

# Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial



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## Summary

**Background** It is unknown whether screening for atrial fibrillation and subsequent treatment with anticoagulants if atrial fibrillation is detected can prevent stroke. Continuous electrocardiographic monitoring using an implantable loop recorder (ILR) can facilitate detection of asymptomatic atrial fibrillation episodes. We aimed to investigate whether atrial fibrillation screening and use of anticoagulants can prevent stroke in individuals at high risk.

**Methods** We did a randomised controlled trial in four centres in Denmark. We included individuals without atrial fibrillation, aged 70–90 years, with at least one additional stroke risk factor (ie, hypertension, diabetes, previous stroke, or heart failure). Participants were randomly assigned in a 1:3 ratio to ILR monitoring or usual care (control) via an online system in permuted blocks with block sizes of four or eight participants stratified according to centre. In the ILR group, anticoagulation was recommended if atrial fibrillation episodes lasted 6 min or longer. The primary outcome was time to first stroke or systemic arterial embolism. This study is registered with ClinicalTrials.gov, NCT02036450.

**Findings** From Jan 31, 2014, to May 17, 2016, 6205 individuals were screened for inclusion, of whom 6004 were included and randomly assigned: 1501 (25·0%) to ILR monitoring and 4503 (75·0%) to usual care. Mean age was 74·7 years (SD 4·1), 2837 (47·3%) were women, and 5444 (90·7%) had hypertension. No participants were lost to follow-up. During a median follow-up of 64·5 months (IQR 59·3–69·8), atrial fibrillation was diagnosed in 1027 participants: 477 (31·8%) of 1501 in the ILR group versus 550 (12·2%) of 4503 in the control group (hazard ratio [HR] 3·17 [95% CI 2·81–3·59];  $p < 0·0001$ ). Oral anticoagulation was initiated in 1036 participants: 445 (29·7%) in the ILR group versus 591 (13·1%) in the control group (HR 2·72 [95% CI 2·41–3·08];  $p < 0·0001$ ), and the primary outcome occurred in 318 participants (315 stroke, three systemic arterial embolism): 67 (4·5%) in the ILR group versus 251 (5·6%) in the control group (HR 0·80 [95% CI 0·61–1·05];  $p = 0·11$ ). Major bleeding occurred in 221 participants: 65 (4·3%) in the ILR group versus 156 (3·5%) in the control group (HR 1·26 [95% CI 0·95–1·69];  $p = 0·11$ ).

**Interpretation** In individuals with stroke risk factors, ILR screening resulted in a three-times increase in atrial fibrillation detection and anticoagulation initiation but no significant reduction in the risk of stroke or systemic arterial embolism. These findings might imply that not all atrial fibrillation is worth screening for, and not all screen-detected atrial fibrillation merits anticoagulation.

**Funding** Innovation Fund Denmark, The Research Foundation for the Capital Region of Denmark, The Danish Heart Foundation, Aalborg University Talent Management Program, Arvid Nilssons Fond, Skibsreder Per Henriksen, R og Hustrus Fond, The AFFECT-EU Consortium (EU Horizon 2020), Læge Sophus Carl Emil Friis og hustru Olga Doris Friis' Legat, and Medtronic.

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## Introduction

Stroke constitutes a major health problem worldwide.<sup>1,2</sup> The risk of stroke is five-times higher in individuals with atrial fibrillation than those without.<sup>2</sup> Approximately 20% of strokes are linked to atrial fibrillation, and strokes secondary to atrial fibrillation are associated with a poor outcome compared with strokes without atrial fibrillation.<sup>3–5</sup> Furthermore, 30% of strokes are so-called cryptogenic, potentially caused by undetected atrial fibrillation.<sup>6,7</sup> As with stroke, the increasing prevalence of atrial fibrillation can be attributed to population ageing and accumulation of other risk factors.<sup>8–10</sup>

Anticoagulation treatment is highly effective in reducing the risk of stroke in patients diagnosed with atrial fibrillation.<sup>11</sup> A major challenge is that patients with atrial fibrillation are often asymptomatic and thus remain undiagnosed, and the proportion of asymptomatic cases increases with age.<sup>12</sup> In patients with cryptogenic stroke, approximately 30% will have atrial fibrillation detected if continuous heart rhythm monitoring is applied with an implantable loop recorder (ILR).<sup>7</sup> Studies of patients with cardiac implantable electronic devices have found that even short, subclinical atrial fibrillation episodes are associated with increased stroke risk.<sup>13</sup>

Published Online  
August 29, 2021  
[https://doi.org/10.1016/S0140-6736\(21\)01698-6](https://doi.org/10.1016/S0140-6736(21)01698-6)  
See Online/Comment  
[https://doi.org/10.1016/S0140-6736\(21\)01785-2](https://doi.org/10.1016/S0140-6736(21)01785-2)

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### Research in context

#### Evidence before this study

Stroke constitutes a growing health challenge worldwide. Atrial fibrillation is a well known risk factor for stroke, but the risk can be mitigated by anticoagulation treatment. The LOOP Study was initiated on the basis that individuals with atrial fibrillation are often asymptomatic and thus remain undiagnosed and untreated. Studies of patients with cardiac implantable electronic devices, such as pacemakers, reported a high prevalence of subclinical atrial fibrillation and evidence was growing that this type of atrial fibrillation was associated with increased stroke risk. In 2014, the Cryptogenic Stroke and Underlying Atrial Fibrillation study reported that 30% of patients with cryptogenic stroke had atrial fibrillation detected when continuous heart rhythm monitoring was applied. These findings sparked a growing interest in atrial fibrillation screening, while new technologies emerged to detect the arrhythmia. The effect on hard outcomes, such as incidence of stroke, remains to be determined.

#### Added value of this study

This study presents outcomes of long-term continuous screening for atrial fibrillation versus usual care in individuals with risk factors for stroke. We found that although atrial

fibrillation was detected and treated much more often, systematic, intensive screening did not have a significant effect on stroke risk, and there was no effect on mortality. However, the time-to-event curves for stroke overlapped during the first 2–3 years after which they appeared to diverge due to increasing event rates in the control group, and a sensitivity analysis suggested that screening might prevent strokes if done per protocol—ie, continuous implantable loop recorder monitoring for 3 years. The study also showed high rates of atrial fibrillation diagnosis without active screening, high acceptance of anticoagulation, and modest bleeding rates.

#### Implications of all the available evidence

In this randomised trial of individuals with stroke risk factors, continuous implantable loop recorder monitoring for atrial fibrillation, and subsequent anticoagulation if atrial fibrillation was detected, did not significantly reduce the risk of stroke or systemic arterial embolism. This result was seen despite a high proportion of atrial fibrillation detection and a high acceptance of anticoagulation therapy and might imply that not all atrial fibrillation is worth screening for, and not all screen-detected atrial fibrillation merits anticoagulation.

European and US guidelines recommend opportunistic screening for atrial fibrillation in people aged 65 years and older using pulse-palpation or standard electrocardiogram (ECG), whereas systematic or more intense screening is recommended in individuals at high risk of stroke.<sup>14–16</sup> These recommendations are based on studies showing that screening is feasible and will detect more cases of atrial fibrillation, whereas the effect on stroke prevention remains unknown.

Given the scarcity of evidence on health benefits of screening for atrial fibrillation, we aimed to investigate whether systematic, intensive atrial fibrillation screening and use of anticoagulants can prevent stroke in individuals at high risk.

## Methods

### Study design and participants

Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals (The LOOP Study) was an investigator-initiated, multicentre, unblinded, randomised controlled trial done at four centres (Rigshospitalet, Bispebjerg and Frederiksberg Hospital, Zealand University Hospital, and Odense University Hospital) covering three of Denmark's five regions. The trial design has been published previously.<sup>17</sup>

Eligible participants were aged 70–90 years and had at least one of four conditions: hypertension, diabetes, previous stroke, or heart failure; and did not have atrial fibrillation, a history of atrial fibrillation, a pacemaker,

anticoagulation medicine, or contraindication to anticoagulation. A complete list of the inclusion and exclusion criteria is provided in the appendix (p 6). A random sample of potentially eligible study participants from the general population was identified by administrative registries. They were sent an invitation letter to an initial screening visit at a study centre. At the screening visit, eligibility was confirmed, and a standard 12-lead ECG was taken to rule out prevalent atrial fibrillation.

The trial was designed and overseen by a steering committee (appendix p 4). The study protocol was approved by the regional scientific ethics committee for the Capital Region of Denmark and the Danish Data Protection Agency. The trial was done in accordance with the Declaration of Helsinki. All analyses were done by the academic coordinating centre for the trial. Oral and written informed consent was obtained from all eligible participants.

### Randomisation

Participants were randomly assigned in a 1:3 ratio to either the ILR group or the control group (usual care involved an annual interview with a study nurse and standard contact with the participant's general practitioner). Randomisation was done with the use of an online system in permuted blocks with block sizes of four or eight participants stratified according to centre. Study nurses randomly assigned participants after enrolment. The trial was not blinded.

See Online for appendix

## Procedures

Baseline assessments included detailed medical history, drug prescriptions, vital signs, and blood samples. Blood pressure and pulse rate were recorded after 5 min of supine rest, with a minimum three automated measurements using the mean of the last two.

Implantation of the ILR (Reveal LINQ, Insertable Cardiac Monitor, Medtronic, Minneapolis, MN, USA) was planned within 4 weeks from random assignment. All participants receiving ILR were followed up by continuous ECG monitoring via automated remote transmissions with physician review of all transmissions on a day-to-day basis (SZD). If atrial fibrillation lasting at least 6 min was detected, the participant was contacted and initiation of oral anticoagulation was recommended. Choice of anticoagulation type and further clinical tests or treatment was left to the treating physician and the patient. Remote monitoring continued until the end of service of the device, patient withdrawal, or death.

Study visits to collect outcomes were scheduled annually until the end of the trial. For the ILR group, in-person visits were planned until year 3, while subsequent follow-up took place by telephone contact and consult of medical records. For the control group, the visit at year 3 was in hospital, whereas other visits took place by telephone contact and consult of medical records.

On Dec 1, 2020, the steering committee decided to close the study, as the prespecified number of primary events had been reached. All participants still in follow-up underwent a final assessment within 2 months, and the last date of follow-up was used to determine censoring for the analysis.

## Outcomes

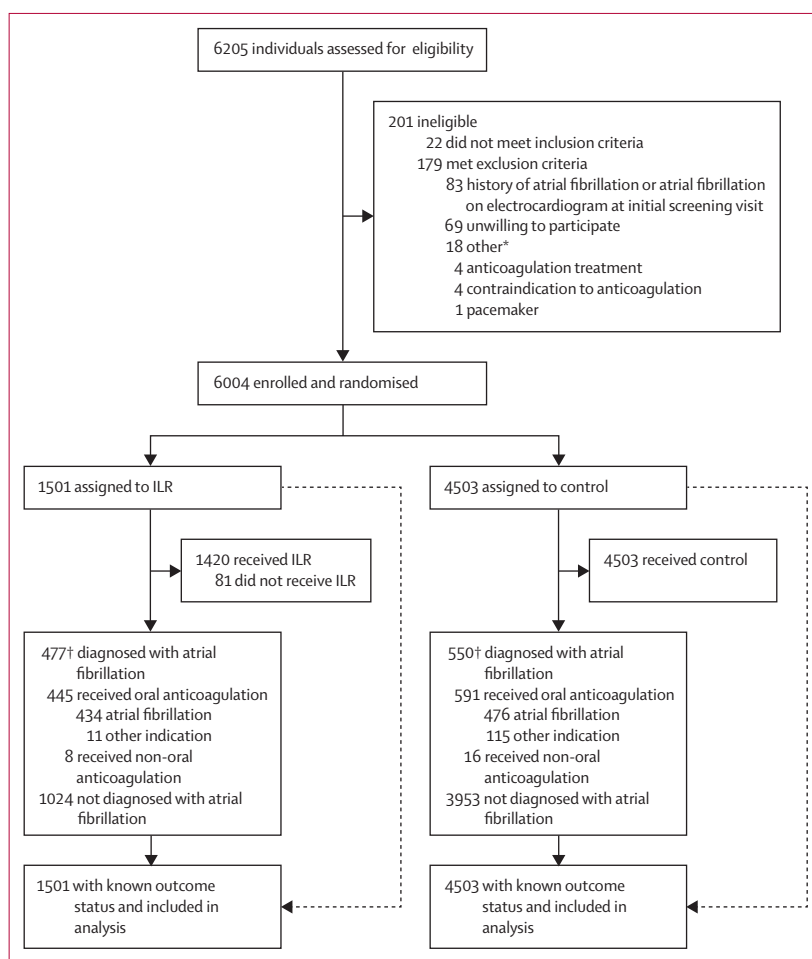
The primary outcome was the combined endpoint of stroke or systemic arterial embolism. Secondary outcomes were: (1) the combined endpoint of ischaemic stroke, transient ischaemic attack, or systemic arterial embolism; (2) the combined endpoint of stroke, systemic arterial embolism, or cardiovascular death; (3) cardiovascular death; and (4) all-cause death. Other outcomes included diagnosis of atrial fibrillation, initiation of anticoagulation, major bleeding as defined by the International Society on Thrombosis and Haemostasis, and haemorrhagic stroke. A clinical endpoint committee unaware of treatment assignments adjudicated all primary and secondary endpoints using prespecified criteria (appendix p 7). New-onset ILR-detected atrial fibrillation episodes lasting at least 6 min were independently adjudicated by at least two consultant cardiologists (JHS, SH, KJH, or AB). For the outcome of anticoagulation initiation, only treatments approved for atrial fibrillation thromboprophylaxis were considered.

## Statistical analysis

The trial was designed to have 80% power to detect a difference of 35% in the primary outcome between the

randomisation groups and was event-driven with a minimum requirement of 279 events. The sample size calculation assumed an annual event rate of 1.00 per 100 person-years in the control group and 0.65 per 100 person-years in the ILR group. The prespecified statistical analysis plan is provided in the appendix (pp 17–25).

Outcomes were analysed as time-to-first-event. Cumulative incidences were calculated, plotted, and compared using the Aalen-Johansen method accounting for competing risk of death for all outcomes but all-cause death, which was analysed according to the Kaplan-Meier method. Corresponding group-wise comparisons were made using cause-specific Cox proportional hazards. The proportional-hazards assumption was assessed with Schoenfeld residuals and any violations were reported. Post-hoc annual event rates and event rate ratios were derived from a Poisson distribution. Multivariable models were examined as a supplement; the first model included age, sex, and centre; the second model



**Figure 1: Trial profile**

ILR=implantable loop recorder. \*Other included malignancy and short life expectancy, among others. †Some participants were not diagnosed with atrial fibrillation but still received anticoagulation so the total number in this box might exceed total participants.

	ILR group (n=1501)	Control group (n=4503)
Sex		
Women	709 (47.2%)	2128 (47.3%)
Men	792 (52.8%)	2375 (52.7%)
Age, years	74.7 (4.1)	74.7 (4.1)
Study centre		
Rigshospitalet	517 (34.4%)	1555 (34.5%)
Bispebjerg and Frederiksberg Hospital	321 (21.4%)	951 (21.1%)
Zealand University Hospital	385 (25.6%)	1166 (25.9%)
Odense University Hospital	278 (18.5%)	831 (18.5%)
Alcohol consumption, units per week	5 (1-10)	5 (1-10)
Smoking status		
Never	597 (39.8%)	1782 (39.6%)
Current	135 (9.0%)	417 (9.3%)
Previous	769 (51.2%)	2302 (51.1%)
Smoking pack years	7 (0-28)	6 (0-28)
Comorbidities		
Hypertension	1378 (91.8)	4066 (90.3%)
Diabetes	422 (28.1)	1288 (28.6%)
Heart failure	67 (4.5%)	199 (4.4%)
Previous stroke	262 (17.5%)	794 (17.6%)
Previous transient ischaemic attack	155 (10.3%)	473 (10.5%)
Previous stroke, transient ischaemic attack, or systemic arterial embolism	370 (24.7%)	1139 (25.3%)
Chronic ischaemic heart disease*	177 (11.8%)	614 (13.6%)
Valvular heart disease	63 (4.2%)	181 (4.0%)
Peripheral artery disease	42 (2.8%)	119 (2.6%)
Chronic obstructive pulmonary disease	110 (7.3%)	330 (7.3%)
Previous thyrotoxicosis	47 (3.1%)	115 (2.6%)
Previous syncope	300 (20.0%)	924 (20.5%)

(Table 1 continues in next column)

	ILR group (n=1501)	Control group (n=4503)
(Continued from previous column)		
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	4 (3-4)	4 (3-4)
2	202 (13.5%)	602 (13.4%)
3	513 (34.2%)	1494 (33.2%)
4	419 (27.9%)	1312 (29.1%)
5	244 (16.3%)	687 (15.3%)
≥6	123 (8.2%)	408 (9.1%)
Medication		
β blockers	354 (23.6%)	1172 (26.0%)
Calcium channel blockers	562 (37.4%)	1684 (37.4%)
Renin-angiotensin inhibitors	991 (66.0%)	2999 (66.6%)
Statins	879 (58.6%)	2621 (58.2%)
Diuretics	495 (33.0%)	1511 (33.6%)
Platelet inhibitors	702 (46.8%)	2204 (48.9%)
Insulins	124 (8.3%)	354 (7.9%)
Other antidiabetic drugs	328 (21.9%)	959 (21.3%)
Systolic blood pressure, mm Hg	150.6 (19.2)	149.8 (19.5)
Diastolic blood pressure, mm Hg	84.7 (11.1)	83.9 (11.3)
Pulse rate, beats per min	71.6 (12.1)	71.3 (12.5)
Height, cm	170.6 (8.9)	170.5 (8.8)
Weight, kg	81.1 (16.1)	80.5 (15.5)
Body-mass index, kg/m <sup>2</sup>	27.8 (4.7)	27.6 (4.5)
Creatinine, μmol/L	84.8 (24.2)	85.8 (26.2)
Estimated glomerular filtration rate, mL/min	76 (19.2)	75.4 (19.4)
High-sensitivity C-reactive protein, mg/L	2 (1-4)	2 (1-4)

Values are presented as n (%), mean (SD), or median (IQR). Missing observations: alcohol consumption n=3; smoking status n=2; systolic blood pressure n=7; diastolic blood pressure n=7; height n=1; weight n=1; body-mass index n=1; pulse rate n=21; creatinine n=31; estimated glomerular filtration rate n=31; and high-sensitivity C-reactive protein n=37. ILR=implantable loop recorder. \*Previous acute myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention.

**Table 1: Baseline characteristics**

further included baseline variables with statistically significant differences between the two groups; the third model included all variables reported in the descriptive statistics.

A predefined sensitivity analysis of the primary outcome included only participants receiving the assigned intervention at randomisation (ILR or control). A second predefined sensitivity analysis further censored participants at premature discontinuation (before 3 years) of ILR monitoring without outcome, atrial fibrillation, or death, with a grace period of 3 months of additional follow-up. Subgroup interaction analyses of the primary outcome were done according to a prespecified set of baseline variables. A two-sided p value of 0.05 or less was considered statistically significant. R, version 4.0.5 was used for the analyses. There was no data monitoring committee. This study is registered with ClinicalTrials.gov, NCT02036450.

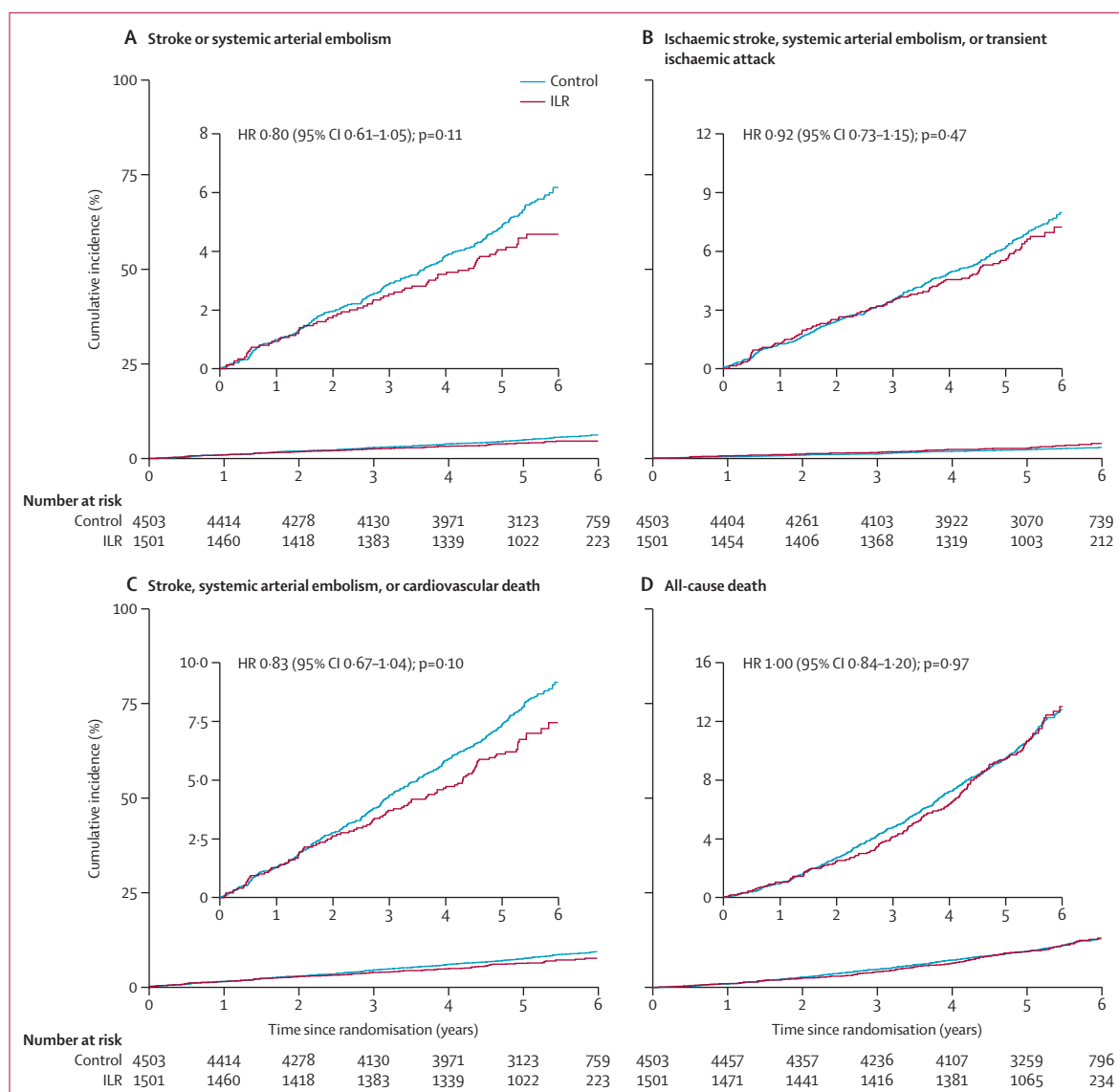
### Role of the funding source

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

### Results

From Jan 31, 2014, to May 17, 2016, 6205 individuals were screened for inclusion and, of these, 6004 were included and randomly assigned. The most frequent reason for exclusion was history of atrial fibrillation or atrial fibrillation on the initial screening ECG (figure 1). 6004 participants were randomly assigned into the trial; 1501 (25.0%) were assigned to the ILR group, and 4503 (75.0%) to control (table 1). The mean age of the participants was 74.7 years (SD 4.1), and 2837 (47.3%) were women.

1420 (94.6%) participants in the ILR group received ILR, and the median time from randomisation to



**Figure 2: Time-to-event curves for primary and secondary outcomes**

Panel A shows the primary outcome, while B, C, and D show secondary outcomes. ILR=implantable loop recorder. HR=hazard ratio.

implantation was 24 days (IQR 27–35). The median duration of monitoring was 39.3 months (IQR 36.8–41.5). Premature discontinuation of ILR monitoring (ie, before 3 years without outcome, atrial fibrillation, or death, with a grace period of 3 months of additional follow-up) occurred in 166 (11.7%) individuals. No participant in the control group received ILR during the trial.

Follow-up data for all outcomes were available up until Jan 28, 2021, and no participants were lost to follow-up. The median follow-up period was 64.5 months (IQR 59.3–69.8). Atrial fibrillation was diagnosed in 477 (31.8%) of 1501 participants in the ILR group versus 550 (12.2%) of 4503 in the control group (hazard ratio [HR] 3.17 [95% CI 2.81–3.59];  $p < 0.0001$ ). In the ILR group, 426 (89.3%) of 477 participants with atrial

fibrillation were diagnosed within 3 years from randomisation, and the corresponding number for the control group was 271 (49.3%) of 550.

Oral anticoagulation was initiated in 445 (29.7%) participants in the ILR group versus 591 (13.1%) in the control group (HR 2.72 [95% CI 2.41–3.08];  $p < 0.0001$ ). In the ILR group, 375 (78.6%) participants with atrial fibrillation initiated oral anticoagulation within the first month after diagnosis, 407 (85.3%) within the first 3 months, and 434 (91.0%) at any time. In the control group, 393 (71.5%) of the participants with atrial fibrillation initiated oral anticoagulation within the first month after diagnosis, 415 (75.5%) within the first 3 months, and 476 (86.5%) at any time. Time-to-event curves and annual event rate ratios for atrial fibrillation



detection and oral anticoagulation initiation are provided in the appendix (pp 30–33).

42 (4·6%) of 910 participants who had atrial fibrillation and initiated oral anticoagulation discontinued the treatment, 25 (5·8%) of 434 in the ILR group and 17 (3·6%) of 476 in the control group, and the median time from initiation to discontinuation of anticoagulation was 16·8 months (IQR 2·73–31·5); 16·4 (2·5–31·5) for the 25 individuals in the ILR group, and 17·1 (4·8–30·5) for the 17 individuals in the control group.

The primary outcome of stroke or systemic arterial embolism occurred in 318 participants (269 ischaemic stroke, 40 haemorrhagic stroke, six stroke of unspecified type, and three systemic arterial embolism): 67 (4·5%) in the ILR group (0·88 events per 100 person-years [95% CI 0·68–1·12]) versus 251 (5·6%) in the control group (1·09 events per 100 person-years [95% CI 0·96–1·24]). No significant difference between the groups was seen (HR 0·80 [95% CI 0·61–1·05];  $p=0\cdot11$ ; figure 2, table 2). The supplementary multivariable models yielded similar results. Annual event rate ratios of the primary outcome are provided in the appendix (p 34). 17 participants in the ILR group had a stroke or systemic embolism after debut of atrial fibrillation. 15 (88·2%) of these 17 had initiated oral anticoagulation, most had only short-lasting episodes, and the time from atrial fibrillation debut to stroke ranged from zero to 42 months (appendix p 29).

Cardiovascular death occurred in 43 (2·9%) participants in the ILR group versus 157 (3·5%) in the control group (HR 0·83 [95% CI 0·59–1·16];  $p=0\cdot27$ ), and death from any cause occurred in 168 (11·2%) participants in the ILR group versus 507 (11·3%) in the control group (HR 1·00 [0·84–1·19];  $p=1\cdot00$ ; table 2).

Annual event rate ratios of all-cause death are provided in the appendix (p 35).

The first sensitivity analysis of the primary outcome, including only participants who received the assigned intervention at random assignment (ILR or control), identified 316 instances of the primary outcome with an HR of 0·81 (95% CI 0·62–1·07;  $p=0\cdot14$ ). The second sensitivity analysis, further censoring participants at premature discontinuation of ILR monitoring without outcome, atrial fibrillation, or death, identified 307 instances of the primary outcome with an HR of 0·70 (0·52–0·94;  $p=0\cdot016$ ). Time-to-event curves for the sensitivity analyses are provided in the appendix (p 36).

The subgroup analyses of the primary outcome are shown in figure 3. There were no significant treatment-by-subgroup interactions across the prespecified baseline variables apart from systolic blood pressure ( $p=0\cdot0073$  for the interaction term). In the subgroup of participants with systolic blood pressure in the highest tertile ( $\geq 157$  mm Hg), the primary outcome rate was significantly lower in the ILR group than the control group (HR 0·51 [95% CI 0·31–0·83];  $p=0\cdot0066$ ; appendix p 37). In the subgroup of participants with systolic blood pressure in the middle tertile (141–156 mm Hg) and the lowest tertile ( $<141$  mm Hg), the primary outcome rate was not significantly different between the ILR group and the control group (HR 1·06 [95% CI 0·68–1·67;  $p=0\cdot80$  for 141–156 mm Hg and HR 0·99 [0·62–1·57];  $p=0\cdot95$  for  $<141$  mm Hg).

Among the 1420 participants who received an ILR, nine (0·6%) participants had complications leading to device explantation, and time from implantation to explantation was a median of 40 days (IQR 22–51). Eight of these

	Number of events		Cumulative incidence rate at 6 years (95% CI)		Events per 100 person-years (95% CI)		Hazard ratio (95% CI)	p value
	ILR group (n=1501)	Control group (n=4503)	ILR group	Control group	ILR group	Control group		
Stroke or systemic arterial embolism	67 (4·5%)	251 (5·6%)	4·61 (3·50–5·73)	6·22 (5·41–7·03)	0·88 (0·68–1·12)	1·09 (0·96–1·24)	0·80 (0·61–1·05)	0·11
Ischaemic stroke, systemic arterial embolism, or transient ischaemic attack	96 (6·4%)	316 (7·0%)	7·20 (5·71–8·70)	7·94 (7·03–8·86)	1·27 (1·03–1·55)	1·39 (1·24–1·55)	0·92 (0·73–1·15)	0·47
Stroke, systemic arterial embolism, or cardiovascular death	104 (6·9%)	376 (8·3%)	7·44 (5·95–8·93)	9·16 (8·20–10·12)	1·36 (1·11–1·65)	1·64 (1·48–1·81)	0·83 (0·67–1·04)	0·10
Cardiovascular death	43 (2·9%)	157 (3·5%)	3·23 (2·16–4·30)	3·77 (3·14–4·40)	0·55 (0·40–0·74)	0·67 (0·57–0·78)	0·83 (0·59–1·16)	0·27
All-cause death	168 (11·2%)	507 (11·3%)	13·02 (10·96–15·08)	12·80 (11·65–13·96)	2·16 (1·84–2·51)	2·16 (1·97–2·35)	1·00 (0·84–1·19)	1·00
Major bleeding	65 (4·3%)	156 (3·5%)	4·88 (3·67–6·10)	3·69 (3·10–4·29)	0·85 (0·66–1·08)	0·67 (0·57–0·79)	1·26 (0·95–1·69)	0·11
Haemorrhagic stroke	11 (0·8%)	34 (0·8%)	0·80 (0·32–1·29)	0·81 (0·53–1·10)	0·14 (0·07–0·25)	0·14 (0·10–0·20)	0·97 (0·49–1·92)	0·94
Traumatic intracranial haemorrhage	10 (0·9%)	36 (0·8%)	0·81 (0·29–1·33)	0·90 (0·59–1·21)	0·13 (0·06–0·24)	0·15 (0·11–0·21)	0·84 (0·41–1·68)	0·61
Atrial fibrillation	477 (31·8%)	550 (12·2%)	32·24 (29·84–34·65)	13·62 (12·47–14·78)	8·04 (7·34–8·80)	2·48 (2·27–2·69)	3·17 (2·81–3·59)	$<0\cdot0001$
Oral anticoagulation	445 (29·7%)	591 (13·1%)	30·25 (27·82–32·67)	14·58 (13·37–15·79)	7·39 (6·72–8·11)	2·68 (2·46–2·90)	2·72 (2·41–3·08)	$<0\cdot0001$

Data are n (%) or as specified. ILR=implantable loop recorder.

**Table 2: Outcomes and adverse events**

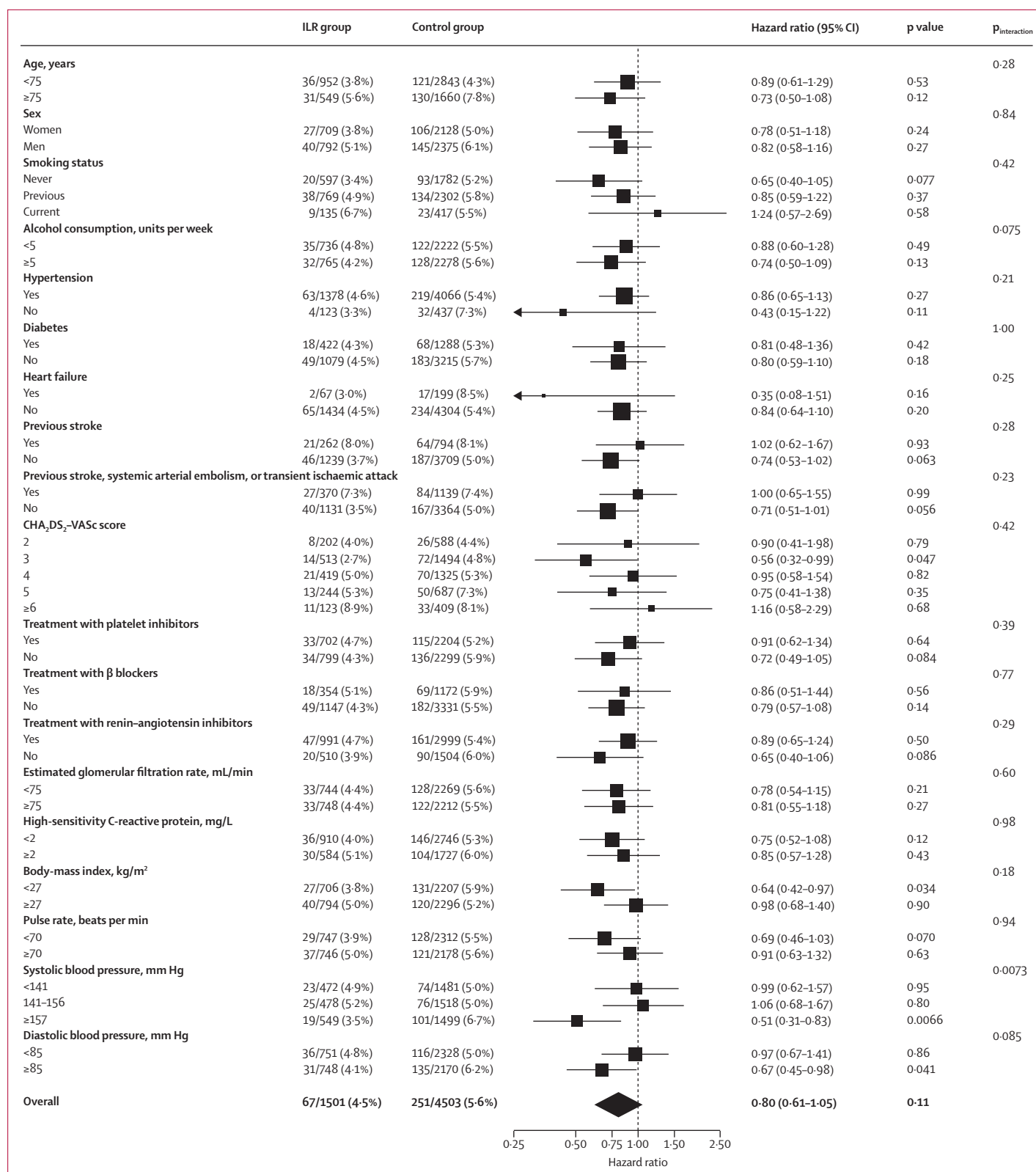


Figure 3: Frequency of the primary outcome grouped by randomisation arm and hazard ratios in prespecified subgroups  
ILR=implantable loop recorder.

participants underwent a new implantation to resume remote monitoring.

Major bleeding occurred in 65 (4.3%) participants in the ILR group versus 156 (3.5%) in the control group (HR 1.26 [95% CI 0.95–1.69];  $p=0.11$ ), and haemorrhagic stroke occurred in 11 participants (0.8%) in the ILR group versus 34 (0.8%) in the control group (HR 0.97 [95% CI 0.49–1.92];  $p=0.94$ ; table 2).

## Discussion

In this randomised trial of individuals with stroke risk factors, continuous ILR monitoring for atrial fibrillation, and subsequent anticoagulation if atrial fibrillation was detected, did not significantly reduce the risk of stroke or systemic arterial embolism. This result was despite a high proportion of diagnosed atrial fibrillation and a high acceptance of anticoagulation therapy and adherence to the treatment. The rates of bleeding were modest despite the low threshold for anticoagulation. There was no effect on cardiovascular or all-cause death.

To exert a health benefit, a screening strategy must first detect the disease, then decrease the disease-associated risk through downstream interventions. To date, no randomised trials have reported on the health benefits of atrial fibrillation screening. At the European Heart Rhythm Association congress in April, 2021, the STROKESTOP trial was presented by Svennberg and colleagues. STROKESTOP used a different screening method, but the authors reported a reduction in the composite outcome of ischaemic stroke, systemic embolism, all-cause death, haemorrhagic stroke, or hospital admission for bleeding with an HR of 0.96 (95% CI 0.92–1.00).<sup>18</sup>

Several randomised studies with atrial fibrillation detection and initiation of anticoagulation as the outcomes of interest have been published.<sup>19–21</sup> The REHEARSE-AF study randomly assigned 1001 participants to be monitored two times per week by AliveCor Kardia monitor or standard care and found four-times more atrial fibrillation in the active arm.<sup>21</sup> The mSToPS study investigated more than 2500 participants who received up to 4 weeks monitoring using a patch system and were randomly assigned to be screened immediately or with a 4-month delay, both compared with matched controls, finding that screening identified more atrial fibrillation and this diagnosis was delayed if screening was delayed.<sup>19</sup> In the SCREEN-AF study, 856 study participants were randomly assigned to 2 weeks of continuous monitoring using a patch system or standard care. The results showed that 11-times more atrial fibrillation was detected by screening than standard care.<sup>20</sup>

Despite the limited evidence with regards to hard outcomes, screening for atrial fibrillation is increasingly applied and is receiving widespread enthusiasm.<sup>22</sup> Numerous studies have shown feasibility of a growing panel of tools, such as smart watches and other so-called wearables, and some of these technologies are even

entering the consumer market.<sup>23</sup> On the one hand, the findings of the current trial indicate that systematic, intensive screening might not decrease stroke rates, even in individuals at high risk, and not all screen-detected atrial fibrillation should merit anticoagulation. On the other hand, the time-to-event curves for stroke overlapped during the first 2–3 years after which they appeared to diverge due to increasing event rates in the control group (figure 2A, appendix p 34). Furthermore, our sensitivity analysis suggested that ILR screening might prevent strokes if done per protocol—ie, continuous screening for 3 years (appendix p 36).

In general, the findings were consistent across subgroups. We did, however, observe an interaction with systolic blood pressure. Although the inclusion criteria mandated that the few participants without a diagnosis of hypertension (9.3%) had to have at least one other stroke risk factor, the interaction suggests that patients with dysregulated hypertension could benefit from this type of screening and concomitant anticoagulation (appendix p 37). Our finding of an effect from screening in those with very high blood pressure is in line with previous studies showing that hypertension, and especially high systolic blood pressure, is a predominant risk factor for atrial fibrillation and stroke alike.<sup>24–26</sup> However, it should be stressed that these findings should only be considered as hypothesis generating.

We aimed to detect a considerable reduction in stroke risk and anticipated a 35% decrease in the primary outcome, which was based on the assumption that 30% of participants would have unknown atrial fibrillation,<sup>13</sup> and the rate of stroke in these untreated individuals would be two per 100 person-years.<sup>27</sup> These assumptions did not account for a possibly lower stroke risk associated with short or intermittent atrial fibrillation detected by ILR compared with clinically diagnosed atrial fibrillation. Although we diagnosed atrial fibrillation in more than 30% of participants in the ILR group and 91% of these initiated oral anticoagulation, the overall risk reduction was only 20% and non-significant. Accordingly, the stroke risk associated with atrial fibrillation detected by continuous monitoring might be lower than that of atrial fibrillation diagnosed by usual care, thus decreasing the effect of such screening and making the current study underpowered. Although a meta-analysis has established short, subclinical atrial fibrillation episodes as a strong marker of stroke risk,<sup>28</sup> a post-hoc analysis of ASSERT indicated that the risk was upheld by patients with longer atrial fibrillation episodes.<sup>29</sup> This finding was supported by a registry study merging clinical databases and device databases of patients with an atrial lead showing that the stroke risk increased significantly when the atrial fibrillation episodes were long-lasting (>23.5 h).<sup>30</sup> Therefore, it is possible that the cutoff of only 6 min might have resulted in participants receiving anticoagulation who were not at risk of atrial fibrillation-related stroke. Among 17 patients in the ILR group who



had a stroke after detection of atrial fibrillation, we found no clear temporal relationship between atrial fibrillation and stroke (appendix p 29), which was in accordance with previous findings.<sup>31</sup> Also, it could be discussed whether a much larger trial powered to detect a risk reduction of 20% (cumulative incidence 4.6 vs 6.2 at 6 years) would be warranted. If we anticipate that the absolute risk reduction of 1.61% (ie 6.22% minus 4.61%; table 2) is the correct estimate, the number needed to screen to avoid one primary outcome after 6 years would be 100 divided by 1.61 (ie, 62 people). Given the even smaller signal for cardiovascular mortality and no signal for total mortality in our trial, one could argue that other events than atrial fibrillation and stroke could be more important in this older population.

Another finding that might have decreased the effect of screening was the high proportion of participants in the control group diagnosed with atrial fibrillation (12.2%; incidence rate 2.5 per 100 person-years) compared with what we anticipated (3.0%). In the control group of the CRYSTAL-AF trial, atrial fibrillation was only detected in about 3% of participants at 3 years,<sup>7</sup> while the population-based Rotterdam study reported incidence rates of only 0.95–1.77 per 100 person-years in participants aged 70–80 years.<sup>8</sup> The high rate of atrial fibrillation detection by usual care could be due to participation in the trial inspiring participants in the control group to consult their physician. Also, atrial fibrillation episodes detected in the control group are likely to have lasted longer than atrial fibrillation detected by ILRs.

Our study has several limitations. First, potential participants were identified from registries and recruited by letter invitation to their homes, which might introduce a healthy user bias. Second, participants in both groups could change their behaviour in relation to detection of atrial fibrillation or management of stroke risk factors as a consequence of participating in the trial. Third, the probability of detecting asymptomatic atrial fibrillation is likely to be higher if the episode is long lasting and the protective effect of anticoagulation on stroke risk might not be similar in short-lasting versus long-lasting atrial fibrillation episodes. Fourth, even though the curves seemed to diverge after 2–3 years, only 982 (16.4%) of the initial 6004 participants were still followed up for the primary outcome at the sixth year follow-up, and the signal at this specific time should be interpreted with a very high degree of caution.

In conclusion, in this trial of individuals at high risk of stroke, screening for atrial fibrillation using long-term continuous monitoring by ILR resulted in a three-times increase in detection of atrial fibrillation and concomitant anticoagulation, but no significant decrease in the risk of stroke or systemic arterial embolism.

#### Contributors

All authors were responsible for conceptualisation of the study. JHS, SZD, SH, DWK, CG, CK, AB, KJH, and LK were part of the steering committee for the study. JHS, SZD, and LK verified the data.

JHS, SZD, and LK did the formal data analysis. JHS acquired funding. All authors were responsible for investigations and methodology. SZD, AGH, and JBN were responsible for the database and software. SZD, JHS, SH, AB, and KJH were responsible for validation of the atrial fibrillation outcome. LK and DWK were responsible for validation of the primary outcome. JHS, SZD, and LK were responsible for writing the first version of the manuscript. All authors vouch for the accuracy and completeness of the data, and adherence to the trial protocol and statistical analysis plan. All authors reviewed the final draft and agree with its content and conclusions. 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

JHS is a member of Medtronic advisory boards and has received speaker honoraria and research grants from Medtronic in relation to this work and outside the submitted work. SZD is a part-time employee of Vital Beats outside the submitted work. DWK is a member of a Medtronic advisory board on stroke and has received speaker honoraria and travel grants from Medtronic, St Jude Medical, and Boehringer Ingelheim, outside the submitted work. AB reports research grants from The Region of Southern Denmark and The Region of Zealand, and Theravance; speaker honoraria from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb; and a travel grant from Biotronik, outside the submitted work. JBN is an employee of Regeneron Pharmaceuticals, outside the submitted work. AGH is an employee of Acesion Pharma, outside the submitted work. KJH reports travel and educational grants from Medtronic, Abbott, and BIOTRONIK; and speaker honoraria from Boehringer Ingelheim, outside the submitted work. LK reports speaker honoraria from Novo, AstraZeneca, Novartis, and Boehringer Ingelheim, outside the submitted work. All other authors declare no competing interests.

#### Data sharing

The LOOP Study data will be part of the AFFECT-EU consortium (supported from EU-Horizon 2020 programme) in which studies on screening for atrial fibrillation will be included in a future meta-analysis. Applications for other collaborations can be submitted to the consortium via JHS.

#### Acknowledgments

The LOOP Study is supported by Innovation Fund Denmark (12-135225), The Research Foundation for the Capital Region of Denmark, The Danish Heart Foundation (11-04-R83-A3363-22625), Aalborg University Talent Management Program, Arvid Nilssons Fond, Skibsreder Per Henriksen, R og Hustrus Fond, The AFFECT-EU Consortium (Horizon 2020, grant number 847770-AFFECT-EU), Læge Sophus Carl Emil Friis og hustru Olga Doris Friis' Legat, and an unrestricted grant from Medtronic. We thank Dan Atar (University of Oslo and Department of Cardiology B, Oslo University Hospital Ullevål, Oslo, Norway), Gregory Y H Lip (The University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK), and Mårten Rosenqvist (Karolinska Institutet and Danderyd Hospital, Stockholm, Sweden), for assisting the study with their expertise in the study's international advisory committee. We thank the research nurses and other colleagues in the Departments of Cardiology at Rigshospitalet, Bispebjerg and Frederiksberg Hospital, Zealand University Hospital, and Odense University Hospital who assisted with study procedures.

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## High-intensity atrial fibrillation screening to prevent stroke



Opportunistic single-timepoint screening for atrial fibrillation is guideline-recommended in people aged 65 years and older to prevent cardioembolic stroke.<sup>1</sup> Such screening is easily done by taking the pulse or by handheld electrocardiogram (ECG) in primary care as part of routine practice,<sup>2</sup> although it is infrequently performed.<sup>3</sup> The stroke risk of atrial fibrillation detected on single-timepoint screening, and the reduction of this risk by oral anticoagulant thromboprophylaxis, is approximated by incidentally detected asymptomatic atrial fibrillation. This incidentally detected atrial fibrillation has the same level of risk as symptomatic atrial fibrillation presentations.<sup>4,5</sup> Although single-timepoint screening detects (largely persistent) atrial fibrillation in 1.4% of individuals aged 65 years and older,<sup>6</sup> paroxysmal atrial fibrillation is often unrecognised and requires more intensive surveillance for detection.<sup>3</sup> Intermittent handheld ECG self-screening as in STROKESTOP<sup>3,7</sup> or 2–4 weeks of continuous patch recording<sup>3,8</sup> identifies an additional 2.5–4.0% of paroxysmal atrial fibrillation. By contrast, many more cases of atrial fibrillation are found by implanted cardiac monitors, sometimes referred to as implantable loop recorders (ILRs).<sup>9</sup>

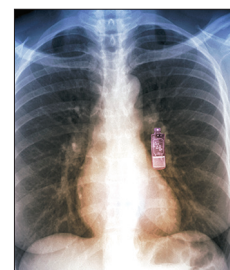
In The LOOP Study,<sup>10</sup> reported by Jesper Hastrup Svendsen and colleagues in *The Lancet*, 6004 volunteers aged 70–90 years (mean 74.7 [SD 4.1]; 2837 [47.3%] women) without atrial fibrillation and with one or more stroke risk factors were randomly assigned 1:3 to intensive monitoring by ILR (n=1501) or usual care (n=4503). In this randomised controlled trial in four centres in Denmark, the primary outcome was time to first stroke or systemic arterial embolism. During a median follow-up of 64.5 months, atrial fibrillation lasting 6 min or more was diagnosed in 477 (31.8%) participants in the ILR group versus 550 (12.2%) in the control group (hazard ratio [HR] 3.17 [95% CI 2.81–3.59]; p<0.0001). Oral anticoagulation was initiated in 445 (29.7%) participants in the ILR group versus 591 (13.1%) in the control group. The primary outcome occurred in 67 (4.5%) participants in the ILR group versus 251 (5.6%) in the control group (HR 0.80 [95% CI 0.61–1.05]; p=0.11). The most frequent adverse event was major bleeding, which occurred in 65 (4.3%) participants in the ILR group and 156 (3.5%) in the control group (HR 1.26 [95% CI 0.95–1.69]; p=0.11). Haemorrhagic stroke occurred in 11 participants (0.8%)

in the ILR group versus 34 (0.8%) in the control group. Complications leading to device explantation occurred in nine (0.6%) participants in the ILR group.

Almost a third of those in the ILR group had atrial fibrillation detected. This proportion is much greater than that seen with less intensive screening, but is not surprising given the large differences in total ECG sampling duration between screening techniques: 30 s for single-timepoint screening, 840 s for intermittent handheld ECGs two times per day for 2 weeks (STROKESTOP),<sup>7</sup> and more than 103 000 000 s for ILR in The LOOP Study.<sup>10</sup>

The LOOP Study<sup>10</sup> was a large, well executed, randomised study, important for the field, with high protocol fidelity, high atrial fibrillation detection, high oral anticoagulant initiation for atrial fibrillation, and long-term oral anticoagulant therapy adherence, with no participants lost to follow-up. It examined whether an ILR strategy would reduce stroke or systemic arterial embolism, and showed a non-significant 20% relative risk reduction in this primary endpoint over 5 years of follow-up compared with controls. Although the results would conventionally be considered as negative, we can learn a lot from this large trial by examining why it did not succeed. The authors posited several potential reasons, including a higher than expected atrial fibrillation incidence in the control group during follow-up (12.2% vs 3.0%), possibly related to a Hawthorne effect, with an increase in health-seeking behaviour of study volunteers randomly assigned to the control group, a potential study limitation. The most important explanation is that shorter atrial fibrillation episodes found by long-term ILRs might not have the same stroke risk as atrial fibrillation detected through single-timepoint or less intense monitoring. In studies of atrial fibrillation detected incidentally by implanted cardiac devices, stroke risk was increased in patients with atrial fibrillation episodes of longer than 5–6 min, but most of the prognostic information was carried by episodes lasting 24 h or longer.<sup>1,9,10</sup> In a subset of participants from The LOOP Study with atrial fibrillation detected on the ILR, the maximum episode duration was between 6 min and 5.5 h in 42% of patients, while only 16% had episodes lasting 24 h or longer.<sup>11</sup>

The cutoff point for atrial fibrillation duration or burden, below which there is no increased stroke risk, is fiercely debated.<sup>1,9</sup> Modelling suggests that less intense



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Published Online  
August 29, 2021  
[https://doi.org/10.1016/S0140-6736\(21\)01785-2](https://doi.org/10.1016/S0140-6736(21)01785-2)  
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intermittent self-screening as seen in STROKESTOP is likely to detect atrial fibrillation with relatively high burden, and miss atrial fibrillation in patients with low burden.<sup>8</sup> This factor might explain why the per-protocol results of STROKESTOP looked impressive.<sup>7</sup> However, in continuous recordings it is difficult to define a safe amount of paroxysmal atrial fibrillation. Regardless of the putative burden cutoff, it would interact with the calculated stroke risk score in each patient, leading to a treatment algorithm that takes both into account.<sup>1,9,10</sup> Further information on the burden cutoff point might come from ongoing randomised trials of oral anticoagulants in implanted device-detected atrial fibrillation.<sup>9</sup>

Technological advances in smartwatches that combine on-demand or prompted ECG recordings with semi-continuous photo-plethysmography to detect pulse irregularity likely to be atrial fibrillation can approximate the high intensity atrial fibrillation screening of ILRs.<sup>2</sup> However, the same caveats of lower stroke risk from short atrial fibrillation episodes are of great relevance to the predominantly brief, low-burden atrial fibrillation found by these devices. Such episodes could underlie the negative results in The LOOP Study. Smartwatch ECGs are now readily available to consumers, although the ECG quality is not as high as that of ILRs. The younger demographic of smartwatch owners are more likely to have false-positive atrial fibrillation alarms and recordings due to lower atrial fibrillation prevalence. For atrial fibrillation diagnoses in this demographic, the low calculated risk of stroke would be associated with a low indication for oral anticoagulants. More evidence of effectiveness of these devices in an appropriate age group is needed. The ongoing HEARTLINE study in people aged 65 years and older (NCT04276441) might provide some answers on atrial fibrillation diagnosis and oral anticoagulant treatment, but stroke and mortality are secondary endpoints in this study.

The absence of a temporal relationship between ILR-detected atrial fibrillation and stroke seen in The LOOP Study<sup>10</sup> and some previous studies,<sup>9,12</sup> together with many observations consistent with atrial fibrillation being more a risk marker for a thrombotic atrial cardiomyopathy than a risk factor for stroke,<sup>12</sup> might explain the difficulty in defining a safe level of paroxysmal atrial fibrillation in prolonged continuous recordings that does not lead to cardioembolic stroke,

and does not require an oral anticoagulant. However, if much of the paroxysmal atrial fibrillation found in The LOOP Study and other device studies is not the actual cause of stroke and is instead predominantly a risk marker,<sup>12</sup> further research is warranted to establish whether a different screening focus and treatment paradigm are required to prevent stroke and other vascular brain injury related to atrial fibrillation.

BF reports grants to the Heart Research Institute, speaker's fees and non-financial support from the Bristol-Myers Squibb-Pfizer Alliance, speaker's fees and non-financial support from Daiichi Sankyo, non-financial support from AliveCor, and speaker's fees and non-financial support from Omron unrelated to the topic of this Comment but related to atrial fibrillation and screening for atrial fibrillation. NL reports grants to the Heart Research Institute from the Bristol-Myers Squibb-Pfizer Alliance unrelated to the topic of this Comment but related to atrial fibrillation and screening for atrial fibrillation.

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