Recanalization Therapy & Secondary Prophylaxis in the Elderly

21st Annual Meeting of the Swiss Stroke Society
Lausanne, 11.01.2018
PD Dr. G. M. De Marchis, MD MSc
Neurology & Stroke Center
University Hospital Basel
Disclosures

- Swiss National Science Foundation; Science Funds [Wissenschaftsfonds] of the University Hospital Basel and University of Basel;
- Bangerter-Rhyner-Stiftung; Swisslife Jubiläumsstiftung for Medical Research; Swiss Neurological Society; Fondazione Dr. Ettore Balli; De Quervain research grant; Thermo Fisher GmbH
- Travel honoraria by Bayer; speaker honoraria by Medtronic and BMS/Pfizer.
Content

- Recanalization Therapies:
  - I.v. tPA & Endovascular Treatment in the Elderly
  - Pre-existing Dementia and Disability

- Secondary Prophylaxis in the Elderly
  - DOAC vs. VKA
  - DOAC vs. DOAC (indirect comparisons)
  - DOAC vs. Aspirin
Stereotype #1

„Older patients do not benefit from i.v. tPA“
Patients >80 years benefit from i.v. tPA as much as patients ≤80 years

Meta-analysis of individual patient data from 6756 patients in 9 randomised trials* comparing alteplase with placebo or open control.

*NINDS A, NINDS B, ECASS I, ECASS II, ATLANTIS A, ATLANTIS B, ECASS III, IST-3
Lancet. 2014;384(9958):1929-35
Age does not significantly affect the interaction between i.v. tPA delay and good outcomes.

\[ P=0.08 \text{ (ie, not significant but, if anything, in the direction of lengthening, not shortening, the period during which alteplase is effective in older people)} \]

Lancet. 2014;384(9958):1929-35
Endovascular Treatment > 80 y.o.
Stereotype #2

„Age is one of the strongest predictor of poor outcomes, so that endovascular treatments are useless in the elderly.“
Patients $\geq$80 years have a worse prognosis, but EVT improves their chances of a good outcome.

Meta-analysis of individual patient data from MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA (n=1287), HERMES collaborators.
Patients $\geq 80$ years do benefit from endovascular treatment

Meta-analysis of individual patient data from MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA (n=1287), HERMES collaborators

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49</td>
<td>158</td>
<td>1.36 (0.75-2.46)</td>
</tr>
<tr>
<td>50-59</td>
<td>218</td>
<td>2.85 (1.72-4.72)</td>
</tr>
<tr>
<td>60-69</td>
<td>333</td>
<td>2.58 (1.49-4.48)</td>
</tr>
<tr>
<td>70-79</td>
<td>371</td>
<td>2.41 (1.55-3.74)</td>
</tr>
<tr>
<td>18-79</td>
<td>1080</td>
<td>2.44 (1.70-3.50)</td>
</tr>
<tr>
<td>$\geq 80$</td>
<td>198</td>
<td>3.68 (1.95-6.92)</td>
</tr>
<tr>
<td>Total</td>
<td>1278</td>
<td>2.49 (1.76-3.53)</td>
</tr>
</tbody>
</table>

Lancet. 2016;387(10029):1723-31
Pre-Existing Dementia & Disability
Stereotype #3

„Patients with dementia bleed more if treated with i.v. tPA“
Stroke & Dementia in the Elderly Share the Same Risk Factors

Dementia

Cerebral small vessel disease (CSVD)
- age- and vascular risk-factor-related CSVD
- cerebral amyloid angiopathy (CAA)

Haemorrhagic
- cerebral microbleeds (CMBs)

Ischaemic
- silent cerebral infarcts
- white matter hyperintensities

Stroke

10% of stroke patients have dementia

High blood pressure
Dyslipidaemia
Diabetes
Smoking
Obesity
APOE4

Dementia→thrombolysis rate 0.56%–10% vs 1–16% in the general population

<table>
<thead>
<tr>
<th>Reason thrombolysis was not given</th>
<th>Dementia (n = 628)</th>
<th>No dementia (n = 7,250)</th>
<th>Standardized difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival more than 3 hours after stroke onset (%)^b</td>
<td>27.1</td>
<td>29.4</td>
<td>0.05</td>
<td>0.29</td>
</tr>
<tr>
<td>Patient condition too mild (e.g., deficit resolved, rapidly improving, or low NIHSS)</td>
<td>13.2</td>
<td>16.8</td>
<td>0.10</td>
<td>0.054</td>
</tr>
<tr>
<td>Patient condition too severe (e.g., decreased level of consciousness or high NIHSS)</td>
<td>4.3</td>
<td>1.4</td>
<td>0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delay in decision to treat</td>
<td>1</td>
<td>0.6</td>
<td>0.04</td>
<td>0.51</td>
</tr>
<tr>
<td>Other contraindications to thrombolysis</td>
<td>7.0</td>
<td>6.0</td>
<td>0.04</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Physician decision</strong></td>
<td>13.5</td>
<td>7.5</td>
<td>0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No reason stated</td>
<td>39.8</td>
<td>41.3</td>
<td>0.03</td>
<td>0.48</td>
</tr>
</tbody>
</table>
### I.v. Thrombolysis in Patients with Pre-existing Dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Dementia (n=207)</th>
<th>Non-Dementia (n=621)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alshekhlee A et al</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Neurology</em> 2011;76:1575–1580</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sICH</td>
<td>5.8%</td>
<td>4.5%</td>
<td>0.45</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>17.4%</td>
<td>14.5%</td>
<td>0.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Dementia (n=99)</th>
<th>Non-Dementia (n=99)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saposnik G et al</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>J Neurol</em> 2012;259:2366–2375</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sICH</td>
<td>11.1%</td>
<td>11.1%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>22.2%</td>
<td>26.3%</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>NO Pre-existing Disability (n=7430)</th>
<th>Pre-existing Disability (n=489)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gensicke H et al</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Stroke</em> 2016; 47:450–456</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sICH</td>
<td>4.8%</td>
<td>4.5%</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

| 3-month poor outcome           | aOR 0.95; 95% CI, 0.75-1.21        |                                  |     |
Oral Anticoagulation in the Elderly
Oral Anticoagulation in the Elderly

- 1/10 person ≥75 years has atrial fibrillation
- ↑Age = ↑Stroke Risk
- Age≥75 y. = 2 points in the CHA₂DS₂-Vasc Score → OAC recommended

BUT:
- Risk of VKA-related bleeding in patients ≥75 y.o.: 5%
- Poor cognitive functions → VKA-nonadherence
- DOAC are increasingly prescribed in the elderly

→ What do we know on the efficacy and safety of DOACs and VKA among patients with atrial fibrillation and ≥75 y.o.?
# Group characteristics of trials on atrial fibrillation

<table>
<thead>
<tr>
<th>Trial Name (Year)</th>
<th>Patients ≥75 years included in the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF (2011)</td>
<td>43%</td>
</tr>
<tr>
<td>Rivaroxaban vs. Warfarin</td>
<td></td>
</tr>
<tr>
<td>RE-LY (2009)</td>
<td>31%</td>
</tr>
<tr>
<td>Dabigatran vs. Warfarin</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (2013)</td>
<td>40%</td>
</tr>
<tr>
<td>Edoxaban vs. Warfarin</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE (2011)</td>
<td>31%</td>
</tr>
<tr>
<td>Apixaban vs. Warfarin</td>
<td></td>
</tr>
</tbody>
</table>
DOAC in full Dose vs. VKA, ≥75 y.o.  
Endpoint = Any Stroke or Systemic Embolism

Meta-Analysis of the 4 RCTs comparing DOAC to VKA in AFIB (n=22,381)

---

**Swiss Med Wkly. 2016;146:w14356**
**Lancet. 2014;383(9921):955-62**
DOAC in **full** Dose vs. VKA, ≥75 y.o.

Endpoint = Major and Clinically Relevant Non-Major Bleeding

→ No difference between DOAC and VKA in the elderly and total population (OR 0.86, 95%-CI 0.73–1.00)
DOAC in low Dose vs. VKA, ≥75 y.o.
Endpoint = Any Stroke or Systemic Embolism

CAVE: Increased risk of ischemic stroke with low dose DOAC
DOAC in *low* Dose vs. VKA, ≥75 y.o.

Endpoint = Major and Clinically Relevant Non-Major Bleeding

Swiss Stroke Society Annual Meeting 2018
*Indirect* Comparison of DOAC, ≥75 y.o.
Indirect comparison of DOAC, ≥75 y.o.

- No RCT available comparing DOACs to each other.
- Indirect comparisons between DOACs using data from RCT are biased.
- Conflicts of interest may influence the interpretation of data.
Indirect Comparison of DOAC, ≥75 y.o.
Endpoint = Any Stroke or Systemic Embolism

No significant difference between DOACs in the prevention of SSE
Indirect Comparison of DOAC, ≥75 y.o.  
Endpoint = Major or Clinically Significant Bleeding

Indirect Comparison: Compared to Apixaban, *apparently* elevated bleeding risk under D150mg (+84%), D110mg (+58%), and Rivaroxaban (+74%). However:

- In patients ≥75 y.o.: lower CHADS2 score in ARISTOTLE (2.7) than in ROCKET (3.7)
- Patients on Aspirin: ARISTOTLE: 31%, RELY: 40%, ROCKET: 40%
- In the RCTs on VTE, Apixaban not shown to be safer

→ *Differences in the trial populations may explain the apparently better safety profile of apixaban.*

---

Swiss Stroke Society Annual Meeting 2018
**Indirect Comparison of DOAC, ≥75 y.o.**
**Endpoint = Major or Clinically Significant Bleeding**

<table>
<thead>
<tr>
<th>DOAC1</th>
<th>vs</th>
<th>DOAC2</th>
<th>OR for Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>D150mg</td>
<td>vs</td>
<td>Edo 60mg</td>
<td><strong>1.49, 95% CI 1.13-1.96</strong></td>
</tr>
<tr>
<td>D110mg</td>
<td>vs</td>
<td>Edo 30mg</td>
<td><strong>2.19, 95% CI 1.62-2.96</strong></td>
</tr>
</tbody>
</table>

→*However*, Patients on Aspirin: RELY: 40%, ENGAGE-AF TIMI: 29%
RCT populations do not entirely reflect the clinical population

- Patients with reduced life expectancy (1 to 2 years depending on the trial) were excluded.

- Likely exclusion of people with dementia (challenging informed consent process), as well as people with psychosocial issues or living in nursing homes for whom follow-up could be difficult

→ We need more clinical studies on DOAC for the elderly, without excluding frail people
Stereotype #4

„Older people fall more often, so that we treat them with aspirin instead of oral anticoagulants regardless of their CHADS-Score.“
What if the patients is unsuited to VKA – No oral anticoagulatio at all?

- Double-blind randomized clinical trial (AVERROES)
- 5599 patients with atrial fibrillation for whom VKA was unsuitable
- Apixaban (2*5mg) vs. Aspirin (81 to 324 mg/d)

Stroke or Systemic Embolism

Hazard ratio with apixaban, 0.45 (95% CI, 0.32–0.62)

N Engl J Med. 2011;364(9):806-817
What if the patients is unsuited to VKA – No oral anticoagulation at all?

„Treating 1000 patients for 1 year with apixaban rather than with aspirin would prevent 21 strokes or systemic emboli, 9 deaths, and 33 hospitalizations for cardiovascular causes, at the cost of 2 major bleeding events“.

*Major Bleeding*

- Hazard ratio with apixaban, 1.13 (95% CI, 0.74–1.75)

Summary

- Age alone should not be an exclusion reason for IV tPA or EVT.
- Neither should mild pre-existing dementia, unless this treatment is precluded because of other reasons.
- Not all patients with dementia are suitable for all interventions.
- All DOACs are effective and safe also in the elderly.
- Indirect DOAC to DOAC comparisons are misleading because of baseline imbalances.
- Older people with atrial fibrillation for whom VKA does not seem a safe option can still benefit from DOACs.
Thank you to the Stroke Team and Many More!