What the general cardiologist should know about arrhythmia
„Stroke prevention in AF"

Peter Ammann
Kantonsspital St. Gallen
What the cardiologist should know about arrhythmia and stroke

• are there real low risk AF patients for ischemic stroke?

• How should we treat «Cryptogenic stroke»?
  • search for the underlying mechanisms?
  • tailored therapy or NOACs for all
  • How should we screen for AF?

• How to treat AF patients with stroke an KI for oral anticoagulation?
Time for a new model

Kamel et al. Stroke 2016

Watson Lancet 2009
Which patients are at risk?
Annual stroke rate in AF patients

AF is an independent risk factor for stroke

Stroke risk persists in AF patients regardless of symptoms and/or rhythm management

Page et al Circulation 2003; Fuster et al JACC 2006,
Discriminatory power of both systems is limited (C-statistic < 0.7) both scoring systems cannot identify real low risk AF patients possibility of other unidentified risk factors (e.g. weight, LA size, race, OSAS, metabolic syndrome...
Risk of stroke versus ICH in «low risk patients»

Chao TF et al JACC 2015
Cryptogenic stroke
• Essential hypertension
• Lone atrial fibrillation
• Idiopathic cardiomyopathy
• Cryptogenic stroke

...we don’t know the underlying mechanism
• **TOAST classification**: stroke of undetermined cause refers to
  – Stroke with incomplete workup
  – More than one potential cause
  – No determined etiology after investigations are complete

• **ASCO classification**: cause is unknown, stroke does not involve
  – Atherosclerosis (A)
  – Small vessel disease (S)
  – Cardiac disease (C)
  – Or other cause (O)
"Cryptogenic Stroke" in PubMed

Year of publication

Number of articles

ESUS

Camm HRS 2016
ESUS Embolic Stroke of Undetermined Source

• ESUS International Working Group 2014

• Non-lacunar infarct in the absence of
  – Extracranial/intracranial atherosclerosis causing > 50% luminal stenosis in the artery supplying the ischemic region
  – Major cardioembolic sources
    • Permanent or paroxysmal AF, atrial flutter, intracardiac thrombus, prosthetic cardiac valve, cardiac tumors, mitral stenosis, MI within past 4 weeks, LVEF < 30%, valvular vegetations
  – No other specific cause of stroke (e.g. dissection)
Patients with acute ischemic stroke or TIA (n=4632)

Acute ischemic stroke (n=3981)

TIA (n=511)
Diffusion negative stroke (n=131)
Others (n=9)

History taking, ECG, brain MRI + MRA

Large artery disease (n=1295)
Cardioembolic stroke (n=693)
Small artery occlusion (n=674)
Others (n=186)

Extensive work-ups

Cardioembolic, other than PAF (n=214)
Undetermined etiology (n=368)
Incomplete evaluation (n=230)

Cryptogenic embolic stroke (n=321)

AAA (n=40)
PFO (n=153)
PAF (n=128)

12%
47%
40%

Ryoo et al J Am Heart Assoc 2016
Sophisticated therapy with AP vs OAK or NOAC for all?

Red thrombus from

A PFO, B ulcerated carotid artery plaque, 
C myxomatous mitral valve, D aortic arch

Hart et al Lancet Neurology 2014
PFO: stroke rate between OAC and APT

<table>
<thead>
<tr>
<th>Study name</th>
<th>events/OAC</th>
<th>events/APT</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toronto</td>
<td>2/25</td>
<td>10/63</td>
<td>1.20 (0.22, 7.58)</td>
</tr>
<tr>
<td>Tiffs</td>
<td>2/40</td>
<td>2/46</td>
<td>1.59 (0.21, 12.08)</td>
</tr>
<tr>
<td>PICSS</td>
<td>7/42</td>
<td>13/56</td>
<td>0.66 (0.24, 1.95)</td>
</tr>
<tr>
<td>Schuchtenz</td>
<td>7/47</td>
<td>24/66</td>
<td>0.32 (0.13, 0.80)</td>
</tr>
<tr>
<td>Sapienza</td>
<td>5/35</td>
<td>4/60</td>
<td>0.46 (0.10, 1.90)</td>
</tr>
<tr>
<td>FORI</td>
<td>4/24</td>
<td>7/93</td>
<td>1.43 (0.30, 6.37)</td>
</tr>
<tr>
<td>Bern Pub</td>
<td>8/42</td>
<td>17/57</td>
<td>2.98 (0.88, 10.30)</td>
</tr>
<tr>
<td>PC Trial</td>
<td>1/61</td>
<td>10/116</td>
<td>0.75 (0.35, 1.60)</td>
</tr>
<tr>
<td>CODICIA</td>
<td>4/82</td>
<td>15/212</td>
<td>0.60 (0.41, 1.58)</td>
</tr>
<tr>
<td>German</td>
<td>12/135</td>
<td>21/161</td>
<td>0.20 (0.03, 1.32)</td>
</tr>
<tr>
<td>CLOSURE</td>
<td>8/114</td>
<td>16/266</td>
<td>0.22 (0.03, 1.72)</td>
</tr>
<tr>
<td>RESPECT</td>
<td>3/105</td>
<td>14/332</td>
<td>1.34 (0.63, 2.84)</td>
</tr>
<tr>
<td>Meta-analysis estimates</td>
<td></td>
<td></td>
<td>0.75 (0.52, 1.12)</td>
</tr>
</tbody>
</table>

No difference

Kent DM et al Eur Heart J 2015
Comparison of Warfarin vs Aspirin for prevention of recurrent ischemic stroke (WARSS) in patients without cardioembolic sources

no difference

Mohr et al NEJM 2001
Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial

VKA vs Aspirin

VKA are not more effective than aspirin for secondary prevention after TIA or minor stroke of arterial origin. Possible effect against ischemic events offset by increased bleeding complications

Lancet Neurol 2007
ESUS and Sinus rhythm in ECG 24 h ECG, 7 day holter, or ILR?
Embrace Event Monitor Belt for Recording AF after a Cerebral Ischemic Event

Cryptogenic after initial 24h ECG within 6 mths

24 h ECG AF in 6 of 277 pts
30 day monitor in 42 of 284 pts

Gladstone D NEJM 2014
AF Detection by ILR in Cryptogenic Stroke
Crystal AF study

Hazard Ratio (95% CI) = 8.8 (3.5, 22.2)
log-rank p-value < 0.0001

Brachmann et al Circ Arrhythm Electrophysiol 2016
ILR or long time monitoring with wearable devices (ILR median 365; wearable 21 days)

Data from 3 RCTs and 13 observational studies

Figure 3. This graph shows that detection of AF was significantly higher with ILR 23.3% (CI: 13.83, 32.29) compared to wearable devices 13.6% (CI: 7.91, 19.32; P < 0.05) in patients with cryptogenic stroke. AF = atrial fibrillation; CI = confidence intervals; ILR = implantable loop recorder.

Afzal et al Pacing Clin Electrophysiol 2015
Device patients with AF in storage when to start OAK?

1 min?
1 hour?
1 day?
1 week?

The higher the CHADS2-VAS2c the lower the duration?
AF Duration and Stroke Relationship

- **MOST Sub-study**: AF >5 minutes → $HR=2.79$ for death or stroke

- **Italian AT500 Study**: AF>24 hours → $HR=3.1$ for thromboembolism

- **Botto Study**: 24 hours + CHADS$_2$ → $HR=6.2$ for thromboembolism

- **TRENDS Study**: AF>5.5 hours → $HR=2.2$ for thromboembolism

- **BioTronik Study**: AF>3.8 hours → $HR=9.4$ for thromboembolism

- **ASSERT Study**: AF>6 minutes → $HR=2.5$ for thromboembolism
Device-detected atrial fibrillation and risk for stroke: an analysis of >10 000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices)

Giuseppe Boriani1*, Taya V. Glotzer2, Massimo Santini3, Teena M. West4, Mirko De Melis4, Milen Seps5, Maurizio Gasparini6, Thorsten Lewalter1, John A. Camm8, and Daniel E. Singer9

1Department of Experimental, Diagnostic and Specialty Medicine, Institute of Cardiology, University of Bologna, 40126 Bologna, Italy; 2Cardiology Department, Sir Francis Drake Hospital, London, UK; 3Cardiology Department, San Filippo Neri Hospital, Rome, Italy; 4Pediatric Cardiology in Center, Manitoba, Canada; 5Cardiology Department, University Hospital Brussels, Brussels, Belgium; 6Department of Cardiology, Humantitie Pirogov Hospital, Moscow, Russia; 7Department of Cardiology, University Hospital, Essen, Germany; 8Cardinale Viscardio Hospital, London, UK; and 9Cardinale Viscardio Hospital, London, UK

Received 22 March 2013; revised 26 September 2013; accepted 7 November 2013; online publish-ahead-of-print 11 December 2013

---

**Figure 1** Atrial fibrillation burden along with time during the follow-up. Kaplan–Meier curve of patients experiencing a first day with at least 5 min of atrial fibrillation burden, among all subjects (n = 10 016).
Contraindication for long term OAK and AF?
Protect AF and Prevail

FIGURE 2 PROTECT AF/PREVAIL Combined: Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>0.79</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.02</td>
<td>0.94</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.95</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>1.56</td>
<td>0.21</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.48</td>
<td>0.006</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73</td>
<td>0.07</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)

Favors Watchman ———— Favors warfarin

Holmes JR et al JACC 2015
The Watchman should only be used in patients

- non-valvular AF
- CHADS2VASc2 ≥ 2
- Are suitable for anticoagulation (not for Amplatzer)

- FAD approved March 2015
After discharge

- OAK for 45 days (INR2-3)
- After 45 days TEE is required to assess the presence of LAA blood flow through and/or around the implant
  - Discontinue OAK if complete LAA occlusion or residual blood flow around the device margins ≤ 5 mm
  - ASS indefinitely and clopidogrel for 6 months

- ASS/Plavix for Amplatzer Amulet 6 mts
Conclusions

• «Atrial fibrillation begets Atrial fibrillation» and begets stroke
• The longer we screen for AF after ESUS the more AF we will find
• In 2016 most AF patients needs lifetime OAC
• My personal opinions:
  – AP therapy will decrease in ESUS patients in the next years even in patients without AF
  – LAA occusion will stay as an option for only a minority of AF patients