Fibrillazione Atriale Fattore di Rischio o Marker di Stroke: Implicazioni Per La Terapia
Giovedì 7/4/2016

11:20 - 13:00  Sessione plenaria 2

Effetti cerebrali delle malattie cardiovascolari
Moderatori: D. Bertoli, Sarzana - G. Masotti, Firenze

Effetto della riduzione della pressione arteriosa nei pazienti con deficit cognitivo: troppo è dannoso (secondo lo studio dell'ospedale Careggi....)
E. Mossello, Firenze

Ipertensione ortostastica ed aumentata mortalità e morbilità cardiovascolare: predittore indipendente o nesso causale?
R. Furlan (Milano)

Dobbiamo alzare il valore di pressione arteriosa ottimale da raggiungere con la terapia antipertensiva? (sembrebbe di sì, in base alle linee guida ESH-ESC....)
A. Ungar, Firenze

Fibrillazione Atriale, fattore di rischio o marker di stroke:
Implicazioni per la terapia
G.L. Botto, Como
Research support:
Boston Scientific, Medtronic; St. Jude Medical, Bayer Healthcare, Gilead, Sanofi

Advisory Board:
Biotronik, Medtronic; St. Jude Medical, MSD, Bayer Healthcare, Boehringer, Sanofi

Speaker Fees:
Boston Scientific, Medtronic, St. Jude Medical, Sorin Group, Bayer Healthcare, Boehringer, BMS, Meda, MSD, Pfizer, Sanofi
Paroxysmal Atrial Fibrillation

Symptomatic vs Asymptomatic

a = symptomatic PAF
b = asymptomatic PAF
c = sinus rhythm

AF can be silent

Courtesy of John Camm
The Clinical Presentation of AF

Asymptomatic Atrial Fibrillation

Crypto Stroke | Ischemic Stroke | Sudden Death | Heart Failure

Cognitive Decline

Dementia

Symptomatic Atrial Fibrillation

Palpitations

Hemodynamic
Dizziness
Heart Failure
Syncope

Tachy Arrhythmias

Medical Attention
Stroke as a First Devastating Sign of Atrial Fibrillation

- 75 yr-old male patient with acute hemi-paresis
- Preceding dyspnea NYHA for 7 days
Cerebrovascular Disease

*Patogenesis*

- **Hemorrhagic Stroke (17%)**
  - Intracerebral Hemorrhage (59%)
  - Subarachnoid Hemorrhage (41%)

- **Ischemic Stroke (83%)**
  - Atherosclerotic Cerebrovascular Disease (20%)
  - Embolism (20%)
  - Cryptogenic (30%)
  - Lacunar (25%)

Acute Stroke With AFIB

The Copenhagen Stroke Study

- 15% of all strokes attributable to AFIB
  *(old data)*

Stroke in pts with AFIB vs w/out-AFIB

- Higher mortality rate
  (OR 1.7; 95% CI 1.2-2.5)

- Longer hospital stay
  (50 vs 40 days; p<0.01)

- Lower discharge rate
  (OR 0.60; 95% CI 0.44-0.85)

- Poorer neurologic and functional outcome

- Explained by initially more severe strokes

*Stroke 1996; 27: 1765-1769*
Comprehensive Management Of AF Should Address The Multiple Impacts Of The Condition

- In addition to stroke prevention and reduction of AF burden, successful management of AF should aim to reduce hospitalisations and CV morbidity and mortality.

Camm AJ, Eur Heart J 2012;33:2719-2747
Relation Between Symptoms and ECG Transmission in AF

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Total (%)</th>
<th>AF</th>
<th>No AF</th>
<th>Odds (P Value) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skipped beats</td>
<td>202 (52)</td>
<td>64</td>
<td>138</td>
<td>0.6 (ns)</td>
</tr>
<tr>
<td>Heart racing</td>
<td>132 (33)</td>
<td>68</td>
<td>64</td>
<td>2.4 (ns)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>65 (17)</td>
<td>33</td>
<td>32</td>
<td>1.9 (ns)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>51 (13)</td>
<td>36</td>
<td>15</td>
<td>5 (0.008)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>42 (11)</td>
<td>30</td>
<td>12</td>
<td>5 (0.01)</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>39 (10)</td>
<td>11</td>
<td>28</td>
<td>0.6 (ns)</td>
</tr>
<tr>
<td>Fainting</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
<td>0.0 (ns)</td>
</tr>
</tbody>
</table>

Vesamreddy et al. J Cardiovasc Electrophysiol 2006; 17: 134-139
Conversion From Symptomatic to Silent AF During AAD Rx

52 patients with PAF with 24 hour Holter

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>47%</td>
<td>22%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>53%</td>
<td>78%</td>
</tr>
<tr>
<td>No PAF on Holter</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>PAF on Holter</td>
<td>74%</td>
<td>73%</td>
</tr>
</tbody>
</table>

AF duration at baseline (s) | 2215 +/- 3843 | 16 +/- 10
AF duration on treatment (s) | 16 +/- 10 | 82 +/- 8
HR at baseline (bpm) | 126 +/- 27 | 82 +/- 8
HR on treatment (bpm) | 126 +/- 27 | 82 +/- 8

Wolk R. Int J: Cardiol 1996; 54: 207-211
Symptomatic vs Asymptomatic AF

- DISCERN AF:
  - Comparison of the incidence of symptomatic and asymptomatic AF before and after AF ablation
- 86% reduction in AF burden post ablation
- 56% of AF burden was asymptomatic
- AF was more asymptomatic post ablation

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic Pre-ablation</th>
<th>Ratio Asymptomatic: Symptomatic Pre-ablation</th>
<th>Asymptomatic Post-ablation</th>
<th>Ratio Asymptomatic: Symptomatic Post-ablation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/AFL episodes</td>
<td>51.9%</td>
<td>1.1</td>
<td>78.7%</td>
<td>3.7</td>
<td>0.002</td>
</tr>
<tr>
<td>AF/AFL burden</td>
<td>35.8%</td>
<td>0.6</td>
<td>67.6%</td>
<td>2.1</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Verma A. Presented at the Late Breaking Clinical Trial session during HRS 2011
Incremental Cost Burden of Undiagnosed AF By Prevalence of Undiagnosed AF

![Graph showing the incremental cost burden of undiagnosed AF by prevalence of undiagnosed AF. The graph compares Baseline (1 in 10 AF cases undiagnosed) and Alternative (1 in 4 AF cases undiagnosed) scenarios. The annual burden in U.S. dollars (billions, 2014 USD) increases as the prevalence of undiagnosed AF increases. The cost burden ranges from $1.9 billion for 60% prevalence to $12.8 billion for 140% prevalence.]

Turakhia MP. AJC 2015, 116: 733-739
Atrial Fibrillation
The More You Look, The More You Find

Incremental Yield of Prolonged ECG Monitoring for the Detection of AF in Pts with Cryptogenic Stroke or TIA.

More intensive monitoring results in more AF detection

Opportunistic Screening of AF

Pulse vs Microlife Tech

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse</td>
<td>Hobbs 2592</td>
<td>M-AFIB 405</td>
</tr>
<tr>
<td>Pulse</td>
<td>Morgan 1099</td>
<td>M-AFIB 73</td>
</tr>
<tr>
<td>M-AFIB</td>
<td>Wiesel 405</td>
<td>M-AFIB 999</td>
</tr>
<tr>
<td></td>
<td>Stergiou 73</td>
<td></td>
</tr>
</tbody>
</table>

Botto GL, Russo G. 2015
AF Detection

24-h Holter: Something Like a Disaster

- 425 Holter ECGs after cerebral ischemic event
- 18.2% of all Holters in the hospital

<table>
<thead>
<tr>
<th></th>
<th>AF diagnosis</th>
<th>OAC start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>9 (2.1%)</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>Holters needed</td>
<td>47</td>
<td>85</td>
</tr>
<tr>
<td>Costs per case</td>
<td>$9,400</td>
<td>$17,000</td>
</tr>
</tbody>
</table>

Schaer B. Stroke 2004; 35: e68-70
Improvement of Device Technology Allows Greater Quantification of AF Burden

Botto GL. JCE. 2009;20:241-248
DRONEDARONE STARTED HERE

Data della visita: 26-Lug-2011 18:41:39

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9987 Version software 7.2
Cardiac Monitoring Set

- Reveal LINQ™ ICM
- MyCareLink™ Patient Monitor
- Patient Assistant
- Mobile Alerts
- Streamlined Reports
- Improved CareLink® User Interface

All patient and clinical data are fictitious and for demonstration purposes only.
Example of Cardiac Compass
(Medtronic Inc. ®)
Performance of Reveal XT in Detecting AF

The XPECT Trial

Hindricks G. Circ Arrhythm Electrophysiol 2010; 3: 141-147
Detection of Silent AF is Crucial

How Much Atrial Fibrillation Is Needed to Cause Thromboembolism?
AF Detected By Dual-Chamber Devices And Risk For Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>n (Patient Population)</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glotzer et al^{16}</td>
<td>312 (SSS)</td>
<td>AHRE identified patients that are &gt;2 times as likely to die or have a stroke and 6 times as likely to develop AF as those without AHRE (median FU 27 months).</td>
</tr>
<tr>
<td>Capucci et al^{35}</td>
<td>725 (history of PAF)</td>
<td>The risk for embolism was 3.1 times increased in patients with device-detected AT/AF episodes lasting &gt;24 hours (median FU 22 months).</td>
</tr>
<tr>
<td>Botto et al^{12}</td>
<td>568 (history of PAF)</td>
<td>Risk stratification can be improved by combining CHADS\textsubscript{2} score with data on AF presence and duration (1-year FU).</td>
</tr>
<tr>
<td>Glotzer et al^{68}</td>
<td>2,486 (≥1 RFS)</td>
<td>Daily AF burden ≥5.5 hours on any of 30 previous days appeared to double the risk for stroke (mean FU 1.4 years).</td>
</tr>
<tr>
<td>Ziegler et al^{21}</td>
<td>163 (PS, no history of PAF)</td>
<td>Newly detected episodes of AF were found via continuous monitoring in 28% of patients with previous stroke (mean FU 1.1 years).</td>
</tr>
<tr>
<td>Boriani et al^{30}</td>
<td>568 (history of PAF)</td>
<td>The combination of data on AF burden with CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc score improved risk stratification for stroke (1-year FU).</td>
</tr>
<tr>
<td>Healey et al^{46}</td>
<td>2580 (age ≥65 years, HTN, no history of PAF)</td>
<td>Device-detected atrial tachyarrhythmias were associated with a 2.5-fold increased risk for ischemic stroke or systemic embolism (mean FU 2.5 years).</td>
</tr>
<tr>
<td>Shammugam et al^{49}</td>
<td>560 (CRT)</td>
<td>In a cohort of heart failure patients, daily AF burden &gt;3.8 hours over 24 hours was associated with a significant increase in the event rate (median FU 370 days).</td>
</tr>
</tbody>
</table>

Atrial High Rate Episode (AHRE) in PMK Recipients for SND

Ancillary MOST Study
- 312 patients
- Event logged if AR >220 bpm / 10 beats / 5 min

AHRE predicts
Total mortality 2.48 [1.25-4.91], p = 0.0091
Death or non-fatal stroke 2.79 [1.51-5.15], p = 0.0011
AF 5.93 [2.88-12.2], p = 0.0001

Glotzer TV. Circulation 2003; 107:1614-9
**ASSERT Trial: Primary Outcome**

- 2582 pts with SSS; HTx and no prior AF (76±7 years, CHADS\(_2\) score 2.41)
- goal AF > 6 min, > 190 bpm in 36% of pts; F-U 2.8 years

<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></td>
<td>events %/year</td>
<td>events %/ year</td>
</tr>
<tr>
<td>Ischemic Stroke or Systemic Embolism</td>
<td>40 0.69</td>
<td>11 1.69</td>
</tr>
<tr>
<td></td>
<td>RR 2.49 95% CI 1.28 – 4.85 p 0.007</td>
<td></td>
</tr>
<tr>
<td>Vascular Death</td>
<td>153 2.62</td>
<td>19 2.92</td>
</tr>
<tr>
<td></td>
<td>RR 1.11 95% CI 0.69 – 1.79 p 0.67</td>
<td></td>
</tr>
<tr>
<td>Stroke / MI / Vascular Death</td>
<td>206 3.53</td>
<td>29 4.45</td>
</tr>
<tr>
<td></td>
<td>RR 1.25 95% CI 0.85 – 1.84 p 0.27</td>
<td></td>
</tr>
<tr>
<td>Clinical Atrial Fibrillation or Flutter</td>
<td>71 1.22</td>
<td>41 6.29</td>
</tr>
<tr>
<td></td>
<td>RR 5.56 95% CI 3.78 – 8.17 p &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Device-Detected AF And Risk For Stroke Or TIA
An Analysis Of >10 000 Pts From The SOS AF Project

Boriani G. European Heart Journal 2014; 35: 508–16
CHADS$_2$ Score, AF Duration and Stroke Risk

568 Pts with MDT AT500 IPG Continuously Monitored for 1 Year

<table>
<thead>
<tr>
<th>CHADS$_2$ score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AF at FU (AT/AF &lt; 5 min in 1 day)</td>
<td>1.7%</td>
<td>0%</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>5 min &lt; AT/AF Episodes &lt; 24 h</td>
<td>1.8%</td>
<td>1.3%</td>
<td>2.4%</td>
<td>0%</td>
</tr>
<tr>
<td>AT/AF Episodes &gt; 24 h</td>
<td>0%</td>
<td>4.4%</td>
<td>4.4%</td>
<td>33%</td>
</tr>
</tbody>
</table>

(3 out of 351 Pts) 0.8% vs 5% (11 out of 217 Pts) P = 0.035

Botto GL. J Cardiovasc Electrophys 2009; 20: 241-248
ASSERT enrolled 2580 PMK&ICD pts aged ≥65 years with a htx of hypertension but w/out a htx of AF

The temporal relationship between SCAF >6 min in duration and stroke or systemic embolism has evaluated

51 pts with S/SE

18 (35%) SCAF before S/SE

4 (8%) SCAF ≤ 30 days

33 (65%) SCAF after S/SE

14 (27%) SCAF > 30 days

the most recent episode @ median interval of 339 days (25°-75th percentile, 211-619) earlier

Brambatti M. Circulation 2014; 129: 2094-9
Patients with Sub-Clinical AF (SCAF)
The mechanisms of Cerebrovascular / Systemic Events in pts with implantable devices may importantly involve mechanisms other than cardioembolism due to atrial tachyarrhythmias.
Mechanism Linking Inflammation and Thrombosis in AF

Guo Y, Lip, GY, Apostolakis S. J Am Coll Cardiol 2012; 60: 2263–70
Electroanatomic Left Atrial Voltage Mapping In Pts With AF

Kottkamp H. European Heart Journal 2013 34, 2731–2738
The net clinical benefit associated with a given therapeutic choice should guide this decision.
Net Clinical Benefit of Warfarin in Patients With AF
A Report From the Swedish Atrial Fibrillation Cohort Study
Net Clinical Benefit of Warfarin in Patients With AF
A Report From the Swedish Atrial Fibrillation Cohort Study

<table>
<thead>
<tr>
<th>CHADS₂</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.7 (0.5-0.9)</td>
<td>0.9 (0.1-2.0)</td>
<td>...</td>
<td>...</td>
<td>0.3 (0.2-0.5)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1</td>
<td>2.0 (1.6-2.3)</td>
<td>2.6 (2.5-3.1)</td>
<td>2.9 (1.9-3.9)</td>
<td>...</td>
<td>...</td>
<td>2.5 (2.3-2.7)</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>3.3 (2.6-4.0)</td>
<td>3.5 (3.1-3.8)</td>
<td>3.9 (3.5-4.3)</td>
<td>2.4 (1.1-3.8)</td>
<td>...</td>
<td>3.6 (3.3-3.8)</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>5.7 (4.9-6.5)</td>
<td>6.8 (6.1-7.1)</td>
<td>6.3 (5.1-7.2)</td>
<td>5.8 (4.5-7.2)</td>
<td>...</td>
<td>6.5 (5.1-11)</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>8.6 (7.7-9.5)</td>
<td>12.1 (10.9-13)</td>
<td>11.5 (8.1-15)</td>
<td>13.0 (10.7-20)</td>
<td>...</td>
<td>10.1 (9.4-11)</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>9.1 (6.6-11)</td>
<td>12.7 (11.1-14)</td>
<td>10.7 (6.9-14)</td>
<td>10.0 (1.2-19)</td>
<td>...</td>
<td>11.8 (10-13)</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>...</td>
<td>10.5 (7.5-14)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>11.9 (9.2-15)</td>
<td>...</td>
</tr>
</tbody>
</table>

| CHA₂DS₂: VASC | 0 | 0.0 (-0.2 to 0.2) | ... | ... | ... | ... | ... |
|               | 1 | 0.4 (0.2-0.7) | ... | ... | ... | ... | ... |

|         | 2 | 1.5 (1.1-1.8) | 2.2 (1.8-2.8) | 2.7 (1.4-5.0) | ... | ... | 1.7 (1.5-2.0) |

Friberg L. Circulation. 2012; 125: 2298-2307
AVERROES

Primary Efficacy and Safety Outcome

Net Clinical Benefit for Warfarin and NOACs by CHA$_2$DS$_2$-VASc and HAS-BLED Score

Banerjee A. Thrombosis Haemost 2012; 107: 584-589
The Effectiveness of OAC for Stroke Prevention in AF is Well Documented, but …

No Data on Similar Strategies in Pts With CIED Detected AF Are Available
Annual Rate of Stroke and SE in Registries Compared to ASSERT

- Singer 2009: 2.29
- Friberg 2012: 4.50
- ASSERT 2012: 1.59
The IMPACT of BIOTRONIK HM Guided Anticoagulation on Stroke Risk

### A. Initiation criteria

<table>
<thead>
<tr>
<th>CHADS(_2) score</th>
<th>AHRE duration (over 48 consecutive hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>48 h</td>
</tr>
<tr>
<td>3 and 4</td>
<td>24 h</td>
</tr>
<tr>
<td>5 and 6 or prior ischemic stroke, TIA or systemic embolism independent of CHADS(_2) score</td>
<td>(\leq 12) h</td>
</tr>
</tbody>
</table>

### B. Interruption criteria

<table>
<thead>
<tr>
<th>CHADS(_2) score</th>
<th>Consecutive days free from AHRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>30</td>
</tr>
<tr>
<td>3 and 4</td>
<td>90</td>
</tr>
<tr>
<td>5 and 6 or prior ischemic stroke, TIA or systemic embolism independent of CHADS(_2) score</td>
<td>Maintain warfarin</td>
</tr>
</tbody>
</table>

Ip J. Am Heart J 2009; 158: 364-370
Atrial Arrhythmia Monitoring To Guide Anticoagulation In Pts With ICD/CRT Devices

The IMPACT Trial

Primary events first stroke, SE, major bleedings

Martin DT. Eur Heart J 2005; 36: 1660–1668
A randomized trial of long-term remote monitoring of pacemaker recipients

The COMPAS trial

Hosp. for A arrhythmias (6 vs. 18) and strokes (2 vs. 8) were fewer (P < 0.05)

Philippe Mabo, Frédéric Victor, Patrick Bazin, Saïd Ahres, Dominique Babuty, Antoine Da Costa, Didier Binet, and Jean-Claude Daubert, on behalf of the COMPAS trial investigators
Atrial Fibrillation and Stroke

*Bread for the Brain*

- Asymptomatic device-detected AHRE are of clinical importance.
- The impact of device-detected atrial high-rate episodes and arrhythmia burden on thrombogenesis and clinical thromboembolism is attracting much interest.
- Thromboembolic risk is not only related to AT/AF episodes, but likely involves a complex interplay of:
  - atrial arrhythmias
  - atrial myopathy
  - endothelial dysfunction related to comorbidity
  - abnormal hemostasis
- The need for anticoagulation Rx is mostly depending on stroke risk factors once a low threshold of AT/AF burden is exceed rather than merely the presence/absence of AF.
- Cost-effectiveness of future approaches needs to be determined.
Silent Atrial Fibrillation and Stroke

**Conclusion**

- Pts with CIEDs are a *unique* population
  - *multiple comorbidities predisposing to AF*
- Diagnosis of silent AF is *more likely* in this group
  - *continuous monitoring increases the chance of early detection*
- AF detected by devices is an independent *predictor of TE events*
- **Optimal management is currently not known**
Silent Atrial Fibrillation and Stroke Prevention

Practical Suggestion

Personal Opinion of the Author

■ Certain pts can be identified based on
  - presence of individual risk factors
  - detected AF duration and burden

■ In case of CHADS2 score …
  \( \text{CHADS}_2 = 0 \)
  *no OAC regardless of the burden of detected AF*
  \( \text{CHADS}_2 = 1-2 \)
  *OAC if a single episode of detected AF exceed … (24 hs ?)*
  \( \text{CHADS}_2 \geq 3 \)
  *OAC if the burden of detected AF exceed … (1 h ?)*