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ORIGINAL ARTICLE
Arrhythmia and electrophysiology

Incident atrial fibrillation and adverse clinical outcomes during extended follow-up of participants recruited to the remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study

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Aims Atrial fibrillation (AF) is an important risk factor for stroke, which is commonly asymptomatic, particularly in older patients, and often undetected until cardiovascular events occur. Development of novel technology has helped to improve detection of AF. However, the longer-term benefit of systematic electrocardiogram (ECG) screening on cardiovascular outcomes is unclear.

Methods and results In the original REHEARSE-AF study, patients were randomized to twice-weekly portable electrocardiogram (iECG) assessment or routine care. After discontinuing the trial portable iECG assessment, electronic health record data sources provided longer-term follow-up analysis. Cox regression was used to provide unadjusted and adjusted hazard ratios (HR) [95% confidence intervals (CI)] for clinical diagnosis, events, and anticoagulant prescriptions during the follow-up period. Over the median 4.2-year follow-up, although a greater number of patients were diagnosed with AF in the original iECG group (43 vs. 31), this was not significant (HR 1.37, 95% CI 0.86–2.19). No differences were seen in the number of strokes/systemic embolisms or deaths between the two groups (HR 0.92, 95% CI 0.54–1.54; HR 1.07, 95% CI 0.66–1.73). Findings were similar when restricted to those with CHADS-VASc ≥ 4.

Conclusion A 1-year period of home-based, twice-weekly screening for AF increased diagnoses of AF for the screening period but did not lead to increased diagnoses of AF or a reduction in cardiovascular-related events or all-cause death over a median of 4.2 years, even in those at highest risk of AF. These results suggest that benefits of regular ECG screening over a 1-year period are not maintained after cessation of the screening protocol.

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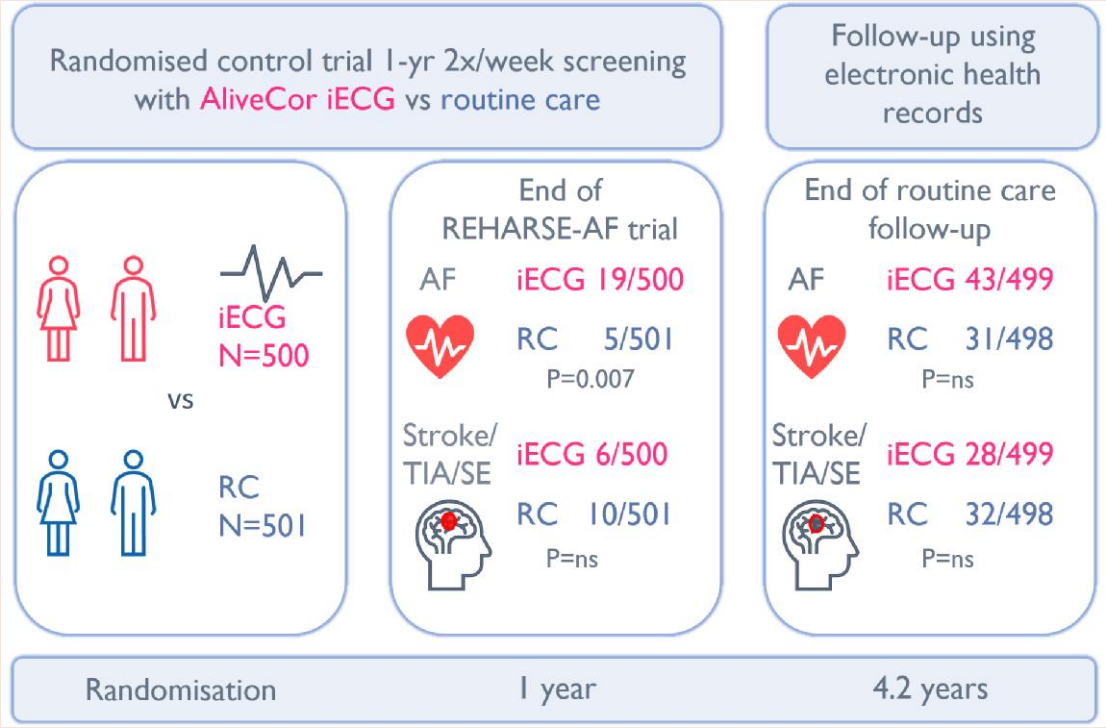
Graphical Abstract



Keywords Atrial fibrillation • Electrocardiography • Mass screening • Preventive medicine • Stroke

Lay summary

A follow-up of patients who had undergone a 1-year screening programme to detect atrial fibrillation (AF) (a heart rhythm problem) was carried out using electronic health records to see if there were differences in AF diagnoses, strokes, or deaths between those who had the screening device and those who had routine care (RC).

- Extended follow-up of the patients showed no overall increase in the diagnosis of AF in the screened population, despite a higher detection rate during the screening period.
- Numbers of strokes/systemic embolisms and deaths were similar in the screened and RC groups over the extended period of follow-up (including the year of screening).

Introduction

Atrial fibrillation (AF) is an important risk factor for stroke, which is commonly asymptomatic, particularly in older patients, and therefore often undetected until diagnosis at the time of an associated cardiovascular event.[1,2] However, identification of AF and subsequent treatment with oral anticoagulants reduce the risk of stroke and other cardiovascular events.[3,4] Development of novel devices and technology allowing easy and accurate electrocardiographic rhythm assessment has facilitated screening of patients, improving identification of those with AF. Indeed, a study (REHEARSE-AF) by our group in patients identified as being at high risk of AF demonstrated that twice-weekly electrocardiogram (ECG) screening with a WiFi-enabled iPod ECG device (iECG) identified significantly more incident AF over a 1-year period than those patients who received normal care.[5] Other studies have also shown that detection of AF can be increased using alternative screening strategies.[6,7]

However, the limited follow-up period of these studies has not allowed a fuller evaluation of the effectiveness of a 1-year screening intervention for preventing cardiovascular events over the longer term, beyond the screening period. Two recent studies, the STROKESTOP and LOOP studies, have looked at the effects of screening on the risk of stroke and other cardiovascular outcomes but with conflicting findings.[8,9]

Linking data from the REHEARSE-AF study to routinely held clinical data for the trial participants, this analysis aimed to explore potential differences in AF diagnoses, strokes, and death rates during the longer-term, routine clinical follow-up in patients who received routine care (RC) vs. those who underwent the twice-weekly iECG monitoring regime for the first year of the extended evaluation period.[5]

Methods

Transparency and openness promotion

The data used in this evaluation are openly available in the Secure Anonymised Information Linkage (SAIL) Databank at Swansea University, Swansea, UK. Due to the sensitive nature of these data, all proposals to

use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). SAIL has an established application process for all projects and users who want to access data via SAIL https://www.saildatabank.com/application-process. This project was approved by the IGRP at Swansea University (SAIL project number 0982).

Original study

The method of the original study is reported in Halcox *et al.*[5] Briefly, in 2015, 1001 patients (53.3% female) over 65 years (mean age 72.6 ± 5.4 years), with a CHADS-VASc score ≥ 2, without a known diagnosis of AF, known contraindication to anticoagulation or permanent cardiac pacing implantation, were recruited and allocated to either RC ($n = 501$) or the intervention arm (iECG, $n = 500$). Participants in the intervention arm undertook twice-weekly recording of a 30 s single-lead iECG trace for 12 months (AliveCor Kardia Mobile system, AliveCor Inc., Mountain View, CA, USA) attached to an iPod (Apple Inc., Cupertino, CA, USA), which was transmitted via an encrypted process to a secure server. Additional traces could be submitted if participants were symptomatic. The iECG traces were analysed by an automated analysis software algorithm [AliveCor version 2.2.0 (build 21)] and transmitted over a secure server for analysis by a physiologist-led electrocardiographic reading service (Technomed Ltd UK). Abnormal and 10% of normal ECGs were overread by a cardiologist. Clinical review and appropriate care were arranged for those with clinically significant arrhythmia. Patients in the RC arm were followed up as normal by their general practitioner (GP). Ethics approval was obtained from the Wales Research Ethics Committee 6 (REC reference 14/WA/1227), and the clinical trial was registered at URL: https://www.isrctn.com (unique identifier: ISRCTN10709813).

Table 1 Baseline characteristics of the study participants with data linkage

	iECG ($n = 499$)	Routine care ($n = 498$)
Age (SD) years	72.60 (5.5)	72.55 (5.4)
Female, *n* (%)	260 (52.1)	273 (54.8)
Heart failure, *n* (%)	5 (1.0)	9 (1.8)
Hypertension, *n* (%)	267 (53.7)	271 (55.0)
Diabetes mellitus, *n* (%)	128 (25.7)	140 (28.2)
Stroke, *n* (%)	35 (7.1)	28 (5.7)
Vascular disease, *n* (%)	71 (14.4)	78 (15.8)
CHADS-VASc score (SD)	2.97 (1.0)	3.01 (1.0)
Mean follow-up period (SD)	1534 (214)	1530 (222)

Vascular disease, ischaemic heart disease, or peripheral vascular disease.

Follow-up

The original study dataset was imported into the SAIL Databank, a world-leading privacy-protecting trusted research environment (TRE) that holds anonymized individual-level, population-scale data, through which access to and linkage of the data were enabled.[10,11] The randomization date into the trial was taken as time zero, and participants were followed up until 31 December 2019. Both the primary care data [Welsh Longitudinal General Practice (WLGP)] and population-scale national secondary care data [Patient Episode Database for Wales (PEDW)] were used to identify any diagnosis of AF, stroke (haemorrhagic or ischaemic), transient ischaemic attack (TIA), systemic embolism (SE), acute coronary syndrome, deep vein thrombosis, pulmonary embolism, and hospitalization for bleeds.[12,13] Prescription of anticoagulation medication was also identified from WLGP data. Death was identified from the Office for National Statistics (ONS) mortality data [Annual District Death Extract (ADDE)].[14]

Statistical analysis

The primary outcome for this study was AF diagnosis, and secondary outcome measures were stroke/TIA/SE (SSE) and death. Hospital admissions for acute coronary syndrome, venous thromboembolism, and bleeding were also assessed. Cox regression was used to provide both unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for clinical events and prescription of anticoagulation therapy during the follow-up period. Variables included in the adjusted model were age ≥ 75, sex, hypertension, diabetes, previous stroke, peripheral artery disease, and CHADS-VASc score ≥ 4. Kaplan–Meier plots were used to estimate event rates for AF diagnosis, SSE, and death between the groups. The CHADS-VASc score had been calculated for all patients in the main study, and the analysis was repeated in those with CHADS-VASc ≥ 4; as in the original analysis, this variable was a significant predictor of AF. SPSS (version 28, IBM Corp., Armonk, NY, USA) and R (version 4.1.3) were used for analysis.

Results

Successful linkage between study data and electronic health record (EHR) data sources within the SAIL Databank was achieved for 99.6% (997 of the original 1001 participants) in the study. The median period of follow-up was 4.2 years (1547 days, IQR 159), including the year of screening. *Table 1* shows the baseline characteristics of those participants included in this analysis by treatment group. There were no differences in the age and sex or medical history of the two groups with linked data, as observed in the original trial.

Over the full period of follow-up, although detection of AF was 38.7% greater in the iECG group compared with RC, this difference was not statistically significant (*Table 2*). There was no difference in the number of deaths, strokes, or TIA between the two groups.

Table 2 Number of clinical events and anticoagulation therapy prescription

Outcome *n* (%)	iECG	Routine care	Unadjusted	Adjusted
Death	35 (7.0)	33 (6.6)	1.05 (0.65–1.69)	1.07 (0.66–1.73)
Atrial fibrillation	43 (8.6)	31 (6.2)	1.41 (0.89–2.24)	1.37 (0.86–2.19)
Stroke/TIA/SE	28 (5.6)	32 (6.4)	0.87 (0.52–1.44)	0.92 (0.54–1.54)
Ischaemic stroke	23 (4.6)	27 (5.4)	0.84 (0.48–1.47)	0.90 (0.51–1.60)
Transient ischaemic attack	13 (2.6)	16 (3.2)	0.81 (0.39–1.68)	0.86 (0.41–1.82)
Acute coronary syndrome	10 (2.0)	21 (4.2)	0.47 (0.22–1.00)	0.45 (0.21–0.97)
Bleed	34 (6.8)	38 (7.6)	0.88 (0.56–1.40)	0.85 (0.53–1.35)
Anticoagulant therapy	50 (10.0)	37 (7.4)	1.38 (0.90–2.11)	1.28 (0.83–1.96)

Unadjusted and adjusted hazard ratios with routine care as the reference.
iECG, iPod ECG; SE, systemic embolism; TIA, transient ischaemic attack.

Although more participants in the iECG group were prescribed anticoagulant therapy, this difference did not reach statistical significance (*Table 2*). Of the 74 patients who developed AF, 66 were treated with anticoagulants (89%), and 8 were not (11%). The SAIL data governance protocol does not permit us to present absolute numbers due to the small number of patients (<5) not being prescribed anticoagulants in one or both groups. However, the proportion of participants who developed AF and were treated with anticoagulants was similar in the two groups ($P = 0.71$). Twenty-one participants received anticoagulant treatment for another indication.

Participants in the iECG care group were less likely to have an acute coronary syndrome event during the follow-up period than in the RC group (10 vs. 21, $P = 0.044$; *Table 2*).

There were no differences between the groups with regard to time to diagnosis of AF, stroke and SE, or death (Kaplan–Meier plots; *Figure 1*).

A subgroup analysis was undertaken in those with a CHADS-VASc score ≥ 4 at baseline, as this was an independent predictor for increased detection of AF with iECG screening. Similar numbers of diagnoses of AF, SSE, and deaths were seen in both groups, with fewer acute coronary syndromes occurring in the iECG group (*Table 3*), as observed in the overall study.

Discussion

Although a 1-year period of iECG monitoring with the AliveCor Kardia Mobile device increased the detection of AF compared with RC during the screening period, there was no overall reduction in the number of strokes, TIA, systemic embolisms, or deaths over a mean follow-up period of 4.2 years from enrolment into the study. In addition, whilst the number of patients diagnosed with AF over the entire follow-up period, including the year of screening, was greater in the screening group, the difference between the groups no longer remained statistically significant over the longer-term follow-up. Hence, the initial advantage in detection of AF was gradually eroded beyond the screening period. Interestingly, patients in the iECG group were less likely to have acute coronary syndrome during follow-up. These findings were replicated when the analyses were restricted to only those with a higher likelihood of an AF diagnosis in the original screening study, who would also be expected to be at greater risk of events (CHADS-VASc score ≥ 4).

The original REHEARSE-AF study showed increased detection of AF (19 iECG vs. 5 RC, $P = 0.007$) and a trend towards fewer associated SSE (6 iECG vs. 10 RC, $P = 0.34$) events in the iECG group during 1 year of monitoring, suggesting that this might be a promising approach to reducing the risk of major complications of AF.[5] These early trends seen during the first year did not translate into a measurable reduction of hard clinical events in a cohort of this size. We note that the original study was not powered to evaluate clinical outcomes. The power of this follow-up is considerably improved with the four-fold increase in the follow-up time and hence the expected event count, but there is still considerable uncertainty in the estimates for clinical event differences, as reflected in the 95% CI for the HR. Thus we cannot exclude small effects on clinical events. We note that the HR point estimate for stroke is centred very close to 1 but with a 95% CI from 0.54 to 1.54. However, as the regular iECG screening approach was discontinued after 1 year, the benefits of screening are only likely to have been realized by those patients in whom AF was diagnosed during the screening period. As such, this analysis cannot determine whether extending the period of screening beyond 1 year would result in further differential increases in AF diagnoses and fewer clinical events in the iECG compared with the RC group. Nonetheless, these findings suggest that the benefit of this screening approach may not be as marked as initially hoped for, if discontinued after 1 year. However, whether the initial promise of this approach to increase AF detection and reduce hard clinical events could be realized by an ongoing screening strategy beyond 1 year would require further study in larger and/or longer clinical trials. Ongoing screening would also agree with the WHO principles of early disease detection, specifically that case finding should be a continuing process and not a 'once and for all project'.[15] However, the clinical and cost-effectiveness of such a strategy would need to be formally evaluated before being recommended.

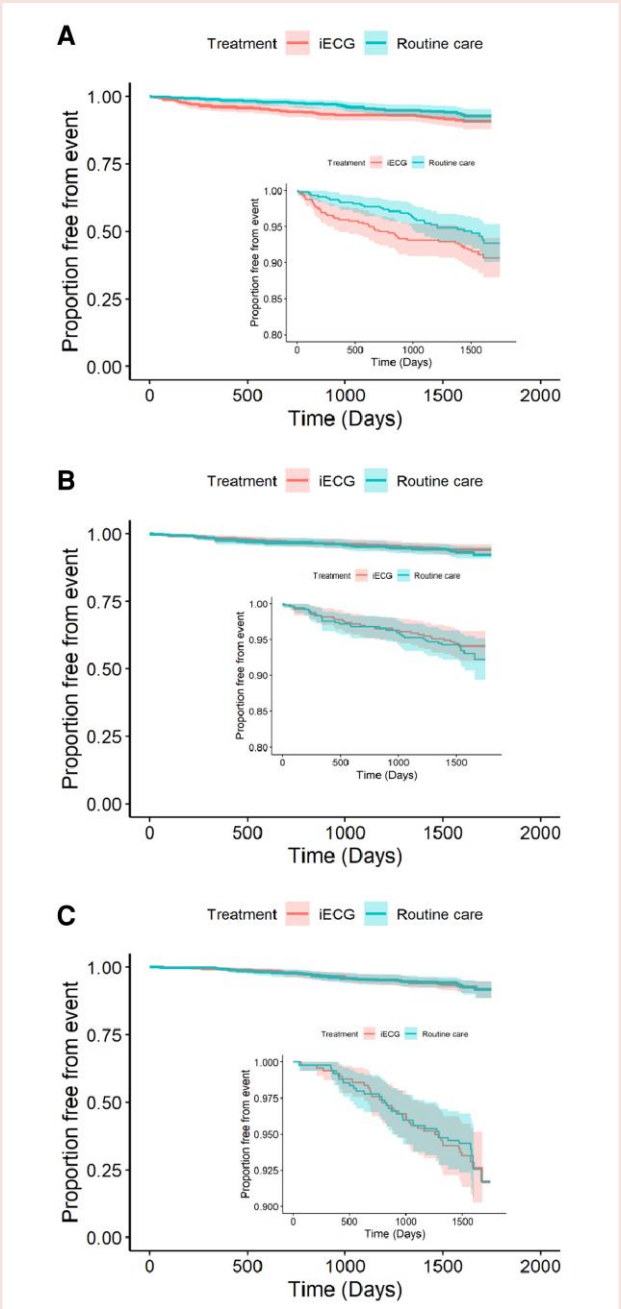


Figure 1 Kaplan–Meier plots describing time-to-event curves for diagnosis of atrial fibrillation (*A*), stroke/transient ischaemic attack/systemic embolism (*B*), and death (*C*). Shaded areas represent 95% confidence regions. Log-rank $P = 0.28$, 0.83, and 0.87 (Mantel–Cox), respectively. Day 0 on the *x*-axis is the point of randomization in the study.

Table 3 Number of clinical events and anticoagulation therapy prescription during the follow-up period in participants with a CHADS-VASc score ≥ 4

Outcome *n* (%)	iECG (*n* = 135)	Routine care (*n* = 136)	Unadjusted	Adjusted
Death	14 (10.4)	13 (9.6)	1.10 (0.52–2.33)	1.16 (0.53–2.53)
Atrial fibrillation	15 (11.1)	10 (7.4)	1.57 (0.71–3.50)	1.46 (0.65–3.27)
Stroke/TIA/SE	15 (11.1)	11 (8.1)	1.42 (0.65–3.10)	1.37 (0.61–3.09)
Ischaemic stroke	13 (9.6)	10 (7.4)	1.35 (0.59–3.07)	1.28 (0.54–3.04)
Transient ischaemic attack	6 (4.4)	<5[a]	2.08 (0.52–8.33)	2.15 (0.53–8.67)
Acute coronary syndrome	<5[a]	10 (7.4)	0.30 (0.08–1.10)	0.23 (0.06–0.83)
Bleed	13 (9.6)	11 (8.1)	1.21 (0.54–2.69)	1.10 (0.49–2.47)
Anticoagulant therapy	18 (13.3)	11 (8.1)	1.75 (0.82–3.70)	1.64 (0.77–3.48)

Unadjusted and adjusted hazard ratios with routine care as the reference.
[a]Governance restrictions within SAIL prohibit the reporting of numbers <5 due to privacy protection and disclosure control.

Two other randomized controlled trials have evaluated the impact of screening for AF on clinical outcomes, with differing results. In the LOOP study, a similar number of strokes and systemic embolisms were seen in patients aged 70–90 years without known AF but one risk factor for stroke undergoing monitoring with an implantable loop recorder ($n = 1420$) compared with controls ($n = 4503$) over a median follow-up period of 5.4 years.[9] However, in the recent STROKESTOP study, which followed 7165 patients who used a single-lead handheld device twice daily for 2 weeks and 14 381 controls for a median of 6.9 years, a reduction in the composite endpoint of any stroke/bleed/death ($P = 0.045$) was observed in the screening group but with no difference in the incidence of ischaemic stroke.[8] Notably, the difference in the composite endpoint emerged between the groups during the later period of follow-up (5–6 years), which was greater than in the current study. Furthermore, the patients in the STROKESTOP study were on average older (all aged 75–76 years on recruitment) than those in the REHEARSE-AF study [mean (SD) 72.6 (55) years] but also included those who already had a diagnosis of AF.

The VITAL-AF study evaluated 30 715 patients aged 65 years and over who attended primary care clinics over a period of 12 months.[16] Practices were randomized to offer iECG assessment with the AliveCor device during patient appointments vs. usual care. Although there were a similar number of diagnoses of AF and major adverse clinical outcomes in both study groups, this was effectively a study of opportunistic single-lead ECG testing in those attending primary care for usual reasons, rather than a trial of systematic screening for AF.

Considered together with the inconsistent results from these outcome studies, the evidence from our study suggests that the ultimate clinical impact of systematic screening for AF using single-lead ECG in at-risk populations remains uncertain and may not be as substantial as initially thought, at least with screening protocols of limited duration. However, we note that a number of larger outcome studies using different approaches in different target populations are ongoing, the results of which are eagerly awaited.[17,18]

Although these studies considered together do not currently support a role for systematic AF screening at present, they do not diminish the value of point-of-care single-lead ECG assessment as a clinical tool, especially in settings where a 12-lead ECG is not readily and/or rapidly available such as primary and community care settings or where they may be used as an alternative to ambulatory monitoring in appropriately selected patients with intermittent symptoms. Indeed, recent UK-based National Institute for Health and Care Excellence (NICE) guidelines have recently recommended the AliveCor for use in patients with suspected paroxysmal AF presenting with symptoms such as palpitations and who have been referred for ambulatory ECG monitoring by their clinician.[19]

The finding of fewer acute coronary syndromes in the iECG group was somewhat unexpected. It is possible that the nature of the monitoring process in this group led to increased interaction with their clinicians and better general preventive advice and treatment. However, a formal evaluation of these issues is outside the scope of this study and can only be speculative. Alternatively, it may also be due to a Type 1 error as this was not a primary outcome, given the relatively small number of events.

Limitations

The patients were predominantly of White European ethnicity and from a single UK regional health authority, which may limit the generalizability of the findings to other populations. Although the follow-up period is >4 years and a longer period may be required to fully evaluate the benefit of this screening approach and tease out potential clinical effects further, the fact that the gap in the proportion of patients with stroke or SE observed during the initial year of study (albeit non-significant) narrowed over the longer-term period of follow-up suggests that this would be unlikely to be the case.

The current guidelines do not discriminate between screen-detected vs. clinically detected AF regarding the recommended approach to management, including the antithrombotic strategy. However, there are fewer data available with regard to the thrombo-embolic risk and net clinical benefit of anticoagulation in screen-detected AF. Nonetheless, several studies have shown a greater risk of adverse outcomes in asymptomatic/screen-detected AF patients at increased cardiovascular disease risk.[20–22] Studies of patients with implanted devices have shown an increased risk of adverse events in patients with atrial high-rate episodes consistent with AF/atrial tachyarrhythmia, but these patients are not necessarily representative of the general population. Further randomized controlled trials are needed to determine the impact on outcome measures.

Conclusions

In conclusion, 1-year of home-based, twice-weekly screening for AF did not lead to a reduction in cardiovascular-related events or all-cause death after a median 4.2-year follow-up compared with patients who had RC, even in those at highest risk of AF. Further research is required to identify a patient population and an ECG testing strategy that may

obtain improved outcomes from a targeted screening programme for AF.

Lead author biography

Elizabeth A. Ellins is a senior research officer based at Swansea University with an interest in cardiovascular disease prevention. She started her career as a vascular technologist specializing in non-invasive measures to assess vascular structure and function at the Institute of Child Health, University College London. She continued this at Cardiff University, where she obtained her PhD. Now at Swansea University, her interests have diversified into data science, using electronic health records to investigate cardiovascular disease prevention with a particular interest in mental and women's health.

Author contributions

J.P.H. and E.A.E. contributed to the conception of the work. E.A.E., D.E.H., M.B.G., and J.P.H. contributed to the analysis and interpretation of data for the work. E.A.E. drafted the manuscript. K.W., M.H., M.G., J.P.B., C.J.P., M.B.G., and J.P.H. were responsible for delivering the REHEARSE-AF clinical trial. K.W., D.E.H., A.A., M.H., M.G., J.P.B., C.J.P., M.B.G., and J.P.H. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

Data availability

The data used in this evaluation are openly available in the Secure Anonymised Information Linkage (SAIL) Databank at Swansea University, Swansea, UK.

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This study makes use of anonymized data held in the SAIL Databank. We would like to acknowledge all the data providers who make anonymized data available for research.

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Conflict of interest: The original study was funded predominantly by the Welsh Government but in part by a project grant from AliveCor. The study data were analysed and reported independently without involvement of the company. J.P.H. had full access to all the study data and takes responsibility for its integrity and data analysis. None of the authors have received personal financial support for speaking or consulting on behalf of AliveCor Inc. There are no other disclosures to report.

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