Long-Term Follow-up of Enhanced Holter-Electrocardiography Monitoring in Acute Ischemic Stroke

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Background and Purpose Prolonged electrocardiography (ECG)-monitoring in stroke patients improves the detection of paroxysmal atrial fibrillation (pAF). However, most randomized studies only had short follow-up. We aimed to provide 3-year follow-up data for AF detection and stroke recurrence risk.

Methods We randomized 402 patients aged ≥60 years with acute ischemic strokes without AF to either enhanced and prolonged monitoring (EPM; 3×10-day Holter-ECG-monitoring) or standard-of-care (≥24 hours ECG-monitoring). The endpoint of the current analysis was AF within 36 months analyzed by intention to treat. Long-term follow-up was performed for 36 months.

Results Two hundred and seventy-four patients (80%) participated in the extended follow-up (median duration of follow-up was 36 months [interquartile range, 12 to 36]). During the first 6 months, more AF was documented in the EPM arm compared to the control arm (13.5% vs. 5.1%; 95% confidence interval, 2.9% to 14.4%; *P*=0.004). During months 6 to 36, AF was less detected in the EPM intervention arm than in the control arm (2.0% vs. 7.3%; 95% confidence interval, 0.7% to 9.9%; *P*=0.028). Overall, the detection rate of AF within 36 months was numerically higher within the EPM group (15.0% vs. 11.1%, *P*=0.30). Numerically less patients in the EPM arm had recurrent ischemic strokes (5.5% vs. 9.1%, *P*=0.18), transient ischemic attacks

(3.0% vs. 4.5%, *P*=0.44) or died (4.5% vs. 6.6%, *P*=0.37).

Conclusions Enhanced and prolonged ECG monitoring increased AF detection during the first six months, but there was significantly more clinical AF during months 6 to 36 observed in the usual-care arm. This suggests that EPM leads to an earlier detection of clinically relevant AF.

Keywords Stroke; Atrial fibrillation; Electrocardiographic monitoring; Randomized controlled trial

Introduction

Atrial fibrillation (AF) is a major cause of ischemic strokes. AF-related strokes are more severe than those of other etiologies[1] and stroke patients with AF exhibit a high risk of recurrent ischemic events.[2] AF might escape routine stroke etiology work-up as paroxysmal AF (pAF) occurs intermittently. The identification of pAF is of major clinical importance as it usually changes the secondary stroke prevention strategy with respect to the initiation of oral anticoagulation instead of antiplatelet therapy. This leads to a 40% relative risk reduction of recurrent strokes events.[3]

So far, three randomized trials have demonstrated that a high proportion of patients with pAF can be identified by prolonged electrocardiography (ECG)-monitoring[4-6] compared to a standard stroke workup. However, the clinical relevance of AF detected by different means is unknown. For instance, short episodes detected by implantable cardiac monitors are a frequent finding in patients with cardiovascular risk factor (29% within 18 months) while the overall stroke rate is low.[7]

A latent or early symptomatic stage is a key principle of a screening program.[8] This principle has not yet been proven for AF detection in stroke patients. We aimed to follow-up patients after a 6-month monitoring period for additional 2.5 years to investigate if (1) detection rate of AF during follow-up is different between both study arms and (2) ischemic stroke rate is different between both study arms.

Methods

Study design and patients

Find-AF_RANDOMISED was an investigator-initiated randomized, controlled, open-label trial, conducted at four certified stroke centers in Germany. It is registered with clinicaltrials.gov (NCT01855035).

The study protocol was approved by the individual ethics boards at each study site. Patients 60 years or older with ischemic strokes and symptoms ≤7 days were prospectively included after signing written and informed consent. Patients with known AF, another indication or a contraindication for oral anticoagulation were excluded. We also excluded those with symptomatic ipsilateral stenoses (>50%, North American Symptomatic Carotid Endarterectomy Trial [NASCET] classification). The details of all inclusion and exclusion criteria have been published previously.[6,9]

In an amendment dated July 22nd, 2014, we extended the follow-up duration to 36 months after the index event. All patients still in the trial after 12 months were contacted in order to acquire informed consent for the extended trial phase.

Randomization and masking

Eligible patients were randomized in a 1:1 ratio to either enhanced and prolonged monitoring (EPM) by means of three 10-day Holter-ECGs which were analyzed in a central core laboratory (intervention group) or standard workup, including ≥24 hours of ECG-monitoring (Holter-ECG and/or telemetry).[6]

Procedures

Clinical follow-up visits took place 3, 6, 12, 18, 24, 30, and 36 months after the index event in both groups. Follow-up visits beyond 12 months were conducted by telephone. We collected information on recent morbidity (including a new diagnosis of AF/atrial flutter), current medication, adverse events, guideline adherence, and disability (modified Rankin Scale). If AF was reported, ECGs tracings were requested from treating physicians/hospitals. Additional diagnostic work-up to identify pAF was not recommended.

Patients in the intervention group received a total of three 10-day two-channel (five-lead) Holter-ECG (CardioMem 3000, Getemed, Teltow, Germany) at baseline and at the 3 and 6 months follow-up visit, respectively. All ECGs in the intervention group were analyzed by an ECG core laboratory, following a predefined standard operating procedure. An alternative thumb-sensor ECG-device was offered to those who refused to repeat the Holter-ECG. The control group received ≥24 hours of ECG-monitoring (telemetry and or Holter-ECG), according to local standards.

AF was defined according to the 2010 European Society of Cardiology guideline[10] including only episodes detected on a 12-lead ECG or that lasted at least ≥30 seconds on a rhythm strip.

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Outcomes

The primary endpoint of the trial was the ECG-documentation of atrial fibrillation (AF) or atrial flutter within 6 months after randomization and before a recurrent stroke. All potential episodes were evaluated by an expert primary endpoint adjudication committee (D.C., U.L., and M.Z.), which was blinded to all other clinical data.

The extended follow-up collected outcome information until 36 months after randomization. Major outcomes included the detection of AF, the recurrence of stroke or systemic embolism, transient ischemic attack (TIA) and death. Events that potentially qualified as recurrent cerebral events (strokes or TIAs) were assessed by an independent stroke adjudication committee (M.K., H.P., and P.U.H.), masked to all data regarding the primary endpoint and to the allocated study group. Stroke was defined according to the criteria of the World Health Organization as an acute onset of focal or global neurologic deficits of presumed vascular origin lasting for more than 24 hours or resulting in death before 24 hours. In case that patients received thrombolytic or recanalization therapy, the event was classified as stroke irrespective of duration of clinical symptoms. If the clinical symptoms last less than 24 hours and the patients were not receiving thrombolytic or recanalization therapy or dying within 24 hours, the event was classified as TIA. TIAs with a corresponding lesion on brain imaging were counted as strokes.

Statistical analysis

Baseline characteristics are presented as means and standard deviation (SD) or frequencies and percentages. For variables that were not normally distributed, the median and interquartile ranges (IQR) are shown. Comparison of event rates in cross tables was performed by chi-square test. Frequency differences are estimated with 95% confidence intervals (CIs).

Because death is a competing risk for detection of atrial fibrillation/flutter, cumulative incidences following the methods of Fine & Gray[11] were calculated, depicted and tested. Times to study end were considered as censored. To separate AF detection in the treatment period (0 to 6 months) from those of the follow-up, conditional survival methods were applied for estimation of cumulative incidence of AF after 6 months. A Cox model with time-dependent covariates was built to model the different risk for AF in the treatment period and afterwards. Time to stroke or death was analyzed by Kaplan-Meier method and log rank test.

Significance level was determined 5% for two-tailed tests. All statistical analyses were performed with SPSS version 26 (IBM Co., Armonk, NY, USA) and R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and results until 12 months of follow-up have been published and are included here to depict the full study results.[6] One thousand six hundred four patients ≥60 years with International Classification of Diseases (ICD) diagnosis 63.x were screened and finally 402 patients were enrolled and randomized at four study centers in Germany from May 8th, 2013 until August 31st, 2014. Four patients were randomized erroneously (two in each group) and were excluded from the final analysis. Two hundred patients were assigned to the intervention group and 198 to the control group. The study population had a mean±SD age of 73±7 years (range, 60 to 96). Forty percentage (160 patients) were female.

Details on the monitoring in the intervention and control group have been published previously.[6] In brief, in the intervention group, 197 patients (99.5%), 128 (75.3% of those remaining in the study and without detected AF) and 116 patients (75.8%) underwent study monitoring at baseline, after 3 and after 6 months, respectively.

In the control group, 188 of 198 patients (95%) underwent Stroke-Unit telemetry for a median duration of 73 hours (IQR, 54 to 84) and 149 of 198 patients (75%) received additional Holter-ECG-monitoring for a median of 24 hours (IQR, 22 to 25). One hundred and eighty-one of 198 patients (91.4%) in the control arm and 178 of 200 patients (89.0%) in the intervention arm had at least 24 hours of monitoring outside the study monitoring.

The primary trial ended as planned after all patients had completed 12 months of follow-up and the last patient's final visit took place on September 16th, 2015. After 12 months, all 342 patients still in the trial were offered an extended follow-up for an additional 2 years, and 274 (80.1%) consented for the extended follow-up. Details are shown in Figure 1 and baseline characteristics of patients consenting for extended follow-up are shown in Table 1. Patients consenting for extended follow-up were on average 3 years younger than those who did not give consent, tended to have less comorbidities, more often had a history of myocardial infarction and coronary artery disease, and had lower initial National Institutes of Health Stroke Scale (NIHSS) score (Supplementary Table 1).

Detection of atrial fibrillation

Within 6 months after randomization, newly diagnosed AF occurred in 13.5% (27 of 200 patients) in the group assigned to EPM, as compared to 5.1% (10 of 198 patients) in the control group (absolute difference, 8.4%; 95% CI, 2.9 to 14.4; *P*=0.004; needed to screen n=12). Details on the AF detection by the study intervention are shown in Supplementary Table 2. One
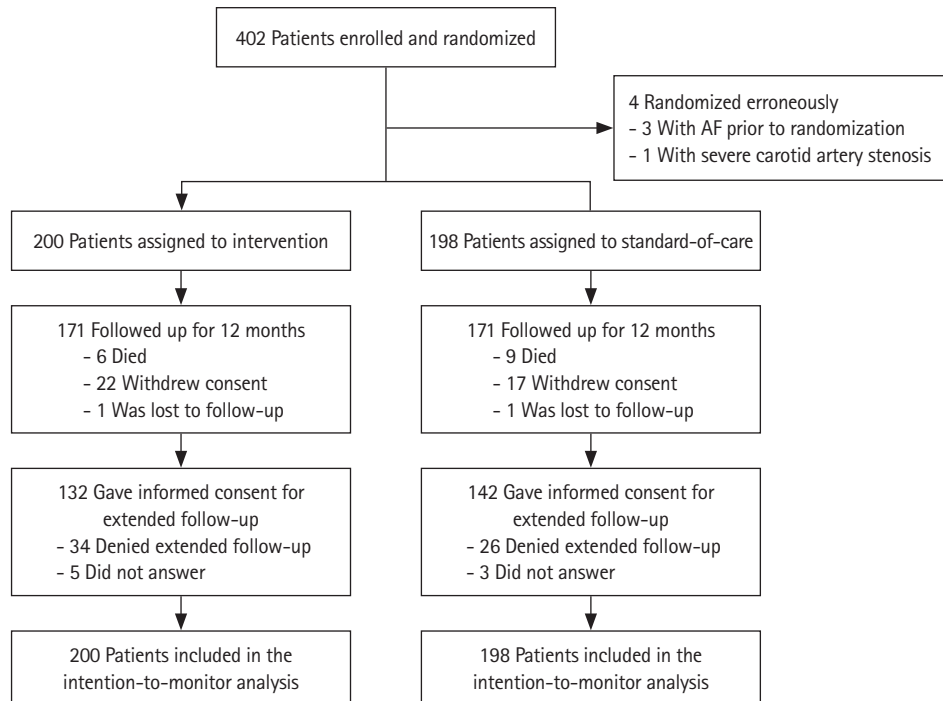
Figure 1. Trial profile. Randomization, electrocardiography monitoring, follow-up, and participation in the extended follow-up. Four hundred and two patients were enrolled and randomized, four patients were randomized erroneously and were excluded from further analysis. Two hundred and seventy-four from 342 participants gave informed consent for extended follow-up. AF, atrial fibrillation.

Table 1. Baseline characteristics of the patients participating in the extended follow-up

Characteristic	Intervention group (n=132)	Control group (n=142)	P
Age (yr)	70.5±6.8	72.3±7.4	0.03
Female sex	51 (38.6)	48 (33.8)	0.45
Medical history			
Hypertension	101 (76.5)	112 (78.9)	0.67
Diabetes	29 (22.0)	35 (24.6)	0.67
Hyperlipidemia	46 (34.8)	64 (45.1)	0.11
Smoking status			
Current smoker	21 (15.9)	24 (16.9)	0.87
Previous smoker	41 (31.1)	42 (29.6)	0.79
Previous ischemic stroke	20 (15.1)	28 (19.7)	0.34
Previous transient ischemic attack	11 (8.3)	14 (9.6)	0.68
Heart failure	5 (3.8)	8 (5.6)	0.58
Myocardial infarction	14 (10.6)	12 (8.5)	0.68
Coronary artery disease	18 (13.6)	26 (18.3)	0.33
Mean creatinine (mg/dL)*	1.0±0.4	1.0±0.3	0.39
Mean ejection fraction (%)†	61±8	60±9	0.85
Symptoms >24 hours	123 (93.2)	134 (94.4)	0.80
Symptoms <24 hours and DWI lesion in MRI	9 (6.8)	8 (5.6)	0.80
Lacunar lesion on brain imaging	42/96 (43.8)	46/94 (48.9)	0.56
TOAST classification			0.02
Large artery atherosclerosis	3 (2.3)	1 (0.7)	
Cardioembolism	37 (28.0)	19 (13.4)	

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Table 1. Continued

Characteristic	Intervention group (n=132)	Control group (n=142)	P
Small-vessel occlusion	40 (30.3)	50 (35.2)	
Stroke of other determined etiology	0 (0)	1 (0.7)	
Stroke of undetermined etiology	52 (39.4)	71 (50.0)	
Score on NIHSS[‡]	3 (1–4)	2 (1–4)	0.11
Time from symptom onset to randomization (day)	3 (2–4)	3 (2–5)	0.34
Mean CHA$_2$DS$_2$VASc score[§]	4.5±1.3	4.7±1.2	0.48
CHA$_2$DS$_2$VASc score			0.32
2	10 (7.6)	7 (4.9)	
3	21 (15.9)	13 (9.2)	
4	32 (24.2)	46 (32.4)	
5	41 (31.1)	41 (28.9)	
6	24 (18.2)	26 (18.3)	
7	4 (3.0)	8 (5.6)	
8	0 (0)	1 (0.7)	
Mean CHADS$_2$ score[‖]	3.3±0.9	3.5±0.9	0.89
CHADS$_2$ score			0.07
2	27(20.5)	16 (11.3)	
3	53 (40.2)	65 (45.8)	
4	42 (32.6)	41 (28.9)	
5	9 (6.8)	20 (14.1)	
6	1 (0.8)	0 (0)	
4–6 pooled	52 (39.4)	61 (43.0)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale.
*Data were missing for one patient in the intervention group; [†]Data were missing in 22 patients in the intervention group and 20 patients in the control group; [‡]Scores on the National Institutes of Health (NIH) Stroke Scale range from 0 to 42, higher scores indicate a greater neurological deficit. Data were missing for one patient in the control group; [§]Scores on the CHA$_2$DS$_2$VASc risk assessment range from 0 to 9, with higher scores indicating a greater risk of thromboembolic events; [‖]Scores on the CHADS$_2$ risk assessment range from 0 to 6, with higher scores indicating a greater risk of thromboembolic events.

case of AF in the control arm was initially not reported by the study site and not included in the primary publication,[6] but was identified during final study close out and was positively adjudicated by the endpoint committee. From the end of the study intervention (6 months) to the end of the follow-up (36 months), there were significantly more new AF cases detected in the control arm than in the intervention arm (12/171 [7.0%] vs. 3/154 [1.9%], absolute difference, 5.1%; 95% CI, 0.6% to 10.1%) (Supplementary Figure 1). The hazard ratio (HR) is 0.33 (95% CI, 0.16 to 0.68; P=0.003) for the estimated AF risk in the control arm up to 6 months calculated with an age-adjusted Cox regression model. In the time period of 6 to 36 month the HR is 10.2 (95% CI, 2.36 to 43.7; P=0.002).

Two thirds of AF cases during extended follow-up were detected by 12-channel surface ECG. Table 2 shows details on AF detection during extended follow-up. The difference in AF incidence between the two arms diminished over time. After 36

months, the cumulative incidence of the AF detection rate was 15.9% in the EPM arm and 12.8% in the control arm (P=0.17) (Figure 2). Of note, 25 of the total 30 AF cases (83%) in the intervention arm were detected by the study intervention. Of all 52 patients, in which AF was detected during follow-up, 18 (34.6%) of the index strokes were documented as cardioembolic, 11 (21.2%) as small vessel occlusion and 19 were classified as stroke of unknown cause (36.5%).

Anticoagulation for atrial fibrillation

Oral anticoagulation was started in all 52 patients with detected AF and the anticoagulation rate was 97% after 12 months, 97% after 18 months, 94% after 24 months, and 100% after 30 and 36 months.

Stroke, transient ischemic attack, and death

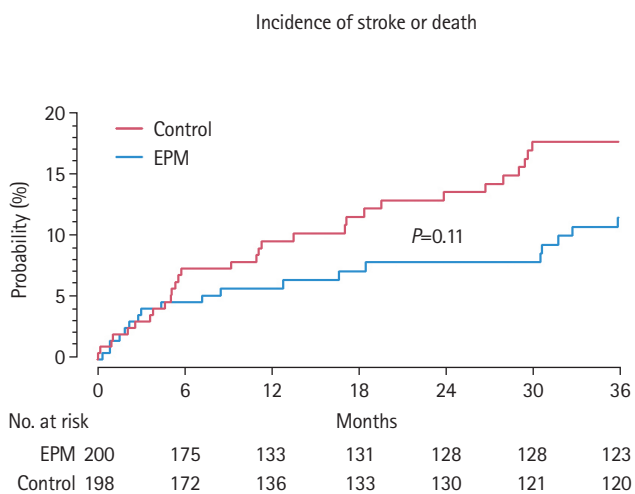During the whole study period, there were 13 stroke events in

Table 2. Endpoints within 3 years of follow-up

	EPM (%) (n=200)	Usual care (%) (n=198)	HR (95% CI)	P
Atrial fibrillation	15.0	11.1	1.45 (0.83–2.51)	0.187
TIA	3.0	4.5	0.65 (0.22–1.98)	0.448
Stroke	5.5	9.1	0.61 (0.29–1.29)	0.191
Death	4.5	6.6	0.71 (0.30–1.65)	0.419
Composite TIA/stroke/death	12.5	19.2	0.65 (0.39–1.07)	0.090

EPM, enhanced and prolonged monitoring; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.
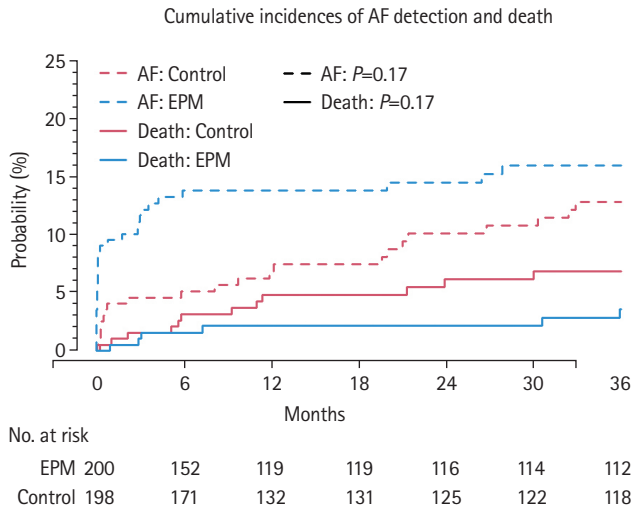
Figure 2. Cumulative incidences of atrial fibrillation (AF) detection in the presence of the competing risk death. EPM, enhanced and prolonged monitoring.

Figure 4. Cumulative incidences of the combined endpoint of transient ischemic attack (TIA), stroke, and death (whatever occurs first). EPM, enhanced and prolonged monitoring.

Figure 3. Cumulative incidences of the combined endpoint of stroke and death (whatever occurs first). EPM, enhanced and prolonged monitoring.

11 patients in the intervention arm (12 ischemic strokes, one hemorrhagic stroke) and 21 stroke events in 18 patients in the control arm (20 ischemic strokes, one hemorrhagic stroke). Event rates after 3 years were estimated 5.5% versus 9.1%

(odds ratio [OR], 0.58; 95% CI, 0.79 to 1.27; P=0.18). Both patients with hemorrhagic stroke also had an ischemic stroke event. Six patients in the intervention arm and nine patients in the control arm had a TIA (one patient in the control arm had two TIAs). No cases of systemic embolism occurred in either group. Nine patients in the intervention arm and 13 patients in the control arm died (P=0.37). Since AF detection and death are competing risks, cumulative incidences were calculated and depicted (Figure 2). Figure 3 shows the incidences of the combined endpoint of stroke and death (whatever occurs first: OR, 0.63; 95% CI, 0.32 to 1.20; P=0.13) and Figure 4 shows the incidences of the combined endpoint of TIA, stroke, and death (whatever occurs first).

Patients with atrial fibrillation and stroke or TIA
Five patients had detection of AF and a recurrent ischemic cerebral event during follow-up. Sixty percentage of AF detections (3 out of 5) occurred in proximity to the recurrent ischemic cerebral event: In one patient in the intervention arm, the detection of AF was 3 days after recurrent ischemic stroke and in two patients in the control arm, the detection of AF was on

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the day of a TIA event. In the two other cases, a recurrent ischemic stroke occurred >1 year after the detection of AF. One patient in the intervention arm was on subtherapeutic dose of apixaban and temporally discontinued anticoagulation for pacemaker implantation when the stroke occurred and in the other patient (control arm), the stroke was associated with an ipsilateral severe carotid artery stenosis while being adequately anticoagulated with phenprocoumon (international normalized ratio [INR] on hospital admission 2.3).

Discussion

We present data on 3 years of follow-up in a study randomizing patients aged ≥60 years with acute ischemic strokes to enhanced and prolonged ECG-monitoring by means of three 10-day Holter-ECGs (EPM) or standard-of care to detect pAF. While there was a significant difference in the primary endpoint of first detection of atrial fibrillation prior to recurrent stroke after 6 and 12 months in the EPM group, this difference diminished over time due to a higher detection rate of AF in the control group and became non-significant beyond 2 years of follow-up. We found a high adherence to anticoagulation in patients with detected new-onset AF. Importantly, there were numerically less strokes, TIAs, and deaths in the EPM arm compared to the control arm.

To date, three large randomized trials for intensified AF detection have been performed in ischemic stroke patients. The 0-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trial[4] applied a 30-day external event recorder in 572 patients with cryptogenic stroke, starting 75 days after the stroke event, while the Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke (CRYSTAL-AF) study[5] used an implantable cardiac monitor in 441 patients with cryptogenic stroke starting 38 days after the stroke event. The third trial is the Find-AF trial,[6] which also included approximately 50% of non-cryptogenic stroke patients and initiated the intervention within a median of 3 days after the qualifying ischemic stroke. All three trials found significantly more cases of AF in the intervention as compared to the control arm. However, the follow-up in EMBRACE was only 90 days and no information on ischemic cerebral events beyond 90 days of follow-up has been reported so far. In CRYSTAL-AF, the minimum duration of follow-up was 12 months, but only a minority of patients was followed beyond 2 years. There were numerically less strokes and TIAs in the intervention arm, but only the combined number of strokes and TIAs (20 vs. 24) has been reported and these events were not blindly adjudicated.[12]

Although the intervention only lasted 6 months in our study, EPM still remained superior to standard-of-care in detecting AF after 12 months (13.5% vs. 6.6%, P=0.021), yet losing significance after 24 months (14.0% vs. 9.1%, P=0.13) and 36 months (14.5% vs. 11.1%, P=0.37). While more patients with AF were detected in the intervention arm in the first 6 months after randomization, there were more AF cases detected in the standard-of-care arm during the following 2.5 years. This suggests that EPM mostly identified AF cases that otherwise would have been detected as clinical AF at a later stage. This is supported by the fact that most AF cases during extended follow-up were diagnosed by routine surface ECG, mostly done by the patients' general practitioner or after having had a recurrent cerebrovascular event. Interestingly, EPM within the first 6 months found as much as 5/6 of all AF cases that were detected during the complete 3 years of follow-up. Our data suggest that AF episodes during a 10-day ECG monitoring are precursors of clinically relevant AF. This might be in contrast to AF episodes >2 minutes detected during continuous monitoring in CRYSTAL-AF: AF was diagnosed in 30% of patients during 36 months of follow-up with an implantable loop recorder, but the detection rate in the control arm was as low as 3% after 3 years.[12] While these differences may also partly be explained by different stroke characteristics (younger patients, lower NIHSS score), the minimum duration of AF that is of clinical relevance may depend on the duration and type of monitoring. We recently showed that AF episodes of 30 seconds or longer (detected by 7-day Holter-ECG) are associated with more severe strokes (comparable to strokes in patients with AF on surface ECG), while episodes lasting <30 seconds were associated with less severe strokes.[13] This is an argument that the threshold of 30 seconds duration of AF on a rhythm strip seems to be adequate for Holter monitoring ≤10 days. Interestingly, in patients with continuous monitoring by implanted pacemakers or defibrillators, but without prior stroke, it has recently been shown that mainly AF episodes that last for >24 hours are associated with a high stroke risk.[14]

The adherence to anticoagulation in monitoring trials seems to be higher than in randomized anticoagulation trials, e.g., the discontinuation rate in Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (NAVIGATE-ESUS)[15] and Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS)[16] was 15% and 25%, respectively. The fact that anticoagulation therapy was mandated by a specific diagnosis (AF in this case) may explain the higher adherence rate in CRYSTAL-AF and Find-AF_{RANDOMISED}.

Although our data imply that short episodes of AF detected during 10-day Holter-ECG are of clinical relevance, this does not prove that they benefit from anticoagulation. Unfortunately, patients with short episodes of AF detected early after stroke have not been included in randomized anticoagulation trials. The question whether prolonged ECG-monitoring for AF after stroke not only increases the AF detection rate, but reduces the risk of recurrent stroke remains unknown and our trial was not powered to provide a definite answer. However, we previously reported numerically fewer stroke, TIAs, and deaths after 12 months in the EPM group[6] and this trend corroborated after 36 months. This is in line with a recent meta-analysis of randomized and observational studies that found a significant reduction of cerebral ischemic events by intensified ECG monitoring.[17] In summary, these findings would support the current clinical practice of treating patients with (short) AF-episodes detected after stroke with anticoagulation. Nevertheless, an adequately powered outcome trial with ischemic stroke and systemic embolism as the primary endpoint is needed to establish prolonged monitoring as an efficacious strategy for secondary stroke prevention. At least one trial, called Find-AF 2 (NCT 04371055) is underway and has already randomised more than 1,100 patients.

Find-AF$_{RANDOMISED}$ should be interpreted in the context of its limitations. The trial was conducted in Germany and we cannot rule out that results would have differed in other countries, health systems or ethnicities. Only 68% and 65% of patients accepted the second and third Holter-ECG. This problem may be solved by more comfortable devices, such as adhesive ECG-patches and/or by an early risk stratification based on age,[18] left atrial size and function,[19] supraventricular ectopy,[20] brain natriuretic peptides,[21,22] or others as recommended in a recent consensus paper.[23]

The decision to extent the follow-up was made during the study conduct and only 80% of patients consented, which is a potential bias. Differences between groups in number of visits to the general practitioner, access to care, socioeconomic status could have resulted in disparities in reporting AF-related symptoms and subsequently receiving an ECG. We tried to address this potential bias by competing risk analysis, but cannot totally excluded it. Moreover, we did not specifically assess the routine monitoring that patients received during extended follow-up. According to registry data from Germany,[24] most patients are treated by their General Practitioner and do not frequently receive prolonged Holter-ECG monitoring. We suppose that our study patients were treated similarly which is in line with 2/3 of AF cases during extended follow-up being detected by 12-lead ECG, and only a minority by implantable loop recorder or prolonged Holter-ECG monitoring.

It was not possible to blind physicians and patients to study assignment. To overcome potential bias, we chose to assess the primary endpoint "detection of AF" and the major secondary endpoint "recurrent cerebral ischemic event" by blinded endpoint committees (prospective randomized open blinded endpoint [PROBE] design). In addition, the sample size and the number of stroke events of this trial were too small to give more than a trend for recurrent cerebral ischemic events. Finally, our results were obtained in stroke patients ≥60 years and AF prevalence is likely to be lower in younger patients.[18]

Conclusions

In conclusion, the extended follow-up of Find-AF$_{RANDOMISED}$ showed that enhanced and prolonged ECG-monitoring detected AF episodes that otherwise would have likely been detected later by clinical practice. The compliance with anticoagulation in AF patients was excellent (>90%) and there was a favorable trend towards fewer strokes, TIAs, and deaths in the EPM arm which might be the result of an earlier initiation of anticoagulation after AF detection. These findings provide the rationale for a larger randomized trial to prove that recurrent or continuous ECG-monitoring for AF and consecutive anticoagulation can reduce recurrent ischemic strokes.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2021.01207.

Disclosure

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Supplementary Table 1. Clinical characteristics of patients giving consent to extended follow-up versus not giving consent

Characteristic	Giving consent for follow-up (n=274)	Not giving consent (n=60)	P
Age (yr)	71.4±7.2	74.5±8.1	0.004
Female sex	99 (36.1)	28 (46.7)	0.128
Medical history			
Hypertension	213 (77.7)	49 (81.7)	0.108
Diabetes	64 (23.4)	21 (35.0)	0.134
Hyperlipidemia	110 (40.1)	24 (40.0)	0.970
Smoking status			
Current smoker	45 (16.4)	15 (25.0)	0.117
Previous smoker	83 (30.3)	15 (25.0)	0.414
Previous ischemic stroke	48 (17.5)	13 (21.7)	0.567
Previous transient ischemic attack	25 (9.1)	3 (5.0)	0.054
Heart failure	13 (4.7)	3 (5.0)	0.428
Myocardial infarction	26 (9.5)	3 (5.0)	0.044
Coronary artery disease	44 (16.1)	5 (8.3)	0.005
Mean creatinine (mg/dL)	1.0±0.3	1.1±0.5	0.297
Mean ejection fraction (%)*	60±9	60±9	0.581
Initial score on NIHSS[†]	2 (1–4)	4 (2–7)	0.001

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

NIHSS, National Institutes of Health Stroke Scale.

*Data were missing in 54 patients in the group giving informed consent and 17 patients in the group not giving informed consent; [†]Scores on the National Institutes of Health (NIH) Stroke Scale range from 0 to 42, higher scores indicate a greater neurological deficit. Data were missing for one patient in the control group.

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Supplementary Table 2. Details of patients with AF detection by the study intervention

Age (yr)	Sex	Days after randomization	Holter ECG (n)	No. of AF episodes	Duration of longest episode (min)
75	F	1	1	1	5,070
76	F	1	1	1	8,940
85	M	1	1	1	1
73	F	1	1	1	0.7
60	M	1	1	12	300
73	M	1	1	2	4,432
74	F	1	1	1	14,400
80	M	2	1	2	1,440
78	M	2	1	1	2
61	M	4	1	1	180
65	F	4	1	2	1
73	F	4	1	4	300
88	M	4	1	1	1,695
72	M	5	1	1	4,380
96	F	6	1	1	913
88	F	6	1	1	4,242
62	M	7	1	1	925
83	F	8	1	1	150
70	M	87	2	1	6
64	M	90	2	1	439
60	F	91	2	3	4
60	M	98	2	1	0.5
75	F	113	2	2	2
72	F	125	2	4	2,790
74	F	187	3	1	0.6

During the first 6 months after randomization, two patients in the intervention arm had AF detection outside of the study intervention.
AF, atrial fibrillation; ECG, electrocardiography.
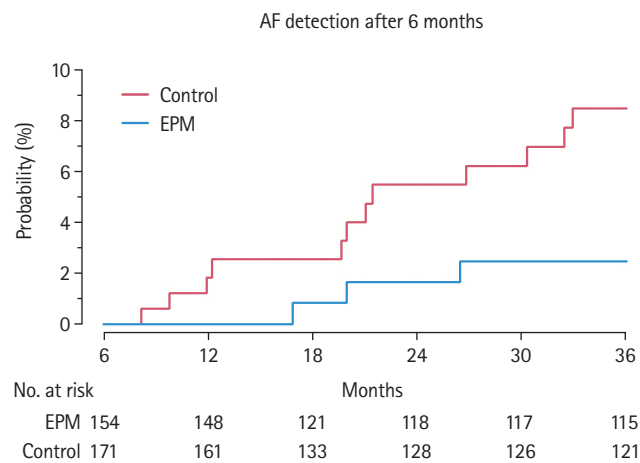
Supplementary Figure 1. Detection of AF conditional on no atrial fibrillation detection until 6 months. EPM, enhanced and prolonged monitoring.