Small vessel disease, microbleeds and intracerebral haemorrhage

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The clinical question

- What is the best anticoagulation treatment?
- Is cerebral small vessel disease (as indicated by microbleeds) a risk factor for ICH in patients with AF treated with anticoagulant drugs?

The most feared complication of anticoagulation
Talk outline

- The importance of the clinical question
- Cerebral small vessel disease, cerebral amyloid angiopathy and cerebral microbleeds
- How could CMBs relate to ICH risk?
- What evidence is available
- “Amyloid spells” in the brain
- CROMIS-2 substudies
AF and anticoagulation-related ICH

- Causes death or disability in up to 75%
- Often occurs with therapeutic INR*
- Age is a strong risk factor
- Likely related to individual age-dependent patient factors affecting cerebral small vessel fragility

- URGENT NEED TO UNDERSTAND MECHANISMS TO PREVENT ICH

*Rosand et al. Arch Int Med 2004
The increasing incidence of anticoagulant-related ICH

Now accounts for 10-15% of all “spontaneous” ICH

Flaherty et al. Neurology 2006
Absolute risk of ICH in patients taking anticoagulants

- Difficult to be sure from RCTs as all of these may have some limitation of external validity
  - Proportion of patients who were new to warfarin
  - Exclusion criteria (cognition, age, previous ICH, etc)
  - Selected as “good candidates” or cases in whom physician was uncertain as to best treatment
  - May not generalize to the “real world” and could underestimate the risk
Absolute risk of ICH in patients taking warfarin for AF: RCTs versus “real life” practice
What about the new oral anticoagulants?

- Dabigatran, rivaroxaban, apixaban, etc.
- Non inferior to warfarin
- Lower ICH rate (~40%-70% RR)
- No data outside RCTs
- Little real world natural history data so far
Patients at highest risk of ICH also have the highest risk of ischaemic stroke

HAS-BLED score includes elements that may correlate with small vessel disease.
Mechanisms of “spontaneous” anticoagulation-associated ICH

- Associated with:
  - Increased age
  - Previous stroke
- Often occurs with therapeutic INR
- The risk of ICH is increased by an age-related disorder of small brain blood vessels

**Bleeding-prone microarteriopathies**

- Genetic and ethnic factors
- Chronic vascular risk factors (e.g. smoking, hypertension)
- Acute precipitants (e.g. hypertension, “stress”)

**Antithrombotic drug treatment**
Cerebral small vessel disease

- The most prevalent brain condition ever described

- The major cause of:
  - vascular cognitive impairment
  - intracerebral haemorrhage

Lancet Neurology, 2010
NEJM, 2006
Cerebral small vessel disease

Cerebral amyloid angiopathy

Hypertensive arteriopathy

Lobar

Deep
Small vessel disease and cerebral microbleeds

A. Charidimou

Deep microbleeds

Leukoaraiosis

Lacunes

A. Cerebral amyloid angiopathy

B. Hypertensive arteriopathy

Lobar microbleeds

Deep microbleeds

A. SWI

B. T2*-GRE
Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study

CE Lovelock, AJ Molyneux, PM Rothwell, on behalf of the Oxford Vascular Study


- Reduction of hypertensive arteriopathy-related ICH
- CAA-related bleeds are increasing
- May be particularly important in relation to antithrombotic-related ICH.
How may CMBs relate to anticoagulation-associated ICH risk?

1. CMBs reflect areas of bleeding from cerebral small vessels.
2. CMBs are common in the populations likely to be exposed to anticoagulant drugs.
3. CMBs develop dynamically over time in a significant proportion of patients.
4. CMBs that arise are usually “sealed off” by haemostatic factors or surrounding tissues, thus not causing obvious clinical symptoms.
5. In the presence of anticoagulation, some CMBs are not effectively limited by these mechanisms, and may develop into a serious symptomatic ICH.
What evidence is available?

- Cross-sectional case-control and case-case comparisons
- Prospective studies

Charidimou et al., in preparation

Lovelock et al., Stroke, 2010

Systematic reviews and meta-analyses
**Intracerebral haemorrhage**
(excess of CMBs in warfarin users not seen in ischaemic stroke cohorts)

### Warfarin-users vs Non-antithrombotic users

<table>
<thead>
<tr>
<th>Study</th>
<th>Number with MBs / Number in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin / no antithrombotic</td>
</tr>
<tr>
<td>Oxford, UK</td>
<td>6 / 10</td>
</tr>
<tr>
<td>Hiroshima, Japan</td>
<td>19 / 23</td>
</tr>
<tr>
<td>Ilsan, Korea</td>
<td>3 / 3</td>
</tr>
<tr>
<td>Tokyo, Japan</td>
<td>1 / 2</td>
</tr>
<tr>
<td>Seoul, Korea</td>
<td>19 / 24</td>
</tr>
<tr>
<td>Lille, France</td>
<td>14 / 25</td>
</tr>
<tr>
<td>Washington, US</td>
<td>8 / 8</td>
</tr>
<tr>
<td>London, UK</td>
<td>2 / 2</td>
</tr>
<tr>
<td>Hokkaido, Japan</td>
<td>2 / 2</td>
</tr>
<tr>
<td>Uppsala, Sweden</td>
<td>3 / 3</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td>77 / 103</td>
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<tr>
<td></td>
<td>575 / 961</td>
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<td></td>
<td>2.7</td>
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<tr>
<td><strong>OR</strong></td>
<td>1.6-4.4</td>
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</tbody>
</table>

Sig: p<0.001       Het: p=0.81

### Antiplatelet-users vs Non-antithrombotic users

<table>
<thead>
<tr>
<th>Study</th>
<th>Antiplatelet / no antithrombotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxford, UK</td>
<td>6 / 15</td>
</tr>
<tr>
<td>Seoul, Korea</td>
<td>21 / 30</td>
</tr>
<tr>
<td>Tokyo, Japan</td>
<td>6 / 9</td>
</tr>
<tr>
<td>Otsu, Japan</td>
<td>8 / 12</td>
</tr>
<tr>
<td>Lille, France</td>
<td>37 / 62</td>
</tr>
<tr>
<td>Hiroshima, Japan</td>
<td>42 / 45</td>
</tr>
<tr>
<td>Ilsan, Korea</td>
<td>22 / 26</td>
</tr>
<tr>
<td>Edinburgh, UK</td>
<td>1 / 3</td>
</tr>
<tr>
<td>Washington, US</td>
<td>24 / 51</td>
</tr>
<tr>
<td>London, UK</td>
<td>14 / 17</td>
</tr>
<tr>
<td>Hokkaido, Japan</td>
<td>10 / 15</td>
</tr>
<tr>
<td>Uppsala, Sweden</td>
<td>7 / 12</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>198 / 297</td>
</tr>
<tr>
<td></td>
<td>630 / 1061</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td>1.3-2.3</td>
</tr>
</tbody>
</table>

Sig: p<0.001       Het: p=0.002

Lovelock et al., Stroke, 2010
Prospective studies: meta-analysis

- High quality prospective studies of CMBs and ICH risk on anticoagulation are not available

Available prospective studies include:
- **CMBs in ischaemic stroke**
- **CMBs in the general population**
- **CMBs in ICH**

<table>
<thead>
<tr>
<th>Study</th>
<th>CMB (-) n/N</th>
<th>CMB (+) n/N</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thijs, 2010</td>
<td>1/358</td>
<td>1/129</td>
<td>2.78 (0.17, 44.04)</td>
<td>10.92</td>
</tr>
<tr>
<td>Gregoire, 2010</td>
<td>0/13</td>
<td>1/8</td>
<td>6.68 (0.28, 157.63)</td>
<td>6.39</td>
</tr>
<tr>
<td>Soo, 2008</td>
<td>4/656</td>
<td>11/251</td>
<td>7.19 (2.31, 22.36)</td>
<td>45.62</td>
</tr>
<tr>
<td>Boulanger, 2006</td>
<td>1/191</td>
<td>1/45</td>
<td>4.24 (0.27, 66.57)</td>
<td>7.86</td>
</tr>
<tr>
<td>Naka, 2005</td>
<td>1/172</td>
<td>9/94</td>
<td>16.47 (2.12, 128.00)</td>
<td>14.57</td>
</tr>
<tr>
<td>Fan, 2003</td>
<td>1/78</td>
<td>4/43</td>
<td>7.26 (0.84, 62.88)</td>
<td>14.65</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $p = 0.938, I^2 = 0.0\%$

Test for overall effect: $p \leq 0.001$

**Presence of CMBs decrease the risk of ICH**

Charidimou et al, in preparation
Spectrum of imaging manifestations of CAA

Charidimou A et al. JNNP 2012;83:124-137
Clinical case

- 75-year old male
- Presented with tingling (and numbness) of the left hand, migrating rapidly up the left arm and into the tongue
- Lasting 2-3 minutes
- Occurred 3 times in 2 days
- Diagnosed as transient ischaemic attacks (TIA)s
- Treated with aspirin and dipyridamole
Clinical case

- Remained well for 6 months
- Then awoke with weakness of his left arm and leg with sensory disturbance in the leg > arm
- Deficit persisted this time
- Diagnosis?
- Investigation?
Diagnosis?

What were these episodes? 

Ischaemia

Bleeding
Transient focal neurological episodes (TFNE) in CAA

- The next most common syndrome described in CAA after ICH?
- Typically recurrent spreading paraesthesias
- Also “aura-like” visual disturbances, limb jerking
- Probably they are misdiagnosed as TIAs

**CLINICAL RELEVANCE:** THESE PATIENTS MAY HAVE A VERY HIGH RISK OF FUTURE ICH (ANTITHROMBOTICS?)

**No systematic studies of:**
- their prevalence in CAA
- clinical and radiological spectrum
- prognostic implications – risk of ICH

Greenberg SM et al. Neurology 1993; 43: 2073-2079
Methods - Study Design

- Multi-centre
- Retrospective cohort of consecutive CAA cases (from prospective databases)
- 4 specialist stroke centres
- MRI routine for all cases of suspected CAA (including T2-W and T2*-GRE)
- Standardised case report forms
- Standardised follow-up and outcomes
- Systematic review of all published cases
Multicentre MRI cohort study and meta-analysis

Inclusion criteria:

✓ CAA defined according to Boston criteria
✓ Clear description of transient (<24h), fully resolving, focal neurological episodes
✓ No other explanation for episodes (e.g. AF, extracranial or intracranial stenosis, structural brain lesion, definite seizures)

Exclusion criteria:

✖ Patients without an adequate medical history or imaging
✖ Patients not meeting the criteria for CAA
✖ Patients with non-focal transient symptoms (e.g. generalized seizures, confusion, disorientation)
Results

- 172 patients with CAA
  (possible=54; probable=115; probable with supportive pathology=2; definite=1)
- 25 (14.5%; 95% CI: 9.6% to 20.7%) had a history of TFNE
  (possible=4; probable=18; probable with supportive pathology=2; definite=1)
- 13 (52%) had predominantly positive symptoms (“aura-like” spreading paraesthesias, positive visual phenomena, or limb jerking)
- 12 (48%) had predominantly negative symptoms (“TIA-like” sudden-onset limb weakness, dysphasia, or visual loss)
Representative T2*-GRE images

Median time from episodes to MRI: 7 days (interquartile range: 6.5-30 days)

Episodes of visual disturbances in the right hemifield: cortical superficial siderosis in the parietal and occipital lobes

Recurrent brief episodes of tingling, starting in the fingers of the left hand and then smoothly migrating to continuous areas of the skin
Results – risk of ICH

- Follow up available on 24/25 cases
- Over a median of 14 months, 50% of TFNE patients had a symptomatic lobar ICH
- Within 2 months of the TFNE 37.5% (95% CI: 21.6% to 59.7%) of the patients experienced a symptomatic lobar ICH
- In the meta-analysis the 2-month risk was 27.6% (95% CI: 18.3% to 40.2%)

![Graph showing time to symptomatic ICH from start of TFNEs]

*Combined with published data*

*Current multicentre cohort*
Patients with TFNE vs. CAA patients without TFNE

<table>
<thead>
<tr>
<th></th>
<th>CAA patients with TFNE*</th>
<th>CAA patients with no TFNE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=25</td>
<td>N=147</td>
<td></td>
</tr>
<tr>
<td>Age, mean (95% CI:), years</td>
<td>69.7</td>
<td>73.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(66.9 to 72.5)</td>
<td>(71.4 to 74.9)</td>
<td></td>
</tr>
<tr>
<td>Sex, female</td>
<td>56%</td>
<td>50%</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52%</td>
<td>67%</td>
<td>NS</td>
</tr>
<tr>
<td>On antithrombotics</td>
<td>32%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td>Previous symptomatic ICH</td>
<td>32%</td>
<td>54%</td>
<td>NS</td>
</tr>
<tr>
<td>Superficial cortical siderosis</td>
<td>50%</td>
<td>19%</td>
<td>0.001</td>
</tr>
<tr>
<td>Focal (≤3 sulci)</td>
<td>17%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td>Disseminated (≥4 sulci)</td>
<td>33%</td>
<td>11%</td>
<td>0.008</td>
</tr>
<tr>
<td>Acute ischaemic lesions (DWI)</td>
<td>6%</td>
<td>11%</td>
<td>NS</td>
</tr>
<tr>
<td>Evidence of chronic lobar ICH</td>
<td>40%</td>
<td>53%</td>
<td>NS</td>
</tr>
<tr>
<td>Evidence of acute lobar ICH</td>
<td>36%</td>
<td>48%</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple lobar CMBs (≥2)</td>
<td>58%</td>
<td>56%</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Median time from the episodes to MRI for CAA patients with TFNE: 7 days (interquartile range: 6.5-30 days)
Conclusions

- Transient focal neurological episodes in CAA are common
- They include both positive and negative neurological symptoms
- Superficial cortical siderosis is more common in CAA patients with TFNE vs. CAA without TFNE
- They signify a very high early future risk of ICH – even if they are clinically TIA-like (so avoid antithrombotics)
- Blood-sensitive MRI sequences are important in the investigation of such episodes

Limitations
- Retrospective design: have we underestimated their true prevalence?
- MRI was performed at different times from TFNE onset
- Lack of availability of acute DWI sequences in all cases
CROMIS-2 (ICH):
Transient focal neurological episodes in ICH substudy

**HISTORY OF TRANSIENT FOCAL NEUROLOGICAL EPISODES**
Research suggests that transient focal neurological episodes can precede ICH in some patients. Often these attacks are described as paraesthesias (“pins and needles”) that move from one part of the body to another. The questions below are important to understand more about these attacks.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can the participant (or a reliable informant, e.g. a relative or close friend) provide a reliable history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Before the patient had an ICH, were there any attacks of the following: Paraesthesia, focal weakness, speech disturbance, limb shaking or jerking, visual disturbances or headaches? |     |    | If NO, please STOP
|                                                                           |     |    |
|                                                                           |     |    |
|                                                                           |     |    | If YES, please continue to answer the questions on the next page If NO, please go to the next section (Family Background)
### CROMIS-2 (ICH): Transient focal neurological episodes in ICH substudy

<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Paraesthesias (&quot;pins and needles&quot;)</td>
<td>Q1: Episodes of focal paraesthesia (pins and needles, tingling affecting part of the face or body)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Q2: If so, was the paraesthesia of a spreading onset (i.e. moving from one part of the body to another over time)</td>
<td></td>
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<tr>
<td>B. Focal Weakness</td>
<td></td>
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<tr>
<td>C. Speech disturbance: Aphasia (altered content of speech)</td>
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<tr>
<td>D. Speech disturbance: Dysarthria (slurred speech)</td>
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<tr>
<td>E. Limb shaking or jerking</td>
<td>History of limb shaking episodes (or episodes of other abnormal movements)</td>
<td></td>
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<tr>
<td>F. Visual disturbances</td>
<td>Q1: History of episodes involving visual symptoms</td>
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<td>Q2: Were these typical of migraine? (zig-zags, flashing lights, objects changing size/shape/black dots)</td>
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<tr>
<td></td>
<td>Q3: Hallucinations (seeing things that are not there)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>G. Headache</td>
<td></td>
<td></td>
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</tbody>
</table>

If YES please complete the table below:

<table>
<thead>
<tr>
<th>Paraesthesias</th>
<th>Focal weakness</th>
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<tbody>
<tr>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Face</td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td></td>
</tr>
<tr>
<td>Foot</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td></td>
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</tbody>
</table>

If YES please complete the table below:

<table>
<thead>
<tr>
<th>History of Limb shaking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Arm</td>
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<tr>
<td>Hand</td>
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<tr>
<td>Leg</td>
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<tr>
<td>Foot</td>
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</tbody>
</table>
CROMIS-2: Other substudies

- Genetics
- Biomarkers
- Retinal changes in cerebral haemorrhage
- Thrombolysis-related ICH
- Predictors of cognitive impairment in AF-related stroke

**Conclusion:** There is consistent evidence supporting an association between AF and increased incidence of dementia in patients with stroke whereas there remains considerable uncertainty about any link in the broader population. The potential association between AF and incident dementia in mild cognitive impairment merits further investigation. *Neurology* 2011;76:914-922

AF-related stroke carries a high risk of future dementia
Summary

- ICH risk and cerebral small vessel disease: many clinical questions remain unanswered
- **URGENT NEED TO UNDERSTAND MECHANISMS TO PREVENT ICH**
- CROMIS-2 study and substudies provide a great opportunity to tackle clinical questions related to small vessel disease, anticoagulation and risk of ICH
- It is very important to do the right MRI sequences
  - T2*-GRE MRI (with standardized sequence parameters)
  - Other required vascular MRI sequences:
    - Axial T2-weighted MRI
    - Axial diffusion-weighted MRI
    - Coronal FLAIR with 3 mm slice thickness
    - Coronal T1-weighted MRI
  - Optional: susceptibility-weighted imaging (SWI) or equivalent
Thank you!

Acknowledgements

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Dr Simone Gregoire
Prof Martin Brown