Screening for atrial fibrillation to prevent stroke: a meta-analysis

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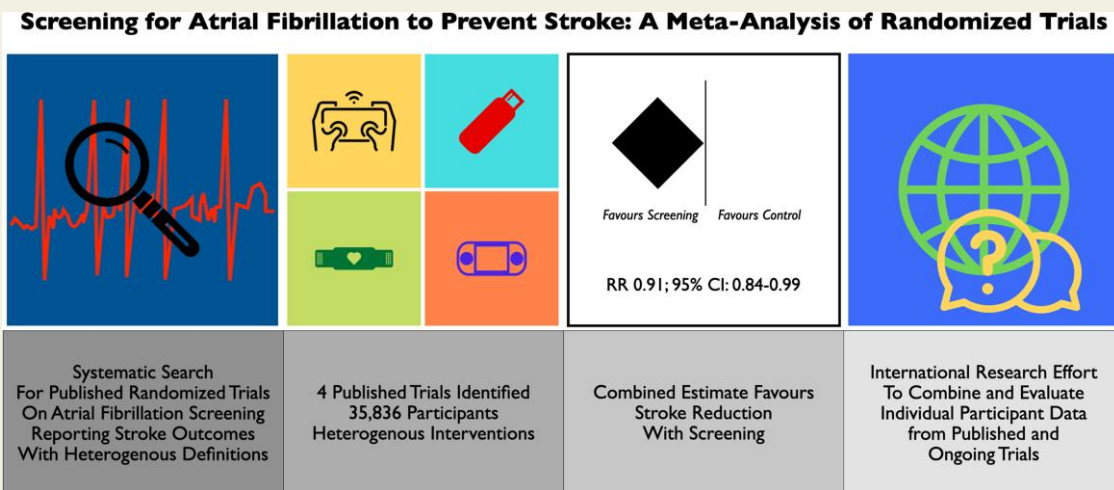|	
Aims	We aimed to summarize existing evidence from published randomized trials that assessed atrial fibrillation (AF) screening for stroke prevention.
Methods and results	We searched MEDLINE for randomized trials that enrolled patients without known AF, screened for AF using electrocardiogram-based methods, and reported stroke outcomes. For this analysis, we excluded studies that focused on post-stroke populations. We combined data using a random-effects model and performed trial sequential meta-analysis using an O'Brien-Fleming alpha-spending function.
	We identified four randomized clinical trials with a total of 35 836 participants. The populations, screening intervention, and definition of stroke varied markedly. As compared with no screening, AF screening was associated with a reduction in stroke (relative risk 0.91; 95% confidence interval: 0.84–0.99]. Trial sequential meta-analysis found that the cumulative z-score did not cross the stopping boundary.
	After polling members of the AF-SCREEN and AFFECT-EU consortia, we identified a further 12 trials that are complete but have not yet reported stroke outcomes or are ongoing and expected to collect stroke outcomes. These consortia are planning an individual participant data meta-analysis which will permit the exploration of methodological heterogeneity.
Conclusions	If and how to screen for AF is an important public health concern. The body of evidence published to date suggests that AF could be effective to prevent strokes in some settings. The AF-SCREEN/AFFECT-EU individual patient data meta-analysis aims to comprehensively assess the benefits and risks of AF screening, and determine how population, screening method, and health-system factors influence stroke prevention.

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Graphical Abstract

Screening for Atrial Fibrillation to Prevent Stroke: A Meta-Analysis of Randomized Trials

Favours Screening   Favours Control

RR 0.91; 95% CI: 0.84-0.99

| Systematic Search For Published Randomized Trials On Atrial Fibrillation Screening Reporting Stroke Outcomes With Heterogenous Definitions | 4 Published Trials Identified 35,836 Participants Heterogenous Interventions | Combined Estimate Favours Stroke Reduction With Screening | International Research Effort To Combine and Evaluate Individual Participant Data from Published and Ongoing Trials |

Table 1   **Ongoing and completed randomized trials assessing atrial fibrillation screening**

Study	Number randomized	Screening intervention	Population
Studies cited in the current report			
LOOP[3]	6004	Implanted monitor	Age ≥70 with risk factors, Denmark
REHEARSE-AF[4]	1001	Hand-held ECG, BID for 1 year	Age 65 + risk factors, UK/Wales
SCREEN-AF[5]	822	14-day ECG Patch, Twice	Age ≥75 with hypertension, Canada/Germany
STROKESTOP[6]	28 768	Hand-held ECG, BID for 14 days	Age 75 and 76, Sweden
Completed trials without published stroke outcomes and/or conducted in post-stroke population			
Find-AF NCT01855035	398	10-day Holter, 0, 3, and 6 months	Post-stroke, Germany
MonDAFIS NCT02204267	3470	7-day Holter, once	Post-stroke, Germany
mSTOPS NCT02506244	2659	12-day ECG Patch, twice	Age >75 or <75 with risk factors, USA
PerDIEM NCTT02428140	300	Implanted monitor	Post-stroke, Canada
VITAL-AF NCT03515057	35 308	Hand-held ECG, once	Age ≥65, USA
Ongoing trials			
AMALFI ISRCTN15544176	5029	14-day ECG patch, once	Age ≥65 with risk factors, UK
DANCAVAS ISRCTN12157806	79 000	3-lead ECG, once	Men, age 60–74, Denmark
FIND-AF2 (high risk) NCT04371055	1040	Implanted monitor	Post-stroke, Germany
FIND-AF2 (low risk) NCT04371055	4160	7-day Holter, once	Post-stroke, Germany
GUARD-AF NCT04126486	11 931	14-day ECG Patch, once	Age ≥70, USA
Heartline NCT04276441	150 000	ECG Watch	Age ≥65, USA
SAFER-Internal Pilot ISRCTN16939438	14 082	Hand-held ECG, QID for 21 days	Age ≥70, UK
SAFER-UK ISRCTN72104369	100 418	Hand-held ECG, QID for 21 days	Age ≥70, UK
SAFER-AUS ISRCTN72104369	2100	Hand-held ECG, QID for 21 days	Age ≥70, Australia
STROKESTOP II NCT02743416	28 712	Hand-held ECG, QID for 14 days	Age 75/76 with elevated NT-ProBNP, Sweden

Atrial fibrillation (AF) is a major cause of disabling stroke worldwide. Once AF is identified, stroke risk can be substantially reduced with oral anticoagulation (OAC). Many medical and consumer-facing technologies can now detect AF, and there is widespread interest in screening for AF, as a means of preventing stroke.[1] However, advisory panels, like the United States Preventative Services Task Force, have concluded that there is currently insufficient evidence to endorse AF screening.[2] We undertook a focused review to summarize

Figure 1 Study selection diagram.
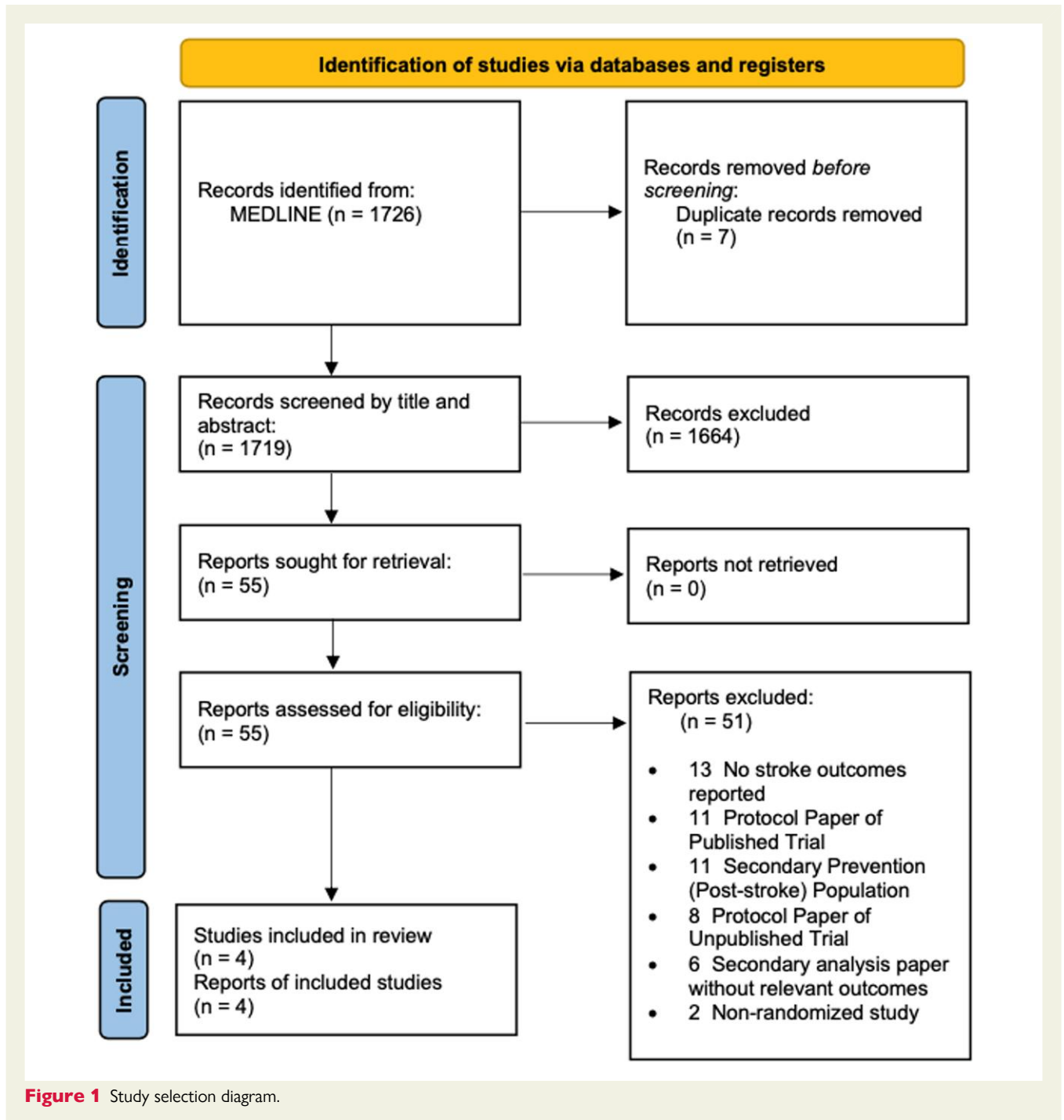
existing evidence from published randomized controlled trials (RCTs) that assessed AF screening for stroke prevention.

We searched MEDLINE for randomized trials that enrolled patients without known AF, screened for AF using electrocardiogram (ECG)-based methods, and reported stroke outcomes. We excluded studies that focused on post-stroke populations. We identified four randomized clinical trials with a total of 35 836 participants (*Table 1* and *Figure 1*).[3–6] *Figure 2*'s lower panel shows the results of a random-effects meta-analysis of stroke outcomes, following the intention-to-treat principle. While the point estimate

[relative risk 0.91; 95% confidence interval (CI): 0.84–0.99] is modestly in favour of AF screening, published trials are heterogenous in their populations, their definition of stroke (*Figure 2* footnote), and their screening methodology (from single time-point ECG to years of invasive monitoring).

Figure 2's upper panel shows a trial sequential analysis of reported studies. The boundary in red is calculated using the observed event rates of studies to date, a two-sided Type-1 error of 5%, 80% power, 50% heterogeneity, and an O'Brien-Fleming alpha-spending function. The trial sequential analysis shows that the cumulative z-score from
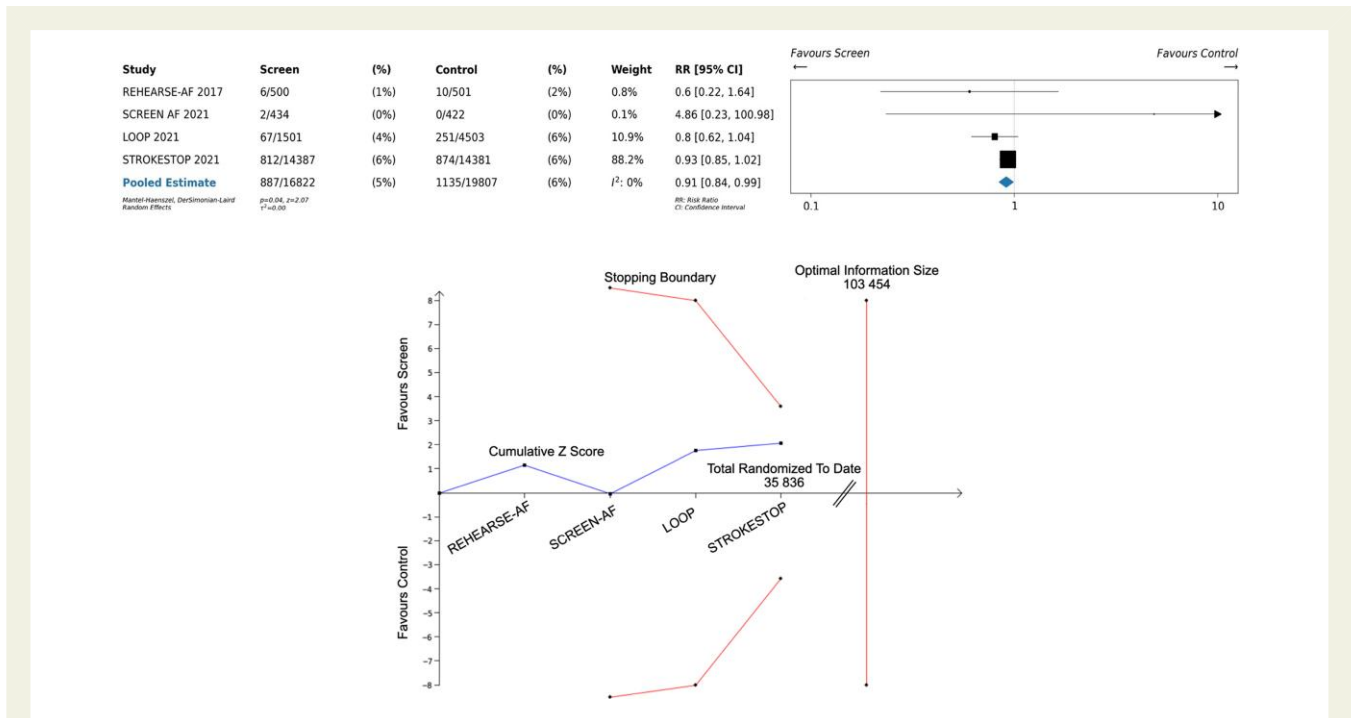
Figure 2 Forest plot (upper panel) and trial sequential analysis (lower panel) of published RCTs of AF screening for stroke prevention. Stroke was defined in REHEARSE-AF as stroke, transient ischaemic attack, or systemic embolism; stroke was defined in SCREEN-AF as ischaemic stroke; stroke was defined in LOOP as stroke or systemic embolism; stroke was defined in STROKESTOP as ischaemic stroke or systemic embolism. *REHEARSE-AF was not penalized at interim look due to low information use (<1%).

published data (blue line) is insufficient to conclude the benefits of screening and calculates an optimal sample size of a total of 103 454 participants randomized, indicating that further trials should be performed.

Atrial fibrillation screening can only prevent strokes in patients who are found to have the disease, and then take OAC as a result of positive screening. Furthermore, AF is only one of many important risk factors for stroke. This means that the relative risk reduction for screening could be small and large numbers of patients need to be studied to demonstrate the efficacy of AF screening for stroke prevention. Still, the number of patients worldwide who are at risk of AF-related stroke is very large, and the absolute benefit of AF screening could be large. Given this potential public health impact of AF screening on stroke, there is a need to systematically collate data on RCTs of AF screening in a variety of healthcare settings.

The International AF-SCREEN collaboration has been working since 2015 to assess the efficacy of AF screening for the prevention of stroke.[1] Members of the group secured a European Union Horizons 2020 grant (*Digital, risk-based screening for atrial fibrillation in the European community*, agreement No 847770), which supports a prospective, individual patient data meta-analysis of RCTs (PROSPERO, Protocol Under Review).[7] The primary outcome of the meta-analysis is stroke. Secondary outcomes include AF detection, OAC prescription, hospitalization, mortality, and bleeding. Anonymized participant data from individual RCTs are being translated into a common format and collated in a central database. Individual participant data will permit pre-specified subgroup and meta-regression analyses to explore heterogeneity in populations,

healthcare settings, screening modalities, and uptake of OAC. To date, study teams from 16 RCTs including nearly 300 000 participants are contributing to the effort; any group conducting an eligible trial is invited to join (*Table 1*).

Conclusion

If and how to screen for AF is an important public health concern. The AF-SCREEN/AFFECT-EU individual patient data meta-analysis aims to comprehensively assess the benefits and risks of AF screening, and determine how population, screening method, and health-system factors influence stroke prevention.

Data availability
All data were abstracted from the referenced publications.

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