Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage (ATACH-2)

N Engl J Med 2016; 375:1033-43

Patients who present with acute intracerebral hemorrhage (ICH) and elevated blood pressure have an increased risk of hematoma expansion, neurologic deterioration, death, and dependency. For these reasons, several prior studies had assessed optimal blood pressure management and targets following acute ICH. The first large, randomized trial was INTERACT2 (2013) which essentially found that it was safe to lower SBPs to <140 following ICH. This prompted new AHA guidelines (2015) recommending target SBPs of <140 post-ICH. Notably, however, although INTERACT2 showed that intensive SBP reduction improved functional outcomes post-ICH, this treatment strategy did not significantly reduce mortality rates or disability post-ICH. The ATACH-2 Trial was meant to re-address this question, and to determine the optimal SBP target post-ICH.

Experimental design and statistics:

- Large multi-center trial, randomized, open-label study (US, Japan, China, Taiwan, South Korea, Germany)
- Total of 1000 patients that were split equally into two groups: intensive SBP reduction (110-139mmHg, intensive group) or standard reduction (140-179mmHg, standard group)
- Treated blood pressure with IV nicardipine (second line: IV labetalol)
- Inclusion criteria: mean SBP of 200, GCS >/= 5, supratentorial ICH <60cm^3 on CT head
- Exclusion criteria: AVM, neoplasm, aneurysm, trauma-associated ICH, coagulopathy
- Randomized within 4.5hr of symptom onset; treatment was started within that 4.5hr period and continued for 24hr; repeat CT head obtained 24hrs after initiation of treatment
- Primary treatment failure: not reaching SBP target w/in 2hrs of randomization
- Secondary treatment failure: hourly minimum SBP was higher than the upper-limit of the target SBP range, for >2hrs during maintenance period
- Primary outcome: proportion of patients of with death or disability (measures by: MRS 4-6) at 3 months
- Secondary outcomes: quality of life scale EQ-5D, hematoma expansion by 33%
- Safety outcomes: neurologic deterioration (2pt drop in GCS or 4pt drop in NIHSS)

Results: The population included patients with a mean age of 61.9, including 38% women, 56.2% Asian (**Table 1**). Of note, the study authors calculated that 1280 participants would be needed for sufficient statistical power, though this trial stopped enrollment early at 1000 participants due to futility. There were no group differences in terms of the primary outcome (death or disability), as this was observed in 38.7% of the intensive group and in 37.7% of the standard group, with no differences in follow-up subgroup analyses (**Fig 3**). The mRS scores at 3 months were also similar between the two groups (**Fig 2**), as were secondary outcomes. Of note, there were no group differences in treatment-related adverse events (w/in 72hrs of randomization), but there was a higher incidence of any serious adverse event at 3 months in the intensive vs. the standard treatment group (25.6% in intensive vs. 20% in standard, RR: 1.30, *p*=0.05). Importantly, there was a higher rate of renal adverse events within 7 days in the intensive treatment group vs. the standard treatment group in a post-hoc analysis (9% vs 4%, *p*=0.002). In addition, 12.2% of study participants in the intensive treatment group experienced primary treatment failure vs. only 0.8% in the standard group, and 15.6% of study participants in the intensive group experienced secondary treatment failure, vs only 1.4% in standard treatment group. Essentially, there

were no differences in the primary outcome, but targeting a lower SBP goal caused more systemic, adverse events, and was harder to achieve and sustain.

Conclusions: Given that there was no difference in the primary outcome with intensive versus standard SBP treatment, and a higher risk for renal injury, this study suggested no clear benefit to more aggressive SBP targets post-ICH. Ultimately, current 2022 AHA guidelines recommend careful titration of SBPs to a target range of 130-150 mmHg, if a patient presents with SBPs from 150-220 mmHg (still per the INTERACT2 trial). Guidelines also recommend avoiding SBPs of <130 in these patients, as this could be harmful (per the ATACH2 trial). The main limitations of this study include the following:

1) Possibly under-powered given the original power calculation based on an event rate of 60%; the actual observed event rate was 38% thus could lead to a false negative study
2) Over 50% of patient population from Asian countries, possibly not a good predictor of American population
3) Higher proportion of primary + secondary treatment failure (achieving and sustaining target SBPs) in the intensive treatment group may have masked a potential, beneficial treatment effect
4) Vs. INTERACT2, all patients enrolled in ATACH-2 had SBPs >200 at study entry, maybe contributing to both higher treatment failure rates, and maybe also to higher adverse event rates in the intensive treatment group of ATACH-2
5) Higher rates of serious adverse events at 3 months in both intervention groups compared to the control group, which leads to a next large, randomized control study with less aggressive blood pressure control; could possibly show a benefit and further change the guidelines

Summary created by Kelly Knolton, DO

Additional Reading, if interested:

Anderson, C. et al., Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage (INTERACT2), NEJM (2013); 368 (25): 2355-2365.