The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk: The TRENDS Study

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support
- Consulting Fees/Honoraria

Company

- Medtronic
- Medtronic, St. Jude
Study Aims

• To assess the relationship between device-detected AT/AF and risk of Thromboembolic Events (TE)

• To determine if there is a threshold value of AT/AF burden which increases TE risk
TRENDS Methods
Patient Selection

• 2814 pts
• Class I/II indication for implantation of a dual chamber pacemaker, ICD, or CRT device
• ≥ 1 stroke risk factor:
  • Diabetes
  • HTN
  • CHF
  • Prior stroke/TIA
• Age ≥ 65
Methods

Follow Up & Outcome

• Device diagnostics downloaded at 3 month intervals
• Clinical evaluation at 6 month intervals
• Antithrombotic therapy was directed by patients’ MDs
• TEs were adjudicated by 3 neurologists

• Primary outcome: Thromboembolic event (TE)
  – Ischemic stroke
  – TIA
  – Systemic embolism
Methods
AT/AF Detection

• All devices were programmed to dual chamber operation with active mode switching

• Threshold for AT/AF episode detection was:
  • Atrial rate >175 beats per minute
  • Lasting at least 20 seconds
TRENDS Methods
AT/AF Burden

• AT/AF burden was defined as the longest total duration of AT/AF in hours (h) on any given day during a 30-day rolling window

• Window is “rolled” in 1-day increments
Results
Assembly of the Cohort

Screened
N = 3045

Enrolled
N = 2813

Excluded
N = 232

30 days Device Data
"Overall Study Group"
N = 2486

Excluded: < 30 days of
Device Data
N = 327
## Results

### Baseline Clinical Features - 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.9 ± 11.1 yrs</td>
</tr>
<tr>
<td>Male</td>
<td>1650 (66.4%)</td>
</tr>
<tr>
<td>CHADS$_2$</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td>CHF</td>
<td>1479 (59.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1887 (75.9%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>783 (31.5%)</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>333 (13.4%)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>133.3 ± 22.5 mmHg</td>
</tr>
</tbody>
</table>
### Results

#### Baseline Clinical Features - 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPG</td>
<td>1234 (49.6%)</td>
</tr>
<tr>
<td>ICD</td>
<td>781 (31.4%)</td>
</tr>
<tr>
<td>CRT</td>
<td>471 (18.9%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>517 (20.8%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1547 (62.2%)</td>
</tr>
<tr>
<td>Documented AT/AF History</td>
<td>498 (20.0%)</td>
</tr>
</tbody>
</table>
Results

• Average follow-up was 1.4 years (3382 patient-years)

• 40 TE events
  • 20 ischemic strokes
  • 17 TIAs
  • 3 systemic emboli

• Annualized TE event rate was 1.2% [0.8, 1.6%]
The median value for maximum daily burden in all 30-day windows with non-zero AT/AF was **5.5 h**.
## TRENDS Results
### Annualized TE Event Rates

<table>
<thead>
<tr>
<th>Burden Level</th>
<th>Annualized Rate</th>
<th>Annualized Rate (Excluding TIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Burden</td>
<td>1.1%/Year</td>
<td>0.5%/Year</td>
</tr>
<tr>
<td>Low Burden &lt; 5.5 hours</td>
<td>1.1%/Year</td>
<td>1.1%/Year</td>
</tr>
<tr>
<td>High Burden ≥ 5.5 hours</td>
<td>2.4%/Year</td>
<td>1.8%/Year</td>
</tr>
</tbody>
</table>

TRENDS Results

Cox proportional hazard model adjusting for baseline stroke risk factors & time dependent AT/AF burden & antithrombotic therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio*</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Burden &lt; 5.5 hours</td>
<td>0.98</td>
<td>0.34 to 2.82</td>
<td>0.97</td>
</tr>
<tr>
<td>High Burden ≥ 5.5 hours</td>
<td>2.20</td>
<td>0.96 to 5.05</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*compared to no AT/AF burden
Summary

• The observed stroke rate in this study was very low compared to prior studies of AF patients with similar risk profiles.

• Our results suggest that device-detected AT/AF burden $\geq 5.5$ h on any day during a 30 day window doubles the risk for TE, independent of known risk factors and antithrombotic therapy.
Newly Detected AF in Patients with a History of TE Event

319 had hx TE event

Enrolled 163

- NDAF defined as ≥ 5 mins
- Enrolled
  - NDAF 45 (28%)
  - No NDAF 118 (72%)

Excluded 156
- hx of AF (n=80)
- Warfarin use (n=56)
- AA drug use (n=20)

Zeigler et al. *Stroke*. 2010;41:256-260
Newly Detected AF in Patients with TE Risk Factors

- Enrolled: N=2,814
- Excluded: 156
  - hx of AF (n=480)
  - Warfarin use (n=380)
  - prior TE event (n=353)
  - CHADS 0 (n=232)
- Analyzed: 1,368
  - NDAF: 416 (30%)
  - No NDAF: 952 (70%)

NDAF defined as ≥ 5 mins

Zeigler et al, Am J Cardiol 2012; 110:1309-1314
What Percent of Patients have NDAF?

Figure 2

Zeigler et al, Am J Cardiol 2012; 110:1309-1314
Percentage of NDAF pts exceeding different AF burden thresholds

Maximal Daily AT/AF Burden (or consecutive day) Threshold

% of NDAF Patients

- Prior TE Patients
- Other Risk Factor Patients
KM Curve for Time to Detection of NDAF

- **Freedom from AT/AF**

<table>
<thead>
<tr>
<th>Time from Device Implant (months)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior TE Patients</td>
<td>163</td>
<td>127</td>
<td>111</td>
<td>106</td>
<td>67</td>
</tr>
<tr>
<td>Other Risk Factor Patients</td>
<td>1428</td>
<td>1091</td>
<td>949</td>
<td>856</td>
<td>592</td>
</tr>
</tbody>
</table>

Numbers at Risk:

- Prior TE: 163
- Other Risk Factors: 1428

HackensackUMC
Is the AF detected by CIEDs directly responsible for Strokes?
Patients with pre-stroke AT/AF burden
# Temporal Relationship of Device-Detected AF to Thromboembolic Events

<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>TRENDS53</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>2014</td>
<td>ASSERT54</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>IMPACT55</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>

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>AF Burden Measure</th>
<th>Hazard ratio for stroke event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>MOST</td>
<td>5 min</td>
<td>6.7 p = 0.020</td>
</tr>
<tr>
<td>2005</td>
<td>Capucci</td>
<td>&gt; 24hrs AF</td>
<td>3.1 p = 0.044</td>
</tr>
<tr>
<td>2009</td>
<td>Botto</td>
<td>CHADS₂ + AF burden</td>
<td>0.8% vs. 5% (6.25)</td>
</tr>
<tr>
<td>2009</td>
<td>TRENDS</td>
<td>5.5 hours</td>
<td>2.4 p = 0.060</td>
</tr>
<tr>
<td>2012</td>
<td>Home monitor CRT</td>
<td>3.8 hours</td>
<td>9.4 p = 0.006</td>
</tr>
<tr>
<td>2012</td>
<td>ASSERT</td>
<td>6 min</td>
<td>2.5 p = 0.008</td>
</tr>
</tbody>
</table>