Blood pressure management in hemorrhagic stroke

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Content
1. What is known from clinical studies?
2. What else should be taken into consideration?
3. Do we need additional trials?

Intensive blood pressure reduction (≤140 mmHg) decreases the risk of hematoma expansion

**Primary endpoint:**
Mean proportional hematoma growth:
- 36.3% (<140-group)
- 13.7% (<180-group)
Difference 22.6%, (95% CI 0.6-44.5%; p=0.04)

Mean absolute increase: 1.7 ml, p=0.12


**INTERACT-2:** Systolic blood pressure levels at and after randomization

Primary outcome, mRS 0-2 vs 3-6:
- Odds ratio (with < 140 mmHG): 0.87; 95% confidence interval [CI], 0.75 to 1.01; p=0.06
- Odds ratio for greater disability (with <180mmHg): 0.87; 95% CI, 0.77 to 1.00; p=0.04

For adults with acute ICH, does altering blood pressure to a particular target or with a specific agent compared to an alternative target or agent:

Recommendation
In acute ICH within 6 hours of onset, intensive blood pressure reduction (systolic target <140 mmHg in <1 hour) is safe and may be superior to a systolic target <180 mmHg. No specific agent can be recommended.

Strength of recommendation: weak
Quality of evidence: moderate

Blood pressure

Recommendation
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).

ATACH-II

What does it add to this?

Primary endpoint: mRS 0-3 vs. 4-6
110-139 mmHg group: 38.7% vs. 140-180 mmHg group: 37.7%
Relative risk, 1.04; 95% CI, 0.85 to 1.27
**Meta-Analysis**

**Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: clinical outcomes and haemorrhage expansion systematic review and meta-analysis of randomised trials**

**Flowchart for studies selection**

- PubMed
- ENSAGE
- Cochrane

**Studies**

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>OR (95% CI)</th>
<th>Wg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large RCTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERACT 1</td>
<td>0.82 (0.68, 0.96)</td>
<td>49/120 55/190 59.87</td>
</tr>
<tr>
<td>INTERACT 2</td>
<td>1.11 (0.83, 1.53)</td>
<td>186/305 18/1309 40.13</td>
</tr>
<tr>
<td>APACHE</td>
<td>0.72 (0.49, 1.02)</td>
<td>485/1233 732/1239 109.00</td>
</tr>
</tbody>
</table>

**3-month mortality risk**

**3-month death or dependency**

**3-month mRS>3**

**Significant haemorrhage expansion at 24 hours**

**Studies**

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<tbody>
<tr>
<td>Small RCTs (-100 patients)</td>
<td>1.09 (0.84, 1.41)</td>
<td>90/175 70/175 0.08</td>
</tr>
<tr>
<td>Small RCTs (-100 patients)</td>
<td>0.91 (0.71, 1.19)</td>
<td>90/175 70/175 0.08</td>
</tr>
</tbody>
</table>

**Significant haemorrhage expansion at 24 hours**

**Studies**

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<td>Large RCTs</td>
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<td></td>
</tr>
<tr>
<td>INTERACT 1</td>
<td>0.39 (0.24, 0.65)</td>
<td>85/170 70/170 1.92</td>
</tr>
<tr>
<td>INTERACT 2</td>
<td>1.10 (0.79, 1.53)</td>
<td>120/275 95/150 9.15</td>
</tr>
<tr>
<td>APACHE</td>
<td>1.07 (0.85, 1.34)</td>
<td>195/350 100/200 3.21</td>
</tr>
</tbody>
</table>

**Flowchart for studies selection**

- PubMed
- ENSAGE
- Cochrane
Blood pressure in acute ICH
Do we need additional trials after INTERACT-2 and ATTACH-II?

1. What is known from clinical studies
2. What else should be taken into consideration?
3. Do we need additional trials?

What else should be taken into consideration?
Ischemia?

PET study: hypo-perfusion in ICH without peri-lesional ischemia

Edema
Blood flow
O2 extraction

PET study: hypo-perfusion in ICH without peri-lesional ischemia

Blood flow
O2 extraction

Moderate BP reduction does not impair CBF (n=14)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Treated</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg, mean +/- SD (range)</td>
<td>143 +/- 10 (120-158)</td>
<td>119 +/- 11 (90-133)</td>
<td>0.846</td>
</tr>
<tr>
<td>MCANS, mean +/- SD</td>
<td>46 +/- 23</td>
<td>46 +/- 26</td>
<td>0.909</td>
</tr>
<tr>
<td>Arterial PCO2, mm Hg, mean +/- SD</td>
<td>36.6 +/- 6.1</td>
<td>35.4 +/- 5.1</td>
<td>0.473</td>
</tr>
<tr>
<td>Arterial O2 saturation, %, mean +/- SD</td>
<td>96.1 +/- 2.3</td>
<td>96.7 +/- 1.5</td>
<td>0.49</td>
</tr>
<tr>
<td>Global CBF, ml/100 g/min, mean +/- SD 95% CI difference</td>
<td>32.1 +/- 7.1</td>
<td>31.5 +/- 8.4</td>
<td>0.402</td>
</tr>
<tr>
<td>Percut CBF, ml/100 g/min, mean +/- SD 95% CI difference</td>
<td>18.9 +/- 9.7</td>
<td>18.1 +/- 8.8</td>
<td>0.402</td>
</tr>
</tbody>
</table>

MCANS = Middle Cerebral Artery Neurological Scale; CBF = cerebral blood flow

ICH-ADAPT

The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial

Kenneth S. Butcher, MD, PhD; Thomas Jeerkovski, MD, MD; Michael Rill, MD, MSc; Andrew M. Domerick, MD, Danduhelkh MD, MD, MD; Meghaj B. Costi, MD; Brettan Goot, BSc; Rebecca McCourt; Nesar Aslangs, MD, MSc, J. Max Fiedley, MD, PhD; Derek Evers, MD, MSc; Ashley Beach, MD, for the ICH-ADAPT Investigators.

Systolic blood pressure (BP) in ICH-ADAPT

Treatment Group
≤ 110 mmHg
≤ 120 mmHg
No relationship between the absolute change in systolic blood pressure (BP) and perihematoma relative cerebral blood flow (rCBF).

What else should be taken into consideration?

Basic difference in trial design: Cerebral ischemia vs intracerebral hemorrhage

Determinants of intracerebral hemorrhage growth

Larger hematomas on the baseline CT were associated with increased absolute ICH growth.
Small intracerebral hemorrhages have a low spot sign prevalence and are less likely to expand.

Baseline volumes and timing in RCT on RR management ICH?

<table>
<thead>
<tr>
<th>Study</th>
<th>MAP &lt;110</th>
<th>110-130</th>
<th>130-150</th>
<th>150-180</th>
<th>&gt;180</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERACT-I</td>
<td>16.2</td>
<td>16.2</td>
<td>11.1</td>
<td>11.1</td>
<td>10.3</td>
</tr>
<tr>
<td>INTERACT-II</td>
<td>16.2</td>
<td>16.1</td>
<td>8.6</td>
<td>8.6</td>
<td>7.3</td>
</tr>
<tr>
<td>ATACH-II</td>
<td>11.1</td>
<td>3.8</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>ADAPT</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>7.3</td>
</tr>
<tr>
<td>RBPR-ICH</td>
<td>7.3</td>
<td>7.3</td>
<td>7.3</td>
<td>7.3</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Mean: 8.5 ± 2.2 9.8 ± 1.7

Onset to randomisation (hours)
<table>
<thead>
<tr>
<th>Study</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERACT-I</td>
<td>3.4</td>
</tr>
<tr>
<td>INTERACT-II</td>
<td>3.7</td>
</tr>
<tr>
<td>ATACH-II</td>
<td>3.6</td>
</tr>
<tr>
<td>ADAPT</td>
<td>3.07</td>
</tr>
<tr>
<td>RBPR-ICH</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Mean: 7.8 ± 2.4

Onset to start of treatment (hours)
<table>
<thead>
<tr>
<th>Study</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERACT-I</td>
<td>4.5</td>
</tr>
<tr>
<td>INTERACT-II</td>
<td>4.5</td>
</tr>
<tr>
<td>ATACH-II</td>
<td>4.5</td>
</tr>
<tr>
<td>ADAPT</td>
<td>4.5</td>
</tr>
<tr>
<td>RBPR-ICH</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Mean: 4.5 ± 1.0

Onset to reach of target pressure (hours)
<table>
<thead>
<tr>
<th>Study</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERACT-I</td>
<td>10.7</td>
</tr>
<tr>
<td>INTERACT-II</td>
<td>10.7</td>
</tr>
<tr>
<td>ATACH-II</td>
<td>10.7</td>
</tr>
<tr>
<td>ADAPT</td>
<td>10.7</td>
</tr>
<tr>
<td>RBPR-ICH</td>
<td>10.7</td>
</tr>
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</table>

Mean: 10.7 ± 2.0

Influence of time, age, IVH-, ICH-volume on ODs for severe disability or death in FAST

Baseline volume >60ml predict mRS 5 or 6

The primary study target

Presence of spot sign depends on onset to CCT time

Reason why to continuously control BP

Course of hematoma expansion

- Hyper-acute (minutes to hours) - is a matter of coagulation and blood pressure
- Sub-acute (hours) - is a matter of inflammation (cell damage) and blood pressure

Prospective studies
Retrospective studies
RCT
Modified Rankin Scale scores from ENOS for ICH at day 90

Randomized < 24 hours (GTN 310 vs. no GTN 319)
Adjusted common odds ratio, 1.04 (95% confidence interval, 0.78–1.38; P=0.81)

However
Mean baseline volumes GTN vs No-GTN
13 ml vs 20 ml

Randomized < 6 hours (GTN 32 vs. no GTN 32)
Adjusted common odds ratio, 0.19 (95% confidence interval, 0.06–0.59; P=0.004)

Mean baseline volumes GTN vs No-GTN

16,2 (17.1) vs 16,2 (16.1)
11 (18-20) vs 11 (18-19)
10,3 (8.5-21.2) vs 10,2 (9.8-19.1)
22,61 (21.35-23,90) vs 23,90 (21.96-28.38)
8.5 (9.8-17.2) vs 9.8 (9.9-17.9)

Mean time to target pressure too long to expect an effect on outcome

-3.4 ± 2.9 (2.6-6.5) vs 3.4 ± 1.7 (2.5-4.6)

Time to treatment > 2.5 hours: predicts mRS 5 or 6

Influence of timing

Results go in different directions

What about chronic hypertension

Do we need to differentiate between patients with and without a history of chronic hypertension?
Preliminary conclusion
with respect to INTERACT-2 and ATACH-2

INTERACT-2: Systolic blood pressure levels at
and after randomization

ATACH-2: Blood pressure courses

Blood pressure in acute ICH
Do we need additional trials after
INTERACT-2 and ATACH-II?

Content
1. What is known from clinical studies
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consideration?
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Suggestions
• RCT
• Adult patients (<70–75 years) with spontaneous ICH (CT
  proven and a systolic pressure >140 mmHg).
• Pre-mRS <1
• Volume 10–60 ml, IVH <5 ml
• Onset to treatment: <3 hours (better 2,5 hours)
• with a fast-acting iv-antihypertensive: Clevidipine
• to a systolic blood pressure >120 and <140 mmHg
• compared to systolic blood pressure 140–160 mmHg
• Outcome: shift in mRS categories

Blood pressure lowering:
• too late
• too weak
• too small
Volumes small

Blood pressure lowering:
• "too much"

No fear - it can be done
there are examples