Implication of Subclinical AF on Stroke and Heart Failure

Session: SPAF 2

Chu-Pak Lau, MD
Honorary Clinical Professor
Queen Mary Hospital
The University of Hong Kong
M/62, L hemiparesis, AF detected 3 m after stroke by ICM
Clinical AF Types & Embolic Risk
Vanassche T et al. EHJ 2015;36:281-287

Patients & Methods: 6,563 aspirin-treated pts with AF from ACTIVE A / AVERROES were re-analysed for embolic risks. Multivariate risks for AF include age ≥ 75yr, sex, prior stroke or TIA and AF types.
AF Detection by ICM

**ASSERT II**
SJM CONFIRM AF, n = 256

- SCAF ≥ 5mins
- SCAF ≥ 30mins
- SCAF ≥ 6hours
- SCAF ≥ 24hours

Cumulative incidence (%)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCAF ≥ 5mins</td>
<td>256</td>
</tr>
<tr>
<td>SCAF ≥ 30mins</td>
<td>256</td>
</tr>
<tr>
<td>SCAF ≥ 6hours</td>
<td>256</td>
</tr>
<tr>
<td>SCAF ≥ 24hours</td>
<td>256</td>
</tr>
</tbody>
</table>

Healey JS. Circ 2017;136:1276-1283

**REVEAL AF**
Medtronic Linq, n = 385

- ≥6 min of AF in a day
- ≥30 min of AF in a day
- ≥1 h of AF in a day
- ≥6 h of AF in a day

Incidence of AF Burden, %

<table>
<thead>
<tr>
<th>No. at risk of AF in a day</th>
<th>Post-ICM Insertion, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6 min</td>
<td>391</td>
</tr>
<tr>
<td>≥30 min</td>
<td>391</td>
</tr>
<tr>
<td>≥1 h</td>
<td>391</td>
</tr>
<tr>
<td>≥6 h</td>
<td>391</td>
</tr>
</tbody>
</table>

Reiffel JA et al. JAMA Cardiol 2017;2:1120-1127

KHRS 2019, Seoul
20 – 22 Jun 2019
Should She be Anticoagulated?

Clinical Features

F80 Implanted with DDDR for SND 1 yr ago, no history of AF
Routine pacemaker check:
Frequent AHRE detected > 5 min. Duration < 24 h. AF Burden 2%
No clinical AF on ECG/Holter
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Device Indication</th>
<th>Clinical Profile of Patients</th>
<th>Follow-up</th>
<th>Incidence of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Gillis et al. 16</td>
<td>PPMs for sinus node disease</td>
<td>All</td>
<td>718±383 days</td>
<td>157/231 (68%)</td>
</tr>
<tr>
<td>2003</td>
<td>MOST5</td>
<td>PPMs for sinus node disease</td>
<td>All</td>
<td>median 27 months</td>
<td>156/312 (50%)</td>
</tr>
<tr>
<td>2006</td>
<td>BEATS21</td>
<td>PPMs for all indications</td>
<td>All</td>
<td>Prospective, 12 months</td>
<td>137/254 (54%)</td>
</tr>
<tr>
<td>2010</td>
<td>TRENDS17</td>
<td>PPMs and ICDs</td>
<td>History of prior stroke</td>
<td>Mean 1.4 years</td>
<td>45/163 (28%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No history of AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No OAC use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥1 stroke risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>TRENDS6</td>
<td>PPMs and ICDs</td>
<td>No history of prior stroke</td>
<td>1.1±0.7 years</td>
<td>416/1368 (30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No history of AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No OAC use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥1 stroke risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>ASSERT7</td>
<td>PPMs and ICDs</td>
<td>History of hypertension</td>
<td>2.5 years</td>
<td>895/2580 (34.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No history of AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No OAC use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Healey et al. 4</td>
<td>PPMs</td>
<td>All</td>
<td>Single center retrospective</td>
<td>246/445 (55.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All indications</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE)

Bulent Gorenek (chair)\(^1\), Jeroen Bax\(^2\), Giuseppe Boriani\(^3\), Nikolaos Dagres\(^5\), Taya V. Glotzer\(^6\), Jeff S. Healey\(^7\), Carsten W. Israel\(^8\), Gulmira Kudaiberdieva\(^9\), Lars-Åke Levin\(^10\), Gregory Y.H. Lip\(^11,12\), David Martin\(^13\), Ken Okumura\(^14\), Jesper H. Svendsen\(^15\), Hung-Fat Tse\(^16\), and Giovanni L. Botto (co-chair)\(^17\)

Document Reviewers: Christian Sticherling (Reviewer Coordinator)\(^18\), Cecilia Linde\(^19\), Valentina Kutyifa\(^20\), Robert Bernat\(^21\), Daniel Scherr\(^22\), Pedro Iturralde\(^24\), Daniel P. Morin\(^25\), and Irina Savelieva (for EP-Europace, UK)\(^26\)
Definitions

**Atrial High Rate Events (AHRE)**
Atrial events > 190 bpm detected by an CIED (implanted atrial lead)

**Subclinical AF (SCAF)**
AHRE > 6 min and < 24h
Asymptomatic
No prior clinical AF

**Silent (asymptomatic) AF**
E.C.G. (or ICM) documented AF without prior symptoms nor diagnosis. Often made with a complication related to AF e.g. Stroke, HF
SCAF and Clinical AF: ASSERT
Healey JS... Lau CP... Hohnloser SH. NEJM 2012;366:120-9

Pts & Methods: 2580 pts ≥65 yrs with HT, no AF, and with pacing/ICD indications were monitored for 2.5 years

Conclusion: 10.1% pts had device recorded SCAF at 3 months, which predicted clinical AF
### SCAF in CIEDs Increased Risk of Clinical AF in Major Trials

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>age</th>
<th>FU (m)</th>
<th>Atrial activity</th>
<th>Duration</th>
<th>AF OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOST</strong> ¹</td>
<td>312</td>
<td>74</td>
<td>27</td>
<td>AHRE ≥220</td>
<td>≥5min</td>
<td>5.9</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Capucci</strong> ²</td>
<td>725</td>
<td>71</td>
<td>22</td>
<td>AF</td>
<td>≥1day</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Botto</strong> ³</td>
<td>568</td>
<td>70</td>
<td>12</td>
<td>AT/AF</td>
<td>&lt; 5min – 24hr</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>TRENDS</strong> ⁴</td>
<td>2486</td>
<td>71</td>
<td>17</td>
<td>AT/AF burden</td>
<td>≥5.5hours</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>ASSERT</strong> ⁵</td>
<td>2580</td>
<td>76</td>
<td>34</td>
<td>AT ≥190</td>
<td>&gt;6min</td>
<td>5.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

3. JCE 2009;20:241
5. NEJM 2012;366:120-9
SCAF and Stroke Risk: ASSERT
Healey JS... Lau CP... Hohnloser SH. NEJM 2012;366:120-9

Pts & Methods: 2580 pts ≥65 yrs with HT, no AF, and with pacing/ICD indications were monitored for 2.5 years

Conclusion: 10.1% pts had device recorded subclinical AF at 3 months, which predicted clinical AF and stroke
### SCAF in CIEDs Increased Risk of Stroke & Systemic Embolism

<table>
<thead>
<tr>
<th></th>
<th>Prior AF</th>
<th>Prior TE</th>
<th>Prior OAC</th>
<th>CHADS₂</th>
<th>Pts with TE</th>
<th>TE (OR)</th>
<th>P</th>
<th>TE %/yr</th>
<th>AHRE (+) Annual TE%</th>
<th>AHRE (-) Annual TE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOST ¹</td>
<td>60%</td>
<td>20%</td>
<td>24%</td>
<td>--</td>
<td>10</td>
<td>2.8</td>
<td>0.001</td>
<td>1.6%</td>
<td>2.2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Capucci ²</td>
<td>100%</td>
<td>1.8%</td>
<td>32%</td>
<td>1.8</td>
<td>14</td>
<td>3.1</td>
<td>0.044</td>
<td>1.2%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Botto ³</td>
<td>100%</td>
<td>1.4%</td>
<td>25.2%</td>
<td>~1.0</td>
<td>14</td>
<td>5.3</td>
<td>--</td>
<td>2.5%</td>
<td>3.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>TRENDS ⁴</td>
<td>20%</td>
<td>13.4%</td>
<td>20.8%</td>
<td>2.2</td>
<td>40</td>
<td>2.2</td>
<td>0.06</td>
<td>1.2%</td>
<td>2.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ASSERT ⁵</td>
<td>0%</td>
<td>12.1%</td>
<td>18%</td>
<td>~1.2</td>
<td>51</td>
<td>2.5</td>
<td>0.008</td>
<td>0.89%</td>
<td>1.78%</td>
<td>0.69%</td>
</tr>
</tbody>
</table>

2. Circ Arrhythmia Electrophysiol 2009;2:474
4. JCE 2009;20:241
5. NEJM 2012;366:120-9
Conclusion: SCAF increases over time in 2.5 yr. SCAF > 24h predicts ischemic stroke or systemic emboli, whereas the risk for < 24h is similar to pts without SCAF.
Absolute TE Risk of SCAF

- **TRENDS study:**
  TE ↑ if AF > 5.5h/day. 2.4%/yr if AT burden detected (CHADS$_2$ = 2.2)

- **ASSERT study:**
  TE ↑ if AF > 17.72h. Annual stroke rate:

<table>
<thead>
<tr>
<th>CHADS$_2$</th>
<th>&lt; 2</th>
<th>2</th>
<th>&gt; 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF-detected</td>
<td>0.56%</td>
<td>1.29%</td>
<td>3.78%</td>
<td>P = 0.35</td>
</tr>
<tr>
<td>No AF-detected</td>
<td>0.28%</td>
<td>0.70%</td>
<td>0.97%</td>
<td>P = NS</td>
</tr>
<tr>
<td>AF in General Population</td>
<td>2.8</td>
<td>4.0</td>
<td>&gt; 5.8%</td>
<td>--</td>
</tr>
</tbody>
</table>

Lau CP. Europace 2015;17:ii40-46
Mechanism of SCAF and Stroke: Temporal Relationship Between SCAF and Embolic Events
Healey J, … , Lau CP. Circulation 2014; 129: 2094-9(2)
# Recommendation for OAC in SCAF

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc score</th>
<th>Duration of AHRE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2</td>
<td>&gt;5.5 h (lower duration if multiple stroke risk factors are present)*</td>
<td>![Heart]</td>
</tr>
<tr>
<td>1 (male) or 2 (female)</td>
<td>&gt;5.5 h*</td>
<td>![Heart]</td>
</tr>
</tbody>
</table>

*Data suggests risk is similarly increased by a mere 5 min. AHRE, atrial high rate episode.*
Recommendations for Treatment of SCAF with OAC (1)

1. Assessment of patient’s stroke risk using the CHA2DS2-VASc score is recommended.

2. No antithrombotic therapy for any patients with CHA2DS2-VASc score of 0 in males or 1 in females, irrespective of AHRE, is recommended.

3. For patients with two additional CHA2DS2-VASc risk factors (i.e. ≥ 2 in males, ≥ 3 in females) OAC is recommended for AF burden > 5.5h/day (if there are no contraindications). Lower duration may merit OAC if multiple risk factors are present.

4. For effective stroke prevention in patients with CHA2DS2-VASc score ≥ 2, oral anticoagulation, whether with well controlled vitamin K antagonist (VKA) with a time in therapeutic range > 70%, or with a non-VKA oral anticoagulant (NOAC, either dabigatran, rivaroxaban, apixaban or edoxaban) is recommended.
1. Apixaban for Reduction of Thrombo-Embolism due to Sub-Clinical AF (ARTESiA). (CT NCT 01938248)

2. NOAH-AFNET 6 (NCT 02618577)

3. ART-CAT (Chi CTR 180001622) OAC vs placebo
## AF and Risks of CVD, CRF and Death

**Odutayo A et al. BMJ 2016;354:i4482 (2)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral arterial disease</td>
<td>1</td>
<td>1.31 (1.19 to 1.45)</td>
<td>1.31 (1.19 to 1.45)</td>
<td>NA</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>66</td>
<td>1.46 (1.39 to 1.53)</td>
<td>1.46 (1.39 to 1.53)</td>
<td>93</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>16</td>
<td>1.61 (1.38 to 1.87)</td>
<td>1.61 (1.38 to 1.87)</td>
<td>86</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3</td>
<td>1.64 (1.41 to 1.91)</td>
<td>1.64 (1.41 to 1.91)</td>
<td>50</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>7</td>
<td>1.88 (1.36 to 2.60)</td>
<td>1.88 (1.36 to 2.60)</td>
<td>78</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>9</td>
<td>1.96 (1.53 to 2.51)</td>
<td>1.96 (1.53 to 2.51)</td>
<td>98</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>3</td>
<td>2.00 (0.67 to 5.96)</td>
<td>2.00 (0.67 to 5.96)</td>
<td>73</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>14</td>
<td>2.03 (1.79 to 2.30)</td>
<td>2.03 (1.79 to 2.30)</td>
<td>76</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>12</td>
<td>2.33 (1.84 to 2.94)</td>
<td>2.33 (1.84 to 2.94)</td>
<td>87</td>
</tr>
<tr>
<td>Stroke</td>
<td>38</td>
<td>2.42 (2.17 to 2.71)</td>
<td>2.42 (2.17 to 2.71)</td>
<td>96</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6</td>
<td>4.99 (3.04 to 8.22)</td>
<td>4.99 (3.04 to 8.22)</td>
<td>93</td>
</tr>
</tbody>
</table>
Progression of SCAF and HF. ASSERT- Substudy

Wong JA... Lau CP... Healey JS. JACC 2018;71:2603-11 (2)

Subclinical atrial fibrillation (SCAF) (episodes lasting >6 minutes and ≤24 hours)

- No progression of SCAF to episodes >24 hours
- SCAF progression (incidence 8.8%/year)

Annual rate of heart failure (HF) hospitalization:
- 2.5%/year
- 8.9%/year

SCAF progression associated with increased risk of HF hospitalization
[HR: 4.58; 95% CI: 1.64 - 12.8; p = 0.004]

Predictors of SCAF progression:
- Older age
- Greater BMI
- SCAF episode duration: 1-hour increase in duration
- 13% increased risk of SCAF progression
Progression of SCAF and HF. ASSERT- Substudy

Wong JA… Lau CP… Healey JS. JACC 2018;71:2603-11 (3)

Mechanisms:

(A) HF $\rightarrow$ AF
But baseline demographics in those with or without SCAF are identical

(B) AF $\rightarrow$ HF
Rapid AF rate, tachy-cardiomyopathy
Loss of atrial contraction
Atrial and ventricular myopathy
Abnormal Calcium handling, RAS & ADH
Conclusions

1. SCAF can be accurately detected by implantable devices such as PPM, ICD and CRT, and predicts occurrence of clinical AF

2. SCAF predicts clinical stroke and thromboembolism if > 5.5 h - 24 h, but the stroke risk of SCAF is lower than clinical AF in those without a history of AF

3. The relationship between SCAF and stroke, be it causal or temporal, is uncertain

4. Primary prevention studies of stroke based on subclinical AF are ongoing. The role of consumer ECG recording devices on AF detection is evolving

5. Progression of SCAF is related to new onset heart failure