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BCS Editorial

AF screening and thromboembolic risk: How much AF is significant?

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Take Home Messages

- AF may go undetected in patients until they experience a complication, such as an AF-related stroke.
- Early diagnosis of AF and initiation of oral anticoagulation may prevent AF-related stroke and death. However, there are knowledge gaps regarding screening strategy and the thromboembolic risk related to duration of AF.
- STROKESTOP and LOOP studies investigated the benefits of systematic screening in high-risk populations with different screening modalities.
- Intermittent ECG screening in STROKESTOP yielded a small but significant net clinical benefit. Yet, there was no significant reduction in stroke and systemic embolism in patients screened with continuous rhythm monitoring and initiated on oral anticoagulation for AF.
- Short-lasting AF episodes may not be clinically significant and the AF burden that warrants anticoagulation is yet to be determined.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. In Europe, the prevalence of AF is projected to more than double and could reach 17.9 million by 2060, driven in part by demographic changes from an ageing population[1]. AF is associated with up to a three-fold increased risk of death and five-fold increased risk of stroke[2-5]. AF-related strokes account for approximately a third of all strokes and tend to be more disabling, more lethal and are more likely to recur[6-8].

Oral anticoagulation, when indicated, is a highly effective stroke prevention strategy with significant reductions in both morbidity and mortality[9]. However, a large proportion of patients are asymptomatic or may only experience brief symptomatic paroxysms of AF, which are not captured on monitoring[10]. AF may, therefore, remain undetected and untreated until patients experience a complication, such as an AF-related stroke or decompensated heart failure [11, 12].

AF screening can lead to early detection which, together with timely initiation of oral anticoagulation, may prevent AF-related strokes and death[13]. However, knowing who should be screened, how and for how long is unclear [14]. Two studies, STROKESTOP and LOOP, published simultaneously in The Lancet used different AF screening strategies in high-risk populations and offer further insights into systematic AF screening (**Table 1**)[15, 16].

About the author

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Table 1. Summary of study design and main outcomes in STROKESTOP and LOOP

	STROKESTOP	LOOP
Study design	Prospective randomised	Prospective randomised
Randomisation	1:1	1:3
Intervention	Intermittent single-lead ECG twice daily for 14 days	ICM (AF ≥ 6 minutes)
Enrolment	2012-2014	2014-2017
Inclusion Criteria	Age: 75-76	Age ≥ 65 and one additional stroke risk factor
Exclusion Criteria	None	History of AF, ongoing or contraindications for OAC
Primary Endpoint	Composite of ischaemic or haemorrhagic stroke, systemic embolism, hospitalisation for bleeding, or death from any cause	Composite of stroke or systemic embolism
Total number of patients (intervention/control group)	28,768 (14,387/14,381)	6,004 (1501/4503)
CHA_2DS_2-VASc score	3.5	4
AF detection after screening		
Intervention	1953 (14.1%) [p=0.005]	477 (31.8%) [p<0.0001]
Control	1794 (12.8%)	550 (12.2%)
Oral anticoagulation		
Intervention	†	455 (29.7%) [p<0.0001]
Control	†	591 (13.1%)
Composite primary endpoint		
Intervention	4456 (31.9%) [p=0.045]	67 (4.5%) [p=0.11]
Control	4616 (33.0%)	251 (5.6%)
Ischaemic stroke		
Intervention	766 (5.5%) [p=0.084]	‡
Control	830 (5.9%)	‡
Haemorrhagic stroke		
Intervention	137 (0.98%) [p=0.27]	11 (0.8%) [p=0.94]
Control	155 (1.1%)	34 (0.8%)
Major bleeding		
Intervention	1431 (10.2%) [p=0.60]	65 (4.3%) [p=0.11]
Control	1448 (10.3)	156 (3.5%)
All-cause death		
Intervention	3177 (22.7%) [p=0.12]	168 (11.2%) [p=1.00]
Control	3287 (23.5%)	507 (11.3%)

AF, atrial fibrillation. ICM, implantable cardiac monitors. OAC, oral anticoagulants.
† Total number of patients on oral anticoagulation is not available only number of patients stratified per year.
‡ Number of ischaemic strokes is not available. Composite primary endpoint combines ischaemic strokes with systemic embolism.

AF screening

The likelihood of detecting new AF during screening depends upon screening intensity (single time-point, intermittent, continuous), screening strategy (opportunistic, systematic) and the demographics of the population being screened[14].

In general, the longer the monitoring window and intensity of screening, the higher the yield (**Figure 1**)[15-24]. The detection rate of new AF in individuals aged ≥ 65 years was 1.4% in a meta-analysis of 19 studies using single time-point assessment vs. a 34% yearly detection rate in the ASSERT-II study which used implantable cardiac monitors (ICM)[17, 23]. Nevertheless, the cohort of patients diagnosed with AF on single time-point screening are likely to have a higher arrhythmia burden, and thus sit more closely with patients who have clinically apparent AF[25]. Though extended screening with continuous rhythm monitoring undoubtedly identifies more AF, this includes short-lasting asymptomatic AF episodes (i.e minutes) of unclear clinical significance and the episode duration or daily AF burden that merits oral anticoagulation is currently unknown.

AF screening strategies have previously been classified as opportunistic, usually during a healthcare visit, or systematic, targeting an entire population. Recent advancements in consumer-facing wearable devices (smartphone applications, smartwatches, bands or rings) have given rise to a third type of AF screening: patient-initiated screening[26]. These new technologies provide exciting new screening tools but there are significant knowledge gaps in their accuracy and use within the current healthcare system.

Opportunistic screening is recommended by many major medical societies[5, 27-29]. Pulse palpation to assess for an irregular pulse followed by an electrocardiogram is recommended by NICE if AF is suspected, and by the European Society of Cardiology (ESC), in individuals aged ≥ 65 years[5, 27]. However, there is less consensus with regards to systematic screening: ESC recommends systematic screening for individuals aged ≥ 75 years old, or at a high stroke risk —albeit with a lower class of recommendation, Class IIa — but UK National Screening Committee and the US Preventive Service do not[29, 30]. The rationale for this is the lack of robust randomised hard outcome data.

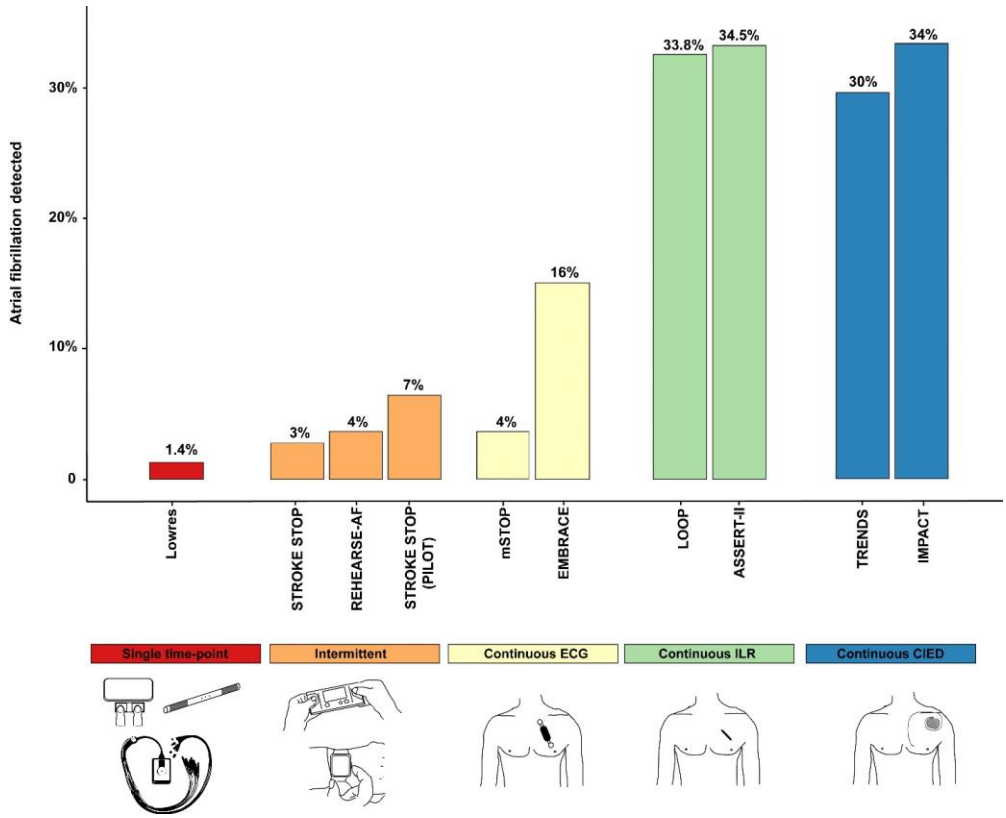

Figure 1. Rates of AF detection with different screening modalities (Adapted from Engdahl et al[25])

STROKESTOP[16] and LOOP[15] – Headline results

The STROKESTOP study randomised 28,768 Swedish residents aged 75-76 years to intermittent AF screening or routine care (control group). Individuals assigned to screening were required to perform a 30-second ECG twice daily with a handheld device (Zenicor) for 14 days. AF was defined as an irregular rhythm without P-waves for 30 seconds or two episodes lasting 10-29 seconds each. If AF was detected or previously untreated, oral anticoagulation was offered. Notably, there was no exclusion criteria. At baseline, the control group had a slightly higher rate of AF than the screening group (12.8% vs 12.1%) but after screening, 262 (1.87%) new AF patients were identified.

Over the course of the study, screening led to a higher proportion of new AF diagnosis in the intervention arm. Although oral anticoagulation initiation in AF patients after one year was higher in the screening group (65.8% vs 59.8%, p= 0.005, respectively), this levelled out during the study. After a median follow-up 6.9 years, fewer patients in the screening group met the primary endpoint (composite of ischaemic or haemorrhagic stroke, systemic thromboembolism, severe bleeding, and all-cause mortality) than those in the control group (4456 vs 4616, respectively). The intention-treat analysis showed only a modest 4% relative risk reduction (HR 0.96: CI 0.92-1.00; p-value=0.045) in the primary endpoint which represents a number needed to screen of 91 patients. The Kaplan-Meier curves start to diverge at around four years, and the overall results appear to be driven by a reduction in ischaemic strokes in the screening arm. The authors concluded that AF screening in the elderly is safe and led to a 'small net clinical benefit'.

The LOOP study was designed to investigate whether continuous rhythm monitoring with ICMs and oral anticoagulation for AF episodes longer than 6 minutes would prevent ischaemic strokes and systemic embolism (primary endpoint). 6,004 Danish patients aged over 70 with an additional risk factor for stroke were randomised in a one-to-three fashion to an ICM (1,501) or routine care (4,503). The median CHA2DS2-VASc was 4 and patients were followed up for a median of 16.8 months. Despite a three-fold increase in AF detection (31.8% vs 12.2%) followed by oral anticoagulation initiation (29.7% vs 13.1%) in the ICM group, there was a non-significant 20% reduction (HR 0.80; 95% CI 0.61-1.05, p = 0.11) in the primary endpoint.

Interpretation – AF burden and thromboembolic risk

How to reconcile the difference in outcomes between these two trials in a similar high-risk population? As the authors of the LOOP study concluded: 'not all AF may be worth screening' [15]; implying that AF burden may play a significant role in the overall thromboembolic risk.

Landmark trials demonstrating the net clinical benefit of oral anticoagulants required electrocardiographic evidence of AF prior to enrolment [31-34]. As a result, they were more likely to include patients with persistent AF or a high burden of paroxysmal AF. A recent meta-analysis demonstrated that the adjusted and unadjusted mortality and stroke risk was higher in persistent AF, supporting the notion that AF burden is a risk modifier in clinical AF[35].

Studies with cardiac implantable electronic devices (CIEDs) provide some insight into the association between AF episode duration and/or AF burden and thromboembolic risk [22, 36-43]. The term 'silent' or 'subclinical' AF was initially coined to refer to asymptomatic AF episodes detected by CIEDs, but it is perhaps used more broadly today to include episodes captured by ICMs and wearable devices. Importantly, these devices have a varying degree of diagnostic accuracy, and all episodes require adjudication to confirm that they truly represent AF and are not false positive detections due to far-field R wave, ectopy, or other atrial tachyarrhythmias.

Patients with subclinical AF have a 5-fold increased risk of developing clinical AF and a significant yearly stroke risk (2.8/100 per person-years) albeit numerically smaller than patients with clinical AF[44]. The AF episode duration associated with increased thromboembolism risk varied considerably amongst studies: 5 minutes in MOST, 6 minutes in ASSERT, 1 hour in SOS, 5.5 hours in TRENDS and Turakhia et al, and 24 hours in studies by Botto et al, Cappuci et al. [22, 36-38, 41, 45]

The LOOP investigators designed their study in line with ASSERT study criteria, which showed an association between subclinical AF episodes ≥ 6 minutes and thromboembolism[39]. However, a post-hoc analysis of the ASSERT study published in 2017 demonstrated that only episodes longer than 24 hours were associated with ischaemic strokes, and, in fact, there was no difference between patients with subclinical AF lasting 6 minutes to 24 hours and those without subclinical AF[43]. In the LOOP study, the AF threshold that triggered oral anticoagulation was likely too low; AF episodes ≥ 24 hours were only seen in 16% of patients which may help the non-significant reduction in ischaemic strokes observed in the study.

STROKESTOP screening strategy required participants to monitor their rhythm for 14 minutes during a 2-week period — approximately 0.07% of the screening window. It therefore included patients with a higher AF burden in whom the stroke risk most closely resembles clinical AF. Moreover, one should take into account that the intervention in STROKESTOP was an invitation for screening and only 51.3% participated. In this 'as-treated' cohort, which represents a younger and healthier group, the results are more compelling with a 24% reduction in ischaemic stroke (HR 0.76; 95% CI 0.68 - 0.87; p < .001).

Other factors, in addition to AF burden, may have influenced the results of the LOOP study. The control arm had an unusually high rate of AF detected (12%); the authors had assumed a 3% detection rate in keeping with other studies, such as CRYSTAL-AF and EMBRACE-AF[21, 46]. This may have diluted the difference in outcomes between the intervention and control arms. Compliance with the ICM was also overestimated; rates of early ICM explants were more than double than anticipated, 12% and 5%, respectively.

Two randomised controlled trials (ARTESiA, NCT01938248; NOAH AFNET 6, NCT02618577) of oral anticoagulation in subclinical AF episodes are currently ongoing and may further inform our understanding[47, 48].

Conclusions – What lessons are we to learn?

Taken together, these two studies strengthen our understanding of AF screening. Firstly, they demonstrate the feasibility of using new technologies with remote monitoring to screen large number of patients. Secondly, they highlight the challenges of screening invitation as an intervention, particularly amongst those in older age groups or lower-socioeconomic status — almost half of those invited did not engage with screening in STROKESTOP. Thirdly, they provide further evidence that short-lasting AF episodes carry a lower thromboembolic risk and may not warrant oral anticoagulation and intermittent ECG monitoring may be a better strategy. Lastly, these studies reinforce current ESC guidance which upgraded systematic screening from class IIb to IIa recommendation; results of HEARTLINE, SAFER and STROKESTOP2 are eagerly awaited (**Table 2**).

Table 2. Summary of selected systematic screening studies currently recruiting.

Study	Study design	Population	Sample size	Intervention	Follow-up	Primary endpoint	Funding
STROKESTOP2 (NCT02743416)	RCT	76-75	28,712	Invitation for screening with handheld 30-secs ECG four times a day for 14 days combined with biomarker (NT-proBNP)	5 years	Incidence of stroke and systemic embolism: 1. Control vs intervention 2. Control vs low-risk (NT-proBNP <125ng/l)	Roche
HEARTLINE (NCT04276441)	RCT	≥ 65	150,000	Intermittent screening with iPhone or Apple Watch	3 years	1. Time to AF diagnosis 2. Days covered by oral anticoagulation	Jansen and Apple
SAFER (ISRCTN72104369)	RCT	≥ 70	120,00	Intermittent screening with handheld 30-sec ECG four times a day for 3 weeks	5 years	Fatal or non-fatal stroke	NIHR

ECG, electrocardiogram. NIHR, National Institute of Health Research. PPG, photoplethysmography. RCT, randomised controlled trial

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