Finding atrial fibrillation in stroke - randomised evaluation of enhanced and prolonged Holter-ECG (NCT01855035)

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Conflicts of interest

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Author Disclosure Information:

R. Wachter: Research Grant; Significant; Boehringer Ingelheim. Speakers' Bureau; Modest; Bayer, Boehringer Ingelheim, BMS/Pfizer, Daiichi. K. Gröschel: Speakers' Bureau; Modest; Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Pfizer. Honoraria; Modest; Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Daiichi Sankyo, Pfizer. G. Gelbrich: None. G.F. Hamann: None. P. Kermer: Speakers' Bureau; Modest; Boehringer Ingelheim. Consultant/Advisory Board; Modest; Boehringer Ingelheim. Other; Modest; Travel Grant, Boehringer Ingelheim. J. Liman: None. J. Seegers: None. K. Wasser: None. A. Schulte: None. F. Jürries: None. A. Messerschmid: None. N. Behnke: None. S. Gröschel: None. T. Uphaus: None. A. Grings: None. T. Ibis: None. S. Klimpe: None. M. Wagner-Heck: None. M. Arnold: None. E. Protsenko: None. P.U. Heuschmann: Research Grant; Modest; From University Göttingen during study conduct (within FIND-AFrandomized, from German Ministry of Research and Education, EU, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert-Koch-Institute, Charité–Universitätsmedizin Berlin (within MonDAFIS; MonDAFIS is supported by an unrestricted research grant to the Charité from Bayer), 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 and Daiichi Sankyo). D. Conen: None. M. Weber-Krüger: None.
Atrial fibrillation (AF) is a common risk factor for (recurrent) stroke, but paroxysmal AF episodes often escape the routine diagnostic workup.

The current AHA/ASA guidelines recommend:
“For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event (Class IIa; Level of Evidence C)” (Kernan et al., Stroke 2014)

Two randomized trials (EMBRACE and CRYSTAL-AF) established that prolonged monitoring detects more AF as compared to standard of care or repetitive Holter-ECG in patients with “cryptogenic strokes”
A shift in paradigm

Retrospection (Cryptogenic stroke, ESUS)

Cerebral events (stroke, TIA)

1st stroke

Time

Anticoagulate & Prevent

Look ahead (Find-AF randomised)

Stroke patients have a high risk of underlying AF irrespective of stroke etiology and should be anticoagulated if AF is detected

Why did this stroke happen? Can I find an explanation? Is it cryptogenic? Does it look embolic? Should I anticoagulate?

AF cluster
Primary Objective

We aimed to determine whether enhanced and prolonged monitoring (3 x 10-day Holter ECG) for atrial fibrillation / atrial flutter (AF) in stroke patients aged 60 years and above results in a higher detection rate of AF (before recurrent stroke) compared to standard-of-care procedures (including at least 24 hours of continuous heart rhythm monitoring)
Primary Endpoint:
Detection of atrial fibrillation or atrial flutter (adjudicated by an independent adjudication committee) before recurrent stroke within 6 months after randomisation.
Study design

- **prospective randomized multicenter trial** (ClinicalTrials.gov NCT01855035)

- **investigator-initiated, academic trial with an unrestricted grant** from Boehringer Ingelheim for the conduct of the study

- **recruitment: 16 months** (May 8th, 2013 to August 31st, 2014) at **four study centers** in Germany; assessments: 0, 3, 6 and 12 months

- **open label design with blinded endpoint assessment** (PROBE) (two endpoint committees: AF and stroke/TIA)

- randomization with variable block size in **1:1 ratio**, stratified by center

- target sample size: 400 (83 % power for 15 % AF-yield in intervention arm vs. 5 % in control arm; 98 % power for 20 % AF-yield in intervention arm vs. 5 % in control arm)

- **intention to monitor analysis**
Intervention

Enhanced and prolonged Holter-ECG monitoring:

*Enhanced monitoring* = analysis in a dedicated ECG core laboratory.

*Prolonged monitoring* = 3 x 10-day Holter-ECG 0, 3 and 6 months after stroke.

Device used: *CardioMem 3000*, getemed, Teltow, Germany (5 leads, continuous recording).

*Alternative thumb-sensor ECG monitoring*

Patients unwilling to repeat the Holter-ECG after 3 or 6 months were alternatively offered to use a thumb-sensor ECG (Zenicor, Stockholm, Sweden). Patients were required to record two 30-second episodes per day on 10 consecutive days.

*Weber-Krüger et al., AHJ 2014*
2848 patients screened
(hospitalization for ischemic stroke, ICD diagnosis I 63.x, age ≥ 60 years)

14 %
402 randomized

4 randomized erroneously
- 3 AF prior to randomization
- 1 severe carotid stenosis

200 assigned to intervention
- 200 received 10-day Holter-ECG

177 followed-up after 6 months,
23 exited the study
- 5 died
- 17 withdrew consent
- 1 lost to follow-up

200 included in the intention-to-monitor analysis

198 assigned to control
- 198 received standard-of-care

180 followed-up after 6 months,
18 exited the study
- 6 died
- 12 withdrew consent

198 included in the intention-to-monitor analysis
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention group (n=200)</th>
<th>Control group (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age - years ± SD</td>
<td>72.1 ± 7.4</td>
<td>73.2 ± 7.5</td>
</tr>
<tr>
<td>female sex - no (%)</td>
<td>85 (42.5 %)</td>
<td>75 (37.9 %)</td>
</tr>
<tr>
<td>symptoms ≥ 24 hours</td>
<td>188 (94.0 %)</td>
<td>189 (95.5 %)</td>
</tr>
<tr>
<td>symptoms &lt; 24 hours but DWI lesion on MRI</td>
<td>12 (6.0 %)</td>
<td>9 (4.5 %)</td>
</tr>
<tr>
<td>median NIHSS score (IQR)</td>
<td>3 (1;5)</td>
<td>2 (1;4)</td>
</tr>
<tr>
<td>mean CHADS&lt;sub&gt;2&lt;/sub&gt; score ± SD</td>
<td>3.5 ± 0.9</td>
<td>3.5 ± 0.9</td>
</tr>
<tr>
<td>Median time from symptom onset to randomization – days (IQR)</td>
<td>3 (2;5)</td>
<td>3 (2;5)</td>
</tr>
</tbody>
</table>
Control arm
ECG-monitoring

**Stroke-Unit telemetry:**
188 patients (95 %)
median duration: 73 (54;84) hours

**Additional Holter-ECG:**
149 patients (75 %)
median duration: 24 (22;25) hours
## Intervention arm

### ECG-monitoring

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>3-month-visit</th>
<th>6-month-visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>scheduled for Holter-ECG by study protocol</td>
<td>200</td>
<td>170</td>
<td>153</td>
</tr>
<tr>
<td>any prolonged study ECG-monitoring</td>
<td>199# (99.5 %)</td>
<td>128 (75.3 %)</td>
<td>116 (75.8 %)</td>
</tr>
<tr>
<td>study Holter-ECG monitoring</td>
<td>199# (99.5 %)</td>
<td>116 (68.2 %)</td>
<td>100 (65.3 %)</td>
</tr>
<tr>
<td>median duration of Holter-ECG (IQR)</td>
<td>9.5 d (8.0; 9.8 d)</td>
<td>9.6 d (8.6; 9.9 d)</td>
<td>9.6 d (8.2; 9.9 d)</td>
</tr>
<tr>
<td>thumb-sensor-ECG (Holter-ECG refused)</td>
<td>na</td>
<td>12 (7.1 %)</td>
<td>16 (10.4 %)</td>
</tr>
</tbody>
</table>

# One patient received no Holter-ECG at baseline for unknown reasons, but continue the intervention at the 3 month visit.
Primary Endpoint:
AF after 6 months (before rec. stroke)

AF detected (% of patients)

- EPM: 13.5%
- Control: 4.5%

Difference 9.0% (CI: 3.5; 14.6%)

p = 0.002

Number needed to screen 11

Months since Randomisation
Duration of Atrial Fibrillation in the Intervention Arm

Duration of longest AF episode

- 30s - 6 minutes: 8 cases
- 6 minutes - 6 hours: 5 cases
- 6 to 24 hours: 3 cases
- > 24 hours: 9 cases
Secondary Endpoint:
AF after 12 months

EPM: 13.5%
Difference: 7.4% (CI: 1.6; 13.2%)
p-value: 0.02
Number needed to screen: 13

Control: 6.1%

N at risk:
- EPM: 200, 163, 150, 144, 143
- Control: 198, 177, 164, 159, 154
Anticoagulation for AF

All patients with newly diagnosed AF in both trial arms were started on oral anticoagulation

97% maintained anticoagulation at the 12 month visit

<table>
<thead>
<tr>
<th></th>
<th>intervention group</th>
<th>control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>after 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anticoagulation for AF</td>
<td>15/174 (8.6 %)</td>
<td>5/170 (2.9 %)</td>
<td>0.02</td>
</tr>
<tr>
<td>after 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anticoagulation for AF</td>
<td>21/166 (12.7 %)</td>
<td>8/163 (4.9 %)</td>
<td>0.01</td>
</tr>
<tr>
<td>after 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anticoagulation for AF</td>
<td>25/166 (15.1 %)</td>
<td>10/166 (6.0 %)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Secondary Endpoint: Recurrent stroke after 12 months

All recurrent strokes were ischemic

p = 0.28

Days from randomization

Incidence of recurrent stroke [%]

Control

EPM

4.5%

2.5%
## Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group (n=200)</th>
<th>Control Group (n=198)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF detection rate after 6 mo. &amp; before recurrent stroke</td>
<td>27 (13.5%)</td>
<td>9 (4.5%)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Major secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF detection rate after 12 mo.</td>
<td>27 (13.5%)</td>
<td>13 (6.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Recurrent strokes after 12 mo.</td>
<td>5 (2.5%)</td>
<td>9 (4.5%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Total deaths after 12 mo.</td>
<td>6 (3.0%)</td>
<td>9 (4.5%)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Other secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA after 12 months</td>
<td>3 (1.5%)</td>
<td>5 (2.5%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Primary Endpoint subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events</th>
<th>Total no.</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL SAMPLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;73 years</td>
<td>11/101</td>
<td>2/97</td>
<td>0.94</td>
</tr>
<tr>
<td>≥73 years</td>
<td>16/99</td>
<td>7/101</td>
<td></td>
</tr>
<tr>
<td>SEX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>12/115</td>
<td>5/123</td>
<td>0.32</td>
</tr>
<tr>
<td>female</td>
<td>15/85</td>
<td>4/75</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>9/89</td>
<td>2/99</td>
<td>0.86</td>
</tr>
<tr>
<td>&gt;2</td>
<td>18/111</td>
<td>7/98</td>
<td></td>
</tr>
<tr>
<td>CHADS-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>12/97</td>
<td>4/101</td>
<td>0.87</td>
</tr>
<tr>
<td>4-6</td>
<td>15/103</td>
<td>5/96</td>
<td></td>
</tr>
<tr>
<td><strong>SYMPTOMS AT ADMISSION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no lacunar symptoms</td>
<td>24/161</td>
<td>9/139</td>
<td>0.53</td>
</tr>
<tr>
<td>lacunar symptoms</td>
<td>2/38</td>
<td>0/59</td>
<td></td>
</tr>
<tr>
<td><strong>LESIONS IN BRAIN IMAGING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-lacunar</td>
<td>19/83</td>
<td>6/73</td>
<td>0.09</td>
</tr>
<tr>
<td>lacunar</td>
<td>4/53</td>
<td>3/56</td>
<td></td>
</tr>
</tbody>
</table>
Limitations

1) study only performed in Germany, Caucasian population → results may differ in other countries, health care systems and ethnicities

2) participation rate for prolonged Holter-ECG monitoring decreased over time → AF rate probably underestimated, yield may be higher with more comfortable devices (e.g. adhesive patches)

3) Role of short AF episodes on risk of stroke and which duration of AF requires antiocoagulation is unknown
Summary

Prolonged and enhanced monitoring by means of 3 times 10 day Holter ECG increased the detection rate of Atrial Fibrillation 3-fold (absolute 9.0 %) as compared to usual care in a cohort of stroke patients aged ≥ 60 years.

There were numerically fewer recurrent strokes, fewer TIA’s and fewer deaths in the intervention group as compared with the control group.
Conclusion

EPM should be considered for all stroke patients in whom the detection of AF is of therapeutic relevance.
TRIAL COMMITTEES

COORDINATING INVESTIGATORS
R. Wachter and K. Gröschel

STEERING COMMITTEE
R. Wachter (chair), K. Gröschel (co-chair), G. Gelbrich (study biometrician), M. Weber-Krüger (study coordinator).

ECG CORE LABORATORY

ATRIAL FIBRILLATION ADJUDICATION COMMITTEE
D. Conen (chair), U. Laufs, M. Zabel.

RECURRENT CEREBRAL ISCHEMIA ADJUDICATION COMMITTEE
P. U. Heuschmann (chair), E. Jüttler, H. Poppert.
PARTICIPATING SITES, INVESTIGATORS AND COORDINATORS*
*sites listed according to patient enrolment (number of randomized patients), names listed alphabetically


Back up slides
Inclusion criteria
1. Recent cerebral ischemia defined as stroke (sudden focal neurologic deficit lasting >24 h consistent with the territory of a major cerebral artery and categorized as ischemic) and/or a corresponding lesion on brain imaging
2. Stroke symptoms started ≤7 days ago
3. Age ≥60 years
4. mRS ≤2 (prior to index event)

Exclusion criteria
1. History of AF/flutter or documented AF/flutter prior to randomization
2. Indication for oral anticoagulation at randomization
3. Absolute contraindication for oral anticoagulation at randomization
4. Intracerebral bleeding in medical history
5. Patient scheduled for Holter ECG or cardiac event-recording monitoring ≥ 48 h
6. Carotid artery stenosis of >50% (NASCET) needing revascularization and ipsilateral to ischemic territory (Amendment 18-NOV-2013: extended to those with significant vertebral artery stenosis ≥ 50%, intracranial stenoses suspicious of atherosclerotic origin and those with acute arterial dissections.)
7. Implanted pacemaker device or cardioverter/defibrillator
8. Life expectancy < 1 year for reasons other than stroke (e.g. metastatic cancer disease)
9. Concomitant participation in another randomized controlled trial
Principal Investigators:
R. Wachter, Göttingen
K. Gröschel, Mainz

4 study sites:
Göttingen (R. Wachter/J. Liman)
Mainz (K. Gröschel)
Sanderbusch (P. Kermer)
Wiesbaden (G. Hamann/S. Klimpe)
## Comparison between Monitoring studies

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Screening modality</th>
<th>Participants (n)</th>
<th>Mean age</th>
<th>Lacunar strokes included</th>
<th>Mean NIHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMBRACE(^1)</td>
<td>30-day Event Recorder</td>
<td>572</td>
<td>73</td>
<td>no</td>
<td>Not reported</td>
</tr>
<tr>
<td>CRYSTAL-AF(^2)</td>
<td>Implantable cardiac monitor</td>
<td>441</td>
<td>62</td>
<td>yes</td>
<td>1.8</td>
</tr>
<tr>
<td>Find-AF randomised(^3)</td>
<td>3x10-day Holter</td>
<td>402</td>
<td>73</td>
<td>yes</td>
<td>3.7</td>
</tr>
</tbody>
</table>
# AF detection rate and cerebral events

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Recruitment rate (patients/study site/month)</th>
<th>Detection rate screening arm (%)</th>
<th>Detection rate control/comparetor arm (%)</th>
<th>NNS</th>
<th>Reduction recurrent stroke/TIA in intervention vs. control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMBRACE⁷</td>
<td>1.1</td>
<td>16.1</td>
<td>3.2</td>
<td>8</td>
<td>Not reported</td>
</tr>
<tr>
<td>CRYSTAL-AF⁸</td>
<td>0.2</td>
<td>8.9</td>
<td>1.4</td>
<td>14</td>
<td>-21% (15 vs. 19 patients)</td>
</tr>
<tr>
<td>Find-AF randomised</td>
<td>6.3</td>
<td>13.5</td>
<td>4.5</td>
<td>11</td>
<td>-43% (8 versus 14 patients)</td>
</tr>
</tbody>
</table>
Why old-fashioned Holter?

Holter ECG

External Event Recorder

Implantable Cardiac Monitor

Wachter and Rybak, Akt Kardiol 2015