How Low Should You Go?
Management of Blood Pressure in Intracranial Hemorrhage

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Pharmacy Grand Rounds
August 21, 2018
Patient Case

- AB is a 64 year old male brought in by ambulance for unilateral weakness that came on suddenly. Imaging reveals a small hemorrhage in the left cerebral hemisphere.
- PMH: Hypertension, hyperlipidemia
- Vitals on arrival: BP 186/98, HR 92, GCS 15
Objectives

• Review the pathophysiology of intracranial hemorrhage (ICH) and risk factors associated with poor outcomes

• Outline current guidelines for management of blood pressure in the acute period following ICH

• Discuss the INTERACT2 and ATACH-2 trials and their potential impact on clinical practice
Types of Stroke

- 85% Ischemic
- 15% Hemorrhagic

Pathophysiology of ICH

Hematoma

Brainstem
Etiology of ICH

• Spontaneous
  • Hypertensive
  • Cerebral Amyloid Angiopathy
  • Vascular abnormalities
  • Intracranial neoplasm
  • Coagulopathy

Qureshi et al. NEJM 2001, 344. 1450-60
Treatment Options for ICH

• Reverse coagulopathy
• Management of hypertension
• Management of Intracranial Pressure
• Surgical intervention
Pathophysiology of Acute Hypertension

- Chronically hypertensive
- Cushing Response
- Hypertension
- Perfusion
- Pain

Qureshi et al. NEJM 2001, 344. 1450-60
Blood Pressure Lowering in ICH

• Hypertension is correlated with hematoma expansion and poor outcomes
• Early trials indicated lowering blood pressure in the acute setting prevented hematoma growth
• Must be balanced with risk of hypoperfusion to unaffected areas of the brain and other vital organs
# Pharmacologic Treatment Options for ICH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Repeat?</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicardipine</td>
<td>5 mg/hr</td>
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<td>Systemic arteriolar vasodilation</td>
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</table>
Assessment Question 1

• An hour after arrival AB remains stable with BP 174/96. He is below the guideline recommended SBP goal of 180 mmHg and no longer at risk of hematoma expansion.
  • True
  • False
Timeline of BP Lowering in ICH

- **Late 1990’s:** Safety established
- **2008:** INTERACT
- **2010:** ATACH
- **2013:** INTERACT2
- **2016:** ATACH-2
- **2015:** AHA Guidelines Published
The INTERACT Trial
Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage: a randomised pilot trial
Be consistent with what side of the slide you're putting references on, and formatting of the references.

Caitlin S Brown, 8/16/2018
Design
• Multinational, open-label trial, blinded to outcome

Population
• Aged >18 with CT confirmed ICH and SBP 150-220 mmHg
• Excluded: structural defect leading to ICH, SBP >220mmHg, neurosurgical intervention

Intervention
• Intensive blood pressure lowering: <140 mmHg
• Guideline lowering: <180 mmHg

Primary Endpoint
• Hematoma growth at 24 hours

Major Results
• Hematoma expansion was significantly higher in SBP <180 group (36% vs 13.7%, p=0.04)
• No significant differences between mortality, mRS or ADE
What do you think of changing the colors of the arrows?

This looks great! Was it \( \geq 18 \) or \( > 18 \)?

Maybe include GCS 3-5 on the slides? could take out structural defect?

Verbalize what they could use for BP lowering

Caitlin S Brown, 8/16/2018
INTERACT

Results – Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>SBP &lt;140 (n=172)</th>
<th>SBP &lt;180 (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline volume (mL)</td>
<td>14.2 ± 14.5</td>
<td>12.7 ± 11.6</td>
</tr>
<tr>
<td>Increase in hematoma*</td>
<td>13.7%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Substantial growth (n)</td>
<td>15%</td>
<td>23%</td>
</tr>
</tbody>
</table>

*P=0.04

- 4 (2%) of patients in Intensive group did not require any antihypertensive agents
- 52 (26%) of patients in Guideline directed group did not require any antihypertensive agents
INTERACT

Takeaways

• Intensive SBP lowering reduces hematoma growth in spontaneous ICH
• Early, intensive BP lowering is safe
• Does reduced hematoma expansion correspond to better outcomes?
• Is there an optimal strategy for lowering SBP?

Timeline of BP Lowering in ICH

Late 1990’s: Safety established

2008
INTERACT

2010
ATACH

2013
INTERACT2

2015: AHA Guidelines Published

2016
ATACH-2
The ATACH Trial
Antihypertensive Treatment of Acute Cerebral Hemorrhage

Design
• Dose escalation, multicenter prospective study

Population
• Aged ≥18 with CT confirmed ICH and SBP ≥170 mmHg presenting within 6 hours of onset

Intervention
• Intravenous nicardipine titrated to goal SBP
• Three cohorts: 110-140 mmHg, 140-170 mmHg or 170 to 200 mmHg

Primary Endpoint
• Feasibility of achieving and maintaining SBP in desired range

Major findings
• No difference between groups in safety endpoints
• Keeping SBP in target range was feasible

**ATACH**

### Outcomes and Conclusions

<table>
<thead>
<tr>
<th>SBP 110-140 (n=22)</th>
<th>SBP 140-170 (n=20)</th>
<th>SBP 170-200 (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>41%</td>
<td>0</td>
</tr>
<tr>
<td>ADE within 72 hr</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Neurological deterioration</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>Asymptomatic expansion</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>3 month mRS 0-2</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

Author conclusions: observed rates of neurologic deterioration and adverse events were below prespecified safety thresholds

Recommend larger, randomized trial
ATACH

Takeaways

- Safety endpoints were not significantly different between any of the SBP target groups
- Feasibility demonstrated at reaching SBP <140 mmHg
- Is it efficacious to reduce SBP <140 mmHg?

Timeline of BP Lowering in ICH

- **Late 1990’s:** Safety established
- **2008** INTERACT
- **2010** ATACH
- **2013** INTERACT2
- **2015:** AHA Guidelines Published
- **2016** ATACH-2
The INTERACT2 Trial
Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

Multicenter, randomized, open-treatment

Randomized within 6 hours of symptom onset

Intensive lowering <140 mmHg (n=719)

Standard therapy <180 mmHg (n=785)

Maintained BP for 7 days (or discharge)

INTERACT2
Trial Design

Primary Endpoint
- Death or major disability (mRS 3-6) at 90 days

Secondary Endpoints
- Death or disability in patients enrolled within 4 hrs
- Health-related quality of life (EQ-5D)
- Duration of hospitalization

Safety Endpoints
- Early neurological deterioration (GCS < 2, NIH + 4)
- Hypotension that required fluids or vasopressors
- Change in hematoma size in patients who underwent repeat imaging

SBP = systolic blood pressure
ICH = intracranial hemorrhage

# INTERACT2

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>SBP &lt; 140 mmHg (n=1399)</th>
<th>SBP &lt; 180 mmHg (n=1430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63 ± 13.1</td>
<td>64.1 ± 12.6</td>
</tr>
<tr>
<td>Males</td>
<td>64.2%</td>
<td>61.7%</td>
</tr>
<tr>
<td>SBP in mmHg on arrival</td>
<td>179 ± 17</td>
<td>179 ± 17</td>
</tr>
<tr>
<td>GCS on arrival</td>
<td>14 (12-15)</td>
<td>14 (12-15)</td>
</tr>
<tr>
<td>Baseline hematoma, mL</td>
<td>11 (6-19)</td>
<td>11 (6-20)</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>38.6%</td>
<td>37.8%</td>
</tr>
</tbody>
</table>

*yr=years  
GCS = glasgow coma scale  
ICU = intensive care unit*

## INTERACT2 Results

<table>
<thead>
<tr>
<th></th>
<th>SBP &lt;140 mmHg (n=1399)</th>
<th>SBP &lt;180 mmHg (n=1430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to treatment from onset, hr</td>
<td>4 (2.9-5.1)</td>
<td>4.5 (3-7)</td>
</tr>
<tr>
<td>Intravenous treatment</td>
<td>90.1%</td>
<td>42.9%</td>
</tr>
<tr>
<td>Single intravenous treatment</td>
<td>60.7%</td>
<td>29%</td>
</tr>
<tr>
<td>Surgical Intervention</td>
<td>5.6%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Mannitol administration</td>
<td>62%</td>
<td>61.7%</td>
</tr>
<tr>
<td>Mean SBP at 1 hr, mmHg</td>
<td>150</td>
<td>164</td>
</tr>
</tbody>
</table>

Only 33% of patients in intensive treatment group reached SBP <140 mmHg
INTERACT2
Mean SBP Across Treatment Period

### INTERACT2

#### Results - Outcomes

<table>
<thead>
<tr>
<th></th>
<th>SBP &lt;140 (n=1399)</th>
<th>SBP &lt;180 (n=1430)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or major disability</td>
<td>52%</td>
<td>55.6%</td>
<td>0.06</td>
</tr>
<tr>
<td>Death by 90 days</td>
<td>12%</td>
<td>12%</td>
<td>0.96</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>20 (12-25)</td>
<td>19 (11-33)</td>
<td></td>
</tr>
<tr>
<td>Health related quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Overall health utility score</td>
<td>0.60 ± 0.39</td>
<td>0.55 ± 0.40</td>
<td>0.002</td>
</tr>
<tr>
<td>Neurologic decline in first 24 hr</td>
<td>14.5%</td>
<td>15.1%</td>
<td>0.62</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>23.3%</td>
<td>23.6%</td>
<td>0.92</td>
</tr>
<tr>
<td>• Recurrent hemorrhage</td>
<td>0.3%</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>• Acute coronary event</td>
<td>0.4%</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>• Severe hypotension</td>
<td>0.5%</td>
<td>0.6%</td>
<td></td>
</tr>
</tbody>
</table>

INTERACT2

Takeaways

• Intensive blood pressure lowering in ICH did not reduce death or severe disability
  • An ordinal analysis of mRS indicated improved functional outcomes with intensive lowering

• Small difference in median SBP between groups across time period

• Does pharmacologic choice matter?

Timeline of BP Lowering in ICH

Late 1990’s: Safety established

2008
INTERACT

2010
ATACH

2013
INTERACT2

2015: AHA Guidelines Published

2016
ATACH-2
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class, LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lowering of SBP to 140 is safe in patients presenting with SBP of 150-220</td>
<td>I, A</td>
</tr>
<tr>
<td>Acute lowering of SBP to 140 can be effective for improving functional outcome</td>
<td>IIb, B</td>
</tr>
<tr>
<td>For initial SBP &gt; 220, it may be reasonable to consider aggressive reduction with continuous infusion and close monitoring</td>
<td>IIb, C</td>
</tr>
</tbody>
</table>

*all values reported in mmHg*
Assessment Question 2

• Five hours after arrival AB’s blood pressure has remained stable at 168/96. AB’s blood pressure management should:
  • Target an SBP <140 mmHg as it is safe and may improve functional outcome
  • Target an SBP of <160 mmHg to mitigate risks of hypotension and decrease risks of expansion
  • Target an SBP <180 mmHg to minimize risk
Timeline of BP Lowering in ICH

- Late 1990’s: Safety established
- 2008: INTERACT
- 2010: ATACH
- 2013: INTERACT2
- 2015: AHA Guidelines Published
- 2016: ATACH-2
The ATACH-2 Trial

Intensive Blood Pressure Lowering in Patients with Acute Cerebral Hemorrhage
Multicenter, randomized, open-label

Randomized within 3-4.5* hours of symptom onset

Intensive lowering <140 mmHg (n=500)

Standard therapy <180 mmHg (n=500)

Qureshi A, et al. NEJM 206:375:1033-43
**Primary Endpoint**
- Death or major disability (mRS 4-6) at 90 days

**Secondary Endpoints**
- Patients with hematoma expansion of 33% or greater at 24 hrs
- Health-related quality of life (EQ-5D)

**Safety Endpoints**
- Early neurological deterioration (GCS <2, NIH + 4)
- Serious adverse events occurring within 72 hours
- Death within 90 days

*Trial was halted early after interim analysis determined futility in reaching a difference in primary endpoint*

Qureshi A, et al. NEJM 206;375:1033-43

18 years of age
SBP >180 mmHg
ICH < 60 mL

Exclude:
- Poor prognosis
- Drop to SBP <140

Initiated on nicardipine
5 mg/hr
+ labetalol PRN
## ATACH-2

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intensive (n=500)</th>
<th>Standard (n=500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62 ± 13.1</td>
<td>61.9 ± 13.1</td>
</tr>
<tr>
<td>Male sex, n</td>
<td>60.8%</td>
<td>63.2%</td>
</tr>
<tr>
<td>Initial SBP, mmHg</td>
<td>200 ± 27.1</td>
<td>201 ± 26.9</td>
</tr>
<tr>
<td>Hematoma, mL</td>
<td>10.3 (2.3 – 85.2)</td>
<td>10.2 (0.98 – 79.1)</td>
</tr>
<tr>
<td>Hematoma &gt;30 mL</td>
<td>9.1%</td>
<td>10.4%</td>
</tr>
</tbody>
</table>
ATACH-2
Mean SBP during Study Period

Minimum Systolic Blood Pressure (mm Hg)

Hours since Randomization

Standard treatment
Intensive treatment
## ATACH-2
### Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive (n=500)</th>
<th>Standard (n=500)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or disability</td>
<td>38.7%</td>
<td>37.7%</td>
<td>0.84</td>
</tr>
<tr>
<td>Hematoma expansion</td>
<td>18.9%</td>
<td>26.4%</td>
<td>0.08</td>
</tr>
<tr>
<td>Neurologic deterioration</td>
<td>11%</td>
<td>8%</td>
<td>0.11</td>
</tr>
<tr>
<td>Treatment related ADE</td>
<td>1.6%</td>
<td>1.2%</td>
<td>0.05</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>0.7 (-0.1-1)</td>
<td>0.7 (0 -1)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

ADE=adverse drug event

### ATACH-2

**Adverse Renal Effects?**

<table>
<thead>
<tr>
<th></th>
<th>SBP&lt;140 (n=500)</th>
<th>SBP&lt;180 (n=500)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious renal AE within 7 days</td>
<td>4</td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>Serious renal AE within 30 days</td>
<td>5</td>
<td>4</td>
<td>0.73</td>
</tr>
<tr>
<td>Any renal AE</td>
<td>45</td>
<td>20</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

Adverse renal events were included if urine output dropped below 30 cc for 1 hour.

Qureshi A, et al. NEJM 206;375:1033-43
ATACH-2
Takeaways

- Utilized a protocolized approach
- Intensive blood pressure lowering following ICH did not result in a lower rate of death or disability
- Median SBP was well below target in both groups
- ADE definitions have limited clinical utility

Qureshi A, et al. NEJM 206;375:1033-43
## INTERACT2 vs. ATACH-2

<table>
<thead>
<tr>
<th></th>
<th>INTERACT2</th>
<th>ATACH-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial SBP</td>
<td>179 mmHg</td>
<td>200 mmHg</td>
</tr>
<tr>
<td>Initial NIH</td>
<td>10-11</td>
<td>11</td>
</tr>
<tr>
<td>Hematoma volume</td>
<td>11 mL</td>
<td>10 mL</td>
</tr>
<tr>
<td>Pharmacologic agent</td>
<td>Variable</td>
<td>Nicardipine + labetalol</td>
</tr>
<tr>
<td>SBP at 1 hr (Tx/control)</td>
<td>150/164</td>
<td>125/140</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Death/disability</td>
<td>Death/disability</td>
</tr>
<tr>
<td>Significant difference</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>Yes, by mRS</td>
<td>No*</td>
</tr>
<tr>
<td>ADE</td>
<td>No</td>
<td>Yes?</td>
</tr>
</tbody>
</table>

*Tx=treatment group in each study

Qureshi A, et al. NEJM 206:375:1033-43
Assessment Question 3

• AB was initiated on intravenous nicardipine infusion in the emergency department. He arrives to the ICU with a BP of 110/65. He should be managed by:
  • Continuing nicardipine at the current rate to decrease risk of hematoma expansion
  • Changing to an oral agent for more consistent control
  • Decreasing the rate of nicardipine but maintaining SBP <140 mmHg
  • Change to an alternate intravenous agent
Acute Hypertension in ICH

SBP in mmHg vs Hours after symptom onset

- **Standard Therapy**
- **Intensive Therapy**
Blood Pressure Variability

- Fluctuation in SBP over a period of time
- Independently predicts
  - Hematoma expansion
  - Neurological deterioration
  - Death

Nicardipine Reduces Blood Pressure Variability After Spontaneous Intracerebral Hemorrhage

*Neurocritical Care 2018*

**Design and Population**
- Retrospective chart review conducted at Mayo Clinic Rochester
- ICH treated with labetalol, hydralazine or nicardipine

**Intervention**
- Labetalol +/- hydralazine
- Nicardipine +/- labetalol +/- hydralazine

**Primary Endpoint**
- Blood pressure variability (defined as standard deviation of SBP)

**Major Results**
- Patients receiving nicardipine based regimens had less BPV and were more likely to achieve SBP < 140
Pearls for Choosing BP Lowering Agents

• Rapid onset
  • Short duration in acute period
• Predictable and easily titratable
• Easy conversion to oral agents
• Few adverse events
## Pharmacologic Treatment Options for ICH

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<td>10-20 mg</td>
<td>q4hr PRN</td>
<td>Systemic arterial vasodilation</td>
</tr>
<tr>
<td>Clevidipine*</td>
<td>1-2 mg/hr</td>
<td>titrate by 1 mg q2min</td>
<td>Calcium channel blockade</td>
</tr>
</tbody>
</table>
Future Directions - Questions Left to be Answered

• What should our target SBP be?
• Is there a pharmacologic agent of choice?
• Does BPV have more impact on outcomes than SBP alone?
Summary of Evidence

• Current guidelines recommend lowering SBP <140 mmHg following ICH

• INTERACT2 found a correlation with improved mRS scores with intensive BP lowering but failed to show an overall benefit

• ATACH-2 did not find a difference in mortality or morbidity with intensive blood pressure lowering

• Optimal target SBP has yet to be elucidated
Recommendations for Treatment

SBP > 150 mmHg
- Monitor

SBP > 220 mmHg
- Lower SBP cautiously with nicardipine and monitor for signs of neurologic deterioration
- Yes
- No
- No

Initiate nicardipine 5 mg/hr for goal SBP <140 mmHg

Unable to achieve SBP <140 mmHg
- Labetalol 10 mg q15min PRN
- Heart rate won’t tolerate
- Hydralazine 10 mg q4h PRN
How Low Should You Go?
Management of Blood Pressure in Intracranial Hemorrhage

Rachael Scott, Pharm.D.
PGY2 Critical Care Pharmacy Resident

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