

Interpretation and Implementation of Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT II)

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The second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT II)¹ randomized 2,839 patients with intracerebral hemorrhage (ICH) within 6 h of symptom onset to intensive systolic blood pressure (SBP) reduction, with a target of <140 mm Hg within 1 h, or guideline-recommended SBP reduction, with a target of <180 mm Hg using a variety of antihypertensive medications. The primary outcome was death or major disability defined by a score of 3–6 on the modified Rankin scale (mRS) at 3 months post-randomization. The proportion of subjects with death or major disability was 719 of 1,382 (52%) in the group randomized to receive intensive BP reduction compared with 785 of 1,412 (55.6%) in the group randomized to receive guideline-recommended treatment (odds ratio [OR] with intensive treatment, 0.87; 95% confidence interval [CI], 0.75–1.01; $p = 0.06$). In the secondary analysis, mRS grades were analyzed as an ordinal scale, which detected significantly lower mRS scores in subjects randomized to intensive SBP reduction (common OR, 0.87; 95% CI, 0.77–1.00; $p = 0.04$).

After the publication, the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II investigators prepared a report for its Data and Safety Monitoring Board to determine implications of INTERACT II on current practice and on ATACH II trial design and conduct (Table 1).

Patient selection

In general, INTERACT II used broad criteria for defining the target population which resulted in relatively fast

patient enrollment but increased the variability in patient population and response to treatment. Certain criteria that raised specific concerns are also discussed below:

Inclusion of patients with only moderate hypertension at baseline

Patients with at least two SBP measurements of ≥ 150 and ≤ 220 mm Hg recorded at least 2 min apart were eligible. The relationship between acute hypertensive response and hematoma enlargement² and mortality³ is most evident in patients with initial SBP > 200 mm Hg. In one study, the mortality rate was 44% in patients with ICH and initial SBP > 196 mm Hg group compared with 18% in those with ≤ 196 mm Hg.³ SBP ≥ 200 mm Hg was seen in 46% and 26% of patients with or without hematoma enlargement in another study.² SBP on admission of ≥ 200 mm Hg predisposed subjects to enlargement in multivariate analysis. The INTERACT I trial⁴ reported that initial SBP ≥ 181 mm Hg was observed in 47% of the 404 patients recruited and early intensive BP reduction resulted in the most prominent reduction in hematoma expansion in this group of ICH patients.

Therefore, inclusion of patients with relatively low SBP may have predispose the overall study sample to have low rates of hematoma enlargement and mortality (ceiling effect) making it difficult to discern the beneficial effect of intensive SBP reduction. The mean SBP was 179 ± 17 mm Hg among subjects recruited in the INTERACT II. A total of 1,488 of 2,839 (52%) subjects were randomized with initial SBP < 180 mm Hg.

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Table 1. Differences between INTERACT II and ATACH II with regard to addressing common issues in trials involving patients with ICH

Trial design issues	INTERACT II design	ATACH II design
Frequent transient or moderate elevation in SBP in subjects with ICH	Inclusion of patients with initial SBP of 150 mm Hg or greater	Inclusion of patients with initial SBP of 180 mm Hg or greater; exclusion of patients with spontaneous reduction in SBP prior to randomization
Short time window for preventing hematoma expansion	Inclusion and treatment of patients with symptom onset of 6 h or less	Inclusion and treatment of patients with symptom onset of 4.5 h or less
Very high likelihood of death within 24 h in patients with high severity	Investigator judgment	Exclusion of patients with parenchymal hematoma volume <60 cc, large amount of IVH, or pontine ICHs
Surgical evacuation of ICH may confound the effect of trial intervention	Investigator judgment	Exclusion of cerebellar hemorrhages and those in whom surgery is indicated at time of randomization
High rate of hematoma expansion associated with anticoagulant related ICHs	Included with INR correction based on investigator discretion	Included but require INR correction to value <1.5 prior to randomization using prothrombin complex concentrate
Imbalance between treatment groups for known factors that influence prognosis or treatment responsiveness	Large sample size; sensitivity analyses after adjusting for potential confounders	Post-randomization adjusted analyses (adjusted for GCS score, IVH, and hematoma volume)
Heterogeneity of IV antihypertensive treatment can reduce effectiveness of SBP lowering and effect ICP	Several BP-lowering protocols using urapidil, labetalol, hydralazine, metoprolol, and nicardipine	Single agent—IV nicardipine, in all patients
Effect of intensive SBP reduction post-24 h independent of hematoma expansion	A SBP level of <140 mm maintained for the next 7 days in intensive SBP reduction group	The SBP goals after first 24 h same in both treatment groups
Time to achieve therapeutic goals important for benefit	33% reaching therapeutic goals within 1 h in those allocated to intensive SBP reduction	ATACH I suggested that 90% of subjects can reach therapeutic goals within 2 h. Interim monitoring in ATACH II demonstrates similar observation
Heterogeneity in intensity of medical care in subjects between sites can affect the rates of death and disability	Not addressed	Review of patient care profile at each site by IOC
Definition of primary outcome easy to interpret with direct clinical relevance	A dichotomous outcome mRS score of 0–2 versus 3–6	A dichotomous outcome mRS score of 0–3 versus 4–6
Ascertainment of safety or adverse events with determination of causal effect of trial intervention	Investigator judgment	Review by IOC regarding relationship to treatment intervention and intensity of medical care
Large magnitude of benefit of trial intervention required to change clinical practices	Absolute risk reduction anticipated $\geq 7\%$; actual 3.6%	Absolute risk reduction anticipated $\geq 10\%$

ICH: intracerebral hemorrhage, SBP: systolic blood pressure, INR: international normalized ratio, IVH: intraventricular hemorrhage, IOC: independent oversight committee, mRS: modified Rankin scale.

Only 1,873 of 2,839 (66%) subjects received any IV antihypertensive medication; 10% and 57% of subjects randomized to intensive or standard SBP reductions, respectively, did not receive any IV antihypertensive medication. Therefore, in almost a third of patients, the SBP profile was a consequence of spontaneous SBP change and not of actual pharmacological SBP reduction. The risk benefit profile associated with spontaneous reduction of SBP may be due to different pharmacological reduction in SBP.

Inclusion of patients with symptom onset ≥ 4 h

INTERACT II recruited subjects who are in whom randomly assigned BP-lowering regimen could be commenced within 6 h of symptom onset. The first 4 h represents the time interval for maximum rates of hematoma expansion. As the hypothesized mechanism of improved outcome after SBP reduction is attenuation of hematoma expansion, inclusion of patients beyond 4 h may dilute any treatment effect, as many of these patients will have already experienced hematoma expansion or are at very low risk for growth.⁵ An estimated 1,173 of 2,839 (41%) were randomized ≥ 4 h after symptom onset. The median time from symptom onset to start

of treatment was 4 h (interquartile range [IQR] 2.9–5.1 h) and 4.5 h (IQR 3.0–7.0 h) in subjects randomized to intensive SBP and standard SBP reductions, respectively. The beneficial effect of rFVIIa (recombinant factor VIIa) or intensive SBP reduction in ameliorating hematoma expansion was at maximum in patients recruited within 2.5 h⁶ or within 3.1 h⁴ in Factor Seven for Acute Hemorrhagic Stroke Trial (FAST) and INTERACT I trials, respectively. Among the subjects recruited in the ATACH I trial,⁷ SBP reduction of ≥ 60 mm Hg prominently reduced rates of hematoma expansion, relative edema expansion, and death and disability in ICH subjects treated within 3.1 h and those treated within 4.5 h.⁸ However, such reduction was not observed in subjects treated within the 6-h time window.

Lack of inclusion criteria based on hematoma volume

Patients with a very high likelihood of death within the next 24 h on the basis of clinical and/or radiological criteria (e.g., massive hematoma with a mid-line shift of the hemisphere or deep coma on presentation, defined by Glasgow Coma Scale [GCS] score of 3–5) were excluded from INTERACT II. The median hematoma

volume in intensive SBP-lowering group and standard SBP-lowering group was similar (11 ml with IQR of 6–19 ml versus 11 ml with IQR 6–20 ml). An estimated 1,980 of 2,839 (70%) patients had a hematoma volume of <15 ml. According to the median hematoma volumes observed in INTRERACT II, patients with large hematoma volume were not included in the trial based on investigator judgment. The FAST subgroup analysis⁶ suggested that if patients aged <70 years, with baseline hematoma <60 ml and baseline IVH volume <5 ml, and with time to onset \leq 2.5 h were selected, the OR for poor outcome at 90 days decreased to 0.28 (95% CI 0.08–1.06) with rFVIIa treatment. To avoid variation between investigators identifying patients who have a low chance of successful outcome, ATACH I and II exclude patients with large hematomas (greater than >60 cc).

Trial intervention

The INTERACT II and ATACH II trials differ with respect to intervention and overall patient management.⁹

Heterogeneity of IV antihypertensive treatment

In INTERACT II, at each site, a standardized, incremental BP-lowering protocol was established using available intravenous medications (e.g., urapidil, labetalol, hydralazine, metoprolol, and nicardipine) for the intensive SBP reduction group. The treatment was to be titrated in a monitored facility. Co-administration of oral antihypertensive agent(s) was to be commenced as soon as practical. The agents included alpha-adrenergic antagonist [urapidil ($n = 645$)], calcium-channel blocker [nicardipine or nimodipine ($n = 349$)], combined alpha- and beta-blocker [labetalol ($n = 285$) and nitroglycerin ($n = 268$)], diuretics [furosemide ($n = 268$), nitroprusside ($n = 197$), hydralazine ($n = 132$), and others ($n = 129$)]. Treatment modalities for BP lowering in the standard SBP reduction group were unlimited at the discretion of the responsible physicians until the recommended target SBP of <180 mm Hg was achieved. The first line treatment in standard SBP reduction group was oral (including nasogastric if required) and/or transdermal routes. In the event of failure of first line medication, IV treatment was started to reach target SBP of <180 mm Hg.

The variation in mode of administration (IV bolus versus infusion) of antihypertensive agents can result in high variability in BP¹⁰ and may predispose to hematoma expansion.¹¹ IV nicardipine-treated ICH and SAH patients had less BP variability, and fewer dosage adjustments compared with IV labetalol or IV nitroprusside-treated patients in previous studies.^{12,13} Hydralazine, nitroglycerin, and nitroprusside were used in 460 of

1,399 (33%) subjects and 137 of 1,430 (10%) in subjects randomized to intensive and standard SBP reduction in INTERACT II, respectively. More patients in the intensive-treatment group than in the standard-treatment group received two or more IV agents to lower their blood pressure (26.6% versus 8.1%, $p < 0.001$). A review of the agents¹⁴ suggested that IV hydralazine and nitroprusside can increase both regional cerebral blood flow (rCBF) and intracranial pressure (ICP).^{15–17} Nitroprusside, nitroglycerine, and nicardipine can increase rCBF without any clear increase in ICP.¹⁴ It has also been shown that labetalol, hydralazine, and enalaprilat do not affect rCBF in acute ICH patients.¹⁸ It remains unclear whether cerebrovascular effects of various antihypertensive agents could have impact on clinical outcomes because of the diverse therapeutic approaches in the INTRERACT II. In one observational study, after adjustment for baseline risk of mortality, the risk of in-hospital mortality was higher among ICH patients treated with nitroprusside compared with nicardipine (OR 1.7, 95% CI 1.3–2.2).¹⁹

Intensive SBP reduction post-24 hours after randomization

In INTERACT II, for participants assigned to receive intensive treatment, the goal was to achieve a SBP level of <140 mm Hg for the next 7 days. Therefore, the SBP levels were much lower in subjects randomized to intensive SBP reduction (compared with standard SBP reduction) in the post-24 h and within 1-week period. There is a possibility that reduction in death and disability observed with intensive SBP reduction may be related to SBP reduction after 24 h. A reduction of vascular events and deaths during the next 12 months was seen in The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study with SBP reduction in the post-24 h and within 1-week period.²⁰ However, the Scandinavian Candesartan Acute Stroke Trial (SCAST), that enrolled 2,029 patients with acute ischemic (85%) or hemorrhagic (14%) stroke and SBP \geq 140 mm Hg within 30 h of onset, did not confirm a therapeutic benefit of post-24-h intensive SBP reduction.²¹

Effectiveness of intervention in achieving target BP goals

For patients allocated to the intensive group (target SBP of <140 mm Hg within 1 h of randomization), mean SBP at baseline was 150 mm Hg [with 462 patients (33.4%) achieving the target SBP of <140 mm Hg] as compared with 164 mm Hg in the standard-treatment group (a difference of 14 mm Hg, $p < 0.001$). It is therefore possible that failure to reach the therapeutic target

resulted in suboptimal benefit. In INTERACT I, SBP goals were achieved in 42% and 66% of the subjects at 1 and 6 h after treatment initiation, respectively.²² On-treatment SBP levels achievement in the first 24 h were associated with both absolute and proportional hematoma growth. Maximum reduction in hematoma growth occurred in the one third of participants with the lowest on-treatment SBP levels (median: 135 mm Hg).²² In ATACH I, the SBP goals were achieved in 90% of the patients by 2 h.²³ Actual lowering of SBP and not just the initiation of treatment goal specified was associated with therapeutic benefit.⁷ Comparing patients having ≤ 54 mm Hg and >54 mm Hg SBP reduction at 2 h, frequencies were 21% versus 31% for hematoma expansion, and 35% versus 48% for death and disability at 3 months. Severe hypotension occurred in 0.5%, acute coronary event in 0.4%, and ischemic or undifferentiated stroke in 0.6% of subjects randomized to intensive SBP reduction in INTERACT II. The rates of these events could be higher if SBP goals of <140 mm Hg were consistently achieved in intensive SBP reduction group.

Clinical management of study subjects

Overall intensity of care in INTRERACT II

In a total of 2,839 participants enrolled at 144 hospitals in 21 countries in INTERACT II, variance in intensity of care can be considerable. Because of the lesser requirements of monitoring, the rate of admission to intensive care unit was 38% (1,061 of 2,779 subjects). The rate of intubation was 7% (189 of 2,779 subjects) in INTERACT II which is much lower than the 22% rate observed in patients with ICH admitted in the United States.²⁴ Approximately 30% supratentorial and all infratentorial ICH patients require intubation.²⁵ Early intubation and mechanical ventilation initiated within 30 min of detection time of GCS score <8 documentation or other indications is considered a quality parameter and adequately performed in 80% of the patients with ICH in one study.²⁶

The rate of prophylactic treatment for deep vein thrombosis (DVT) was 610 of 2,779 subjects (22%) in INTERACT II. In two audits conducted at one of the United States hospital, DVT prophylaxis was achieved in 52%–68% of the patients with ICH.^{26,27} Timely administration of prophylactic treatment for DVT has been considered a quality indicator due to the relatively high prevalence of DVT among patients with ICH.^{28–30} The first 48 h after symptom onset is considered the appropriate time to initiate prophylaxis based on consis-

tent safety and effectiveness data provided by clinical trials in ICH patients.^{28–30}

Difference in intensity of care between the two treatment groups

The median time from the onset of the ICH to the initiation of IV treatment was shorter in the intensive-SBP reduction group than in the standard-SBP reduction group (4 h [IQR, 2.9–5.1] versus 4.5 h [IQR, 3.0–7.0], $p < 0.001$); the median time from randomization to initiation of treatment was also shorter in the intensive-SBP reduction group (6 min versus 19 min).

Hemostatic therapy including the use of fresh-frozen plasma, vitamin K, and rFVIIa was used in 4.1% and 2.9% of patients randomized to intensive and standard SBP reduction ($p = 0.07$), respectively. Huttner *et al*³¹ reported that early INR reversal (<2 h) reduced proportion of patients with hematoma growth (absolute reduction of 16%). Therefore, INR reversal (<1.4) within 2 h of first elevated INR was recommended as a quality parameter in patients with ICH.²⁷ The possibility that more rapid reversal of INR was undertaken in intensive SBP reduction group cannot be excluded.

A decision to withdraw active treatment and care was made more frequently among participants in the intensive-SBP reduction group than in the standard-treatment group [75 participants (5.4%) versus 46 participants (3.3%), $p = 0.005$]. A differential rates of withdrawal of care could influence the rate of risk-adjusted mortality in treatment groups independent of age, GCS, ICH volume, and IVH.³²

Statistical considerations

The INTRERACT II used a trial sample size of 2,800 participants, to provide 90% power to detect a 14% relative reduction (or an absolute difference of 7%) in the primary outcome, from 50% in the standard-SBP reduction group to 43% in the intensive-SBP reduction group. The definition of “clinically meaningful” difference can vary considerably. Trials evaluating therapies with higher associated risk such as rFVIIa have used a threshold of 15% or greater absolute reduction in death or disability to define clinical benefit.³³ Setting the bar very low may achieve more “positive” outcomes of clinical trials at the expense of very large sample sizes; however, the approval of mediocre therapies may hinder the development of truly effective treatments. In the ATACH II trial, a 10% or greater difference in proportion of death and disability at 3 months is being evaluated between intensive SBP reduction and standard BP reduction among patients with ICH. An absolute reduc-

tion of 5% would translate into a minor reduction of approximately 781 deaths from annualized mortality of 15,625 ICH deaths.²⁴

Another issue is whether an absolute difference of 10% or greater (instead of 7% as sought in INTERACT II) in the primary event can be reasonably expected. The 14% relative risk reduction in INTERACT II was based on the pilot phase findings where a 10–14 mm Hg difference in SBP between treatment groups resulted in 1.7 ml absolute difference in hematoma growth. Thus, a difference in hematoma growth of 2 ml (0–6 h) from BP lowering should result in at least a 14% relative (7% absolute) relative reduction in poor outcome from ICH. To observe an absolute reduction of 10% in the rate of poor outcomes, a mean difference of greater than 3 ml may be required between the intensive and standard BP treatment groups which was seen in INTERACT I if analysis confined to only patients recruited within 4 h of symptom onset (3.4 ml) similar to ATACH II.

Summary

INTRERACT II as a definitive trial

The writing group considered the results as hypothesis generating but not compelling to change standard of care based on the following observations:

1. Statistical significance was not achieved in primary analysis and the impact was further reduced after adjustment for confounders such as NIHSS score, hematoma volume, and IVH. Statistical significance was achieved in secondary analysis, but not after adjustment for confounders such as National Institutes of Health Stroke Scale (NIHSS) score, hematoma volume, and IVH.
2. Intensive SBP reduction as applied in INTERACT II resulted in benefit of small magnitude with no effect on hematoma expansion. Similarly, the benefit was of small magnitude (absolute benefit of 3.6%) on rate of severe disability and death.
3. Antihypertensive treatment in the intensive SBP reduction group did not achieve the target SBP value of less than 140 mm Hg in a large proportion of patients. The risk benefit profile maybe different with greater magnitude of SBP reduction if implemented into clinical practice.
4. There is discordance between the proposed and observed therapeutic benefit of intensive SBP reduction in INTERACT II. The lack of early

reduction in hematoma expansion (at 24 h) and death and disability (both at 7 days or 1 month) in subjects randomized to intensive SBP reduction suggests possible therapeutic effect of variable impact on other differences in treatment groups such as post-24-h SBP reduction.

5. The safety or benefit of intensive SBP reduction was not tested in patients with large volumes hematomas; a group most likely at risk for global cerebral perfusion compromise due to high ICP. The lack of a clear cut off for hematoma size in INTRERACT II prevents implementation of a reproducible method to exclude such patients in clinical practice.
6. Without a more focused therapeutic measure, such as the one adopted by ATACH II in which only IV nicardioie is the antihypertensive therapy, it is difficult to define the most optimal antihypertensive therapy based on INTERACT II findings.

Implications for ATACH II trial

The ATACH II writing group identified certain aspects of trial design and conduct to be implemented or monitored in the ATACH II trial. These are summarized below:

1. Efforts are undertaken to ensure that intensive SBP reduction meets the SBP goals (<140 mm Hg) effectively and consistently. A mere difference from standard SBP reduction may not adequately test the primary hypothesis or provide clinically meaningful SBP reduction treatment goals.
2. The time to initiate treatment and post-24-h BP management must be monitored to avoid differences secondary to the unblinded nature of the trial. (There is a probable weakness here because the BP management post-24 h is not standardized. Without a more standardized protocol to regulate BP, post-24-h BM management may affect the outcomes because diverse modes are applied in the post-24-h to 3-month trial period leading to treatment variables that may dilute the effect of intensive BP management in the 24-h period.)
3. Since the release of INTERACT II results, no modification in inclusion/exclusion criteria was considered necessary as no heterogeneity of the treatment effect on the primary outcome in eight prespecified groups in INTERACT II was seen.

4. The ATACH II trial should maintain a low proportion of untreated patients to adequately test “pharmacological SBP reduction” as an intervention in patients with ICH.

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