

# Control of elevated blood pressure in acute intracerebral hemorrhage

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## Abstract

Intracerebral hemorrhage remains a challenging worldwide clinical problem with no proven treatments. In the acute phase of the illness, there has been some controversy regarding the appropriate management of elevated blood pressure. Recently published and ongoing clinical trials are beginning to shed some light on appropriate blood pressure management in acute intracerebral hemorrhage. This brief review focuses on these trials. In the next few years, it is hoped that clinical uncertainty regarding this issue will be obviated after completion of these trials.

## Introduction and context

Spontaneous intracerebral hemorrhage (ICH) occurs in an estimated 2 million people worldwide each year [1,2]. ICH has a 30-day mortality of 32-50% [3,4] and only 20% of survivors are functionally independent at 6 months [5]. No proven therapies exist for ICH. Elevated blood pressure at presentation is one of the factors that has been consistently associated with worse outcomes in ICH [6-8]. It remains unclear whether elevated blood pressure is an epiphenomenon of severe ICH or an independent risk factor for poor outcome. The rate of blood pressure decline in the first 24 hours after ICH has also been associated with poor outcomes [9]. Thus, there is clinical concern that markedly elevated blood pressure may contribute to early hematoma expansion, while overly aggressive blood pressure reduction may compromise cerebral blood flow to perihematomal regions of the brain.

Since phase III clinical trial data are lacking, recent guidelines do not have Class I recommendations for blood pressure reduction in ICH [3,10]. The European Stroke Initiative Guidelines recommend a target mean arterial pressure (MAP) of 125 mmHg in patients with a history of hypertension and 110 mmHg in those without a history of hypertension [10]. The American

Heart Association Guidelines recommend keeping MAP at less than 130 mmHg while maintaining cerebral perfusion pressure at more than 60 mmHg in patients with elevated intracranial pressure. A goal MAP of 110 mmHg is recommended for patients without elevated intracranial pressure [3]. This review focuses on recently published and ongoing clinical trials that may directly impact blood pressure management in acute ICH within the next few years.

## Recent advances

The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) is the largest study published to date on blood pressure management in acute ICH [11]. INTERACT enrolled ICH patients diagnosed by computed tomography within 6 hours of symptom onset with elevated systolic blood pressure (150-220 mmHg). A total of 404 patients were randomized to intensive blood pressure reduction (target systolic blood pressure 140 mmHg; n = 203) or standard guideline-based management of blood pressure (target systolic blood pressure 180 mmHg; n = 201). The primary endpoint was change in hematoma volume at 24 hours. Safety and clinical outcomes were assessed for up to 90 days.

From randomization to 1 hour, mean systolic blood pressure was 153 mmHg in the intensive group and 167 mmHg in the guideline group ( $P < 0.0001$ ); from 1 hour to 24 hours, it was 146 mmHg in the intensive group and 157 mmHg in the guideline group ( $P < 0.0001$ ). The relative risk of hematoma expansion was 36% lower (95% confidence interval 0-59%,  $P = 0.05$ ) in the intensive group than in the guideline group. Intensive blood pressure reduction did not alter the risks of adverse events or outcomes at 90 days. The authors concluded that early blood pressure reduction is clinically feasible, well tolerated, and may reduce hematoma expansion in ICH [11].

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial is another recently published study of blood pressure management in acute ICH [12]. The objective of ATACH was to determine the safety and feasibility of three levels of systolic blood pressure reduction within 6 hours of symptom onset in ICH patients with initial systolic blood pressure greater than or equal to 170 mmHg. Intravenous nicardipine was infused for a target systolic blood pressure of 170-200 mmHg in the first cohort of patients ( $n = 18$ ), 140-170 mmHg in the second cohort ( $n = 20$ ) and 110-140 mmHg in the third cohort ( $n = 22$ ). Primary outcomes were feasibility of treatment, neurological deterioration within 24 hours, and serious adverse events within 72 hours. No significant adverse events above the pre-specified safety stopping points were observed [12].

### Implications for clinical practice

The INTERACT study provides the best available evidence to date for aggressive early blood pressure reduction in ICH. Overall, INTERACT suggests that for patients similar in clinical characteristics to those enrolled in the study, reducing systolic blood pressure to 140 mmHg is safe and may reduce risk of hematoma expansion. The Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) is the phase III follow-up study to INTERACT. An estimated 2800 patients will be enrolled by the planned December 2011 study completion date [13]. This study may provide clinicians with an answer regarding an age-old clinical question in the management of acute ICH. The ATACH investigators are also proceeding with a phase III follow-up study, although recruitment has not begun for that study. It should be noted that INTERACT excluded patients with the severest injury (Glasgow Coma Score [GCS] 3-5), and enrolled patients had mean ICH volumes of 12 mL (guideline) and 14 mL (intensive). INTERACT was also not powered to detect clinical outcomes. ATACH included only patients with a GCS of greater than 8 and hematoma volume of less than

60 mL. Therefore, the findings in these trials may not be applicable to all ICH patients.

In summary, while many clinical questions remain regarding the acute management of ICH, recent and ongoing trials are shedding light on the management of blood pressure in acute ICH. It is anticipated that Class I recommendations for blood pressure management in ICH will be generated by ongoing trials.

### Abbreviations

ATACH, Antihypertensive Treatment of Acute Cerebral Hemorrhage; GCS, Glasgow Coma Score; ICH, intracerebral hemorrhage; INTERACT, Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial; MAP, mean arterial pressure.

### Competing interests

OA is on the speakers' bureau for EKR Therapeutics.

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