Sporadic or short episodes of paroxysmal atrial fibrillation - still a need for antithrombotic therapy?

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Patterns of AF

- Terminates spontaneously
- Generally last ≤7 days
- Recurrent

Camm, ESC AF Guidelines, EHJ 2010
Increased risk of stroke versus normal population

Relative Risk of Patients with Atrial Fibrillation Compared with Controls

- Framingham
- Whitehall Regional Heart Study
- Manitoba
- Framingham (no Heart Disease)
- Framingham (overall)
CHADS2 - risk stratification for thromboembolism in AF

- Scoring system based on presence of risk factors → numerical stratification of stroke risk within each patient (score 0 – 6)

**Predicted yearly stroke rates based on risk scores**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Recent congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 yrs</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S2 History of stroke or transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>

Stroke risk with paroxysmal AF versus chronic AF: Incidence and Predictors

- SPAF (Stroke Prevention in Atrial Fibrillation) cohort study:
  - 460 intermittent AF patients vs 1,552 sustained AF patients (aspirin treated, FU mean 2 yrs.

Annualized rate of ischemic stroke similar in paroxysmal (3.2%) and permanent (3.3%) AF (during aspirin).

ESC guidelines – anticoagulation in AF pats

ESC 2010 Guidelines on Management of AF

<table>
<thead>
<tr>
<th>Recommendations for prevention of thromboembolism</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those at low risk (lone AF aged &lt;65 years or contraindications)</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

Paroxysmal AF

The stroke and thromboembolic risk in paroxysmal AF is less well defined, and such patients have represented the minority (usually <30%) in clinical trials of thromboprophylaxis. Stroke risk in paroxysmal AF is not different from stroke risk in persistent or permanent AF (10), and is dependent upon the presence of stroke risk factors (see Section 4.1.1). Therefore, patients with paroxysmal AF should receive OAC according to their risk score.
Paroxysmal AF

Need for antithrombotic therapy if:

1. **Sporadic AF episodes**? **Frequency**?
   - Once monthly, once annually, clusters seldomly?

2. **Short episodes**? **Duration**?
   - Runs of PACs, nonsust. AF, minutes, few hours?
Atrial High Rate Episodes Detected by PM Diagnostics Predict Death and Stroke - Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST)

- N=312 pat, analyzed for presence of PM detected AHRE lasting > 5 min, during median FU of 27 months.
- Any AHRE - independent predictor of total mortality (HR 2.48 [1.25, 4.91], \(P=0.0092\)); death/nonfatal stroke (HR 2.79 [1.51, 5.15], \(P=0.0011\)); and atrial fibrillation (HR 5.93 [2.88, 12.2], \(P=0.0001\)).

Kaplan-Meier plot of death/nonfatal stroke after 1 yr FU in pats with and without AHREs.

\[ P=0.001. \]

Figure 1. Documented AF in patients with AHREs vs patients without AHREs; \(P=0.0001\). AHRE indicates atrial high rate episodes; AF, atrial fibrillation.

Glotzer, MOST trial, Circulation 2003
Monitored AF Duration Predicts Arterial Embolic Events in Pats Suffering From Bradycardia and AF, Implanted With Antitachycardia PM

- 725 pats, DDDR PM
- AF episodes lasting > one day - risk of embolism increased 3.1 times (95% CI 1.1 to 10.5, p=0.044).

Kaplan-Meier cumulative survival from embolic events for pats with AF episodes > one day vs those without AF recurrences or with AF < one day.

Capucci, JACC 2005.
AF duration – stroke risk

• PM detected atrial high rate episodes > 5 min - two-fold increased risk of death or stroke in SSS pats.
  – Mode Selection Trial (MOST) ¹

• Device-detected AF recurrences >1 day - 3.1-fold increased risk of embolism in comparison with pats without or with shorter AF recurrences².

• BUT, these studies did not combine these parameters with CHADS2 score.

Incidence of embolic events related to CHADS2 score and AF presence/duration.

- 568 pats with PM and a history of AF.
  - 365-days continuous monitoring = true history of pat rhythm.
  - 3 AF groups:
    - AF-free = <5-min AF on 1 day (29.2%)
    - AF-5 min = >5-min AF on 1 day but <24 hours (31.5%)
    - AF-24 h = AF episodes >24 hours (39.2%)

By combining data on AF presence, absence, duration with all CHADS2 score - subdivide population into 2 subgroups with significantly different risks of thromboembolic events.

Botto, JCE 2009
Presence and Duration of AF Detected by Continuous Monitoring: Crucial Implications for the Risk of Thromboembolic Events

2 risk groups identified:

- Low risk profile (0.8%) vs High risk profile (5%, P = 0.035).
  - AF-free + CHADS2 ≤2, or
  - AF-5 min + CHADS2 ≤1, or
  - AF-24 hours + CHADS2 = 0.

- Risk stratification - improved by combining CHADS2 score with AF duration.

Botto, JCE 2009
TRENDS study

- Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk
- Prospective, observational study,
- N=2486 pats with CHADS2 ≥1 + PM/ICD that monitor (AT)/AF burden.
  - AT/AF burden = longest total AT/AF dur. during prior 30-day period
- Annualized thromboembolic rates according to AT/AF burden subsets;
  - Zero,
  - Low (<5.5 hours),
  - High (>5.5 hours)
- Mean follow-up: 1.4 years
- AT/AF burden >5.5 hours on any of 30 prior days - double thromboembolic risk.

Table 3. Hazard Ratios for Thromboembolic Events Associated With AT/AF Burden Adjusted for Stroke Risk Factors and Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT/AF burden</td>
<td>Low burden vs zero burden</td>
<td>0.98 (0.34, 2.82)</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>High burden vs zero burden</td>
<td>2.20 (0.96, 5.05)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Glotzer, Circ Arrhythmia Electrophysiol. 2009
### Monitoring of AF by implantable devices and outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Device/monitoring</th>
<th>1’ and 2’ end point</th>
<th>FU</th>
<th>Sponsored</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRENDS</td>
<td>Interrogate 3 mo, AF burden/mo (AHRE ≥20 sec)</td>
<td>Stroke, TIA (ischemic)/AF progression, QoL, HE</td>
<td>1,4 yrs</td>
<td>Medtronic</td>
</tr>
<tr>
<td>ASSERT</td>
<td>Interrogate 6 mo (AHRE &gt; 6 min)</td>
<td>Stroke + embolism/AF, MI, death, bleed</td>
<td>2.75 yrs</td>
<td>St Jude</td>
</tr>
<tr>
<td>IMPACT</td>
<td>HF trends, home monitor for AF &gt; 48h - OAC</td>
<td>Stroke, embolism, major bleed/AF burden, QoL, HR</td>
<td>Results expect: 2014</td>
<td>Biotronic</td>
</tr>
<tr>
<td>RATE registry</td>
<td>Advanced AT/AF diagnostics</td>
<td>AT/AF burden, CHF, stroke, QoL, mortality….</td>
<td>Results expect: 2014</td>
<td>St Jude</td>
</tr>
</tbody>
</table>

Glotzer, Circ Arrhythmia Electrophysiol. 2009
Patients’ symptoms - unreliable surrogate parameter for AF burden

- Incidence of **asymptomatic AF** varies in different studies - depends on intensity of FU and monitoring systems used.
  - Low intensity monitoring systems
    • Asympt. AF incidence 10 - 40 % (Psaty 1997, Benjamin 1994)
  - More intense monitoring strategies

- **Asymptomatic AF recurrences** – still at risk of thromboembolism

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Paroxysmal AF

Need for antithrombotic therapy if:

1. Sporadic AF episodes? Frequency?
   - Once weekly, -monthly, clusters annually?

2. Short episodes? Duration?
   - Runs of PACs, nonsustAF, minutes, few hours?

3. Which monitoring methods can assess AF burden?

4. Will AF type remain constant?
Monitoring AF

• Standard methods of AF monitoring to evaluate antithrombotic strategy in pats at risk of stroke may be inaccurate
• 568 pats with PM and a history of AF.
• Mean sensitivity in detecting AF episode lasting > 5 min;
  – 24-hour Holter: 44.4%
  – 1-week Holter: 50.4%
  – 1-month Holter 65.1%, resp.

Sensitivity of simulated methods in detecting a 5-minute AF episode always < 70%

Botto, JCE 2009
Monitoring AF - Comparison of continuous versus intermittent monitoring of atrial arrhythmias

- 574 PM pats
  - PM detected amount of AT/AF each day analyzed retrospectively over 1 year.
- Simulated intermittent monitoring
  - annual, quarterly, and monthly 24-hour Holter; 7-day and 30-day annual long-term recordings.
- Symptom-based monitoring
  - analyzing days when pats indicated symptoms with external activator.
- All intermittent and symptom-based monitoring - significantly lower sensitivity (range 31%–71%) and negative predictive value (range 21%–39%) for identification of pats with any AT/AF ($P< .001$) and underestimated AT/AF burden vs continuous monitoring ($P <.001$)
  - Sensitivity for identifying pats with long-duration episodes ranged from 23% to 58%.

Ziegler 2006
Continuous monitoring with implantable devices

- Enables detection of AF in all patients with AF burden > 1%
  - High sensitivity (96.1%) and
- Enables correct exclusion of AF in most patients who do not have AF
  - High negative predictive value (97.4%)
Paroxysmal AF

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1. Sporadic AF episodes? Frequency?
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2. Short episodes? Duration?
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3. Which monitoring methods can assess AF burden?

4. Will AF type remain stable – progression?
Progression of AF

Canadian Registry of AF (CARAF)
- N = 757 Parox. AF pts; FU: 8 yrs.

Kerr CR, Am Heart J. 2005

Probability of progression to any AF
- Chronic AF: 63.2%
- Paroxysmal AF: 24.7%

- N = 5333 AF pts; FU: 1 yrs.
- PAF: 18% → persist/perm AF
- Persist. AF: 30% → perm AF.

Nieuwlaat, EurHeart J 2008; 29,1181–89
Conclusions

• Prospective, large-scale trials needed to assess relation between stroke risk and AF burden in different populations, and to establish the most appropriate anti-thromboembolic treatment in terms of risk-benefit ratio.

• If CHADs score $>2 +$ any sustained recurrent AF
  – consider conventional antithrombotic treatment or
  – repeat risk re-evaluations during follow-up.