Critical Review Form
Therapy

Qureshi AI, Palesch YY, Barsan WG, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. N Engl J Med. 2016 Sep 15;375(11):1033-43.

Objectives: **"to determine the efficacy of rapidly lowering the systolic blood-pressure level in patients in an earlier time window after symptom onset than that evaluated in previous trials." (p. 1034)**

Methods: **This randomized, multicenter, open-label trial was conducted at 110 sites in the US, Japan, China, Taiwan, South Korea, and Germany between May 2011 and September 2015. Patients aged 18 years or older with spontaneous intracranial hemorrhage (ICH) with at least one systolic blood pressure (SBP) measurement of 180 mmHg or more, in whom the initiation of IV antihypertensive treatment and randomization could occur within 4.5 hours of symptom onset, were eligible for inclusion. Patients were also required to have a GCS of 5 or more and initial intraparenchymal hematoma volume of 60 cm^3.**

Patients were randomized to either a goal SBP of 140-179 mmHg or 110-139 mmHg for a period of 24 hours following randomization. A nicardipine infusion was used as the first-line agent for BP control, followed by IV labetalol if the BP was still above the goal after using a maximal dose of nicardipine (15 mg/hr).

A repeat head CT was performed at 24 hours, and initial and repeat had CTs were evaluated by a reader who was blinded to treatment group and clinical findings to assess for change in hematoma size. Patients were followed up at one month by telephone interview and at 3 months by clinic visit. The primary outcome was the proportion of patients with a modified Rankin Scale (mRS) score of 4 to 6 at 3 months. Secondary outcomes included quality of life (based on scores on the EQ-5D utility index) at 3 months and the proportion of patients with hematoma volume expansion of 33% or more at 24 hours. Safety outcomes included neurologic deterioration (decrease in GCS of 2 or more or increase in NIHSS or 4 or more), serious adverse events occurring within 72 hours of randomization that were felt to be related to treatment, and deaths within 3 months.

One thousand patients were randomized, 500 to the intensive-treatment group and 500 to standard care. The mean age was 61.9 years and 38.0% were women. Just over half of the patients were Asian. The mean SBP at baseline was 200.6±27.0 mmHg.

Guide		Comments
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. "Randomization was performed centrally through the trial website with the use of a minimization algorithm combined with the biased coin method to ensure a balance of treatment assignment within and across clinical sites, baseline GCS score, age (divided into seven strata), and presence or absence of intraventricular hemorrhage at baseline." (p. 1034)
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?	Yes. The use of a central randomization system should ensure adequate allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "The prespecified primary analysis was conducted under the intention-to-treat principle..." (p. 1036)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, sex, race, baseline GCS, initial SBP, NIHSS, hematoma volume, time interval between symptom onset and randomization, and location of hemorrhage. There was a slightly higher incidence of intraventricular hemorrhage in the standard-treatment group than in the intensive-treatment group (28.9% vs. 24.6%).
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?	No. Baseline and 24-hour CTs were reviewed by a blinded assessor in order to determine hematoma volume. Data collection at 3 months

		was performed by an investigator who was not involved in randomization or treatment of the patients, and who was presumably blinded to treatment group.
4.	Was follow-up complete?	Mostly yes. Primary outcome data was missing in only 39 patients (3.9% of the study population), 20 from the standard-treatment group and 19 from the intensive-treatment group.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• The primary outcome (mRS score of 4-6 at 3 months) occurred in 186 patients (38.7%) in the intensive-treatment group vs 181 (37.7%) in the standard-treatment group: unadjusted RR 1.02 (95% CI 0.83-1.25), adjusted RR 1.04 (95% CI 0.85-1.27). • There was no difference in the ordinal distribution of the mRS. • There was no difference in quality of life measured by the EQ-5D. • Patients in the standard-treatment group were more likely to have hematoma expansion at 24 hours compared to the intensive-treatment group, but this did not achieve statistical significance: 24.4% vs. 18.9%, RR 0.78 (95% CI 0.59-1.04). • There were no differences in treatment-related serious adverse events within 72 hours. There were slightly more treatment-related serious adverse events within 3 months in the intensive-treatment group: RR 1.30 (95% CI 1.00-1.69).
2.	How precise was the estimate of the treatment effect?	See above. This was a relatively large study with narrow CIs.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Uncertain. While these were patients with spontaneous ICH presenting to the ED, most of the patients were recruited outside of the US and around half were Asian. The authors do not provide information regarding medical comorbidities (i.e. preexisting hypertension) or use of illicit substances that increase risk of

		ICH (i.e. cocaine). It does, however, seem likely that treatment efficacy would be similar in patients treated at our institution compared to patients in the study.
2.	Were all clinically important outcomes considered?	Mostly yes. The authors did not consider cost, hospital length of stay, or amount of physician/nursing care required to maintain the SBP in the target range.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. This is a fairly methodologically sound study, and despite some understandable limitations (such as lack of blinding) it seems internally valid and likely generalizable to patients in our institution. The study found no benefit with regards to clinically relevant outcomes, with a slightly higher rate of adverse events at 3 months with intensive blood pressure lowering.

Limitations:

1. **The study was stopped early for a perceived futility of the intervention being studied. This practice has been called into question as it has the potential to result in missing a benefit.**

2. **While the study is understandably open-label, and blinding would not have been possible given the interventions involved. such lack of blinding raises the potential for performance bias on the part of the clinicians.**

3. **This study was performed in multiple countries, and it is not stated how many were recruited in the US. About half of the patients were Asian. The results may not be generalizable to patients in our institution (external validity), though it seems likely that they are.**

Bottom Line:

This large, multi-center, randomized controlled trial found no benefit to more intensive lowering of blood pressure in patients with spontaneous ICH. For the primary outcome, risk of a mRS score of 4-6, the unadjusted RR was 1.02 (95% CI 0.83-1.25), with a slightly high rate of adverse events related to treatment at 3 months. The fact that half of the patients in the study were Asian raises concerns regarding external validity, but on the whole it seems likely that these results would be generalizable to patients at our institution.