

**Critical Review Form
Therapy**

[Anderson CS, Heeley E, Huang Y, et al; INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013 Jun 20;368\(25\):2355-65.](#)

Objectives: "to determine the safety and effectiveness of early intensive lowering of blood pressure in patients with intracerebral hemorrhage." (p. 2356).

Methods: This international, multicenter, prospective, randomized trial was conducted from October 2008 to August 2012 at 144 hospitals in 21 countries. Patients with spontaneous intracerebral hemorrhage (ICH) seen on CT or MRI with a systolic blood pressure (SBP) between 150 and 220 mmHg in whom BP lowering treatment could be started within 6 hours of symptom onset were eligible for inclusion. Exclusion criteria included a structural cause for the ICH, a Glasgow Coma Scale (GCS) score of 3 to 5, massive hematoma with a poor prognosis, and early surgery planned for hematoma evacuation.

Patients were randomized to either intensive or guideline-recommended management of BP. For patients in the intensive management group, the goal was to attain a SBP of < 140 mmHg within one hour of randomization, and to maintain this level for the next 7 days. Patients in the guideline-recommended group were to receive BP lowering treatment if their SBP was > 180 mmHg with no lower level stipulated.

GCS and National Institutes of Health Stroke Scale scores were evaluated at baseline and again at 24 hours and 7 days (or at the time of discharge if this occurred before 7 days). All patients underwent brain CT (or MRI) at baseline; a subgroup of patients underwent repeat imaging at ~24 hours either as part of routine practice at some locations or for research purposes. All patients were followed up at 28 days and 90 days either in person or by telephone interview by staff who were blinded to treatment group.

The primary outcome was the proportion of patients with a [modified Rankin Scale](#) (mRS) score of 3 to 5 at 90 days after randomization. A key secondary outcome (defined AFTER completion of the study but prior to data analysis) was an [ordinal analysis](#) of the mRS score across all 7 levels. Other secondary outcomes included mortality, quality of life as assessed by the [European Quality of Life-5 Dimensions](#) (EQ-5D) questionnaire, duration of hospital stay, residence in a residential care facility at 90 days, mRS score at 7 and 28 days, and serious adverse events.

A total of 2839 patients were enrolled, with a mean age of 63.5 years; 62.9% were male. There were 1403 patients assigned to early intensive treatment and 1436 assigned to guideline-recommended treatment.

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. Patients were randomized via "a secure Web-based randomization system...with the use of a minimization algorithm to ensure that the groups were balanced with respect to country, hospital, and time (≤ 4 hours vs. >4 hours) since the onset of the intra-cerebral hemorrhage." (p. 2356)
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 Web-based randomization system should allow for adequate allocation concealment .
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "Participants who did not receive the assigned treatment or who did not adhere to the protocol were followed up in full, and their data were included in the analyses according to the intention-to-treat principle." (p. 2357)
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, baseline systolic and diastolic BP, baseline NIHSS and GCS, past medical history, baseline hematoma volume,
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. For the primary outcome and most of the secondary outcomes, "Participants were followed up in person or by telephone at 28 days and at 90 days by trained local staff who were unaware of the group assignments." (p. 2357) For change in hematoma volume, it is not stated whether radiologists reviewing the imaging studies were blinded to group allocation.
4.	Was follow-up complete?	Mostly yes. "The primary outcome was determined for 1382 of the participants (98.5%) in the intensive-treatment group and for 1412 (98.3%) in the standard-treatment group." (p. 2360) This represents excellent follow-up.
II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	<ul style="list-style-type: none"> • The primary outcome (mRS of 3 to 5 at 90 days) occurred in 719 patients (52.0%) in the intensive-treatment group and 785 patients (55.6%) in the standard-treatment group: OR 0.87, 95% CI 0.75 to 1.01. • Using ordinal analysis, there was a significant shift toward improved outcomes in the intensive-treatment group, with a pooled OR for a shift to a higher mRS score of 0.87, 95% CI 0.77 to 1.00, p = 0.04. • EQ-5D scores at 90 days were overall higher in the intensive-treatment group than the standard-treatment group: mean [\pmSD] utility score, 0.60\pm0.39 vs. 0.55\pm0.40; P=0.002. • All-cause mortality was similar between the groups (11.9% vs. 12.0%) as was the percent of mortality attributed to the ICH itself (61.4% vs. 65.3%). • There was no statistically significant difference in duration of hospital stay, residence in a residential care facility at 90 days, mRS score at 7 and 28 days, and serious adverse events between the two groups.
2.	How precise was the estimate of the	

	treatment effect?	
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 68% were recruited in China. 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 considered functional status, quality of life, length of hospital stay, and hematoma volume. They did not assess cost.
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. While there was a shift towards better outcomes with the use of ordinal analysis, the decision to perform this analysis was made <i>post hoc</i> and this is considered a secondary outcome. As such, it is thought provoking, but not practice changing.

Limitations:

- 1. 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.**
- 2. This study was performed in multiple countries and around 68% of patients were Chinese. The results may not be generalizable to patients in our institution (external validity), though it seems likely that they are.**
- 3. While an ordinal analysis of functional outcomes did reveal a statistically significant improvement in the intensive-treatment group, this was performed as a**

***post-hoc* secondary analysis. While thought provoking, such an analysis should not influence management without confirmation.**

Bottom Line:

This large, methodologically sound, multicenter study compared intensive lowering of blood pressure (to a SBP of < 140 mmHg within one hour) to standard BP management in patients with spontaneous ICH. There was no difference in the primary outcome (poor functional status) between the groups at 90 days, with an OR of 0.87 (95% CI 0.75 to 1.01). While an ordinal analysis of functional outcomes did reveal a statistically significant improvement in the intensive-treatment group, this was performed as a *post-hoc* secondary analysis. While thought provoking, such an analysis should not influence management without confirmation.