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Rapid Blood Pressure Lowering According to Recovery at Different Time Intervals after Acute Intracerebral Hemorrhage: Pooled Analysis of the INTERACT Studies

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Key Words
Intracerebral hemorrhage · Pattern of recovery · Blood pressure lowering · INTERACT · Clinical trial

Abstract
Background and Purpose: Early intensive blood pressure (BP) lowering has been shown to improve functional outcome in acute intracerebral hemorrhage (ICH), but the treatment effect is modest and without a clearly defined underlying explanatory mechanism. We aimed at more reliably quantifying the benefits of this treatment according to different time periods in the recovery of participants in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) studies. ***Methods:*** Pooled analysis of the pilot INTERACT1 (n = 404) and main INTERACT2 (n = 2,839) involving patients with spontaneous ICH (<6 h) and elevated systolic BP (SBP 150–220 mm Hg) who were randomized to intensive (target SBP <140 mm Hg) or guideline-recommended (target SBP <180 mm Hg) BP lowering treatment. Treatment effects were examined according to repeated measures analysis of an ordinal ('shift') across all 7 levels of the modified Rankin Scale (mRS) assessed during follow-up at 7, 28, and 90 days, post-randomization. Clinical trial registration information: http://www.clinicaltrials.gov, NCT00226096 and NCT00716079. ***Results:*** Intensive BP lowering resulted in a significant favorable distribution of mRS scores for better functioning (odds ratio 1.13, 95% confidence interval 1.00–1.26; p = 0.042) over 7, 28 and 90 days, and the effect was consistency for early (7–28 days) and later (28–90 days) time periods (p homogeneity 0.353). Treatment effects were also consistent across several pre-specified patient characteristic subgroups, with trends favoring those randomized early, and with higher SBP and milder neuro-

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logical severity at baseline. ***Conclusions:*** Intensive BP lowering provides beneficial effects on physical functioning that manifests consistently through the early and later phases of recovery from ICH.

Introduction

Acute intracerebral hemorrhage (ICH) is the most lethal and disabling form of stroke, affecting several million people worldwide each year [1–3], most of whom reside in Asia [1]. One of the most promising approaches to the acute treatment is early and sustained control of elevated blood pressure (BP) in ICH. Recently, the main phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) showed that early intensive blood pressure (BP) lowering is safe and improves functional outcomes [4]. However, the primary outcome in the trial was analyzed according to the pre-specified conventional binary analysis of the modified Rankin Scale (mRS) at 90 days was not significant at the $p < 0.05$ level, as was the effect on hematoma growth at 24 h in a subgroup of patients, raising concerns over the robustness of the results [5]. This has prompted us to quantify in more detail the treatment effects on the recovery pattern from ICH using repeated measurements of the mRS assessed at 7, 28 and 90 days in a pooling of the pilot phase (INTERACT1) and INTERACT2 datasets to maximize statistical power. Our aim was to determine whether the treatment effects of early intensive BP lowering differed across different time periods after ICH and in several patient subgroups, to better understand whether the benefits may relate to earlier (i.e., hematoma growth) or later (i.e., perihematomal edema) mechanisms.

Methods

The INTERACT studies were international, multicenter, open, blinded endpoint, randomized controlled trials, as described in detail elsewhere [4, 6, 7]. Briefly, 404 (INTERACT1) and 2,839 (INTERACT2) patients with spontaneous ICH within 6 h of onset and elevated systolic BP (SBP, 150–220 mm Hg) were randomized to receive intensive (target SBP <140 mm Hg within 1 h) or guideline-recommended (target SBP <180 mm Hg) BP-lowering treatment. The study protocols were approved by appropriate ethics committees at each site and written informed consent was obtained from each patient or, where appropriate, by an authorized surrogate.

Demographic, clinical characteristics, medical history including current medications, and CT findings were recorded at the time of enrolment. Stroke severity was measured using the National Institutes of Health stroke scale (NIHSS) at baseline, 24 h, and at Day 7 (or earlier, upon discharge from hospital). Participants were assessed by telephone or in-person assessments were conducted for evaluating the functioning and health-related quality of life by a researcher independent of the treating service at 28 and 90 days.

The primary outcome for these analyses was repeated measures of physical function across all 7 levels of the modified Rankin Scale (mRS) [8] at 7, 28, and 90 days, as determined with the use of an ordinal (shift) analysis [9]. The outcome was also determined according to the conventional binary measure (mRS 0–2 vs. 3–6). As repeated measures of the mRS were available from the same individuals, generalized estimating equations (GEE) [10] were used to examine the effects of BP-lowering treatment in proportional odds GEE models, with time (days post-randomization) as a covariate. Time was considered a continuous variable, and the interaction methods between time and randomized BP lowering treatment were tested and rejected. We assessed the heterogeneity of the treatment effect on the outcome in 8 patient characteristic subgroups by adding an interaction term to the GEE model. Patients were stratified as <20 and ≥20 [11] on the baseline NIHSS to determine whether the treatment effects differed according to the initial severity of illness, as the NIHSS enables greater discriminative assessment of neurological deficits than the GCS [12, 13]. Two secondary analyses using two restricted time epochs, Day 7 to Day 28 and Day 28 to Day 90, were undertaken to determine whether the treatment effect differed between earlier and later phases of recovery. We also used a GEE model with time included as a covariate, to test the effects of BP-lowering treatment using binary (0–2 vs. 3–6) outcome on the mRS. Data are reported with odds ratios (OR) and 95% confidence intervals (CI), and significance was declared when the p value was <0.05. All of the data were analyzed using SAS version 9.3 (SAS Institute).

Results

Table 1 shows the baseline characteristics of participants. Compared with INTERACT1, those in INTERACT2 were less often from China and had higher NIHSS and larger hematoma at baseline. For the INTERACT1 and INTERACT2 combined group, the baseline characteristics were well balanced by randomized BP-lowering treatment, except that the use of warfarin anticoagulation was slightly more frequent in those who received intensive BP-lowering treatment.

Table 2 indicates that more patients in the intensive group than in the guideline group received intravenous or oral BP-lowering agents over 90 days. However, the frequency of BP-lowering treatment decreased over time in the intensive group while it was near stable in the guideline group. The mean SBP levels differed significantly from 15 minutes to Day 7 post-randomization between the groups, as shown elsewhere [4].

Table 1. Baseline characteristics of INTERACT participants, by study and randomized treatment

Variable	Total (n = 3,233)	Study			BP lowering treatment		
		INTERACT1 (n = 404)	INTERACT2 (n = 2,829)	p value	intensive (n = 1,602)	guideline (n = 1,631)	p value
Time from ICH to randomization, h	3.7 (2.8–4.7)	3.7 (2.9–4.8)	3.7 (2.8–4.7)	0.985	3.7 (2.8–4.8)	3.7 (2.9–4.7)	0.626
Age, years	63 (13)	62 (13)	64 (13)	0.075	63 (13)	64 (13)	0.063
Male sex	2,042 (63)	262 (65)	1,780 (63)	0.452	1,021 (64)	1,021 (63)	0.504
Recruited from China	2,304 (71)	384 (95)	1,920 (68)	<0.0001	1,140 (71)	1,164 (71)	0.897
Systolic blood pressure, mm Hg	179 (17)	181 (18)	179 (17)	0.080	179 (17)	180 (17)	0.176
Diastolic blood pressure, mm Hg	101 (15)	103 (14)	101 (15)	0.021	101 (15)	102 (15)	0.624
NIHSS score†	10 (6–15)	9 (5–15)	11 (6–16)	0.032	10 (6–15)	11 (6–16)	0.534
NIHSS score ≥20	358 (11)	42 (10)	316 (11)	0.620	184 (12)	174 (11)	0.482
GCS score‡	14 (12–15)	14 (13–15)	14 (12–15)	0.886	14 (12–15)	14 (12–15)	0.728
History of hypertension	2,348 (73)	300 (74)	2,048 (73)	0.451	1,163 (73)	1,185 (73)	0.948
Current use of antihypertensive drugs	1,449 (45)	175 (43)	1,274 (45)	0.505	712 (45)	737 (45)	0.660
Prior intracerebral hemorrhage	275 (9)	46 (11)	229 (8)	0.027	142 (9)	133 (8)	0.473
Prior ischemic/undifferentiated stroke	369 (11)	46 (11)	323 (11)	0.980	178 (11)	191 (12)	0.588
Prior acute coronary event	95 (3)	14 (4)	81 (3)	0.505	46 (3)	49 (3)	0.821
Diabetes mellitus	339 (11)	34 (8)	305 (11)	0.145	176 (11)	163 (10)	0.360
Use of warfarin anticoagulation	85 (3)	4 (1)	81 (3)	0.028	53 (3)	32 (2)	0.017
Use of aspirin or other antiplatelet agent	297 (9)	32 (8)	265 (9)	0.343	142 (9)	155 (10)	0.526
Baseline hematoma volume, ml	10.7 (5.6–19.3)	9.1 (4.8–17.5)	11.0 (5.8–19.5)	0.008	10.6 (5.5–18.9)	10.8 (5.7–19.5)	0.871
Deep location of hematoma§	2,479 (83)	297 (83)	2,182 (84)	0.631	1,233 (84)	1,246 (83)	0.639
Left hemisphere site of hematoma	1,491 (50)	178 (52)	1,313 (50)	0.676	726 (50)	765 (51)	0.314
Intraventricular hemorrhage	821 (28)	81 (23)	740 (28)	0.055	416 (28)	405 (27)	0.475

Data are means (SD), medians (IQR), or numbers (%). † Scores range from 0 (normal) to 42 (coma with quadriplegia). ‡ Scores range from 15 (normal) to 3 (deep coma). § Location in the basal ganglia or thalamus.

Table 2. Blood pressure (BP)-lowering treatment at various stages of follow-up among participants of the INTERACT studies

Randomized group/number of agents	First 24 h, n (%)	Day 2 to 7, n (%)	Day 28, n (%)	Day 90, n (%)
Intensive				
Any	1,553 (97)	1,472 (92)	1,290 (81)	1,252 (78)
≥2 drugs	1,001 (63)	1,160 (72)	764 (48)	685 (43)
Number of intravenous drugs				
1	982 (61)	749 (47)	–	–
2	354 (22)	246 (15)	–	–
≥3	71 (4)	75 (5)	–	–
Number of oral drugs				
1	510 (32)	428 (27)	–	–
2	291 (18)	477 (30)	–	–
≥3	113 (7)	406 (25)	–	–
Guideline				
Any	1,142 (70)	1237 (76)	1,205 (74)	1,204 (74)
≥2 drugs	533 (33)	775 (48)	582 (36)	565 (35)
Number of intravenous drugs				
1	489 (30)	409 (25)	–	–
2	104 (6)	102 (6)	–	–
≥3	31 (2)	30 (2)	–	–
Number of oral drugs				
1	492 (30)	476 (29)	–	–
2	226 (14)	364 (22)	–	–
≥3	71 (4)	272 (17)	–	–

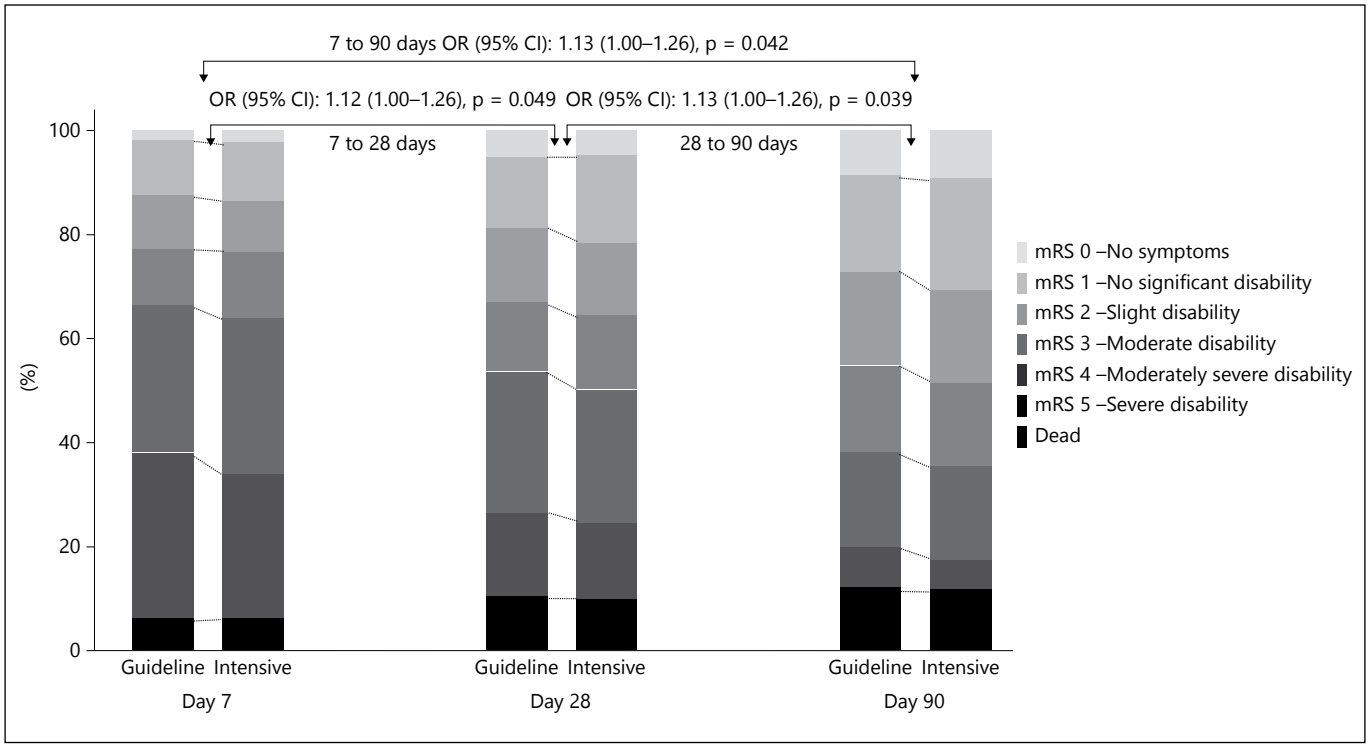

Fig. 1. Effects of blood pressure (BP)-lowering treatment across different time points of assessment, post-randomization. The odds ratio (OR) and 95% confidence interval (CI) represent the effect of treatment between specific time points.

Ordinal analysis showed a significant favorable shift in the distribution of scores on the mRS with intensive BP-lowering treatment (OR for shift toward better function, 1.13, 95% CI 1.00–1.26; p = 0.042) (fig. 1). The treatment effects were consistent between early and later time epochs (interaction between time and randomized BP-lowering treatment, p homogeneity 0.353). Secondary analyses showed similar favorable shifts in mRS scores at early (7 to 28 days) (OR 1.12, 95% CI 1.00–1.26; p = 0.049) and later (28 to 90 days) (OR 1.13, 95% CI 1.01–1.27; p = 0.039) time epochs. The treatment effects were consistent across all pre-specified subgroups (all p for homogeneity are not significant), although slightly larger favorable shift was found in patients randomized within 4 h of ICH onset, with baseline SBP ≥180 mm Hg, and with baseline NIHSS score <20 (fig. 2).

The proportion of participants with a good outcome was higher in the intensive treatment group compared to the guideline group at all follow-up time points (fig. 3). Although the recovery pattern was not significantly different between the 2 treatment groups, the intensive group showed slightly greater benefit over time (OR 1.11, 95% CI 0.98–1.26; p = 0.107).

Discussion

This pooling analysis of the INTERACT studies provides further support for the main findings of the INTERACT2 study in showing that early intensive BP lowering significantly improves functional outcomes through an ordinal analysis of mRS during the different phases of recovery over 90 days after the onset of acute ICH. The benefits of treatment were better defined in those patients who received early treatment (randomized <4 h), with higher baseline SBP (≥180 mm Hg), and with less severe neurological impairment (NIHSS scores <20), and applied equally over the early (within the first few weeks) and later (1–3 months) phases after ICH.

These findings also complement our results regarding intra-individual SBP variability in both the hyperacute (<24 h) and acute (over 7 days) phases of ICH, being an important determinant of outcome independent of mean level of achieved SBP. All these data imply that it is not only important to rapidly lower elevated BP within the first few hours of ICH, but also to ensure that there is consistent and sustained control of BP over the subsequent several days [14]. Although INTERACT did not include

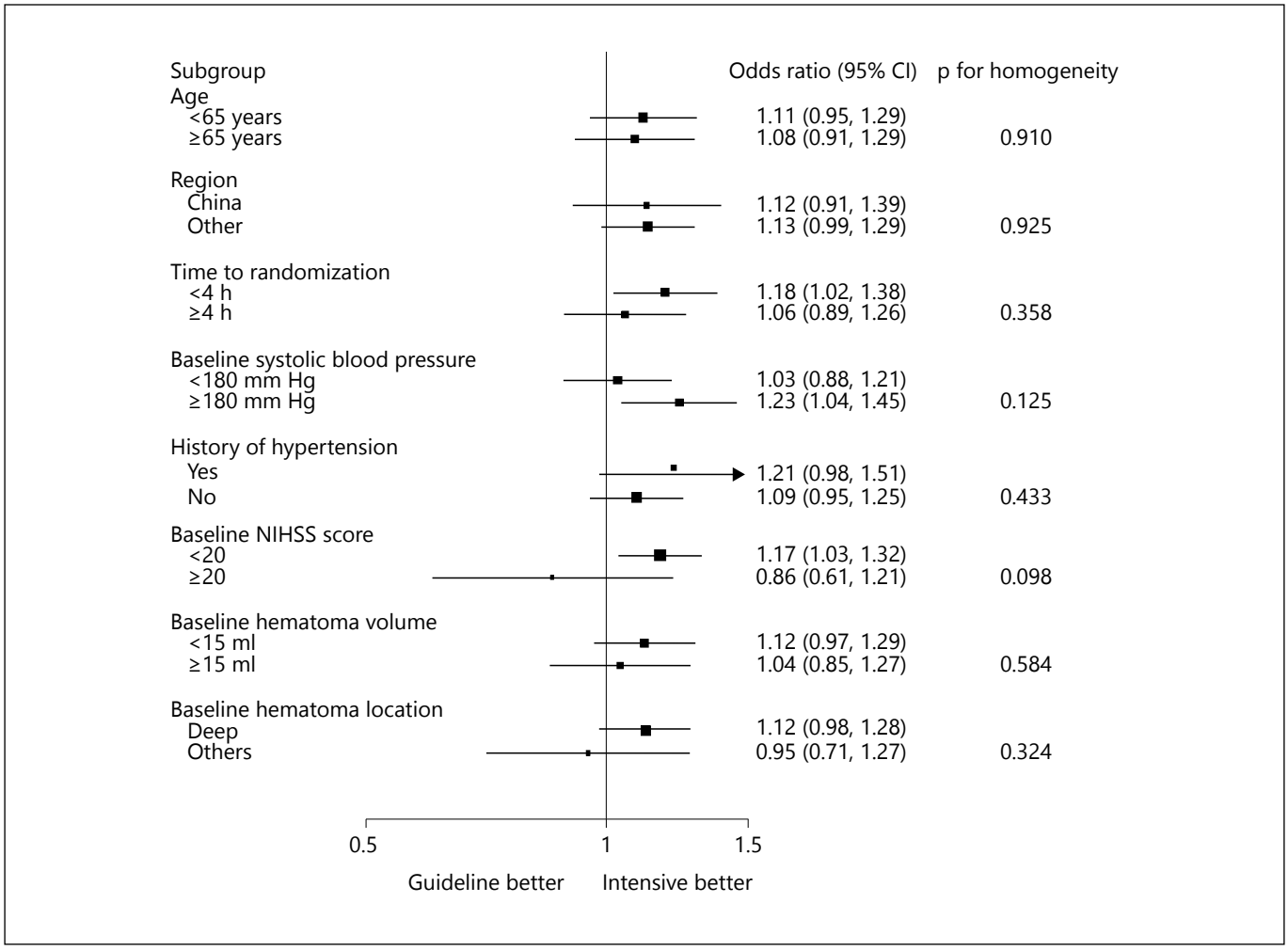

Fig. 2. Effects of blood pressure (BP)-lowering treatment on the outcome, according to pre-specified subgroups. The outcome was repeated measures of physical function across all 7 levels of the modified Rankin Scale (mRS) at 7, 28, and 90 days, as determined with the use of an ordinal (shift) analysis. The black squares represent the odds ratio (OR), and the horizontal lines represent 95% confidence interval (CI).

systematic information on BP levels at 28 and 90 days post-ICH, information on the number of BP-lowering agents prescribed during follow-up indicates that participants continued using BP-lowering drugs beyond being discharged from hospital. As the present analysis indicates that the treatment effects are consistent over the duration of follow-up from 7 to 90 days, it provides further evidence that the control of BP beyond 7 days may also important in promoting early recovery from ICH.

One important mechanism underlying the beneficial effects of BP reduction in ICH is the reduction in hydrostatic pressure at the site of the hemorrhage with subsequent attenuation of early hematoma expansion. This may explain why patients who were treated earlier and those presenting with higher SBP showed a clearer trend toward better outcome [15–17]. Secondary analysis of the INTERACT studies suggests that early control of elevated BP is likely to provide greater protection against hematoma growth, which could lead to a better outcome [18, 19]. Other mechanisms involve reduction in the risks of re-bleeding, perihematomal edema, and early stroke recurrence [20–22]. These data indicate that patients who present with ICH associated with less severe neurological severity, assessed by the NIHSS score, especially benefit from intensive BP lowering, and in particular, as they have the greater potential to survive albeit with less residual disability. However, as our dataset included fewer cases of severe ICH, there remains uncertainty as to

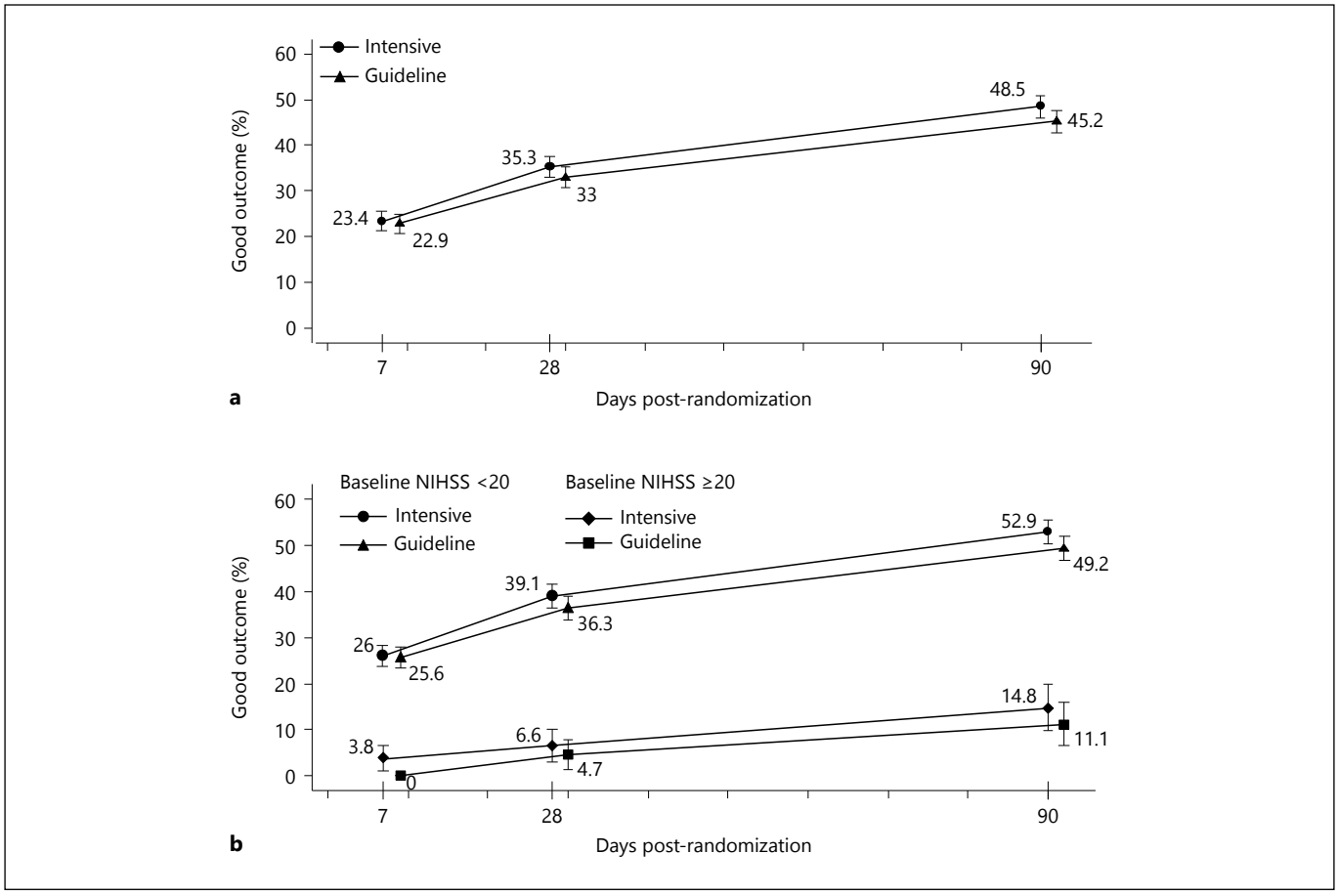

Fig. 3. a Frequency of patients with a good outcome at each time point on follow-up, post-randomization. **b** Frequency of patients with a good outcome at each time point on follow-up, post-randomization, by baseline NIHSS. Solid boxes represent the percentage of patients with a good outcome. Vertical lines represent 95% confidence intervals (CI).

whether more aggressive BP control, alone or as an adjuvant to decompressive procedures for the hematoma, may improve outcomes.

Strengths of this study included the repeated observations at the individual level, which enhanced the power to assess the treatment effects on outcomes over 90 days, by virtue of being able to study the individual development of a certain outcome variable over time. The large sample size provides reassurance over precision and reliability around the estimates of association. The wide range of patients who were included from a variety of hospitals in many countries, along with the use of a range of BP-lowering regimes, enhanced the generalizability of these results. However, there were also some limitations, particularly related to the selection bias associated with this being a clinical trial population, where patients with severe ICH or early planned surgery were excluded. Moreover, differences in socioeconomic and management factors between countries and over time may have influenced outcomes, while the heterogeneity of treatments used may create uncertainty over the most desirable agent and BP-lowering dosing protocol. Additionally, because only 358 participants presented with high (≥20) NIHSS scores, power was limited to reliably assess the treatment effects in this subgroup. Finally, we had not collected data on BP levels at 28 and 90 days, and so with only the use of BP-lowering medication, we were unable to provide detailed information about how well BP was controlled beyond 7 days. Similarly, we were unable to assess the influence of comorbid variables and management of residual disability beyond the in-hospital acute phase on outcomes.

In summary, intensive BP-lowering appears beneficial across the trajectory of recovery over 90 days after the onset of ICH, especially in those treated early, with higher SBP, and less severe forms of this illness.

Contributors

X.W. contributed to data analysis and wrote the first draft of the report. H.A., R.A.S., and C.S.A. supervised the analyses, contributed to the concept and rationale for the study, and wrote the report. M.W., E.H., C.S., P.M.L., T.R., Y.H., J.W., and C.D. provided comments on data interpretation and the report.

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Disclosure Statement

None related to this paper.

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