Screening for atrial fibrillation to prevent stroke in elderly individuals with or without preexisting cardiovascular disease

A post hoc analysis of the randomized LOOP Study

Xing, Lucas Yixi; Diederichsen, Søren Zöga; Højberg, Søren; Krieger, Derk W.; Graff, Claus; Olesen, Morten S.; Brandes, Axel; Køber, Lars; Haugan, Ketil Jørgen; Svendsen, Jesper Hastrup

Published in:
International Journal of Cardiology

DOI (link to publication from Publisher):
10.1016/j.ijcard.2022.10.167

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

International Journal of Cardiology 370 (2023) 197–203

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Screening for atrial fibrillation to prevent stroke in elderly individuals with or without preexisting cardiovascular disease: A post hoc analysis of the randomized LOOP Study☆

Lucas Yixi Xing [a,b], Søren Zöga Diederichsen [a,c], Søren Højberg [c], Derk W. Krieger [d,e], Claus Graff [f], Morten S. Olesen [a,g], Axel Brandes [h,i], Lars Køber [a,j], Ketil Jørgen Haugan [b], Jesper Hastrup Svendsen [a,j,*]

[a] Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Inge Lehmanns Vej 7, 2100 Copenhagen, Denmark
[b] Department of Cardiology, Zealand University Hospital Roskilde, Sygehusvej 10, 4000 Roskilde, Denmark
[c] Department of Cardiology, Bispebjerg Hospital, Copenhagen University Hospital, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark
[d] Department of Neurology, Mediclinic City Hospital, Building 37 - 26th St, Dubai, United Arab Emirates
[e] Department of Neuroscience, Mohammed Bin Rashid University of Medicine and Health Science, Al Razi St, Dubai, United Arab Emirates
[f] Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7 D2, 9220 Aalborg, Denmark
[g] Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, DENMARK
[h] Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Winsløwparken 19, 5000 Odense C, Denmark
[i] Department of Cardiology, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense, Denmark
[j] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark

ARTICLE INFO

Keywords:
Atrial fibrillation
Stroke prevention
Cardiovascular disease
Continuous rhythm monitoring

ABSTRACT

Background: An evidence-based approach for risk stratification of subclinical atrial fibrillation (AF) and hereby AF screening is lacking. This study aimed to investigate whether established cardiovascular diseases (CVD) could help to identify the population more likely to benefit from AF screening.

Methods: The LOOP Study randomized AF-naïve individuals aged ≥70 years and with additional stroke risk factors to either screening with implantable loop recorder (ILR) and subsequent anticoagulation upon detection of new-onset AF episodes ≥6 min, or usual care. In this sub-study, all participants were divided into two risk groups according to the presence/absence of CVD (defined as ischemic heart disease, heart failure, previous stroke, valvular heart disease, or peripheral artery disease).

Results: A total of 1997 (33.3%) had CVD at baseline and experienced higher incidences of stroke or systemic arterial embolism (SAE), ischemic stroke, stroke/SAE/cardiovascular death, and all-cause death (adjusted HR 1.34 [1.06–1.69], 1.31 [1.02–1.69], 1.49 [1.23–1.79], and 1.59 [1.36–1.85], respectively) than those without. For ILR screening versus usual care, there was no decrease in stroke/SAE, ischemic stroke, or stroke/SAE/cardiovascular death among participants with CVD (adjusted *p*-values >0.05), whereas significant reductions in these outcomes were obtained by screening among those without CVD (adjusted HR 0.64 [0.44–0.93], 0.54 [0.35–0.82], 0.64 [0.46–0.87], respectively); adjusted p-values for interaction ≤0.05.

Conclusions: In an elderly, at-risk population, ILR screening did not prevent stroke significantly in individuals with CVD, whereas screening was associated with approximately 40% stroke risk reduction among those without CVD. However, these findings should be considered as hypothesis-generating and warrant further study.

Abbreviations: AF, Atrial fibrillation; CI, Confidence interval; CVD, Cardiovascular disease; HR, Hazard ratio; IHD, Ischemic heart disease; ILR, Implantable loop recorder; OAC, Oral anticoagulation; PAD, Peripheral artery disease; SAE, Systemic arterial embolism; SBP, Systolic blood pressure; SD, Standard deviation.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Inge Lehmanns Vej 7, 2100 Copenhagen, Denmark.
E-mail address: Jesper.Hastrup.Svendsen@regionh.dk (J.H. Svendsen).

https://doi.org/10.1016/j.ijcard.2022.10.167
Received 8 September 2022; Received in revised form 13 October 2022; Accepted 27 October 2022
Available online 31 October 2022

1. Introduction

Globally, stroke is the second leading cause of death and has a 70% increase in incidence over the last two decades [1]. As a potential cause of cardioembolism [2], atrial fibrillation (AF) increases the stroke risk by five-fold [3]. In patients with clinically diagnosed AF, CHA_2DS_2-VASc score constitutes a well-established scheme to guide stroke prevention with oral anticoagulation (OAC) [4–6]. However, as the rapid technological progress enables more feasible screening for previously unknown AF, an evidence-based risk assessment approach with respect to management of subclinical AF is urgently needed [6].

The LOOP Study (*Atrial Fibrillation detected by Continuous ECG Monitoring using Implantable Loop Recorder to prevent Stroke in High-risk Individuals*) was a randomized controlled trial to assess systematic AF screening with implantable loop recorder (ILR) in elderly individuals [7]. Nevertheless, it reported only a 20% non-significant stroke risk reduction by screening, without any remarkable interaction with CHA_2DS_2-VASc score [8]. Indeed, better risk stratification of subclinical AF is demanded. It is well known that various cardiovascular diseases (CVD) predispose AF patients to additional stroke risk [3–6,9–13]. The key question to address would be whether these conditions could contribute to identify the appropriate population to warrant screening for subclinical AF and subsequent OAC initiation upon AF detection.

With this post hoc analysis of the LOOP Study, we aimed to investigate the influence of preexisting CVD on effects of long-term continuous AF screening, which will aid to fill the knowledge gaps about risk stratification of subclinical AF.

2. Methods

2.1. The LOOP Study

In the LOOP Study, participant enrolment and intervention assignment (by a computer-generated randomization scheme) were done at four centers in Denmark between January 2014 and May 2016. Eligible participants were 70–90 years old and with at least one of four conditions: arterial hypertension, diabetes mellitus, congestive heart failure, or previous stroke. The main exclusion criteria were history of AF, cardiovascular implantable electronic device, and treatment with OAC. The participants were randomized in a ratio 1:3 to either the intervention group with ILR monitoring and subsequent OAC initiation when any new-onset AF episodes lasting ≥6 min were detected, or a control group with usual care. Details of the trial design and the main results from the primary analysis have been published previously [7,8].

The trial was registered at Clinical-Trials.gov (NCT02036450) and approved by the Regional Scientific Ethics Committee for the Capital Region of Denmark (H-4-2013-025) before study conduct. All participants gave oral and written informed consent at inclusion. The trial was done in accordance with the Declaration of Helsinki.

2.2. Study population

In this post hoc analysis, all LOOP participants were included and further divided into two cardiovascular risk groups, i.e. participants with and without established CVD at baseline (eFig. 1 in the Supplement). Here, established CVD included any history of *ischemic heart disease* (*IHD*, as defined by acute myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention), *congestive heart failure, stroke, valvular heart disease, or peripheral artery disease* (*PAD*, as defined by peripheral artery bypass graft or percutaneous peripheral intervention). Participants with a history of hypertension and/or diabetes alone were not considered as having CVD.

2.3. Outcomes

The primary outcome was a composite endpoint of stroke or systemic arterial embolism (SAE). Secondary outcomes included: 1) ischemic stroke; 2) the composite of stroke, SAE, or cardiovascular death; and 3) all-cause death. Other outcomes of interest were AF diagnosis, OAC initiation, ILR-detected AF episodes ≥5.5 hours and ≥24 hours.

A clinical endpoint committee blinded to randomization assignment was responsible for adjudication of the primary and secondary outcomes [7]. Any ILR-detected AF episodes with duration ≥6 min were evaluated by at least one experienced physician.

2.4. Statistical analysis

Baseline characteristics are presented as means with standard deviations (SD) and compared using *t*-test for continuous variables, whereas categorical variables are presented as frequencies with percentages and compared using chi-squared test.

The outcomes were analyzed with the time-to-first-event principle. Crude event rates (events per 100 person-years) were calculated by a Poisson distribution, while cumulative incidences were estimated using the Kaplan-Meier estimator for all-cause death and the Aalen-Johansen estimator with death as competing risk for all other outcomes. For groupwise comparisons, hazard ratio (HR) was determined in Cox proportional-hazards models. The interactions between CVD and ILR screening efficacy was assessed by adding an interaction term. The Cox models were also subjected to multivariate adjustment for the following baseline characteristics: sex, age, alcohol consumption, smoking pack years, body mass index, hypertension, diabetes mellitus, and the number of baseline CVD (not included for comparisons across CVD strata). The influence of baseline CVD on ILR screening efficacy was further evaluated according to sex and age, which are both well-known stroke risk factors in patients with clinical AF [3–6,12]. Here, a restricted cubic spline method was applied to examine age as a continuous variable, with separate effects of age on hazards of the outcomes estimated in each randomization group. Additionally, risk factor management between the randomization groups was explored by assessing systolic blood pressure (SBP) changes for 3-year follow-up versus baseline in a constrained linear mixed model with unstructured covariance pattern, as high blood pressure is a predominant and modifiable stroke risk factor [14–16].

In a supplementary analysis, all study participants were reclassified into two new risk groups according to the presence of atherosclerotic phenotypes (defined as *stroke*, *IHD*, or *PAD* at baseline). Thus, ILR screening effects on the primary and secondary outcomes were determined among participants with and without stroke/IHD/PAD.

The statistical analysis was performed using R version 4.1.0 and a statistical significance was defined by two-sided *p*-values ≤0.05.

3. Results

Of 6004 participants included, 4007 (66.7%) had no CVD at baseline and 1997 (33.3%) had a history of ≥1 CVD. Baseline characteristics in participants with and without CVD are summarized in Table 1. Participants without CVD were significantly younger, more likely to be female, and had lower tobacco exposure and slightly higher body mass index. Among participants with CVD at baseline, the majority (77.8%) had only one CVD, with previous stroke being the most common (52.9%).

3.1. Baseline CVD and outcomes

Cumulative incidences of the primary and secondary outcomes according to preexisting CVD in the entire study cohort are displayed in Figure 1. The primary outcome of stroke/SAE occurred in 132 participants with CVD (130 strokes and two SAEs) and 186 participants without CVD (185 strokes and one SAE). The event rates were 1.32 [95% confidence interval (CI): 1.11–1.57] and 0.90 [95% CI: 0.78–1.04] per 100 person-years, respectively. The risk difference between these two groups was significant (HR 1.47 [95% CI: 1.18–1.84]) and remained

Table 1
Overview of baseline characteristics according to preexisting cardiovascular disease.

	Without cardiovascular disease[a] ($n = 4007$)	With cardiovascular disease[a] ($n = 1997$)	p-value
Assignment to ILR group (%)	1002 (25.0)	499 (25.0)	>0.99
Male sex (%)	1872 (46.7)	1295 (64.8)	< 0.001
Age, years (SD)	74.6 (4.0)	75.0 (4.3)	< 0.001
Alcohol consumption, standard drink per week (SD)	7.2 (8.1)	7.4 (8.2)	0.33
Smoking pack years (SD)	15.0 (21.9)	20.8 (25.5)	< 0.001
Body mass index, kg/m^2 (SD)	27.8 (4.7)	27.4 (4.3)	< 0.001
Systolic blood pressure, mmHg (SD)	150.9 (19.1)	148.1 (20.1)	< 0.001
Diastolic blood pressure, mmHg (SD)	84.9 (10.9)	82.6 (11.7)	< 0.001
Pulse rate, beats per min (SD)	72.5 (12.4)	69.2 (12.1)	< 0.001
CHA_2DS_2-VASc score (%)			
2	755 (18.8)	35 (1.8)	< 0.001
3	1738 (43.4)	269 (13.5)	
≥4	1514 (37.8)	1693 (84.8)	
Number of cardiovascular diseases[a] (%)			
0	4007 (100.0)	–	–
1	–	1554 (77.8)	
2	–	372 (18.6)	
≥3	–	71 (3.6)	
Comorbidities (%)			
Hypertension	3776 (94.2)	1668 (83.5)	< 0.001
Diabetes Mellitus	1234 (30.8)	476 (23.8)	< 0.001
Heart Failure	–	266 (13.3)	–
Previous stroke	–	1056 (52.9)	–
Ischemic heart disease[b]	–	791 (39.6)	–
Valvular heart disease	–	244 (12.2)	–
Peripheral artery disease[c]	–	161 (8.1)	–
Concomitant medication (%)			
Beta-blockers	799 (19.9)	727 (36.4)	< 0.001
Calcium channel blockers	1553 (38.8)	693 (34.7)	0.002
Digoxin	1 (0.0)	7 (0.4)	0.004
Renin-angiotensin inhibitors	2746 (68.5)	1244 (62.3)	< 0.001
Mineralocorticoid receptor antagonists	112 (2.8)	102 (5.1)	< 0.001
Thiazide diuretics	918 (22.9)	344 (17.2)	< 0.001
Loop diuretics	323 (8.1)	233 (11.7)	< 0.001
Platelet inhibitors	1265 (31.6)	1641 (82.2)	< 0.001
Statins	1970 (49.2)	1530 (76.6)	< 0.001
Antidiabetic drugs	1088 (27.2)	426 (21.3)	< 0.001

Abbreviation: ILR, implantable loop recorder; SD, standard deviation.
Missing observations: Alcohol consumption $n = 3$; Body mass index n = 1; Blood pressure $n = 7$; Pulse rate $n = 21$.

[a] Cardiovascular disease defined as any history of ischemic heart disease, congestive heart failure, stroke, valvular heart disease, or peripheral artery disease.

[b] Ischemic heart disease defined as previous acute myocardial infarction, coronary bypass surgery, or percutaneous coronary intervention.

[c] Peripheral artery disease defined as previous peripheral artery bypass surgery or percutaneous peripheral intervention.

present in the multivariate model (adjusted HR 1.34 [95% CI: 1.06–1.69]). For the secondary outcomes, the presence of CVD was associated with significantly increased risks of ischemic stroke (adjusted HR 1.31 [95% CI: 1.02–1.69]), stroke/SAE/cardiovascular death (adjusted HR 1.49 [95% CI: 1.23–1.79]), and all-cause death (adjusted HR 1.59 [95% CI: 1.36–1.85]) compared with no CVD (eTable 1 in the Supplement).

In total, 625 (15.6%) of 4007 participants without preexisting CVD had AF during follow-up: 288 (28.7%) in the ILR group versus 337 (11.2%) in the control group. For participants with CVD ($n = 1997$), AF was diagnosed in 402 (20.1%): 189 (37.9%) in the ILR group versus 213 (14.2%) in the control group. A history of CVD was associated with increased likelihood of AF diagnosis both in the ILR group (adjusted HR 1.32 [95% CI: 1.09–1.59]) and the control group (adjusted HR 1.24 [95% CI: 1.03–1.48]); eTable 2 and eFigure 2 in the Supplement. Participants with preexisting CVD were also more likely to develop AF episodes ≥5.5 hours and ≥24 hours as detected by ILR, than those without (adjusted HR 1.39 [95% CI: 1.07–1.79] and 1.64 [95% CI: 1.05–2.56], respectively).

3.2. ILR screening efficacy according to baseline CVD

Among participants with CVD, ILR screening did not reduce the risk of stroke/SAE (HR 1.05 [95% CI: 0.71–1.56]; adjusted HR 1.13 [95% CI: 0.76–1.68]) as compared with usual care (Table 2; eFigure 3 in the Supplement). For those without CVD, stroke/SAE occurred at a rate of 0.64 [95% CI: 0.44–0.90] per 100 person-years in the ILR group and 0.99 [95% CI: 0.84–1.16] per 100 person-years in the control group, corresponding to HR 0.65 [95% CI: 0.44–0.94]. This screening benefit remained significant after multivariate adjustment (adjusted HR 0.64 [95% CI: 0.44–0.93]); adjusted p-value for interaction 0.041. Based on the 6-year cumulative incidences among participants without CVD (3.25% [95% CI: 2.11%–4.38%] for the ILR group versus 5.86% [95% CI: 4.85%–6.86%] for the control group), the number needed to screen was estimated to be 39 in this participant group to avoid one stroke/SAE after six years. For secondary outcomes, the event rates were comparable across the randomization groups in the presence of CVD (Fig. 2). Among participants without CVD, ILR screening appeared to be beneficial with respect to ischemic stroke and stroke/SAE/cardiovascular death (adjusted HR 0.54 [95% CI: 0.35–0.82] and 0.64 [95% CI: 0.46–0.87], respectively), but not all-cause death. The interactions between baseline CVD and randomization were significant for all secondary outcomes (adjusted p-value for interaction ≤0.05 for all).

ILR screening effects on the primary and secondary outcomes according to sex in participants with and without CVD are presented in eFigure 4 in the Supplement. The influence patterns of preexisting CVD were similar in men as in women, and no statistical significance was reached for interactions between sex and ILR screening efficacy in either CVD risk group. Likewise, no significant effect modifications of age on screening benefits were found in either participants with or without CVD (eFigure 5–8 in the Supplement).

An increased incidence of AF diagnosis was obtained by ILR screening both among participants with and without CVD (eTable 2 in the Supplement), corresponding to adjusted HR of 3.59 [95% CI: 2.94–4.38] and 3.09 [95% CI: 2.64–3.61], respectively. This increase was comparable across the randomization groups (adjusted p-value for interaction 0.25). With respect to OAC initiation, the event rates for ILR versus usual care were 9.79 [95% CI: 8.41–11.33] per 100 person-years versus 3.07 [95% CI: 2.68–3.50] per 100 person-years in the CVD group (adjusted HR 3.20 [95% CI: 2.62–3.90]), and 6.33 [95% CI: 5.59–7.14] per 100 person-years versus 2.49 [95% CI: 2.24–2.75] per 100 person-

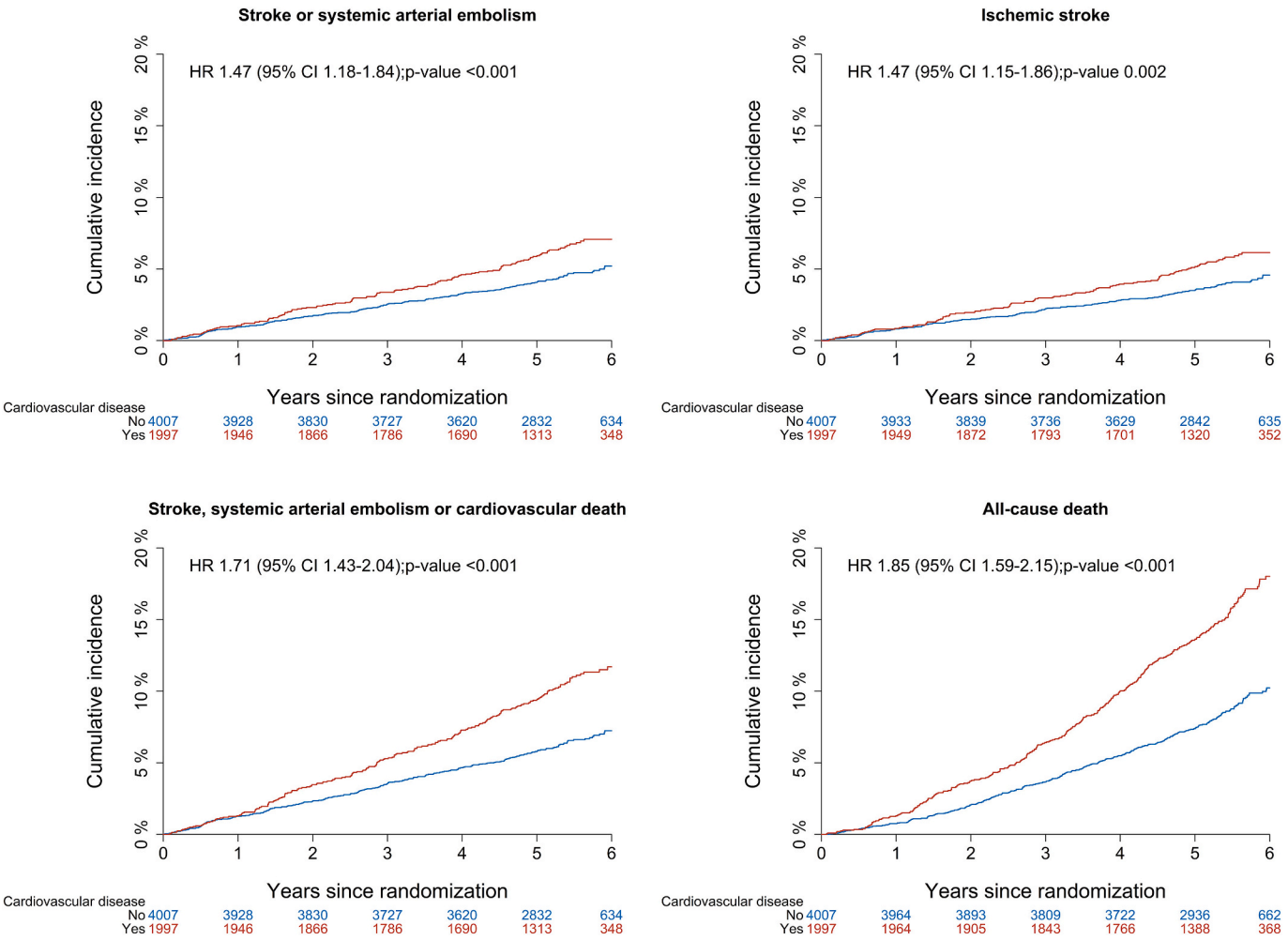

Fig. 1. Cumulative incidences of primary and secondary outcomes according to cardiovascular disease at baseline in the entire study cohort.
Graphical presentation of cumulative incidences of primary and secondary outcomes in the entire study cohort, according to the presence of cardiovascular disease (defined as any history of ischemic heart disease, congestive heart failure, stroke, valvular heart disease, or peripheral artery disease). Cumulative incidences were plotted using the Kaplan-Meier method for all-cause death and the Aalen-Johansen method for all other outcomes with death as competing risk. Hazard ratios were based on univariate Cox proportional-hazards regression.
Abbreviation: HR, hazard ratio; CI, confidence interval.

years in the risk group without preexisting CVD (adjusted HR 2.54 [95% CI: 2.17–2.98]).

3.3. Blood pressure management

The average SBP at baseline was 150.90 mmHg and 148.12 mmHg for participants without and with CVD, respectively. Over the first three years of follow-up, there was no difference in SBP reduction between the ILR group (4.00 mmHg [95% CI: 2.32–5.68]) and the control group (3.64 mmHg [95% CI: 2.54–4.75]) among participants with CVD. For participants without CVD, SBP reduction was significantly greater in the ILR group (3.73 mmHg [95% CI: 2.57–4.89]) than the control group (2.34 mmHg [95% CI: 1.58–3.10]); *p*-value for difference 0.036.

3.4. ILR screening efficacy according to atherosclerotic phenotypes

When investigating participants according to stroke/IHD/PAD at baseline in the supplementary analysis, similar screening effects were observed; eFig. 9 in the Supplement. ILR screening led to significant risk reduction in stroke/SAE only among participants without stroke/IHD/PAD (adjusted HR 0.62 [95% CI: 0.43–0.90]), but not those with (adjusted HR 1.23 [95% CI: 0.82–1.85]); adjusted p-value for interaction 0.017.

4. Discussion

This post hoc analysis of the LOOP Study investigated the effects of ILR screening for AF in an elderly, at-risk population according to the presence/absence of established CVD. The main findings were as follows: 1) the history of CVD was associated with increased risks of AF diagnosis and cardiovascular outcomes; 2) participants with CVD experienced higher excess of longer AF episodes (≥5.5 hours and ≥24 hours) as detected by ILR, than those without; and 3) in the absence of CVD, an approximately 40% stroke risk reduction was obtained by ILR screening, whereas no significant screening benefits were observed among participants with CVD.

The increased availability of consumer-based technologies for heart rhythm monitoring has accentuated the interest in AF screening [6], as AF itself constitutes a predominant risk factor for morbidity and mortality [3,17]. Nevertheless, data on benefits of anticoagulation upon detection of subclinical AF are scarce and hence, an evidence-based risk assessment approach for identification of the appropriate population for AF screening has yet to be developed [6]. The LOOP Study intended to evaluate the best-case scenario for AF screening in a selected population

Table 2
Event rates, relative risks, and interactions between cardiovascular disease at baseline and randomization assignment on the primary and secondary outcomes.

		Events per 100 person-years (95% CI)		Relative risk		Interaction between cardiovascular disease[a] and ILR screening	
		ILR group	Control group	Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[b]	*p*-value	Adjusted p-value[b]
Stroke or systemic arterial embolism	Participants with cardiovascular disease[a]	1.37 (0.95–1.92)	1.31 (1.06–1.59)	1.05 (0.71–1.56)	1.13 (0.76–1.68)	0.08	0.04
	Participants without cardiovascular disease[a]	0.64 (0.44–0.90)	0.99 (0.84–1.16)	0.65 (0.44–0.94)	0.64 (0.44–0.93)		
Ischemic stroke	Participants with cardiovascular disease[a]	1.21 (0.82–1.73)	1.12 (0.89–1.38)	1.09 (0.72–1.65)	1.18 (0.77–1.79)	0.02	0.01
	Participants without cardiovascular disease[a]	0.48 (0.31–0.71)	0.88 (0.74–1.04)	0.55 (0.36–0.84)	0.54 (0.35–0.82)		
Stroke, systemic arterial embolism, or cardiovascular death	Participants with cardiovascular disease[a]	2.30 (1.74–2.98)	2.14 (1.82–2.49)	1.08 (0.80–1.46)	1.20 (0.89–1.63)	0.03	0.005
	Participants without cardiovascular disease[a]	0.91 (0.67–1.21)	1.40 (1.22–1.60)	0.66 (0.48–0.90)	0.64 (0.46–0.87)		
All-cause death	Participants with cardiovascular disease[a]	3.34 (2.67–4.13)	3.05 (2.67–3.47)	1.09 (0.85–1.40)	1.23 (0.96–1.59)	0.33	0.05
	Participants without cardiovascular disease[a]	1.58 (1.26–1.96)	1.72 (1.52–1.94)	0.92 (0.72–1.18)	0.86 (0.67–1.11)		

Crude rates in the ILR group and the control group are presented as events per 100 person-years (95% CI). Hazard ratios and assessment of interaction were based on Cox proportional-hazards model.
Abbreviation: ILR, implantable loop recorder; CI, confidence interval.
[a] Cardiovascular disease defined as any history of ischemic heart disease, congestive heart failure, stroke, valvular heart disease, or peripheral artery disease.
[b] Multivariate model adjusted for sex, age, alcohol consumption, smoking pack years, body mass index, history of hypertension, history of diabetes, and the number of preexisting cardiovascular disease.

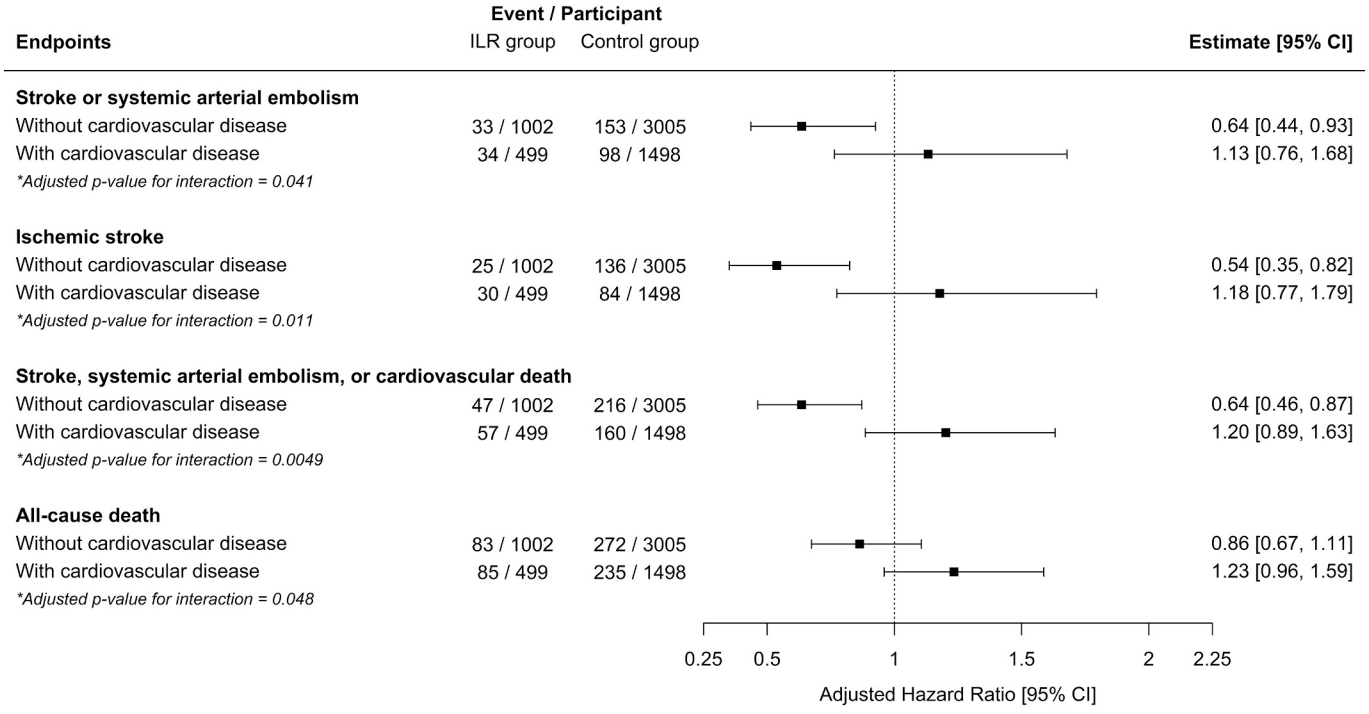

Fig. 2. ILR screening efficacy on primary and secondary outcomes according to cardiovascular disease at baseline (adjusted analysis).
Results of multivariate models for the primary and secondary outcomes according to baseline cardiovascular disease (defined as any history of ischemic heart disease, congestive heart failure, stroke, valvular heart disease, or peripheral artery disease), adjusting for sex, age, alcohol consumption, smoking pack years, body mass index, history of hypertension, history of diabetes mellitus, and the number of preexisting cardiovascular disease. Adjusted hazard ratios with 95% CI and adjusted *p*-values for interaction of baseline cardiovascular disease on ILR screening effects on the primary and secondary outcomes were shown.
Abbreviation: ILR, implantable loop recorder; CI, confidence interval.

of elderly individuals with high stroke risks based on CHA_2DS_2-VASc score, where all AF episodes ≥6 min were expected to be detected by ILR and lead to initiation of OAC [7,8]. As a recent meta-analysis of studies of patients with clinical AF reported indifferent stroke risks between asymptomatic and symptomatic AF [18], the lack of a significant screening benefit in the LOOP Study would thus imply that subclinical AF may constitute a different entity than clinical AF. Indeed, a previous sub-analysis of the ILR group found no association between symptoms and device-detected AF burden, and more importantly, a spontaneous reduction in AF burden among the majority of the participants with AF

[36]. Moreover, the absence of any noticeable interactions between screening effects and CHA_2DS_2-VASc scores in the primary analysis might also indicate a potential limitation of using this scheme for risk stratification for AF screening.

The present study demonstrated that a history of CVD was associated with an increased risk of stroke/SAE. This seemingly accords with numerous prior studies linking CVD to heightened stroke risk in patients with clinical AF [3–6,9–13]. In the ASSERT study (*Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial*), the absolute stroke rates in patients with device-detected atrial tachyarrhythmias were also reported to be positively correlated with $CHADS_2$ score [19]. Additionally, we found higher incidences of AF diagnosis and longer AF episodes ($\geq$5.5 hours and $\geq$24 hours) detected by ILR among participants with CVD than those without. Especially the latter is noteworthy and could partly explain the increased stroke risk in the CVD group, as an association between AF duration and stroke risk has been ascertained by several studies [20–22]. However, in our study, ILR screening and subsequent OAC did not successfully reduce the stroke risk among CVD participants, compared with usual care. On the other hand, a significant screening benefit on stroke prevention was achieved among participants without CVD. Our findings tie well with a previous Danish nationwide registry study wherein Christiansen et al. observed that the AF-related increase in stroke risk became more modest when other concomitant stroke risk factors were present [10]. Furthermore, the lack of screening benefits among participants with established CVD seems less likely to be caused by higher AF detection with usual care during study follow-up, as the relative risks of AF diagnosis for ILR versus controls were comparable across the CVD risk strata. Nevertheless, it could be speculated that high level patient care and monitoring due to established CVD might already have been able to detect those most clinically relevant AF, why ILR screening did not appear to contribute to additional stroke prevention in this patient population. Another possible explanation could also be "competing" stroke etiologies, as high-risk individuals with several other cardiovascular risk factors that could drive non-cardioembolic strokes, might barely benefit from AF screening. Specifically, IHD, PAD, and calcific valvular stenosis – as an expression of underlying systemic atherosclerosis – are interrelated to coexisting extracranial and intracranial atherosclerosis [23–26], thus predisposing to heightened risks of large-artery strokes and atherosclerotic lacunar strokes [27–31]. This could potentially explain the lacking response on ILR screening in the presence of CVD in our study. Indeed, it is noteworthy that reclassifying the study participants according to the presence of atherosclerotic phenotypes (stroke/IHD/PAD) yielded similar screening effects in the supplementary analysis. The notion about competing etiology is further supported by a previous study of 777 patients with embolic stroke of undetermined source, which reported a lesser extent of AF detected in the patients with carotid atherosclerosis than those without [32]. Likewise, another study of patients with cryptogenic stroke also pointed to the existence of a negative correlation between carotid atherosclerosis and patent foramen ovale [33]. Hence, both studies indicate that atherosclerotic diseases could act as competing conditions to other established stroke causes. Moreover, an interesting observation in this study was the slightly better blood pressure management in the ILR group than the control group among participants without CVD, while SBP reduction appeared to be of similar magnitude for both randomization groups in the presence of CVD. As elevated SBP is a well-known stroke risk factor [15,16], our finding may well translate into a greater possibility of further optimization of risk factor management upon AF detection in individuals without established CVD, which could partly explained the remarkable screening benefits in this risk group, but not those with CVD.

Current European guidelines recommend systematic electrocardiogram screening to be considered in individuals aged $\geq$75 years or at high stroke risk [6], while the most recent US Preventive Services Task Force Recommendation Statement states a lack of sufficient evidence to endorse AF screening [34]. However, this post hoc analysis of the LOOP Study demonstrates that the effects of systematic AF screening on stroke prevention was considerably upheld by high-risk individuals without established CVD. This finding is arguably consistent with that of the STROKESTOP study (*Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden*), where Svennberg et al. reported a significant benefit of intermittent screening in individuals at high stroke risk as solely based on age without requirement of specific comorbidities [35]. Hence, further studies on the interaction between cardiovascular risk profile and AF screening efficacy are needed to inform screening strategy and clinical management of subclinical or screen-detected AF.

4.1. Study limitations

Several limitations may warrant further consideration. First, this was a post hoc analysis and our findings would thus only be hypothesis generating. Second, CVD definition was based on baseline comorbidities, which would lead to misclassification bias of the participants who had acquired a CVD diagnosis during follow-up. Third, the medical history of valvular heart disease was recorded at randomization by the study nurses without any formal disease definition specified in the protocol, while further details about types of valvular heart disease and information about other cardiac disease such as congenital heart disease were lacking.

5. Conclusions

Among individuals aged $\geq$70 years with additional stroke risk factors, the presence of CVD conferred increased risks of AF diagnosis and cardiovascular outcomes. However, continuous AF screening did not prevent stroke significantly in individuals with preexisting CVD, whereas screening was associated with an approximately 40% stroke risk reduction in those without CVD. These findings should be considered as hypothesis-generating and warrant further study.

Funding

The LOOP Study was funded by Innovation Fund Denmark [grant number 12–1352259], The Research Foundation for the Capital Region of Denmark, The Danish Heart Foundation [grant number 11–04-R83-A3363–22625], Aalborg University Talent Management Program, Arvid Nilssons Fond, Skibsreder Per Henriksen, R og Hustrus Fond, the European Union's Horizon 2020 program [grant number 847770 for AFFECT-EU consortium], Læge Sophus Carl Emil Friis og hustru Olga Doris Friis' Legat, and an unrestricted grant from Medtronic. The employment of the first author, LYX, is funded by the European Union's Horizon 2020 program [grant number 847770] via AFFECT-EU consortium.

Declaration of Competing Interest

SZD reports to be a part-time employee of Vital Beats and a member of Bristol-Myers Squibb/Pfizer advisory boards not related to this work. DWK reports to be a Medtronic Focus Group member. AB reports research grants from The Region of Southern Denmark and The Region of Zealand, The Canadian Institutes of Health Research, and Theravance, and speaker honoraria from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb, and a travel grant from Biotronik not related to this work. LK reports speaker honoraria from Novo, AstraZeneca, Novartis, and Boehringer, not related to this work. KJH reports travel and educational grants from Medtronic, Abbott, and Biotronik and speaker honoraria from Boehringer-Ingelheim not related to this work. JHS reports to be a member of Medtronic advisory boards and to have received speaker honoraria and research grants from Medtronic in relation to this work and outside this work. LYX, SH, CG and MSO have no conflicts of

interest to report.

Acknowledgements

We thank Christian Kronborg (University of Southern Denmark, Denmark) for contributing with his expertise in the Trial Steering Committee of the LOOP Study. We thank Dan Atar (Oslo University Hospital, Norway), Gregory Y. H. Lip (Liverpool Heart and Chest Hospital, United Kingdom), and Mårten Rosenqvist (Danderyd Hospital, Sweden), for contributing with their expertise in the Advisory Committee of the LOOP Study. We thank our colleagues in the Departments of Cardiology at Rigshospitalet, Bispebjerg and Frederiksberg Hospital, Zealand University Hospital, and Odense University Hospital, for assisting with the conduct of the LOOP Study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.167.

References

[1] V.L. Feigin, Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019, Lancet Neurol. 20 (10) (2021) 1–26.
[2] B.B. Love, B.H. Bendixen, Classification of subtype of acute ischemic stroke definitions for use in a multicenter clinical trial, Stroke. 24 (1) (1993) 35–41.
[3] P.A. Wolf, R.D. Abbott, W.B. Kannel, Atrial fibrillation as an independent risk factor for stroke: the Framingham study, Stroke. 22 (8) (1991) 983–988.
[4] L. Friberg, M. Rosenqvist, G.Y.H. Lip, Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish atrial fibrillation cohort study, Eur. Heart J. 33 (12) (2012) 1500–1510.
[5] J.B. Olesen, G.Y.H. Lip, M.L. Hansen, et al., Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: Nationwide cohort study, BMJ. 342 (7792) (2011) 320.
[6] G. Hindricks, T. Potpara, N. Dagres, et al., 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), Eur. Heart J. 42 (5) (2021) 373–498.
[7] S.Z. Diederichsen, K.J. Haugan, L. Køber, et al., Atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (the LOOP study): rationale and design of a large randomized controlled trial, Am. Heart J. 187 (2017) 122–132.
[8] J.H. Svendsen, S.Z. Diederichsen, S. Højberg, et al., Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP Study): a randomised controlled trial, Lancet. 398 (10310) (2021) 1507–1516.
[9] C. Andreasen, G.H. Gislason, L. Køber, et al., Incidence of ischemic stroke in individuals with and without aortic valve stenosis: a Danish retrospective cohort study, Stroke (2020) 1364–1371.
[10] C.B. Christiansen, T.A. Gerds, J.B. Olesen, et al., Atrial fibrillation and risk of stroke: a nationwide cohort study, Europace. 18 (11) (2016) 1689–1697.
[11] H.L. Casele, Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials, Arch. Intern. Med. 158 (12) (1998) 1316–1320.
[12] L. Frost, G. Engholm, S. Johnsen, H. Møller, S. Husted, Incident stroke after discharge from the hospital with a diagnosis of atrial fibrillation, Am. J. Med. 108 (1) (2000) 36–40.
[13] R. Philippart, A. Brunet-Bernard, N. Clementy, et al., Prognostic value of CHA2DS2-VASc score in patients with “non-valvular atrial fibrillation” and valvular heart disease: the Loire Valley atrial fibrillation project, Eur. Heart J. 36 (28) (2015) 1822–1830.
[14] L.Y. Xing, S.Z. Diederichsen, S. Højberg, et al., Systolic blood pressure and effects of screening for atrial fibrillation with long-term continuous monitoring (a LOOP substudy), Hypertension. 79 (9) (2022) 2081–2090.
[15] K. Kitagawa, Y. Yamamoto, H. Arima, et al., Effect of standard vs intensive blood pressure control on the risk of recurrent stroke: a randomized clinical trial and Meta-analysis, JAMA Neurol. 76 (11) (2019) 1309–1318.
[16] E. Rapsomaniki, A. Timmis, J. George, et al., Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people, Lancet. 383 (9932) (2014) 1899–1911.
[17] E.J. Benjamin, P.A. Wolf, R.B. D'Agostino, H. Silbershatz, W.B. Kannel, D. Levy, Impact of atrial fibrillation on the risk of death: the Framingham heart study, Circulation. 98 (10) (1998) 946–952.
[18] D. Sgreccia, M. Manicardi, V.L. Malavasi, et al., Comparing outcomes in asymptomatic and symptomatic atrial fibrillation: a systematic review and meta-analysis of 81,462 patients, J. Clin. Med. 10 (17) (2021) 3979.
[19] J.S. Healey, S.J. Connolly, M.R. Gold, et al., Subclinical atrial fibrillation and the risk of stroke, N. Engl. J. Med. 366 (2) (2012) 120–129.
[20] I.C. Van Gelder, J.S. Healey, H.J.G.M. Crijns, et al., Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT, Eur. Heart J. 38 (17) (2017) 1339–1344.
[21] T.V. Glotzer, E.G. Daoud, D.G. Wyse, et al., The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk the trends study, Circ. Arrhythm. Electrophysiol. 2 (5) (2009) 474–480.
[22] B.A. Steinberg, A.S. Hellkamp, Y. Lokhnygina, et al., Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF trial, Eur. Heart J. 36 (5) (2015) 288–296.
[23] I. Bytyçi, R. Shenouda, P. Wester, M.Y. Henein, Carotid atherosclerosis in predicting coronary artery disease: a systematic review and Meta-analysis, Arterioscler. Thromb. Vasc. Biol. 41 (2021) E224–E237.
[24] G. Novo, F.P. Guarneri, G. Ferro, R. Russo, K. Fattouch, S. Novo, Association between asymptomatic carotid atherosclerosis and degenerative aortic stenosis, Atherosclerosis. 223 (2) (2012) 519–522.
[25] L. Razzouk, C.B. Rockman, M.R. Patel, et al., Co-existence of vascular disease in different arterial beds: peripheral artery disease and carotid artery stenosis - data from life line screening®, Atherosclerosis. 241 (2) (2015) 687–691.
[26] K.S. Mathur, S.K. Kashyap, V. Kumar, Correlation of the extent and severity of atherosclerosis in the coronary and cerebral arteries, Circulation. 27 (1963) 929–934.
[27] S. Parish, M. Arnold, R. Clarke, et al., Assessment of the role of carotid atherosclerosis in the association between major cardiovascular risk factors and ischemic stroke subtypes, JAMA Netw. Open 2 (5) (2019).
[28] D.H. O'Leary, J.F. Polak, R.A. Kronmal, T.A. Manolio, G.L. Burke, S.K. Wolfson, Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults, N. Engl. J. Med. 340 (1) (1999) 14–22.
[29] P.J. Touboul, A. Elbaz, C. Koller, et al., Common carotid artery intima-media thickness and brain infarction: the etude du profil genetique de l'infarctus cerebral (GENIC) case-control study, Circulation. 102 (3) (2000) 313–318.
[30] D.O. Kleindorfer, A. Towfighi, S. Chaturvedi, et al., 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack; a guideline from the American Heart Association/American Stroke Association, Stroke. 52 (2021) E364–E467.
[31] S. Yaghi, E. Raz, D. Yang, et al., Lacunar stroke: mechanisms and therapeutic implications, J. Neurol. Neurosurg. Psychiatry 92 (8) (2021) 823–830.
[32] G. Ntaios, K. Perlepe, G. Sirimarco, et al., Carotid plaques and detection of atrial fibrillation in embolic stroke of undetermined source, Neurology. 92 (23) (2019) e2644–e2652.
[33] A. Jaffre, B. Guidolin, J.B. Ruidavets, N. Nasr, V. Larrue, Non-obstructive carotid atherosclerosis and patent foramen ovale in young adults with cryptogenic stroke, Eur. J. Neurol. 24 (5) (2017) 663–666.
[34] K.W. Davidson, M.J. Barry, C.M. Mangione, et al., Screening for atrial fibrillation, JAMA. 327 (4) (2022) 360.
[35] E. Svennberg, L. Friberg, V. Frykman, F. Al-Khalili, J. Engdahl, M. Rosenqvist, Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial, Lancet. 398 (10310) (2021) 1498–1506.
[36] S.Z. Diederichsen, K.J. Haugan, A. Brandes, et al., Natural history of subclinical atrial fibrillation detected by implanted loop recorders, J. Am. Coll. Cardiol. 74 (22) (2019) 2771–2781.