**Critical Review Form**
**Therapy**

Butcher KS, Jeerakathil T, Hill M, et al; ICH ADAPT Investigators. The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial. Stroke. 2013 Mar;44(3):620-6.

**Objectives:** **To evaluate the hypothesis that "early acute BP reduction would not result in significantly lower perihematoma CBF [cerebral blood flow] than that in patients managed conservatively." (p. 620)**

**Methods:** **This multicenter, prospective, randomized, open-label trial was conducted between January 28, 2007 and December 6, 2011. Patients aged 18 years or older with spontaneous intracranial hemorrhage (ICH) on noncontrast CT within 24 hours of symptom onset were eligible for inclusion if they had at least 2 systolic blood pressure (SBP) readings of 150 mmHg or more at least 5 minutes apart. Patients with a secondary cause of the hemorrhage (i.e. AVM), those with a planned surgical resection, and those with contraindication to IV contrast were excluded.**

**Patients were randomized to a target SBP of < 150 mmHg or < 180 mmHg within 1 hour of randomization. All patients underwent a head CT with contrast two hours after randomization with CT perfusion (CTP) imaging, as well as a repeat noncontrast head CT at ~24 hours after randomization. Patients were also clinically evaluated at 2 hours, 24 hours, 30 days, and 90 days after randomization and had an NIHSS score assessed. Patients also had a Barthel index and modified Rankin Scale (mRS) calculated at 24 hours, 30 days, and 90 days following randomization. The primary endpoint was perihematoma relative cerebral blood flow (rCBF), a measure of change in perfusion relative to unaffected contralateral homologous regions.**

**A total of 75 patients were randomized, 39 with a target SBP of < 150 mmHg and 36 with a target SBP of < 180 mmHg. All patients in the < 150 group were treated with IV antihypertensives, compared to 44% of patients in the < 180 group. The target BP was achieved in 79% of patients in the < 150 group and 100% of patients in the < 180 group.**

| Guide | | Comments |
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| **I.** | **Are the results valid?** | |
| **A.** | **Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?** | |
| 1. | Were patients randomized? | Yes. "A block randomization design (6 |

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| | | patients/block), stratified by onset to treatment time (≤ 6 hours and 6-24 hours), was used." (p. 621) |
| 2. | Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group? | Uncertain. The authors provide no information regarding the method of randomization or attempts at allocation concealment. |
| 3. | Were patients analyzed in the groups to which they were randomized? | Yes. Patients were analyzed by intention to treat principles, regardless of whether they achieved target BP goals or not. As stated, 21% of patients randomized to a target SBP of < 150 mmHg did not achieve this BP in the first hour as planned. |
| 4. | Were patients in the treatment and control groups similar with respect to known prognostic factors? | Yes. Patients were similar with respect to age, gender. past medical history (including hypertension), baseline BP, HR, GCS, and NIHSS, hematoma location, and intraparenchymal hematoma volume. Patients in the more aggressive SBP management group had smaller intraventricular hematoma volume compared to the less aggressive management group (2.09 vs. 4.25 mL), but this does not seem as if it would be clinically significant. |
| **B.** | **Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?** | |
| 1. | Were patients aware of group allocation? | Yes. It seems unlikely, though possible, that performance bias on the part of the patient would have affected outcomes. |
| 2. | Were clinicians aware of group allocation? | Yes. It is possible that performance bias on the part of the patient would have affected outcomes. |
| 3. | Were outcome assessors aware of group allocation? | Yes. For the primary outcome, "Images were postprocessed and measured centrally by readers (B.G. and R.M.) blinded to clinical outcome and treatment group." (p. 621) Also, NIHSS, mRS score, and Barthel index scores were assessed by investigators blinded to BP treatment. |
| 4. | Was follow-up complete? | Mostly yes. It would seem that primary outcome data was missing for 2 patients in the aggressive SBP management group. Data for all other outcomes was available for all |

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| | | patients. |
| **II.** | **What are the results (answer the questions posed below)?** | |
| 1. | How large was the treatment effect? | • Perihematoma rCBF was similar in patients randomized to a target SBP < 150 mmHg and those randomized to a target SBP < 180 mmHg (0.86±0.12 vs. 0.89±0.09; p = 0.18; absolute difference 0.03, 95% CI -0.018 to 0.078).<br>• Perihematoma relative cerebral blood volume (rCBV) was similar between the groups (0.90±0.14 vs. 0.91±0.15; p = 0.73).<br>• Ipsilateral rCBF was lower in patients randomized to the < 150 mmHg group compared to the < 180 mmHg group (0.95±0.05 vs. 0.99±0.05; p = 0.0013).<br>• There was no statistically significant difference in mortality, NIHSS, mRS, and Barthel index measurements between the groups. The median 90-day mRS was lower in patients in the < 150 mmHg group compared to the < 180 mmHg group (2.5 vs. 4), but this did not achieve statistical significance (p=0.65). |
| 2. | How precise was the estimate of the treatment effect? | See above. This was a small study, and while 95% CIs were not provided for clinical outcomes, these would likely be quite wide. |
| **III.** | **How can I apply the results to patient care (answer the questions posed below)?** | |
| 1. | Were the study patients similar to my patient? | Not necessarily. This study enrolled patients with symptoms up to 24 hours old. Most of our patients would likely be managed sooner, and most other studies enroll patients with symptoms of much shorter duration (4.5 hours in ATACH-2 and 6 hours in INTERACT-2) as the majority of hematoma expansion occurs within the first few hours (Brouwers 2013). The inclusion of patients with longer duration of symptoms may mask the potential benefit of early aggressive BP management. |
| 2. | Were all clinically important outcomes considered? | No. The primary outcome in the study, for which the study was powered, is a surrogate outcome of unclear clinical significance. The study was vastly underpowered to detect |

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| | | improvements in patient-centered outcomes (such as mRS score). The authors did not assess quality of life, length of hospital/ICU stay, or cost. |
| 3. | Are the likely treatment benefits worth the potential harm and costs? | Uncertain. This trial showed no difference in changes in relative CBF between those patients treated with more aggressive BP management and those treated with more traditional BP goals. Unfortunately, the inclusion of patients with a much longer duration of symptoms than traditionally enrolled in such studies may mask the potential benefit of early aggressive BP management. Additionally, the study was underpowered to detect improvements in clinically relevant outcomes. |

**Limitations:**

1. **The authors do not provide details regarding the method of randomization sequence generation or attempts at allocation concealment.**

2. **Patients with symptoms up to 24 hours were included, despite evidence that the majority of hematoma expansion occurs within the first few hours (Brouwers 2013). The inclusion of patients with longer duration of symptoms may mask the potential benefit of early aggressive BP management.**

3. **The primary outcome, relative cerebral blood flow, is a surrogate outcome. The study was underpowered to detect statistically significant differences in more clinically relevant outcomes.**

4. **This was understandably an open-label study, but it is possible that performance bias on the part of the clinician would have affected some of the outcomes.**

**Bottom Line:**

**This small, open-lab, randomized trial found no difference in changes in rCBF between those patients treated with more aggressive BP management and those treated with more traditional BP goals. Unfortunately, the inclusion of patients with symptom duration out to 24 hours may result in an underestimation of benefit in those treated with early aggressive BP management. Additionally, the primary outcomes in this study were surrogate outcomes, and the study was underpowered to detect statistically significant differences in more patient-centered outcomes.**