

**Degree and timing of intensive blood pressure lowering on hematoma growth in
intracerebral hemorrhage: INTERACT2 results**

Cheryl Carcel MD,^{1,2,3} Xia Wang MMed,^{1,2} Shoichiro Sato MD PhD,^{1,4} Christian Stapf MD,⁵
Else Charlotte Sandset MD PhD,^{1,6} Candice Delcourt MD,^{1,2,3} Hisatomi Arima MD,^{1,7}
Thompson Robinson MD,⁸ Pablo Lavados MD MPH,⁹ John Chalmers MD PhD,^{1,2,3} and
Craig S Anderson MD PhD,^{1,2,3} on behalf of the INTERACT 2 Investigators*

¹The George Institute for Global Health, Sydney, Australia

² Sydney Medical School, The University of Sydney, Sydney, Australia

³ Royal Prince Alfred Hospital, Sydney, Australia

⁴ Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center,
Suita, Osaka, Japan

⁵ Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM),
Département de Neurosciences, Université de Montréal, Montréal, QC, Canada

⁶ Department of Neurology, Oslo University Hospital, Oslo, Norway

⁷ Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka
University, Fukuoka, Japan

⁸ Department of Cardiovascular Sciences and NIHR Biomedical Research Unit in
Cardiovascular Disease, University of Leicester, Leicester, UK

⁹ Unidad de Neurología vascular, Servicio de Neurología, Departamento de Medicina, Clínica
Alemana; Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile

*See Online Supplement.

Author for correspondence:

Professor Craig S Anderson
The George Institute for Global Health
PO Box M201, Missenden Road, NSW 2050, AUSTRALIA
T: +61-2-9993-4500; F: +61-2-9993-4502
Email: canderson@georgeinstitute.org.au

Tables: 0 **Figures:** 3 **Supplemental Table:** 6

Word Count: 1999; abstract 185, Title 16

Key Words: blood pressure control, intracerebral hemorrhage, hematoma growth

Abstract

Background and Purpose: Degree and timing of blood pressure (BP) lowering treatment in relation to hematoma growth were investigated in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).

Methods: INTERACT2 was an international clinical trial of intensive (target systolic BP [SBP] <140 mmHg) versus guideline-recommended (SBP <180 mmHg) BP lowering in 2839 patients within 6 hours of spontaneous intracerebral hemorrhage (ICH) and elevated SBP (150-220 mmHg), in whom 964 had repeat cranial CT at 24 hours. Analysis of covariance models assessed categories of SBP reduction and time to target SBP on 24 hour hematoma growth.

Results: Greater SBP reduction was associated with reduced hematoma growth (13.3, 5.0, and 3.0 mL for <10, 10-20, and $\geq$ 20 mmHg, respectively; *P* trend <0.001). In the intensive treatment group (n=491), the least mean hematoma growth was in patients who achieved target SBP <1 hour (2.6 mL) versus to those in target at 1-6 (4.7 mL) and >6 hours (5.4 mL). The smallest mean absolute hematoma growth (2.0 mL) was in those achieving target SBP 5-8 times versus 3-4 (3.1 mL) and 0-2 (5.2 mL) times.

Conclusions: Intensive BP lowering with greater SBP reduction, achieved quickly and maintained consistently, appears to provide protection against hematoma growth over 24 hours.

Clinical Trial Registration Information: URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00716079.

Elevated systolic blood pressure (SBP) is common after acute spontaneous intracerebral hemorrhage (ICH). Attenuation of hematoma growth is the most plausible mechanism for any beneficial effect of intensive BP lowering, but this was not confirmed in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT),^{1,2} leaving uncertainty over any heterogeneity of the treatment by timing and degree of BP lowering. We assessed the effects of degree and consistency of BP lowering on hematoma growth in INTERACT2 participants.

Materials and Methods

INTERACT2 was an international, multicenter, open, blinded endpoint, randomized controlled trial, as described elsewhere.² In brief, 2839 spontaneous ICH patients (<6 hours of onset) and elevated SBP (150-220 mmHg) were randomly assigned to intensive (target SBP <140 mmHg within 1 hour) or guideline-recommended (target SBP <180 mmHg) BP lowering.³ The study is registered with ClinicalTrials.gov, number NCT00716079.

Demographic and clinical characteristics were recorded, including SBP every 15 minutes in the first hour post-randomization, and 6 hourly until 24 hours; the number of readings <140 mmHg were noted. In a substudy, baseline and 24±3 hours CT brain scans were performed and analysed centrally.

Analysis of covariance models assessed associations of SBP reduction on 24 hour hematoma growth.

Results

Among 2839 participants of the INTERACT2 study, 964 (40%) were included in the CT substudy. Compared to patients without a follow-up CT, they were more often on anticoagulation or antiplatelet therapy, had higher National Institute of Health Stroke Scale (NIHSS) scores, and shorter time from symptoms onset to randomization at baseline

(Supplemental Table I). However, the two groups were similar with regard to baseline SBP, ICH volume and location, and allocation to intensive BP lowering treatment. Supplemental Table II shows the patient characteristics by degree of SBP reduction: those with the smallest Δ SBP (<10 mmHg) were older and those with greatest Δ SBP (≥ 20 mmHg) were more often female, with a history of ICH, higher baseline BP, and more often included to intensive BP lowering group (420 [59%]; $P < 0.001$). A greater degree of SBP reduction was associated with less hematoma growth: Δ SBP_{1-24H} at <10 , 10-20, and ≥ 20 mmHg reduction were associated with hematoma growth (mL) of 13.3 (9.0-17.5), 5.0 (1.6-8.4), and 3.0 (0.5-5.4), respectively (P trend < 0.001). A similar trend was observed for the same degrees of Δ SBP_{15-60M} but this was not statistically significant (Figure 1). There was no significant difference in the relation of SBP reduction and hematoma growth in patients with baseline SBP levels above or below 180 mmHg for any of Δ SBP_{1-24H} or Δ SBP_{15-60M} (P homogeneity 0.133 and 0.999, respectively; Supplemental Table III). The results were similar in a sensitivity analysis stratified for trial treatment without any heterogeneity (Supplemental Table IV).

Supplemental Table V shows the participants' baseline characteristics, grouped by time from symptom onset to randomization, were broadly similar between groups, except more patients allocated intensive treatment were on anticoagulation in at 3-4.5 hours. There was no association of intensive treatment with hematoma growth in these subgroups by time to treatment in crude or adjusted models (P trend 0.691 and 0.702, respectively; Figure 2 and Supplemental Table VI).

Of 491 patients randomized to intensive BP lowering, the SBP target was achieved in 242 (49%) and 125 (25%) <1 and 1-6 hours, respectively; 124 (25%) did not achieve target <6 hours. The least hematoma growth (mL) was in those achieving target SBP early (≤ 1 hour, 2.6; 95% CI 0.1-5.2) compared to later periods 1-6 hour (4.7; 95% CI 1.8-7.5) and >6 hours (5.4; 95% CI 2.4-8.3) (P trend =0.029) (Figure 3a).

Hematoma growth was 5.2 (95% CI 2.7-1.8), 3.1 (0.3-6.0) and 0.4 (-1.1-5.1), respectively, according to 0-2, 3-4, and 5-8 times to target SBP (*P* trend 0.018; Figure 3b)

Discussion

These analyses of INTERACT2 show that a greater fall in SBP was associated with less hematoma growth, irrespective of whether patients received intensive or guideline-based BP lowering treatment. Patients with the least hematoma growth were those who achieved target SBP of <140 mmHg within the first hour and in those who sustained this target throughout the first 24 hours. These data are relevant for patient management, where early, intensive and consistent lowering of SBP appears to offer the greatest potential to improve outcome in ICH, including better functional recovery in those with smooth BP control.⁴ These results also support recent guideline recommendations for more intensive BP management in ICH.

Outcome in ICH depends on the size and growth of the underlying hematoma,^{5,6} which are related to mechanisms of intravascular hydrostatic pressure, local tissue pressure and mechanical injury to brain tissue and blood vessels, cerebral blood flow, plasma protein induction and inflammation.^{7,8} Other important factors that may influence hematoma growth include timing of imaging and baseline hematoma volume. Greater SBP reduction and shorter time to target SBP being associated with the least hematoma growth could relate to intensive BP lowering producing larger and faster decreases in intravascular hydrostatic pressure secondary arteriolar rupture. This analyses could not confirm the other mechanisms stated above. Our earlier analyses have shown a linear relationship between achieved SBP and disability in both the hyperacute (1–24 hours) and acute (2–7 days) phases,⁹ and similar findings have been reported in other populations.^{10,11}

While our study included a large and heterogeneous population with rigorous prospective and systematic evaluations of both BP and hematoma growth, the analyses are limited by selection

- 1 bias, inability to establish a causal relationship with treatment and in being post-hoc and not
- 2 pre-specified.
- 3 In conclusion, these analyses suggest potential beneficial effects of early and controlled BP
- 4 lowering treatment through attenuation of hematoma growth.
- 5

Acknowledgements

C.C., X.W., S.S., C.S., C.S.A. contributed to the concept of the study. S.S. and C.D. undertook the CT scan analysis. X.W. contributed to statistical analysis. All authors participated in interpreting results, drafting and approval of the final manuscript, and take responsibility for the content of this article.

Sources of Funding

The INTERACT2 was supported by Program (571281) and Project Grants (512402 and 1004170) from the National Health and Medical Research Council (NHMRC) of Australia.

Conflicts of Interest

C.S.A. is employed by The George Institute for Global Health (TGI), holds a Senior Principal Research Fellowship, NHMRC grants, reports membership of Advisory Boards for Astra Zeneca and Medtronic, receives travel reimbursement and honorarium from Takeda China. JC has received research grants from Servier, administered through the University of Sydney, as principal investigator for the ADVANCE trial and ADVANCE-ON post-trial study, and received honoraria from Servier for speaking about those studies at scientific meetings. PL has received a research grant from TGI.

References

1. Arima H, Huang Y, Wang JG, Heeley E, Delcourt C, Parsons M, et al. Earlier blood pressure-lowering and greater attenuation of hematoma growth in acute intracerebral hemorrhage: INTERACT pilot phase. *Stroke* 2012;43:2236-2238
2. Anderson CS, Chalmers J, Stapf C. Blood-pressure lowering in acute intracerebral hemorrhage. *New Engl J Med* 2013;369:1274-1275
3. Morgenstern LB, Hemphill JC, 3rd, Anderson C, Becker K, Broderick JP, Connolly ES, Jr., et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2010;41:2108-2129
4. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: A post-hoc analysis of interact2, a randomised controlled trial. *Lancet Neurol* 2014;13:364-373
5. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J Neuropath Exp Neurol* 1971;30:536-550
6. Schlunk F, Greenberg SM. The pathophysiology of intracerebral hemorrhage formation and expansion. *Translational Stroke Res* 2015;6:257-263
7. Wartenberg KE, Mayer SA. Reducing the risk of ICH enlargement. *J Neurol Sci* 2007;261:99-107
8. Brouwers HB, Greenberg SM. Hematoma expansion following acute intracerebral hemorrhage. *Cerebrovascular Dis* 2013;35:195-201
9. Arima H, Heeley E, Delcourt C, Hirakawa Y, Wang X, Woodward M, et al. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT. *Neurology* 2015;84:464-471

- 1 10. Sakamoto Y, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, et al. Systolic
2 blood pressure after intravenous antihypertensive treatment and clinical outcomes in
3 hyperacute intracerebral hemorrhage: The stroke acute management with urgent risk-
4 factor assessment and improvement-intracerebral hemorrhage study (SAMURAI-
5 ICH). *Stroke* 2013;44:1846-1851
- 6 11. Itabashi R, Toyoda K, Yasaka M, Kuwashiro T, Nakagaki H, Miyashita F, et al. The
7 impact of hyperacute blood pressure lowering on the early clinical outcome following
8 intracerebral hemorrhage. *J Hypertension* 2008;26:2016-2021

9

1 **Figure Legends**

2 **Figure 1. The effect of BP reduction on hematoma growth by time and absolute**
3 **hematoma growth stratified by baseline SBP**

4 *Adjusted by age, sex, Chinese region of recruitment, prior ICH, hematoma location, baseline
5 hematoma volume, baseline SBP, time from ICH onset - baseline CT scan, randomized
6 treatment

7 **Figure 2. Treatment effect on hematoma growth by time**

8 *Time = Date and time of ICH onset - Date and time of randomization

9 ** Adjusted by baseline hematoma volume and hematoma location

10 **Figure 3a. The effect of time to treatment target SBP<140 on hematoma growth among**
11 **patients in the intensive treatment group**

12 *Adjusted by age, sex, Chinese region, prior ICH, hematoma location, baseline hematoma
13 volume, baseline SBP, time from ICH onset - baseline CT scan

14 **Figure 3b. The effect of the number of times SBP achieved treatment target SBP within**
15 **24 hours on hematoma growth among patients in the intensive treatment group**

16 *Adjusted by age, sex, Chinese region, prior ICH, hematoma location, baseline hematoma
17 volume, baseline SBP, time from ICH onset - baseline CT scan

18