

Large-scale screening studies for atrial fibrillation – is it worth the effort?

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Atrial fibrillation (AF) is a common disease with increasing prevalence, approximately 3.2% in the adult population. In addition, about one third of AF cases are considered asymptomatic. Due to increased longevity, increased detection and increased prevalence of risk factors, the prevalence of AF is expected to at least double by the year 2060. Patients with AF have an increased risk for ischaemic stroke, heart failure, death and cognitive decline. Treatment with oral anticoagulation reduces the risk of ischaemic stroke and mortality, and the effect on cognitive decline is being studied. Based on the increasing prevalence of AF, its often asymptomatic and paroxysmal presentation and

the efficacy of oral anticoagulation treatment, screening for AF has been proposed. AF seems to fulfil most of the Wilson–Jungner criteria for screening issued by the World Health Organization, but some knowledge gaps remain, gaps that will be addressed by several ongoing studies. The knowledge gaps in AF screening consist of the magnitude of the net benefit or net harm inflicted by AF screening because the oral anticoagulation treatment will also increase the risk of bleeding, and the psychological effects of AF screening are not very well studied. So far, the AF screening recommendations issued by the European Society of Cardiology have had limited impact on national and regional AF screening activities. Several large-scale AF screening studies will report results on hard endpoints within the next few years, and these results will hopefully manifest AF as a cardiovascular disease which we need to pay more attention to.

Keywords: atrial fibrillation, ECG, screening, stroke.

Introduction

Atrial fibrillation (AF) is a common disease with increasing prevalence, approximately 3.2% in the adult population [1]. In addition, about one third of AF cases are considered asymptomatic [2,3]. Due to increased longevity, increased detection and increase in prevalence of risk factors, the prevalence of AF is expected to at least double by the year 2060 [4–6].

In patients with AF, there is an increased risk for stroke, heart failure and death [7]. Although the mechanism is not fully elucidated, there is also a strong association between AF and cognitive dysfunction [8]. Treatment using oral anticoagulants (OAC) is efficacious in reducing the risk for ischaemic stroke and death. Recent register studies strongly indicate that OAC treatment is also

associated with lower incidence of cognitive dysfunction in AF patients [9, 10].

AF is common and associated with several negative outcomes. There is a large proportion of undiagnosed asymptomatic cases, and there is treatment available to reduce the risk of clinical events, and therefore, it has been proposed that AF should be subjected to screening.

The aim of this paper is to review the available data on AF screening methods as well as the design and outcome of large AF screening studies.

Atrial fibrillation epidemiology

For a long time, AF prevalence only considered permanent or persistent forms of the arrhythmia [11]. Because the majority of patients have paroxysmal AF [12], this led to a gross underestimation

of the prevalence [13]. An estimation from Sweden including hospitalized cases and outpatients from specialized care and primary care reported a total prevalence of 3.2% in the adult population [1]. When considering different age strata amongst elderly populations, an Italian study reported a prevalence of AF of 6.6% in a population aged above 65 years [4], and a Swedish screening study reported an AF prevalence of 9.3% in a 75/76-year-old population [3]. The AF prevalence increased to 12.3% after AF screening in the same study, indicating a considerable proportion of clinically undiagnosed cases in this age group. A Norwegian AF screening study reported a prevalence of 5.8% in a 65-year old population with at least one additional stroke risk factor, increasing to 7.6% after AF screening [14]. Men seem to have a higher prevalence than women in all age strata [1].

Several reports on the future projections of AF prevalence from different parts of the world all report at least a doubling of the prevalence in the nearest 30–40 years [4–6]. This is most likely due to increased longevity.

The age-adjusted incidence and lifetime risk of AF are lower in women than in men. The lifetime risk of developing AF is estimated as 1 in 3 individuals [15, 16]. Incidence of AF is depending on the presence of several risk factors, of which the most important are hypertension, obesity and age [17].

Patients with AF and risk factors have an increased risk for ischaemic stroke and systemic embolism. This risk is associated with both structural and functional changes in the atria and in particular the left atrial appendix, which will generate a prothrombotic environment [18].

For patients with an increased risk of ischaemic stroke and systemic embolism due to AF, oral anticoagulation (OAC) offers a major risk reduction in the region of 70% [19, 20], though it comes with an increased risk of bleeding. During the vitamin K antagonist (VKA)-era, undertreatment with OAC in patients with AF was common and antiplatelet therapy was often used as a treatment option instead [21]. Since the introduction of non-vitamin K oral anticoagulants (NOACs) more than a decade ago, guideline adherence has improved with regard to OAC treatment [22], and a decrease in ischaemic stroke rate has been reported [23, 24].

To estimate the stroke risk in patients with AF, the risk factor scoring system CHA₂DS₂-VASc [25] is now widely used; however, alternatives have been developed [26].

A lesser known complication of AF is the association with cognitive dysfunction and dementia, including not only vascular dementia but other common subtypes [27]. Two large-scale register studies have noted a reduction in dementia incidence in AF patients treated with OAC, including AF patients aged 65 years or older [9, 10]. Although these data have to be confirmed in randomized clinical trials, the possibility to prevent dementia could be another reason for AF screening.

The costs for society inflicted by AF and its complications are difficult to estimate since a share of this cost will comprise long-term care of stroke survivors, a share that is not always accounted for in healthcare expenses. However, a Scottish study reported an annual cost of almost £3800 for AF patients [28], and Swedish data have reported that the majority of AF costs derive from complications [29].

Why is atrial fibrillation a candidate for medical screening?

Wilson and Jungner presented the World Health Organization (WHO) guidelines for medical screening in 1968 [30]; see Table 1. AF seems to fulfil most of these criteria, but there are remaining uncertainties.

As stated in the previous section, AF is a common disease with a rising prevalence, even if only the symptomatic cases are considered. Atrial fibrillation undoubtedly has asymptomatic forms [31]. It is common to find episodes of AF with and without symptoms within the same individual [32–34]. Even if less is known about predictors for symptoms in AF, asymptomatic forms seem to be more common with persistent forms and with a normal heart rate [35].

As there is no diagnostic test with 100% sensitivity or specificity, the screening process will result in false-positive and false-negative cases. The diagnostic performance of a screening test is summarized in a two-by-two table as in Fig. 1. For most individuals with risk factors for stroke, the risk of having AF without OAC treatment is higher than the risk of having OAC treatment without an AF diagnosis. Hence, a missed diagnosis of AF

Table 1. Example of screening yield

WHO criteria	Applicability for AF screening
1. The condition sought should be an important health problem	The prevalence of AF is high and further increasing. AF increase the risk for ischemic stroke manifold and implies an increased risk for heart failure, death, and arrhythmia symptoms. AF is also associated with cognitive decline
2. There should be an accepted treatment for patients with recognized disease	There is overwhelming evidence that oral anticoagulation treatment reduces the risk of ischemic stroke and death in patients with AF and risk factors
3. Facilities for diagnosis and treatment should be available	Availability of ECG recording equipment and diagnostic expertise is varying widely between and within health care systems. Technological development, and in particular development of smartphones and smart watches will increase availability of ECG or heart rhythm recording devices
4. There should be a recognizable latent or early symptomatic stage	The natural course of AF is not yet fully elucidated, it is however well established that AF, regardless of AF subtype, could be asymptomatic
5. There should a suitable test or examination	At present, an ECG recording is necessary for the diagnosis of AF. All available ECG recording modalities are suitable for diagnosing AF including intracardiac recordings. ECG recordings are dependent on the qualifications of the interpreter. Pulse taking is available to detect irregular pulse suggestive of AF, but this modality is hampered by low positive predictive value
6. The test should be acceptable to the population	In general, there is no risk of physical harm associated with ECG recordings. High tolerability has been reported from AF screening studies. For certain long-term ECG modalities, moderate skin irritation may occur with the use of adhesive skin electrodes
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood	The natural history of AF is not entirely investigated, particularly so in the general population. For subgroups like patients with cardiac implantable devices and/or patients undergoing AF ablation, some data are available. It has been proposed that AF will progress from paroxysmal to permanent forms, but data from cardiac device studies suggest that progression could be slow or absent
8. There should be an agreed policy on whom to treat as patients	For patients diagnosed with AF using 12-lead ECG, via external long-term ECG recordings or inpatient ECG telemetry, there are unanimous recommendations to offer patients with risk factors treatment with OAC regardless of symptoms. However, for the group of asymptomatic patients with paroxysmal AF, the net benefit of OAC treatment is less studied. For patients with short episodes of AF recorded via implantable devices, the net benefit of OAC is not yet supported by randomised trials
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	So far, simulation studies have reported cost-effectiveness for AF screening
10. Case finding should be a continuing process and not a 'once and for all' project	At this time, there are no continuous national screening programs for AF

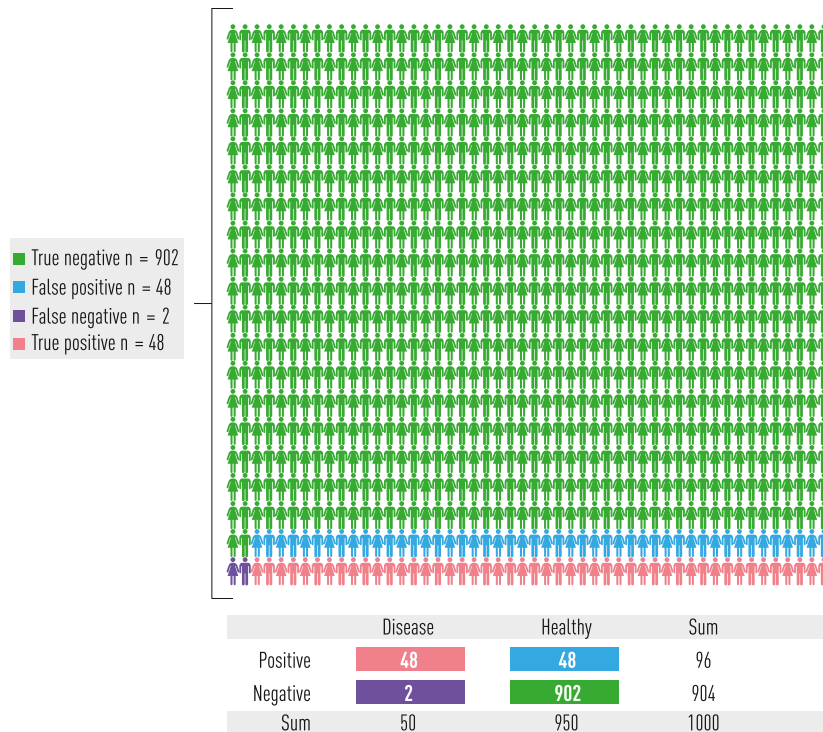


Fig. 1 Distribution of screening yield in a population of 1000 individuals, a undetected disease prevalence of 5% and a sensitivity and specificity of both 95%.

constitutes a higher risk than a falsely positive diagnosed AF, and a high sensitivity is very important for the screening test. On the other hand, if the disease prevalence is low in the screened population, the proportion of false positives will be of growing importance in the balance between sensitivity and specificity. For example, with an untreated disease prevalence of 5% and sensitivity and specificity of 95%, a screening of 1000 individuals will result in 48 true positives, 2 false negatives, 902 true negatives and 48 false positives (Fig. 1). Notably, the disease prevalence expressed as the detection rate in AF screening has been reported to vary within wide limits depending on the population studied and to vary even more depending on the screening device used [36]. The specificity of most AF screening devices is at least 90% [37]. In comparison, specificity for mammography in mammary cancer screening is reported to be 90.5% [38].

One could speculate that many of the patients being falsely diagnosed with AF during screening,

particularly when using one-lead ECG recordings, have an excess of premature atrial contractions (PACs) and/or short runs of PACs. Excess of PACs and runs of PACs are associated with an increased risk for incident AF, stroke and mortality [39-41]. Thus, one could further speculate that individuals falsely diagnosed with AF due to supraventricular activity could have some benefit from OAC treatment, but there are no prospective trials yet on the benefit of OAC on this indication.

The diagnostic performance of several newer ECG recording devices has been reported [37]. However, these validation studies are mostly performed in an office setting – compared to the gold standard of 12-lead ECG. In most cases, this setting does not resemble the actual screening setting in which participants are expected to record multiple intermittent ECG recordings or a continuous ECG recording in an ambulatory setting. Furthermore, patients diagnosed with AF in screening studies using long-term ECG often have multiple paroxysmal AF episodes [3, 42], which should increase the

diagnostic accuracy. The true diagnostic performance of newer ECG devices during ambulatory use is therefore partly unknown, as most detected cases of AF are paroxysmal and comparison with the gold standard of 12-lead ECG in this setting is not possible.

The diagnostic performance of ECG is also very dependent on the qualifications of the reader. The aspects of inter- and intrareader variations are less often reported in the validation of newer ECG recording devices. Although some of the ECG devices used for AF screening have reported diagnostic performance for the automated ECG interpretation algorithm [37], the performance is not yet of a standard that would allow for relying on the algorithms only, particularly not for positive recordings. However, the prediction of AF using Artificial Intelligence (AI) in the interpretation of 12-lead ECG in sinus rhythm has been reported with encouraging results [43].

Even if the ECG or pulse palpation measurements made in connection to AF screening have to deal with the trade-off between sensitivity and specificity, there is no grading in the response to a positive recording; that is, if an individual is diagnosed with AF during screening, risk factors for stroke should be assessed and OAC treatment started as appropriate. An exception to this is if a suspicion of AF has been raised by irregular pulse palpation or by pulse plethysmographic (PPG) recordings. In these examples, the AF diagnosis must be confirmed by an ECG recording.

In contrast, other cardiovascular screening programmes like abdominal aortic aneurysm screening, the result from screening will be a continuous variable (abdominal aortic diameter) to which there are different follow-up options, some of which will include further examinations but not necessarily any intervention [44].

Screening for AF is so far mostly targeted at reducing the risk of ischaemic stroke in the screened population by commencing OAC treatment in detected cases. Further possible benefits from AF screening would be lower mortality, lower risk of cognitive decline and a possibility to address undetected structural heart disease and untreated cardiovascular risk factors such as hypertension, obesity, alcohol consumption and sleep apnoea.

There is overwhelming evidence from the late 20th century that OAC treatment reduces the stroke risk and mortality in patients with clinically diagnosed AF [19], that is patients seeking medical attention for AF-related symptoms. On the other hand, there are less data on the net benefit of OAC treatment in patients with asymptomatic or screen-detected AF because this particular group has not yet been evaluated separately in prospective trials with regard to stroke risk and net benefit or net harm using OAC treatment.

There are, however, several studies suggesting that patients diagnosed with asymptomatic AF have similar or worse prognosis than patients with clinical diagnosed AF [45, 46]. It has also been demonstrated that patients with screening-detected AF are highly motivated to initiate and adhere to OAC treatment, even in the long term [3, 47].

Several studies are now underway with the aim of assessing the value of AF screening and treatment with OAC in newly diagnosed cases, which will be discussed below.

Screening strategies

The two strategies used in AF screening are systematic and opportunistic screening.

In systematic screening, an entire population or a stratum of a population is targeted for screening. Examples of systematic screening programmes in Swedish health care include blood test for phenylketonuria in newborns, mammary cancer screening by mammography in all women aged 40–74 and abdominal aortic arch aneurysm screening in all men aged 65. Systematic screening will give a complete population coverage of the screening effort but will also introduce some downsides.

For systematic AF screening, the age of the invitees will have a large impact on the screening yield because the prevalence of AF is highly dependent on age. This must be considered when choosing the screening age group. On one hand, a higher age will give a higher screening yield, but on the other hand a higher age could lead to lower participation due to co-morbidities and frailty. To illustrate this point, the participation in a Norwegian study inviting 65-year-olds had an uptake of 94% and a detection rate of 0.9% [14], whilst the Swedish STROKESTOP study, inviting 75- and 76-year-olds

had an uptake of 54% and an AF detection rate of 3.0% [3]. The inverse relationship between uptake and screening yield of AF in relation to age has also been reported in the SAFE trial [48].

A screening invitation in a population will introduce bias, resulting in lower participation rates amongst individuals with lower socio-economic status, longer distance to the screening site and with more co-morbidities [49]. Participation can be increased by multiple invitations and locating screening sites in targeted areas [50]. One would expect that siteless, digital inclusion of participants would improve uptake as compared to invitations to physical screening visits, but experiences from the mSToPS trial show that uptake was far lower than corresponding conventional systematic screening studies [51].

Inviting an entire population or an age stratum of a population will also give a defined denominator for the screening population. Screening studies using only non-targeted advertising for screening recruitment do not have the same possibility to report how many individuals have considered participation in the study.

Opportunistic screening is a strategy in which the participant is offered screening during a healthcare visit not caused by a suspicion of the screened disease. Opportunistic screening has several advantages. First, it will use the existing structure of the healthcare system and there is no need to organize a separate system for screening examinations. Secondly, since patients with chronic disease often have regular visits, they have a high probability of being offered screening in this setting, that is patients with risk factors which will give enrichment to the screening process. Thirdly, a participant could have particular confidence for the screening examination offered by their regular healthcare contact, that is their general practitioner [52]. There are also drawbacks of opportunistic screening. Individuals never visiting healthcare facilities will not be offered screening in this setting. It is further possible that the pre-existing workload of healthcare professionals will limit the screening capacity, both in terms of performing a test and in terms of handling positive findings. In AF screening, the diagnostic test is the ECG, a test that requires reading qualifications, which has been shown to vary in primary care [53]. Automated algorithms for ECG interpretation have not yet entirely solved this issue [37].

Following the advent of heart rhythm recording devices for consumers – mainly smartwatches, smartphones, wearables and handheld units – consumer-initiated AF screening has become increasingly prevalent. The availability of these devices makes it possible for the user to make their own heart rhythm investigation without involving healthcare services. The increased availability could give some advantages such as increased detection, but there are also several other aspects in this development. First, many of these devices do not record ECG but PPG, and any suspicion of arrhythmia must be confirmed using ECG. Secondly, none of the automated interpretations algorithms in the devices have a specificity of 100%, and many users will get a false-positive notification of arrhythmias, which could cause unnecessary worries to the user and further investigations consuming healthcare resources. Thirdly, the risk groups that should be targeted for screening, that is the elderly and those with chronic cardiovascular risk factors, are most likely less frequently users of the devices. Finally, in publicly financed healthcare systems, there is a risk that consumer-initiated screening to some extent will displace other patient groups in the competition for healthcare resources. Two very large trials have reported from the use of smartwatches or wearables for AF screening [54, 55]. The mean age of the participants in these trials was low (35 and 41 years, respectively), and the AF yield was similarly low, 0.09% and 0.04%. As expected, AF detection was strongly age dependent, but participants aged above 65 years constituted minorities of 2-6%. The consequences of false-positive recordings are yet to be reported from these trials.

Screening tools

Pulse taking is a very simple and inexpensive test. Recent studies, however, have reported low sensitivity and low specificity (Figs 2 and 3). Low specificity is a limitation amongst screening tests because individuals without the disease who are tested will be falsely diagnosed as positive and must wait for a confirmative ECG recording. Furthermore, paroxysmal AF will in many cases be missed by pulse palpation because AF episodes are often short, and the majority of patients have a relatively low AF burden [56].

Pulse can be analysed using pulse plethysmography. With this technique, pulse waves are studied with an optical sensor that measure shifts in blood

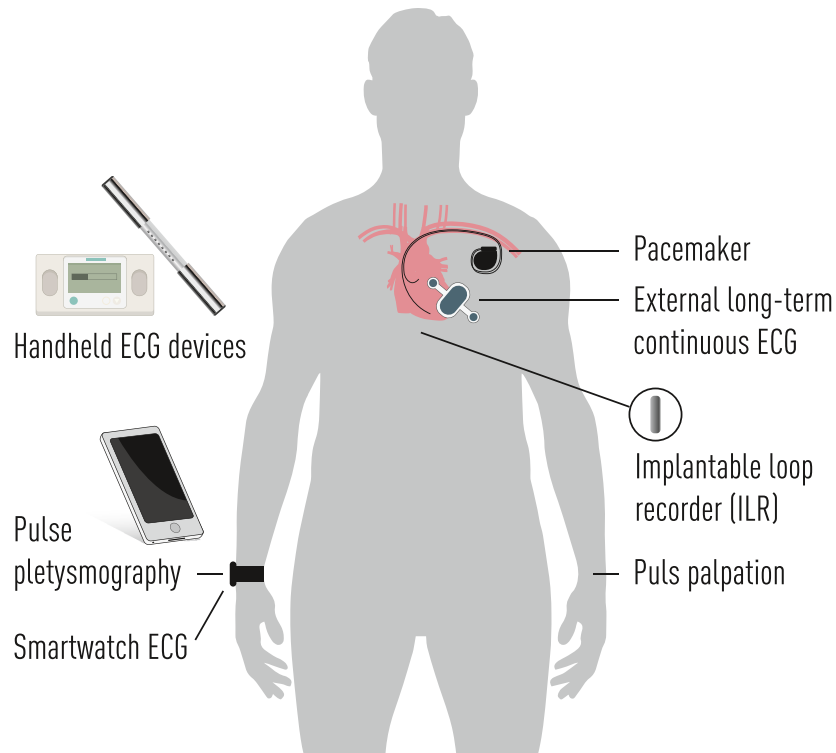


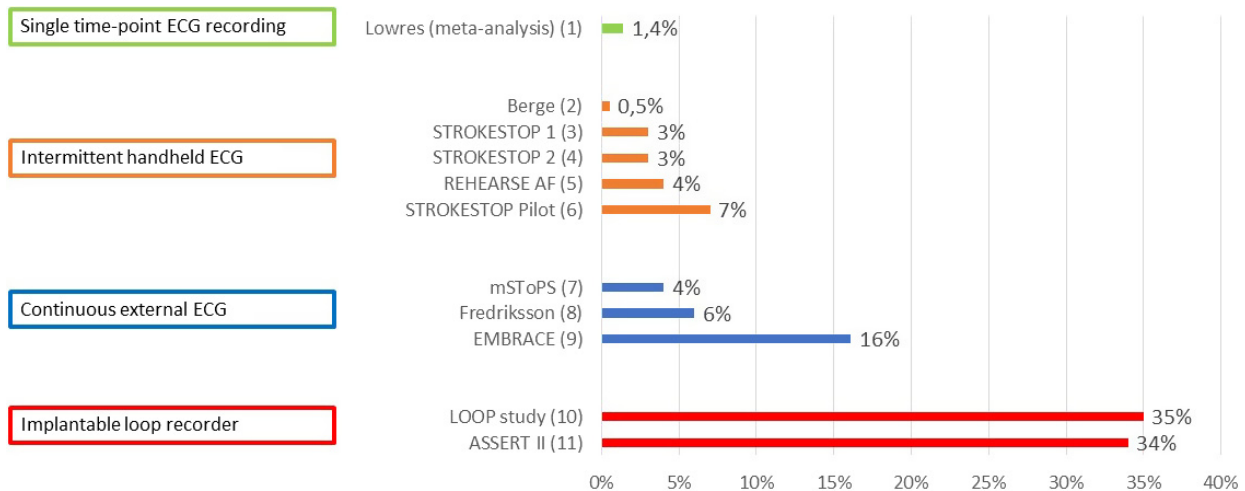
Fig. 2 Examples of methods and devices used for atrial fibrillation screening.

volume in the peripheral circulation, that is in a fingertip. PPG techniques for heart rhythm studies are available in smartphones, smartwatches and wearables. As with pulse taking, there are currently insufficient data regarding the use of PPG for heart rhythm diagnosis, making a confirmatory ECG recording necessary. Considering the high availability of these devices, this modality has a potential for screening large populations with very low device costs for healthcare systems [54, 55]. Several issues remain however to be resolved in the field of consumer-initiated AF screening as noted above.

Handheld ECG devices record in most cases ECG lead I and may be used for one-time or intermittent screening. No confirmatory ECG recording is necessary given that sensitivity and specificity in most validations have been reported to be well above 90% [37]. These devices have been used for repeated intermittent ECG recordings which gives the possibility for long-term screening without electrode attachment. This is because the ECG signal is acquired by the intermittent application of the user's hands to the device. There is a risk of

underdiagnosing paroxysmal AF using this technique [57, 58], and the signal quality is very much dependant on participant adherence to instructions. Handheld ECG recording is also available in some smartwatches, and the use of these for population screening is currently being studied [59].

External long-term continuous ECG devices are available with a recording time from 24 h to several weeks. Continuous ECG has a higher diagnostic yield than corresponding intermittent ECG, but continuous ECG is limited by the risk of skin irritation which can affect compliance. With a similar ECG recording technique using electrode attachment, arrhythmias can be detected by *event recording*. With this technique, continuous time loops of ECG are analysed and stored in the case of predefined arrhythmia or in case of symptom annotation. This both requires less storage memory compared to the storage of full disclosure ECG and allows for longer recordings but is hampered by the limited duration of stored ECG strips and the issue of making the patient comply to several weeks of device attachment.



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Fig. 3 Diagnostic yield in relation to ECG recording modalities in atrial fibrillation screening.

Implantable loop recorders (ILR) are small devices which are inserted subcutaneously on the chest and are used for long-term ECG event recording, up to several years. At present, these devices are mainly used in syncope investigations. ILRs have also been used for AF screening in high-risk patients in several studies, and in general, a very high yield of AF (30%) has been reported [42, 58, 60]. The use of ILR in AF screening is limited by the invasive procedure needed for implantation, the high cost for devices and the high workload associated with adjudication of long-term monitoring. For the moment, one ongoing randomized study is recording the impact of ILR-guided AF screening on stroke incidence [61].

Modern pacemakers and implantable cardioverter defibrillators (ICDs) allow for monitoring, storage and adjudication of arrhythmias including AF. Incident AF is a very common finding in patients with cardiac devices [62]. The threshold of AF burden needed to justify OAC in these patients is not established [63], but several studies addressing this knowledge gap are ongoing [64, 65].

Screening intensity

As noted above, the yield of AF screening is dependent on the screening intensity, that is the duration of ECG recordings. In the same

population, intermittent repeated ECG recordings will give a higher yield than a single ECG recording [3], and a continuous ECG recording of the same duration as the intermittent will give an even higher yield [57]. A meta-analysis including 141 200 cases reported a yield of previously undiagnosed AF in 1.44% of participants older than 65 years and 2.73% of those above 85 years of age [66] using single time screening. In the STROKESTOP study, the AF yield using a single ECG recording was reported to be 0.5% and 3.0% using intermittent ECG recordings [3].

Simulations have reported considerable differences in screening yield between implantable and external ECG recording devices [58, 67], but the stroke risk associated with brief episodes of AF recorded via implantable devices is still to be defined [63].

There is an inverse relationship between the intensity of screening and AF burden in those detected with arrhythmia. Hence, individuals diagnosed with AF on a single ECG recording experience a high risk of persistent arrhythmia. Individuals detected with AF during intermittent recording of short ECG strips will have a high arrhythmia burden since these recordings will cover a very small proportion of time. On the other hand, implantable devices were able to detect very short episodes and very small AF burdens [68]. Because

AF burden is associated with stroke risk [69], this could have implications for the net benefit of OAC treatment after AF screening and detection.

Who should be screened?

Few guideline recommendations on AF screening exist, and their implementation is perhaps even rarer. As for primary prevention, the current AF guidelines from the European Society of Cardiology [7,70] (ESC) recommend opportunistic AF screening by pulse taking or ECG rhythm strip amongst those aged above 65 (class I, level B recommendation) and consideration of systematic AF screening in patients aged >75 years or those at high risk (class IIa, level B recommendation). There is also a recommendation on the regular interrogation of implanted cardiac devices to detect atrial high rate episodes (AHRE) suggestive of atrial fibrillation. In a consensus document from European Heart Rhythm Association [71] (EHRA) endorsed by the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society (APHRS) and the Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE), the primary prevention screening recommendations from the ESC [7] are applied. The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand issued AF guidelines in 2018, including AF screening recommendations for opportunistic point-of-care screening in those aged above 65 years as well as AF screening by interrogation of cardiac devices [72]. For now, there are no specific recommendations on AF screening issued by the American Heart Association. No national-level AF screening programmes have been introduced so far.

Mainly based on the lack of randomized studies on the stroke reduction efficacy of AF screening and on the lack of data on stroke risk of shorter asymptomatic AF episodes, the United States Preventive Services Task Force (USPSTF) [73] and the UK National Screening Committee (NSC) [74] have recommended against AF screening.

What are the harms of AF screening and treatment?

The possible harms of the screening procedure include, amongst other things, the consequences of sensitivity and specificity below 100%, which will lead to false negatives and false positives. In the British SAFE trial, the 12-lead ECG reading accuracy of general practitioners was studied and

resulted in a sensitivity of 80% and a specificity of 92% [53]. Further data on ECG reading accuracy and diagnostic performance in AF screening in the ambulatory setting are scarce, and the diagnostic performance will depend on screening modality, its signal quality and the ECG reading qualifications of the interpreter. False positives will result in OAC treatment in individuals without AF, exposing them to the increased risk for bleeding. As with the stroke risk, the bleeding risk inflicted by OAC in individuals without AF is not well defined and probably lower than the risk reported in patients with AF. Participants with false-negative examination will be exposed for the risks of AF without OAC treatment.

There are limited data on the psychological effects of AF screening. The UK SAFE study collected data on anxiety levels and quality of life before and after screening. The screening seemed tolerable to most participants, but anxiety levels were higher amongst those screened positive for AF [48]. Despite this, a high compliance to OAC treatment has been reported amongst patients diagnosed in AF screening [47].

In their recommendation statement on AF screening, the USPSTF raised concerns about the potential harm that would result from additional investigations following AF screening. Specifically, USPSTF had concerns that ECG abnormalities noted during AF screening would lead to additional testing including invasive procedures like coronary angiography and coronary revascularization, procedures associated with increased risk for bleeding, contrast-induced nephropathy and allergic reactions. Similar risks exist for electrophysiological investigation and ablation treatment for AF. No AF screening study has so far reported the healthcare utilization and the frequency of these invasive procedures following the screening procedure, but one can expect that the need for cardioversion, AF ablation and invasive coronary treatment should be low as patients are mostly asymptomatic.

Overview over selected studies

SAFE

The first randomized AF screening trial at scale was conducted in the UK [48] (Table 2). The SAFE study was designed to determine the most cost-effective method of screening for AF in the population aged 65 years and over, using a single time-point ECG. The study used a multicentre, controlled

Table 2. Summary of selected studies arranged by year of recruitment start

		Recruitment						
Study name	Country	Recruitment start	Design	Sample size	Enrolment setting	Population age	Screening modality	
SAFE	UK	2001	Interventional, randomized	14 802	Systematic screening with invitation or opportunistic screening	65+	12-lead ECG (systematic arm) or pulse taking (opportunistic arm)	
STROKESTOP 1	Sweden	2012	Interventional, randomized	28 768	Systematic invitation by mail in age group	75–76 years	Handheld ECG, one lead	
LOOP study	Denmark	2014	Interventional, randomized	6000	Advertising	75 + years and co-morbidities	Implantable loop recorder, one lead	
BRAIN AF	Canada	2015	Interventional, randomized	3250	Clinical recruitment of low-risk AF patients.	30–62 years	MMSE, MOCA, Quality of life tests	
mSToPS	United States	2015	Interventional, randomized	2659	Invitation by email or mail to health plan members	75 + or male 55+ / female 65 + with co-morbidities	ECG patch, one lead, immediate or delayed monitoring	
ARTESIA	Canada	2015	Interventional, randomized	4000	Patients with permanent pacemaker, defibrillator or insertable cardiac monitor with at least one episode of SCAF > 6 minutes	55 + with additional risk factors	Device monitoring, intracardiac or subcutaneous	
STROKESTOP 2	Sweden	2016	Interventional, randomized, enriched by NT-proBNP levels	28 712	Systematic invitation by mail in age group	75–76 years	Handheld ECG, one lead	
Apple Heart Study	United States	2017	Interventional, single group	419 297	Advertising in mobile app	22+	PPG in smartwatch, ECG confirmation using ECG patch	
SAFER	UK	2018	Interventional, cluster randomized	120 000	Primary care	70+	Handheld ECG, one lead	

Table 2 (Continued)

		Recruitment					
Study name	Country	start	Design	Sample size	Enrolment setting	Population age	Screening modality
GUARD AF	United States	2019	Interventional, randomized	52 000	Primary care	70+	iRhythm Zio patch, one lead
Heartline	United States	2020	Interventional, randomized	150 000	Advertising to Medicare beneficiaries	65 + years	Apple watch/iPhone or iPhone only
		Frequency, duration of ECG or visits		Primary endpoint		Duration of follow-up	
Study name	SAFE	Single time-point ECG or pulse taking	Newly diagnosed AF	Acceptability to screening tools	Other endpoints	Results	
STROKESTOP 1	30 s twice daily for 14 days	Composite of stroke, systemic embolism, bleeding, death from any cause	Incidence of dementia, cardiovascular hospitalization, cost effectiveness, compliance to OAC therapy	5 years	New AF diagnosed in 3.0%, untreated AF noted in 5.1% and 3.7% started OAC treatment. Primary endpoint not yet reported	Mean age 75 years. New AF diagnosed in 1.6% in both systematic and opportunistic arms compared to 1.0% in control arm	
LOOP study	Continuous, 3 years	Time to stroke or systemic embolism	Mortality, bleeding, quality of life, brain imaging on MRI, cost effectiveness, cardiac MRI parameters and more.	Event driven, 4 years	34% diagnosed with AF with duration > 6 minutes after 40 months of monitoring. Primary endpoint not yet reported		
BRAIN AF	Yearly visits	Composite endpoint of stroke, TIA and neurodegenerative decline with Rivaroxaban compared to ASA	Mortality, cardiovascular hospitalization, bleeding, rate of decline of MMSE and MOCA score	Event driven, minimum 2 years	Primary endpoint not yet reported		

Table 2 (Continued)

Study name	Frequency, duration of ECG or visits	Primary endpoint	Other endpoints	Duration of follow-up	Results
mSToPS	Continuous, 14 days	AF > 30 s newly diagnosed by the device or new AF diagnosis in claims data	Prevalence of AF. Time to first combined endpoint of systemic emboli/stroke/MI in monitored vs. control cohorts. Health care utilization.	3 years	New AF diagnosed in 3.9% in immediate group compared to 0.9% in delayed group. Secondary endpoints not yet reported
ARTESIA	Continuous in cardiac devices	Ischemic stroke and systemic embolism, major bleed	Myocardial infarction, cardiovascular death, all-cause death	Event driven, 3 years follow-up anticipated	Primary endpoint not yet reported
STROKESTOP 2	30 s four times daily for 14 days	Stroke incidence in low-risk group compared to control group.	Cost effectiveness, diagnostic performance of a wide variety of biomarkers, performance of ECG recording modalities	5 years	New AF diagnosed in 4.4% in high-risk group. NT-proBNP strongest predictor for new AF. Primary endpoint not yet reported
Apple Heart Study	Intermittent photoplethysmography, ECG patch if irregular rhythm	AF > 30 s on ECG patch, simultaneous AF on ECG patch and irregular photoplethysmogram	Simultaneous AF on ECG patch, irregular pulse notification and contact with health care provider	117 days (median monitoring time)	Mean Age 41 years. Irregular pulse noted in 0.5%. Overall AF yield 0.04%
SAFER	30 s four times daily for 21 days	Fatal or non-fatal stroke	Proportion of new AF and OAC treatment in both arms, psychological and functional status outcome	5 years	Primary endpoint not yet reported
GUARD AF	Continuous, 14 days	Stroke or bleeding leading to hospitalization	OAC prescriptions	2.5-5 years	Primary endpoint not yet reported

Table 2 (Continued)

Study name	Frequency, duration of ECG or visits		Primary endpoint	Other endpoints	Duration of follow-up		Results
	ECG or visits	Intermittent			Duration of follow-up	Duration of follow-up	
Heartline			Time to AF diagnosis, percent days covered by OAC (known AF cohort)	Time to major adverse cardiovascular events, cost of care, health care utilization, cost effectiveness	3 years	3 years	Primary endpoint not yet reported

AF, Atrial Fibrillation; ASA, Acetylsalicylic Acid; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; MRI, Magnetic Resonance Imaging; OAC, Oral Anticoagulation Therapy; SCAF, Subclinical atrial fibrillation; TIA, Transient Ischaemic Attack.

randomized design. It was set in general practice, using 25 practices for intervention and 25 practices for control. In the intervention practices, patients were randomly allocated to systematic ($n = 5000$) or opportunistic ($n = 5000$) screening. AF screening was performed using pulse taking followed by an ECG recording in cases with irregular pulse. In both systematic and opportunistic arms, AF detection was higher (1.63%) in the screened population compared to the control population (1.04%), and similar proportions of patients with new AF were detected using opportunistic or systematic approach. This was the first study demonstrating that AF screening detects additional cases over current practice.

STROKESTOP 1

The STROKESTOP 1 study is a Swedish randomized study that aimed to study the effect of systematic AF screening in a population aged 75 and 76. It is the first large-scale AF screening study using ambulatory ECG. The population of Stockholm and Halland Regions in Sweden aged 75 and 76 ($n = 28\ 768$) were randomized 1:1 to intervention and control. The intervention group was offered AF screening using intermittent handheld ECG for 30 s twice daily for 14 days. Patients with newly diagnosed AF or previously known AF without OAC treatment were offered OAC treatment at a cardiologist consultation. Results of recruitment and screening yield have been reported [3]. New AF was diagnosed amongst 3.0% of participants, and another 2.1% had known AF without OAC treatment. In total, 3.7% of participants started OAC treatment for AF because of their participation. Uptake was 50% and affected by socio-demographic factors [49]. A five-year follow-up including incidence of stroke in the intervention and control group is expected in 2021.

LOOP study

The Danish LOOP study is a randomized multicentre study using ILR in the intervention arm for AF detection [61]. The study will evaluate the effectiveness and cost effectiveness of ILR as an AF screening tool. Participants at least 70 years of age and with at least one risk factor of hypertension, diabetes mellitus, heart failure or previous stroke were randomized 1:3 to intervention ($n = 1500$) or control. Those randomized to intervention received implantation of an ILR. The LOOP study also collects data on quality of life, cognitive

decline, echocardiographic data, serologic risk markers and imaging using brain and cardiac MRI. This study offers a unique possibility to study in detail the impact of silent arrhythmias, the significance of AF burden, natural history of AF and the stroke risk associated with subclinical AF. The primary endpoint is time to first stroke or systemic embolism. Study duration is event driven.

BRAIN AF

Addressing this risk of cognitive impairment associated with AF, the Canadian BRAIN AF study will examine if anticoagulation reduces the cognitive decline in patients with AF and low stroke risk [8]. The study is a randomized, controlled, multicentre design, recruiting patients with low-risk non-valvular AF and randomizing them to low-dose rivaroxaban (15 mg daily) or standard of care. The primary endpoint is a composite of stroke, transient ischaemic attack and cognitive decline. The study plans to enrol 3,250 patients at 130 sites and will provide important data on the possibility to reduce cognitive decline in AF patients not eligible for OAC treatment according to current guidelines.

The mHealth Screening to Prevent Strokes (mSToPS)

To determine the effect of a self-applied wearable ECG patch for screening of AF, the mSToPS clinical trial used a siteless study design and recruited participants via email and regular mail from a large health insurance plan's members in the United States [75]. The study included individuals older than 75 years, or males aged above 55 years and females aged above 65 years with specified comorbidities. The participants were intended to make two separate 2-week recordings using an ECG patch with 3 months between recordings. Participants were also randomized to immediate (within 2 weeks) or delayed (4 months later) screening. There were no physical visits within this trial; all communication, including participants' consent and instructions, was digital except for a share of the invitations which were sent by regular mail. Notably, only 4.3% of the eligible invitees who were sent an email ($n = 52\,553$) and only 0.76% of the 50 000 invited by regular mail invitation were enrolled. In the immediate screening group, 3.9% were identified with new AF as compared to 0.9% in the delayed group. Monitored individuals had higher rates of AF diagnosis, greater initiation of OAC treatment and increased healthcare

consumption at one year. This important study shed light on several important aspects of AF screening, such as the possibility to use siteless and digital enrolment of participants using the patch ECG device. However, it also revealed the very limited response rate to invitations which led to optimization of the recruitment process [51].

ARTESiA

Another study focusing on silent episodes of AF recorded in implanted devices is the multinational, multicentre ARTESiA trial [65]. This trial is a prospective, randomized, controlled trial recruiting patients with an implanted pacemaker, defibrillator or cardiac monitor. Participants with subclinical episodes of AF < 24 h and stroke risk factors are eligible and randomized 1:1 to treatment with apixaban or aspirin, and the primary outcome is a composite of stroke and systemic embolism. The study will include approximately 4000 participants and address the important knowledge gap if short, often asymptomatic episodes of AF recorded in cardiac implanted devices will have a net benefit from OAC treatment. This trial is projected to complete inclusion in 2020.

STROKESTOP 2

Following the STROKESTOP 1 study, the STROKESTOP 2 study started recruitment in 2016. STROKESTOP 2 is a Swedish population screening study for AF aimed at studying the effect of AF screening on stroke incidence in the screened population, using plasma biomarkers as enrichment. The plasma peptide NT-proBNP has been demonstrated to be elevated in individuals with incident AF [76], including silent, paroxysmal disease [77]. As in STROKESTOP 1, the entire population ($n = 28\,712$) of 75- and 76-year-olds in the Stockholm region were randomized 1:1 to intervention or control. Participants with NT-proBNP > 125 ng L⁻¹ were offered screening using intermittent handheld ECG four times daily for 14 days. OAC treatment was suggested to participants as in STROKESTOP 1. Results of ECG screening revealed 2.6% new AF detection in total, with a yield of 4.4% in the high-risk group with elevated NT-proBNP [78]. Furthermore, 94% of patients with new AF accepted to start OAC treatment. Five-year results in terms of incident stroke, mortality and bleeding are expected in 2024. This is the first large-scaled AF screening study using serological biomarkers for enrichment. The biobank created during the study will give further data on

how future serological markers can be utilized in identifying individuals with increased risk for AF.

Apple Heart Study

The Apple Heart Study poses another example of digital recruitment and examination in AF screening, at an even larger scale [55]. In this extraordinary AF screening study, a prospective, single-group, open-label siteless design was applied. The study recruited US individuals using a smartphone app being 22 years or older possessing compatible Apple iPhone and Apple Watch. The participants recorded the heart rhythm using the PPG sensor in the Apple Watch, creating 1-minute tachograms which were classified as either regular or irregular. Given that ECG confirmation is necessary in AF-suspicious recordings made by PPG, those with irregular rhythm were offered a teleconsultation and also an offer to wear an ECG recording patch up to 7 days in non-urgent cases. Of the 419 297 individuals enrolled, mean age was 41 years. There were 2161 (0.5%) participants with a notification of irregular pulse. Of those, 450 (0.1%) returned an analysable ECG patch. AF was noted in 153 of those 450. The frequency of irregular rhythm notifications was strongly age-correlated as one would expect, with very low rates below 55 years of age. Apart from the size of this study, the very low diagnostic yield in the studied age group and the difficulties with a stepwise diagnostic approach, making the participants performing another examination based on a suspicion from the first, is notable. Because ECG recording is available in newer generations of smart watches, Apple will study its use in the ongoing Heartline study [59].

SAFER

The SAFER study is by far the largest AF screening study directed towards risk groups. It will recruit participants aged 65 or older [79]. The project is coordinated by the University of Cambridge, UK, and aims at studying if AF screening is effective in reducing stroke and other key outcomes. The study will use handheld intermittent ECG for ambulatory ECG recording. After the feasibility trial, a pilot trial and a randomized trial are planned. The randomized trial will include 300 general practices involving 120 000 participants. One hundred of those practices will include patients in the intervention arm, and 200 practices will serve as control. The study also has a comprehensive

programme for qualitative studies and other sub-studies. Follow-up will be completed in 2026.

GUARD AF

The ReducinG stroke by screening for Undiagnosed atrial fibrillation in elderly individuals (GUARD AF) study is sponsored by Bristol Myers Squibb and Pfizer Alliance. It aims to fill the knowledge gap of the impact of hard endpoints of stroke and bleeding from AF screening [80]. U.S. citizens aged above 70 years in the Medicare system will be included in primary care. The study will deploy a 14-day continuous ECG recording using patch ECG. The primary endpoints are hospitalization for stroke or bleeding. With the aim of randomizing 52 000 participants from 300 sites to usual care or AF screening during 24 months, this is one of the largest and ambitious AF screening trials projected.

Heartline

Heartline is another large-scale trial involving Apple and, in this case, in collaboration with Johnson & Johnson [59, 81]. This is a virtual, siteless, controlled randomized trial aiming to study the health impact of AF screening. Screening and inclusion are completed using the Heartline App. Participants are aged > 65 years and recruited from the United States. The study has the objectives of detecting new AF using Apple Watch and improving OAC adherence amongst patients with existing AF. Participants in the AF screening arm will be randomized 3:1 to either AF screening using the Apple Watch or usual care. Those randomized to intervention are offered to purchase or be loaned Apple Watches. The study is planned for a three-year follow-up, the first two years of which are dedicated to active participation. The primary endpoints are time from randomization to AF diagnosis (AF screening arm) and percentage of days covered by OAC treatment (OAC adherence arm). There will also be reimbursement for the participants. This study has the potential to give us deepened knowledge on the completely digital screening design and is a logical sequel to the Apple Heart Study. The most notable differences are that the Heartline study will use enrichment with a lower age limit of 65 years and that ECG recording will be available directly in the Apple watch; hence, no stepwise ECG investigation is needed.

Summary and future perspectives

Screening for AF is attractive for several reasons. Atrial fibrillation is a major risk factor for ischaemic stroke, mortality, heart failure and cognitive dysfunction. Many of these complications can be prevented by OAC. About one third of AF patients are asymptomatic and thus have a risk of being undetected and untreated. AF also seems to fulfil most WHO criteria for screening.

Several heart rhythm recording methods are available for AF screening, significantly increasing AF detection compared to standard of care. However, there are still no data on the impact of AF screening on hard endpoints like stroke and bleeding because studies have so far only reported data on AF detection and OAC treatment initiation in the screened populations.

The optimal screening procedure is yet to be defined. For the moment, there are less data on the use of opportunistic recruitment in large scale, but ongoing trials like the SAFER trial [79] will bring more clarity to this point.

In the near future, we can expect data on further enrichment of the screening process. Serum biomarkers, imaging such as echocardiography and AI interpretation of ECG recordings have already shown promising results in identifying high-risk individuals. The dissemination of heart rhythm recordings via smartphone and smart watches will contribute to low-cost alternatives to ECG recording devices, but the smartphones/watches will probably have limited coverage in high-risk groups. The smartphone/watches with PPG recording only will still need a confirmatory ECG recording for an AF diagnosis.

Hence, we still lack data on the net benefit or net harm of OAC treatment initiated in a screening setting. However, several ongoing studies like SAFER [79], GUARD AF [80], STROKESTOP 1 [3] & 2 [78] and the LOOP study [61] will report data within a few years on hard endpoints after randomization to AF screening or not. These large-scale studies are an absolute necessity to get evidence on hard endpoints in AF screening. It could be considered a strength that these trials are designed using different ECG devices and different populations, even if the age span between these study populations is limited. However, AF screening in age groups below 65 years has been proven

to have very low yield. The cost for OAC treatment with NOACs will drop in the years to come, making cost effectiveness for AF screening even more plausible.

Evaluation of the ongoing large-scale AF screening trials will be crucial. The conditions for recruitment, participation, OAC treatment and follow-up data acquisition could differ between healthcare systems and studies, and outcomes may not be generalizable in all cases.

So far, surprisingly few countries or regions have implemented the AF screening recommendations issued by the ESC. The recommendation to perform systematic AF screening in individuals aged >75 years has been upgraded from class IIb to class IIa in the 2020 ESC AF guidelines [70], and we hope this will stimulate the very limited AF screening focus in clinical practice, as well as stimulate further large-scale AF screening studies.

Positive results from the ongoing large-scale AF screening trials will also increase the awareness of AF as a relevant and often silent cardiovascular disease with strong prognostic implications. We already know that we, to a large extent, are able to prevent the different complications associated with AF, and whilst waiting for the results from the screening trials, we should ensure that all our AF patients in clinical practice benefit from the current evidence on AF treatment.

Conflict of interest

JE has received consultancy or lecture fees from Pfizer, Medtronic, Merck Sharpe & Dome and Bristol Myers Squibb. Dr. Rosenqvist received honorarium from Abbott, Bristol Myers Squibb-Pfizer, Medtronic and Zenicor.

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Author contribution

Johan Engdahl: Conceptualization (equal); Investigation (equal); Methodology (equal); Project administration (equal); Writing-original draft (equal); Writing-review & editing (equal). **Mårten Rosenqvist:** Conceptualization (equal); Investigation (equal); Methodology (equal); Project administration (equal); Writing-original draft (equal); Writing-review & editing (equal).

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