

## Editorial

# Evolution of Blood Pressure Parameters in Spontaneous Intracerebral Hemorrhage

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## Editorial

Blood pressure parameters in the setting of an acute spontaneous Intracerebral Hemorrhage (ICH) has been a topic of controversy for decades. It had led to multiple randomized controlled trials and meta-analyses even after which we still do not have a good grasp on an ideal target blood pressure goal after an ICH. Advocates of targeting lower threshold systolic blood pressures (SBP less than 140 mm Hg) cite evidence pertaining to peri-hematoma expansion in the early hours after an ICH leading to worse clinical outcomes. Advocates of targeting a higher threshold systolic blood pressure (SBP less than 180 mm Hg) argue that aggressive lowering of blood pressure causes more complications relating to hypotension, decreased cerebral perfusion pressures and ischemia. Recent data from the ATACH 2 trial has not been able to give us the optimal answer most physicians were hoping for, causing us to rethink management strategies.

The first guidelines for the management of spontaneous intracerebral hemorrhage by the American Heart Association and American Stroke Association (AHA/ASA) were published in 1999 [1]. At the time there were very few prospective studies and no randomized controlled trials. A recommendation of keeping the systolic blood pressure less than 180 mm Hg and a mean arterial blood pressure less than 130 mm Hg was made with suggested antihypertensive agents including labetalol, esmolol, nitroprusside, hydralazine and enalapril (Level of Evidence V, Grade C). These guidelines were updated in 2007 at which time there was still little prospective evidence existing to support a specific blood pressure threshold [2]. Subjects for the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH 1) and Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT 1) randomized controlled trials were being enrolled at this time. A recommendation of targeting a systolic blood pressure of 160 mm Hg and a MAP of less than 110 mm Hg were made with the addition of nicardipine and nitroglycerin added to the list of suggested antihypertensive agents (Class IIb; Level of Evidence C).

The INTERACT 1 and ATACH 1 trials had been completed by the time the guidelines were revised in 2010 [3]. The INTERACT 1 trial [4], published in 2008, consisted of 403 patients that were randomized to an intensive treatment group (SBP less than 140 mm

Hg) and a standard guideline based group (SBP less than 180 mm Hg) who presented with a spontaneous ICH within 6 hours of onset. The primary outcome was proportional change in hematoma volume at 24 hours. The ATACH 1 trial [5], published in 2010, consisted of 80 patients that were subdivided into tiers; tier one SBP  $\geq$  170 mm Hg and  $<$  200 mm Hg, tier two (SBP  $\geq$  140 mm Hg and  $<$  170 mm Hg), and tier three (SBP  $\geq$  110 mm Hg and  $<$  140 mm Hg). Primary outcomes were treatment feasibility, neurologic deterioration within 24 hours and serious adverse events within 72 hours. Both INTERACT 1 and ATACH 1 showed that intensive blood pressure lowering was clinically feasible and potentially safe. The recommendations for target blood pressures remained unchanged in the 2010 AHA/ASA guidelines, however based on the results of INTERACT 1 and ATACH 1, a new recommendation was made and it was deemed safe to reduce the systolic blood pressure down to 140 mm Hg acutely in patients with spontaneous ICH (Class IIa; Level of Evidence B).

The latest AHA/ASA guidelines were published in 2015 [6]. By this time, the phase 3, INTERACT 2 trial had been completed. The INTERACT 2 trial [7], published in 2013, consisted of 2839 patients that were randomized to an intensive treatment group (SBP less than 140 mm Hg) and a standard group (SBP less than 180 mm Hg) who presented with a spontaneous ICH within 6 hours of onset. The primary outcome was death or major disability. The results of the INTERACT 2 trial were rather underwhelming; they found no difference in the rate of the primary outcome of death or severe disability between the two groups. However now we had Class 1, Level A evidence that intensive lowering of blood pressure to less than 140 mm Hg was safe and as effective as the standard 180 mm Hg. A further recommendation of aggressive treatment of SBP  $>$  220 was made in these guidelines. We still did not have a clear optimal blood pressure parameter by this time, but the trend had now become to generally opt for the lower end of the spectrum and aim for a SBP of 140 mm Hg.

The ATACH 2 trial [8], was published in 2016 and has managed to keep the controversy for optimal blood pressure after a spontaneous ICH ongoing. This trial consisted of 1000 patients that were randomized to an intensive treatment arm (SBP goal of 110 – 139) and a standard treatment arm (SBP goal of 140 – 179). The primary outcome was death or disability (modified Rankin scale score of 4 to 6) at 3 months after randomization. The trial found no difference in outcomes at three months between the two treatment groups. However it was noted that patients in the intensive treatment arm had a higher rate of renal complications compared to those in the standard treatment arm (9.0% vs. 4.0%,  $P = 0.002$ ).

After roughly 2 decades of scientific study and research, we are still contemplating the ideal blood pressure parameter after a spontaneous ICH. The fact that there were higher renal complications in the ATACH 2 trial with intensive treatment may lead to a change

in recommendations in the next AHA/ASA guidelines. A lower blood pressure parameter may not be as safe as was previously thought, however it is important to note that the overall mortality and severe disability did remain non-significant for both the treatment arms in ATACH 2. There was a higher rate of hematoma expansion in the standard arm compared to the intensive arm in both ATACH 2 and INTERACT 2, albeit it was non-significant. The adverse events relating to hypotension were also non-significant in both these trials.

Similar to the debatable preventative management of ischemic stroke with antiplatelet therapy (aspirin *vs.* clopidogrel *vs.* dipyridamole *vs.* ticagrelor), it seems that the blood pressure parameters in spontaneous ICH are just as elusive. Of course, the recommendations made by all these trials and studies can be limited and management should be directed on an individual case by case basis. However, for patients fitting the inclusion criteria of these trials, it still seems that it is up to the physicians' best judgment for optimal blood pressure parameters at this point in time.

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