



Protocol for a Systematic Review and Individual Participant Data Meta-Analysis of Randomized Trials of Screening for Atrial Fibrillation to Prevent Stroke

The AF SCREEN and AFFECT-EU Collaborators*

Thromb Haemost 2023;123:366–376.

Address for correspondence William McIntyre, MD, PhD, Population Health Research Institute, 237 Barton St E, Hamilton, Ontario L8L 2×2, Canada (e-mail: william.mcintyre@phri.ca).

Abstract

Introduction Atrial fibrillation (AF) is a common cause of stroke. Timely diagnosis of AF and treatment with oral anticoagulation (OAC) can prevent up to two-thirds of AF-related strokes. Ambulatory electrocardiographic (ECG) monitoring can identify undiagnosed AF in at-risk individuals, but the impact of population-based ECG screening on stroke is uncertain, as ongoing and published randomized controlled trials (RCTs) have generally been underpowered for stroke.

Methods and analysis The AF-SCREEN Collaboration, with support from AFFECT-EU, have begun a systematic review and individual participant data meta-analysis of RCTs evaluating ECG screening for AF. The primary outcome is stroke. Secondary outcomes include AF detection, OAC prescription, hospitalization, mortality, and bleeding.

After developing a common data dictionary, anonymized data will be collated from individual trials into a central database. We will assess risk of bias using the Cochrane Collaboration tool, and overall quality of evidence with the Grading of Recommendations Assessment, Development and Evaluation approach.

We will pool data using random effects models. Prespecified subgroup and multilevel meta-regression analyses will explore heterogeneity. We will perform prespecified trial sequential meta-analyses of published trials to determine when the optimal information size has been reached, and account for unpublished trials using the SAMURAI approach.

Impact and Dissemination Individual participant data meta-analysis will generate adequate power to assess the risks and benefits of AF screening. Meta-regression will permit exploration of the specific patient, screening methodology, and health system factors that influence outcomes.

Trial registration number PROSPERO CRD42022310308.

Keywords

- ▶ atrial fibrillation
- ▶ screening
- ▶ stroke/prevention

Description of the Problem

Atrial fibrillation (AF) is the most common heart rhythm abnormality worldwide, and is associated with a significantly

*Prepared on behalf of the AF SCREEN and AFFECT-EU Collaborators. The names of the collaborators are present in the supporting Appendix section.

received
June 3, 2022
accepted
October 28, 2022

DOI <https://doi.org/10.1055/s-0042-1760257>.
ISSN 0340-6245.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

increased risk of ischemic stroke. This risk can be reduced by approximately two-thirds with oral anticoagulation (OAC).¹ However, as AF is often intermittent and asymptomatic, and requires an electrocardiogram (ECG) to confirm the diagnosis, there are millions of individuals worldwide with undiagnosed AF.² Patients with no symptoms or atypical symptoms of AF may have worse prognoses than those with typical symptoms,^{3,4} and stroke can be the initial clinical manifestation of AF.^{5,6} Undiagnosed AF is thought to be responsible for about 10% of all strokes.⁷ Estimates of the proportion of AF cases that are undiagnosed range anywhere from 15 to 85%.^{2,8} In the United States alone, costs in this population exceed \$3.1 billion per year.^{2,9} Given the widespread availability of modern ambulatory ECG technologies, the global burden of stroke, the convenience, safety, and efficacy of contemporary OAC, and the possibility of intervening early in the disease course to slow disease progression, there is great interest in screening at-risk patients for AF.⁷

Although studies have demonstrated that a variety of screening tools and methods can detect AF in a wide range of populations, many have identified important challenges for the translation of AF detection into stroke prevention.^{10–13} Screening studies pose unique challenges; only a limited number of participants have the condition of interest (AF) and will screen positive. Depending on the screening method, the diagnostic yield can be low, meaning that only a minority of individuals screened would be eligible for stroke prevention therapy. Further, among these only a fraction would be expected to experience the outcome of interest (stroke) during early follow-up. To prevent stroke, AF detection must lead to OAC therapy. Coupling of screening with structured follow-up is essential to ensuring initiation and persistent use of OAC. Finally, the population-attributable risk of AF to stroke could be small. In the INTERSTROKE study, estimates of the population-attributable risk of AF to stroke ranged from as low as 3.1% (95% confidence interval [CI] 1.9–5.0%) in South Asia, to as high as 17.1% (13.8–21.1%) in Western Europe, North America, and Australia with a worldwide estimate of 9.0% (8.0–10.1%).¹⁴

Still, researchers have done modeling studies that suggest that screening for AF is likely to be a cost-effective method to prevent stroke.^{15,16} However, organizations such as the United States Preventative Services Task Force have not endorsed population-based AF screening due to a lack of direct randomized controlled trial (RCT) data showing a reduction in stroke.¹⁷ The European Society of Cardiology Guidelines Committee and the International SCREEN-AF Collaboration have called for further evaluation of the risks and benefits of systematic AF screening programs in at-risk populations.^{7,18}

Description of the Intervention

A number of contemporary tools can be used to screen for AF in the ambulatory setting. These range from traditional resting 12-lead ECGs, to handheld ECG devices, to 1- to 3-lead continuous ambulatory monitors wearable for up to 30 days, to implantable continuous monitors which monitor

the heart rhythm for up to 3 to 4 years.^{7,19} There are also non-ECG based technologies, such as pulse palpation and pulse plethysmography.²⁰ These monitors can be used in traditional and nontraditional health care settings; some are marketed directly to consumers.¹⁰

Observational studies using continuous, implantable monitors have detected high rates of previously unrecognized AF, with 6.1 to 12% of participants having AF lasting >5 minutes within the first 30 to 90 days of monitoring.^{8,12,21,22} The rate of AF detection increases with the age of the screened population, with an increased prevalence of stroke and AF risk factors, and importantly with the duration and quality of ECG monitoring.^{23,24} The positive-predictive value of ECG-based AF detection increases with the prevalence of undiagnosed AF in the specific population.^{7,10} The rate of AF detection is also dependent on the minimum duration of AF required to define an individual as “screen positive.”²⁵ AF screening programs must not only contend with the logistics, costs, and psychological consequences of false-positive screening results, but must also ensure that individuals with true-positive results are connected with medical care, receive OAC where appropriate, and persist with therapy for the long term to prevent stroke.^{11,13} There is wide-spread enthusiasm among patients and physicians about the value of AF screening and many RCTs have been completed or are underway.^{26–37}

Why is this Review Important?

Because of the inherent challenges of screening studies and the many causes of stroke other than AF, the sample size needed to definitively assess the risks and benefits of AF screening for primary or secondary stroke prevention is very large (►Fig. 1). This results in single RCTs often being statistically underpowered. This is illustrated in two recent RCTs that had point estimates that favored reductions in stroke or systemic embolism with screening, but were statistically nonsignificant (LOOP,²⁸ $n = 6,004$, hazard ratio [HR] 0.80 [95% CI 0.61–1.05] and STROKESTOP,³⁴ $n = 28,768$, HR 0.92 [95% CI 0.84–1.02]). Therefore, a systematic review and meta-analysis is essential not only to summarize all of the available evidence, but to generate the required power to adequately assess this question. Meta-regression using individual patient data will permit exploration of the impact of differences in study participants and design outcomes.

Research Question

In patients without a diagnosis of AF, does ECG-based screening for AF reduce the risk of stroke?

This systematic review and meta-analysis will examine the impact of ECG-based AF screening on the primary outcome of stroke. Secondary outcomes will include: rate of AF detection, all-cause mortality, OAC use, all-cause hospitalization, and major bleeding. Subgroup analyses and meta-regression will explore the relationship of patient factors (e.g., age, race, sex, socioeconomic factors, clinical stroke risk factors, etc.), screening methods (type of

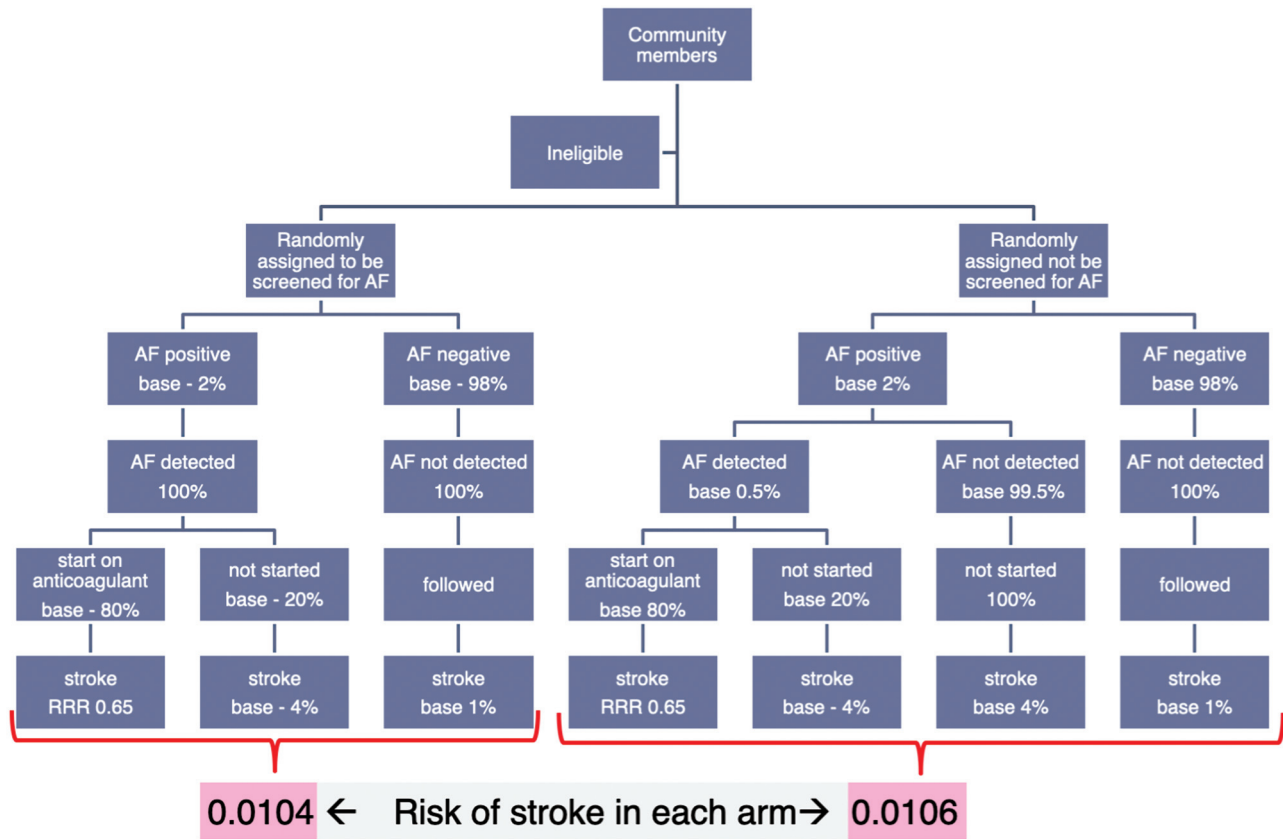


Fig. 1 Patient flow in a randomized trial of atrial fibrillation (AF) screening for stroke prevention: assumptions for sample size estimation.

screening device, frequency and duration of screening, etc.), and health care settings (community-based, physician-based, regional/national health care model, etc.) with outcomes of AF screening. Sensitivity analyses will be undertaken, including on-treatment analyses, which examine only those individuals who actually underwent AF screening for the majority of the prescribed duration, and only those individuals who received OAC in response to screen-detected AF.

Methods

The AF-Screen International Collaboration (www.AFSCREEN.org) was formed to facilitate collaboration between researchers, clinicians, and patient groups with an interest in AF screening and with the shared goal to determine if screening for AF can prevent strokes.⁷ Several members of this group were successful in obtaining a Horizon 2020 grant from the European Union (AFFECT-EU, *Digital, risk-based screening for atrial fibrillation in the European community*, grant agreement N°847770), which includes resources to conduct an individual participant data meta-analysis of RCTs of ECG-based AF screening to prevent stroke. Since 2016, the leaders of major AF screening trials have met at the annual AF-SCREEN conference, have networked to identify other ongoing or planned RCTs, and have discussed the logistics of pooled analyses of individual participant data from randomized ECG-based screening trials. The list of SCREEN-AF and

AFFECT-EU Investigators appears in **Appendix A**. To date, 16 randomized trials have been identified, which include nearly 300,000 participants (**Table 1**).²⁶⁻³⁷

Methods for Systematic Review

In order to capture the entirety of the published literature, we are conducting a formal systematic review, using Cochrane CENTRAL, MEDLINE, and EMBASE, to identify any additional, relevant studies. The search will be from database inception, using pretested filters to select for RCTs. The search string includes keywords and Medical Subject Headings for AF and screening. The search string will be updated iteratively as known trials are published and indexed (**Appendix B**). In addition, we are reviewing Clinicaltrials.gov, ISRCTN Register, and World Health Organization International Clinical Trials Registry Platform for relevant unpublished studies. We are also reviewing the references of included studies and prior systematic reviews on the topic for other potentially relevant studies. Finally, we will poll members of the AF-SCREEN collaboration to see if they are aware of other relevant studies.

Study Selection Process

Two independent reviewers, following the same criteria, will assess eligibility of each study. Pairs of reviewers will independently assess titles and abstracts of each reference. Any reference deemed relevant by either reviewer will be retrieved for full-text article review. Two reviewers will

Table 1 List of randomized atrial fibrillation screening trials

	Country	Rand. level	N	Screening tool	Screening method	Setting	Population	Follow-up duration	Status	AF definition
AMALFI amalftrial.org	UK	Patient	5,029	ECC patch	Continuous monitoring for 14 d	Primary care	Age ≥ 65, and CHA ₂ DS ₂ -VASC score ≥ 3 M, ≥ 4 W	5 y (primary outcome at 2.5 y)	In follow-up	ECC algorithm, > 30 s
DANCAVAS ²⁷	Denmark	Patient	79,000	3-lead ECG	Single time point	Community	Men, age 60–74	Mean 5 y	In follow-up	If AF was suspected during CT, an ECG or 7 d of Holter monitoring was used to confirm
LOOP ²⁸	Denmark	Patient	6,004	Implanted monitor	Continuous monitoring for 3–4 y	Community	Age ≥ 70 + ≥ 1 of HTN, DM, HF, prior stroke	64.5 mo (59.3–69.8)	Completed	Adjudicated AF ≥ 6 min
Find-AF randomized ³⁷	Germany	Patient	398	10-d Holter	Baseline, 3 and 6 mo	Post-stroke	Age ≥ 60, within 1 wk of ischemic stroke	3 y	Completed	Duration ≥ 30 s on rhythm strip or 12-lead ECG
FIND-AF2 Low risk stratum NCT04371055	Germany	Patient	4,160	7-d Holter	0, 3 and 12 mo, then annually	Post-stroke	Age ≥ 60, within 1 mo of ischemic stroke	2–4 y (minimum 2 y for individual patient)	Recruitment ongoing	Duration ≥ 30 s on rhythm strip or 12-lead ECG
FIND-AF2 High risk stratum NCT04371055	Germany	Patient	1,040	Implanted monitor	Continuous monitoring	Post-stroke	Age ≥ 60, within 1 mo of ischemic stroke	2–4 y (minimum 2 y for individual patient)	Recruitment ongoing	Duration ≥ 30 s on rhythm strip or 12-lead ECG
GUARD-AF ⁵⁰	USA	Patient	11,931	ECC patch	Continuous monitoring for 14 d	Primary care	Age ≥ 70	2.5 y	In follow-up	≥ 30 s
Heartline NCT04276441	USA	Patient	28,000	Watch	Continuous wear	Community	Age ≥ 65	3 y	Recruitment ongoing	30 s
MonDAFIS ²⁹	Germany	Patient	3,470	In-hospital ECG monitoring	In-hospital, post-stroke	Hospital	Age ≥ 18 + stroke or TIA ≤ 72 h of symptoms	24 mo	Completed	≥ 30 s
mSTOPS ³⁰ (first 4 mo)	USA	Patient	2,659	ECC patch	12 d × 2	Population	Age ≥ 75 or men > 55 or women > 65 with one risk factor	4 mo for primary endpoint. Total duration 3 y	Completed	≥ 30 s or new diagnosis in claims data
PerDIEM ³¹	Canada	Patient	300	Implanted monitor External loop recorder	Continuous 30 d	Post-stroke	Age > 18, within 6 mo of ischemic stroke	12 mo	Completed	≥ 2 min
REHEARSE-AF ²² (first 4 mo)	UK/Wales	Patient	1,001	Handheld ECG	Twice weekly for 1 y	Primary care	Age ≥ 65 + CHA ₂ DS ₂ -VASC ≥ 2	12 mo	Completed	≥ 30 s
SAFER-Internal Pilot safer.phpc.cam.ac.uk	UK	Cluster	14,082	Handheld ECG	Four times daily for 21 d	Primary care	Age ≥ 70, not on OAC	5 y	Ongoing	≥ 30 s

(Continued)

Table 1 (Continued)

	Country	Rand. level	N	Screening tool	Screening method	Setting	Population	Follow-up duration	Status	AF definition
SAFER-UK safer.phpcc.cam.ac.uk	UK	Patient	100,418	Handheld ECG	Four times daily for 21 d	Primary care	Age \geq 70, not on OAC	5 y	Ongoing	\geq 30 s
SAFER-AUS safer.phpcc.cam.ac.uk	Australia	Patient	2,100	Handheld ECG	Four times daily for 21 d	Primary care	Age \geq 70, not on OAC	5 y	Ongoing	\geq 30 s
SCREEN-AF ³³	Canada/Germany	Patient	822	ECG patch	14 d \times 2	Primary care	Age \geq 75 with hypertension	6 mo	Completed	\geq 5 min or on 12-lead ECG
STROKESTOP ³⁴	Sweden	Patient	28,768	Handheld ECG	Two times daily for 14 d	Population	Age 75 and 76	Median 6.9 y	Completed	At least 30 s irr or two episodes 10–29 s
STROKESTOP II ³⁵	Sweden	Patient	28,712	Handheld ECG	Four times daily for 14 d	Population	Age 75 and 76 + NT-ProBNP > 125 ng/L	Minimum 5 y	Ongoing	At least 30 s irr
VITAL-AF ³⁶	USA	Cluster	35,308	Handheld ECG	Single time point	Primary care	Age \geq 65	2 y	Completed	Electronic health record

Abbreviations: AF, atrial fibrillation; CT, computed tomography; DM, diabetes mellitus; ECG, electrocardiogram; HF, heart failure; HTN, hypertension; NT-ProBNP, N-terminal pro-B-type natriuretic peptide; OAC, oral anticoagulation; TIA, transient ischemic attack; irr, irregular.

independently review the full text of each study and indicate the main reason for exclusion of any study not meeting criteria.³⁸ Studies that meet all eligibility criteria will be included in the systematic review. Disagreements will be resolved through consensus discussion, and the inclusion of a third reviewer where necessary. Study authors will be contacted in order to clarify any ambiguities that may affect eligibility. The lead investigators of all relevant studies will be invited to participate and provide data for the participant-level meta-analysis. In the event that individual studies cannot provide participant-level data, summary data and subgroup data will be sought.

Study Eligibility

This review and meta-analysis will include RCTs—both individual participant randomized and cluster randomized—that evaluate an ECG-based method (handheld, wearable, or implanted) of AF screening and evaluate the clinical endpoint of stroke. Pseudo-randomized and observational studies will be excluded. We will not impose any language restrictions. The population of interest includes adults (18 years of age and older) without a documented history of AF.

Baseline individual patient data will be captured including demographics, cardiovascular and stroke risk factors, heart rate, blood pressure, and medication use. The type of ECG monitor, duration of monitoring, screening setting (e.g., community-based, physician office-based, etc.), health care environment (public vs. private; for-profit vs. not for-profit), and income status (using World Bank definitions) of the country where screening is performed will also be recorded.

Outcomes

The primary clinical endpoint will be the *time to the first occurrence* of stroke, using the definitions of the individual studies. Sensitivity analyses will examine subtypes of stroke (all-cause, ischemic, unspecified, hemorrhagic) and systemic emboli. Secondary outcomes include AF detection, OAC prescription, hospitalization, major bleeding (with primary analysis using the International Society on Thrombosis and Haemostasis definition³⁹), and mortality.

Data Collection

The AFFECT-EU collaboration has developed a data sharing agreement and rules for publication, timing of analyses, and access to the pooled database. Derived data supporting the findings of this study will be available from the corresponding author on request, following publication of a final study report.

A data dictionary for the data elements to be included in the pooled data set has been developed and contributing studies will adapt, where possible, their data to these definitions and format (► Table 2). A central database has been created at the Copenhagen University Hospital – Rigshospitalet, where data will be stored on a secure server. Data will be transmitted as a .csv file (or equivalent method) from participating studies, without unique patient identifiers. Raw data sets will be saved in their original formats and then converted to a common format by renaming variables

Table 2 List of data elements

Type of data		
Study level		Country in which study was carried out Number of participants randomized Number allocated to the Screening Group Number allocated to the Standard Care Group Setting (primary care, pharmacies, other) Did the study measure quality of life (which tool) Details of intervention (frequency of testing, actions, etc.) Details of comparator (frequency of review, actions, etc.)
Individual participant	Baseline characteristics - demographics	Age Sex Weight Height Smoking status Date of entry into study/date of randomization Allocated to screening or standard care Race
Individual participant	Baseline characteristics – medical history	History of heart failure or LVEF < 40% History of hypertension History of diabetes mellitus History of myocardial infarction/ PCI/CABG/vascular disease History of stroke, TIA, or systemic embolism
Individual participant	Follow-up data - clinical	Date of visit Clinical NYHA class Left ventricular ejection fraction Resting heart rate Systolic blood pressure Diastolic blood pressure
Individual participant	Follow-up data - medications	OAC initiation
Individual participant	Follow-up data - quality of life	Quality of life if collected (derived scores if available)
Individual participant	Clinical outcomes	Date of death Cause of death (cardiovascular or noncardiovascular) Hospital admission/cardiovascular event Presence/absence and date of stroke or systemic embolism Presence/absence and date of major bleeding event Lost to follow-up? Date of last follow-up

Abbreviations: CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association, OAC, oral anticoagulation; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

from each study in a consistent format. The central statistical team will perform quality checks on the data and clarify discrepancies with study authors. For each study, completeness and accuracy of data in the common database will be checked against values in the original publication. Data sets will then be combined into the pooled, master data set, including a variable indicating the study of origin.

For studies from which individual participant data are not available, data extraction will be performed independently and in duplicate using prepiloted forms. We will collect data on study characteristics, population characteristics, details of screening method (including modality, frequency, and duration), follow-up, as well as the incidence of primary and secondary outcomes as described above. Disagreements will be resolved through consensus discussion, and the inclusion of a third reviewer where necessary. Study authors will be contacted in order to clarify any data ambiguities, or to provide additional data. Data will be deemed unavailable if

no response is received after two contact attempts over a 4-week period.

Assessment of Risk of Bias

Two reviewers will use the Cochrane Collaboration tool to independently assess the risk of bias for each included study, using the variant for cluster-randomized trials where appropriate.⁴⁰ The reviewers will evaluate risk of bias as “low,” “high,” “probably low,” or “probably high” in five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Overall risk of bias for each study will be considered “low” if all risk of bias domains are ranked “low”; “some concerns” if at least one domain (other than blinding of participants and personnel) is ranked “unclear” without any domains ranked as “high,” and “high” if one or more

domains (other than blinding of participants and personnel) is ranked as “high” risk of bias.

Data Analyses and Assessment of Heterogeneity

Our preferred outcome variable is time to the first occurrence of the clinical endpoint of stroke, so that HRs will be estimated using a Cox proportional hazards regression model for each trial. This approach was chosen because we expect differences in follow-up time both within and between studies. The primary analyses will use the “intention-to-treat” populations of each study. We will combine data using a one-step individual patient data meta-analysis approach.⁴¹

If individual participant data is not obtained for a particular study, we will request that HRs be shared with us. Where only risk ratios (RRs) or proportions of events are available, we will assume that $RR = HR$, under the restrictive situation of “shorter follow-up, rarer end points, and risks closer to 1.”⁴² We will perform sensitivity analyses that assess the impact of excluding any or all such studies. We will combine effect estimates across studies using the DerSimonian and Laird random effects model method.⁴³ We will assess variance and adjust for outcomes with zero observations by substituting a value of 0.5 and adjust for clustering in cluster-randomized studies.⁴⁴ Additionally, we will calculate the pooled relative and absolute risk differences using the observed event rates in included studies. We will assess heterogeneity using the chi-square test for homogeneity and the I^2 and D^2 statistics. Substantial heterogeneity will be defined as $I^2 > 50\%$. In cases of substantial heterogeneity, we will conduct subgroup analyses to assess clinical and methodological sources of heterogeneity.

A cumulative z-score will be calculated each time a new study is added to the pooled database.⁴⁵ We will use the SAMURAI approach to conduct sensitivity analysis to estimate the potential impact of unpublished registered trials.⁴⁶ For each outcome, we will assess for publication bias using funnel plots. We will perform an arcsine test in cases where visual inspection of the funnel plot suggests potential publication bias and ≥ 10 studies are available. We will assess our confidence in the pooled effects estimates using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.⁴⁷

A Priori Hypotheses to Explain Clinical Heterogeneity

We expect that between-study clinical heterogeneity will exist due to differences in study populations (e.g., age of participants or recruitment in clinical or community settings) and design (e.g., varying screening methodology or AF episode cutoffs to recommend OAC). We will estimate subgroup effects by estimating interaction terms between treatments and covariates within studies, and combining them in a uniform way between studies.⁴⁸

In order to account for heterogeneity among studies, our meta-analyses will use the random effects model. However, given the expected large heterogeneity among studies due to individual- and study-level characteristics, we will conduct meta-regression, incorporating both patient-specific factors as well as study-specific factors. We will build these meta-

regression models in stages, that is, incorporating only study-level variables initially, and then adding the patient-level variables, as available. Participant-specific factors include: (1) age categorized as < 65 (reference), 65 to 74, 75 to 84, and ≥ 85 years; (2) history of stroke, transient ischemic attack, or systemic embolism; (3) sex; and (4) components of the CHA_2DS_2 -VASc score (other than age and sex). Study-level characteristics include: (1) if study is conducted in a public health system setting versus private or hybrid; (2) if the screening method is single time point versus repeated screening versus continuous screening and by the duration of screenings and cutoffs used for AF episode duration; (3) by ECG-only methods versus multicomponent interventions (e.g., paired with blood pressure, imaging, etc.); (4) by downstream interventions in case of positive or negative screening, OAC versus not and referral to cardiologist versus not; (5) by region: North America versus Europe versus other and by World Bank income level, as available; (6) by setting: community (including pharmacies and health centers) versus primary care versus specialist care; and (7) by risk of bias of individual studies: low versus moderate or high.

To prevent stroke, it is crucial that AF detection leads to appropriate use of OAC. Thus, an additional subgroup analysis will assess results after grouping studies as above or below the median rate of OAC initiation in screen-positive individuals.

Our primary analysis will be “intention to treat” and include all participants regardless of whether they undertook the screening intervention and/or took OAC in the case of AF detection. One “on-treatment” sensitivity analysis will use participant-level data to identify those individuals who screen positive for AF who are started on OAC. Screen-positive individuals who are not started on OAC will be censored for analysis of outcome events. An additional “on-treatment” sensitivity analysis will exclude data from participants who were randomized to screening, but did not take part in screening.

Sample Size and Interim Analyses

We performed an exploratory sample size estimate using trial sequential analysis (TSA).⁴⁹ This calculation was based on the following assumptions: acceptable risk of type I error (α): 5%; minimum important effect size of a 30% relative risk reduction (RRR) in stroke; statistical power: 80%; stroke event rate of 1% in the control arm, stroke event rate of 0.5% in the treatment (screened) arm; and heterogeneity (diversity index, D^2) = 75% (because we expect the body evidence to be made up of mostly smaller trials). In sensitivity analyses, we calculated the optimal information size (OIS) for RRRs of 40 and 20% and control event rates of 0.5 and 2%. The base TSA returned an OIS of 117,600 participants (→ **Table 3**). Sensitivity analyses returned OISs ranging from 30,896 to 562,580 participants. The OIS for the “worst-case scenario” is comparable to the planned final number of randomized participants among all known planned trials.

Dissemination Plans

The Writing Committee, who will regularly monitor z-scores and the potential impact of unpublished studies, will make

Table 3 Optimal information size assuming 5% alpha, 80% beta, and 75% heterogeneity

Incidence of stroke in control arm	Relative risk reduction		
	40%	30%	20%
2%	30,896	58,296	138,740
1%	62,292	117,600	280,020
0.5%	125,080	236,204	562,580

Abbreviation: OIS, optimal information size.

Note: OIS denotes the total number of patients (2N) that need to be randomized.

decisions about the production interim and final publications. We will report the findings from this meta-analysis according with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses including those recommended for individual participant data meta-analysis.³⁸ We will target presentation of our findings at a major international cardiovascular meeting and publication in a peer-reviewed general medical or cardiovascular journal.

Discussion

There is great interest in assessing the efficacy of AF screening as a public health strategy to prevent stroke. While many ECG-based technologies have demonstrated that AF can be accurately detected in a variety of populations, direct evidence for stroke reduction is lacking, and endorsement of AF screening is heterogeneous.^{7,17,18} Several large randomized trials are currently underway and it is unlikely that any of them will have sufficient statistical power to reliably detect a reduction in stroke with AF screening. Thus, analysis of all available trials, which include nearly 300,000 participants, will provide the most sensitive evaluation of the impact of AF screening. Meta-regression of trials with different study populations, recruitment procedures, screening methodologies, and downstream interventions will help to clarify if there are more suitable patient populations, screening methods, or settings to conduct screening for AF. The inclusion of trials from different regions and health care systems will permit a better understanding of the generalizability of the results.

Registration

The protocol for this individual participant data meta-analysis has been registered with PROSPERO, the international prospective register of systematic reviews (PROSPERO CRD42022310308).

Strengths and Limitations of this Study

- Rigorous search strategy including gray literature and nonindexed trials.
- Broad range of screening approaches, populations, and health care settings with prespecified measures to explore heterogeneity.
- Individual participant data meta-analysis.
- Quality of evidence assessment using the GRADE framework.

- Sensitivity analysis considering unpublished registered trials.
- Ongoing analysis of OIS with publication of new trials.

Disclosures

Dr. Bowman reports research grants from Novartis, The Medicines Company, UK Medical Research Council, British Heart Foundation, NIHR. Dr. Brandes reports personal fees (honoraria) from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, travel grants from Biotronik, and research grants from Theravance outside the submitted work. Dr. Buck reports receiving research funding from Alberta Innovates Health Solutions. Dr. Casadei reports in-kind support for clinical studies from iRhythm and Roche Diagnostics. Dr. Chen Reports NIH Grants. Dr. S. Diederichsen reports personal consulting fees from Bristol-Myers Squibb Pfizer, Vital Beats, and Acesion Pharma, personal speaker fees from Bristol-Myers Squibb Pfizer, and institutional travel grants from Abbott and Medtronic. Dr. Engdahl reports consultancy or lecture fees from Pfizer, Roche Diagnostics, Philips, Boehringer Ingelheim, and Bristol-Myers Squibb. Dr. Freedman reports grants to the Institution for investigator-initiated studies from the BMS-Pfizer Alliance, the Medical Research Future Fund (Federal government), and NSW State Health, consulting fees from the BMS-Pfizer Alliance, and loan of hand-held ECG devices from Alivacor for investigator-initiated studies. Dr. Gibson reports research support from Johnson & Johnson. He receives consulting support from AstraZenca, Johnson & Johnson, Janssen & Bayer. Dr. Haesler reports speaker's honoraria, consulting fees, lecture honoraria, and/or study grants from Abbott, Amarin, Alexion, AstraZeneca, Bayer Healthcare, Sanofi, Biotronik, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer, Portola, SUN Pharma, W.L. Gore and Associates, and Edwards Lifesciences. Dr. Healey reports research grants and speaking fees from BMS/Pfizer, Medtronic, Boston Scientific, Consulting from Boston Scientific, and Bayer, speaking fees from Servier. Dr. Hobbs reports part support as Director of the NIHR Applied Research Collaboration (ARC) Oxford Thames Valley, and Theme Lead of the NIHR OUH BRC. F.D.R.H. has also received occasional fees or expenses for speaking or consultancy from AZ, BI, Bayer, BMS/Pfizer, and Novartis. Dr. Lip reports consultant and speaker fees

for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally. G.Y.H.L is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. Dr. Lopes reports individual consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Glaxo Smith Kline, Medtronic, Merck, Pfizer, Portola, and Sanofi; institution Grant Support from Bristol-Myers Squibb, Daiichi Sankyo, Glaxo Smith Kline, Medtronic, Pfizer, and Sanofi. Dr. Lubitz is a full-time employee of Novartis as of July 18, 2022. Dr. Lubitz previously received research support from NIH grants R01HL139731 and R01HL157635, and American Heart Association 18SFRN34250007. Dr. Lubitz received sponsored research support from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Fitbit, Medtronic, Premier, and IBM, and has consulted for Bristol Myers Squibb, Pfizer, Blackstone Life Sciences, and Invitae. Dr. Mant reports honoraria from BMS/Pfizer. Dr. McIntyre reports speaking fees Bayer and Servier outside the submitted work. Dr. McManus reports honorary, speaking/consulting fees, or grants from Heart Rhythm Society, Flexcon, Rose Consulting, Bristol-Myers Squibb, Pfizer, Boston Biomedical Associates, and Avania. David D. McManus has received honorary, speaking/consulting fees, or grants from Heart Rhythm Society, Flexcon, Rose Consulting, Bristol-Myers Squibb, Pfizer, Boston Biomedical Associates, Avania Consulting, Samsung, Phillips, Mobile Sense, CareEvolution, Flexcon, Boehringer Ingelheim, Biotronik, Otsuka Pharmaceuticals, and Sanofi. Dr. McManus also declares financial support for serving on the Steering Committee for the GUARD-AF study (NCT04126486) and Advisory Committee for the Fitbit Heart Study (NCT04176926). Dr. Rosenqvist reports paid consultancy for Zenicor and Medtronic and Pfizer. Dr. Sandhu reports research support from Servier Alberta Innovation in Health Fund and BMS/Pfizer Quality Improvement Grant. Dr. Schnabel reports funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under the grant agreement No 648131, from the European Union's Horizon 2020 research and innovation programme under the grant agreement No 847770 (AFFECT-EU) and German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103 and 81Z0710114); German Ministry of Research and Education (BMBF 01ZX1408A) and ERA-CoSysMed3 (031L0239), Wolfgang Seefried project funding German Heart Foundation. Dr. Singer reports research support from Bristol Myers Squibb. Dr. Svendsen reports research support from Innovation Fund Denmark, The Research Foundation for the Capital Region of Denmark, The Danish Heart Foundation, and Medtronic and speaker's fees from Medtronic. Dr. Svennberg reports research support from Research Position Stockholm County Council, Åke Wiberg Foundation, Swedish Heart Foundation, and consulting fees from

Bayer, Bristol-Myers Squibb-Pfizer, Johnson & Johnson, and Merck Sharp & Dohme. Dr. Zink reports research support from START-GRANT, University RWTH Hospital Aachen, and consulting fees from BMS Pfizer. Dr. Wachter reports research support from Boehringer Ingelheim, Medtronic, Bundesministerium für Bildung, and Forschung, Deutsche Forschungsgemeinschaft, Deutsches Zentrum für Herz-Kreislaufforschung, and the European Union and personal fees from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, CvRx, Daiichi Sankyo, Novartis, Pfizer, Pharmacosmos, Sanofi, Servier, SOBI, Sciarc, and Vifor. Dr. Tieleman reports grants from Medtronic and Abbott all outside the submitted work. Dr. Tieleman is co-inventor of the MyDiagnostick, not receiving royalties for the past 5 years. Dr. Tieleman reports personal fees from Boehringer Ingelheim, Bayer and Pfizer/Bristol Meyer Squibb all outside the submitted work.

Drs. Bangdiwala, Benz, Connolly, A. Diederichsen, Dolovich, Halcox, Lucassen, Quinn, Siu, Smyth and Steinhubl has no disclosures.

Funding

This work is funded by a grant from the Horizons-2020 program of the European Union N°847770, and with funds from the Canadian Stroke Prevention Intervention Network, which is funded by the Canadian Institutes of Health Research.

Conflict of Interest

None declared.

References

- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146(12):857–867
- Turakhia MP, Shafrin J, Bogner K, et al. Estimated prevalence of undiagnosed atrial fibrillation in the United States. *PLoS One* 2018;13(04):e0195088–e0195088
- Siontis KC, Gersh BJ, Killian JM, et al. Typical, atypical, and asymptomatic presentations of new-onset atrial fibrillation in the community: characteristics and prognostic implications. *Heart Rhythm* 2016;13(07):1418–1424
- Tsang TS, Barnes ME, Pellicka PA, et al. 173 Silent atrial fibrillation in Olmsted county: a community-based study. *Can J Cardiol* 2011; 27:S122–S122
- Gladstone DJ, Spring M, Dorian P, et al; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370(26):2467–2477
- Lubitz SA, Yin X, McManus DD, et al. Stroke as the initial manifestation of atrial fibrillation: the Framingham Heart Study. *Stroke* 2017;48(02):490–492
- Freedman B, Camm J, Calkins H, et al; AF-Screen Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation* 2017;135(19):1851–1867
- Healey JS, Connolly SJ, Gold MR, et al; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366(02):120–129
- Turakhia MP, Shafrin J, Bogner K, et al. Economic burden of undiagnosed nonvalvular atrial fibrillation in the United States. *Am J Cardiol* 2015;116(05):733–739

- 10 Perez MV, Mahaffey KW, Hedlin H, et al; Apple Heart Study Investigators. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019;381(20):1909–1917
- 11 Sandhu RK, Dolovich L, Deif B, et al. High prevalence of modifiable stroke risk factors identified in a pharmacy-based screening programme. *Open Heart* 2016;3(02):e000515
- 12 Healey JS, Alings M, Ha A, et al; ASSERT-II Investigators. Subclinical atrial fibrillation in older patients. *Circulation* 2017;136(14):1276–1283
- 13 Tieleman RG, Plantinga Y, Rinkes D, et al. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace* 2014;16(09):1291–1295
- 14 O'Donnell MJ, Chin SL, Rangarajan S, et al; INTERSTROKE investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016;388(10046):761–775
- 15 Hill NR, Sandler B, Mokgokong R, et al. Cost-effectiveness of targeted screening for the identification of patients with atrial fibrillation: evaluation of a machine learning risk prediction algorithm. *J Med Econ* 2020;23(04):386–393
- 16 McIntyre WF, Yong JHE, Sandhu RK, et al. Prevalence of undiagnosed atrial fibrillation in elderly individuals and potential cost-effectiveness of non-invasive ambulatory electrocardiographic screening: the ASSERT-III study. *J Electrocardiol* 2020;58:56–60
- 17 Davidson KW, Barry MJ, Mangione CM, et al; US Preventive Services Task Force. Screening for atrial fibrillation: US Preventive Services Task Force recommendation statement. *JAMA* 2022;327(04):360–367
- 18 Hindricks G, Potpara T, Dagres N, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42(05):373–498
- 19 Khurshid S, Healey JS, McIntyre WF, Lubitz SA. Population-based screening for atrial fibrillation. *Circ Res* 2020;127(01):143–154
- 20 Pluymaekers NAHA, Hermans ANL, van der Velden RMJ, et al. Implementation of an on-demand app-based heart rate and rhythm monitoring infrastructure for the management of atrial fibrillation through teleconsultation: TeleCheck-AF. *Europace* 2021;23(03):345–352
- 21 Reiffel JA, Verma A, Kowey PR, et al; REVEAL AF Investigators. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: the REVEAL AF study. *JAMA Cardiol* 2017;2(10):1120–1127
- 22 Diederichsen SZ, Haugan KJ, Brandes A, et al. Incidence and predictors of atrial fibrillation episodes as detected by implantable loop recorder in patients at risk: from the LOOP study. *Am Heart J* 2020;219:117–127
- 23 Diederichsen SZ, Haugan KJ, Kronborg C, et al. Comprehensive evaluation of rhythm monitoring strategies in screening for atrial fibrillation: insights from patients at risk monitored long term with an implantable loop recorder. *Circulation* 2020;141(19):1510–1522
- 24 Haeusler KG, Gröschel K, Köhrmann M, et al. Expert opinion paper on atrial fibrillation detection after ischemic stroke. *Clin Res Cardiol* 2018;107(10):871–880
- 25 Chen LY, Chung MK, Allen LA, et al; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation* 2018;137(20):e623–e644
- 26 Uittenbogaart SB, Verbiest-van Gorp N, Lucassen WAM, et al. Opportunistic screening versus usual care for detection of atrial fibrillation in primary care: cluster randomised controlled trial. *BMJ* 2020;370:m3208
- 27 Diederichsen AC, Rasmussen LM, Søgaard R, et al. The Danish Cardiovascular Screening Trial (DANCAVAS): study protocol for a randomized controlled trial. *Trials* 2015;16:554
- 28 Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet* 2021;398(10310):1507–1516
- 29 Haeusler KG, Kirchhof P, Kunze C, et al; MonDAFIS Investigators. Systematic monitoring for detection of atrial fibrillation in patients with acute ischaemic stroke (MonDAFIS): a randomised, open-label, multicentre study. *Lancet Neurol* 2021;20(06):426–436
- 30 Steinhubl SR, Waalen J, Edwards AM, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mStoPS randomized clinical trial. *JAMA* 2018;320(02):146–155
- 31 Buck BH, Hill MD, Quinn FR, et al. Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: the PERDIEM randomized clinical trial. *JAMA* 2021;325(21):2160–2168
- 32 Halcox JJJ, Wareham K, Cardew A, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation* 2017;136(19):1784–1794
- 33 Gladstone DJ, Wachter R, Schmalstieg-Bahr K, et al; SCREEN-AF Investigators and Coordinators. Screening for atrial fibrillation in the older population: a randomized clinical trial. *JAMA Cardiol* 2021;6(05):558–567
- 34 Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet* 2021;398(10310):1498–1506
- 35 Kemp Gudmundsdottir K, Fredriksson T, Svennberg E, et al. Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study. *Europace* 2020;22(01):24–32
- 36 Lubitz SA, Atlas SJ, Ashburner JM, et al. Screening for atrial fibrillation in older adults at primary care visits: VITAL-AF randomized controlled trial. *Circulation* 2022;145(13):946–954
- 37 Wachter R, Weber-Krüger M, Hamann GF, et al; Find-AFRANDOMISED Investigators and Coordinators. Long-term follow-up of enhanced Holter-electrocardiography monitoring in acute ischemic stroke. *J Stroke* 2022;24(01):98–107
- 38 Stewart LA, Clarke M, Rovers M, et al; PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;313(16):1657–1665
- 39 Franco L, Becattini C, Beyer-Westendorf J, et al. Definition of major bleeding: prognostic classification. *J Thromb Haemost* 2020;18(11):2852–2860
- 40 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898
- 41 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;341(8842):418–422
- 42 Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. *J Clin Epidemiol* 2002;55(09):893–899
- 43 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(03):177–188
- 44 Abo-Zaid G, Guo B, Deeks JJ, et al. Individual participant data meta-analyses should not ignore clustering. *J Clin Epidemiol* 2013;66(08):865–873.e4
- 45 Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin Trials* 1997;18(06):580–593, discussion 661–666

- 46 Kim NY, Bangdiwala SI, Thaler K, Gartlehner G. SAMURAI: sensitivity analysis of a meta-analysis with unpublished but registered analytical investigations (software). *Syst Rev* 2014;3:27
- 47 Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol* 2011;64(04):380–382
- 48 Thompson SG, Higgins JPT. Treating individuals 4: can meta-analysis help target interventions at individuals most likely to benefit? *Lancet* 2005;365(9456):341–346
- 49 Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017;17(01):39
- 50 Singer DE, Atlas SJ, Go AS, et al. Reducing stroke by screening for Undiagnosed atrial fibrillation in elderly individuals (GUARD-AF): Rationale and design of the GUARD-AF randomized trial of screening for atrial fibrillation with a 14-day patch-based continuous ECG monitor. *Am Heart J* 2022;249:76–85