Where next for generating evidence for intensive blood pressure lowering in ICH?

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Challenges to studying ICH

- **Relative low rate / frequency** – multicenter, international cooperation essential
- **High early mortality** – potential differential effects of treatments on mortality and function
- **Confounding from other management factors** - early withdrawal of care, neurosurgery, other medical interventions (eg mannitol, TCM, etc)
- **Outcome assessments** - reliability, timing of primary outcome (3, 6 or 12 months) and deciding on the appropriate method of analysis (eg. shift or dichotomous mRS)
Randomized trials of early intensive BP lowering in ICH

ICH ADAPT 2013 (n=75)

INTERACT2 2013 (n=2794)

INTERACT1 2008 (n=320)

ATACH2 2016 (n=1000)

RBPR 2008 (n=42)
Comparison of mRS categories

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Intensive</td>
<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>
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<tr>
<td>Guideline</td>
<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>
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Odds ratio 0.87
P=0.04

Odds ratio 1.1
P=0.56
Effects of early intensive BP lowering on hematoma growth

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large RCTs</strong></td>
<td></td>
</tr>
<tr>
<td>INTERACT1</td>
<td>0.6 (0.3 – 1.0)</td>
</tr>
<tr>
<td>INTERACT2</td>
<td>1.0 (0.7 – 1.3)</td>
</tr>
<tr>
<td>ATACH2</td>
<td>0.7 (0.5 – 1.0)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.8 (0.6 – 1.1)</td>
</tr>
<tr>
<td><strong>Small RCTs</strong></td>
<td></td>
</tr>
<tr>
<td>RBPR ICH</td>
<td>1.1 (0.3 – 3.8)</td>
</tr>
<tr>
<td>ICH ADAPT</td>
<td>1.1 (0.4 – 3.3)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1.1 (0.5 – 2.5)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0.8 (0.7 – 1.0)</td>
</tr>
</tbody>
</table>

Favors intensive

Favors control
PATICH (Perioperative Antihypertensive Treatment in Patients with Spontaneous Intracerebral Hemorrhage)


**Design:** Single center, active comparison, blinded outcome

**Patients:** N=201, 75% male, av. age 54 yr
baseline hematoma vol, av. 36 mL
hypertensive (150-220mmHg), open surgery <24 hrs, no contraindication

**Interventions:**
- **Active** - 140-160 mmHg <1 hr post-randomization 120-140 mmHg immediately prior and after surgery for 7 days
- **Control** – 140-180mmHg pre and post-surgery
- **Both** - 90-140 mmHg intra-operatively

**Outcomes:** **Primary** – re-bleeding within 7 days
**Secondary** – mortality 7, 30 and 90 days
- neurological function, disability, HRQoL at 90 days
- safety
PATICH (Perioperative Antihypertensive Treatment in Patients with Spontaneous Intracerebral Hemorrhage)


No significant between group differences

- Rebleeding
- Mortality 7 days
- Mortality 90 days
- Cerebral ischemia
- Acute coronary event
- Acute renal failure
Recommendations for the control of blood pressure in ICH patients

Acute treatment

1. For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class IIa; Level of Evidence B). (Revised from the previous guideline)

2. For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (Class IIb; Level of Evidence C). (New recommendation)
Pre-hospital paramedical care - RIGHT2 and other planned trials
30% of stroke calls are true stroke
30% of true strokes due to ICH
30% of ICH with hypertension and eligible for clinical trial
Endpoint – hematoma growth?
A multicenter, stepped-wedge, cluster clinical trial of early intensive control of hypertension and other physiological variables in acute intracerebral haemorrhage

A collaboration between the Department of Neurosurgery of West China Hospital (Professor YOU Chao) and The George Institute China (Professor Craig ANDERSON)
Benefits of the approach

- Evaluation of the implementation of evidence into clinical practice
- Include a broad range of patients who were excluded from previous trials – in particular surgical patients and those with large ICH
Care Bundle – all to commence as soon as possible after presentation (<6 hours of ICH onset)

- **Early intensive BP lowering** – INTERACT2 protocol - achieve a systolic BP 130-140mmHg within 1 hour of initiation and maintain for the next 7 days (or hospital separation if earlier).

- **Glucose monitoring and control** to achieve target blood glucose level of <7.5 mmol/L in both diabetic and non-diabetic patients

- **Treatment of pyrexia** to achieve a core body temperature level <37.5°C of treatment and to maintain this temperature level.

- **Early correction of anticoagulation related ICH**
Protocol schema

Sample size of 8621 in a stepped-wedge trial of 3 groups and 4 phases - 75 hospitals randomised to 3 groups of 25 hospitals - each recruiting an average of 29 patients per phase, provides 90% power to assess 20% improvement in functional recovery (shift mRS) (4% absolute effect).

Study sites

Randomization

Sequence 1
- Step 0: control
- Step 1: Intensive management
- Step 2: Intensive management
- Step 3: Intensive management

Sequence 2
- Step 0: control
- Step 1: control
- Step 2: Intensive management
- Step 3: Intensive management

Sequence 3
- Step 0: control
- Step 1: Intensive management
- Step 2: control
- Step 3: Intensive management

Data collection by sites at 0, 1, 7 days

Blinded assessment of outcome at 6 months

Standard Nursing and Medical Care (Local Guidelines)
UK Care bundle proposal
Adrian Parry-Jones, Niki Spriggs and others

- **Stepped wedge design** – 40 hospitals, 3200 pts, 14% RRR

- **ABCD-ICH protocol**
  
  A = anticoagulation reversal within 90 min
  B = Blood pressure control, SBP target 130-140 mmHg within 2 hours
  C = care pathway for neurosurgery
  D = DNR limited use
To determine benefits of more intensive long-term BP control in ICH

An investigator, multicenter, international, double-blinded, placebo-controlled, parallel-group, randomised controlled trial of a fixed low-dose combination BP lowering pill (“Triple Pill” – telmisartan, amlodipine, indapamide) on top of standard of care in 4300 ICH patients
PROGRESS - stroke occurrence by severity and subtype

<table>
<thead>
<tr>
<th></th>
<th>Strokes active</th>
<th>Strokes placebo</th>
<th>Favours active</th>
<th>Favours placebo</th>
<th>Risk reduction (95%CI)</th>
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<tbody>
<tr>
<td>Fatal/disabling</td>
<td>123</td>
<td>181</td>
<td></td>
<td></td>
<td>33% (15 to 46%)</td>
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<tr>
<td>Other stroke</td>
<td>201</td>
<td>262</td>
<td></td>
<td></td>
<td>24% (9 to 37%)</td>
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<tr>
<td>Ischaemic stroke</td>
<td>246</td>
<td>319</td>
<td></td>
<td></td>
<td>24% (10 to 35%)</td>
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<tr>
<td>Cerebral haemorrhage</td>
<td>37</td>
<td>74</td>
<td></td>
<td></td>
<td>50% (26 to 67%)</td>
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<tr>
<td>Stroke type unknown</td>
<td>42</td>
<td>51</td>
<td></td>
<td></td>
<td>18% (-24 to 45%)</td>
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<tr>
<td>Total</td>
<td>307</td>
<td>420</td>
<td></td>
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<td>28% (17 to 38%)</td>
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</table>
Effects blood pressure lowering by ICH subtype  
Arima et al. Stroke 2010; 41: 394-396

<table>
<thead>
<tr>
<th></th>
<th>Number of Events</th>
<th>Favors</th>
<th>Favors</th>
<th>Risk Reduction</th>
<th>P for</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>(95% CI)</td>
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<tr>
<td>Probable CAA-related ICH</td>
<td>3</td>
<td>13</td>
<td></td>
<td></td>
<td>77% (19 to 93%)</td>
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<tr>
<td>Probable HT-related ICH</td>
<td>18</td>
<td>33</td>
<td></td>
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<td>46% (4 to 69%)</td>
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<tr>
<td>Unclassified ICH</td>
<td>16</td>
<td>28</td>
<td></td>
<td></td>
<td>43% (-5 to 69%)</td>
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<td>Overall</td>
<td>37</td>
<td>74</td>
<td></td>
<td></td>
<td>50% (26 to 67%)</td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)
PROGRESS - stroke risk by achieved systolic BP
Arima et al. J Hypertension 2006; 24: 1201-08
Management of BP in clinical practice

Relative risk of disease

Systolic blood pressure (mmHg)

Normotensive
No BP lowering therapy
BP lowering for acute ICH - summary

- Early intensive, smooth and sustained BP lowering in acute ICH to target <140mmHg seems appropriate in acute ICH
- More intensive BP control <120mmHg for secondary prevention of ICH
- More trials necessary to determine best outcomes for patients and implementation of evidence into clinical practice
Thank you for our attention