Blood Pressure Lowering in Acute Intracerebral Haemorrhage: How low?

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Prevalence of high blood pressure intracerebral haemorrhage

NHAMCS n = 563,704

Mechanisms – hypertensive response

• Inadequately treated or undiagnosed
• Stress response
• Activation of neuroendocrine systems
• Damage to autonomic centres in the brain
• Cushing reflex
Course of blood pressure in ICH

Christensen et al. Acta Neurol Scand 2002;106:142-147
Cerebral autoregulation

Stroke

Strandgaard S et al BMJ 1973
High blood pressure
Low blood pressure, ICH and ischemia

Systolic blood pressure and risk of death or disability

$n = 1,760$
Objectives and design

- Randomized, open-treatment, blinded endpoint
- Inclusion criteria:
  - Spontaneous ICH
  - SBP 150 – 220 mmHg
  - Treatment within 6 hours of symptom onset
- Management:
  - SBP ≤ 140mmHg vs ≤ 180mmHg
- Endpoint:
  - mRS (0-2 vs 4-6) at 90 days
## INTERACT 2 baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive N= 1399</th>
<th>Standard N=1430</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>3.7 (2.8 – 4.8)</td>
<td>3.7 (2.9 – 4.8)</td>
</tr>
<tr>
<td>Age (age)</td>
<td>63 ± 13.1</td>
<td>64.1 ± 12.6</td>
</tr>
<tr>
<td>Recruited from China (%)</td>
<td>67.7</td>
<td>61.7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>179 ± 17</td>
<td>179 ± 17</td>
</tr>
<tr>
<td>NIHSS</td>
<td>10(6 – 15)</td>
<td>11 (6 – 16)</td>
</tr>
<tr>
<td>Hematoma volume, (ml)</td>
<td>11 (6-19)</td>
<td>11 (6 – 20)</td>
</tr>
<tr>
<td>GCS median</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Previous hypertension (%)</td>
<td>72.4</td>
<td>72.5</td>
</tr>
</tbody>
</table>

Anderson et al NEJM 2013
Systolic BP control

Anderson et al NEJM 2013
mRS scores at 90 days

Odds ratio 0.87 (95% CI 0.77-1.00), p=0.04

Intensive

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1%</td>
<td>21.1%</td>
<td>18.7%</td>
<td>15.9%</td>
<td>18.1%</td>
<td>6.0%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Standard

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.6%</td>
<td>18.0%</td>
<td>18.8%</td>
<td>16.6%</td>
<td>19.0%</td>
<td>8.0%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Disability but independent | Major disability | Death

Benefit per thousand treated: 81; NNT: 13

Anderson et al NEJM 2013
### Effects of intensive BP lowering on mRS according to baseline BP levels

<table>
<thead>
<tr>
<th>Baseline SBP (mmHg)</th>
<th>Outcome (rate)</th>
<th>Favors</th>
<th>Favors</th>
<th>Risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Guideline</td>
<td>intensive</td>
<td>guideline</td>
</tr>
<tr>
<td>&lt;160</td>
<td>85 (45%)</td>
<td>85 (49%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>160-179</td>
<td>148 (50%)</td>
<td>139 (52%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>170-179</td>
<td>139 (53%)</td>
<td>176 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180-189</td>
<td>140 (55%)</td>
<td>153 (59%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥190</td>
<td>207 (52%)</td>
<td>232 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVERALL</td>
<td>719 (51%)</td>
<td>785 (55%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Arima H. et al, Neurology 2014
Effects of achieved SBP on mRS at 90 days

Arima H. et al, Neurology 2014
BP lowering and hematoma growth

A

P trend 0.078

B

P trend <0.001

Carcel C. et al, Stroke 2016
Haematoma growth, time and achieved blood pressure target

A

P trend 0.029

Absolute growth (ml)

≤1 1-6 ≥6

Time to target SBP<140mmHg (hour)

B

P trend 0.018

Absolute growth (ml)

0-2 3-4 5-8

Number of times of achieving target SBP <140 mmHg within 24 hours of ICH

Carcel C. et al, Stroke 2016
• Randomized, multicenter, two-group, open-label
• Inclusion criteria:
  – Spontaneous supratentorial hemorrhage
  – SBP > 180 mmHg
  – 4.5 hours of symptom onset
• Management:
  – IV nicardipine with BP goal: ≤ 140 mmHg vs ≤ 180 mmHg
• Endpoint:
  – mRS (0-2 vs 4-6) at 90 days

Qureshi et al NEJM 2016
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive N= 500</th>
<th>Standard N=500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (minutes)</td>
<td>182.2±57.2</td>
<td>184.7±56.7</td>
</tr>
<tr>
<td>Age (age)</td>
<td>62 ± 13.1</td>
<td>61.9 ± 13.1</td>
</tr>
<tr>
<td>Recruited from Asian site (%)</td>
<td>52.8</td>
<td>54.6</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>200 ± 27.1</td>
<td>201 ± 26.9</td>
</tr>
<tr>
<td>NIHSS</td>
<td>11 (0 – 40)</td>
<td>11 (0 – 40)</td>
</tr>
<tr>
<td>Hematoma volume, (cm³)</td>
<td>10.3 (2.3 – 85.2)</td>
<td>10.2 (0.98 – 79.1)</td>
</tr>
<tr>
<td>GCS 15 (%)</td>
<td>55.0</td>
<td>56.8</td>
</tr>
<tr>
<td>Previous hypertension (%)</td>
<td>82.2</td>
<td>76.4</td>
</tr>
</tbody>
</table>

Qureshi et al NEJM 2016
ATACH II—death or disability

Adjusted OR, 1.04; 95% CI, 0.85 - 1.27

Qureshi et al NEJM 2016
ATACH-2 vs INTERACT-2

SBP, mmHg

- ATACH 2 mean BP baseline
- ATACH 2 mean minimum BP
- INTERACT 2 mean BP

Baseline  2 hours  6 hours
ICH ADAPT: Design and outcome

- Randomised, open-label, blinded end-point
- Primary ICH, within 24 hours of symptom onset
- Target SBP < 150 vs 180 mmHg
  - Labetalol, hydralazine, enalapril
- CT perfusion after 2 hours
- Cerebral blood flow in borderzone and perihematoma tissue

Butcher et al Stroke 2013
ICH ADAPT: Outcome

No difference in CBF in borderzone and perihematoma tissue
Challenges of BP lowering in acute ICH

- **Time**
  - Too late?

- **Hematoma volume**
  - Too small?

- **Intensity**
  - Too much?

- **Agent**
  - Nicardipine vs various antihypertensives agents

- **Previous hypertension**
**BASC**  
Blood pressure in Acute Stroke Collaboration

**Ongoing work**

**BASC**  
Individual patient data metaanalysis 2018?

**RiGHT-2**  
Pre-hospital trial GTN vs no GTN

**ICH ADAPT 2**  
SBP < 140 vs <180 mm Hg DWI lesion frequency 270 patients
Concluding remarks

- Moderate and early BP lowering treatment is safe and probably beneficial.
- Intensive BP lowering (< 120 mmHg) should be avoided.
- Remember potential shifts in autoregulation in patients with chronic hypertension.
Thank you for your attention!

John Fabre Exhibit, Palma de Mallorca, 2014