

RESEARCH PAPER

Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: clinical outcomes and haemorrhage expansion. Systematic review and meta-analysis of randomised trials

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ABSTRACT

Introduction It is unclear whether intensive lowering of blood pressure (BP) at the acute phase of intracerebral haemorrhage (ICH) is beneficial. We performed a meta-analysis of randomised controlled trials (RCTs) to assess whether intensive BP lowering in patients with acute ICH is safe and effective in improving clinical outcomes.

Methods We searched PubMed, EMBASE and the Cochrane databases for relevant RCTs and calculated pooled OR for 3-month mortality (safety outcome) and 3-month death or dependency (modified Rankin Scale (mRS) ≥ 3 ; efficacy outcome), in patients with acute ICH randomised to either intensive BP-lowering or standard BP-lowering treatment protocols. We also investigated the association between treatment arm and ICH expansion at 24 hours. Random effects models with DerSimonian-Laird weights were used.

Results Five eligible studies including 4360 patients with acute ICH were pooled in meta-analysis. The risk of 3-month mortality was similar between patients randomised to intensive BP-lowering treatment and standard BP-lowering treatment (OR: 0.99; 95% CI: 0.82 to 1.20, $p=0.909$). Intensive BP-lowering treatment showed a (non-significant) trend for an association with lower 3-month death or dependency risk compared with standard treatment (OR: 0.91; 95% CI: 0.80 to 1.02), $p=0.106$). Intensive BP reduction was associated with a trend for lower risk of significant ICH expansion compared with standard treatment (OR: 0.82; 95% CI: 0.68 to 1.00, $p=0.056$), especially in larger RCTs.

Conclusions For patients with acute ICH similar to those included in RCTs and without contraindication to acute BP treatment, intensive acute BP lowering is safe, but does not seem to provide an incremental clinical benefit in terms of functional outcomes. The effect of intensive BP lowering on significant haematoma expansion at 24 hours warrants further investigation.

beneficial effect of BP-targeted treatments in the hyperacute phase of ICH on clinical outcome remains unclear.³

The current American Heart Association guidelines suggest that the early lowering of BP to 140 mm Hg is safe and can be effective for patients with ICH presenting with a 150–220 mm Hg systolic BP (SBP) and without contraindication to acute BP treatment.² These recommendations are mainly based on the results of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT 2) study,⁶ a large randomised controlled trial (RCT), that demonstrated the safety and showed modest trends of a better functional outcome in those patients treated with intensive lowering of BP, regardless of the presenting BP.³ In 2014, a meta-analysis of four RCTs^{6–9} evaluating acute lowering of BP in patients with ICH demonstrated similar trends,¹⁰ and documented a significant association between intensive BP management and reduction of haemorrhage expansion at 24 hours, potentially mediating the effect on clinical outcome.

More recently, the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-II trial results were published.¹¹ In this study, the acute reduction of BP to a target SBP of 110–139 mm Hg did not yield significantly better clinical outcome when compared with a target of 140–179 mm Hg. The results of ATACH-II contribute a significant number of patients for an updated meta-analysis and may help advancing clinical evidence on the effect of BP lowering in patients with acute ICH.

We therefore performed a new comprehensive systematic review and meta-analysis including the latest RCTs data on the topic to assess whether intensive BP lowering in patients with acute ICH is safe and effective in improving outcomes and significant haemorrhage expansion.

METHODS

This report was prepared with reference to the Preferred Reporting Items for Systematic reviews and Meta-Analyses¹² and the Cochrane Handbook for Systematic Reviews of Interventions.¹³ The study was performed according to a prespecified summary protocol developed in house in May 2016 (not published or registered). This study was designed, conducted and analysed, and the manuscript was written independently of industry.

INTRODUCTION

Intracerebral haemorrhage (ICH) accounts to 15% of all strokes and its prognosis remains poor.¹ In contrast to patients with ischaemic stroke, very limited treatment options have demonstrated their efficacy in the acute phase of ICH.² Multiple lines of evidence suggest that higher blood pressure (BP) after an ICH is associated with higher case fatality and worse functional recovery.^{3–5} However, the



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Search strategy and selection criteria

We identified RCTs reporting functional outcomes of acute (<24 hours) BP lowering in patients with ICH using PubMed (including MEDLINE and Pre-MEDLINE databases), EMBASE and the Cochrane Controlled Trials Register (CENTRAL and DARE) databases (last search conducted on 10 June 2016). Observational series were excluded from the analysis. The detailed search strategy is provided in the online supplementary material (online supplementary appendix).

Data extraction

Data were extracted independently by three authors (AM, GB and AC) using a standardised critical appraisal and data extraction form. The data extraction form was subdivided into five sections: (1) study characteristics, (2) baseline characteristics, (3) definition of outcome, (4) outcome measures (case fatality and unfavourable outcome as defined below). Study quality was critically appraised based on the seven-point tool for assessing risk of bias by the Cochrane collaboration,¹⁴ by the three authors who reviewed the literature.

Outcome measures

Primary outcome measures included 3-month mortality, as the safety outcome measure and 3-month mortality or significant disability (using the modified Rankin Scale (mRS) score, 3–6, higher values indicating lower functional recovery). Secondary outcome measures included the rate of ‘substantial’ haemorrhage expansion as defined in each study, as well as the rate of serious adverse events (when available).

Statistical analysis

Data were pooled in a meta-analysis when at least two studies with relevant data were available. In all analyses, we used a random effects model with DerSimonian-Laird weights.¹⁵ We quantified the strength of the association between intensive BP-lowering treatment and standard BP-lowering treatment and (1) 3-month mortality (safety outcome) and (2) 3-month death or dependency (efficacy outcome). In a secondary analysis, we investigated the association between acute ICH treatment arm and significant ICH expansion at 24 hours as defined in included studies. For all pooled analyses, we used OR and their corresponding 95% CIs, with the inverse variance method for weighting.

To account for methodological variability in study design, in subanalyses we stratified studies by sample size, that is, large RCT and RCT including <100 patients. As a sensitivity analysis, where available for the main outcomes we pooled the covariate-adjusted ORs as provided from relevant multivariable models in included studies. OR values >1 denote a positive association between intensive BP reduction and the outcomes under investigation.

We assessed statistical heterogeneity using I^2 statistics and visually through forest plot inspection. We explored publication bias with funnel plots. We used a random-effect univariable meta-regression to explore whether certain key baseline characteristics of all included patient populations could have affected our estimates. Meta-analyses were performed using Stata V. 13.0 (Stata).

RESULTS

The initial search strategy yielded 1495 original records. After a full screen of these records (see figure 1 for details) we included five RCTs in the final analyses.^{6–9 11} General characteristic of included studies and patients characteristics by treatment are

Figure 1 Flowchart for studies selection. ICH, intracerebral haemorrhage; IS, ischaemic stroke. + As defined within each trial RPBR, Rapid blood pressure reduction trial.

summarised in table 1, and detailed inclusion/exclusion criteria are provided in online supplementary table 1.

The risk of 3-month mortality was similar between patients randomised to intensive BP-lowering treatment and standard BP-lowering treatment (OR: 0.99; 95% CI: 0.82 to 1.20, $p=0.909$), without evidence of statistical heterogeneity (figure 2A). In the subanalysis, the 3-month mortality rates were higher for standard BP-lowering treatment in small RCTs (including <100 patients), but this result was not statistically significant (figure 2A). Intensive BP-lowering treatment showed a trend for an association with lower risk of 3-month death or dependency compared with standard treatment, but this trend was non-significant (OR: 0.91; 95% CI: 0.81 to 1.03, $p=0.136$) and seemed to be driven by the large RCTs (figure 2B). No evidence of substantial statistical heterogeneity was found using I^2 tests while visual inspection of the funnel plots and the Egger’s statistical test revealed no evidence of publication bias. Two of the large RCTs (INTERACT-2⁶ and ATACH-2,¹¹ $n=3839$) provided adjusted estimates for risk of 3-month death or dependency in the two arms: the pooled adjOR was 0.945 (95% CI: 0.79 to 1.13; $p=0.525$), with some degree of statistical heterogeneity ($I^2=41.5\%$, $p=0.191$) (forest plot not presented). No significant confounding was noted in univariable meta-regression analyses according to age, sex and initial stroke severity (as measured by National Institute of Health Stroke Scale and Glasgow Coma Scale (GCS)), hypertension, baseline ICH volume, ICH location (lobar and deep), intraventricular haemorrhage presence and mean SBP at presentation for any of the outcomes (all p values >0.1). These two trials also reported the full distribution of the mRS scores according to treatment group. In a post hoc analysis, using different 3-month mRS cut-offs (mRS >1 and mRS >3), intensive versus standard BP lowering was not associated with better functional outcomes (figure 3).

All trials provided data on significant ICH expansion using slightly different definitions (table 1). Intensive BP reduction was associated with a trend for lower significant ICH expansion risk compared with standard treatment (OR: 0.82; 95% CI: 0.68 to 1.00, $p=0.056$) (figure 4). When stratified by RCT size, this trend was evident only in the large studies (OR: 0.79; 95% CI: 0.59 to 1.05, $p=0.099$ and OR: 1.07; 95% CI: 0.46 to 2.50, $p=0.894$ in large and smaller studies respectively), but with moderate statistical heterogeneity (figure 4).

Two of the included studies provided extractable data on severe adverse events associated with BP-lowering treatment (INTERACT-1⁷ and ATACH-2,¹¹ $n=1404$). In a pooled analysis, intensive BP-lowering treatment compared with standard BP-lowering treatment was not associated with increased risk of severe adverse events (OR: 1.235; 95% CI: 0.902 to 1.691, $p=0.188$, $I^2=27.2\%$, $p=0.241$).

DISCUSSION

The results of our meta-analysis suggest that intensive BP lowering in patients with acute ICH is safe but does not seem to improve functional outcome or mortality at 3 months. In addition, we observed an association between intensive BP reduction and

Table 1 Characteristics of included studies and patients per treatment arm protocol

Study characteristics	INTERACT 1, 2008		RBPR ICH, 2008		ICH ADAPT, 2013		INTERACT 2, 2013		ATACH 2, 2016	
Country	International		USA		International		International		International	
Patient population	<6 hour since onset SBP (150–220) mm Hg		<8 hour since onset		<24 hour since onset SBP>150 mm Hg		<6 hour since onset SBP (150–220) mm Hg		3 & 4.5 hour since onset	
Definition of poor outcome*	90 days mRS (3–6)		90 days mRS (3–6)		90 days mRS (3–6)		90 days mRS (3–6)		90 days mRS (4–6)	
Definition of ICH expansion	>33% or >12.5 cc at 24 hours		>30% at 24 hours		>33% or >6 cc at 24 hours		>33% or >12.5 cc at 24 hours		>33% at 24 hours	
Baseline characteristics	Intensive	Standard	Intensive	Intensive	Standard	Intensive	Standard	Intensive	Standard	
Target BP (mm Hg)*	140	180	<110	(110–130)	150	180	140	180	(110–139)	(140–179)
Patients/group	203 (50%)	201 (50%)	21 (50%)	21 (50%)	39 (52%)	36 (48%)	1382 (50%)	1412 (50%)	500 (50%)	500 (50%)
Age (years)	63±12	62±13	61±13	60±11	70.7±12.5	68.7±11.1	63±13.1	64.1±12.6	62±13.1	61.9±13.1
Male (%)	60.6	69.1	42.9		66.7	77.8	64.2	61.7	60.8	63.2
Hypertension (%)	74.4	74.1	85.0		66.7	75.0	72.4	72.5	82.2	76.4
Antiplatelets (%)	9.3	6.5	33.3		10.2	0.0	8.8	9.9	–	–
Anticoagulants (%)	1.5	0.5	4.7		2.5	8.3	3.6	2.2	–	–
NIHSS	9 (5–14)	9 (5–16)	10.9±6.5		10 (6–18)	11 (5.5–15.5)	10 (6–15)	11 (6–16)	11 {0–40}	11 {0–40}
GCS	14 (13–15)	14 (13–15)	13.5 (9–15)	15 (10–15)	14 (4–15)	15 (6–15)	14 (12–15)	14 (12–15)	15 (12/14–15)	15 (12/14–15)
Onset to randomisation (hours)	3.4 (2.5–4.5)	3.4 (2.5–4.5)	3.2±2.2		7.8 (3.3–16.8)	8.54 (3.8–15.9)	3.7 (2.8–4.8)	3.7 (2.9–4.7)	3.04±0.95	3.07±0.94
Deep ICH location	73.4%	73.6%	88.0%		74.4%	75.0%	83.8%	83.2%	90.3%	87.6%

Values are expressed as absolute number (% of total), mean±SD, median (minimum–maximum) or median (25%–75% quantiles).

*'Intensive' and 'standard' denote the treatment group (intensive or standard management of BP in each trial).

*All target BPs are SBPs except for RBPR³ where target BP is the mean arterial pressure low risk of bias was found in each item of the items of the assessment tool¹⁴ for included studies, except for a constant high risk in regard to the blinding of personnel and participants (all open-label studies) (see online supplementary table 1 for details).

BP, blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; ICH ADAPT, Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure.

lower risk for significant ICH expansion, although not statistically significant.

The main underlying assumption behind the equipoise of decreasing blood pressure at the acute phase of ICH is that it may meliorate outcomes by limiting early haemorrhage expansion, a known (potentially modifiable) predictor of bad outcome.¹⁶ However, large RCTs as well as our aggregate level analysis failed to demonstrate that a clear clinical benefit derived from such strategy.¹⁷ Several reasons might explain these findings.

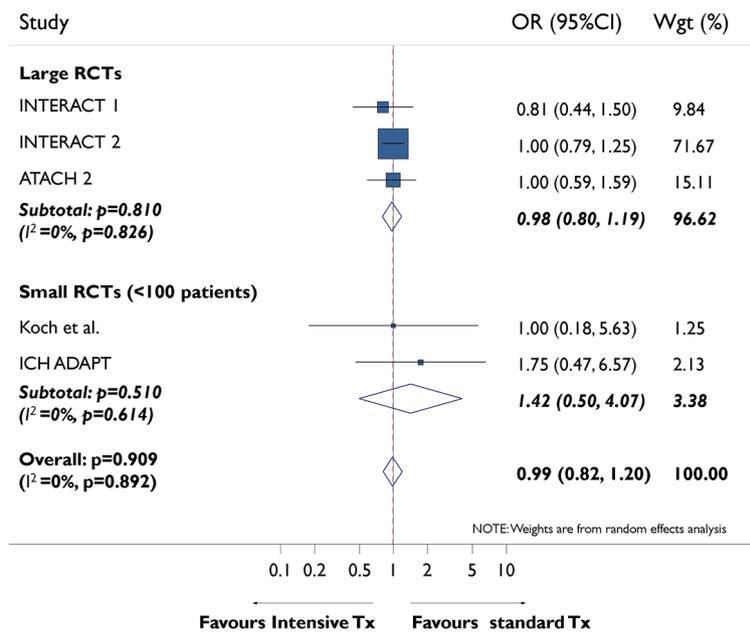
The first potential explanation is that completed BP-lowering RCTs did not specifically randomise patients at highest risk of expansion (specifically, enrolled patients demonstrated disproportionately small baseline ICH volumes and a very low proportion of warfarin-associated haematomas). This was probably driven by the fact that patients at highest risk of expansion (larger volumes, anticoagulation related) also have an important risk of unfavourable outcome. While this approach ultimately increases the external validity of the intervention and improves feasibility of trial enrolment, reductions in haematoma expansion in the target population are diluted over the entire sample, which may in part explain the lack of clear therapeutic benefit. Ongoing or recently halted trials' results using specific markers such as the spot sign (ClinicalTrials.gov STOP-AUST, NCT01702636;

STOP-IT, NCT00810888; SPOTLIGHT, NCT01359202) or more stringent inclusion criteria (NCT02281838) to select patients at highest risk of expansion are therefore awaited, but face difficulties with enrolment.¹⁷ It should be noted, that the absolute effect of intensive BP treatment on ICH expansion appeared to be small in previous reports (absolute reduction of haematoma growth <2 mL).⁷ Therefore, despite the plausible hypothesis that BP lowering may indeed decrease haemorrhage expansion rate, any possible beneficial effect of reduced haematoma growth may be masked by stronger predictors of outcome, such as admission GCS, age and presence of intraventricular extension.¹⁸

Secondary complications may also have a significant influence on ICH prognosis¹⁹ and the heterogeneity in medical management of patients with ICH outside of the hyperacute phase may be an important confounder.

Finally, there is no established consensus on the optimal BP reduction protocol and some BP-lowering agents may be associated with rebound hypertension and increased intracranial pressure.^{20,21} In addition, several studies reported significant difficulties and delay in achieving the optimal BP target.⁶ Heterogeneity in BP management beyond the acute phase (>24 hours) may also underlie the conflicting results of different studies^{6,11}

A. 3-month mortality



B. 3-month death or dependency

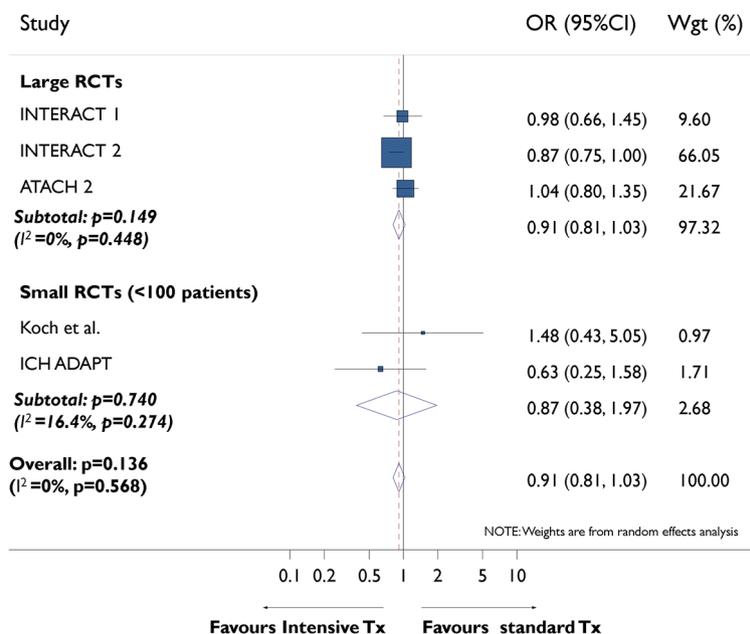


Figure 2 Safety and efficiency of intensive versus standard blood pressure lowering Forest plot of the effect of intensive versus standard blood pressure lowering on (A) 3-month mortality risk and (B) 3-month death or dependency in patients with acute intracerebral haemorrhage (ICH). RCT, randomised controlled trial.

(increased BP variability has been shown for example to be associated with poor outcomes).²²

Because of the larger sample size compared with other studies, patients enrolled in INTERACT II are highly represented in our meta-analysis. Some important differences between INTERACT II and other studies, in particular ATACH II should be considered, since they may affect the effect estimates.^{6 11 23} Compared with ATACH II, the INTERACT II study had a lower admission SBP cut-off (SBP >150 mm Hg vs SBP >180 mm Hg) and a longer time window (6 vs 4.5 hours from stroke onset) for

inclusion. ICH expansion occurs more frequently in the first 6–12 hours after stroke onset and therefore any delay in BP treatment may have a negative influence on the extent of bleeding.²⁴ INTERACT II patients had lower admission SBP values (179 vs 200 mm Hg) and ATACH-II allowed the inclusion of patients that received antihypertensive treatment before randomisation. A wide range of BP-lowering medications with different modes of administration (intravenous bolus or continuous infusion) were used in INTERACT II, whereas all patients enrolled in ATACH II were treated with intravenous infusion of nicardipine.

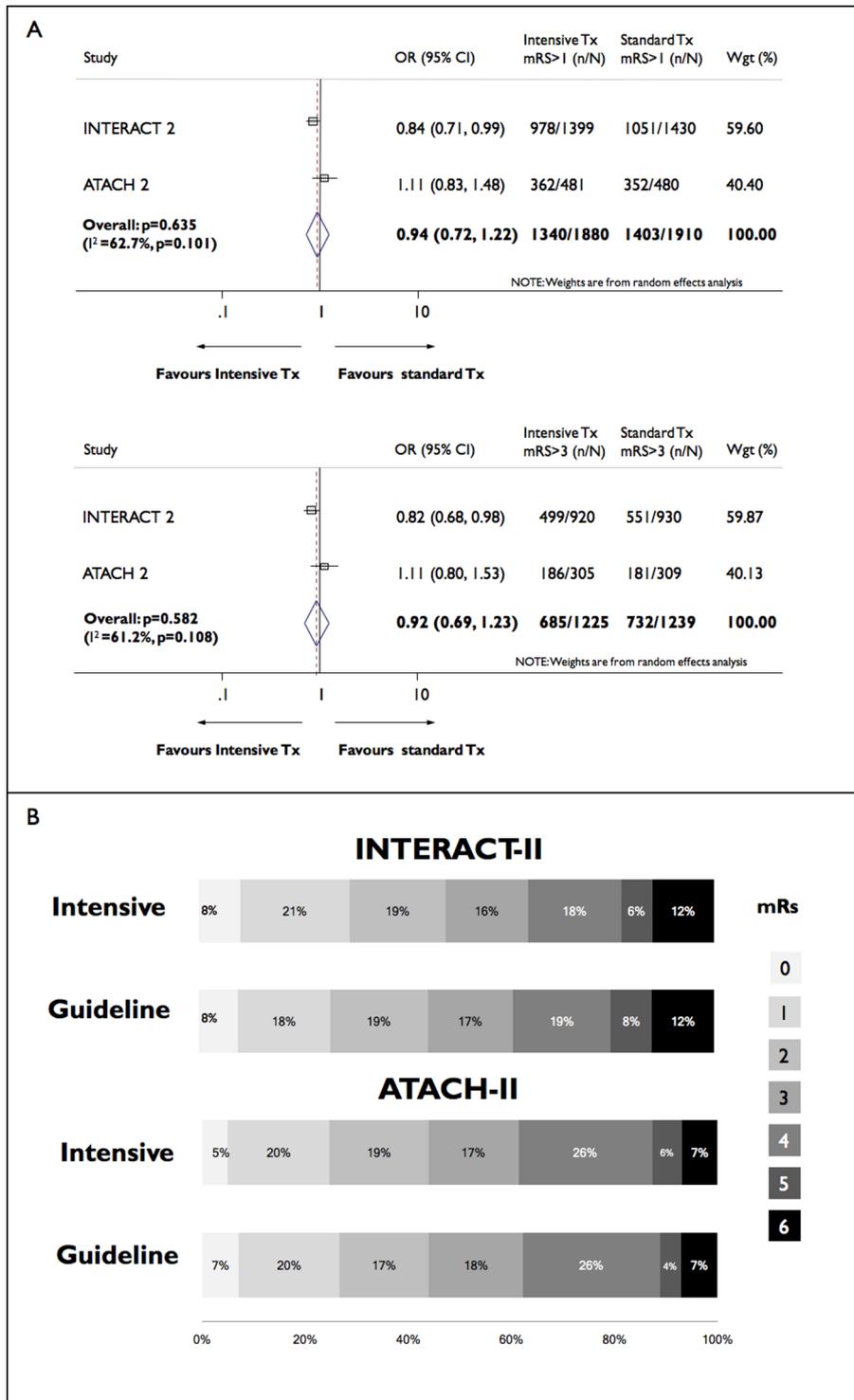


Figure 3 Detailed mRS analysis in ATACH II and INTERACT II. **(A)** Post hoc analysis forest plots of the effect of intensive versus standard blood pressure lowering on 3-month mRS>1 (top panel) or 3-month mRS>3 (bottom panel) in patients with acute intracerebral haemorrhage included in INTERACT-2 and ATACH-2. **(B)** Distribution of mRS scores according to treatment group in these two large trials. The percentage of participants with each score on the mRS is shown in each cell. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden and incontinent) and 6 death. mRS, modified Rankin Scale.

Finally, the rate of primary treatment failure (SBP >140 mm Hg) was higher in INTERACT II (66% vs 12.2%) although measured at slightly different time points (1 hour from randomisation in INTERACT II vs 2 hours from randomisation in ATACH II).

The methodological aspects of included studies discussed can influence the findings of our meta-analysis. Some additional limitations of the current analysis deserve consideration. Despite the quality control of included studies indicates low risk of bias

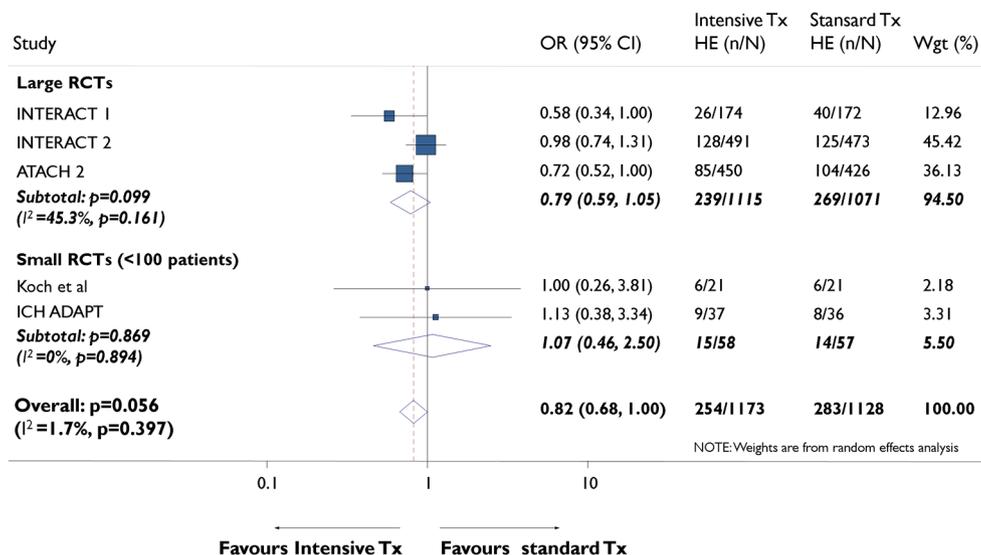


Figure 4 Significant haemorrhage expansion at 24 hours in intensive versus standard blood pressure-lowering treatment. Post hoc analysis of the (A) crude (data available from four RCTs) and (B) adjusted absolute haematoma growth (data available from two RCTs) at 24 hours after baseline CT scan in patients randomised to intensive versus conservative blood pressure lowering. RCT, randomised controlled trial.

overall, other important sources of heterogeneity cannot be fully excluded. Importantly, we acknowledge that the definitions used for qualifying for haemorrhage expansion differed between the trials, and while it is unlikely that these slight differences are of clinical relevance, we could not account for them in our analyses. Individual patients level data meta-analysis are needed to further explore this question.

In addition, several important variables that can potentially influence the main outcomes were not adjusted for in the analyses. Reassuringly, the adjusted pooled estimates provided in ATACH-2 and INTERACT-1 were consistent with the main results. However, these trials represent only around 20% of included patients in all studies. Finally, the meta-regression is not sufficient to account for potential confounding since it is based on overall population characteristic. Further individual patient data meta-analysis on the topic might be of interest to explore these issues in detail.

To conclude, for patients with acute ICH with characteristics similar to those included in RCTs (ie, mild to moderate severity) and without contraindication to acute BP treatment, intensive acute BP lowering is safe, but does not seem to provide an incremental clinical benefit in terms of reduced mortality and better functional outcomes. For patients with acute ICH with large haematomas and increased intracranial pressure, who have a higher risk of cerebral hypoperfusion, the safety and benefit of BP reduction is still unclear. The data presented here on the effect of intensive BP lowering on significant haematoma expansion at 24 hours warrant further investigation in large multi-centre studies.

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