Atrial fibrillation

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Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck
(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA<sub>2</sub>DS<sub>2</sub>-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thrombo-embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female sex)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
<tr>
<td>CHA\textsubscript{2}DS\textsubscript{2} -VASc score</td>
<td>Patients (n = 73538)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>0</td>
<td>6369</td>
</tr>
<tr>
<td>1</td>
<td>8203</td>
</tr>
<tr>
<td>2</td>
<td>12771</td>
</tr>
<tr>
<td>3</td>
<td>17371</td>
</tr>
<tr>
<td>4</td>
<td>13887</td>
</tr>
<tr>
<td>5</td>
<td>8942</td>
</tr>
<tr>
<td>6</td>
<td>4244</td>
</tr>
<tr>
<td>7</td>
<td>1420</td>
</tr>
<tr>
<td>8</td>
<td>285</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
</tr>
</tbody>
</table>

Therefore:

- One single condition, non-valvular AF, associated with extremely variable risk of stroke, from <1%/year to >6%/year
- Lone AF has a risk of stroke similar to that of the normal population (<1%/year)
- The presence of AF alone is not sufficient to increase the risk of stroke
- The presence of risk factors largely determines the prothrombotic state in AF
Left atrial/Left atrial appendage thrombosis – Virchow revisited

**Localizing factor**

- Atrial fibrillation per se

- The blood

- The atrial endothelial lining

- The flow
Components of Virchow’s triad for thrombogenesis in atrial fibrillation

Flow abnormalities

- Blood stasis in the atria an obvious common denominator in AF, greater with mitral stenosis, less severe with associated mitral regurgitation
- Blood stasis increases with LA size
- Exacerbated by the occurrence of ventricular tachycardia, reducing the diastolic filling time and the atrial contribution to ventricular filling
- Documentable as spontaneous echo-contrast at TEE and as reduced Doppler flow velocities in the LAA
- ... but blood flow stasis is present also in lone AF, where the thromboembolic risk is similar to that of the general population, therefore stasis alone CANNOT explain the increased risk of stroke in AF

Atrial endocardial damage

- Electron-microscopy aspects of atrial endocardial damage\(^1\) and of a “rough” endothelium\(^2\)
- Aspects of LAA endocardial fibroelastosis\(^3\)
- Systemic and vascular inflammation described in AF, as documented by elevated CRP levels\(^4\)
- Increased fibrosis and levels of MMPs/TIMP in the atria correlating with risk factors\(^5\)
- Increased atrial endothelial expression of tissue factor, again as a correlate of risk factors

Inflammation and AF burden
Step-wise elevation of CRP with increasing burden of AF

Probability of new-onset AF as a function of higher-than median or lower-than median baseline CRP

Abnormalities of blood constituents

- Platelets
- Coagulation
Platelet abnormalities in AF


- However plasma levels of P-selectin were unrelated to estimated stroke risk among patients in the SPAF III trial despite associations between soluble P-selectin levels and atherothrombotic risk factors, such as smoking and peripheral vascular disease (Conway DSG, et al. Circulation 2002;106:19627)
The ACTIVE Program

Documented AF + ≥1 risk factor:
Age ≥75, Hypertension, Prior stroke/TIA, LVEF<45, PAD, Age 55-74 + CAD or diabetes

ACTIVE W
6706 patients
Clopidogrel+ASA vs. OAC

ACTIVE A
7662 patients
Clopidogrel+ASA vs. ASA

Contra-indications to OAC or Unwilling

No Exclusion criteria for ACTIVE I

ACTIVE I
9022 patients
Irbesartan vs placebo

Partial Factorial Design
ACTIVE-W: Primary Endpoint
Stroke, Non-CNS Systemic Embolism, MI & Vascular Death

Cumulative Hazard Rates

Years

# at Risk
C+A: 3335, 3149, 2387, 916
OAC: 3371, 3220, 2453, 911

RR = 1.45
P = 0.0002

5.64%/year
3.93%/year

Clopidogrel+ASA
OAC

ACTIVE Writing Group, Lancet 2006;367:1903
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Partial Factorial Design
ACTIVE-A outcomes - Stroke

HR = 0.72 (0.62-0.83) p < 0.00002

Cumulative Hazard Rates

Aspirin

Clopidogrel + Aspirin

No. at Risk
C+A  3772
ASA  3782

C+A  3491  3229  2570  1203
ASA  3458  3155  2517  1186

Years
Event-free survival as a function of D-dimer levels under VKA in atrial fibrillation

Platelet abnormalities play some role in thrombogenesis in AF. This may occur because of the cross talk between primary and secondary hemostasis. But in any case, the contribution of coagulation is probably higher.
Reversing coagulation abnormalities in AF

- An AFASAK-2 substudy reported that only dose-adjusted warfarin (INR 2–3) had an effect on the amounts of prothrombin fragments 1 and 2 after 3 months’ treatment.

- Fixed low-dose warfarin, combined low-dose warfarin and aspirin, or aspirin alone had little effect on prothrombin fragments.

- Similarly, fixed low-dose warfarin or aspirin-warfarin combination treatment did not substantially reduce other markers of thrombogenesis in AF, whereas dose-adjusted warfarin did.

What drives the prothrombotic state in atrial fibrillation?

- Inflammation
- Growth factors
- Excessive extracellular matrix turnover
- Decreased NO
- Activation of the renin-angiotensin-alderosterone system
Interactions of the elements in Virchow’s triad in determining thrombus formation in AF

Risk factors

Prothrombotic state

Blood stasis

Atrial wall changes

THROMBUS
Thus, knowledge and understanding of the mechanisms by which risk factors prompt a thrombogenic state may help in risk stratifying and in guiding new therapies in atrial fibrillation.
Inflammation and thrombosis – testing the hypothesis with anti-inflammatory drug trials

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INFLAMMATORY PATHWAYS AS POTENTIAL TARGETS FOR Atherosclerotic Therapies

Ongoing large randomized controlled trials designed to evaluate the effect of anti-inflammatory drugs on atherosclerosis, including CANTOS and CIRT, also assess the impact of anti-inflammatory therapy on incident VTE, will shed light on the hypothesis of inflammation-mediated thrombosis.

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…but let’s not forget that not all strokes in atrial fibrillation are thromboembolic…
The multi-factorial etiology of stroke in AF

- **Structural**
  - Mitral valve prolapse?
  - Mitral annular calcification

- **Stasis**
  - Large LA
  - Large LV/low EF

- **Risk factors/markers**
  - Atherosclerosis
    - aortic, cerebrovascular

Frequency: ?

75% ?

25% ?

*Gersh et al, 1995*
Thank you!