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Original Article

Effects of population-based screening for atrial fibrillation on quality of life

Emilie Katrine Kongebro [a], Christian Kronborg [b], Lucas Yixi Xing [a], Ketil Jørgen Haugan [c], Claus Graff [d], Søren Højberg [e], Morten S Olesen [a,f], Derk Krieger [g,h], Axel Brandes [i,j], Lars Køber [a,k], Jesper Hastrup Svendsen [a,k,1], Søren Zöga Diederichsen [a,1,*]

[a] Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Inge Lehmanns Vej 7, 2100, Copenhagen, Denmark
[b] Department of Economics, University of Southern Denmark, Campusvej 56, 5230, Odense
[c] Department of Cardiology, Zealand University Hospital Roskilde, Sygehusvej 10, 4000, Roskilde, Denmark
[d] Department of Health Science and Technology, Aalborg University, Selma Lagerløfs Vej 249, 9260, Gistrup, Denmark
[e] Department of Cardiology, Bispebjerg Hospital, Copenhagen University Hospital, Bispebjerg Bakke 23, 2400, Copenhagen, Denmark
[f] Department of Biomedical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200, Copenhagen, Denmark
[g] Mohammed Bin Rashid University of Medicine and Health Sciences, Al Razi St - Umm Hurair 2 - Dubai Healthcare City, Dubai, United Arab Emirates
[h] Department of Neurology, Mediclinic Parkview Hospital, Umm Suqeim St - Arjan-Dubailand - Al Barsha South, Dubai, United Arab Emirates
[i] Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Finsensgade 35, 6700, Esbjerg, Denmark
[j] Department of Cardiology, Esbjerg Hospital – University Hospital of Southern Denmark, Finsensgade 35, 6700, Esbjerg, Denmark
[k] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200, Copenhagen, Denmark

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ABSTRACT

Background: Screening for atrial fibrillation is rising and may worsen or improve quality of life.
Methods: We assessed quality of life (EQ-5D-5L) data in 6,004 participants with stroke risk factors randomised to usual care (n=4,503) or implantable loop recorder with anticoagulation upon detection of atrial fibrillation (n=1,501). Five domains (mobility, selfcare, usual activities, pain/discomfort, anxiety/depression) each scored from one to five were calculated into individual index scores (worst=-0.76, best=1.00). Changes in the index score and the visual analogue scale score (EQ VAS (0=worst, 100=best)) from baseline to year three were the primary outcomes, which were analysed using linear mixed models. Major problem was defined as a domain score ≥3 and analysed with logistic regression in year three.
Results: Of 6,004 participants, 5,733 (95 %) were alive after three years, and 5,162 (86 %) had complete EQ-5D-5L data. The baseline index score of 5,733 participants was 0.88 ±0.16, which decreased by -0.05 (-0.05; -0.04) in the control vs -0.04 (-0.05; -0.03) in the screening group after three years, and a baseline EQ VAS score of 78.4 ±16.2, which decreased by -6.06 (-6.54; -5.57) in control vs -5.18 (-5.95; -4.40) in the screening group after three years, with no significant difference between the groups (p=0.063 and p=0.056, respectively). The most frequent problem was major pain/discomfort (1,202 of 5,162 (23.3 %)), and any major problem occurred equally in the groups after three years (OR 0.91 (0.79;1.05)).
Conclusion: A population-based, long-term, and continuous screening for atrial fibrillation in high-risk individuals did not translate into increased quality of life.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of stroke, heart failure, and mortality [1]. Many cases of AF remain undetected due to no or subtle symptoms – a condition called device-detected AF [1]. This has increased the interest in systematic AF screening to prevent stroke via early detection and anticoagulation. Previous studies found even short-lasting

Abbreviations: AF, atrial fibrillation; BP, blood pressure; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EQ VAS, euroqol 5d-5L visual analogue scale; EQ domain, euroqol 5d-5L domain; ILR, implantable loop recorder; TIA, transient ischemic attack; OR, odds ratio; SD, standard deviation; SAE, systemic arterial embolism; VAS, visual analogue scale.

* Corresponding author at: Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Inge Lehmanns Vej 7, 2100, Copenhagen, Denmark.
E-mail address: soeren.zoega.diederichsen@regionh.dk (S.Z. Diederichsen).

[1] denotes equal contribution

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device-detected AF to be associated with increased stroke risk [2], that potentially can be reduced with anticoagulant treatment, although, at the cost of increased bleeding risk, that may tip the net benefit balance towards harm [3–5]. European guidelines 2024 recommend clinicians to consider AF population-based screening in older persons with risk factors, although the few trials with clinical outcomes did not convincingly show efficacy for stroke prevention [6,7], and the US Preventive Services Task Force concluded that current trial evidence is insufficient to assess the balance between harms and benefit [8]. Thus, it remains unknown which patients may benefit from AF screening – and who may not – and how screening should be performed.

Concerns can be raised about the adverse effects of AF screening, including the unknown impact on quality of life [9,10]. Population screening for cardiovascular diseases may increase emotional distress, but may also elicit a feeling of reassurance in those with negative results [11]. Overtreatment and overdiagnosis may affect quality of life in screened persons more than unscreened, as the risks of complications and hospitalisations may increase with systematic screening compared to an opportunistic strategy. The adverse effects of any screening should arguably be investigated adequately before systematic screening is implemented [12]. In this paper, we present results on quality of life changes associated with a large, randomised trial comparing population-based systematic screening for AF to usual care, as quality of life is an important outcome for patients, physicians, and healthcare systems.

2. Methods

2.1. Study design

The LOOP study was an open-label, randomised, controlled, multicentre trial conducted in Denmark. The trial aimed to prevent stroke events attributed to AF by using continuous screening with implantable loop recorder (ILR) compared to usual care. Participants were 70–90 years of age and diagnosed with at least one known risk factor for stroke: hypertension, diabetes, previous stroke, or heart failure. Exclusion criteria included baseline diagnosis of AF, treatment with heparin or anticoagulation, or any contraindications to anticoagulation [13]. Potential participants were identified through the Danish health registries and received an invitation letter. Upon the initial visit to the study site, eligibility was confirmed by obtaining a detailed medical history, and a thorough physical examination, including a 12-lead electrocardiogram to rule out AF, and followed by blood samples. Eligible persons were randomised in a one-to-three ratio to continuous monitoring with an ILR (screening group) or usual care (control group). Randomisation was performed in permuted blocks of four or eight persons and stratified according to study centres. ILR insertion was performed shortly after randomisation to screening and lasted until death, withdrawal, or end of life of the device. Potential AF episodes were adjudicated daily, and anticoagulation treatment was recommended upon adjudicated AF and initiated by the treating physician according to the study protocol. Quality of life was evaluated with the EQ-5D-5L questionnaire [14]. Quality of life assessments were conducted on-site in the screening group from baseline through year three. The control group received assessment on-site at baseline and year three and assessment by letter in year one and two. Additional data was collected annually via remote contacts and look-up in medical records [13].

2.2. Consent

All participants gave informed consent before enrolment. The local Ethics Committee and the Danish Data Protection Agency approved the study (H-4–2013–025), which was registered at ClinicalTrials.gov (NCT02036450).

2.3. Outcomes

The primary outcome of this substudy was the prespecified analysis of change in the EQ-5D-5L index and EQ Visual analogue scale (EQ VAS) scores from baseline to year three. Secondary outcomes included the occurrences of any problem, major problem, and worsening problem in the screening group compared to the control group, both overall and in the life domains separately (see definitions below).

2.4. Quality of life data

The EQ-5D-5L questionnaire comprises five separate domains (mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression) accompanied by EQ VAS. The EQ-5D-5L domains (EQ domains) are each scored on a five-level scale ranging from [1] to [5], with [1] translating to “no impairment” and [5] referring to an “extreme problem”. All domain scores were transformed from an ordinal scale to a continuous scale using validated and country-specific weights, rendering one EQ-5D-5L index score for every participant [14]. The Danish EQ-5D-5L index scores range from -0.76 to 1.00, with 1.00 being the full state of health and -0.76 being worse than dead (health equivalent to death= 0.00) [14]. The EQ VAS is the participant’s own reported global health in the range [0–100], with 100 referring to the best imaginable health and 0 as the worst imaginable health. The EQ-5D-5L index and EQ VAS scores together constitute the result of the health-related quality of life assessment. The outcome of any problem was defined as level [2–5] in any domain of EQ-5D-5L. The outcome of major problem was defined as level [3–5], and worsening problem was defined as an increment in level by one or two.

2.5. Statistics

Baseline characteristics were presented as frequencies with percentages for categorical variables (compared by Chi-squared tests), mean values ± standard deviations for continuous variables with a normal distribution (*t*-tests), or medians with first and third quartile for continuous variables with non-normal distributions (Wilcoxon rank-sum tests). Linear model estimates and Odds ratio (OR) were presented with 95 % confidence intervals (CI). A linear mixed-effects regression model with an unstructured covariance pattern accounting for repeated measurements was used to estimate the mean changes in EQ-5D-5L index and EQ VAS scores for each randomisation arm [15]. The model included four time points for annual visits/contacts and an interaction term between the randomisation arm and time points to allow a dynamic screening effect. The participants who died after randomisation and before the third-year visit were removed from the analyses and reported as a separate outcome. Logistic regression models were used to estimate the OR for encountering any problem, major problem, or worsening problem and were adjusted for baseline problems. We investigated the effect of screening on major problem in subgroups, which was performed using logistic regression adjusted for major problem at baseline. We investigated the baseline characteristics of the 0–25th percentile and 75–100th percentile of the EQ-5D-5L index scores, respectively. Sensitivity analyses for EQ-5D-5L index and EQ VAS scores accounting for missing data included additional covariates of age, sex, smoking (pack years), prior stroke, transient ischemic attack (TIA), or systemic arterial embolism (SAE), diabetes, chronic obstructive pulmonary disease (COPD) and educational level into the linear mixed model. Sensitivity analyses for major, worsening and any problems were also performed with the additional covariates and imputations for missing data. All statistics were performed in R version 4.3.2 or newer.

3. Results

From 2014 to 2016, a total of 6004 participants were randomised in four Danish centres: 1501 to ILR screening and 4503 to usual care

(control group). The mean age was 75 years (±4.1), and 47 % were women (Table 1). Common diagnoses were hypertension (90.7 %), diabetes (28.5 %), and prior stroke, TIA, or SAE (25.1 %). Approximately 40 % were non-smokers, and the median BMI was 27.1 kg/m^2 (±4.6). Roughly 80 % had completed high school or equivalent, and 10 % completed a master's degree. The median duration of ILR monitoring was approximately 40 months (IQR 4.7), and the median follow-up duration was 64.5 months (IQR 10.5). The study population has been described in previous studies [6].

During the study period, 211 (4.7 %) participants in usual care and 60 (4.0 %) participants in the screening group died before the last assessment at year three. After three years, 5733 participants were still under follow-up (4292 (95.0 %) in the control group and 1441 (96 %) in the screening group), 637 (11.1 %) had been diagnosed with AF (241 (5.6 %) in the control group and 396 (27.5 %) in the screening group), 643 (11.2 %) had initiated anticoagulation (265 (6.2 %) in the control group and 378 (26.2 %) in the screening group), and 5162 (86.0 %) had complete EQ-5D-5L data in all domains from baseline through year three (3815 (84.7 %) in the control group and 1347 (89.7 %) in the screening group).

Table 1
Baseline characteristics.

		Control (n=4503)	Screening (n=1501)	Total (n=6004)
Age, years		74.7 (4.1)	74.7 (4.1)	74.7 (4.1)
Female sex		2128 (47.3)	709 (47.2)	2837 (47.3)
Smoking status	never	1782 (39.6)	597 (39.8)	2379 (39.6)
	current	417 (9.3)	135 (9.0)	552 (9.2)
	previous	2302 (51.1)	769 (51.2)	3071 (51.2)
Alcohol consumption, units/week		5 (1–10)	5 (1–10)	5 (1–10)
Education	Primary School	747 (17.4)	284 (19.5)	1031 (17.9)
	High School/ equivalent	1734 (40.3)	608 (41.8)	2342 (40.7)
	Bachelors's degree	1397 (32.5)	416 (28.6)	1813 (31.5)
	Master's degree	420 (9.8)	146 (10.0)	566 (9.8)
DIAGNOSES				
Hypertension		4066 (90.3)	1378 (91.8)	5444 (90.7)
Diabetes		1288 (28.6)	422 (28.1)	1710 (28.5)
Stroke, TIA or SAE		1139 (25.3)	370 (24.7)	1509 (25.1)
COPD		330 (7.3)	110 (7.3)	440 (7.3 %)
Heart failure		199 (4.4)	67 (4.5)	266 (4.4)
CHA_2DS_2-VA Score		3 (1)	3 (1)	3 (1)
PHYSICAL EXAMINATION				
Systolic BP, mmHg		149.8 (19.5)	150.6 (19.2)	150 (19.4)
Diastolic BP, mmHg		83.9 (11.3)	84.7 (11.1)	84.1 (11.2)
Pulse rate, beats/ min		71.3 (12.5)	71.6 (12.1)	71.4 (12.4)
BMI, kg/m2		27.6 (4.5)	27.8 (4.7)	27.7 (4.6)
Creatinine, umol/L		85.8 (26.2)	84.8 (24.2)	85.6 (25.7)
MEDICATION				
Platelet inhibitor		2204 (48.9)	702 (46.8)	2906 (48.4)
Betablocker		1172 (26.0)	354 (23.6)	1526 (25.4)
Diuretics		1511 (33.6)	495 (33.0)	2006 (33.4)
Statin		2621 (58.2)	879 (58.6)	3500 (58.3)
Renin-angiotensin inhibitor		2999 (66.6)	991 (66.0)	3990 (66.5)
Insulin		354 (7.9)	124 (8.3)	478 (8.0)

TIA; transient ischemic attack, SAE; systemic arterial embolism, COPD; chronic obstructive pulmonary disease, BP; blood pressure, BMI; body mass index

3.1. Occurrence of major problem

At baseline, 1571 of 5162 (30.4 %) participants reported any major problem, 1202 (23.3 %) reported major pain/discomfort problem, 666 (12.9 %) reported major mobility problem, and 83 (1.6 %) reported major selfcare problem (Fig. 1a, b, c).

After the first three years of follow-up, 1539 of 3815 (40.3 %) participants in the control group and 533 of 1347 (39.6 %) participants in the screening group reported any major problem with an OR 0.91 (0.79;1.05), p=0.2, which was confirmed by the sensitivity analyses. The occurrence of any problem and worsening problem were equal in the screening group compared to the control group (OR 0.91 (0.77;1.07), p=0.25 and OR 0.93 (0.82,1.05), p=0.24).

At year three, major pain/discomfort rose 2 % in the control group compared to the screening group (OR 0.84 (0.72;0.98), p=0.03), and major selfcare problem occurred more often in the control group compared to the screening group (OR 0.70 (0.49–1.01), p=0.056) (Table 2a). The sensitivity analyses resulted in non-significant estimates of major problem in all EQ domains.

The screening group had lower odds of any and worsening problem in each EQ domain compared to the control group, but most estimates did not reach statistical significance (Table 3, Table 4). Worsening pain/discomfort problem was reduced in the screening group compared to the control group (OR 0.86

(0.75–0.99), p=0.03), as were major selfcare problem (OR 0.79 (0.63–0.99), P=0.047). When the outcome of worsening problem was defined by a decline of at least two points, the results similarly favoured screening, but all were statistically indifferent, which was confirmed by sensitivity analyses.

3.2. Effect of AF screening on overall quality of life

For the 5733 participants who were alive after three years, the baseline EQ-5D-5L index score was 0.88 (±0.16) and the EQ VAS score was 78.3 (±16.2) (Table 5, Figs. 2a+2b)). At year one, the estimates for EQ-5D-5L index and EQ VAS scores were slightly higher in the screening group (0.008 (-0.001; 0.017), p=0.055 and 1.2 (0.43;2.03), p=0.002) compared to the control group. After three years, the EQ-5D-5L index score had decreased by -0.05 (-0.05; -0.04) in the control group vs. -0.04 (-0.05; -0.03) in the screening group, and the EQ VAS score decreased by -6.06 (-6.54; -5.57) in the control group vs. -5.18 (-5.95; -4.40) in the screening group, resulting in no statistically significant difference between the groups (p=0.063 and p=0.056, respectively). Participants in the screening group who were diagnosed with AF, the EQ-5D-5L index score at year three decreased by -0.04 (-0.05;-0.02) and the EQ VAS score by -5.6 (-7.1;-4.2), and the scores were not significantly different compared to screened participants without AF (EQ-5D-5L index score difference: 0.002 (-0.02;0.02) and EQ VAS difference: -0.5 (-2.3;1.3)). The sensitivity analyses (Table 6) for both EQ-5D-5L index and EQ VAS scores resulted in minimal changes.

3.3. Screening effect in subgroups

The odds of any major problem did not differ between randomisation groups in subgroups with baseline diagnoses of heart failure, stroke, or diabetes (Fig. 3). Female participants had lower odds (OR 0.79 (0.64–0.98), p=0.03) of any major problem after screening compared to usual care, with a p-value for interaction between sex and randomisation arm of 0.08. We also examined the baseline characteristics of

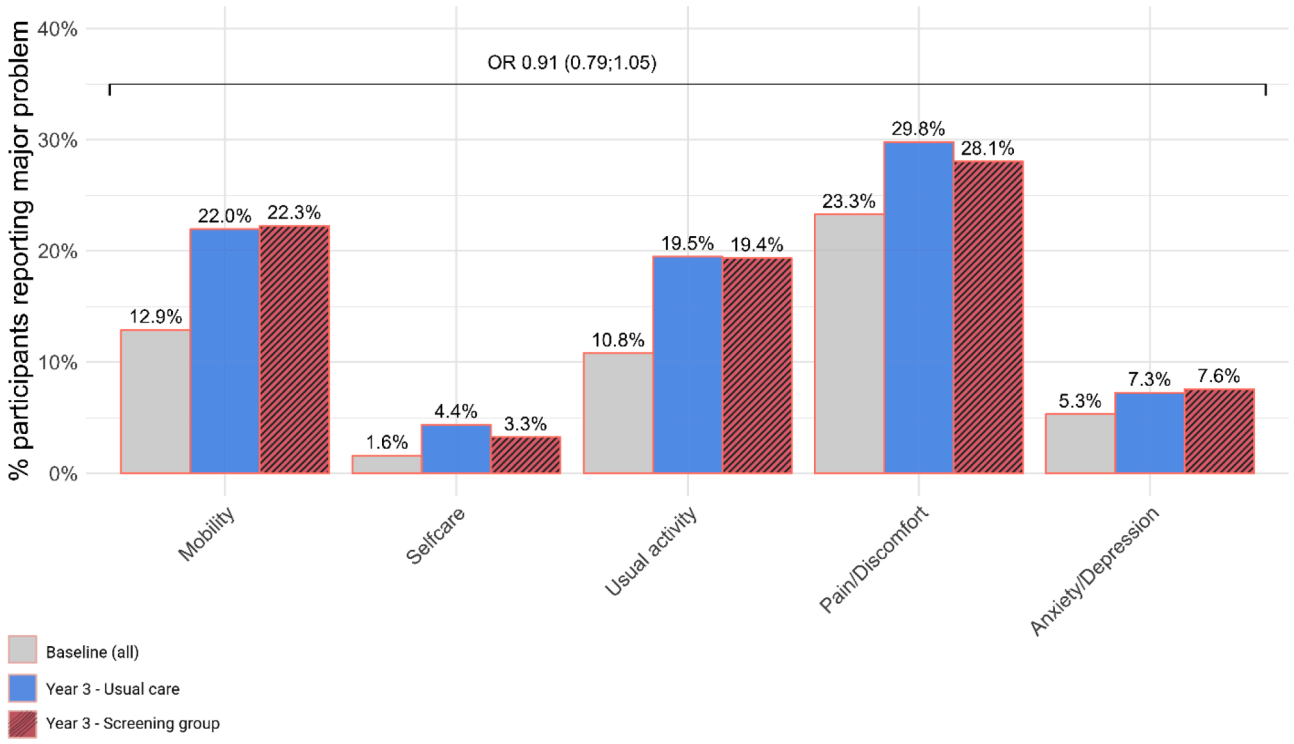

Fig. 1a. Any major problem across EQ domains – from baseline to year three.

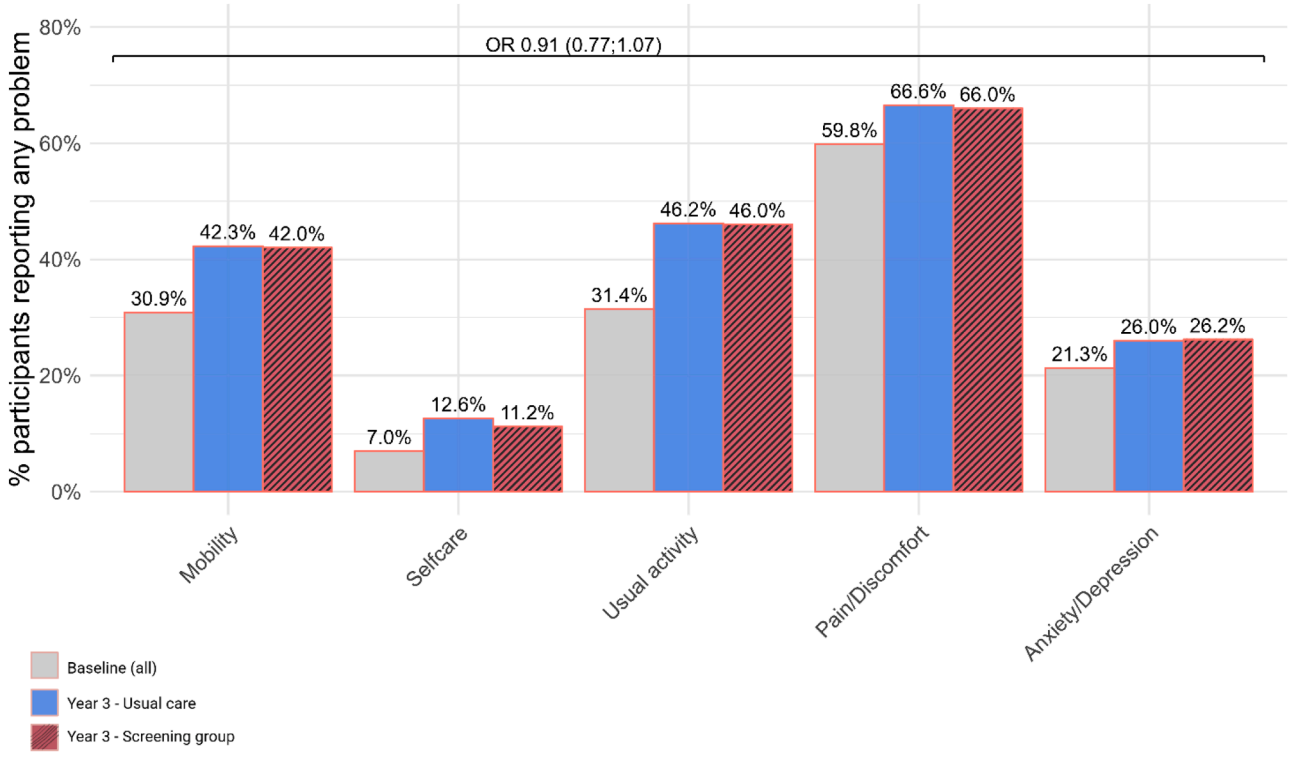

Fig. 1b. Any problem across EQ domains – from baseline to year three.

participants in the lowest and highest quartiles of the EQ-5D-5L index score. The lowest quartile of the EQ-5D-5L index was more likely to be associated with older age, female sex, higher burden of comorbidity (diabetes, previous stroke and COPD), lower education and active smoking (Supplementary Table 2 and 3).

In the separate EQ domains, screening was associated with lower odds of major pain/discomfort problem in several subgroups (Supplementary Figure 2). Participants with no baseline diagnoses of stroke, or heart failure, or diabetes had significantly lower odds for major pain/discomfort associated with screening compared to usual care (OR 0.84 (0.71–1.00), OR 0.85 (0.72–0.99) and OR 0.82 (0.68–0.99)). Former smokers and those with an educational level of primary school had

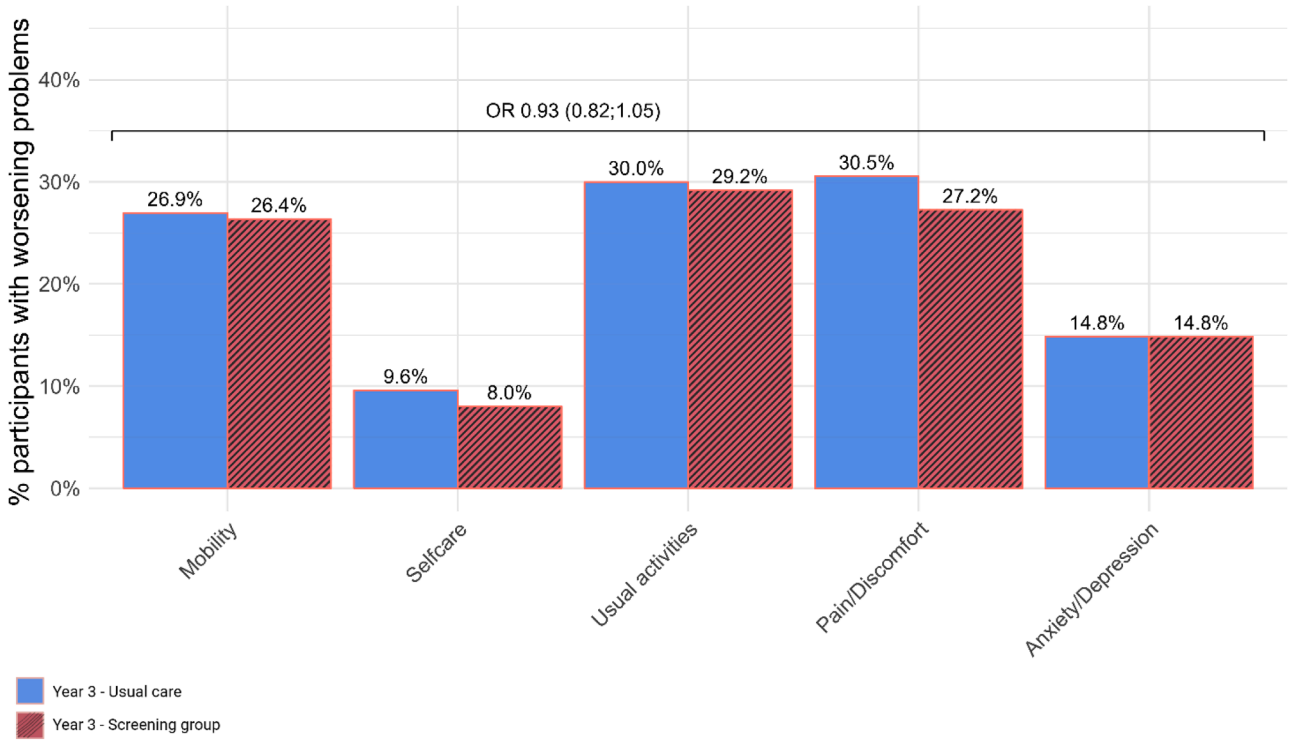

Fig. 1c. Worsening problem across EQ domains – from baseline to year three.

Table 2
Major problem in EQ domains after three years.

	Mobility		Selfcare		Usual activities		Pain/Discomfort		Anxiety/Depression	
	Odds Ratios	*p*	*Odds Ratios*	*p*	*Odds Ratios*	*p*	*Odds Ratios*	*p*	*Odds Ratios*	*p*
Screening effect*	1.02 (0.86 – 1.20)	0.84	0.70 (0.48 – 1.00)	0.056	1.01 (0.86 – 1.20)	0.87	0.84 (0.72 – 0.98)	**0.031**	1.03 (0.80 – 1.32)	0.82

* Difference between the screening group and the control group in year three

Table 3
Any problem in EQ domains after three years.

	Mobility		Pain/Discomfort		Usual activities		Anxiety/Depression		Selfcare	
	Odds Ratios	*P*	*Odds Ratios*	*P*	*Odds Ratios*	*P*	*Odds Ratios*	*P*	*Odds Ratios*	*P*
Screening effect*	0.93 (0.81 – 1.08)	0.36	0.94 (0.81 – 1.09)	0.40	0.96 (0.83 – 1.10)	0.53	0.97 (0.82 – 1.14)	0.68	0.86 (0.70 – 1.07)	0.18

* Difference between the screening group and the control group in year three

Table 4
Worsening problem in EQ domains after three years.

	Mobility		Selfcare		Usual activities		Pain/Discomfort		Anxiety/Depression	
	Odds Ratios	*p*	*Odds Ratios*	*p*	*Odds Ratios*	*p*	*Odds Ratios*	*p*	*Odds Ratios*	*p*
Screening effect*	0.96 (0.83 – 1.11)	0.59	0.79 (0.63 – 0.99)	**0.047**	0.95 (0.83 – 1.09)	0.51	0.86 (0.75 – 0.99)	**0.034**	0.99 (0.83 – 1.18)	0.92

* Difference between the screening group and the control group in year three

lower odds of major pain/discomfort (OR 0.77 (0.62–0.97) and OR 0.68 (0.47–0.98)) after screening compared to usual care. In the mobility domain, female participants had lower odds of major problems after screening compared to usual care with a significant test for interaction (OR 0.84 (0.66–1.07, p=0.15 and p for interaction=0.03)). The subgroup analyses of major selfcare problem resulted in borderline-significant estimates for persons with no baseline diagnoses of diabetes or heart failure, non-smokers, and participants aged ≥ 79 years (Supplementary Figure 5). All other estimates for age subgroups were not associated with screening or usual care, and did not reach statistical significance overall or in separate EQ domains (Supplementary Figure 1–5).

4. Discussion

To our knowledge, this is the first study from a randomised trial presenting data on quality of life associated with long-term, continuous, and population-based screening for atrial fibrillation. In 6004 AF-naïve participants with stroke risks, we found no convincing impact on quality of life in patients screened for AF using ILR, neither in the combined EQ-

Table 5
Changes in quality of life associated with screening for atrial fibrillation.

	EQ-5D-5L index change		EQ VAS change	
	Mean (sd)		*Mean (sd)*	
All participants at baseline	0.880 (±0.16)		78.4 (±16.2)	
	Mean (95 % CI)	*P value*	*Mean (95 % CI)*	*P value*
Screening effect* year one	0.008 (-0.0002 ; 0.017)	0.055	1.22 (0.43 ; 2.03)	**0.002**
Screening effect* year two	0.002 (-0.008; 0.011)	0.72	0.74 (-0.13; 1.60)	0.09
Screening effect* year three	0.009 (-0.0005; 0.018)	0.063	0.88 (-0.02; 1.79)	0.056

Sd; standard deviation, CI; Confidence interval
* Difference in change between the screening group and the control group

5D-5L index score nor in the global health EQ VAS score. Furthermore, we did not find an overall difference in quality of life in screened participants diagnosed with AF compared to screened participants without AF at year three. No difference was seen across the five domains of quality of life, except a separate reduction in pain/discomfort in the screening group, which was not robust to sensitivity analysis for missing data. In other words, screening for AF did not seem to elicit harm or benefits on quality of life. This is supported by the lack of difference between screened participants with AF and without AF. In the first year only, screening appeared to improve the EQ-5D-5L index and EQ VAS scores slightly compared with usual care. However, the sensitivity analysis removed or reduced the confidence for these signals, and there were no convincing estimates for improved quality of life in the longer term. It is fairly surprising that the systematic and continuous screening intervention did not improve reported quality of life compared to usual care. The screening group regimen in the LOOP trial included contact with study personnel, direct initial management, and thorough assessment routines. Medical management or interventions can heavily affect quality of life outcomes, even if these have no clinical effect compared to control [16,17]. This was, for example, seen in the ISCHEMIA trial, where angina-related quality of life improved in the intervention arm, even though the five-component primary endpoint showed no difference compared to the control group [18]. A markedly improved quality of life was also seen in both randomisation arms in the RELIEVE-HF trial, [19] after either implantation of an interatrial shunt to relieve heart failure or a placebo procedure, while the primary composite endpoint did not reveal a difference [19]. The ILR screening in this open-label trial may have promoted a feeling of relief or reassurance. Therefore, we may speculate this potential effect on quality of life conveyed by screening could have masked an actual harmful effect of the intervention. Increased levels of anxiety have been associated with screening itself and with AF, [10,20–22] but did not seem to differ between the randomisation groups in this study. The impact of a screening strategy without guidance, scheduled visits, and follow-up may affect health-related quality of life differently than observed in our study. Lastly, the ILR device used in the intervention was safe, with a very low number of procedure-related complications [23].

A substudy on quality of life from the DANCAVAS and VIVA screening trials for cardiovascular diseases revealed similar outcomes [11]. The authors concluded that screening had minimal effect on

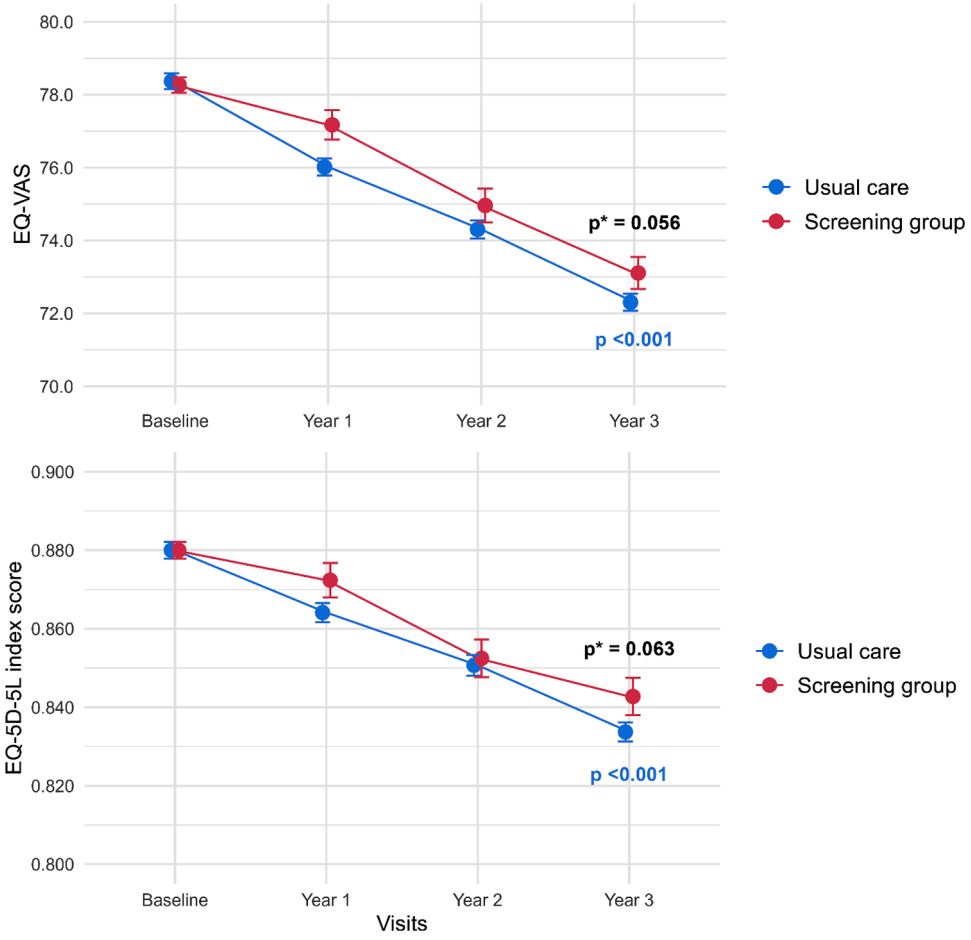

Fig. 2a. "Quality of life during screening for atrial fibrillation vs usual care".
p for change from baseline until year three, p* for difference in deline between the screening group and usual care at year three.

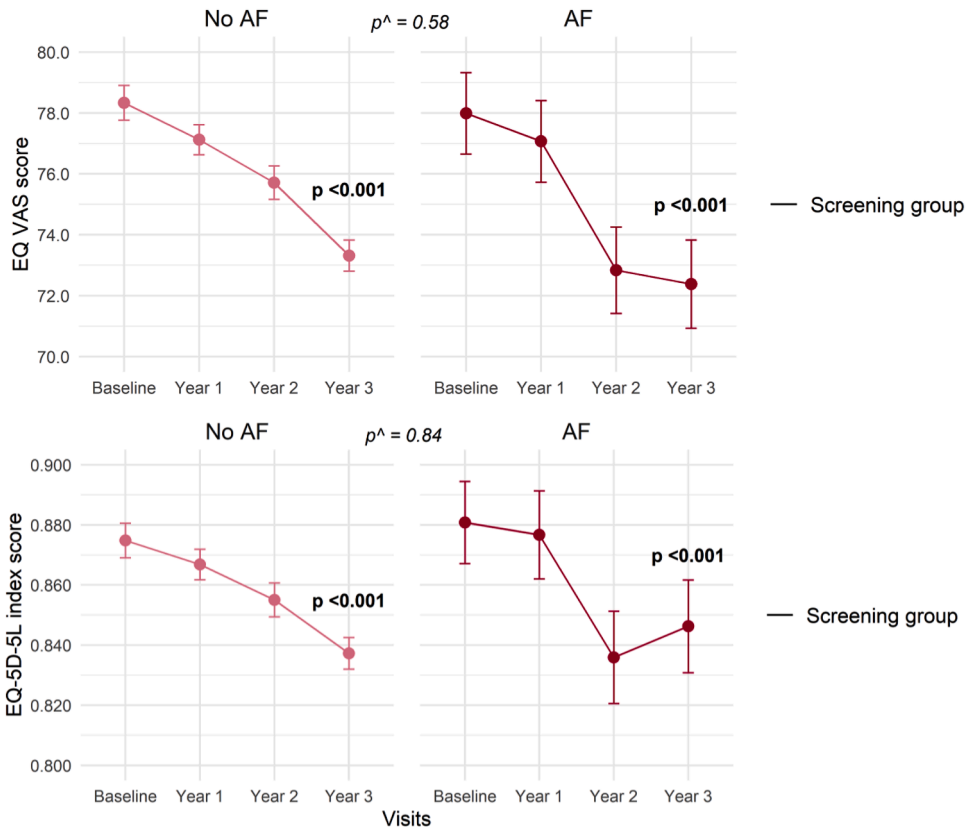

Fig. 2b. "Quality of life with or without atrial fibrillation diagnosis after three years of screening ".
p for change from baseline until year three, pˆ for difference in decline between AF and no AF in the screening group at year three. AF; Atrial fibrillation

Table 6
Sensitivity analyses: Changes in quality of life associated with screening for atrial fibrillation.

	EQ-5D-5L index change		EQ VAS change	
	Mean (sd)		*Mean (sd)*	
All particpants at baseline	0.88 (±0.16)		78.4 (±16.2)	
	Mean (95% CI)	*P value*	*Mean (95 % CI)*	*P value*
Screening effect* year one	0.008 (-0.001 ; 0.017)	0.06	1.08 (0.05; 2.12)	**0.041**
Screening effect* year two	0.002 (-0.008; 0.011)	0.73	0.59 (-0.50; 1.68)	0.29
Screening effect* year three	0.009 (-0.001; 0.018)	0.07	0.73 (-0.40; 1.86)	0.20

Sd; standard deviation, CI; Confidence interval
* Difference in change between the screening group and the control group

overall quality of life compared to controls, yet randomisation to screening resulted in initially higher EQ-5D-5L index score compared to participants randomised to no screening [11]. Furthermore, the EQ VAS score seemed to alternate more than EQ-5D-5L index score in accordance with adverse events or test results, possibly indicating the EQ VAS score to be an earlier sign of quality of life change [11]. In our study, the EQ VAS and EQ-5D-5L index scores had very similar trajectories in each group, which we believe increases the strength of the overall results since these outcomes are typically strongly correlated [24]. The quality of life estimates declined during the course of the study, which could be a natural effect of increasing age [24,25]. Still, as an older and moderately comorbid population, the LOOP participants had fairly high quality of life estimates in the study compared to other European or Asian countries [26,27]. It could be argued that a screening intervention could have a less positive impact on participants with a high quality of life compared to those with a lower quality of life, making a potential positive screening effect more difficult to detect in this population.

4.1. *Quality of life problems in life domains*

We explored quality of life changes as the occurrence of major problem. Despite using different cut-off values (*major, worsening* by one point, *worsening* by two points, or *any*), we found no overall difference between the screening group and usual care.

Our results suggested the reduction in major pain/discomfort after screening to represent a potential screening effect, yet the mechanism is unclear. The pain/discomfort domain has the inherent uncertainty of pooling two dimensions. A study reviewing this domain found responders to mostly answer according to pain, [28] which may influence the interpretation of these results. As pain is not a typical symptom associated with AF, the reduced occurrence of pain/discomfort suggested in our results could relate to a sense of relief or a screening-related focus on general health management. Even though pain/discomfort was the most frequent problem at baseline and in year three as well, we did not find the impact of pain or discomfort to transfer into the domains of usual activities, mobility, or selfcare, which may indicate less pain burden or severity. The estimate was not robust after imputating missing data, and the difference seen in pain/discomfort between the groups could be due to multiple testing.

4.2. *Quality of life in subgroups*

Overall and in the mobility domain, female participants seemed to report improved health after screening. This signal was not significant in the other domains, and did not have an overall significant test for interaction, leaving the results on sex difference quite uncertain.

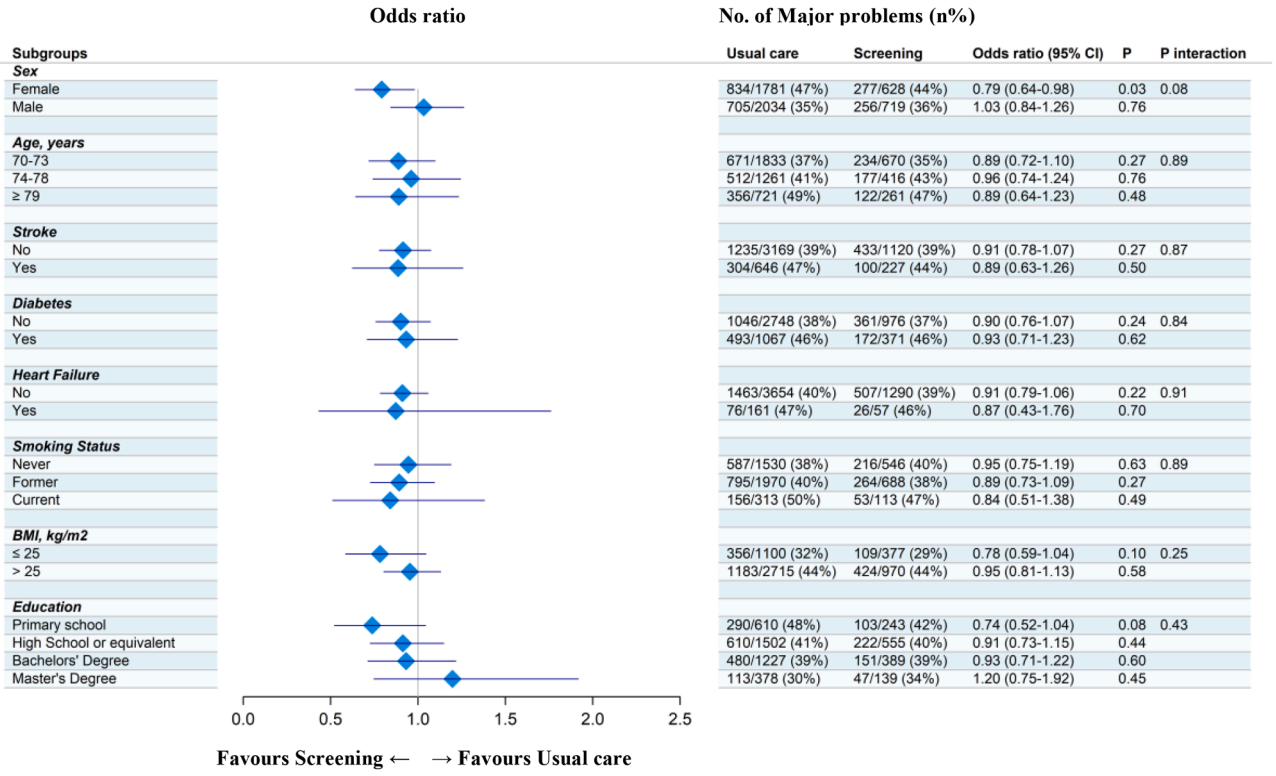

Fig. 3. Subgroups: Odds ratio of any major problem in year three.

Furthermore, these results are in contrast to cancer screening studies, where female participants responded more negatively to screening compared to men [21], and to studies on females reporting impairments in quality of life more often than men [24,27]. In AF patients, quality of life is often impaired in selected subgroups and has been reported reduced in females, with younger age, and with increased comorbidity burden [1,29]. A few other estimates across the separate domains favoured screening, which we view as a result of multiple testing, as the tests for interactions were also negative. We anticipated that patients with pre-existing diagnoses of diabetes, stroke, or heart failure might have responded in favour of screening, as these subgroups often have an increased risk of stroke [29]. Participants with the lowest quality of life at year three were more often female, had higher age, increased burden of comorbidity, lower education and higher BMI. These characteristics could also be associated with increased frailty [30,31], which was not measured formally in the LOOP trial. However, since we did not detect differences associated with screening in the subgroup analyses, we believe there were no differences associated with screening itself in the selected subgroups.

4.3. Clinical perspectives

The LOOP study aimed to prevent stroke through AF screening and the screening group had an approximately three times higher rate of AF diagnosis and anticoagulation compared to usual care, though this did not result in a significant reduction in stroke risk [6]. Screening increased the risk of major bleeding in participants on anticoagulants in both the screening group and the control group [32]. The conclusion from the main paper was that not all AF may be worth screening for, and not all screening-detected AF may warrant anticoagulation. Anticoagulation in patients with device-detected subclinical AF has later shown efficacy for stroke prevention in a meta-analysis of two recent trials, though the absolute risk of stroke was smaller than that associated with clinical AF, and the increase in major bleeding was higher than the decrease in stroke risk [5]. This may indicate that the potential adverse effects from systematic screening and treatment could tip the net benefit towards harm. In the current study, quality of life after was unaffected by screening; thus, long-term ILR screening does not seem to induce harm. On the other hand, the screening group did not benefit from screening, for example in reducing anxiety or improving mobility.

More than 30 % of at-risk populations will be diagnosed with AF if screened continuously, although the AF burden is lower when the diagnosis is established through screening [6,33–35]. This means that choice of screening strategy is highly predictive of screening yield – the more we screen, the more we detect. AF detected by intensive screening may pose less stroke risk compared to AF diagnosed by usual care, as indicated by the main results of the LOOP study. This calls for thorough consideration of potential overdiagnosis and harms, as anticoagulation-mediated bleeding, hospitalization, and other adverse effects will likely increase with screening intensity, with the potential to worsen quality of life [36]. Long-term reductions in quality of life have been reported after false-positive results in relation to mamma cancer screening [37], whereas the impact on quality of life has been largely unknown in AF population screening. Before implementing systematic screening, further studies should investigate and confirm the results on quality of life in population-based screening for AF, particularly in persons with screening-related adverse events.

4.4. Limitations

This was a substudy with prespecified primary outcomes. In the secondary analyses, however, the risk of type one errors and spurious findings is inherently increased, although most of these resulted in negative findings. Quality of life data was collected by letter in year one and year two in the control group, which could have introduced a sampling bias. Quality of life data can be complex to interpret, change over short periods, and be affected by factors not measured in the study. We included all visits in our primary analyses to handle this complexity and performed subgroup analyses to investigate whether selected subgroups had a large impact on our results. Incomplete data not attributed

to death was addressed using advanced linear mixed models, which effectively use correlations to estimate the missing data points, and sensitivity analyses based upon additional covariates and imputations. However, we cannot exclude that this affected the estimates of quality of life in especially years one and two. In addition, our subgroup analyses could be underpowered to demonstrate a difference, despite the relatively large population size. Lastly, all participants were recruited by letter invitation, which could have introduced a healthy-user selection bias in the trial population.

5. Conclusion

In this population-based trial of 6004 individuals with a high risk of AF and stroke, long-term and continuous screening for AF with anticoagulation upon detection did not decrease or improve quality of life at three years compared to no screening, despite a much higher detection of AF and initiation of treatment.

Trial registration

The LOOP study is registered at ClinicalTrials.gov, identifier: NCT02036450

Data sharing statement

The study data underlying this article cannot be shared publicly for ethical reasons, but the methodology will be shared on reasonable request to the corresponding author (SZD).

Declaration of competing interest

DWK reports to be a Medtronic Focus Group member. JHS reports research grants and speaking honoraria from Medtronic, Boston Scientific, Bristol-Myers Squibb/Pfizer, and Servier, and consulting fees from Boston Scientific and Bayer not related to this work. AB reports research grants from The Region of Zealand, The Canadian Institutes of Health Research, The Danish Heart Foundation, and Theravance, and speaker honoraria from Boehringer Ingelheim and Bristol-Myers Squibb, not related to this work. LK reports speaker honoraria from Novo Nordisk, AstraZeneca, Novartis, and Boehringer, not related to this work. SZD reports to be a part-time employee of VitalBeats and advisor to Bristol-Myers Squibb/Pfizer and Acesion Pharma and Cortrium, and a speaker for Bristol-Myers Squibb/Pfizer and Bayer and to have received travel grants from Abbott and Boston Scientific, not related to this work. Other authors have no conflicts of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.12.035.

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