AF and implantable devices

Which AF definition to characterize the risk?

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Disclosures

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Stroke risk in clinical AF
Prevalence of AF in patients with an ILR and CIED
Stroke risk in AHRE/ subclinical AF depending on duration episodes
Virchow’s triad for stroke in AF

- Changes in vessel wall
  - Atrial tissue changes
  - Endothelial dysfunction
- Changes in atrial flow
  - Stasis
- Changes in blood biomarkers
  - Hypercoagulability
  - Platelets
  - Inflammation
Individuals with stroke

47 countries – 15,400 AF pts admitted to emergency dept
1 year follow-up
11% died: 6% with primary AF; 16% with secondary AF
4% had stroke: 3% vs 5%

Healey RE-LY registry Lancet 2016
Stroke risk in clinical AF

**CHA₂DS₂-VASc: Development and Validation**

- Birmingham scheme proposed for NICE recommendations in 2006, refined in 2009
- Validated in the Euro Heart Survey cohort of 1084 NVAF patients not on OAC and known TE outcome (n = 25)
- OR for stroke if:
  - Female: 2.53 (1.08 – 5.92), p=0.029;
  - Vascular disease: 2.27 (0.94 – 5.46), p=0.063
- Further validated based on the Danish patient registry in 73,538 NVAF patients not on OAC
- TE included stroke, peripheral TE, PE

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke at 1 year, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>Euro Heart</td>
</tr>
<tr>
<td>n</td>
<td>1084</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.3*</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>

*TE rates at 1 year 0.6%, adjusted for ASA 0.7%
Post-hoc stroke risk assessment based on SPORTIF trials

Clinical AF: Stroke risk depending on burden?
N=6563, ASA-treated

Stroke risk exceeds treatment threshold even for paroxysmal AF

Thus, there is an association between type of AF and stroke but type of AF does NOT influence decision to anticoagulate
Clinical PAF: Stroke risk depending on burden?

- 1965 patients
- Mean age 69; 45% women
- Median CHA$_2$DS$_2$-VASc = 3
- AF burden during 14 days continuous monitoring
- Primary outcome: ischemic stroke while not on OAC

Median AF burden 4.4%
Clinical PAF: Stroke risk depending on burden?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 1965)</th>
<th>Tertile 1 (n = 679 [0.01%-2.03%])</th>
<th>Tertile 2 (n = 652 [2.05%-11.28%])</th>
<th>Tertile 3 (n = 634 [11.36%-99.99%])</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>68.8 (11.8)</td>
<td>68.5 (12.4)</td>
<td>69.4 (11.2)</td>
<td>68.5 (11.6)</td>
<td>.27</td>
</tr>
<tr>
<td>Women</td>
<td>880 (44.8)</td>
<td>341 (50.2)</td>
<td>290 (44.5)</td>
<td>249 (39.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/European</td>
<td>1469 (74.8)</td>
<td>500 (73.6)</td>
<td>485 (74.4)</td>
<td>484 (76.3)</td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>100 (5.1)</td>
<td>46 (6.8)</td>
<td>35 (5.4)</td>
<td>19 (3.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>266 (13.5)</td>
<td>91 (13.4)</td>
<td>85 (13.0)</td>
<td>90 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>130 (6.6)</td>
<td>42 (6.2)</td>
<td>47 (7.2)</td>
<td>41 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>198 (10.1)</td>
<td>72 (10.6)</td>
<td>64 (9.8)</td>
<td>62 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ATRIA stroke risk score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.3 (2.8)</td>
<td>4.3 (2.8)</td>
<td>4.4 (2.8)</td>
<td>4.3 (2.9)</td>
<td>.61</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.0 (2.0-7.0)</td>
<td>4.0 (1.0-7.0)</td>
<td>4.0 (2.0-7.0)</td>
<td>4.0 (2.0-7.0)</td>
<td>.70</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.6 (1.6)</td>
<td>2.6 (1.6)</td>
<td>2.6 (1.6)</td>
<td>2.6 (1.7)</td>
<td>.97</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.0 (1.0-4.0)</td>
<td>3.0 (1.0-4.0)</td>
<td>3.0 (1.0-4.0)</td>
<td>2.0 (1.0-4.0)</td>
<td>.95</td>
</tr>
</tbody>
</table>
Clinical PAF: Stroke risk depending on AF burden?

After adjusting for CHA<sub>2</sub>DS<sub>2</sub>-VASc and ATRIA scores highest tertile (＞11.3%) associated with 3-fold adjusted rate of TEC while not on OAC (adj HR 3.13 [1.50-6.56] and 3.16 [1.50-6.62] compared with lower 2 tertiles.
Clinical AF: OAC depending on burden?

- Clinical AF
  - “Burden” of AF does NOT influence decision to anticoagulate
  - Stroke risk exceeds 2% per year for paroxysmal AF

Stroke risk exceeds 2% per year for paroxysmal AF

Clinical AF: OAC depending on burden?
SCAF or AHRE is a variant of clinical AF but differs in that SCAF:
- would not be detected by means other than an implanted device with continuous (24/7) long-term recording
- is often asymptomatic; episodes short in duration (minutes to hours)
Incidence ILR detected AHRE in **high risk patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Device</th>
<th>Inclusion</th>
<th>Rate of AF detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSERT-II⁹</td>
<td>250</td>
<td>SJM confirm</td>
<td>Age &gt; 65 and CHADS-VASc ≥2 or OSA or BMI &gt; 30; and LA &gt; 58 mL or NT-ProBNP &gt; 290 pg/mL</td>
<td>≥5 min 34.4% at 1 year</td>
</tr>
<tr>
<td>GRAF (NCT01461434)</td>
<td>200</td>
<td>MDT REVEAL-XT</td>
<td>Age ≥ 18 and CHADS-VASc≥4</td>
<td>Pending</td>
</tr>
<tr>
<td>REVEAL-AF⁴⁰</td>
<td>450</td>
<td>MDT REVEAL-XT</td>
<td>Age ≥ 18, CHADS≥3, or CKD/COPD/OSA/CAD</td>
<td>29.3% at 18 months</td>
</tr>
<tr>
<td>PREDATE-AF⁴¹</td>
<td>245</td>
<td>REVEAL-LINQ</td>
<td>Age &gt; 18 and CHADS-VASc≥2</td>
<td>≥6 min 22.4% at 451 days</td>
</tr>
<tr>
<td>DANISH LOOP⁴²</td>
<td>6000</td>
<td>REVEAL-LINQ (1500)</td>
<td>Age &gt; 70 One of hypertension, diabetes mellitus, HF, or stroke</td>
<td>Pending</td>
</tr>
</tbody>
</table>

**Note that incidence rate is higher than in post-stroke trials**
- EMBRACE-AF: 16.1% in 30 days triggered monitoring vs 3.2% in control group at 3 mths (patients included > 55 yrs)
- CRYSTAL AF: 12.4% in ICM group vs 2.0% in control group at 1 year (pts > 40 years)
Incidence CIED detected AHRE in high risk patients

AHRE in 10-30% of high risk patients without known AF
# Temporal relationship of device detected AF and TE

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Number of patients with TE Event</th>
<th>Definition of AF episode</th>
<th>Any AF Detected Prior to TE Event</th>
<th>AF Detected only after TE Event</th>
<th>No AF in 30 Days Prior to TE Event</th>
<th>Any AF in 30 Days Prior to TE Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>TRENDS</td>
<td>40</td>
<td>5 minutes</td>
<td>20/40 (50%)</td>
<td>6/40 (15%)</td>
<td>29/40 (73%)</td>
<td>11/40 (27%)</td>
</tr>
<tr>
<td>2012</td>
<td>ANGELS</td>
<td>33</td>
<td>5 minutes</td>
<td>21/33 (64%)</td>
<td>NA</td>
<td>22/33 (77%)</td>
<td>11/33 (33%)</td>
</tr>
<tr>
<td>2014</td>
<td>ASSERT</td>
<td>51</td>
<td>6 minutes</td>
<td>18/51 (35%)</td>
<td>8/51 (16%)</td>
<td>47/51 (92%)</td>
<td>4/51 (8%)</td>
</tr>
<tr>
<td>2014</td>
<td>IMPACT</td>
<td>69</td>
<td>36/48 atrial beats ≥200bpm</td>
<td>20/69 (29%)</td>
<td>9/69 (13%)</td>
<td>65/69 (94%)</td>
<td>4/69 (6%)</td>
</tr>
</tbody>
</table>

TRENDS: Subclinical AF burden and stroke

<table>
<thead>
<tr>
<th>AT/AF burden subset</th>
<th>AT/AF burden</th>
<th>HR for TE high vs zero burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero AT</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Low AT (&lt;5.5 h)</td>
<td>1.1%</td>
<td>0.98 [0.34, 2.82]</td>
</tr>
<tr>
<td>High AT (≥5.5 h)</td>
<td>2.4%</td>
<td>2.20 [0.96, 5.05]</td>
</tr>
</tbody>
</table>
Risk of ischemic stroke or embolism in SCAF

- 2580 patients with hypertension, > 65 yrs
- no AF, pacemaker or ICD
- Follow-up: 2.5 years
- Subclinical AF: > 6 min > 190 bpm
## ASSERT: relation between AF and stroke

Both absolute and relative risks of stroke with SCAF are lower than with clinical AF.

<table>
<thead>
<tr>
<th>Event</th>
<th>Device-Detected Atrial Tachyarrhythmia</th>
<th>Device-Detected Atrial Tachyarrhythmia Present vs. absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent N=2319</td>
<td>Present N= 261</td>
</tr>
<tr>
<td>Ischemic Stroke or Systemic Embolism</td>
<td>40 0.69</td>
<td>11 1.69</td>
</tr>
<tr>
<td>Vascular Death</td>
<td>153 2.62</td>
<td>19 2.92</td>
</tr>
<tr>
<td>Stroke / MI / Vascular Death</td>
<td>206 3.53</td>
<td>29 4.45</td>
</tr>
<tr>
<td>Clinical Atrial Fibrillation or Flutter</td>
<td>71 1.22</td>
<td>41 6.29</td>
</tr>
</tbody>
</table>

Healey New Engl J Med 2012 ASSERT Study
Longer subclinical AF: higher risk of stroke

- 2580 patients with hypertension, > 65 yrs
- no AF, pacemaker or ICD
- Follow-up: 2.5 years
- Subclinical AF: > 6 min > 190 bpm

Van Gelder, Healey for the ASSERT Investigators Eur Heart J 2017
Longer subclinical AF: higher risk of stroke

- Pooled analysis from 5 prospective studies (no permAF, with CIED)
- 10,016 patients mean age 70 yrs
- Aim: stroke rate with pre-specified cut-off points of AF burden
- 24 months FU: 43% at least 1 day with 5 min of AF burden
- Cox regression: AF burden independent predictor of ischaemic stroke
- 1 hour associated with highest HR: 2.11 (95% CI: 1.22-3.64, p=0.008)
Stroke Risk and AF Duration

- Analysis of 21,768 CIED non-coagulated patients from the Optum EMR
- Increased stroke risk with higher AF duration and higher CHA$_2$DS$_2$-VASc

<table>
<thead>
<tr>
<th>Maximum Daily AF Duration</th>
<th>CHA$_2$DS$_2$-VASc Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>n=2922 (13.4%)</td>
</tr>
<tr>
<td>No AF</td>
<td>0.33% 40 events</td>
</tr>
<tr>
<td>AF 6 min–23.5 h</td>
<td></td>
</tr>
<tr>
<td>n=3381 (15.5%)</td>
<td>0.52% 11 events</td>
</tr>
<tr>
<td>AF &gt;23.5h</td>
<td></td>
</tr>
<tr>
<td>n=1572 (7.2%)</td>
<td>0.86% 4 events</td>
</tr>
</tbody>
</table>

University Medical Center Groningen

Kaplan Circulation 2019
## Longer subclinical AF: higher risk of stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample size</th>
<th>Follow-up (years)</th>
<th>Adjudication</th>
<th>AF at time of enrollment</th>
<th>Cut-off for AF/AHRE detection and duration associated with stroke risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary MOSTT</td>
<td>Retrospective observational</td>
<td>372</td>
<td>2.3</td>
<td>0</td>
<td>Sinus node dysfunction. Sinus rhythm at randomization</td>
<td>Atrial rate &gt; 120 bpm for 10 consecutive beats. AHRE &gt; 5 min episode. Medtronic pacemakers</td>
</tr>
<tr>
<td>Capucci</td>
<td>Prospective multicentre observational</td>
<td>725</td>
<td>1.8</td>
<td>1</td>
<td>Bradycardia with dual chamber pacing indication. Previous AF. Permanent AF excluded</td>
<td>24 h AF (cardiac compas) episode during period of observation. Medtronic pacemakers</td>
</tr>
</tbody>
</table>
| Basso | Retrospective observational | 568 | 1 | 0 | Brady-tachy syndrome. Permanent AF excluded | PR loge 

### TRENDS

- Prospective observational
- Patients with or without prior PAF. CHAOSD ≥ 1. Permanent AF excluded
- Atrial rate > 175 bpm for > 10 h

### ASSIST

- Randomized
- Excluded prior AF, Hypertension
- Atrial rate > 110 bpm for > 6 min

### Home CARE and everETT

- Prospective observational
- Prior history of AF in 178 of 382 patients. Heart failure cohort. Permanent AF excluded
- Atrial rate > 160 bpm for 58 consecutive beats or 36/48 consecutive cycles, 14.4 min/day (16% home monitor burden) for detection.

### SOS AF

- Three registries
- Prior history of paroxysmal or persistent AF included. Permanent AF excluded
- Atrial rate > 175 bpm for > 10 h

### IMPACT

- Randomized
- CHAOSD ≥ 1. Only permanent AF included
- > 16 of 24 consecutive R-R cycle lengths ≤ 200 bpm.
- > 5.5 h AF burden. Biotronik ICDs/CRT ICDs

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Mahajan, Sanders systematic review and meta analysis Eur Heart J 2018
Risk of stroke and requirement for therapy

Subclinical AF strongly predicts clinical AF and is associated with elevated absolute stroke risk albeit lower than risk described for clinical AF.
Increased stroke risk according to AF burden

Piccini Editorial to Go et al. JAMA Cardiol 2018
But is not only AF!
It is the number of risk factors next to AF that matters

- Community cohort UK Biobank
- 502,637 participants (2006-2010)
- Age 37-73 years, 32% female
- FU 7 years
- 3,651 (0.7%) developed AF
- All cause mortality 6.7%

- Presence of AF and > 4 risk factors:
  6-fold increased all cause mortality risk
SCAF: OAC depending on burden?

- Subclinical AF (AHRE)
  - Treatment of SCAF with anticoagulation has no proven benefit and has the possibility for harm. Stroke risk is lower!
  - Two large RCTs ongoing: NOAH-AFNET 6 and ARTESIA
  - With no indication for anticoagulation for the treatment of SCAF, AF burden cannot influence the treatment decision
SCAF: start OAC depends on burden?

- **Search for AF on ECG or Holter**
- **Anticoagulate when AF is documented by ECG**
- **Do not anticoagulate merely because of AHRE**
- **If you consider OAC, discuss as off licence therapy**
Conclusions and take home messages

- In clinical AF stroke risk is influenced by number of comorbidities (higher CHA₂DS₂-VASc score)
- But also by type of AF
- SCAF/ AHRE differs from clinical AF!
- SCAF/ AHRE has a lower stroke risk
- For now SCAF duration matters
- Once SCAF/ AHRE has been seen: try to document clinical AF
Thank you for your attention