Cerebral microbleeds and intracranial haemorrhage risk in patients with atrial fibrillation after acute ischaemic stroke or transient ischaemic attack: multicentre observational cohort study


on behalf of the CROMIS-2 collaborators
A common clinical dilemma

- Ischaemic stroke or TIA with atrial fibrillation
- MRI scan with blood-sensitive imaging shows cerebral microbleeds
Hypothesis

Coagulation cascade initiation limit bleeding

Damaged small vessel with red cell extravasation

Coagulation cascade inhibited by anticoagulants

Cerebral microbleed

Macroscopic intracerebral haemorrhage

WHAT IS THE CLINICAL RELEVANCE OF CEREBRAL MICROBLEEDS?

SHOULD THEY AFFECT MY DECISION TO ANTICOAGULATE?
Study design and participants

- Prospective observational multicentre observational inception cohort study
- 79 centres throughout UK (and one in the Netherlands)
- Recent ischaemic stroke or TIA with proven atrial fibrillation
- Treated with VKA or DOAC
- Patients followed up for 2 years.
- Multiple overlapping ascertainment methods
  - GP and patient questionnaires
  - Telephone interviews
  - NHS information centre data
  - Hospital visits and records
Neuroimaging

- Patients underwent MRI brain using a pre-defined protocol parameter range, designed to detect markers of cerebrovascular disease
- Analysed using consensus criteria and validated scales

Outcomes

PRE-SPECIFIED STATISTICAL ANALYSIS PLAN

• Primary outcome: symptomatic intracranial haemorrhage
• Secondary outcomes:
  – Symptomatic ischaemic stroke
  – Death
  – Intracerebral haemorrhage
  – Composite outcome (death Ischaemic stroke, Symptomatic intracranial haemorrhage)
• All outcomes adjudicated blinded to baseline imaging
Results

- 1490 patients included
- 1447 (97%) had follow-up data and were included in survival analysis
- Mean age 76 years (SD 10)
- 631 (42%) female
- 311 (21%) patients had CMBs

Diagram:

- Potentially eligible for study and provided consent: 1686
- Appropriate MRI imaging available for analysis: 1496
- Included in final study analysis after imaging quality assurance: 1490
- Follow-up data available for survival analysis: 1447

- MRI not done (n=114)
- MRI done but did not meet protocol specifications (no T2* GRE (n=49), inadequate encryption or anonymization (n=18), incorrect date or patient details (n=9))
- TE too low (n=3)
- T2* GRE of poor quality due to motion artefact (n=3)
- No follow-up information available (n=43)
Results

• Intra-rater and inter-rater reliability for the presence of CMBs were excellent
  – Kappas 0.93 (95% CI 0.86 to 1.00) and 0.85 (95% CI 0.74 to 0.96)

• CMB distribution
  – Strictly lobar 116 patients
  – Strictly non-lobar (deep) 120 patients
  – Mixed 75 patients
  – Modified Boston criteria for CAA 46 patients
Results: primary outcome

• The 1447 patients provided 3366 patient-years of follow-up data (mean follow-up 850 (SD 373) days

• During follow-up there were:
  – 14 symptomatic intracranial haemorrhages
    • 11 intracerebral
    • Two subdural
    • One subarachnoid
<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with symptomatic intracranial haemorrhage (n=14)</th>
<th>Patients without symptomatic intracranial haemorrhage (n=1433)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years median (IQR)</td>
<td>79 (10)</td>
<td>76 (10)</td>
<td>0·32</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>5 (36)</td>
<td>606 (42)</td>
<td>0·62</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>8 (57)</td>
<td>898 (64)</td>
<td>0·62</td>
</tr>
<tr>
<td>Hyperlipidaemia n (%)</td>
<td>8 (57)</td>
<td>653 (45)</td>
<td>0·36</td>
</tr>
<tr>
<td>Diabetes mellitus n (%)</td>
<td>6 (43)</td>
<td>236 (17)</td>
<td>0·0086</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1 (7)</td>
<td>238 (17)</td>
<td>0·34</td>
</tr>
<tr>
<td>Previous ischaemic stroke n (%)</td>
<td>2 (15)</td>
<td>138 (10)</td>
<td>0·50</td>
</tr>
<tr>
<td>Previous intracerebral haemorrhage n (%)</td>
<td>0 (0)</td>
<td>8 (0·6)</td>
<td>1·00</td>
</tr>
<tr>
<td>Alcohol use &gt;14 units/week n (%)</td>
<td>1 (8)</td>
<td>212 (15)</td>
<td>0·50</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White n (%)</td>
<td>14 (100)</td>
<td>1356 (97)</td>
<td></td>
</tr>
<tr>
<td>Asian n (%)</td>
<td>0 (0)</td>
<td>29 (2)</td>
<td></td>
</tr>
<tr>
<td>Black n (%)</td>
<td>0 (0)</td>
<td>17 (1)</td>
<td></td>
</tr>
<tr>
<td>Platelet count median (IQR)</td>
<td>212 (167 to 225)</td>
<td>220 (185 to 264)</td>
<td>0·25</td>
</tr>
<tr>
<td>CHA2DS2-VASC score median (IQR)</td>
<td>6 (4 to 6)</td>
<td>5 (4 to 6)</td>
<td>0·23</td>
</tr>
<tr>
<td>HAS-BLED score median (IQR)</td>
<td>2 (2 to 3)</td>
<td>3 (2 to 3)</td>
<td>0·14</td>
</tr>
<tr>
<td>Anticoagulation started n (%)</td>
<td>14 (100)</td>
<td>1385 (97)</td>
<td>0·49</td>
</tr>
<tr>
<td>DOAC use n (%)</td>
<td>2 (14)</td>
<td>510 (37)</td>
<td>0·081</td>
</tr>
<tr>
<td>Concurrent antiplatelets n (%)</td>
<td>1 (7)</td>
<td>56 (4)</td>
<td>0·54</td>
</tr>
<tr>
<td>Poor therapeutic time in range n (%)</td>
<td>0 (0)</td>
<td>133/862 (15)</td>
<td>0·145</td>
</tr>
<tr>
<td>Total white matter hyperintensity (ARWMC) score median (IQR)</td>
<td>1·5 (0 to 5)</td>
<td>1 (0 to 3)</td>
<td>0·97</td>
</tr>
<tr>
<td>CMB presence n (%)</td>
<td>7 (50)</td>
<td>297 (21)</td>
<td>0·0075</td>
</tr>
<tr>
<td>CMB median (IQR)</td>
<td>0·5 (0 to 3)</td>
<td>0 (0 to 0)</td>
<td>0·0036</td>
</tr>
<tr>
<td>CMB range</td>
<td>0 to 12</td>
<td>0 to 107</td>
<td>N/A</td>
</tr>
<tr>
<td>cSS presence n (%)</td>
<td>1 (7)</td>
<td>4 (0·3)</td>
<td>&lt;0·0001</td>
</tr>
</tbody>
</table>
Primary outcome

- The symptomatic intracranial haemorrhage event rates were:
  - 10 per 1000 patient-years (95% CI 4 to 20) in patients with CMBs
  - 3 per 1000 patient-years (95% CI 1 to 5) in patients without CMBs

- The absolute rate increase associated with CMBs was 7 per 1000 patient-years (95% CI 3 to 15)
Intracranial haemorrhage rates according to CMB status

Pre-specified model adjusted for age and hypertension

Secondary outcomes: ischaemic stroke

- There were 56 recurrent ischaemic strokes during 3312 patient-years of follow-up.

- The recurrent ischaemic stroke rates were:
  - 24 per 1000 patient-years (95% CI 14 to 39) in patients with CMBs
  - 15 per 1000 patient-years (95% CI 11 to 20) in patients without CMBs

- The **absolute rate increase** associated with CMBs was 9 per 1000 patient-years (95% CI 3 to 19)
Secondary outcome: ischaemic stroke

- CMB presence was not significantly associated with recurrent ischaemic stroke in regression analyses:
  - univariable (HR 1·62 95% CI 0·92 to 2·87)
  - multivariable (HR 1·53; 95% CI 0·85 to 2·76)
    (adjusted for age, sex, hypertension, diabetes, previous ischaemic stroke prior to study entry, and age-related white matter hyperintensities score)
## Intracranial haemorrhage and ischaemic stroke rates

<table>
<thead>
<tr>
<th>Symptomatic intracranial haemorrhage</th>
<th>Rate per 1000 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 CMBs</td>
<td>2.6 (1.1 to 5.4)</td>
</tr>
<tr>
<td>1 CMB</td>
<td>5.4 (0.7 to 19.7)</td>
</tr>
<tr>
<td>Multiple CMBs</td>
<td>14.4 (4.7 to 33.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent ischaemic stroke</th>
<th>Rate per 1000 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 CMBs</td>
<td>15.0 (10.6 to 20.4)</td>
</tr>
<tr>
<td>1 CMB</td>
<td>24.9 (11.4 to 47.2)</td>
</tr>
<tr>
<td>Multiple CMBs</td>
<td>23.4 (10.1 to 46.2)</td>
</tr>
</tbody>
</table>
Prediction models for intracranial haemorrhage

- **HASBLED only**
  \[ \text{C-index 0.41 (95\% CI 0.29-0.53)} \]

- **Model 1: HASBLED + CMBs**
  \[ \text{C-index 0.66 (95\% CI 0.53-0.80)} \]

- **Model 2: HASBLED+DM+OAC+CMBs**
  \[ \text{C-index 0.74 (95\% CI 0.60-0.88)} \]

- Models including CMBs predicted symptomatic intracranial haemorrhage significantly better compared to HAS-BLED score alone
  - **C index (diff) model 1:** 0.25 (95\% CI 0.07-0.43, p=0.007)
  - **C index (diff) model 2:** 0.33 (95\% CI 0.14-0.51, p=0.00059)
Conclusions

• CMB presence is associated with an increased hazard of symptomatic intracranial haemorrhage but not recurrent ischaemic stroke
• Including CMB presence as a neuroimaging biomarker improves the predictive value of a commonly used bleeding risk score based on clinical data alone (the HAS-BLED score)
• However, even in patients with CMBs the absolute incidence of symptomatic intracranial haemorrhage was lower than that of recurrent ischaemic stroke
• Large international pooled analyses are needed to confirm our findings, validate risk scores including CMBs (including burden), and establish whether CMBs can identify patients at risk of net harm from OAC
Acknowledgements

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