Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial

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Summary

Background Atrial fibrillation is a leading cause of ischaemic stroke. Early detection of atrial fibrillation can enable anticoagulant therapy to reduce ischaemic stroke and mortality. In this randomised study in an older population, we aimed to assess whether systematic screening for atrial fibrillation could reduce mortality and morbidity compared with no screening.

Methods STROKESTOP was a multicentre, parallel group, unmasked, randomised controlled trial done in Halland and Stockholm in Sweden. All 75–76-year-olds residing in these two regions were randomly assigned (1:1) to be invited to screening for atrial fibrillation or to a control group. Participants attended local screening centres and those without a history of atrial fibrillation were asked to register intermittent electrocardiograms (ECGs) for 14 days. Treatment with oral anticoagulants was offered if atrial fibrillation was detected or untreated. All randomly assigned individuals were followed up in the intention-to-treat analysis for a minimum of 5 years for the primary combined endpoint of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation, and all-cause death. This trial is registered with ClinicalTrials.gov, NCT01593553.

Findings From March 1, 2012, to May 28, 2014, 28 768 individuals were assessed for eligibility and randomly assigned to be invited to screening (n=14 387) or the control group (n=14 381). 408 individuals were excluded from the intervention group and 385 were excluded from the control group due to death or migration before invitation. There was no loss to follow-up. Of those invited to screening, 7165 (51·3%) of 13 979 participated. After a median follow-up of 6·9 years (IQR 6·5–7·2), significantly fewer primary endpoint events occurred in the intervention group (4456 [31·9%] of 13 979; 5·45 events per 100 years [95% CI 5·52–5·61]) than in the control group (4616 [33·0%] of 13 996; 5·68 events per 100 years [5·52–5·85]; hazard ratio 0·96 [95% CI 0·92–1·00]; p=0·045).

Interpretation Screening for atrial fibrillation showed a small net benefit compared with standard of care, indicating that screening is safe and beneficial in older populations.

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Introduction

Atrial fibrillation is associated with increased mortality and morbidity, and is a dominant, yet preventable, cause of cardioembolic stroke, which has more severe outcomes than other ischaemic stroke causes if left untreated.[1,2] Treatment of atrial fibrillation with oral anticoagulants has increased steadily due to its substantial effects on reduction of atrial fibrillation-related mortality and morbidity.[2,3]

Early diagnosis of atrial fibrillation might enable oral anticoagulant therapy and prevent unwanted consequences of undetected disease, leading to the suggestion that screening for atrial fibrillation might be beneficial in populations at risk.[4] The absence of studies reporting on hard clinical endpoints in atrial fibrillation screening has led to differences in recommendations globally. Most notably, systematic screening for atrial fibrillation is to be considered according to 2020 European guidelines,[5] whereas the US Preventive Services Task Force concluded that current evidence is insufficient to assess the balance of benefits and harms of screening for atrial fibrillation.[6]

In this randomised, population-based study in people aged 75–76 years, we aimed to assess whether screening for atrial fibrillation and appropriate oral anticoagulant treatment leads to a net benefit in the screened population, with a reduced incidence of stroke, systemic embolism, and all-cause mortality without an increase in severe bleeding compared with a control group.

Research in context

Evidence before this study

We searched PubMed on March 21, 2021, with no language restrictions, using the following search terms: (atrial fibrillation [MeSH Terms]) AND (screening [MeSH Terms]) AND (cerebral stroke [MeSH Terms]) and identified 90 studies. Adding a filter for randomised controlled trials limited the number of studies to eight. Of these studies, one described the rationale behind a planned study using an electrocardiogram (ECG) patch for detection of atrial fibrillation with a secondary outcome of time to first adjudicated transient ischaemic attack, stroke, arterial thromboembolism, myocardial infarction, hospitalisation overall, and bleeding events. One study was a pilot study, one study included only patients with stroke, and four were substudies. One study included a secondary analysis comparing opportunistic screening for atrial fibrillation with systematic screening. Filtering for clinical trials identified one additional study, which compared detection of atrial fibrillation using a single-lead ECG device with a blood pressure monitor in primary care. We identified no studies with clinical outcome data from randomised clinical trials of atrial fibrillation. Overall, there were no randomised controlled clinical trials reporting on clinical outcomes as a primary outcome in screening for atrial fibrillation compared with a control group.

Added value of this study

To our knowledge, this is the first randomised trial to assess the net clinical outcome of screening for atrial fibrillation. This study reports both data on stroke reduction and on mortality, but also on potential negative consequences of oral anticoagulant therapy with bleeding events. We found that screening for atrial fibrillation significantly reduced the risk of our combined endpoint of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation, and all-cause death.

Implications of all the available evidence

Taken together, our findings suggest that screening for atrial fibrillation in an older population has a net beneficial effect and should be considered as part of health-care policy.

Methods

Study design and participants

The STROKESTOP trial was a multicentre, parallel group, unmasked randomised controlled trial done in the regions of Halland and Stockholm in Sweden to evaluate a screening programme for atrial fibrillation. The regions differ in size and population density, with Stockholm having a larger population and higher population density. The study design has been described previously.[7,8] All living residents aged 75 or 76 years (born in 1936 or 1937) in the two regions who were identified using their person identification number were eligible for inclusion in the study. There were no exclusion criteria. All enrolled participants were followed up for a minimum of 5 years using patient registries for the prespecified outcomes.

The study complied with the Declaration of Helsinki. The protocol was approved by the regional ethics committee (DNR 2011-1363-31/3). Written, informed consent was obtained from all participants in the screening programme.

Randomisation and masking

Residents were randomly assigned (1:1) to a group invited to screening or to a parallel control group. The computer randomisation was done by Statistics Sweden on Nov 30, 2011. There was no masking.

Procedures

Residents randomly assigned to be invited to screening received up to three written invitations to attend one centralised screening centre in Stockholm, or one of six regional screening centres in Halland between March 1, 2012, and May 28, 2014. Individuals randomly assigned to the control group did not receive any intervention.

Identification of endpoint events, exposure to anticoagulant drugs during follow-up, and information about comorbidity and socioeconomic conditions was obtained through linkage of civic identification numbers with nationwide Swedish registers. These numbers are given to all permanent residents in Sweden and are used in all contacts with authorities including the health-care system. The registers used were the National Patient register, the Prescribed Drug register, the Cause of Death register, and the Longitudinal Integrated Database for Health Insurance and Labor Market Studies. These registers are used for epidemiological research and have a high sensitivity and specificity for diagnoses related to discrete events.[9–12] The Prescribed Drug register holds information about all dispensed prescription drugs in the country and was used to assess oral anticoagulant exposure during follow-up. Ongoing treatment was defined as at least one dispensing during the preceding 6 months.

Individuals invited to screening who chose to participate in the study were termed participants and those choosing not to participate were termed non-participants. Participants stating a history of atrial fibrillation and not treated with oral anticoagulants were referred to a cardiologist for follow-up and confirmation of the diagnosis. Participants without a history of atrial fibrillation were instructed on using a hand-held single-lead electrocardiogram (ECG; Zenicor II, Zenicor, Stockholm, Sweden). If the index ECG did not show atrial fibrillation, participants were asked to record

ECGs twice daily for 2 weeks. Participants unable to use single-lead ECGs, or for whom single-lead ECGs were uninterpretable, were offered other means of long-term ECG monitoring. The diagnostic criteria for atrial fibrillation were at least one episode of completely irregular heart rhythm without p-waves lasting 30 s, or two or more episodes of 10–29 s duration. If new atrial fibrillation was detected during monitoring, participants were referred to a cardiologist for follow-up and, if there were no contraindications, initiation of oral anticoagulant therapy. The results of detection rates of atrial fibrillation and oral anticoagulant initiation have been reported previously.[13]

Outcomes

At study start in 2012, the primary endpoint was set to be ischaemic stroke. During the study period, there was a major shift in the care of patients with atrial fibrillation following the introduction of direct oral anticoagulants (DOACs), leading to vastly increased treatment with stroke preventive therapy. In parallel, ischaemic stroke incidence decreased by more than 40% between 2012 and 2017.[14]

Death is a more frequent outcome and a competing risk for patients with atrial fibrillation compared with ischaemic stroke.[5] Earlier studies found that oral anticoagulation with warfarin had the potential also to reduce mortality.[2] Newer studies of DOACs added strength to the data and showed that DOACs could reduce mortality even further in patients with atrial fibrillation.[15] Hence, participants with a new atrial fibrillation diagnosis receiving oral anticoagulants or DOACs would have a lower risk of mortality in addition to stroke. After discussion within the steering committee, and before any data were extracted, the primary endpoint was changed to a combined endpoint of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation (at least one overnight stay), and all-cause mortality (appendix p 2). This change was because a net benefit of the screening programme was deemed more clinically relevant as an endpoint. Secondary endpoints were detection of atrial fibrillation, death from any cause; death from cardiovascular disease; hospitalisation (at least one overnight stay) due to cardiovascular disease; ischaemic stroke; dementia (new clinical diagnosis); a composite of ischaemic stroke and systemic thromboembolism; venous thromboembolism; an addition of cardiovascular hospitalisation to the primary endpoint; and initiation and compliance to oral anticoagulant therapy. A cost–efficacy analysis was also a secondary endpoint, the results of which will be reported elsewhere (appendix p 2). The revision of the endpoints was registered at ClinicalTrials.gov in November, 2017, several years before the extraction of data (appendix p 1). The appendix (p 3) shows the definitions of diagnoses in medical history.

In a post-hoc analyses, we also looked at the composite endpoint of ischaemic stroke, haemorrhagic stroke, or dementia, in order to look at all outcomes that have an impact on the brain.

The index date for participants was defined as the date of the visit to the screening facility or, in the case of non-participants, the date they had been sent the invitation to participate. Individuals in the control population were randomly assigned the same index dates that occurred in the intervention group. Individuals who died, emigrated, or moved out of the region before the index date were not included in the analysis. Time at risk was counted from index and lasted until the specified event, emigration, death, or Dec 31, 2019.

Statistical analysis

In our initial power calculation, we estimated that the annual risk of stroke in untreated patients with atrial fibrillation was 7% and that the protective effect of oral anticoagulant therapy was 70%, leading to an annual risk of stroke in treated patients with atrial fibrillation of 2%. The annual risk of stroke in the general population was 1·2%. With a 55% participation rate, we estimated that 11 397 individuals needed to be included in each group to evaluate the primary outcome at a 5% two-sided significance level with 80% power. However, newer studies showed that the annual ischaemic stroke risk was substantially lower (3·0%) in the untreated group.[14,16] This decrease in ischaemic stroke risk was unaccounted for in our initial power calculation. The endpoint was subsequently changed to a combined endpoint with more similar risks to the ones we had calculated initially in the untreated group.[16]

The primary results were analysed in the intention-to-screen population (all randomly assigned individuals). All secondary endpoints were analysed in the intention-to-treat population with the exception of incidence of ischaemic stroke or systemic thromboembolism, which

See Online for appendix

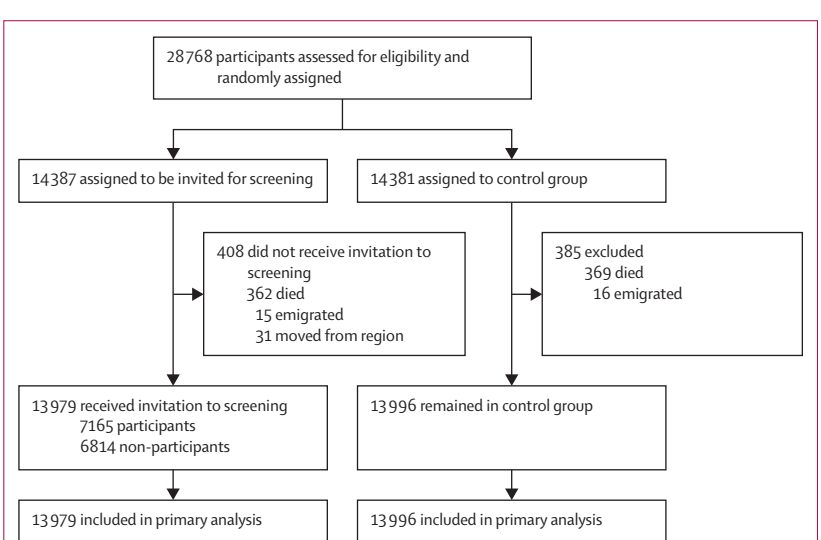


Figure 1: **Trial profile**

	Randomly assigned groups		Within the invited to screening group		
	Invited to screening (n=13 979)	Control group (n=13 996)	Participants (n=7165)	Non-participants (n=6814)	p value*
Demographic and socioeconomic factors					
Age, years	76·0 (75·5–76·6)	76·0 (75·5–76·6)	75·8 (75·3–76·3)	76·2 (75·7–76·8)	<0·0001
Women	7637 (54·6%)	7636 (54·6%)	3863 (53·9%)	3774 (55·4%)	0·081
Living alone	7125 (51·0%)	7095 (50·7%)	3222 (45·0%)	3903 (57·3%)	<0·0001
Born outside of Sweden	2865 (20·5%)	2857 (20·4%)	1076 (15·0%)	1789 (26·3%)	<0·0001
Income in highest quartile	3552 (25·4%)	3522 (25·2%)	2256 (31·5%)	1296 (19·0%)	<0·0001
University or college education	3964 (28·4%)	3937 (28·1%)	2465 (34·4%)	1499 (22·0%)	<0·0001
Alcohol index†	352 (2·5%)	378 (2·7%)	88 (1·2%)	264 (3·9%)	<0·0001
Medical history					
CHA_2DS_2VASC‡ score	3·5 (1·3)	3·5 (1·3)	3·3 (1·1)	3·7 (1·4)	<0·0001
Ischaemic stroke, transient ischaemic attack, or systemic embolism	1557 (11·1%)	1513 (10·8%)	634 (8·8%)	923 (13·5%)	<0·0001
Heart failure	1045 (7·5%)	1098 (7·8%)	341 (4·8%)	704 (10·3%)	<0·0001
Hypertension	4963 (35·5%)	4980 (35·6%)	2262 (31·6%)	2701 (39·6%)	<0·0001
Vascular disease§	1632 (11·7%)	1686 (12·0%)	649 (9·1%)	983 (14·4%)	<0·0001
Diabetes	2115 (15·1%)	2107 (15·1%)	829 (11·6%)	1286 (18·9%)	<0·0001
Chronic kidney disease	303 (2·2%)	356 (2·5%)	77 (1·1%)	226 (3·3%)	<0·0001
Cancer¶	1767 (12·6%)	1864 (13·3%)	898 (12·5%)	869 (12·8%)	0·70
Dementia	465 (3·3%)	408 (2·9%)	72 (1·0%)	393 (5·8%)	<0·0001
Drugs dispensed within preceding 6 months‖					
Oral anticoagulant	1282 (9·2%)	1313 (9·4%)	574 (8·0%)	708 (10·4%)	<0·0001
Aspirin	3525 (25·2%)	3702 (26·5%)	1634 (22·8%)	1891 (27·8%)	<0·0001
β blocker	4752 (34·0%)	4764 (34·0%)	2154 (30·1%)	2598 (38·1%)	<0·0001
ACE inhibitor or angiotensin receptor blocker	5476 (39·2%)	5361 (38·3%)	2632 (36·7%)	2844 (41·7%)	<0·0001
Statin	4183 (29·9%)	4238 (30·3%)	2042 (28·5%)	2141 (31·4%)	<0·0001

Data are median (IQR), n (%), or mean (SD). ACE=angiotensin converting enzyme. *p value comparing participants with non-participants within the intervention group. †For the alcohol index a set of International Classification of Disease codes used by the Swedish Board of Health and Welfare for annual reporting of alcohol-related mortality in the Swedish population was used (E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90–91, Z502, and Z714). ‡For CHA_2DS_2-VASc score 1 point each for: heart failure, hypertension, age 65–74 years, diabetes, vascular disease, or female sex, and 2 points each for age 75 years or more, stroke, systemic embolism, or transient ischaemic attack was used. §Vascular disease as in CHA_2DS_2-VASc—ie, previous myocardial infarction or peripheral artery disease. ¶Cancer within 3 years before index. ‖Not counting dispensings made on the index date.

Table 1: **Baseline characteristics**

was also analysed in the group participating in screening (as treated) compared with the control group. Continuous variables are reported as means with 95% CIs and tested for differences between groups with Student's *t* test. Categorical data are reported as proportions and absolute values, and differences assessed with χ^2 tests. Incidences are reported as the number of events per 100 years at risk. Censoring was done at event, emigration, or death. Hazard ratios (HRs) were obtained by Cox regression without adjustment for cofactors.

In a post-hoc analysis of outcomes in the participants group, an adjusted analysis was done including all variables that differed significantly between participants and non-participants, with the exception of CHA_2DS_2-VASc score, oral anticoagulant use, and aspirin use (appendix p 5).

A prespecified interim analysis using data extracted until Dec 31, 2016, was done in February, 2018. This analysis showed numerically fewer events in the group randomly assigned to be invited to screening compared with the control group.

Two-tailed tests were used and p values less than 0·05 were considered significant. Data management and statistical analyses were done with Stata 16.1 software from StataCorp. The study is registered with ClinicalTrials.gov, NCT01593553.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From March 1, 2012, to May 28, 2014, 28 768 individuals were assessed for eligibility and randomly assigned to be invited to screening or to a control group (figure 1). The randomisation was done at the end of 2011 and 793 individuals had died or migrated before the start of the study. 13 979 received the invitation to screening, and 13 996 were analysed in the control group. There was no loss to follow-up. All individuals included in the analysis were followed up for a minimum of 5·6 years (median 6·9 years [IQR 6·5–7·2]). Baseline characteristics for the two groups are shown in table 1. In the intervention group, 7165 (51·3%) of the 13 979 invited to screening chose to participate in the screening programme (participants). Within the intervention group, non-participants had significantly more comorbidities, medications, and unfavourable sociodemographic factors compared with participants (table 1).

In analysis of the primary endpoint, consisting of ischaemic or haemorrhagic stroke, systemic embolism, bleeding requiring hospitalisation, and all-cause mortality, there were significantly fewer events per 100 years in the group invited to screening than in the control group (table 2; figure 2A). In both groups combined, the majority of events in the primary endpoint were all-cause mortality (6464 [71·2%] of 9072), while 2879 (31·7%) events were hospitalisation due to major bleeding, 1596 (17·6%) were ischaemic stroke, 292 (3·2%) were haemorrhagic stroke, and 114 (1·3%) were systemic embolism. There was no significant difference in any of the individual components of the primary endpoint between the group invited to screening and the control group (table 2; figure 2B). The number needed to invite to screening to avoid one primary endpoint event was 91.

1691 (12·1%) of 13 979 in the intervention group and 1794 (12·8%) of 13 996 in the control group had atrial

	Invited to screening			Control group			Hazard ratio (95% CI)	p value
	Events*	Years at risk	Events per 100 years (95% CI)	Events*	Years at risk	Events per 100 years (95% CI)		
Composite primary endpoint†	4456	81757	5·45 (5·29–5·61)	4616	81262	5·68 (5·52–5·85)	0·96 (0·92–1·00)	0·045
Ischaemic stroke	766	85068	0·90 (0·84–0·97)	830	84574	0·98 (0·92–1·05)	0·92 (0·83–1·01)	0·084
Haemorrhagic stroke	137	86727	0·16 (0·13–0·19)	155	86309	0·18 (0·15–0·21)	0·88 (0·70–1·11)	0·27
Systemic embolism	60	86808	0·07 (0·05–0·09)	54	86531	0·06 (0·05–0·08)	1·10 (0·76–1·59)	0·60
Hospitalisation for major bleeding	1431	83490	1·71 (1·63–1·81)	1448	83084	1·74 (1·66–1·83)	0·98 (0·91–1·06)	0·65
Death from any cause	3177	86930	3·65 (3·53–3·78)	3287	86614	3·79 (3·67–3·93)	0·96 (0·92–1·01)	0·12
Ischaemic stroke or systemic thromboembolism as randomly assigned	812	84952	0·96 (0·89–1·02)	874	84514	1·03 (0·97–1·11)	0·92 (0·84–1·02)	0·10
Ischaemic stroke or systemic thromboembolism as treated	372	47203	0·79 (0·71–0·87)	874	84514	1·03 (0·97–1·11)	0·76 (0·67–0·85)	<0·0001
New clinical diagnosis of dementia	1164	84258	1·38 (1·30–1·46)	1217	83805	1·45 (1·37–1·54)	0·95 (0·88–1·03)	0·20
Cardiovascular death	1211	86930	1·39 (1·32–1·47)	1197	86614	1·38 (1·31–1·46)	1·01 (0·93–1·09)	0·87
Cardiovascular hospitalisation	3633	76265	4·76 (4·61–4·92)	3659	75919	4·82 (4·67–4·98)	0·99 (0·94–1·04)	0·63
Primary endpoint with the addition of cardiovascular hospitalisation	6101	74283	8·21 (8·01–8·42)	6191	73834	8·38 (8·18–8·60)	0·98 (0·95–0·01)	0·26
Ischaemic or haemorrhagic stroke or dementia	1981	79982	2·48 (2·37–2·59)	2077	79724	2·61 (2·50–2·72)	0·95 (0·89–1·01)	0·098
Pulmonary embolism or venous thromboembolism	577	84873	0·68 (0·63–0·74)	564	84809	0·67 (0·61–0·72)	1·02 (0·91–1·15)	0·71

*Only the first event of each category was counted; therefore, one individual could have had several events of the same kind. †Primary endpoint was a composite of: ischaemic or haemorrhagic stroke, systemic embolism, hospitalisation for bleeding, or death from any cause.

Table 2: **Outcomes**

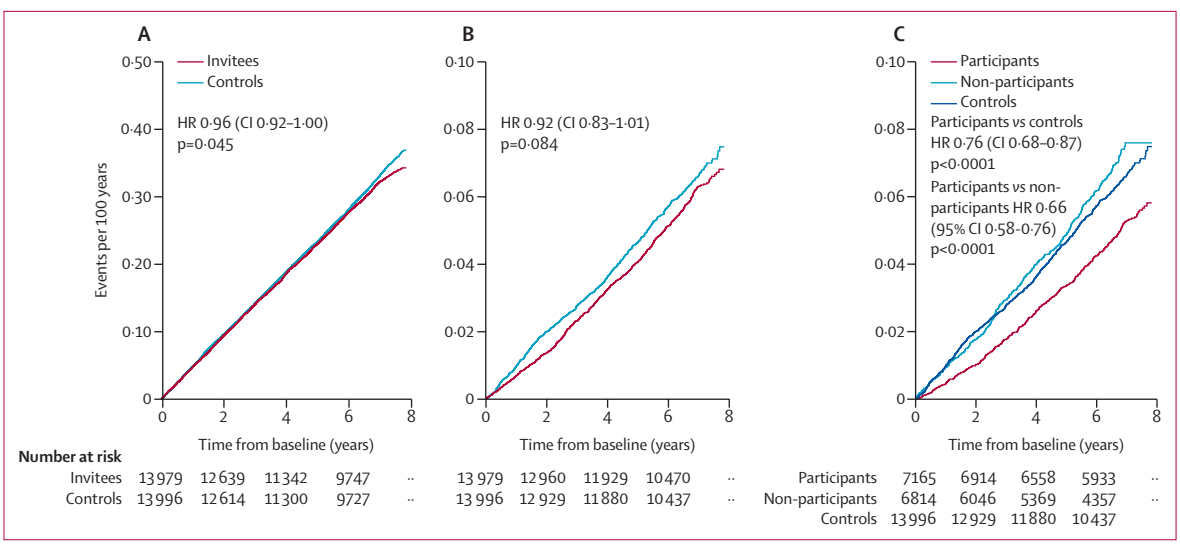
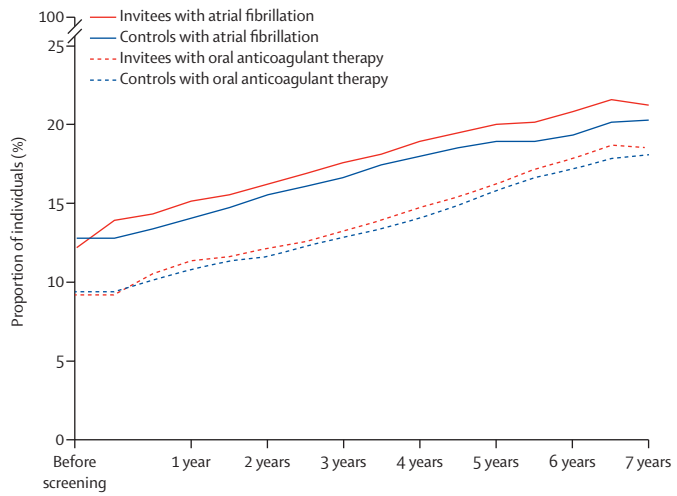


Figure 2: **Events per 100 years for the composite primary endpoint and the secondary endpoint of ischaemic stroke**
(A) Events per 100 years for the primary endpoint of ischaemic or haemorrhagic stroke, systemic embolism, major bleeding leading to hospitalisation, or death from any cause in all randomly assigned individuals (regardless of participation). (B) Events per 100 years for the secondary endpoint of ischaemic stroke in all randomly assigned individuals. (C) Events per 100 years in the unadjusted analysis of the secondary endpoint of ischaemic stroke in individuals choosing to participate in the screening programme compared with non-participants and the control group. HR=hazard ratio.

fibrillation at baseline (figure 3; appendix p 4). Within the intervention group, atrial fibrillation was more common at baseline among non-participants (959 [14·1%] of 6814) than participants (732 [10·2%] of 7165; p<0·0001). Immediately after the screening intervention, the proportion of individuals with diagnosed atrial fibrillation was significantly greater in the intervention group than in the control group (appendix p 4). During follow-up, the proportion with diagnosed atrial fibrillation increased gradually to more than 20% in both groups (figure 3).



n (number at risk)								
Invitees with atrial fibrillation	1691 (13 979)	2047 (13 552)	2127 (13 110)	2229 (12 689)	2312 (12 248)	2348 (11 751)	2281 (10 906)	987 (4 638)
Controls with atrial fibrillation	1794 (13 996)	1919 (13 591)	2037 (13 145)	2118 (12 696)	2193 (12 217)	2227 (11 729)	2114 (10 884)	843 (4143)
Invitees with oral anticoagulant therapy	1282 (13 979)	1526 (13 552)	1604 (13 110)	1682 (12 689)	1804 (12 248)	1902 (11 751)	1949 (10 906)	860 (4638)
Controls with oral anticoagulant therapy	1313 (13 996)	1463 (13 591)	1531 (13 145)	1620 (12 696)	1728 (12 217)	1849 (11 729)	1876 (10 884)	750 (4143)

Figure 3: **Proportion of individuals with diagnosed atrial fibrillation and oral anticoagulant therapy in the invited to screening group and the control group**

Throughout the study period, the higher proportion of diagnosed atrial fibrillation in the intervention group persisted compared with the control group (figure 3).

The use of oral anticoagulants was similar in the intervention group and the control group at baseline (appendix p 4). Within the intervention group, oral anticoagulants were initiated in 262 (3·7%) of 7165 participants (those who agreed to screening) due to newly diagnosed or previously known and undertreated atrial fibrillation. The proportion of individuals using oral anticoagulants was not significantly different between the intervention group and the control group throughout the study (figure 3; appendix p 4). During follow-up, oral anticoagulant use almost doubled in both groups (figure 3; appendix p 4). Oral anticoagulant use among those with a diagnosis of atrial fibrillation increased from approximately 60% to 70% during the study in both groups (appendix p 6). The proportion of participants with atrial fibrillation using oral anticoagulants in the first year after screening (682 [65·8%] of 1037) was greater than non-participants (604 [59·8%] of 1010; p=0·0052) but became similar over time (appendix p 6).

Over the total follow-up period, the annual incidence of ischaemic stroke among individuals with atrial fibrillation at the beginning of follow-up who were unexposed to oral anticoagulants was 3·4 per 100 years at risk (95% CI 2·7–4·2), in both groups.

In the unadjusted analysis of the primary and secondary endpoints in participants in the invited to screening group (only those who participated in the screening) compared with the control group, screening was associated with significant benefits for all endpoints, except venous thromboembolism (appendix p 5). Non-participants had significantly worse outcomes than both participants and the control group for the primary outcome and the secondary outcome of ischaemic stroke (figure 2C; appendix p 5).

In a post-hoc analysis adjusting for differences between participants and non-participants, the adjusted HR for the combined primary endpoint and for the secondary endpoint of ischaemic stroke were significant for participants compared with controls, and for participants compared with non-participants (appendix p 5).

Discussion

To our knowledge this is the first randomised population screening study for atrial fibrillation assessing the net benefits of screening. We found a benefit of screening with regard to the primary endpoint, which was a composite of ischaemic or haemorrhagic stroke, systemic embolism, bleeding requiring hospitalisation, and all-cause death. There were no differences between the groups in any of the individual components of the primary endpoint. There were no significant benefits regarding the prespecified secondary endpoints, including ischaemic stroke, in the group randomly assigned to screening compared with the control group.

The screening programme was successful both in detecting atrial fibrillation and initiating oral anticoagulant treatment in participants with newly detected atrial fibrillation.[8] In the general population, an increase in wearable technologies has increased awareness and enabled a higher spontaneous detection of arrhythmias in the past few years.[17,18] The introduction of novel direct oral anticoagulants and widened indications for oral anticoagulant treatment in recent guidelines was probably part of the explanation for the doubling of the proportion of oral anticoagulant users in both groups of our study from 2012 to 2019.[5,19,20] In the Swedish population overall between 2012 and 2019, the number of oral anticoagulant users increased substantially, paralleled by a substantial reduction in the incidence of ischaemic stroke.[10] With a high spontaneous detection rate of atrial fibrillation and use of oral anticoagulants in the general population, the potential gain from atrial fibrillation screening is smaller. Thus, the same trial design might show a clearer benefit of screening if applied to a population with lower spontaneous atrial fibrillation detection and oral anticoagulant use than in Sweden.

The participants in our screening study (those who accepted the invitation) had overall better health outcomes than non-participants. At baseline, non-participants had more comorbidities overall, a lower grade of education, were more likely to live alone, and had a lower income compared with the participants,

showing that efforts need to be made to target these groups within screening programmes in order to improve public health. The high event rates in non-participants indicate that this group could have benefited from screening. Those most reluctant to participate are often the ones most likely to benefit from screening.[21] Measures to increase participation are therefore essential.[22] Such measures could be to reduce the geographical distance to the screening centre, which has been shown to be important.[22] Participation in our study was higher in the smaller, rural region of Halland where there were several screening centres. Opportunistic screening, for example at general practitioners, might lead to increased participation.[23]

The optimal method for atrial fibrillation screening has not yet been identified. Pulse palpation has been used in previous studies to identify individuals at risk of atrial fibrillation but, with the advent of more modern technologies, other methods with higher accuracy are now easily available in most practices.[5] In our trial, we invited individuals at high risk, as decided solely by age without regard for comorbidities, and used single-lead ECGs for 2 weeks. Other screening studies have used enriched screening criteria such as adding hypertension, diabetes, or biomarkers to identify those at high risk and using other methods of atrial fibrillation detection.[24–26] In the systematic STROKESTOP II study, 75–76-year-olds with biomarker NT-proBNP concentrations of 125 ng/L or more were offered screening with intermittent ECG four times daily for 2 weeks, with an overall new detection of atrial fibrillation in 165 (2·6%) of 6315 participants.[24] Another screening study, the REHEARSE-AF study,[26] used intermittent ECGs twice per week during a year, which significantly increased the detection of atrial fibrillation compared with a control group. In the randomised mSToPS trial, older individuals (mean age 72·4 years [SD 7·3]) were offered a self-applied, wearable ECG patch to use for up to 4 weeks and new atrial fibrillation was identified in 53 (3·9%) of 1366 participants at 4 months.[25] Studies focusing on detection in a population at high risk or using longer windows of atrial fibrillation detection often show a higher rate of detection of atrial fibrillation. The advantage of increased detection with repeated screening should be weighed against the increased cost and burden on the participating individuals. The net burden of atrial fibrillation warranted for oral anticoagulation therapy is unknown. A low burden of atrial fibrillation detected on continous monitoring might infer a lower risk of ischaemic stroke compared with a higher burden of atrial fibrillation or clinically detected atrial fibrillation (studies in this area are ongoing—eg, NCT01938248, NCT02618577, also LOOP NCT02036450). Identification of subpopulations with high atrial fibrillation prevalence, high stroke risk, and a low oral anticoagulant usage might obtain a more substantial net benefit of atrial fibrillation screening.

A major strength of this study is that it focused on screening an entire subset of the population based solely on age, enabling a simple strategy for population screening. The endpoints of the study focused on the net clinical benefits of screening, including potential harms of associated therapies. No individuals were lost to follow-up, and all individuals were followed up regarding treatment with oral anticoagulants and incident atrial fibrillation for a median of almost 7 years. More studies are needed to confirm our findings in other populations but, based on our results, screening in an older population similar to the one included in our study can be safely recommended.

Our study has several limitations. When the trial and the power calculations were made in 2010, the incidence of stroke was much higher than today. The assumed annual stroke risk with untreated atrial fibrillation of 7% at age 75 years was higher than our outcome of 3·4%. One reason for this overestimation could be that earlier studies on atrial fibrillation epidemiology and stroke risk had mostly considered populations with permanent atrial fibrillation.[5] In addition, after the introduction of DOACs, stroke incidence in Sweden greatly decreased during our study period.[14] In our study, we counted all individuals with atrial fibrillation, including paroxysmal atrial fibrillation, which might confer a lower risk of stroke.[27] Inclusion of a higher proportion of individuals at low risk contributed to a lower stroke incidence. The effect of our overestimation of the stroke incidence among patients with untreated atrial fibrillation was that the study was underpowered to detect a difference in ischaemic stroke. However, it is important to note that the trial was not underpowered for the primary composite endpoint. The endpoint events were not adjudicated but were obtained from routine clinical data. Some events could have been misdiagnosed or missed despite the high validity of diagnoses for discrete events in the Swedish patient register.[9]

The combined endpoint used to reflect net clinical benefit of screening for patients with atrial fibrillation used major bleeding as a proxy for harm. In our study of older individuals with asymptomatic arrhythmia, few received treatment to achieve rhythm control.[28] This might differ in different health-care systems, and increased investigations and therapy to achieve rhythm control might lead to adverse events related to the procedure or anti-arrhythmic drugs that has not been reflected in our findings.

The endpoint of newly diagnosed dementia should be regarded as exploratory because clinical diagnoses of dementia are not made until late in the disease process and have low sensitivity.[9] Dementia generally develops slowly through a prodromal phase of cognitive decline. It would be expected that a study of oral anticoagulant treatment to prevent atrial fibrillation-related dementia would need several years to show a difference.[29] Against this background, it is interesting to note that the

incidence of newly diagnosed dementia was slightly lower in the group invited to screening than in the control group.

In analyses comparing outcomes between participating and non-participating individuals, interpretation should be made with caution because of attrition bias, even if attempts have been made to adjust for some differences between the groups. In analyses comparing participants with controls, the non-participants with their higher risk burden have been excluded. This might have made the intervention group appear healthier when compared with the control group. Data for the non-participating group show the group's high risk factor burden. It is possible that with a higher participation rate among the invited group, our findings might have shown more benefits of screening with regards to the hard endpoints.

There are very few data comparing the harms of screening with no screening for atrial fibrillation, but it is possible that screening for atrial fibrillation using ECG can potentially lead to harm.[30] Screening can lead to distress in participants having their heart rhythm assessed daily. In addition, the screening intervention only examined the heart rhythm for a very short period of time, and an absence of arrhythmia during this time could lead to false reassurance that a participant with a rare, paroxysmal arrhythmia, or a participant developing an arrhythmia post-intervention, is free of heart rhythm disturbances. This could lead to the risk of a participant refraining from seeking health care for arrhythmia-related symptoms on the assumption that the heart rate is normal based on the previous screening. In contrast with most screening programmes in which an initial test (eg, a faecal occult blood test) is usually followed by a more detailed investigation (eg, colonoscopy) before intervention, a single-lead ECG is in itself diagnostic for atrial fibrillation.[5] Hence, a false-positive result in atrial fibrillation screening would lead to a wrongful diagnosis, probably increase the use of health-care resources, potentially lead to health anxiety associated with a diagnosis, and would be likely to trigger oral anticoagulant therapy with its associated risk of bleeding. This needs to be carefully balanced against the benefits of the screening intervention.[5] The rate of false positives is related to the underlying prevalence in the population and hence our results might not be generalisable to other populations with lower prevalence of atrial fibrillation. The cost–efficacy of our intervention will be reported elsewhere.

Screening for atrial fibrillation in an older population showed a significant benefit by reducing hard clinical outcomes. Screening for atrial fibrillation is likely to show a greater difference in outcomes in populations with lower spontaneous detection of atrial fibrillation, as well as in settings with higher participation rates.

Contributors

ES contributed to the conceptualisation, investigation, methodology, project administration, and data validation, wrote the initial draft of the manuscript, and contributed to the review and editing of the manuscript. LF contributed to the methodology, data validation, and the review and editing of the manuscript. VF contributed to the methodology, project administration, and the review and editing of the manuscript. FA-K contributed to the methodology, project administration, and the review and editing of the manuscript. JE contributed to the conceptualisation, funding acquisition, investigation, methodology, project administration, and the review and editing of the manuscript. MR contributed to the conceptualisation, funding acquisition, methodology, project administration, supervision, and the review and editing of the manuscript. ES and LF accessed and validated the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ES reports personal fees from Bayer, Bristol Myers Squibb–Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, and Sanofi Aventis outside the submitted work. FA-K reports personal fees from Bayer, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, and Sanofi Aventis outside the submitted work. JE reports grants from Stockholm County Council and Carl Bennet AB, during the conduct of the study; and personal fees from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, BioTel Sweden, and Medtronic outside the submitted work. MR reports consulting fees from Zenicor, Bristol Myers Squibb, and Boehringer Ingelheim; payment or honoraria for lectures or presentations from Bristol Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim, and Merck Sharp & Dohme; and support for travel and attending meetings from Bristol Myers Squibb, Pfizer, and Boehringer Ingelheim. LF and VF declare no competing interests.

Data sharing

Individual participants' data collected for the study will not be shared. The study protocol is published and available.[7] Informed consent form and health questionnaires are available upon request from the corresponding author (emma.svennberg@sll.se) in the original language.

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