Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation

The REHEARSE-AF Study

Editorial, see p 1795

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BACKGROUND: Asymptomatic atrial fibrillation (AF) is increasingly common in the aging population and implicated in many ischemic strokes. Earlier identification of AF with appropriate anticoagulation may decrease stroke morbidity and mortality.

METHODS: We conducted a randomized controlled trial of AF screening using an AliveCor Kardia monitor attached to a WiFi-enabled iPod to obtain ECGs (iECGs) in ambulatory patients. Patients ≥65 years of age with a CHADS-VASc score ≥2 free from AF were randomized to the iECG arm or routine care (RC). iECG participants acquired iECGs twice weekly over 12 months (plus additional iECGs if symptomatic) onto a secure study server with overread by an automated AF detection algorithm and by a cardiac physiologist and/or consultant cardiologist. Time to diagnosis of AF was the primary outcome measure. The overall cost of the devices, ECG interpretation, and patient management were captured and used to generate the cost per AF diagnosis in iECG patients. Clinical events and patient attitudes/experience were also evaluated.

RESULTS: We studied 1001 patients (500 iECG, 501 RC) who were 72.6±5.4 years of age; 534 were female. Mean CHADS-VASc score was 3.0 (heart failure, 1.4%; hypertension, 54%; diabetes mellitus, 30%; prior stroke/transient ischemic attack, 6.5%; arterial disease, 15.9%; all CHADS-VASc risk factors were evenly distributed between groups). Nineteen patients in the iECG group were diagnosed with AF over the 12-month study period versus 5 in the RC arm (hazard ratio, 3.9; 95% confidence interval=1.4–10.4; P=0.007) at a cost per AF diagnosis of $10 780 (£8255). There was a similar number of stroke/transient ischemic attack/systemic embolic events (6 versus 10, iECG versus RC; hazard ratio=0.61; 95% confidence interval=0.22–1.69; P=0.34). The majority of iECG patients were satisfied with the device, finding it easy to use without restricting activities or causing anxiety.

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

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Clinical Perspective

What Is New?

- This is the first prospective randomized trial evaluating the ability of remote ECG acquisition and transmission with a handheld device with remote interpretation to screen for atrial fibrillation (AF) in at-risk people >65 years of age over an extended period of time (1 year).
- This approach is at least 3 times more likely to identify incident AF than routine care at a cost of just over $10 000 per case identified and is a highly acceptable approach in this group of patients. A CHADS-VASc score of ≥4 was the strongest predictor of incident AF.

What Are the Clinical Implications?

- Our findings suggest that this approach could be considered for AF screening in routine practice, particularly in the highest-risk patients.
- Although strokes and transient ischemic attacks were numerically fewer in monitored patients, the study was not statistically powered to evaluate hard clinical outcomes, and this difference was not statistically significant.
- These results support consideration of evaluation in an appropriately powered, event-driven randomized trial to confirm clinical and cost-effectiveness of such an approach to stroke prevention in AF.

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

The annual stroke risk conferred by AF increases with age and other common risk factors and can be estimated with the CHADS-VASc score in those without rheumatic mitral valve disease or metallic valvular prosthesis.[7] Stroke risk can be reduced by about two thirds by the use of oral anticoagulant (OAC) therapy (including non–vitamin-K antagonist OAC [NOACs]).[8,9]

Presentation with AF may be atypical or asymptomatic, especially in older subjects.[10] Data from a range of sources (including the retrospective MOST study [Mode Selection Trial] and the TRENDS study [A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics]) have shown that asymptomatic AF may potentially pose a greater thromboembolic risk than when symptoms are typical.[10–14] AF may also occur on an intermittent basis (paroxysmal AF), with an increased stroke risk[15,16] and recommendations for antithrombotic management identical to those for permanent AF.

AF incidence varies according to the population characteristics and diagnostic strategy.[17] Single-time-point electrocardiographic recording in a general population ≥65 years of age identified AF in 1.4%.[18] Furthermore, twice-daily intermittent single-lead electrocardiographic recording over 2 weeks with a handheld device identified AF in 3.0% of 75- to 76-year-old participants, including 7.4% of those screened who had ≥1 additional stroke risk factor.[19,20] A recent expert consensus article has confirmed that AF identified at screening is not benign and justifies consideration of anticoagulation in those with stroke risk factors.[21] Although validated handheld electrocardiographic recording devices are already considered appropriate technologies for AF screening, expert groups recognize that large prospective trials are required to strengthen the evidence base and to refine population screening strategies.[21]

We therefore undertook a 1-year randomized controlled trial of twice-weekly monitoring with the AliveCor Kardia device (a smartphone/tablet–based single-lead electrocardiographic capture system) versus routine clinical care (RC) in patients >65 years of age with ≥1 additional stroke risk factor.[22] The primary endpoint was time to diagnosis of AF.

METHODS

The online-only Data Supplement provides the full methods.

Study Population

Individuals >65 years of age with a CHADS-VASc score ≥2 not in receipt of OAC therapy without a known diagnosis of AF currently, a known contraindication to anticoagulation, or permanent cardiac pacing implantation were recruited. Participants were required to have access to the internet via WiFi and to be able to operate the AliveCor Kardia system (AliveCor Inc, Mountain View, CA) attached to an iPod (Apple Inc, Cupertino, CA) after simple instruction. Eligibility was confirmed by a brief history, physical examination, and single-lead ECG recorded with the AliveCor device (iECG). Written consent was obtained, and eligible participants were randomized (1:1) to an intervention (iECG) group or RC group. Ethics approval was obtained from the Wales Research Ethics Committee 6 (REC reference 14/WA/1227).

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

Patients With Identified AF

AF was defined as a 30-second iECG recording with irregular rhythm without p waves.[23] All new AF diagnoses were confirmed and reviewed by a senior study cardiologist who made arrangements for OAC initiation and clinical management according to current UK (National Institute for Health and Care Guidelines) guidance.[24] RC participants with AF were diagnosed and managed by local clinicians, with all AF diagnoses validated by a study cardiologist.

Clinical Event Monitoring

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

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, if 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 about 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 with the AliveCor device were estimated from the perspective of the UK National Health Service and Personal Social Services[25] using data from study activity and relevant costs.[26–28]

Statistical Methods

The study sample size of 500 participants per study arm was estimated to provide 92% power to detect a significant difference (α=5%) in the time to AF diagnosis between groups (PS: Power and Sample Size Calculation, version 3.1.2, 2014).[29]

Baseline characteristics were compared by use of a χ^2 test (for groups), Fisher exact test, or *t* test. Compliance with submission of the ECG was evaluated with 1-way ANOVA. The primary outcome of time to AF diagnosis and relationships between baseline characteristics and AF outcome were evaluated with Cox regression. Major adverse outcomes were also compared between groups with Cox regression. Comparison of the distribution of questionnaire responses was done with the Wilcoxon rank-sum test. All analyses were performed with SPSS version 22.0 (released 2013, IBM SPSS Statistics for Macintosh, IBM Corp, Armonk, NY).

RESULTS

Participants

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

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

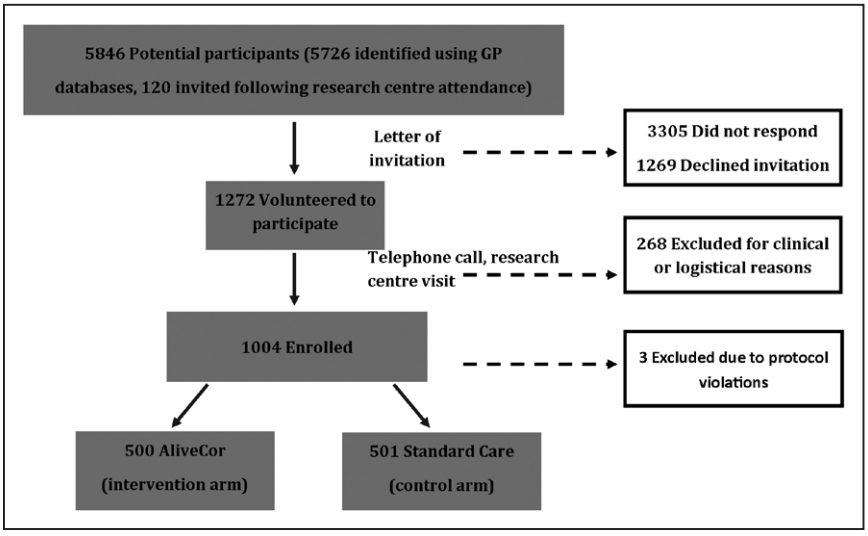

Figure 1. Recruitment of local participants >65 years of age with CHADS-VASc score ≥2.
GP indicates general practitioner.

Age, sex, and clinical characteristics of the study participants were similar in the iECG and RC groups (Table 1). All risk factors were well represented except for heart failure (n=14). Baseline medication prescription was similar in both study groups (Table I in the online-only Data Supplement). All randomized participants were in sinus rhythm at baseline.

We were able to access the National Health Service records of all patients to establish mortality and cardiovascular admissions during the study period. Three participants in the iECG arm withdrew (1 after completing the 12-week and 2 after the 12- and 32-week follow-up calls), and 2 were lost to follow-up (1 after participation in the 12-week and 1 after the 12- and 32-week follow-up). All other patients completing the study participated fully in all telephone interviews at 12, 32, and 52 weeks except for 1 follow-up call missed at 32 weeks by an iECG participant. All practices responded to our requests concerning whether AF had been diagnosed in their respective patients.

iECG Recording and Transmission

The participants in the iECG arm recorded 60 440 ECGs over the 12-month follow-up period. Seventy-four percent of participants completed the trial without missing a single week of submission of the ECG. Recommended twice-weekly ECGs were submitted successfully on average by the iECG participants in 39 of the 52 weeks, and at least 1 weekly ECG was submitted in 48 of the 52 weeks of the trial. Approximately 4 of 5 of participants submitted at least 1 weekly iECG during ≥90% and at least 2 iECGs during ≥75% of the study weeks (Figure 2). Increasing participant age did not affect compliance; the mean number of study weeks with iECG transmitted on 2 (or more) separate days was similar in those 65 to 75, 75 to 79, and ≥80 years of age (77%, 73%, and 74%, respectively; *P*=0.143).

Table 1. Baseline Characteristics of the Study Participants

	iECG (n=500)	RC (n=501)	*P* Value
Sex, M/F, n (%)	241/259 (48/52)	225/276 (45/55)	0.30
Mean age (SD), y	72.6 y (5.4)	72.6 y (5.4)	0.98
Age 65–74 y, n	328	330	0.93
Age ≥75 y, n*	172	171	0.93
Heart failure, n (%)	5 (1)	9 (2)	0.28
Hypertension, n (%)	268 (54)	272 (55)	0.75
Diabetes mellitus, n (%)	129 (26)	140 (28)	0.43
Stroke or TIA, n (%)	35 (7)	28 (6)	0.37
Vascular disease, n (%)	71 (14)	79 (16)	0.50
CHADS-VASc score (SD)	3.0 (1.0)	3.0 (1.0)	0.57

iECG indicates iPod ECG; RC, routine care; and TIA, transient ischemic attack.
*Sixty-five patients in the iECG arm and 56 in the RC arm were at least 80 years of age.

Of the 76% of iECGs that were reported normal by the automated algorithm, none were finally confirmed to be AF; only 6 iECGs of the 21% reported as undetermined were finally confirmed to be AF; only 5% of the ≈1% iECGs reported as AF by the device were finally confirmed to be AF; and 2.2% of iECGs were reported as unreadable.

Newly Diagnosed AF

Nineteen patients in the iECG group were diagnosed with AF during the 12-month study period versus 5 in the RC arm (hazard ratio, 3.9; 95% 95% confidence interval (CI)=1.4–10.4; *P*=0.007; Figure 3). Ten iECG patients had a ventricular rate >100 bpm at the time of diagnosis, and the other 9 had rates between 60 and 100 bpm. There were no significant differences in compliance between those diagnosed with AF (iECG group, n = 19) and those not diagnosed with AF (mean study weeks with iECG submitted on 2 separate days in those diagnosed versus not diagnosed with AF, 69% versus 76%, respectively; 1-way ANOVA; *P*=0.11).

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

Eight (42%) of the iECG patients were asymptomatic at the time of diagnosis, with only 4 (21%) experiencing palpitations and 7 (37%) aware of other symptoms. In the RC arm, 2 (40%) were diagnosed with AF during palpitations, and the other 3 (60%) were diagnosed during other symptoms.

Trends for the relationship between baseline variables and development of AF were as expected, although only age (>75 years), CHADS-VASc score (≥4), and arterial disease were statistically significantly associated with an increased likelihood AF diagnosis (Table 2). When all variables were included in a regression model (excluding heart failure, which was rare), only CHADS-VASc score ≥4 remained a significant predictor of AF (adjusted hazard ratio=4.0; 95% CI, 1.1–15.2l; *P*=0.04). Similar findings were noted when only significant variables were included in a single model (less susceptible to overfitting given the relatively small event rate). The hazard ratio and significance for the difference between treatment groups also remained unchanged in a model adjusted for baseline variables (in any combination). For example, with adjustment for CHADS-VASc score ≥4, the hazard ratio between study groups was 3.9 (95% CI, 1.5–10.4; *P*=0.007). CHADS-VASc score ≥4 also remained significant in the mutually adjusted model. The study arm (iECG) also remained

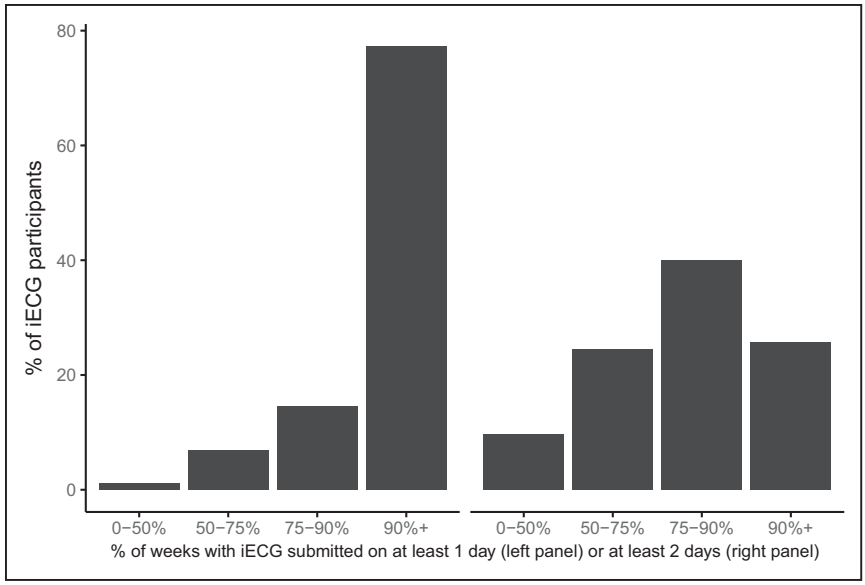

Figure 2. Compliance in the iPod electrocardiogram (iECG) arm can be measured as the proportion of weeks in which a participant submits the recommended number of iECGs.
Here, we show the proportion of patients who submitted iECGs at least once per week (**left**) or at least twice per week (**right**) vs the percent of study weeks when this was achieved (<50%, 50%–75%, 75%–90%, or >90% of the study weeks).

significantly associated with an increased likelihood of AF diagnosis after adjustment for CHADS-VASc score in a further model.

Patients diagnosed with AF in the iECG arm were all treated promptly with anticoagulation (9 with warfarin and 10 with a NOAC). In the RC arm, 3 were treated with warfarin, 1 with NOAC, and 1 with clopidogrel.

Clinical Events

There were no significant differences in the number of serious adverse clinical events occurring in each arm. Although numerically fewer, there was no statistically significant difference in the number of strokes or transient ischemic attacks (TIAs; 6 versus 10 in the iECG and RC arms, respectively; hazard ratio=0.61; 95% CI=0.22–1.69; *P*=0.34; Table 3 and Figure I in the online-only Data Supplement). There were no peripheral arterial embolic events. In the iECG arm, 1 participant had a hemorrhagic stroke (not previously found to be in AF/anticoagulated), and 1 had an ischemic stroke during a complicated postoperative course after aortic valve replacement surgery. The other 4 events in the iECG group were of undetermined origin. In the RC arm, 2 of these events were embolic resulting from AF diagnosed after presentation with stroke, 6 strokes/TIAs were of undetermined origin, and 2 were due to carotid disease. Thus, 4 ischemic strokes or TIAs were due to an uncertain cause in the iECG group and 8 to AF or uncertain cause in the RC group (hazard ratio=0.51; 95% CI=0.15–1.7; *P*=0.27).

We noted 2 clinically significant bleeds (both lower gastrointestinal tract) in the iECG arm and 1 (ocular) in the RC arm. None of these bleeds occurred in patients who had been anticoagulated after AF diagnosis. There were no differences between the study groups

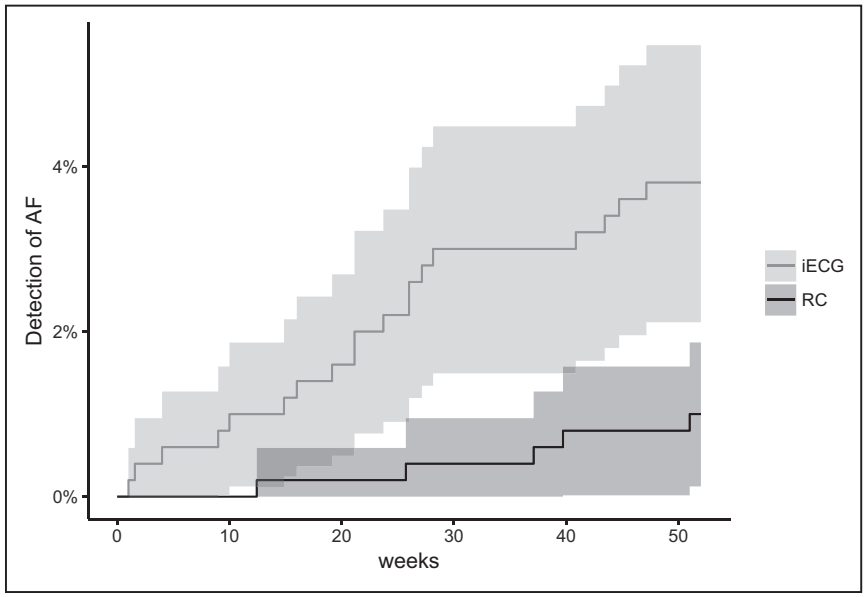

Figure 3. Kaplan-Meier plot showing the estimated detection probabilities for atrial fibrillation (AF) in each study arm over the 52 weeks of the trial.
Shaded areas represent 95% confidence regions. Log-rank *P*=0.004 (Mantel-Cox). RC indicates routine care.

Table 2. Baseline Variables as Predictors of Atrial Fibrillation

	Hazard Ratio (95% CI)	*P* Value
M/F sex	1.9 (0.9–4.5)	0.11
Age ≥75 y	2.3 (1.0–5.1)	0.04
Hypertension	0.91 (0.6–1.4)	0.68
Diabetes mellitus	1.1 (0.7–1.6)	0.79
Stroke or TIA	1.2 (0.6–2.5)	0.64
Arterial disease	1.5 (1.0–2.4)	0.05
CHADS-VASc score ≥4	2.3 (1.0–5.1)	0.04

The table shows results from separate Cox regression models. When variables were combined in a multivariable model, only CHADS-VASc score of ≥4 was independently associated with an increased risk of being diagnosed with AF.

CI indicates confidence interval; and TIA, transient ischemic attack.

in the incidence of all-cause mortality or significant adverse clinical events resulting from other causes (Table 3).

Participant Experience Surveys

Participants' experience (reported with a 1–10 visual analog scale) showed small increases in the iECG arm in the reported awareness of the risk (mean score, 6.8 versus 6.1; *P*=0.001) but slightly less anxiety about the risk of heart rhythm abnormalities and stroke (mean score, 2.2 versus 2.5; *P*=0.003) and slightly lower reported likelihood of intending to visit their physician regarding concerns about their heart rhythm (mean score, 7.1 versus 7.5; *P*=0.04). Notably, RC participants reported a considerably greater preference to have been able to switch to the other study arm (mean score, 1.9 versus 6.2; *P*<0.0001).

Participants in the iECG group were further asked about their experience with the AliveCor device during the study (measured on a 5-point Likert scale). The vast majority of iECG participants were not at all or slightly anxious about using the device; not at all restricted by the device; extremely or very confident using the device; extremely or very comfortable with the process of sharing clinical, iECG, and personal information with the study team; and generally extremely or very satisfied with use of the device (Figure 4).

Table 3. Adverse Clinical Events

Adverse Event	iECG, n	RC, n	*P* Value
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
Other neurological	3	2	0.65
Orthopedic/musculoskeletal/fall	14	14	0.99
Gastroenterological	10	10	0.99
Renal/urologic	2	5	0.26
Other	7	6	0.78

Raw numbers of events in each arm of the study are shown. Comparison between groups (*P* values) was calculated with Cox regression.

DVT indicates deep vein thrombosis; iECG, iPod ECG; PE, pulmonary embolism; RC, routine care; SE, systemic embolism; and TIA, transient ischemic attack.

Health Economic Analysis

The overall cost of the intervention was $204 830 (£156 837). This consisted of device costs of $28 698 (£21 974), patient training costs of $3750 (£2871), and defective technology costs of $2194 (£1680). A total of 60 440 ECGs were recorded, which amounted to a cost of $116 823 (£89 451) in commercial overreads of the ECG. The cost of pathway coordination of the ECGs was $37 793 (£28 938), and 704 ECGs were identified as AF by AliveCor, producing a cost of $7972 (£6104) for cardiologist overread. In addition, 74 review appointments were made: 44 were nurse reviews and 30 were cardiologist reviews. Overall, 19 cases of AF were detected; thus, the intervention cost was $10 780 (£8255) per AF diagnosis.

DISCUSSION

In this study, we found that regular twice-weekly iECG recording and submission is logistically feasible over a 1-year period and highly acceptable to people >65 years of age with increased risk of AF and stroke. This approach results in an almost 4-fold increase in the likelihood of a diagnosis of AF being made over the course of a year at a cost of $10 780 (£8255) per additional AF diagnosis. The overall incidence of stroke plus TIA was similar in both groups; however, this study was not statistically powered to detect a difference in clinical events in this population.

Outcome of Screening Strategy

To be worthwhile, screening tests should use a low-risk, accurate methodology with acceptable cost-effectiveness. The success of such a strategy depends on the incidence/prevalence of the condition in the screened population and the accuracy of the testing strategy. Because age is the strongest predictor of AF,[1] a screening age cutoff of ≥65 years is recommended on the basis of expert consensus[30] because the clinical effectiveness and cost-effectiveness of different screening strategies remain to be confirmed in randomized controlled trials powered to evaluate outcomes.[21]

We found 19 (1.84%) of the 1033 individuals to be in AF at the time of screening, despite careful preassessment to identify and exclude those with known AF. This

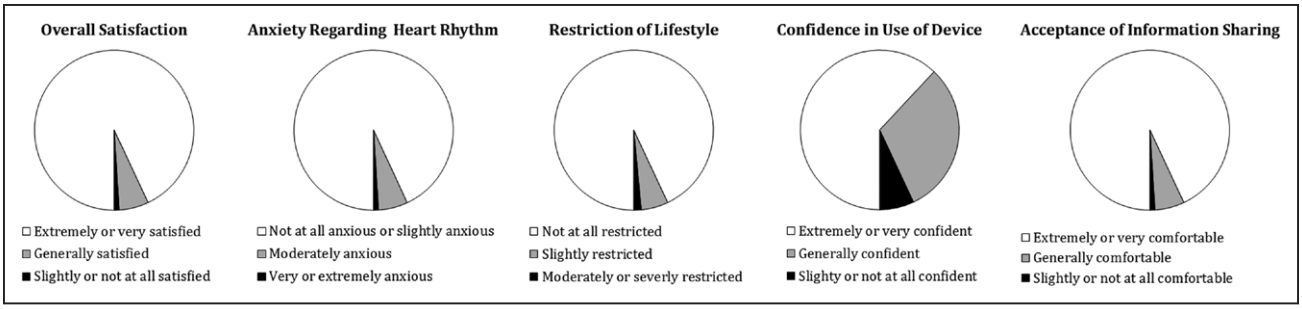

Figure 4. Pie charts showing iPod ECG participant experience questionnaire responses about the use of the AliveCor device in the study.

compares favorably with new AF diagnosis in an iECG screening study of patients ≥65 years of age visiting a community pharmacy (1.5%).[31] These findings contrast with the 0.5% diagnosed with AF at initial electrocardiographic screening in a community study of 75- to 76-year-old patients.[19,31] However, in that study, new AF was diagnosed in a further 218 patients (3.0%; 95% CI, 2.7–3.5) during 2 weeks of twice-daily electrocardiographic recording.

Studies evaluating the incidence of AF with continuous monitoring/implantable devices have shown that atrial "high-rate events" (usually AF) are generally associated with strokes or systemic thromboembolism, although temporal discordance frequently is noted between the "AF" and thromboembolic event, suggesting other contributing risk factors in these individuals.[21] The Registry of Atrial Tachycardia and Atrial Fibrillation Episodes shows that short (15- to 20-second) episodes of AF/atrial tachycardia were not associated with an increased risk of stroke in patients with a device, whereas prolonged episodes were independently associated, as were episodes lasting >5minutes in the MOST study and at least 6 minutes in the ASSERT study (Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial).[12,14,32] In contrast, other studies have found that only device-detected AF duration of several hours was associated with increased risk.[13,33,34] A pooled analysis of 3 studies suggested that at least 1-hour duration of device-detected atrial tachycardia/AF was the best predictor of risk.[35] We found that 63% of newly diagnosed AF was paroxysmal versus 37% persistent/permanent in the iECG arm; we have not further subdivided the latter because accurate classification would have required longer-term follow-up of the patients' subsequent care and should not affect consideration of stroke risk and indication for anticoagulation. It is unclear how the risk associated with increasing duration of AF identified with an implantable device compares with the risk associated with asymptomatic paroxysmal AF of uncertain frequency and duration diagnosed during routine/screening evaluation. Nonetheless, recurrent episodes of paroxysmal AF are common, and because CHADS-VASc scores were high in iECG patients (all ≥2, most ≥3), we made the decision to anticoagulate all patients identified with paroxysmal AF according to European Society of Cardiology and local guidance.[24,30]

We found that age, arterial disease, and CHADS-VASc scores were associated with an increased likelihood of AF diagnosis, but only a CHADS-VASc score ≥4 independently predicted AF. In the STROKESTOP study (Systematic NT-proBNP and ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm, Sweden), increasing CHADS-VASc score increased the likelihood of AF diagnosis, as did heart failure, which was relatively underrepresented in our study.[19]

iECG Device and Monitoring Strategy

We used the AliveCor device to record and upload iECGs in this study. This handheld technology involves the use of a pair of electrodes linked to a mobile device to provide a single-lead rhythm strip comparable to lead 1 of a standard ECG. It uses a US Food and Drug Administration–cleared automatic algorithm with 98% sensitivity and 97% specificity reported for AF diagnosis.[22] AliveCor technology is already widely used for the remote detection of AF and common arrhythmias in routine clinical practice, having several attractive features, including the quality of the trace, a validated AF reporting algorithm, remote access for clinicians over a secure server, and Health Insurance Portability and Accountability Act compliance. However, other validated technologies are available,[36–40] suggesting a need for comparative studies evaluating their relative effectiveness and acceptability.

Mondays and Wednesdays were selected for recording and transmission of the ECGs. Because the small study team was routinely available only Monday through Friday, this approach allowed the study coordinator to review the electrocardiographic reports the following day and to arrange clinical evaluation within 24 to 48 hours of an abnormal ECG being uploaded. This approach could be varied in routine practice according to the size and availability of the clinical team.

Clinical Events

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

Health Economic Evaluation

We found the cost per diagnosis of AF to be $10 780 (£8255) according to current UK National Health Service tariffs. Further detailed health economic analyses will permit modeling of the potential cost-effectiveness of this approach to stroke prevention in the community. This will require imputation of multiple detailed assumptions, including the accuracy of the detection rate, the estimated net risk reduction in those identified and treated, and the specific costs of the systems required to implement the ongoing electrocardiographic surveillance program, which are beyond the remit of this clinical study. Previous studies have suggested that point-of-care screening for AF in those >65 years of age in primary care, in a community pharmacy, or at influenza immunization could be cost-effective,[31,42,43] as could the 2-week, twice-daily period of electrocardiographic recording in the STROKESTOP study.[19] Our preliminary health economic findings are aligned with the conclusions from these and other studies,[19,31] including a systematic review with cost-effectiveness analysis.[44] These indicated that both systematic opportunistic screening and systematic population screening followed by NOAC therapy, when indicated, are likely to be cost-effective compared with no screening (current practice). The costs per AF diagnosis in our study (in which the mean age was 72.6 years) are lower than the costs derived by the economic model, but given that the aim of the study was to assess the costs of identifying AF, we have not yet factored the management of such patients into the overall costs and the longer-term benefits. It is unlikely that the additional costs of NOAC therapy will inflate the costs to such a degree that it would not represent value for money. Indeed, given the proportion of iECG patients with AF provided with NOAC in our study (53%), we estimate that this approach is likely to result in an incremental net benefit (based on a cost per quality-adjusted life-year of $26 118 [£20 000]) with a ratio of incremental cost to quality-adjusted life-year of <$13 058 (<£10 000). Evidence from screening study cost-effectiveness modeling and systematic review highlights that at ages <65 and >80 years, screening strategies are less cost-effective but nevertheless remain within acceptable limits.[19,31,44] Nonetheless, the full morbidity and mortality benefits and consequent health economic outcome, including specifically the impact of variation in uptake and effectiveness of anticoagulation in practice, can be realistically determined only by prospective randomized controlled outcome trials.

Uptake of Anticoagulation

All patients diagnosed with AF in the iECG arm were started promptly on anticoagulation (53% with NOAC). We did not routinely collect data on medication concordance or time in therapeutic range on warfarin because they were outside the scope of this screening study. These issues will influence the clinical effectiveness of a screening program and require evaluation in a prospective outcome study.

Limitations

Our study is the first randomized prospective study to examine the effectiveness of longer-term intermittent electrocardiographic recording to diagnose AF in an at-risk population. Patients who did not have access to the Internet or could not use the device were excluded from participation in the study, excluding those who could not comply with the monitoring protocol, likely including a proportion of those at highest risk. This introduces a potential selection bias toward our findings being representative of this approach in the more independent, educated elderly who would likely still benefit considerably from lower AF-related stroke risk. Nonetheless, we were still able to recruit a large number of older patients who were no less compliant than the younger patients in our population. All study patients required Internet access and documentation of proficiency with the device at screening, excluding additional bias between groups. The majority of iECG patients submitted traces on 2 occasions per week. Despite their generally

very good concordance with the monitoring protocol and higher AF diagnosis rate, it is likely that asymptomatic paroxysmal AF has been missed in some participants, although it is unlikely that persistent/permanent AF was missed. Increasing the frequency of iECG acquisition should increase the AF detection rate but would increase the logistical and financial demands on clinical services and would further burden participants. Although longer-term continuous external monitoring or use of implantable devices to identify incident AF would be expected to increase the capture of clinically relevant AF episodes, such approaches would not be without an adverse effect on patients in terms of convenience, discomfort, risk, and acceptability. We were interested to note that participants were generally very satisfied with the AliveCor device and study protocol, with most finding it easy and acceptable to use without increasing anxiety about their heart or likelihood of consulting with their physician. It was particularly noteworthy that RC participants expressed a far greater preference to have been allocated to the iECG arm. These findings provide reassurance that if such a program is considered clinically and economically viable in the future, it will also be highly acceptable to the target population.

Only the iECG patients were contacted and brought back for clinical review with or without further testing when clinically indicated by their iECG results. There was no specific instruction for how to manage RC patients, and data on the nature and frequency of these visits for comparison have not been formally evaluated. Although we did not undertake a full face-to-face clinical evaluation and chart review of all patients at the completion of the study, all patients underwent detailed questioning at 12, 32, and 52 weeks with specific reference to heart rhythm abnormalities and major clinical events, accounting for those dying, withdrawing, or being lost to follow-up, with only 1 missed call. Furthermore, patients and practitioners tended to notify us at the time of most relevant clinical events during follow-up, with deaths and cardiovascular admissions confirmed through the National Health Service Wales clinical information technology system. Although it is possible that events were underreported because patients did not remember or chose not to report them, participants were on the whole very engaged with the study and happy to volunteer relevant clinical information. It is possible that the closer contact between the study team and iECG participants would make it more likely that relevant events would have been missed in RC patients.

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

The study was not blinded, with electrocardiographic overreads, diagnosis of AF, and determination of clinical outcomes undertaken by the senior physician investigators. Although electrocardiographic and clinical diagnoses were validated, an element of observer bias cannot be excluded. The study was conducted in a single center based in a UK University Hospital with the majority of participants of white European ethnicity; thus, the findings may not be generalizable to different patient populations or healthcare systems. We could not be certain that patients were truly free from (paroxysmal) AF before enrollment, but we excluded anyone with a record of AF in the primary care record and anyone who reported a prior diagnosis of AF, as well as the 19 who were found to be in (asymptomatic) AF on their initial iECG (including 1 participant who was inappropriately randomized and excluded because of protocol violation). We excluded those with cardiac pacing because we felt that identification of asymptomatic high-atrial-rate episodes during routine pacing checks could potentially bias the results of the study. We acknowledge that this could have been a useful control, but because the numbers would have been small, any question of diagnostic superiority of internal versus intermittent external monitoring could not be answered definitively in this study.

The study data were analyzed and reported independently and without involvement of the device manufacturer. The investigators do not have any fiduciary involvement with the company.

Conclusions

Regular twice-weekly iECG screening is highly acceptable to people >65 years of age at increased risk of AF and stroke and results in an almost 4-fold increase in the diagnosis of AF over the course of a year. This impact on AF detection and the lower incidence of ischemic strokes/TIAs resulting from AF or undetermined cause with this monitoring strategy suggest a potential clinical benefit warranting further evaluation in a larger outcome trial.

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FOOTNOTES

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REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837–847. doi: 10.1161/CIRCULATIONAHA.113.005119.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly: the Framingham study. *Arch Intern Med*. 1987;147:1561–1564.
3. Saposnik G, Gladstone D, Raptis R, Zhou L, Hart RG; Investigators of the Registry of the Canadian Stroke Network (RCSN) and the Stroke Outcomes Research Canada (SORCan) Working Group. Atrial fibrillation in ischemic stroke: predicting response to thrombolysis and clinical outcomes. *Stroke*. 2013;44:99–104. doi: 10.1161/STROKEAHA.112.676551.
4. Friberg L, Rosenqvist M, Lindgren A, Terént A, Norrving B, Asplund K. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke*. 2014;45:2599–2605. doi: 10.1161/STROKEAHA.114.006070.
5. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, Crotty M, Whitford D, Jannes J, Lee A, Greenhill J. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. *Stroke*. 2013;44:1226–1231. doi: 10.1161/STROKEAHA.113.675140.
6. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation: the Framingham study. *Stroke*. 1996;27:1760–1764.
7. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584.
8. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449–57.
9. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962. doi: 10.1016/S0140-6736(13)62343-0.
10. Siontis KC, Gersh BJ, Killian JM, Noseworthy PA, McCabe P, Weston SA, Roger VL, Chamberlain AM. Typical, atypical, and asymptomatic presentations of new-onset atrial fibrillation in the community: characteristics and prognostic implications. *Heart Rhythm*. 2016;13:1418–1424. doi: 10.1016/j.hrthm.2016.03.003.
11. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: a systematic review of age/gender differences and cardiovascular outcomes. *Int J Cardiol*. 2015;191:172–177. doi: 10.1016/j.ijcard.2015.05.011.
12. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA; MOST Investigators. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation*. 2003;107:1614–1619. doi: 10.1161/01.CIR.0000057981.70380.45.
13. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2:474–480. doi: 10.1161/CIRCEP.109.849638.
14. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120–129. doi: 10.1056/NEJMoa1105575.
15. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ; ACTIVE W Investigators. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol*. 2007;50:2156–2161. doi: 10.1016/j.jacc.2007.07.076.
16. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J*. 2010;31:967–975. doi: 10.1093/eurheartj/ehn599.
17. Arya A, Piorkowski C, Sommer P, Kottkamp H, Hindricks G. Clinical implications of various follow up strategies after catheter ablation of atrial fibrillation. *Pacing Clin Electrophysiol*. 2007;30:458–462. doi: 10.1111/j.1540-8159.2007.00693.x.
18. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation: a systematic review. *Thromb Haemost*. 2013;110:213–222. doi: 10.1160/TH13-02-0165.
19. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP Study. *Circulation*. 2015;131:2176–2184. doi: 10.1161/CIRCULATIONAHA.114.014343.
20. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation*. 2013;127:930–937. doi: 10.1161/CIRCULATIONAHA.112.126656.
21. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao TF, Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ, Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P, Kowey PR, Krieger D, Lee VWY, Levin LÅ, Lip GYH, Lobban T, Lowres N, Mairesse GH, Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H, Rienstra M, Sandhu RK, Schnabel RB, Siu CW, Steinhubl S, Svendsen JH, Svennberg E, Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC, Verma A, Wachter R, Yan BP; AF-Screen

Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation*. 2017;135:1851–1867. doi: 10.1161/CIRCULATIONAHA.116.026693.
22. Lau JK, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway CD, Albert DE, Freedman SB. iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke. *Int J Cardiol*. 2013;165:193–194. doi: 10.1016/j.ijcard.2013.01.220.
23. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.
24. National Institute for Health and Care Excellence. Atrial Fibrillation: Management: NICE clinical guideline (CG180). 2014. https://www.nice.org.uk/guidance/cg180/chapter/1-Recommendations. Accessed July 17, 2017.
25. National Institute for Health and Clinical Excellence. Assessing cost impact: methods guide. 2011. https://www.nice.org.uk/Media/Default/About/what-we-do/Into-practice/Costing_Manual_update_050811.pdf. Accessed July 17, 2017.
26. Curtis L, Burns A. Unit costs of health and social care 2015: Personal Social Services Research Unit, University of Kent, Canterbury. 2015. http://www.pssru.ac.uk/project-pages/unit-costs/2015/. Accessed July 17, 2017.
27. Curtis L, Burns A. Unit costs of health and social care 2016: Personal Social Services Research Unit, University of Kent, Canterbury. 2016. http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php. Accessed July 17,2017.
28. Department of Health. NHS Reference Costs 2015/2016 (Microsoft Excel spreadsheet). 2016. https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016. Accessed July 17, 2017.
29. Dupont WD, Plummer WD Jr. Power and sample size calculations: a review and computer program. *Control Clin Trials*. 1990;11:116–128.
30. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210.
31. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Freedman SB. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies: the SEARCH-AF study. *Thromb Haemost*. 2014;111:1167–1176. doi: 10.1160/TH14-03-0231.
32. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E, Qu F, Slawsky MT, Turkel M, Waldo AL; RATE Registry Investigators. Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes. *Circulation*. 2016;134:1130–1140. doi: 10.1161/CIRCULATIONAHA.115.020252.
33. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G, Ricci R, Favale S, Zolezzi F, Di Belardino N, Molon G, Drago F, Villani GQ, Mazzini E, Vimercati M, Grammatico A; Italian AT500 Registry Investigators. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. *J Am Coll Cardiol*. 2005;46:1913–1920. doi: 10.1016/j.jacc.2005.07.044.
34. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK, Bauer WR, Paul V, Sack S. Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace*. 2012;14:230–237. doi: 10.1093/europace/eur293.
35. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, Gasparini M, Lewalter T, Camm JA, Singer DE. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J*. 2014;35:508–516. doi: 10.1093/eurheartj/eht491.
36. Kearley K, Selwood M, Van den Bruel A, Thompson M, Mant D, Hobbs FR, Fitzmaurice D, Heneghan C. Triage tests for identifying atrial fibrillation in primary care: a diagnostic accuracy study comparing single-lead ECG and modified BP monitors. *BMJ Open*. 2014;4:e004565. doi: 10.1136/bmjopen-2013-004565.
37. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Posma JL, Cator R, Hofman C, Houben RP. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace*. 2014;16:1291–1295. doi: 10.1093/europace/euu057.
38. Vaes B, Stalpaert S, Tavernier K, Thaels B, Lapeire D, Mullens W, Degryse J. The diagnostic accuracy of the MyDiagnostick to detect atrial fibrillation in primary care. *BMC Fam Pract*. 2014;15:113. doi: 10.1186/1471-2296-15-113.
39. Doliwa PS, Frykman V, Rosenqvist M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. *Scand Cardiovasc J*. 2009;43:163–168. doi: 10.1080/14017430802593435.
40. Marazzi G, Iellamo F, Volterrani M, Lombardo M, Pelliccia F, Righi D, Grieco F, Cacciotti L, Iaia L, Caminiti G, Rosano G. Comparison of Microlife BP A200 Plus and Omron M6 blood pressure monitors to detect atrial fibrillation in hypertensive patients. *Adv Ther*. 2012;29:64–70. doi: 10.1007/s12325-011-0087-0.
41. Yaghi S, Elkind MS. Cryptogenic stroke: a diagnostic challenge. *Neurol Clin Pract*. 2014;4:386–393. doi: 10.1212/CPJ.0000000000000086.
42. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies M, Lip G. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over: the SAFE study. *Health Technol Assess*. 2005;9:iii–iv, ix.
43. Jacobs MS, Kaasenbrood F, Postma MJ, van Hulst M, Tieleman RG. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands [published online ahead of print October 12, 2016]. *Europace*. doi: https://doi.org/10.1093/europace/euw285. https://academic.oup.com/europace/article-abstract/doi/10.1093/europace/euw285/2952432/Cost-effectiveness-of-screening-for-atrial?redirectedFrom=fulltext.
44. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, Okoli G, Sterne JA, Feder G, Eaton D, Hingorani A, Fawsitt C, Lobban T, Bryden P, Richards A, Sofat R. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2017;21:1–236. doi: 10.3310/hta21290.