New insights into the anticoagulation treatment of atrial fibrillation beyond the best-known data of the clinical trials

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1. New risk scores in AF
2. Influence of gender on outcome in AF
3. Minor/moderate bleeding and outcome
4. History of falling and outcome in AF
5. Valvular heart disease and outcome in AF
6. Digoxin and risk of death in AF
7. Importance of "extensive" education
1. New risk scores in AF

**ABC score for prediction of stroke/SE**

- **Points**
  - Prior stroke/TIA:
    - No
  - Age:
    - 44, 55, 65, 75, 90
  - Troponin I (ng/L):
    - 1, 2, 5, 10, 30, 75, 180
  - NT-proBNP (ng/L):
    - 25, 50, 100, 200, 400, 800, 1500, 3000, 5900

- **Total Points**

- **1-year risk of stroke/SE**

- **3-year risk of stroke/SE**

*Hijazi et al. Eur Heart J 2016.*
Based on ARISTOTLE, validated in RE-LY

NEW in the ESC AF guidelines 2016: “Biomarkers such as high-sensitivity troponin and natriuretic peptide may be considered to refine stroke risk in AF (class IIb).”

### 2. Influence of gender on outcome in AF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate, men</th>
<th>Rate, women</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.35</td>
<td>1.57</td>
<td>0.91 (0.74-1.12)</td>
<td>0.38</td>
</tr>
<tr>
<td>All-cause death</td>
<td>3.98</td>
<td>3.26</td>
<td>0.63 (0.55-0.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death</td>
<td>2.09</td>
<td>1.58</td>
<td>0.62 (0.51-0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.62</td>
<td>2.58</td>
<td>0.86 (0.74-1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Major or non-major clinically relevant bleeding</td>
<td>5.08</td>
<td>4.92</td>
<td>0.89 (0.80-1.00)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Implication:** female sex is not an important risk factor for stroke in anticoagulated AF patients.

“*These results should be further explored in order to verify the hypothesis that female sex might not be incorporated in the assessment of risk score of patients with AF.*”

NEW in ESC AF guidelines 2016

Use $\text{CHA}_{2}\text{DS}_{2}-\text{VASc}$, but without $\text{Sc}$ (“sex category”)!
3. Minor/moderate bleeding and outcome

Implication: even moderate and minor bleedings are associated with a higher risk of death and subsequent major bleeding.

_Bahit et al. Heart 2017._
**FDA: “modified” ISTH definition**

**Significant Bleeding (modified ISTH definition)**

**ISTH Major Bleeding:**
- Symptomatic bleeding in a critical area or organ
- Bleeding associated with reduced haemoglobin $\geq 2 \text{ g/dL}$ or transfusion of $\geq 2$ units of blood or packed cells
- Fatal bleed

**OR**

**“Modified” ISTH significant bleeding:**
Not meeting criteria for a major bleed but prompts $\geq 1$ of:
- Hospital admission
- Physician-guided medical or surgical treatment
4. History of falling and outcome in AF

Falls = main “fear” (≈ bleeding) for not prescribing anticoagulants in AF

History of falling increases bleeding and death

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>1.21 (0.80-1.82)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.39 (1.05-1.84)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>1.25 (1.11-1.41)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>1.87 (1.02-3.43)</td>
</tr>
<tr>
<td>Subdural bleeding</td>
<td>2.45 (0.92-6.52)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.70 (1.36-2.14)</td>
</tr>
</tbody>
</table>

The benefits of NOACs compared with warfarin were consistent in patients with an history of falling. 

In anticoagulated patients with AF, AS is associated with a higher risk of stroke/systemic embolism, bleeding, and death, whereas MR and AR are not.

Implication for NOACs?

Apixaban was better than warfarin for ALL TYPES of VHD.

Implication: ESC AF guidelines 2016 - “valvular” AF term is misleading.
Implication: Patients with these echocardiographic findings should not be postponed from undergoing cardioversion, if they are on appropriate anticoagulation therapy.

6. Digoxin and risk of death in AF

All-cause death by digoxin concentration at baseline

Digoxin and risk of sudden death in AF

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**SUDDEN DEATH BY DIGOXIN STATUS**

![Graph showing the estimated probability of sudden cardiac death over time from digoxin start (months).](image)

- **Adjusted HR (95% CI):** 2.14 (1.11–4.12)
- **P = 0.0230**

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7. Importance of “extensive” education

1-year adjusted OR (95% CI): 3.28 (1.67, 6.44); P=0.0002

Baseline 6 months 12 months
Δ_{12-month} = 9.1%

N = 2281

Making a big impact!

HR (95% CI): 0.48 (0.23, 0.99)
log-rank p=0.043
1. Biomarkers may be considered to refine stroke risk in AF;

2. Female sex might not be a risk factor for stroke and, therefore, might not be incorporated in the assessment of risk score;

3. Moderate/minor bleedings are associated with a higher risk of death, and subsequent major bleeding;

4. History of falling increases the risk of bleeding and death, but NOACs better than warfarin;
5. AS is associated with a higher risk of stroke/SE, bleeding, and death, but NOACs better than warfarin for AS, MR, and AR; SEC, LA/LAA thrombus, complex aortic plaque are not associated with an increased risk of stroke/SE in anticoagulated patients with AF;

6. Death is related linearly to digoxin concentration; starting digoxin in AF is associated with higher risk of sudden death;

7. A customized and multilevel intervention involving education of patients with AF and their providers, with regular monitoring and feedback, results in a significant increase in the proportion of patients treated with anticoagulation, associated with a significant reduction in stroke.
Thank you!

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