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### **Paper:**

Halcox, J., Wareham, K., Cardew, A., Gilmore, M., Barry, J., Phillips, C. & Gravenor, M. (2017). Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. *Circulation*, 136, CIRCULATIONAHA.117.030583

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1 Assessment of **REmote HEArt Rhythm Sampling** using the AliveCor heart monitor to  
2 scrEen for **Atrial Fibrillation**: The REHEARSE-AF Study

3

4 Short title. The REHEARSE-AF Study

5

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22

23 Word count:

1 **ABSTRACT**

2

3 **Background:**

4 Asymptomatic Atrial fibrillation (AF) is increasingly common in the ageing population  
5 and implicated in many ischaemic strokes. Earlier identification of AF with appropriate  
6 anticoagulation may decrease stroke morbidity and mortality.

7

8 **Methods:**

9 We conducted a randomized controlled trial (DOI 10.1186/ISRCTN10709813) of AF  
10 screening using an AliveCor Kardia monitor attached to a Wifi enabled iPod to obtain  
11 electrocardiograms (iECG) in ambulatory patients. Patients  $\geq 65$ y with CHADS-VASc  $\geq 2$   
12 free from AF were randomized to iECG arm or routine care (RC). iECG participants  
13 acquired iECGs twice-weekly over 12-months (+ additional iECGs if symptomatic) onto  
14 a secure study server with over-read by an automated AF detection algorithm and also  
15 by cardiac physiologist +/- consultant cardiologist. Time to diagnosis of AF was the  
16 primary outcome measure. The overall cost of the devices, ECG interpretation and  
17 patient management was captured and utilized to generate the cost per AF diagnosis in  
18 iECG patients. Clinical events and patient attitudes/experience were also evaluated.

19

20 **Results:**

21 We studied 1001 patients (500 iECG, 501 RC) aged 72.6+/-5.4y, 534 female. Mean  
22 CHADS-VASc score was 3.0 (heart failure = 1.4%; hypertension = 54%; diabetes mellitus  
23 = 30%; prior stroke/TIA = 6.5%; arterial disease = 15.9%. All CHADS-VASc risk factors  
24 were evenly distributed between groups).

25

1 Nineteen patients in the iECG group were diagnosed with AF over the 12 month study  
2 period vs 5 in the RC arm (Hazard Ratio 3.9, 95%CI = 1.4-10.4, p = 0.007) at a cost per  
3 AF diagnosis of \$10,780 (£8,255). There were a similar number of stroke/TIA/systemic  
4 embolic events (6 vs 10 iECG vs RC HR=0.61, 95%CI = 0.22-1.69, p=0.34)  
5 The majority of iECG patients were satisfied with the device, finding it easy to use,  
6 without restricting activities or causing anxiety.

7

8 **Conclusions:**

9 Screening using twice-weekly single lead iECG with remote interpretation in  
10 ambulatory patients ≥65y at increased risk of stroke is significantly more likely to  
11 identify incident AF than RC over a 12-month period. This approach is also highly  
12 acceptable to this group of patients, supporting further evaluation in an appropriately-  
13 powered, event-driven clinical trial.

14

15 **Clinical Trial Registration:**

16 ISRCTN10709813 DOI 10.1186/ISRCTN10709813

17

18 <https://www.isrctn.com/ISRCTN10709813?q=Assessment%20of%20REmote%20HEArt%20Rhythm%20Sampling%20using%20the%20AliveCor%20heart%20monitor%20to%20OscrEen%20for%20Atrial%20Fibrillation&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search>

22

1 **Clinical Perspective**

2

3 **What is new?**

4 • This is the first prospective randomized trial evaluating the ability of remote ECG  
5 acquisition and transmission using a handheld device with remote interpretation  
6 to screen for atrial fibrillation (AF) in at risk people over 65y over an extended  
7 period of time (1y).

8 • This approach is at least 3 times more likely to identify incident AF than routine  
9 care at a cost of just over \$10,000 per case identified and is a highly acceptable  
10 approach in this group of patients. A CHADS-VASc score of  $\geq 4$  was the strongest  
11 predictor of incident AF.

12

13 **What are the clinical implications?**

14 • Our findings suggest that this approach could be considered for AF screening in  
15 routine practice, particularly in the highest risk patients.

16 • Although strokes and TIAs were numerically fewer in monitored patients, the  
17 study was not statistically powered to evaluate hard clinical outcomes and this  
18 difference was not statistically significant.

19 • These results support consideration of evaluation in an appropriately-powered,  
20 event-driven randomised trial to confirm clinical and cost-effectiveness of such  
21 an approach to stroke prevention in AF.

22

## 1 INTRODUCTION

2

3 Atrial fibrillation (AF) is a common cardiac arrhythmia, affecting an estimated 33.5  
4 million individuals worldwide.<sup>1</sup> AF is an important risk factor for stroke, being  
5 implicated in up to 1 in 3 cases<sup>2-4</sup> and often not diagnosed beforehand.<sup>5</sup> AF-related  
6 strokes commonly result in greater disability than ischemic stroke secondary to arterial  
7 disease.<sup>6</sup>

8

9 The annual stroke risk conferred by AF increases with age and other common risk  
10 factors and can be estimated using the CHADS-VASc score in those without rheumatic  
11 mitral valve disease or metallic valvular prosthesis.<sup>7</sup> Stroke risk can be reduced by  
12 around two thirds by the use of oral anticoagulant (OAC) therapy (including  
13 nonvitamin-K antagonists (N)OACs).<sup>8,9</sup>

14

15 Presentation with AF may be atypical or asymptomatic, especially in older subjects.<sup>10</sup>  
16 Data from a range of sources (including the retrospective MOST study and the TRENDS  
17 study), have shown that asymptomatic AF may potentially pose a greater  
18 thromboembolic risk than where symptoms are typical.<sup>10-14</sup> AF may also occur on an  
19 intermittent basis (“paroxysmal” [PAF]), with an increased stroke risk<sup>15, 16</sup> and identical  
20 recommendations for antithrombotic management as permanent AF.

21

22 AF incidence varies according to the population characteristics and diagnostic  
23 strategy.<sup>17</sup> Single-timepoint ECG recording in a general population  $\geq 65$  years of age  
24 identified AF in 1.4%.<sup>18</sup> Furthermore, twice-daily intermittent single lead ECG recording  
25 over two weeks using a handheld device identified AF in 3.0% of 75-76 year olds,

1 including 7.4% of those screened who had  $\geq 1$  additional stroke risk factor.<sup>19, 20</sup> A recent  
2 expert consensus paper has confirmed that AF identified at screening is not benign and  
3 justifies consideration of anticoagulation in those with stroke risk factors.<sup>21</sup> Whilst  
4 validated handheld electrocardiogram (ECG) recording devices are already considered  
5 appropriate technologies for AF screening, expert groups recognize that large  
6 prospective trials are required to strengthen the evidence base and refine population  
7 screening strategies.<sup>21</sup>

8  
9 We therefore undertook a 1-year randomized controlled trial of twice weekly  
10 monitoring with the AliveCor Kardia device (a smartphone/tablet-based single lead ECG  
11 capture system) versus routine clinical care in patients over the age of 65 with  $\geq 1$   
12 additional stroke risk factor.<sup>22</sup> The Primary outcome was incidence and time to  
13 diagnosis of AF.

## 15 **METHODS** (*Full methods: Supplement 1*)

### 16 **Study Population**

17 Individuals over 65y with a CHADS-VASc score  $\geq 2$  without a known diagnosis of AF,  
18 currently in receipt of OAC therapy, a known contraindication to anticoagulation or  
19 permanent cardiac pacing implant were recruited. Participants were required to have  
20 access to the internet via Wifi and be able to operate the AliveCor Kardia system  
21 (AliveCor inc. Mountain View, CA) attached to an iPod (Apple inc. Cupertino CA) after  
22 simple instruction. Eligibility was confirmed by a brief history, physical examination  
23 and single lead ECG recorded with the AliveCor device (iECG). Written consent was  
24 obtained and eligible participants were randomised (1:1) to an “intervention” (iECG)

1 group or routine care (RC) group. Ethical approval was obtained from the Wales  
2 Research Ethics Committee 6 (REC Reference 14/WA/1227).

3

4 Participants in the “intervention” iECG arm were instructed to undertake twice weekly  
5 recording and transmission of a 30 second single lead iECG trace to a secure server  
6 (Monday and Wednesday recommended, plus additional submissions if symptomatic),  
7 over a 12 month period. iECG traces were analyzed by an automated analysis software  
8 algorithm (AliveCor version 2.2.0 [build 21]) and also sent for offline analysis by a  
9 physiologist-led ECG reading service (Technomed Ltd UK). Abnormal ECGs were over  
10 read by a cardiologist with clinical review and appropriate care arranged for those with  
11 AF or other clinically significant arrhythmia. Patients in the RC arm were followed up as  
12 normal by their general practitioner. All patients were contacted by a member of the  
13 study team at 12, 32 and 52 weeks to assess progress. Clinical events were followed up  
14 and confirmed by clinical chart review.

15

### 16 **Patients with Identified AF**

17 AF was defined as a 30-second iECG recording with irregular rhythm without p waves.<sup>23</sup>  
18 All new AF diagnoses were confirmed and reviewed by a senior study cardiologist who  
19 made arrangements for OAC initiation and clinical management according to current UK  
20 (NICE) guidance.<sup>24</sup> RC participants with AF were diagnosed and managed by local  
21 clinicians, with all AF diagnoses validated by a study cardiologist.

22

### 23 **Clinical Event Monitoring**

24 Adverse events (AEs) were reported either at the time of event or identified by  
25 telephone at 12, 32 and 52 weeks, with confirmation from source clinical records.



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## **Participant Experience Survey**

All study participants were invited to participate in a survey at the end of the study. They were asked if they were more anxious about and more aware of heart rhythm problems, whether they were more likely to visit their doctor or if they would prefer to switch study group (Responses reported via 10-point visual analog scale). iECG patients were also asked about ease of use, restriction of activities, anxiety, concern regarding data security and their general satisfaction with the device (Responses reported via 5-point Likert scale).

## **Health Economic Evaluation**

The costs associated with screening for AF using AliveCor device were estimated from the perspective of the UK NHS and personal social services,<sup>25</sup> utilising data from study activity and relevant costs.<sup>26-28</sup>

## **Statistical Methods**

The study sample size of 500 participants per study arm was estimated to provide 92% power to detect a significant difference ( $\alpha = 5\%$ ) in the time to AF diagnosis between groups (PS: Power and Sample Size Calculation version 3.1.2, 2014).<sup>29</sup> Baseline characteristics were compared using either a Chi-square test (for groups), Fisher's Exact tests, or t-test. Compliance with ECG submission was evaluated using one-way ANOVA. The primary outcome of time to AF diagnosis and relationships between baseline characteristics and AF outcome were evaluated using Cox regression. Major adverse outcomes were also compared between groups using Cox regression. Comparison of the distribution of questionnaire responses was made using the

1 Wilcoxon rank-sum test. All analyses were performed using SPSS version 22.0 (IBM  
2 Corp. Released 2013. IBM SPSS Statistics for Macintosh, Armonk, NY: IBM Corp).

### 3 **RESULTS**

#### 4 **Participants**

5 We invited 5846 individuals to participate (5726 identified via GP records, 120 in  
6 person during attendance at clinical research facility for other study-related visit). Of  
7 these, 3305 did not reply and 1269 declined participation. The 1272 volunteers were  
8 reviewed further by telephone/verbal screening, of whom 240 did not meet criteria for  
9 inclusion (24 with AF not identified on initial notes review, 22 taking warfarin, 4 with  
10 permanent pacemaker 127 with no internet access and 63 miscellaneous) and were not  
11 invited to attend for further screening. A further 28 of the 1032 who attended for a  
12 screening visit were excluded, 18 due to a new AF diagnosis on screening iECG ; 10 for  
13 other reasons (including inability to obtain interpretable iECG traces or to use the  
14 device properly [N=5], lack of access to the internet [N=2] or previously unidentified  
15 exclusion criteria [N=3]).

16

17 We randomized 1004 participants, of whom 3 were excluded immediately after  
18 enrolment for protocol violations: one who was noted to have been in AF on their  
19 baseline iECG trace (missed at the time of screening) one with an uninterpretable iECG  
20 at baseline and one who was found to have had prior hemorrhagic stroke on further  
21 review of their medical notes (Figure 1).

22

23 Age, sex and clinical characteristics of study participants were similar in iECG and RC  
24 groups (Table 1). All risk factors were well represented except for heart failure (N=14).

1 Baseline medication prescription was similar in both study groups (Supplement 2  
2 Table). All randomized participants were in sinus rhythm at baseline.

3

4 We were able to access the NHS records of all patients to establish mortality and  
5 cardiovascular admissions during the study period. Three participants in the iECG arm  
6 withdrew (1 after completing 12 week and 2 after 12 and 32 week follow-up calls) and  
7 2 were lost to follow up (1 after participation in 12 week and 1 after 12 and 32 week  
8 follow-up). All other patients completing the study participated fully in all telephone  
9 interviews at 12, 32 and 52 week except for 1 follow-up call missed at 32 weeks by an  
10 iECG participant. All practices responded to our requests regarding whether or not AF  
11 had been diagnosed in their respective patients

12

### 13 **iECG recording and transmission**

14 The participants in the iECG arm recorded 60,440 ECGs over the 12-month follow-up  
15 period. 74% of participants completed the trial without missing a single week of ECG  
16 submission. Recommended twice-weekly ECGs were submitted successfully on average  
17 by the iECG participants in 39 of the 52 weeks and at least one weekly ECG was  
18 submitted in 48 out of the 52 weeks of the trial. Approximately 4 out of 5 of participants  
19 submitted at least 1 weekly iECG during  $\geq 90\%$  and at least 2 iECGs during  $\geq 75\%$  of the  
20 study weeks (Figure 2). Increasing participant age did not affect compliance; mean  
21 number of study weeks with iECG transmitted on 2 (or more) separate days was similar  
22 in those aged 65-75y, 75-79y and 80y+ ( 77%, 73% and 74% respectively,  $p = 0.143$ ).  
23 Of the 76% of iECGs that were reported normal by the automated algorithm, none were  
24 finally confirmed to be AF; only 6 iECGs of the 21% reported as undetermined were  
25 finally confirmed to be AF; only 5% of the approximately 1% iECGs reported as AF by

1 the device were finally confirmed to be in AF and 2.2% of iECGs were reported as  
2 unreadable.

3

#### 4 **Newly Diagnosed AF**

5 Nineteen patients in the iECG group were diagnosed with AF during the 12-month study  
6 period vs 5 in the RC arm (Hazard Ratio 3.9, 95%CI = 1.4-10.4, p = 0.007)(Figure 3). Ten  
7 iECG patients had a ventricular rate >100/min at the time of diagnosis and the other 9  
8 between 60-100/min. There were no significant differences in compliance between  
9 those diagnosed with AF (iECG group n = 19) and those not diagnosed with AF (mean  
10 study weeks with iECG submitted on 2 separate days in those diagnosed vs not  
11 diagnosed with AF=69% vs 76% respectively, one way ANOVA p = 0.11).

12 The iECG patients diagnosed with AF had CHADS-VASc scores of 2(N=3), 3(N=5), 4(N=7,  
13 5(N=2) and 6(N=1); RC AF patients had CHADS-VASc scores of 2 (N=1), 3(N=2) and  
14 4(N=2). Twelve (63%) of the iECG patients diagnosed with AF had paroxysmal AF at the  
15 time of diagnosis and 7 (37%) were in persistent AF, compared with 0 (0%) and 5  
16 (100%) respectively in the RC arm.

17

18 Eight (42%) of the iECG patients were asymptomatic at the time of diagnosis, with only  
19 4 (21%) experiencing palpitations and 7 (37%) aware of other symptoms. In the RC  
20 arm, two (40%) were diagnosed with AF during palpitations and the other 3 (60%)  
21 during other symptoms.

22

23 Trends for the relationship between baseline variables and development of AF were as  
24 expected, although only age (>75), CHADS-VASc (≥4) and arterial disease were  
25 statistically significantly associated with an increased likelihood AF diagnosis (Table 2).

1 Including all variables in a regression model (excluding HF which was rare) only  
2 CHADS-VASc  $\geq 4$  remained a significant predictor of AF (adjusted hazard ratio=4.0, 95%  
3 CI 1.1 to 15.2,  $p = 0.04$ ). Similar findings were noted when only significant variables  
4 were included in a single model (less susceptible to over-fitting given the relatively  
5 small event rate). The hazard ratio, and significance, for the difference between  
6 treatment groups also remained unchanged in a model adjusting for baseline variables  
7 (in any combination). For example, adjusting for CHADS-VASc  $\geq 4$ , the hazard ratio  
8 between study groups was 3.9 (95% CI 1.5-10.4)  $p = 0.007$ . CHADS-VASc  $\geq 4$  also  
9 remained significant in the mutually adjusted model. Study arm (iECG) also remained  
10 significantly associated with an increased likelihood of AF diagnosis after adjustment  
11 for CHADS-VASc in a further model.

12

13 Patients diagnosed with AF in the iECG arm were all treated promptly with  
14 anticoagulation (9 with warfarin and 10 with a non-coumadin OAC [NOAC]). In the RC  
15 arm, 3 were treated with warfarin, 1 with NOAC and 1 with clopidogrel.

16

## 17 **Clinical Events**

18 There were no significant differences in the number of serious adverse clinical events  
19 occurring in each arm. Although numerically fewer, there was no statistically significant  
20 difference in the numbers of strokes or TIAs (6 vs 10 in iECG and RC arms respectively,  
21 hazard ratio = 0.61, 95%CI = 0.22-1.69,  $p=0.34$ ). Table 3, Supplement 3 Figure). There  
22 were no peripheral arterial embolic events. In the iECG arm, one participant suffered a  
23 hemorrhagic stroke (not previously found to be in AF/anticoagulated) and one suffered  
24 an ischemic stroke during a complicated post-operative course following aortic valve  
25 replacement surgery. The other 4 events in the iECG group were of undetermined

1 aetiology. In the RC arm, two of these events were embolic due to AF diagnosed  
2 following presentation with stroke, 6 stroke/TIA were of undetermined aetiology and 2  
3 were due to carotid disease. Thus 4 ischemic strokes or TIAs were due to an uncertain  
4 cause in the iECG group and 8 due to AF or uncertain cause in the RC group (hazard  
5 ratio = 0.51, 95%CI (0.15, 1.7) p = 0.27).

6 We noted 2 clinically significant bleeds (both lower GI) in the iECG arm and 1 (ocular) in  
7 the RC arm. None of these bleeds occurred in patients who had been anticoagulated  
8 following AF diagnosis. There were no differences between the study groups in the  
9 incidence of all cause mortality or significant adverse clinical events due to other causes  
10 (Table 3).

11

## 12 **Participant Experience Surveys**

13 Participants' experience (reported using a 1-10 visual analogue scale), showed small  
14 increases in the iECG arm in the reported awareness of the risk (mean score 6.8 vs 6.1, p  
15 = 0.001) but slightly less anxiety about the risk of heart rhythm abnormalities and  
16 stroke (mean score 2.2 vs 2.5, p = 0.003) as well as slightly lower reported likelihood of  
17 intending to visit their physician regarding concerns about their heart rhythm (mean  
18 score 7.1 vs 7.5, p = 0.04). Notably, RC participants reported a considerably greater  
19 preference to have been able to switch to the other study arm (mean score 1.9 vs 6.2, p  
20 < 0.0001).

21

22 Participants in the iECG group were further asked about their experience using the  
23 AliveCor device during the study (measured on a 5 point Likert scale). The vast majority  
24 of iECG participants were "Not at all" or "slightly anxious", "Not at all restricted" by,

1 “Extremely” or “Very” confident in using the device, “Extremely” or “Very” comfortable  
2 with the process of sharing clinical, iECG and personal information with the study team  
3 and were generally “Extremely” or “Very” satisfied with use of the device. (Figure 4)

4

#### 5 **Health Economic Analysis**

6 The overall cost of the intervention was \$204,830 (£156,837). This consisted of device  
7 costs of \$28,698 (£21,974), patient training costs of \$3,750 (£2,871) and defective  
8 technology costs of \$2,194 (£1,680). A total of 60,440 ECGs were recorded, which  
9 amounted to a cost of \$116,823 (£89,451) in commercial ECG over-reads. The cost of  
10 ECG pathway co-ordination was \$37,793 (£28,938) and 704 ECGs were identified as ‘AF’  
11 by AliveCor, producing a cost of \$7,972 (£6,104) for cardiologist over-read. In addition,  
12 74 review appointments were made; 44 were nurse reviews and 30 cardiologist  
13 reviews. Overall, 19 cases of AF were detected thus the intervention cost was \$10,780  
14 (£8,255) per AF diagnosis.

## 1 **DISCUSSION**

2 In this study we found that regular twice-weekly iECG recording and submission is  
3 logistically feasible over a 1 year period and highly acceptable to people over 65 with  
4 increased risk of AF and stroke. This approach results in an almost four-fold increase in  
5 the likelihood of a diagnosis of AF being made over the course of a year at a cost of  
6 \$10,780 (£8,255) per additional AF diagnosis. The overall incidence of stroke+TIA was  
7 similar in both groups, however, this study was not statistically powered to detect a  
8 difference in clinical events in this population.

9

### 10 **Outcome of Screening Strategy**

11 To be worthwhile, screening tests should employ a low-risk, accurate methodology with  
12 acceptable cost effectiveness. The success of such a strategy depends on the  
13 incidence/prevalence of the condition in the screened population and the accuracy of  
14 the testing strategy. As age is the strongest predictor of AF,<sup>1</sup> a screening cutoff  $\geq 65$ y is  
15 recommended based on expert consensus,<sup>30</sup> as the clinical- and cost-effectiveness of  
16 different screening strategies remains to be confirmed in randomized control trials  
17 (RCT) powered to evaluate outcomes.<sup>21</sup>

18

19 We found 19 (1.84%) of the 1033 individuals to be in AF at the time of screening,  
20 despite careful pre-assessment to identify and exclude those with known AF. This  
21 compares favourably with new AF diagnosis in an iECG screening study of patients  $\geq 65$ y  
22 visiting community pharmacy (1.5%).<sup>31</sup> These findings contrast with the 0.5%  
23 diagnosed with AF at initial ECG screening in a community study of 75-76 year old  
24 patients.<sup>19,31</sup> However, in that study, new AF was diagnosed in a further 218 patients  
25 (3.0% 95%CI 2.7-3.5%) during 2 weeks of twice daily ECG recording.



1  
2 Studies evaluating incidence of AF with continuous monitoring/implantable devices  
3 have shown that atrial “high rate events” (usually AF) are generally associated with  
4 strokes or systemic thromboembolism, although there is frequently temporal  
5 discordance noted between the “AF” and thromboembolic event suggesting other  
6 contributing risk factors in these individuals.<sup>21</sup> The RATE registry shows that short (15-  
7 20s) episodes of AF/AT were not associated with an increased risk of stroke in device  
8 patients, whereas prolonged episodes were independently associated as were episodes  
9 lasting over 5min in the MDe Selection Trial and at least 6 minutes in the ASSERT  
10 study.<sup>12, 32, 14</sup> In contrast, other studies have found that only device-detected AF  
11 duration of several hours was associated with increased risk,<sup>13, 33, 34</sup> A pooled analysis of  
12 3 studies suggested at least an hour’s duration of device-detected AT/AF was the best  
13 predictor of risk.<sup>35</sup> We found that 63% of newly diagnosed AF was paroxysmal vs 37%  
14 persistent/permanent in the iECG arm; we have not further subdivided the latter as  
15 accurate classification would have required longer term follow-up of their subsequent  
16 care and should not affect consideration of stroke risk and indication for  
17 anticoagulation. It is unclear how the risk associated with increasing duration of AF  
18 identified with an implantable device compares with the risk associated with  
19 asymptomatic PAF of uncertain frequency and duration diagnosed during  
20 routine/screening evaluation. Nonetheless, recurrent episodes of PAF are common and  
21 as CHADS-VASc scores were high in iECG patients (all  $\geq 2$ ; most  $\geq 3$ ), we made the  
22 decision to anticoagulate all patients identified with (P)AF according to ESC and local  
23 guidance.<sup>24, 30</sup>

24

1 We found that age, arterial disease and CHADS-VASc scores were associated with an  
2 increased likelihood of AF diagnosis, but only a CHADS-VASc score  $\geq 4$  independently  
3 predicted AF . In the STROKESTOP study increasing CHADS-VASc score increased the  
4 likelihood of AF diagnosis, as did heart failure, which was relatively underrepresented  
5 in our study.<sup>19</sup>

6

### 7 **iECG Device and Monitoring Strategy**

8 We used the AliveCor device to record and upload iECGs in this study. This handheld  
9 technology involves use of a pair of electrodes linked to a mobile device to provide a  
10 single-lead rhythm strip comparable to Lead 1 of standard ECG. It employs an FDA-  
11 cleared automatic algorithm with 98% sensitivity and 97% specificity reported for AF  
12 diagnosis.<sup>22</sup> AliveCor technology is already widely used for remote detection of AF and  
13 common arrhythmias in routine clinical practice, having several attractive features  
14 including the quality of the trace, a validated AF reporting algorithm, remote access for  
15 clinicians over a secure server, and HIPAA compliance. However, other validated  
16 technologies are available,<sup>36-40</sup> suggesting a need for comparative studies evaluating  
17 their relative effectiveness and acceptability.

18

19 Mondays and Wednesdays were selected for ECG recording and transmission. As the  
20 small study team was only routinely available Monday to Friday this approach would  
21 allow the study coordinator to review the ECG reports the following day and arrange  
22 clinical evaluation within 24-48 hours of an abnormal ECG being uploaded . This  
23 approach could be varied in routine practice according to size and availability of the  
24 clinical team.

25

## 1 **Clinical Events**

2 There were no significant differences in the number of serious adverse clinical events  
3 occurring in each arm. Although numerically fewer, there was no statistically significant  
4 difference in the numbers of strokes or TIAs. Of note, two patients presenting with  
5 strokes in the RC arm were found to have asymptomatic AF, one diagnosed at the time  
6 of and one shortly after presentation with stroke, whereas none of these events in iECG  
7 patients were due to previously undetected/untreated AF. Indeed, numerically fewer  
8 ischemic stroke/TIA in iECG participants were of uncertain aetiology (N=4) than in the  
9 RC arm of which 8 were due to definite AF or uncertain aetiology, although not  
10 statistically significantly different. Up to 30% of strokes of undetermined aetiology may  
11 be a consequence of previously undetected/untreated AF, with incidence varying  
12 according to the population characteristics and monitoring strategy.<sup>41</sup> It is therefore  
13 possible that 1 in 3 or 4 of these events in our higher-risk population could have been  
14 due to undetected AF. Thus, our findings raise the possibility that remote iECG  
15 monitoring may not only increase detection of AF, but could also reduce the incidence of  
16 ischaemic stroke. This would clearly require a large RCT, appropriately powered to  
17 evaluate major clinical outcomes.

18

## 19 **Health Economic Evaluation**

20 We found the cost per diagnosis of AF to be £8,255 (\$10,750) according to current UK  
21 National Health Service tariffs. Further detailed health economic analyses will permit  
22 modelling of the potential cost effectiveness of this approach to stroke prevention in the  
23 community. This will require imputation of multiple detailed assumptions including the  
24 accuracy of the detection rate, the estimated net risk reduction in those identified and  
25 treated and the specific costs of the systems required to implement the ongoing ECG

1 surveillance programme, which are beyond the remit of this clinical manuscript.  
2 Previous studies have suggested that point of care screening for AF in over 65s in  
3 primary care, community pharmacy or at influenza immunization could be cost  
4 effective<sup>31, 42, 43</sup> as could the 2 week, twice daily period of ECG recording in the  
5 STROKESTOP study.<sup>19</sup> Our preliminary health economic findings are aligned with the  
6 conclusions from these and other studies<sup>19, 31</sup> including a systematic review with cost-  
7 effectiveness analysis.<sup>44</sup> These indicated that both systematic opportunistic screening  
8 and systematic population screening followed by NOAC therapy, when indicated, are  
9 likely to be cost-effective compared with no screening (current practice). The costs per  
10 AF diagnosis in our study (where the mean age was 72.6) are lower than the costs  
11 derived by the economic model, but given that the aim of the study was to assess the  
12 costs of identifying AF, we have not yet factored the management of such patients into  
13 the overall costs and the longer-term benefits. It is unlikely that the additional costs of  
14 NOAC therapy will inflate the costs to such a degree that it would not represent value  
15 for money. Indeed, given the proportion of iECG AF patients provided with NOAC in our  
16 study (53%), we estimate that this approach is likely to result in an incremental net  
17 benefit (based on a cost/QALY of \$26,118 (£20,000) with an incremental cost-QALY  
18 ratio of <\$13,058 (<£10,000). Evidence from screening study cost-effectiveness  
19 modelling and systematic review highlights that at ages lower than 65 years and over  
20 80 years, screening strategies are less cost-effective but nevertheless remain within  
21 acceptable limits.<sup>19, 31, 44</sup> Nonetheless, the full morbidity and mortality benefits and  
22 consequent health economic outcome, including specifically the impact of variation in  
23 uptake and effectiveness of anticoagulation in practice, can only be realistically  
24 determined by prospective randomized controlled outcome trials.

25

## 1 **Uptake of Anticoagulation**

2 All of the patients diagnosed with AF in the iECG arm were started promptly on  
3 anticoagulation (53% with NOAC). We did not routinely collect data on medication  
4 concordance, nor time in therapeutic range on warfarin, as that was outside the scope of  
5 this screening study. These issues will influence the clinical effectiveness of a screening  
6 programme and require evaluation in a prospective outcome study.

7

## 8 **Limitations**

9 Our study is the first randomized, prospective study to examine the effectiveness of  
10 longer-term intermittent ECG recording to diagnose AF in an at risk population. Patients  
11 who did not have access to the Internet or could not use the device were excluded from  
12 participation in the study, excluding those who could not comply with the monitoring  
13 protocol which likely include a proportion of those at the highest risk. This introduces a  
14 potential selection bias towards our findings being representative of this approach in  
15 the more independent, educated elderly who would likely still benefit considerably  
16 from lower AF-related stroke risk. Nonetheless, we were still able to recruit a large  
17 number of older patients who were no less compliant than the younger patients in our  
18 population. All study patients required internet access and documentation of  
19 proficiency with the device at screening, excluding additional bias between groups. The  
20 majority of iECG patients submitted traces on two occasions per week. Despite their  
21 generally very good concordance with the monitoring protocol and higher AF diagnosis  
22 rate, it is likely that asymptomatic paroxysmal AF has been missed in some participants,  
23 albeit unlikely that persistent/permanent AF was missed. Increasing the frequency of  
24 iECG acquisition should increase AF detection rate, but would increase logistical and  
25 financial demand on clinical services as well as further burden participants. Although

1 longer-term continuous external monitoring or use of implantable devices to identify  
2 incident AF would be expected to increase the capture of clinically relevant AF episodes,  
3 such approaches would not be without an adverse effect on patients in terms of  
4 convenience, discomfort, risk and acceptability. We were interested to note that  
5 participants were generally very satisfied with the AliveCor device and study protocol,  
6 with most finding it easy and acceptable to use, without increasing anxiety regarding  
7 their heart or likelihood of consulting with their physician. It was particularly  
8 noteworthy that RC participants expressed a far greater preference to have been  
9 allocated to the iECG arm. These findings provide reassurance that if such a programme  
10 is considered clinically and economically viable in the future, it will also be highly  
11 acceptable to the target population.

12

13 Only the iECG patients were contacted and brought back for clinical review +/- further  
14 testing where clinically indicated by their iECG results. There was no specific instruction  
15 regarding how to manage RC patients and data on nature and frequency of these visits  
16 for comparison have not been formally evaluated. Although we did not undertake a full  
17 face to face clinical evaluation and chart review of all patients at the completion of the  
18 study, all patients underwent detailed questioning at 12, 32 and 52 weeks with specific  
19 reference to heart rhythm abnormalities and major clinical events with only one missed  
20 call accounting for those dying, withdrawing or being lost to follow-up. Furthermore,  
21 patients and practitioners tended to notify us at the time of most relevant clinical events  
22 during follow up, with deaths and cardiovascular admissions confirmed through the  
23 NHS Wales clinical IT system. Whilst it is possible that events were underreported  
24 because patients did not remember or chose not to report them, participants were on  
25 the whole very engaged with the study and happy to volunteer relevant clinical

1 information. It is possible that the closer contact between the study team and iECG  
2 participants would make it more likely that relevant events would have been missed in  
3 RC patients.

4  
5 We have not yet completed a full assessment of the diagnostic performance of the  
6 device and the reporting service. This is an extensive undertaking and beyond the scope  
7 of this manuscript. Our initial analysis of the diagnostics shows that a normal  
8 automated iECG report provides excellent negative predictive ability to exclude AF, but  
9 there appears to be a relatively high false positive rate in the small proportion of those  
10 reported as AF by the device, with these data and patients requiring careful review. A  
11 full, detailed evaluation of agreement between the automated algorithm and  
12 overreading physiologist and cardiologist has not been completed and will be the  
13 subject of a further manuscript. Patients often submitted multiple ECGs when the  
14 automated report suggested AF or undetermined and clinical review with confirmatory  
15 testing required in several cases. These factors have been considered in the health  
16 economic evaluation.

17  
18 The study was not blinded, with ECG over reads, diagnosis of AF and determination of  
19 clinical outcomes undertaken by the senior physician investigators. Although ECG and  
20 clinical diagnoses were validated, an element of observer bias cannot be excluded. The  
21 study was conducted in a single centre, based in a UK University Hospital with the  
22 majority of participants of white European ethnicity and thus the findings may not be  
23 generalizable to different patient populations or healthcare systems. We could not be  
24 certain that patients were truly free from (paroxysmal) AF prior to enrolment, but we  
25 excluded anyone with a prior record of AF in their primary care record or reported a

1 prior diagnosis of AF as well as the 19 who were found to be in (asymptomatic) AF on  
2 their initial iECG (including one who was inappropriately randomised and excluded due  
3 to protocol violation). We excluded cardiac pacing subjects as we felt that identification  
4 of asymptomatic high atrial rate episodes during routine pacing checks could  
5 potentially bias the results of the study. We acknowledge that this could have been a  
6 useful control, but as the numbers would have been small, any question of diagnostic  
7 superiority of internal vs intermittent external monitoring could not be answered  
8 definitively in this study.

9 The study data were analysed and reported independently and without involvement of  
10 the company. The investigators do not have any fiduciary involvement with the  
11 company.

12

### 13 **Summary and Conclusions**

14 Regular twice-weekly iECG screening is highly acceptable to people over 65 at increased  
15 risk of AF and stroke and results in an almost four-fold increase in the diagnosis of AF  
16 over the course of a year. This impact on AF detection and lower incidence of ischemic  
17 stroke/TIA due to AF or undetermined cause with this monitoring strategy, suggests a  
18 potential clinical benefit warranting further evaluation in a larger outcome trial.

19

20



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13

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25

## 1 **References**

2

3 1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum  
4 RF, Kim YH, McAnulty JH, Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati  
5 M and Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of  
6 Disease 2010 Study. *Circulation*. 2014;129:837-47.

7 2. Wolf PA, Abbott RD and Kannel WB. Atrial fibrillation: a major contributor to  
8 stroke in the elderly. The Framingham Study. *Arch Intern Med*. 1987;147:1561-4.

9 3. Saposnik G, Gladstone D, Raptis R, Zhou L and Hart RG. Atrial fibrillation in  
10 ischemic stroke: predicting response to thrombolysis and clinical outcomes. *Stroke*.  
11 2013;44:99-104.

12 4. Friberg L, Rosenqvist M, Lindgren A, Terent A, Norrving B and Asplund K. High  
13 prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke*.  
14 2014;45:2599-605.

15 5. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, Crotty M,  
16 Whitford D, Jannes J, Lee A and Greenhill J. Adelaide stroke incidence study: declining  
17 stroke rates but many preventable cardioembolic strokes. *Stroke*. 2013;44:1226-31.

18 6. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ and D'Agostino  
19 RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27:1760-4.

20 7. Lip GY, Nieuwlaat R, Pisters R, Lane DA and Crijns HJ. Refining clinical risk  
21 stratification for predicting stroke and thromboembolism in atrial fibrillation using a  
22 novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*.  
23 2010;137:263-72.

- 1 8. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation.  
2 Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*.  
3 1994;154:1449-57.
- 4 9. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD,  
5 Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T and Antman EM. Comparison  
6 of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial  
7 fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-62.
- 8 10. Siontis KC, Gersh BJ, Killian JM, Noseworthy PA, McCabe P, Weston SA, Roger VL  
9 and Chamberlain AM. Typical, atypical, and asymptomatic presentations of new-onset  
10 atrial fibrillation in the community: Characteristics and prognostic implications. *Heart*  
11 *Rhythm*. 2016;13:1418-24.
- 12 11. Xiong Q, Proietti M, Senoo K and Lip GY. Asymptomatic versus symptomatic  
13 atrial fibrillation: A systematic review of age/gender differences and cardiovascular  
14 outcomes. *Int J Cardiol*. 2015;191:172-7.
- 15 12. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J,  
16 Paraschos A, Love J, Radoslovich G, Lee KL and Lamas GA. Atrial high rate episodes  
17 detected by pacemaker diagnostics predict death and stroke: report of the Atrial  
18 Diagnostics Ancillary Study of the M0de Selection Trial (MOST). *Circulation*.  
19 2003;107:1614-9.
- 20 13. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D  
21 and Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from  
22 implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm*  
23 *Electrophysiol*. 2009;2:474-80.

- 1 14. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain  
2 E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES and Hohnloser SH.  
3 Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med.* 2012;366:120-9.
- 4 15. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S and Connolly SJ.  
5 Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking  
6 oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll*  
7 *Cardiol.* 2007;50:2156-61.
- 8 16. Friberg L, Hammar N and Rosenqvist M. Stroke in paroxysmal atrial fibrillation:  
9 report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J.* 2010;31:967-75.
- 10 17. Arya A, Piorkowski C, Sommer P, Kottkamp H and Hindricks G. Clinical  
11 implications of various follow up strategies after catheter ablation of atrial fibrillation.  
12 *Pacing Clin Electrophysiol.* 2007;30:458-62.
- 13 18. Lowres N, Neubeck L, Redfern J and Freedman SB. Screening to identify  
14 unknown atrial fibrillation. A systematic review. *Thromb Haemost.* 2013;110:213-22.
- 15 19. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V and Rosenqvist M.  
16 Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation.*  
17 2015;131:2176-84.
- 18 20. Engdahl J, Andersson L, Mirskaya M and Rosenqvist M. Stepwise screening of  
19 atrial fibrillation in a 75-year-old population: implications for stroke prevention.  
20 *Circulation.* 2013;127:930-7.
- 21 21. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM,  
22 Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao TF,  
23 Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ,  
24 Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P,  
25 Kowey PR, Krieger D, Lee VWY, Levin LA, Lip GYH, Lobban T, Lowres N, Mairesse GH,

1 Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H,  
2 Rienstra M, Sandhu RK, Schnabel RB, Siu CW, Steinhubl S, Svendsen JH, Svennberg E,  
3 Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC,  
4 Verma A, Wachter R and Yan BP. Screening for Atrial Fibrillation: A Report of the AF-  
5 SCREEN International Collaboration. *Circulation*. 2017;135:1851-1867.

6 22. Lau JK, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway CD, Albert DE and  
7 Freedman SB. iPhone ECG application for community screening to detect silent atrial  
8 fibrillation: a novel technology to prevent stroke. *Int J Cardiol*. 2013;165:193-4.

9 23. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-  
10 Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna  
11 P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le  
12 Heuzey JY, Ponikowski P and Rutten FH. Guidelines for the management of atrial  
13 fibrillation: the Task Force for the Management of Atrial Fibrillation of the European  
14 Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369-429.

15 24. National Institute for Health and Care Excellence. Atrial Fibrillation:  
16 Management. NICE clinical guideline (CG180). 2014.  
17 <https://www.nice.org.uk/guidance/cg180/chapter/1-Recommendations>. Accessed July  
18 2017

19 25. National Institute for Health and Clinical Excellence. Assessing cost impact.  
20 Methods guide. 2011. Retrieved from  
21 [https://www.nice.org.uk/Media/Default/About/what-we-do/Into-](https://www.nice.org.uk/Media/Default/About/what-we-do/Into-practice/Costing_Manual_update_050811.pdf)  
22 [practice/Costing\\_Manual\\_update\\_050811.pdf](https://www.nice.org.uk/Media/Default/About/what-we-do/Into-practice/Costing_Manual_update_050811.pdf). Accessed July 2017

23 26. Curtis L and Burns A. *Unit Costs of Health and Social Care* 2015. *Personal Social*  
24 *Services Research Unit, University of Kent, Canterbury*. 2015. Retrieved from  
25 <http://www.pssru.ac.uk/project-pages/unit-costs/2015/>. Accessed July 2017

- 1 27. Curtis L and Burns A. *Unit Costs of Health and Social Care 2016. Personal Social*  
2 *Services Research Unit, University of Kent, Canterbury.* 2016. Retrieved from  
3 <http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php>. Accessed July 2017
- 4 28. Department of Health. NHS Reference Costs 2015/2016 (Microsoft Excel  
5 spreadsheet). 2016. Retrieved from  
6 [https://www.gov.uk/government/publications/nhs-reference-costs-collection-](https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016)  
7 [guidance-for-2015-to-2016](https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016). Accessed July 2017
- 8 29. Dupont WD and Plummer WD, Jr. Power and sample size calculations. A review  
9 and computer program. *Control Clin Trials.* 1990;11:116-28.
- 10 30. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener  
11 HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten  
12 U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S,  
13 Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G,  
14 Fitzsimons D, Gorennek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A,  
15 McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P,  
16 Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL and  
17 Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed  
18 in collaboration with EACTS. *Eur Heart J.* 2016;37:2893-2962.
- 19 31. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA,  
20 Briffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW and Freedman  
21 SB. Feasibility and cost-effectiveness of stroke prevention through community  
22 screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study.  
23 *Thromb Haemost.* 2014;111:1167-76.
- 24 32. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E, Qu F,  
25 Slawsky MT, Turkel M and Waldo AL. Clinical Implications of Brief Device-Detected

1 Atrial Tachyarrhythmias in a Cardiac Rhythm Management Device Population: Results  
2 from the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes. *Circulation*.  
3 2016;134:1130-1140.

4 33. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G, Ricci R, Favale S,  
5 Zolezzi F, Di Belardino N, Molon G, Drago F, Villani GQ, Mazzini E, Vimercati M and  
6 Grammatico A. Monitored atrial fibrillation duration predicts arterial embolic events in  
7 patients suffering from bradycardia and atrial fibrillation implanted with  
8 antitachycardia pacemakers. *J Am Coll Cardiol*. 2005;46:1913-20.

9 34. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK, Bauer WR, Paul  
10 V and Sack S. Detection of atrial high-rate events by continuous home monitoring:  
11 clinical significance in the heart failure-cardiac resynchronization therapy population.  
12 *Europace*. 2012;14:230-7.

13 35. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, Gasparini M,  
14 Lewalter T, Camm JA and Singer DE. Device-detected atrial fibrillation and risk for  
15 stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn  
16 Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J*.  
17 2014;35:508-16.

18 36. Kearley K, Selwood M, Van den Bruel A, Thompson M, Mant D, Hobbs FR,  
19 Fitzmaurice D and Heneghan C. Triage tests for identifying atrial fibrillation in primary  
20 care: a diagnostic accuracy study comparing single-lead ECG and modified BP monitors.  
21 *BMJ Open*. 2014;4:e004565.

22 37. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Pasma JL, Cator R, Hofman C and  
23 Houben RP. Validation and clinical use of a novel diagnostic device for screening of  
24 atrial fibrillation. *Europace*. 2014;16:1291-5.

- 1 38. Vaes B, Stalpaert S, Tavernier K, Thaelts B, Lapeire D, Mullens W and Degryse J.  
2 The diagnostic accuracy of the MyDiagnostick to detect atrial fibrillation in primary care.  
3 *BMC Fam Pract.* 2014;15:113.
- 4 39. Doliwa PS, Frykman V and Rosenqvist M. Short-term ECG for out of hospital  
5 detection of silent atrial fibrillation episodes. *Scand Cardiovasc J.* 2009;43:163-8.
- 6 40. Marazzi G, Iellamo F, Volterrani M, Lombardo M, Pelliccia F, Righi D, Grieco F,  
7 Cacciotti L, Iaia L, Caminiti G and Rosano G. Comparison of Microlife BP A200 Plus and  
8 Omron M6 blood pressure monitors to detect atrial fibrillation in hypertensive patients.  
9 *Adv Ther.* 2012;29:64-70.
- 10 41. Yaghi S and Elkind MS. Cryptogenic stroke: A diagnostic challenge. *Neurol Clin*  
11 *Pract.* 2014;4:386-393.
- 12 42. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies  
13 M and Lip G. A randomised controlled trial and cost-effectiveness study of systematic  
14 screening (targeted and total population screening) versus routine practice for the  
15 detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health*  
16 *Technol Assess.* 2005;9:iii-iv, ix-x, 1-74.
- 17 43. Jacobs MS, Kaasenbrood F, Postma MJ, van Hulst M and Tieleman RG. Cost-  
18 effectiveness of screening for atrial fibrillation in primary care with a handheld, single-  
19 lead electrocardiogram device in the Netherlands. *Europace.* 2016; euw285. doi:  
20 <https://doi.org/10.1093/europace/euw285>.
- 21 44. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, Okoli G,  
22 Sterne JA, Feder G, Eaton D, Hingorani A, Fawsitt C, Lobban T, Bryden P, Richards A and  
23 Sofat R. Screening strategies for atrial fibrillation: a systematic review and cost-  
24 effectiveness analysis. *Health Technol Assess.* 2017;21:1-236.

25



1 **Figure legends**

2 **Figure 1:** *Recruitment of local participants over 65 years of age with CHADS-VASc $\geq$ 2.*

3

4 **Figure 2:** *Compliance in the iECG arm can be measured as the proportion of weeks in*  
5 *which a participant submits the recommended number of iECG. Here we show proportion*  
6 *of patients who submitted iECGs at least once per week (left panel) or at least twice per*  
7 *week vs the % of study weeks when this was achieved (fewer than 50%, 50-75%, 75-90%,*  
8 *or over 90% of the study weeks).*

9

10 **Figure 3:** *Kaplan-Meier plot showing the estimated detection probabilities for AF in each*  
11 *arm of the study over the 52 weeks of the trial. Shaded areas represent 95% confidence*  
12 *regions. Log-rank  $p = 0.004$  (Mantel-Cox).*

13

14 **Figure 4:** *Pie charts showing iECF participant experience questionnaire responses to*  
15 *regarding use of AliveCor device in the study*

16

1 **Tables**

	<b>iECG (N=500)</b>	<b>Routine Care (N=501)</b>	<b>p-value</b>
<b>Sex M/F</b>	241/259 (48%/52%)	225/275 (45%/55%)	0.30
<b>Mean age (SD)</b>	72.6 y (5.4)	72.6 y (5.4)	0.98
<b>Age 65-74 y</b>	328	330	0.93
<b>Age &gt;= 75 y*</b>	172	171	0.93
<b>Heart Failure</b>	5 (1%)	9 (2%)	0.28
<b>Hypertension</b>	268 (54%)	272 (55%)	0.75
<b>Diabetes Mellitus</b>	129 (26%)	140 (28%)	0.43
<b>Stroke or TIA</b>	35 (7%)	28 (6%)	0.37
<b>Vascular Disease</b>	71 (14%)	79 (16%)	0.50
<b>CHADS-VASc (SD)</b>	3.0 (1.0)	3.0 (1.0)	0.57

2

3 **Table 1:** Baseline characteristics of study participants. TIA=transient ischaemic attack.

4 \*65 patients in the iECG and 56 in the RC arm were at least 80 years of age.

5

1

	<b>Hazard Ratio (95% CI)</b>	<b>p-value</b>
<b>Gender M/F</b>	1.9 (0.9, 4.5)	0.11
<b>Age &gt;= 75</b>	2.3 (1.0, 5.1)	0.04
<b>Hypertension</b>	0.91 (0.6, 1.4)	0.68
<b>Diabetes Mellitus</b>	1.1 (0.7, 1.6)	0.79
<b>Stroke or TIA</b>	1.2 (0.6, 2.5)	0.64
<b>Arterial Disease</b>	1.5 (1.0, 2.4)	0.05
<b>CHADS-VASc Score ≥4</b>	2.3 (1.0, 5.1)	0.04

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3 **Table 2:** Baseline variables as predictors of AF. The table shows results from separate Cox  
4 regression models. When variables were combined in a multivariable model, only CHADS-  
5 VASc score of ≥4 was independently associated with an increased risk of being diagnosed  
6 with AF.

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<b>Adverse event</b>	<b>iECG (N)</b>	<b>RC (N)</b>	<b>p-value</b>
Death	3	5	0.51
Stroke/TIA/SE	6	10	0.34
Clinically Significant Bleeds	2	1	0.56
DVT/PE	3	1	0.31
Other cardiovascular	8	13	0.27
Respiratory	7	3	0.20
Neurological	3	2	0.65
Orthopaedic/Musculoskeletal/Fall	14	14	0.99
Gastroenterological	10	10	0.99
Renal / Urological	2	5	0.26
Other	7	6	0.78

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2 **Table 3:** Adverse clinical events. Raw numbers of events in each arm of the study.

3 Comparison between groups (p-values) were calculated using Cox regression.

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