Atrial Fibrillation Screening Post-Stroke

Peter Higgins

Specialty Training Registrar & Honorary Teaching Fellow
☐ Study funded through Chief Scientist Office (Scotland) grant

☐ Study software & hardware donated by Novacor

☐ No other declarations
Therapeutic importance of AF detection after stroke

How should we investigate for AF & PAF?
  - Guidelines
  - Evidence for different strategies
  - Patient groups & RCTs

Uncertainties & Recommendations
AF as a risk factor for stroke

- AF increases risk of stroke in general population \(^1\)
- Risk increased further 2-3 fold in patients with prior TIA / IS \(^2,3\)
- High long term risk \(^4,5\)
- Early recurrence risk high \(^6\)
  - 5% within 14 days in RCT populations

1. Wolf, Stroke 1991
2. Easton, Lancet Neurol 2012
3. Lip, Chest 2010
5. Kolominsky, Stroke 2001
6. Hart, Stroke 2002
- 6 trials, n = 2,900
- Mean age 69 years
- Adjusted-dose warfarin vs placebo
- Reduction in stroke
  - 64% (95% CI, 49% to 74%)
- ARR
  - Primary, 2.7% / year
  - Secondary, 8.4% / year
- HR-adjusted 0.34; 95% CI, 0.20 – 0.57) vs. placebo
- HR-adjusted 0.38; 95% CI, 0.23 – 0.64) vs. ASA

Lancet 1993;342(8882):1255-62
11 trials, n = 11,748 (mean 70 years)

- Adjusted-dose warfarin vs antiplatelet

- Reduction in stroke
  - 37% (95% CI, 23% to 48%)

- ARR
  - Primary, 0.9% / year
  - Secondary, 7.0% / year (n=3,647)

⇒ Large differential benefit of modified secondary prevention in AF

Ann Intern Med. 2007;146(12):857-867
Anticoagulant therapy in cryptogenic stroke

- Recurrent ischaemic stroke
  - Medium intensity OAC; RR 0.80 (95% CI 0.56 – 1.14)
  - High intensity OAC; RR 1.02 (95% CI 0.49 – 2.13)

- Major bleeding complication
  - Medium intensity OAC; RR 1.93 (95% CI 1.27 – 2.94)
  - High intensity OAC; RR 9.0 (95% CI 3.9 – 21)

⇒ In absence of AF, guidelines recommend antiplatelet therapy

Cochrane Database Syst Rev 2012:9;CD001342
AF as a risk factor for stroke
AF as a risk factor for stroke

- Strong risk factor for recurrent stroke
- Highly modifiable
  - Anticoagulation vs. Antiplatelet increment
- Anticoagulation only supported if AF identified
  - Detection of AF a function of investigative strategy
- Rationale for investigation for AF & occult PAF
Detection of AF following Stroke
Detection of AF following Stroke

- What do the guidelines recommend?
- On what basis?
  - Evidence for investigative strategies
- What scenarios do we face?
- How do RCT data assist?
<table>
<thead>
<tr>
<th>Modality</th>
<th>SIGN</th>
<th>NICE</th>
<th>ESO</th>
<th>AHA / ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-lead ECG</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Continuous cardiac monitoring</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>24-hour ECG monitoring (Holter)</td>
<td></td>
<td>✔ ∗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Investigation</td>
<td></td>
<td>✔ ∗</td>
<td>✔ ∗</td>
<td>✔ ∗</td>
</tr>
</tbody>
</table>

* - If no other cause found

Other Investigation:
- “Cardiac monitoring”; Cardiac event monitoring
Guidelines reflect evidence

- Observational data
- Retrospective; Selected populations
- Direct comparisons lacking
- Few randomised studies

Limited recommendations

- Under-detection?
- Aetiological risk factors co-exist \(^1,2\)

1. Schulz et al, Stroke 2003
2. Kim, Stroke 2011
Diagnostic Investigations - 12-lead ECG
AF is identified in 11.8% presenting with TIA \(^1\)

AF is identified in 18% of patients presenting with IS \(^2\)

- Likely to be higher in elderly \(^3\)

Repeated 12-lead at 24 hours:

- AF identified in an additional 4.5\% \(^4\)

1. Lopes et al, Stroke 2001
2. OCSP, BMJ 1992
## Detection Strategies – Ward Monitoring

<table>
<thead>
<tr>
<th>Modality</th>
<th>Duration</th>
<th>Design</th>
<th>Sample (n)</th>
<th>AF detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous monitoring (^1)</td>
<td>72 hours</td>
<td>Prospective</td>
<td>496</td>
<td>5.4%</td>
</tr>
<tr>
<td>- Centralised &amp; automated</td>
<td></td>
<td>Selected</td>
<td>80.4%</td>
<td></td>
</tr>
<tr>
<td>Continuous Monitoring (^2)</td>
<td>24 hours</td>
<td>Retrospective</td>
<td>133</td>
<td>0%</td>
</tr>
<tr>
<td>- Bedside monitor</td>
<td></td>
<td>Selected</td>
<td>75.9%</td>
<td></td>
</tr>
</tbody>
</table>

1. Rizos et al, Stroke 2012
2. Lazarro et al, J Stroke & Cerebr Dis 2012
• **24-hour Holter**
  - Systematic review: Prospective studies with consecutive patients \(^1\)
  - Estimates range 3.8 – 6.1%; Combined estimate 4.6% (n = 558)

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1. Liao et al, Stroke 2007
2. Schuchert et al, Pacing & Clin Electrophys 1999
3. Stahrenberg et al, Stroke 2010
• 24-hour Holter
  • Systematic review: Prospective studies with consecutive patients
  • Estimates range 3.8 – 6.1%; Combined estimate 4.6% (n = 558)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample (n) IS/TIA (%)</th>
<th>24 hours</th>
<th>48 hours</th>
<th>72 hours</th>
<th>168 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuchert</td>
<td>Prospective</td>
<td>82</td>
<td>1.2%</td>
<td>3.7%</td>
<td>6.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consecutive</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stahrenberg</td>
<td>Prospective</td>
<td>229</td>
<td>4.8%</td>
<td>6.4%</td>
<td></td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>Consecutive</td>
<td>68.6%</td>
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<td></td>
<td></td>
<td></td>
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<th>Sample (n)</th>
<th>IS /TIA (%)</th>
<th>AF detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive CEM ¹</td>
<td>96 hours</td>
<td>Prospective</td>
<td>55</td>
<td>73.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consecutive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantable CEM ²</td>
<td>2 weeks</td>
<td>Cryptogenic</td>
<td>24</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Implantable CEM ³</td>
<td>6 months</td>
<td>RCT</td>
<td>441</td>
<td>100%</td>
<td>8.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cryptogenic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-invasive CEM ⁴</td>
<td>30 days</td>
<td>RCT</td>
<td>572</td>
<td>62.9%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

2. Dion et al, J of Intervent Cardiac Electrophys 2010
3. Sanna et al, NEJM 2014
Detection Strategies – Summary

• Several investigation options
• Diagnostic yield increases with duration of monitoring
• Systematic review prospective consecutive studies & RCTs
  - $\geq 12$ hours monitoring
  - Unselected populations detection – 6.2%; 95% CI, 4.4 – 8.3%
  - Selected populations detection - 13.4%; 95% CI, 9.0 – 18.4%
• Few comparative studies

1. Kishore et al, Stroke 2014
• Patients in whom no cause has been identified
  – Cryptogenic stroke

• Patients in whom investigations incomplete / other cause identified, e.g. LAA
• Patients in whom no cause has been identified
  – Cryptogenic stroke
  – CRYSTAL-AF; EMBRACE

• Patients in whom investigations incomplete / other cause identified, e.g. LAA
  – Glasgow RCT
• Cryptogenic stroke, n=441
  – Negative 24-hour Holter; excluded LAA & SVD & any other cause
  – < 3 months from event, mean 38 days

- Implantable Cardiac Event Monitor
  – vs. No specific investigation

• Primary endpoint:
  – Difference in detection of AF episodes of 30 seconds duration at 6/12

Sanna et al, NEJM 2014
• Median time to AF detection 41 days (IQR, 14 – 81 days)
• Removal required in 2.4%

Sanna et al, NEJM 2014
• **Cryptogenic stroke, n=572**
  - Negative 24-hour Holter; excluded LAA & SVD
  - < 6 months from event, mean 75 days

• **Non-invasive CEM for 30 days**
  - vs. 24-hour Holter

• **Primary endpoint:**
  - Difference in detection of AF episodes of 30 seconds duration at 3/12 days

Gladstone et al, NEJM 2014
**Detection in CEM group at 90 days**

- 16.1% in CEM group; 3.2% in control group, P<0.001
- 50% of detected cases < 2/52
- 75% of detected cases < 3/52

Gladstone et al, NEJM 2014
Conclusions from RCTs

- In “cryptogenic stroke”
  - 4/52 non-invasive CEM superior to repeat 24-hour Holter
  - 6/12 implantable CEM superior to no routine investigation
  - Initial investigation NPV low

- What about unselected patients?
What about unselected patients?

- Immediately after stroke
- Patient to whom guidelines apply
- Not “fully” investigated
- Other aetiological factors evident

Hypothesis:

- Routine investigation for AF superior to guideline based approach
Novacor R-test device

- External objective reporting

- “Any” PAF: Evidence of paroxysmal AF (including brief episodes)

- “Sustained” PAF: Evidence of paroxysms > 20 seconds duration
Methods

Assessment for eligibility (ASU/TIA clinic)

Informed Consent

Randomisation (1:1 basis):

IS < 7 days

+ 1 day

+ 3 days

+ 7 days

+ 14 days

+ 90 days

“Standard Care” alone

12-lead ECG / 24-hour ECG / Echo
(as directed by clinical team)

Cardiac event download

Plus

Cardiac event download

Plus

AF detection & AC treatment evaluation

AF detection & AC treatment evaluation

“Intensive” Investigation

Cardiac event download + 12-lead ECG

Cardiac event download + 12-lead ECG

Cardiac event download

Cardiac event download

Cardiac event download

Cardiac event download

Cardiac event download
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard Care</th>
<th>Intensive investigation</th>
<th>P value for difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 50</strong></td>
<td><strong>n = 50</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>64.6 (13.3)</td>
<td>67.1 (11.1)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Sex Male</strong></td>
<td>64%</td>
<td>48%</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Ictus to randomisation, Median (IQR)</strong></td>
<td>1 (2)</td>
<td>1 (1)</td>
<td>0.87 *</td>
</tr>
<tr>
<td><strong>Qualifying event Stroke</strong></td>
<td><strong>66%</strong></td>
<td><strong>70%</strong></td>
<td>0.67</td>
</tr>
<tr>
<td><strong>NIHSS (stroke patients), Median (IQR)</strong></td>
<td>2 (3.5)</td>
<td>2 (4)</td>
<td>0.82 *</td>
</tr>
<tr>
<td><strong>TACS</strong></td>
<td>14%</td>
<td>14%</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>PACS</strong></td>
<td>42%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td><strong>LACS</strong></td>
<td>30%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td><strong>POCS</strong></td>
<td>14%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic BP, mean (SD)</strong></td>
<td>154.4 (25.3)</td>
<td>155.2 (29)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Diastolic BP, mean (SD)</strong></td>
<td>81.5 (14.4)</td>
<td>81.5 (14.7)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
### “Standard Care” Investigations

#### 14 days

<table>
<thead>
<tr>
<th></th>
<th>Standard investigation group (n = 50)</th>
<th>Additional investigation group (n = 50)</th>
<th>P value for difference in proportions between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-lead ECG</td>
<td>16%</td>
<td>12%</td>
<td>0.564</td>
</tr>
<tr>
<td>24-hour ECG monitoring (Holter)</td>
<td>16%</td>
<td>26%</td>
<td>0.216</td>
</tr>
<tr>
<td>Echo</td>
<td>30%</td>
<td>42%</td>
<td>0.208</td>
</tr>
</tbody>
</table>

#### 90 days

<table>
<thead>
<tr>
<th></th>
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<th>Additional investigation group (n = 50)</th>
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<tbody>
<tr>
<td>12-lead ECG</td>
<td>28%</td>
<td>18%</td>
<td>0.231</td>
</tr>
<tr>
<td>24-hour ECG monitoring (Holter)</td>
<td>60%</td>
<td>46%</td>
<td>0.157</td>
</tr>
<tr>
<td>Echo</td>
<td>62%</td>
<td>54%</td>
<td>0.416</td>
</tr>
</tbody>
</table>
“Any PAF” at 90 days
“Any PAF” at 90 days

Graph showing cumulative proportion with event over time (days). Group comparisons with Log Rank p < 0.001.
“Sustained PAF” at 90 days

Stroke 2013: 44; 2525-2531
“Sustained PAF” at 90 days

Log Rank  p < 0.05

Stroke 2013: 44; 2525-2531
Anticoagulation (any indication, absolute difference)

- 14 days: 18% higher in intensive investigation (95% CI, 7.4–28.6%)
- 90 days: 16% higher in intensive investigation (95% CI, 1.2–30.7%)
<table>
<thead>
<tr>
<th>Modality</th>
<th>Completed %, (95% CI)</th>
<th>“Any PAF” detected %, (95% CI)</th>
<th>“Sustained PAF” %, (95% CI)</th>
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<td>72-hour 12-lead ECG</td>
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<tr>
<td>24-hour R-test download</td>
<td>94%, (83.5 – 98.7%)</td>
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<tr>
<td>72-hour R-test download</td>
<td>90%, (78.1 – 96.7%)</td>
<td>38%, (24.7 – 52.8%)</td>
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</tr>
<tr>
<td>168-hour R-test download</td>
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### “Intensive Investigation” breakdown

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*Stroke 2013: 44; 2525-2531*
Randomised evidence in unselected patients

Routine investigation
- Well tolerated
- High PAF detection rate
- Significantly exceeds guideline based investigation

Treatment influenced by increased detection

Unresolved questions
Should we treat all extended monitoring detected PAF equally?

– What is the predictive value of early PAF detection?

– What is the burden of PAF which justifies modified treatment?
  • Paroxysmal vs. Persistent vs. Permanent
  • Paroxysm frequency & duration

What is the optimal, most cost-efficient investigation strategy?
All IS & TIA patients should be considered for investigation

Guideline based investigation / 24-hours monitoring insufficient

RCT evidence for extended investigation in “unselected” & “cryptogenic”

Optimal strategy to be defined

- Subgroups, modality, duration

- Research to address this & unresolved prognostic issues
Acknowledgements

- PW MacFarlane, J Dawson, GT McIness, P Langhorne, K McArthur, KR Lees
- E Colquhoun, R Graham, B Manak, L Campbell, P MacKenzie
- S Latif, J Watts, K McLaren, L Inglis
- M McNeela
• Any Questions?
• Any Questions?