Treatment of anticoagulant-associated intracerebral haemorrhage

Adrian Parry-Jones
NIHR Clinician Scientist & Honorary Consultant Neurologist
Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Salford, UK
Anticoagulant-associated ICH – a growing problem?

Changing profile of ICH
• ↑ incidence > 75 years old
• ↓ incidence < 60 years old
• Greater use of antithrombotic drugs

<table>
<thead>
<tr>
<th></th>
<th>1985-92</th>
<th>1993-2000</th>
<th>2001-08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelets</td>
<td>2 (10%)</td>
<td>9 (20%)</td>
<td>14 (25.5%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>1 (5%)</td>
<td>5 (11.1%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Total ICHs</td>
<td>126</td>
<td>151</td>
<td>164</td>
</tr>
</tbody>
</table>

Salford Royal Hospital – recent registry data

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No anticoag</td>
<td>32</td>
<td>39</td>
<td>39</td>
<td>39</td>
<td>36</td>
<td>43</td>
<td>59</td>
<td>49</td>
<td>65</td>
<td>72</td>
<td>63</td>
<td>61</td>
<td>28</td>
</tr>
<tr>
<td>VKA</td>
<td>2</td>
<td>6</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>14</td>
<td>3</td>
<td>8</td>
<td>6</td>
<td>11</td>
<td>6</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>DOAC</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

MANCHESTER

The University of Manchester
Outcomes and baseline characteristics

30-day case fatality around 40-50%
Haematoma expansion risk doubled
Worse baseline clinical characteristics?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Anticoag (n=100)</th>
<th>Others (n=612)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>79.5 (57.1 – 81.1)</td>
<td>69.1 (55.3 – 79.8)</td>
</tr>
<tr>
<td>Pre-mRS (0-2)</td>
<td>81 (81%)</td>
<td>487 (79.6%)</td>
</tr>
<tr>
<td>GCS</td>
<td>15 (11-15)</td>
<td>14 (10-15)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>16 (16%)</td>
<td>73 (11.9%)</td>
</tr>
<tr>
<td>IVH</td>
<td>39 (39%)</td>
<td>248 (40.5%)</td>
</tr>
<tr>
<td>ICH volume (ml)</td>
<td>18.2 (4.9 – 64.7)</td>
<td>18.4 (5.3 – 50.0)</td>
</tr>
</tbody>
</table>
VKA-ICH vs. DOAC-ICH

International, multicentre pooled analysis
13 centres – Europe, Asia, North America
500 patients (97 DOAC-ICH; 403 VKA-ICH)

<table>
<thead>
<tr>
<th>Variable</th>
<th>DOAC-ICH (n=97)</th>
<th>VKA-ICH (n=403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>80 (74-85)</td>
<td>80 (72-85)</td>
</tr>
<tr>
<td>GCS</td>
<td>14 (12-15)</td>
<td>15 (13-15)</td>
</tr>
<tr>
<td>ICH vol</td>
<td>14.4 (3.6-38.4)</td>
<td>10.6 (4.0-27.9)</td>
</tr>
<tr>
<td>IVH</td>
<td>42 (43)</td>
<td>146 (36)</td>
</tr>
<tr>
<td>Pre-mRS</td>
<td>1 (0 to 3)</td>
<td>0 (0 to 2)</td>
</tr>
</tbody>
</table>

Wilson et al, ESOC Conference, May 2016
VKA-ICH vs. DOAC-ICH

Wilson et al, ESOC Conference, May 2016
Treatment of VKA-ICH

What do the guidelines say?

- RCP (2016): Urgent reversal with PCC and VK
- AHA/ASA (2015): Receive therapy to replace VK dependent clotting factors; ‘PCC might be considered over FFP’
- ESO (2014): ‘cannot make strong recommendations’

Options for reversal:

- Fresh frozen plasma
- PCC (3-factor, 4-factor)
- Factor VII
Multicentre, pooled registry study

- 1547 patients - VKA-ICH (INR>1.3)
- 16 centres, 9 countries
- Cox regression analysis:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP &amp; 3F PCC</td>
<td>131</td>
<td>reference</td>
<td>-</td>
</tr>
<tr>
<td>PCC</td>
<td>585</td>
<td>1.45 (1.01–2.06)</td>
<td>0.041</td>
</tr>
<tr>
<td>FFP</td>
<td>377</td>
<td>1.34 (0.93–1.93)</td>
<td>0.112</td>
</tr>
<tr>
<td>None</td>
<td>454</td>
<td>2.54 (1.78–3.62)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, ICH volume, infratentorial location, IVH, baseline INR, GCS

INCH trial

• Randomised, open-label, blinded-endpoint trial
• Within 12 h of onset, INR ≥ 2
• 20 mL/kg FFP vs. 30 IU/kg 4F PCC
• 23 FFP & 27 PCC treated
• Outcomes:
  – INR<1.3 by 3h: 9% FFP vs. 67% PCC
  – 90d mortality: 35% FFP vs. 19% PCC
  – Increased expansion with FFP

## Current management of DOAC-ICH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half life</th>
<th>Mode of action</th>
<th>Coagulation tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>12-17 h</td>
<td>Direct thrombin (II)</td>
<td>aPTT, TT</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>7-11 h</td>
<td>Factor Xa</td>
<td>PT, anti Xa</td>
</tr>
<tr>
<td>Apixaban</td>
<td>8-15 h</td>
<td>Factor Xa</td>
<td>anti Xa</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>10-14 h</td>
<td>Factor Xa</td>
<td>PT, anti Xa</td>
</tr>
</tbody>
</table>

### Options for reversal:
- PCC (3-factor, 4-factor)
- Idarucizumab (for dabigatran)
- Andexanet alpha (for Xa inhibitors)
Current management of DOAC-ICH

What do the guidelines say?

• RCP (2016): idarucizumab for dabigatran; 4F PCC for others
• AHA/ASA (2015): PCC or rFVIIa ‘might be considered’; Activated charcoal might be used if <2 h since last dose; Haemodialysis for dabigatran.
• ESO (2014): No recommendation

PCC:

• Animal and healthy volunteer data suggests partial reversal
• British Committee for Standards in Haematology (2013)
Idarucizumab

- Dabigatran antidote, humanised Fab
- Dabigatran - 350x higher affinity for idarucizumab than thrombin
- Rapid & complete reversal
- No prothrombotic effects in volunteers; 1 in 90 pts (RE-VERSE AD)
- RE-VERSE AD included 18 ICHs
- £2400 per dose (5 g)

Andexanet alpha

- recombinant modified human factor Xa decoy protein
- Reverses direct & indirect Xa inhibitors
- ANNEXA-4 trial ongoing
  - 67 patients with acute, major bleeding within 18 h of Xa inhibitor dose
  - Andexanet bolus and 2 h infusion
  - Outcomes: Anti-factor Xa activity and clinical haemostatic efficacy
  - 67 patients reported: 32 rivaroxaban; 31 apixaban; 4 enoxaparin
  - 28 were ICH

Andexanet alpha - rivaroxaban

Andexanet alpha - apixaban

Time is brain in ICH too....

Improving door-to-needle times

Three key changes:

1. PCC stock in the ED
2. Point-of-care INR device
3. Standard protocol to deliver PCC without Haematology referral for every case

Anticoagulant reversal – DNT for PCC

QI project commenced
Education and awareness work, Quick reference sheet produced
Conclusion

• Anticoagulant-associated ICH may be increasing and profile changing
• Increasing number of DOAC-ICH vs. VKA-ICH
• VKA-ICH
  • Management guided by INR
  • Treatment with PCC then VK
• DOAC-ICH
  • Can not rely on standard coagulation tests for treatment
  • Idarucizumab for dabigatran, Andexanet currently unlicensed
  • PCC for Xa inhibitors currently
• Whatever you do – do it quickly!
Acknowledgements

- Data pooling studies: Atte Meretoja, David Werring, Duncan Wilson
- Salford ICH QI team: H Patel, Kyri Paroutaglou, Mark Massyn, Luca Cecchini, Josh Rowland, Lydia Baxter

Funding & support: