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Originalpublikation: *Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFrandomised): an open-label randomised controlled trial. In: Lancet Neurology, Epub ahead of print Feb 07, 2017. DOI: 10.1016/S1474-4422(17)30002-9*

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Zusammenfassung des wissenschaftlichen Inhalts
(Rolf Wachter)

Vorhofflimmern ist eine häufige Ursache des ischämischen Schlaganfalles, aber es wird häufig nicht diagnostiziert, weil es nur anfallsweise auftritt. Die Detektion von Vorhofflimmern bei Schlaganfallpatienten hat eine klinische Konsequenz, weil die Sekundärprävention üblicher Weise von einer Plättchenhemmung auf eine orale Antikoagulation umgestellt wird. Bisher wurde eine erweiterte Diagnostik nach Vorhofflimmern erst durchgeführt, wenn nach ausführlicher Diagnostik keine Ursache für den Schlaganfall gefunden wurde. Die Hypothese der hier vorgestellten Find-AF randomised Studie war, dass Patienten älter als 60 Jahre mit Schlaganfall generell von einem verlängerten Herzrhythmusmonitoring profitieren.
398 Patienten wurde innerhalb von 7 Tagen nach einem ischämischen Schlaganfall in die randomisierte Find-AF randomised-Studie eingeschlossen. Die Hälfte der Patienten bekamen ein Langzeit-EKG über 3x 10 Tage (zum Studieneinschluss, nach drei und nach sechs Monaten, Interventionsarm). Die andere Hälfte bekam die übliche Diagnostik, inklusive mindestens 24 Stunden Aufzeichnung des Herzrhythmus (Kontrollarm). Der primäre

Endpunkt war die Detektion von Vorhofflimmern (über mindestens 30 Sekunden), adjudiziert durch ein unabhängiges Endpunktkommitee. Sekundäre Endpunkte waren unter anderen erneute Schlaganfälle und transitorisch ischämische Attacken.

13,5 % der Patienten im Interventionsarm und 4,5 % der Patienten im Kontrollarm wurden nach 6 Monaten mit Vorhofflimmern diagnostiziert (p=0.002), number needed to screen 11.

Im Interventionsarm gab es numerisch weniger erneute Schlaganfälle (5 versus 9) und transitorisch ischämische Attacken (3 versus 5) als im Interventionsarm (p=n.s.).

Diese Daten stellen den späten Beginn eines Rhythmusmonitoring und die Beschränkung auf kryptogene Schlaganfälle in Frage und unterstützen ein Konzept einer frühen verlängerten Rhythmusdiagnostik unabhängig von der Schlaganfallätiologie.

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Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF$_{RANDOMISED}$): an open-label randomised controlled trial

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Summary

Background Atrial fibrillation is a major risk factor for recurrent ischaemic stroke, but often remains undiagnosed in patients who have had an acute ischaemic stroke. Enhanced and prolonged Holter-electrocardiogram-monitoring might increase detection of atrial fibrillation. We therefore investigated whether enhanced and prolonged rhythm monitoring was better for detection of atrial fibrillation than standard care procedures in patients with acute ischaemic stroke.

Methods Find-AF$_{RANDOMISED}$ is an open-label randomised study done at four centres in Germany. We recruited patients with acute ischaemic stroke (symptoms for 7 days or less) aged 60 years or older presenting with sinus rhythm and without history of atrial fibrillation. Patients were included irrespective of the suspected cause of stroke, unless they had a severe ipsilateral carotid or intracranial artery stenosis, which were the exclusion criteria. We used a computer-generated allocation sequence to randomly assign patients in a 1:1 ratio with permuted block sizes of 2, 4, 6, and 8, stratified by centre, to enhanced and prolonged monitoring (ie, 10-day Holter-electrocardiogram [ECG]-monitoring at baseline, and at 3 months and 6 months of follow-up) or standard care procedures (ie, at least 24 h of rhythm monitoring). Participants and study physicians were not masked to group assignment, but the expert committees that adjudicated endpoints were. The primary endpoint was the occurrence of atrial fibrillation or atrial flutter (30 sec or longer) within 6 months after randomisation and before stroke recurrence. Because Holter ECG is a widely used procedure and not known to harm patients, we chose not to assess safety in detail. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01855035.

Findings Between May 8, 2013, and Aug 31, 2014, we recruited 398 patients. 200 patients were randomly assigned to the enhanced and prolonged monitoring group and 198 to the standard care group. After 6 months, we detected atrial fibrillation in 14% of 200 patients in the enhanced and prolonged monitoring group (27 patients) versus 5% in the control group (nine of 198 patients, absolute difference 9·0%; 95% CI 3·4–14·5, p=0·002; number needed to screen 11).

Interpretation Enhanced and prolonged monitoring initiated early in patients with acute ischaemic stroke aged 60 years or older was better than standard care for the detection of atrial fibrillation. These findings support the consideration of all patients aged 60 years or older with stroke for prolonged monitoring if the detection of atrial fibrillation would result in a change in medical management (eg, initiation of anticoagulation).

Funding Boehringer Ingelheim.

Background

Atrial fibrillation is a major risk factor for ischaemic stroke. Atrial fibrillation-related strokes can be more severe than those from other causes[1] and patients with stroke and atrial fibrillation have a high risk of recurrent ischaemic events.[2] The detection of atrial fibrillation in patients with acute ischaemic stroke is of major clinical relevance,[3] because it usually shifts the secondary prevention therapy from antiplatelet drugs to oral anticoagulation. Oral anticoagulation therapy leads to a 60–70% relative risk reduction of recurrent strokes in those with atrial fibrillation, compared with placebo.[4] However, atrial fibrillation might escape routine short-term electrocardiogram (ECG)-monitoring if it occurs intermittently, because the episodes are often short, occur in irregular patterns, and are frequently asymptomatic.[5] Guidelines recommend that patients with atrial fibrillation should be given oral anticoagulants, irrespective of whether they have paroxysmal (defined as episodes of at least 30 s, but occurring for fewer than 7 days) or persisting atrial fibrillation.[6,7]

Results from observational studies[8–12] and one small randomised trial[13] showed that the detection of paroxysmal atrial fibrillation after cerebral ischaemia can be increased by prolonged monitoring. According to national and international stroke guidelines,[14–16] patients with acute ischaemic stroke should be monitored with immediate 12-channel surface ECG, continuous stroke unit monitoring, or additional Holter-ECG-monitoring. Two surveys showed that these guidelines are widely

Lancet Neurol 2017

Published Online February 7, 2017 http://dx.doi.org/10.1016/S1474-4422(17)30002-9

See Online/Comment http://dx.doi.org/10.1016/S1474-4422(17)30016-9

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Research in context

Evidence before this study

We searched PubMed, Web of Science, and available meta-analyses for "randomised/randomized trial monitoring atrial fibrillation stroke" between June 10–17, 2016 for papers published between January, 2010, and June 17, 2016. There were no language restrictions. Two randomised multicentre trials were identified, and both were confined to "cryptogenic strokes" and the study participants were highly selected based on inclusion and exclusion criteria. Another small randomised trial (n=100) was done in only two centres. All three studies were published after the initiation of our trial. Although using different monitoring techniques and different monitoring periods, these trials showed that, in patients with cryptogenic stroke, more patients with atrial fibrillation were diagnosed in the intervention as compared with the control group.

Added value of this study

In our multicentre trial, 402 patients with stroke aged 60 years and older, in whom the detection of atrial fibrillation had a potential therapeutic consequence, were randomly assigned to three times 10-day-Holter electrocardiogram (ECG) monitoring or usual care. We found an absolute 9% higher incidence of atrial fibrillation in the intervention group than in the control group, with no significant interaction in all predefined subgroups, similar to the detection rate in the previous randomised trials in cryptogenic stroke. This finding raises questions about the current practice to only apply prolonged monitoring to patients with cryptogenic stroke. Moreover, our study reported numerically fewer strokes, transient ischaemic attacks, and deaths in the intervention than in the control group during 1 year of follow-up. Only one of the above mentioned trials reported recurrent ischaemic events and similarly showed a non-significant reduction in events in the monitoring group.

Implications for all the available evidence

Our study supports the application of ECG-monitoring to a broad population of patients with stroke, specifically, those aged 60 years and older with stroke, irrespective of suspected stroke cause, in whom the detection of atrial fibrillation is of therapeutic importance.

adopted in routine care,[17,18] but less than 20% of patients with stroke receive prolonged ECG-monitoring exceeding 24 h. However, prolonged ECG-monitoring is adequate, if underlying paroxysmal atrial fibrillation is suspected. The 2016 Atrial Fibrillation guideline of the European Society of Cardiology recommends at least 72 h of Holter monitoring and gives implantable cardiac monitors a class IIa recommendation.[19] In clinical practice, infrequent prolonged ECG-monitoring might lead to underdiagnosis of underlying atrial fibrillation.

Hence, we hypothesised that, in patients with acute ischaemic stroke presenting with sinus rhythm, enhanced and prolonged Holter-ECG-monitoring reveals more underlying atrial fibrillation than does usual care (according to stroke guidelines) irrespective of the suspected stroke cause. This monitoring might lead to a reduction in the occurrence of recurrent strokes.

Methods

Study design and participants

Find-AF$_{RANDOMISED}$ was an investigator-initiated randomised, controlled, open-label multicentre trial done in four centres in Germany (University Medicine Göttingen [Göttingen], University Medicine Mainz [Mainz], Horst-Schmidt-Kliniken Wiesbaden [Wiesbaden], and Nordwest-Krankenhaus Sanderbusch [Sande]). We assessed atrial fibrillation or atrial flutter and recurrent stroke or transient ischaemic attack (TIA) through independent blinded expert adjudication committees (prospective randomised open-label blinded endpoint evaluation [PROBE] design).

See Online for appendix

For the **study protocol** see http://www.herzzentrum-goettingen.de/de/media/20140910_391_Find-AF-randomised_Studienprotokoll_3_0%20(2).pdf

All study centres had a stroke unit certified by the German Stroke Society. The study protocol was approved by the local ethics board at each study site.

Eligible patients were 60 years or older with acute (clinical symptom onset ≤7 days) ischaemic strokes (documentation of an acute lesion on brain imaging or duration of symptoms ≥24 h). We included patients for whom the detection of atrial fibrillation has therapeutic consequences and for whom no evidence-based therapy is available after minimal diagnostic work-up (admission ECG and ultrasonography of the brain supplying arteries). We excluded patients with known or documented atrial fibrillation, those with an indication or contraindication for oral anticoagulation, and those with a relevant symptomatic ipsilateral carotid stenosis (>50% according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET] classification), as this is a cause of stroke with evidenced-based therapeutic recommendations. In a protocol amendment on Nov 18, 2013, this criterion was extended to patients with clinically significant vertebral artery stenosis of more than 50%, intracranial stenosis suspicious of atherosclerotic origin, and those with acute arterial dissections, because many of these patients require dual antiplatelet therapy. The complete details of all inclusion and exclusion criteria are shown in the appendix and have been published previously.[20] Patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to enhanced and prolonged monitoring (EPM) by means of three 10-day Holter-ECGs (ECG analysis in a central core laboratory) within 6 months (intervention group) or standard of care workup, including 24 h or longer ECG (Holter or telemetry)-monitoring according to

guidelines.[21] Permuted-block randomisation with block sizes of 2, 4, 6, and 8 was stratified by each participating study centre. Randomisation was done using sequentially numbered, opaque sealed envelopes, to be opened in consecutive order. The computer-generated random allocation sequence was provided by the Institut für anwendungsorientierte Forschung und klinische Studien (IFS) Göttingen, Germany. Participants were enrolled and assigned to study interventions by the local study teams. These study teams took care of the study participants during the entire trial, but were not involved in Holter ECG analysis. Participants and study physicians were not masked to group assignment, but both endpoint committees (one for adjudication of atrial fibrillation, and one for cerebral ischaemic events) were.

Procedures

Patients in the intervention group were monitored with a 10-day two-channel (five-lead) Holter-ECG (CardioMem 3000, Getemed, Teltow, Germany) at baseline, at 3 months and at 6 months (during scheduled follow-up visits), similarly to a previous observational study.[22] Once atrial fibrillation was detected and confirmed by the independent atrial fibrillation endpoint committee, no further Holter-ECG was done. Patients who refused to repeat the Holter-ECGs at the follow-up visits were offered to use a thumb-sensor ECG-device (Zenicor-EKG; Zenicor, Stockholm, Sweden) and were encouraged to record at least two 30 s ECG-episodes per day on 10 consecutive days to provide a compensatory form of prolonged ECG-monitoring. All ECG recordings in the intervention group were assessed by a central ECG core-laboratory (led by JS) and the analysis followed a predefined standard operating procedure.

We did clinical follow-up visits 3, 6, and 12 months after randomisation in both groups. Patients in the intervention group received the second Holter-ECG at 3 months, and the third at 6 months. Information on recent morbidity (including a new diagnosis of atrial fibrillation or flutter), current medication, adverse events, and guideline adherence was collected. Vital signs, neurological deficits (National Institute of Health Stroke Scale and modified Rankin Scale), quality of life (visits after 3 and 12 months), and health-care use (visits after 6 and 12 months) were reassessed. Results for quality of life and health-care use will be reported separately. We obtained a 12-channel surface ECG after 12 months in both groups.

The 2010 European Society of Cardiology guideline on atrial fibrillation[7] characterises the arrhythmia as showing absolutely irregular RR-intervals (without any repetitive ECG pattern), lacking a distinct P-wave on surface ECG (though apparently regular electrical activity may be visible in some leads), and showing an atrial cycle length of less than 200 milliseconds (or >300 beats per min), if visible. We included only episodes that lasted long enough to record a 12-lead ECG or at least 30 s on a rhythm strip.

New onset of atrial flutter was defined as any episode of supraventricular tachycardia specified as such by an expert in electrophysiology and lasting at least 30 s. These episodes typically show an atrial frequency of 250–340 beats per min.

Outcomes

The primary endpoint of the trial was the detection of atrial fibrillation or atrial flutter on ECG within 6 months after randomisation and before a recurrent stroke. All episodes potentially qualifying for the primary endpoint were assessed by an expert primary endpoint adjudication committee (led by DC), which was masked to all other clinical data. The assessment was done centrally and coordinated by the centre for clinical trials at Würzburg University, Würzburg, Germany.

Major secondary outcomes included the detection of atrial fibrillation within 12 months; the recurrence of stroke, systemic embolism, or death within 12 months; and the detection of atrial fibrillation within 12 months, but censored by hospital admission for atrial fibrillation. Events that potentially qualified as recurrent cerebral ischaemic events (strokes or TIAs) were assessed by an expert stroke adjudication committee (led by PUH) masked to all data regarding the primary endpoint and to the allocated study group. We report primary endpoints, major secondary endpoints, and the TIA endpoint. Other secondary endpoints will be reported separately as some analyses are ongoing.

The trial did not have a data safety monitoring board because Holter ECG is a widely used procedure and not known to harm patients. We therefore chose not to assess safety in detail.

Statistical analysis

The sample size estimation is based findings of the previous trial Find-AF,[9] in which we found newly detected atrial fibrillation after cerebral ischaemia by 7 days of Holter monitoring in 12·5% of patients. In Find-$AF_{RANDOMISED}$, we did 23 additional days of ECG-monitoring and therefore estimated to find atrial fibrillation in at least 15% of patients. For the control arm, we assumed an atrial fibrillation detection rate of 5% within 6 months. A sample size of 400 patients and a projected dropout rate of 15% would lead to 340 patients to be analysed. This gave our study a power of 83% to distinguish between atrial fibrillation detection rates of 15% (intervention arm) versus 5% (control arm) and 98% power to distinguish between detection rates of 20% versus 5%.

The primary analysis was the comparison of the crude rates of atrial fibrillation or flutter detection. The incidence curves for atrial fibrillation detection were computed from the competing risk analysis. Stroke, systemic embolism, and death were regarded as competing risks, and discontinuation of study participation was treated as a dropout. The subgroup analyses were done with crude atrial fibrillation detection rates. To find out whether the effect of EPM was similar in specific subgroups, respective

analyses were done for age, sex, baseline $CHADS_2$ score (a score that reflects the risk of thromboembolism in patients with atrial fibrillation; sum of congestive heart failure [1 point if present], hypertension [1 point], age >75 years [1 point], diabetes [1 point], and stroke or transient ischaemic attack [2 points]), National Institutes of Health Stroke Scale (NIHSS), and presence of lacunar symptoms on admission (table). Differences of crude rates in EPM and controls were computed within each subgroup. For each subgroup variable, the difference of the differences was assessed, ie, (EPMsub1-controlsub1)-(EPMsub2-controlsub2). 95% CI and p-values were computed using the Gaussian approximation. Patients with missing values in a subgroup variable were excluded from the respective analysis. All statistical analyses were done with SPSS (version 23.0).

In the first version of the statistical analysis plan, Kaplan-Meier estimates for the discovery rates in both groups and their difference with 95% CI were chosen as the method for the primary analysis. The prespecified secondary analysis of the primary endpoint was defined as presentation of the crude discovery rates and their difference (atrial fibrillation or flutter detected: yes or no). That a patient might have reached the primary endpoint if they would not have died or had a recurrent stroke is not relevant from this perspective.

However, we noticed that the Kaplan-Meier analysis (although often carried out in this context) is not suitable, because it censors patients with recurrent strokes or death. Kaplan-Meier estimation assumes non-informative censoring, which means that, after having been censored, participants had endpoints at the same rate as those who have not been censored. In fact, after recurrent stroke or death, the endpoint might not occur by definition. Therefore, we decided to drop Kaplan-Meier

	Intervention group (n=200)	Control group (n=198)
Mean age (years)	72·1 (SD 7·4)	73·2 (SD 7·5)
Age ≥73 years	99 (49·5%)	101 (51·0%)
Women	85 (42·5%)	75 (37·9%)
Medical history		
Hypertension	157 (78·5%)	159 (80·7%)
Diabetes	56 (28·0%)	52 (26·4%)
Hyperlipidaemia	77 (38·5%)	87 (44·2%)
Smoking status		
Current smoker	34 (17·0%)	36 (18·2%)
Previous smoker	57 (28·5%)	59 (29·8%)
Previous ischaemic stroke	34 (17·0%)	43 (21·7%)
Previous transient ischaemic attack	13 (6·5%)	18 (9·1%)
Heart failure	11 (5·5%)	9 (4·6%)
Myocardial infarction	20 (10·0%)	18 (9·1%)
Coronary artery disease	27 (13·5%)	34 (17·3%)
Mean creatinine (μmol/L) *	92 (SD 41)	91 (SD 51)
Mean ejection fraction (%)†	60 (SD 9)	60 (SD 10)
Ejection fraction <50%†	16 (8·0%)	11 (5·6%)
Symptoms >24 h	188 (94·0%)	189 (95·5%)
Symptoms <24 h and DWI lesion in MRI	12 (6·0%)	9 (4·5%)
Lacunar lesion on brain imaging	53/143 (37·1%)	56/136 (44·1%)
Medium or high risk sources of cardioembolism	60 (30·0%)	56 (28·3%)
TOAST classification		
Large Artery Atherosclerosis	6 (3·0%)	1 (0·5%)
Cardioembolism	45 (22·5%)	30 (15·2%)
Small-vessel occlusion	55 (27·5%)	63 (31·8%)
Stroke of other identified cause	0 (0·0%)	1 (0·5%)
Stroke of unknown cause	94 (47·0%)	103 (52·0%)
Score on NIH stroke scale‡	3 (IQR 1–5)	2 (1–4)
NIH stroke scale >2 – no (%)	111 (55·5%)	98 (49·5%)
(Table continues in next column)		

	Intervention group (n=200)	Control group (n=198)
(Continued from previous column)		
Time from symptom onset to randomisation (days)	3 (IQR 2–5)	3 (2–5)
Time from symptom onset to start of study monitoring (days)	4 (3–5)	NA
Lacunar syndrome*	38 (19·1%)	59 (29·8%)
Mean CHA_2DS_2VASC score§	4·8 (SD 1·3)	4·8 (SD 1·2)
CHA_2DS_2VASC score		
2	11 (5·5%)	7 (3·5%)
3	29 (14·5%)	17 (8·6%)
4	36 (18·0%)	57 (28·8%)
5	58 (29·9%)	59 (29·8%)
6	51 (25·5%)	45 (22·7%)
7	13 (6·5%)	12 (6··1%)
8	2 (1·0%)	1 (0·5%)
Mean $CHADS_2$ score¶	3·5 (SD 0·9)	3·5 (SD 0·9)
$CHADS_2$ score ¶		
2	34 (17·0%)	20 (10·1%)
3	63 (31·5%)	82 (41·4%)
4	77 (38·5%)	69 (34·8%)
5	24 (12·0%)	27 (13·6%)
6	2 (1·0%)	0 (0·0%)
4–6	103 (51·5%)	96 (48·5%)

Data are n (%), unless otherwise specified. DWI=Diffusion-weighted imaging. TOAST=Trial of Org 10172 in Acute Stroke Treatment. CHADS=Sum of congestive heart failure (1 point if present), hypertension (1 point), age >75 years (1 point), diabetes (1 point), and stroke or transient ischaemic attack (2 points). *Data were missing for one patient in the intervention group. †Data were missing in 44 patients in the intervention group and 37 patients in the control group. ‡Scores on the National Institutes of Health (NIH) Stroke Scale range from 0 to 42, and higher scores indicate a greater neurological deficit. Data were missing for one patient in the control group. §Scores on the CHA_2DS_2VASC 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.

***Table*: Baseline characteristics of the study participants**

analysis and chose an analysis of the crude rates to be the primary analysis (compared with a Fisher's exact test). Analysis was based on the intention-to-treat population.

Role of the funding source

The funder had no role in the trial design and conduct, data analysis or interpretation, or publication and authorship decisions of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 8, 2013, and Aug 31, 2014, 2848 patients aged 60 years and older were admitted with an ICD diagnosis I 63.x (cerebral infarction) in the four study centres in Germany, based on data from each hospital database. These patients comprise the screening population. We enrolled and randomised 402 patients (figure 1). Four patients were randomised erroneously (two to each group) and were excluded from the final analysis. 200 patients were assigned to the intervention group and 198 to the control group. 357 (90%) of 398 patients completed the 6-month follow-up. The trial ended as planned after all patients had completed 12 months of follow-up, and the last patient's final visit was on Sept 16, 2015. For the two largest study centres, which randomly assigned 251 patients, detailed information for the patients who did not enter the study is provided in the appendix (page 5).

The study population had a mean age of 73 years (SD 7, range 60–96 years). 160 of 398 patients were women. The median time from symptom onset to randomisation was 3 days (IQR 2–5). Baseline characteristics are shown in the table. All 398 patients had carotid artery ultrasonography. 198 of 200 patients in the intervention group and 195 of 198 patients in the control group had intracranial imaging. 162 of 200 patients in the intervention group and 171 of 198 patients in the control group had intracranial duplex sonography. 98 of 200 patients in the intervention group and 93 of 198 patients in the control group underwent magnetic resonance angiography or CT angiography of the entire cerebrovascular tree. After the diagnostic stroke work-up had been completed at the discretion of the local investigator, 197 patients were classified as having cryptogenic stroke[23] and 201 as having non-cryptogenic stroke, mostly small vessel occlusion (118 patients) and cardioembolic stroke (75 patients).

In the intervention group, 199 of 200 patients had Holter-ECG-monitoring at baseline (median duration 9·5 days (IQR 7·9–9·8). The procedure was initiated a median of 3·5 days (3·0–5·0) after symptom onset and 0·0 (0·0–1·0) days after randomisation. After 3 months, 116 patients (68% of those remaining in the study and without detected atrial fibrillation) were monitored, with median duration 9·6 days (IQR 8·6–9·9). After 6 months, 100 patients (65% of those remaining in the study and without detected atrial fibrillation) had Holter-ECG-monitoring (median duration 9·6 days, IQR 8·2–9·9). The details of the study monitoring are shown in the appendix (pp 9–10).

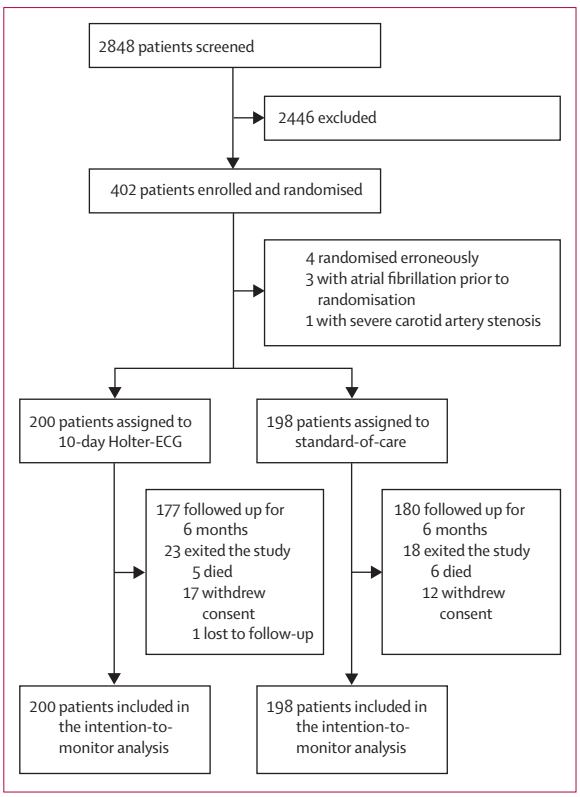

Figure 1: **Trial profile**

In the control group, 188 of 198 patients had stroke-unit telemetry for a median duration of 73 h (IQR 54–84) and 149 of 198 patients received additional Holter-ECG-monitoring for a median of 24 h (22–25). 181 of 198 patients in the control group and 178 of 200 patients in the intervention group had at least 24 h of monitoring outside of monitoring done in the study.

The detection rate of newly diagnosed atrial fibrillation before recurrent stroke or systemic embolism within 6 months of randomisation was 13·5% (27 of 200 patients) in the group assigned to EPM, compared with 4·5% (nine of 198 patients) in the control group (absolute difference 9·0%, 95% CI 3·5–14·6; p=0·002, number needed to screen 11; figure 2A). The Kaplan-Meier estimate of incidence was 13·6% in the intervention group and 4·6% in the control group, leading to a similar estimate for the difference (difference 9·1%, 95% CI 3·5–14·8; log-rank p=0·002). Additional analyses computed from a competing risk model showed similar results (13·7% in the intervention group *vs* 4.6% in the control group; difference 9·2%, 95% CI 3·6–15·2; p=0·004). The mean time and SD from randomisation to atrial fibrillation detection were similar in both groups (33 days, SD 51 *vs* 36 days, SD 56; p=0·88).

No patient with detected atrial fibrillation had a recurrent stroke or systemic embolism before the detection of atrial fibrillation within 6 months (appendix pp 9–10). One of the 27 patients in the EPM group had atrial flutter. The median duration of the longest atrial fibrillation episode during Holter monitoring was 5 h (IQR 2 min to 46 h) and the number of detected atrial fibrillation episodes ranged from 1–12, median 1 episode (IQR 1–2). 17 of 25 atrial fibrillation episodes detected by EPM were longer than 6 min. Details on the duration of the atrial fibrillation episodes are shown in figure 3.

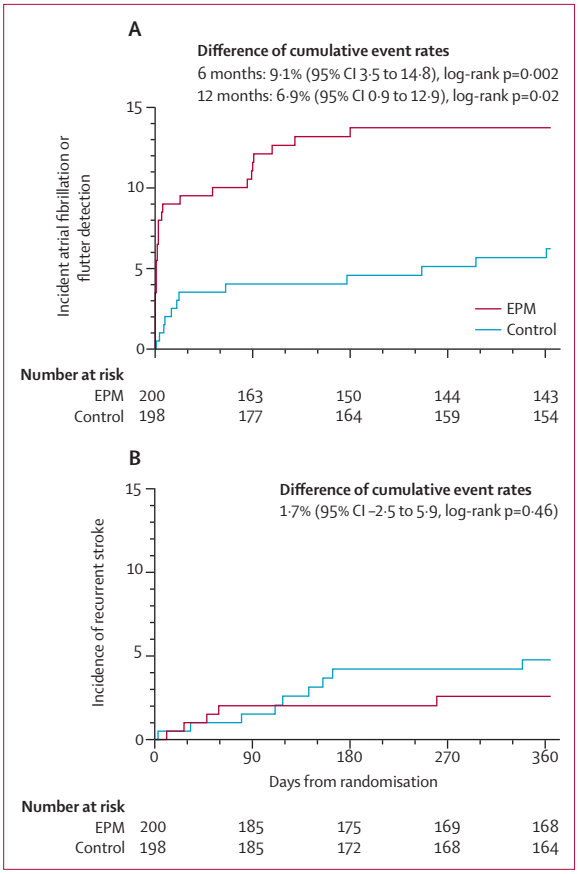

***Figure 2*: Incidence of atrial fibrillation and recurrent stroke**
(A) Time to first detection of atrial fibrillation showing crude rates. (B) Time to first occurrence of recurrent stroke, analysed with death as a competing risk and accounting for dropouts. These incidence curves were computed from competing risk analysis. EPM=enhanced and prolonged monitoring.

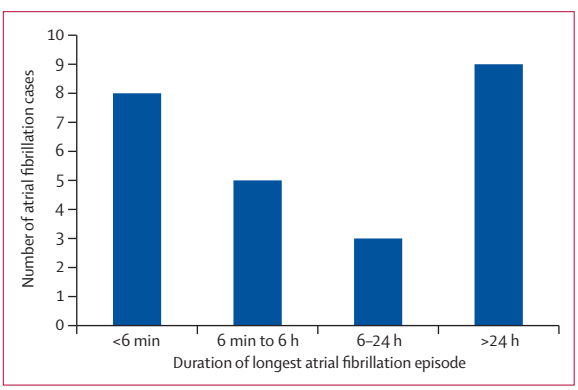

***Figure 3*: Number of cases with atrial fibrillation, according to its duration**
Atrial fibrillation cases in the intervention group, according to the duration of the longest atrial fibrillation episodes. The analysis includes the 25 patients with atrial fibrillation detected with Holter-ECG monitoring. Two cases were detected outside the study monitoring and are not included.

Within the EPM group, atrial fibrillation was detected after randomisation by means of prolonged Holter-ECG monitoring in 25 patients (18 during the first 10-day episode, six during the second 10-day episode, and one during the third 10-day episode), and in two patients by means of routine clinical procedures between hospital discharge and the 3-month visit. Figure 4 shows findings on the first atrial fibrillation detection day within the three Holter ECGs for 25 of 27 patients with atrial fibrillation in the EPM group. 12 (7%) patients in the intervention group had the alternative thumb-sensor ECG instead of Holter-ECG after 3 months and 16 (10%) patients had the alternative thumb-sensor ECG instead of Holter-ECG after 6 months. No cases of atrial fibrillation were detected by the thumb-sensor ECG.

In the control group, seven patients were diagnosed with atrial fibrillation within the first month after the index stroke, one patient in month 3, and one patient in month 6. After the completion of 12 months of follow-up, three additional cases of atrial fibrillation were detected in the control group, resulting in a total 6·1% (12 of 198 patients), and the detection rate remained 13·5% (27 of 200 patients) in the EPM group (absolute difference 7·4%, 95% CI 1·6–13·2; p=0·02, number needed to screen 13; figure 2A). Kaplan-Meier analysis yielded event rates of 13·7% in the intervention group and 6·9% in the control group (difference 6·9%, 95% CI 0·9–12·9; log-rank p=0·02). Similar results were obtained in a competing risk analysis (13·7% in the intervention group *vs* 6·2% in the control group, difference 7·5%; 95% CI 1·8–14·1, p=0·02). Atrial fibrillation after 12 months censored by hospital admission was similar to the previous detection rate (13·5% in the intervention group *vs* 6·1% in the control group, p=0·02). Recurrent strokes after 12 months occurred in five patients in the intervention group versus nine patients in the control group, p=0·28; and the number of total deaths after 12 months was six in the intervention group versus nine in the control group, p=0·45.

Oral anticoagulation was initiated in all 39 patients with detected atrial fibrillation and 34 of 35 patients received oral anticoagulation at the 12-month visit (two patients with atrial fibrillation died before the 12-month visit, one patient with atrial fibrillation withdrew consent, and one patient had atrial fibrillation detected at the 12-month visit by 12 channel surface ECG and was given anticoagulation drugs thereafter). Anticoagulation was stopped in one patient in the intervention group. More patients received anticoagulation in the intervention

group (18%) than in the control group (13%, p=0·17). Details on the anticoagulation therapy in both groups including the reasons for anticoagulation are shown in appendix pp 11–12. Within 12 months, there were two gastrointestinal bleeds (both in the intervention group), one secondary haemorrhagic transformation (in the control group), and one case of epistaxis in a patient taking oral anticoagulation (in the intervention group).

Within 12 months of follow-up, eight (five recurrent strokes and three TIAs) patients in the intervention group and 14 (nine recurrent strokes and five TIAs) patients in the control group had recurrent cerebral ischaemic events. Two patients (one in each group) had two recurrent strokes per person. Figure 2B shows the major secondary endpoint of stroke recurrence within 12 months in both groups. Kaplan-Meier stroke rate was 5·4% in the control group and 3·7% in the intervention group, difference 1·7% (95% CI –2·5 to 5·9, p=0·46). No cases of systemic embolism occurred in either group. Kaplan-Meier rate for death after 12 months was 4·3% in the intervention group versus 4·8% in the control group, difference –0·5% (95% CI –3·7 to 4·7, p=0·82).

The figure in the appendix p 8 shows analyses for the primary outcome in various prespecified subgroups, and in patients with cryptogenic versus those with non-cryptogenic stroke. No significant interactions were observed by age, sex, NIHSS, CHADS-2, symptoms at admission, or cryptogenic stroke.

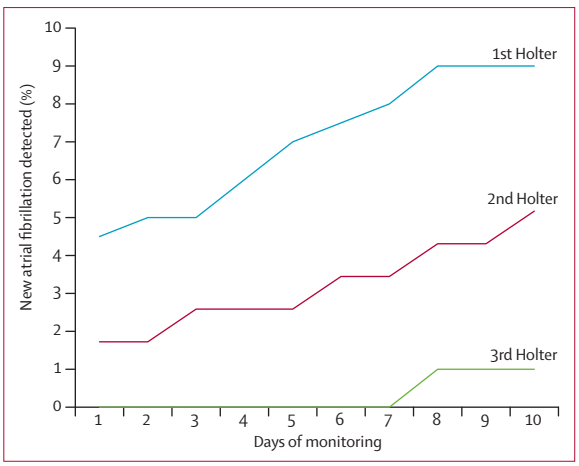

Figure 4: **Cumulative incidence of detected atrial fibrillation within the three 10-day periods of Holter ECG monitoring in 199 (1st Holter), 116 (2nd Holter), and 100 (3rd Holter) patients**
18 cases of atrial fibrillation (blue line) were detected within the first 10-day monitoring, six cases (red line) within the second 10-day and one case (green line) within the third 10-day

Discussion

We compared enhanced and prolonged ECG-monitoring by means of three 10-day Holter-ECGs (EPM) with standard care procedures in patients with acute ischaemic stroke aged years or older. EPM resulted in a significantly higher detection rate of atrial fibrillation and atrial flutter. Although the intervention only lasted 6 months, EPM was still superior to usual care in detecting atrial fibrillation after 12 months. This finding implies that the atrial fibrillation cases revealed by EPM could have been missed or detected later by means of conventional diagnostics. In contrast with a previous report,[22] the second and third ECG-monitoring episode revealed markedly less atrial fibrillation compared with the first.

Two other randomised trials have investigated atrial fibrillation detection by intensified ECG-monitoring in patients with acute ischaemic stroke. The EMBRACE trial[24] applied a 30-day loop-recording-belt, and the CRYSTAL-AF study[5] used an implantable cardiac monitor. Both trials were confined to patients with cryptogenic strokes. The protocols of both trials required various diagnostic procedures before randomisation, which caused delays in the initiation of the atrial fibrillation detection method (randomisation could be realised 75 days after symptom onset in EMBRACE[24] and 38 days in CRYSTAL-AF;[5] implantation occurred within 10 days thereafter in 89% of patients in CRYSTAL-AF). In contrast, we used a more pragmatic approach, which required only minimal diagnostic work-up (12-lead ECG and ultrasonography of brain supplying arteries) and allowed intensified atrial fibrillation screening to be initiated early (3 days after symptom onset and monitoring), which has been considered advantageous.[25] A more thorough diagnostic work-up before randomisation might have led to a selection bias that could have affected the generalisability of the study results because patients with findings suggestive of a specific stroke cause, (eg, hypokinetic left ventricular segment or persistent foramen ovale) but no 12 (7%) patients in the intervention group had the alternative thumb-sensor ECG instead of Holter-ECG after 3 months and 16 (10%) patients had the alternative thumb-sensor ECG instead of Holter-ECG after 6 months. No cases of atrial fibrillation were detected by the thumb-sensor ECG. option might have been excluded before the initiation of an intensified ECG monitoring. We did not find any difference in the atrial fibrillation detection rate between patients with cryptogenic and non-cryptogenic stroke.

Due to the pragmatic inclusion criteria, 370 of 1604 admitted patients with ischaemic stroke (appendix p 5) during the recruitment period met the eligibility criteria of our trial, The broad inclusion criteria support the generalisability of our findings. Acknowledging that the cause of recurrent stroke might vary from the initial event in nearly half of the patients,[26] our hypothesis considered all patients with stroke to be at high risk for future cardiovascular events, and aimed to identify undetected atrial fibrillation as a potential risk factor irrespective of the suspected cause of the qualifying event. Moreover, our monitoring strategy might be easier to implement into the routine work-up of patients with stroke than specialised external loop recorders or implanted devices. Holter-ECG-monitoring has the advantage of being widely available, cheap, non-invasive,

familiar to most physicians and, within our trial, had better compliance than reported previously.[9] Furthermore, unlike automatically triggered devices, Holter-ECGs document the onset and ending of suspicious episodes. and devices with a second ECG-channel have a greater chance of capturing a clearly visible P wave. Both of these aspects are helpful to make a more valid diagnosis of atrial fibrillation and a better differentiation from artifacts compared with external or internal loop recording devices.[27] The analysis in an ECG core laboratory allows a standardised and thorough analysis of all ECG data.[28] It helps to identify even short episodes of atrial fibrillation that might otherwise escape routine clinical practice and thus guarantees a high accuracy of the atrial fibrillation diagnosis.

The detection of atrial fibrillation is of major clinical importance and, in accordance with guidelines, the detection is prompted the initiation of oral anticoagulation in all qualifying patients. As expected, more patients were given anticoagulants for atrial fibrillation in the EPM group than in the control group after 3, 6, and 12 months.

The ultimate goal of enhanced and prolonged ECG-monitoring is the reduction of subsequent cerebral ischaemic events by prescribing anticoagulation to patients with newly detected atrial fibrillation. The incidence of recurrent strokes and TIAs was lower in the intervention group of our trial than in the control group, and similar to the 21% fewer cerebral ischaemic events after 12 months in the intervention group of CRYSTAL-AF.[5] However, our trial was not powered for this clinical endpoint, and a larger trial is needed to show that intensified atrial fibrillation monitoring reduces the rate of recurrent strokes.

67% of atrial fibrillation cases in the intervention group were detected within the first 10-day Holter ECG. We therefore propose a stepwise approach to detect atrial fibrillation in patients with stroke. All patients in whom the detection of atrial fibrillation is of therapeutic relevance should receive prolonged Holter-ECG monitoring for 7–10 days, initiated within the first days after symptom onset. If the initial monitoring episode is negative, the individual risk of atrial fibrillation should be assessed and those with suggestive factors (eg, repeated cryptogenic strokes or embolic stroke of unknown source,[29] frequent supraventricular ectopies,[30] elevated natriuretic peptides,[31] left atrial enlargement, or reduced atrial contractility[32]) should undergo additional intensified monitoring.

Find-AF$_{\text{RANDOMISED}}$ should be interpreted in the context of its limitations. The trial was done in Germany and we cannot rule out that results would have differed in other countries, health systems, or in people of different ethnic origins. The participation rate during the second and third Holter-ECG was lower (116 of 170 patients after 3 months and 100 of 153 patients after 6 months, respectively) than during the first Holter-ECG (appendix p 9) and the yield of repeated monitoring could be higher, assuming better compliance. This problem might be solved by the use of more comfortable devices, such as adhesive ECG-patches. More prolonged monitoring approaches, such as implanted devices, might have yielded an even higher rate of atrial fibrillation in this cohort. Whether or not short atrial fibrillation episodes detected by means of extensive heart rhythm monitoring should be treated similarly to conventionally detected atrial fibrillation, and especially in which duration of atrial fibrillation anticoagulation treatment is required, remains unknown and must be established in future trials, such as the ongoing ARTESIA trial (NCT01938248) and the ongoing NOAH-AFNET6 trial (NCT02618577). We did not measure the quality of anticoagulation therapy. As the study design did not allow masking of patients or physicians, we chose to assess the primary endpoint of detection of atrial fibrillation and the major secondary endpoint of recurrent cerebral ischaemic event by masked endpoint committees (PROBE design). The classification of baseline strokes into the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria was based on information provided by the local investigators and a structured analysis from an independent panel might have led to different results. Finally, our results were obtained in patients aged 60 years or older, and atrial fibrillation prevalence is likely to be lower in younger patients.[33]

Find-AF$_{\text{RANDOMISED}}$ showed that enhanced and prolonged ECG-monitoring using three 10-day Holter-ECG recordings resulted in a higher detection rate of atrial fibrillation compared with standard-care procedures in a cohort of patients with stroke aged 60 years or older with stroke. Most of the atrial fibrillation cases were detected within the first 10-day Holter-ECG. Prolonged and enhanced monitoring should be used in all patients with stroke if the detection of atrial fibrillation would lead to anticoagulation therapy.

Contributors

RW wrote the first draft of the report with input from KG, MWK, and RW edited the manuscript. GG did the statistical analysis. JS lead the ECG core lab, and DC and PUH lead the core-labs for endpoint adjudication and contributed to design and conduct of the endpoint classification (atrial fibrillation and cerebral events, respectively). All other authors contributed to data collection, analysis, and interpretation. All authors critically revised the manuscript.

Declaration of interests

The Find-AF$_{\text{RANDOMISED}}$ trial (NCT 01855035) was sponsored by an unrestricted research grant from Boehringer Ingelheim to the University of Göttingen, Germany. RW reports having been an investigator or consultant for, or received fees from Bayer, Berlin Chemie, Bristol-Myers-Squibb, Boehringer Ingelheim, Boston Scientific, CVRx, Gilead, Johnson & Johnson, Medtronic, Novartis, Pfizer, Relypsa, Sanofi, Servier since 2003. He received research grants from Boehringer Ingelheim, European Union and Bundesministerium für Bildung und Forschung (BMBF). KG reports personal fees and non-financial support from Bayer, personal fees and non-financial support and grant from Boehringer Ingelheim, personal fees from Bristol-Meyers Squipp, personal fees from Daiichi Sankyo, personal fees and non-financial support from Pfizer. GG reports grants from University Göttingen within the FIND-AF-randomised trial (FIND-AF-randomised is supported by an unrestricted grant to the University Göttingen from Boehringer Ingelheim), during the conduct of the study; grants from University Göttingen within DZHK analysis projects (the DZHK is funded by a BMBF grant), personal fees from

Charité - Universitätsmedizin Berlin within the TIM-HF-II trial for data safety and monitoring board membership (TIM-HF-II is supported by a BMBF grant to the Charité), grants from University Hospital Würzburg within the MOOD-HF trial for biometry and steering committee membership (MOOD-HF is supported by a BMBF grant and an unrestricted grant to the University Hospital Würzburg from Lundbeck) and grants from Reha-Klinikum and CaRita-S,. PK reports grant and personal fees from Boehringer Ingelheim, personal fees from Bayer, personal fees from Bristol-Myers Squibb. JL reports personal fees from Pfizer and grants from Boehringer Ingelheim. PUH reports grants from University Göttingen (within FIND-AF randomized; FIND-AF randomized is supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), during the conduct of the study; grants from German Ministry of Research and Education, grants from European Union, grants from Charité – Universitätsmedizin Berlin grants from Berlin Chamber of Physicians, grants from German Parkinson Society, grants from University Hospital Würzburg, grants from Robert Koch Institute, grants from German Heart Foundation, grants from Charité – Universitätsmedizin Berlin (within Mondafis; Mondafis is supported by an unrestricted research grant to the Charité from Bayer), grants from University Hospital Heidelberg (within RASUNOA-prime; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo). DC has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, Bayer, Bristol-Myers-Squibb and Daiichi-Sankyo; he also received consultant or speaker fees from Bayer, Bristol-Myers-Squibb, Boehringer Ingelheim and Daiichi-Sankyo. SG, AM, NB, EP, MW-K, AS, and AG report grants from Boehringer Ingelheim, during the conduct of the study. MA reports grants from Boehringer Ingelheim, during the conduct of the study; and grants from Bayer.

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