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RESEARCH ARTICLE

Hypertension management in elderly with severe intracerebral hemorrhage

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Abstract

Objective: To explore the effect of individualized blood pressure (BP)-lowering treatment on the outcomes of elderly patients with severe intracerebral hemorrhage (ICH). **Methods**: We performed an exploratory analysis of Controlling Hypertension After Severe Cerebrovascular Event (CHASE) trial, which was a multicenter, randomized, controlled clinical trial. Patients with severe ischemic or hemorrhagic stroke (defined as GCS $\leq$ 12 or NIHSS $\geq$ 11) were randomized into individualized versus standard BP-lowering treatment in CHASE trial. In this exploratory analysis, patients with severe ICH were included. The primary outcome was the percentage of patients with 90-day functional independence defined as modified Rankin Scale (mRS) $\leq$2. **Results**: We included 242 patients with severe ICH in the present analysis, consisting of 142 patients aged <65 years and 100 patients aged $\geq$65 years. There were significant differences between patients aged $\geq$65 years and <65 years in the proportion of functional independence (47.9% vs. 15.0%, $P < 0.001$) and good outcome (73.9% vs. 50.0%, $P < 0.001$) at day 90. In patients aged $\geq$65 years, the adjusted individualized BP-lowering treatment had an unequivocal effect on the functional independence at day 90 (21.6% vs. 8.2%, odds ratio [OR]: 4.309, 95% confidence interval [CI]: 1.040-17.859, $P = 0.044$) and improved the neurological deficits at discharge (Δ NIHSS $\geq$ 4: 64.7% vs. 34.7%, OR: 4.300, 95% CI: 1.599-11.563, $P = 0.004$). **Interpretation**: Compared with the younger counterparts, the elderly patients ($\geq$65 years) with acute severe ICH might benefit more from individualized BP-lowering treatment.

Introduction

Intracerebral hemorrhage (ICH) accounts for about 10–20% of all types of stroke and 30% of ICH are severe stroke requiring mechanical ventilation and ICU management.[1–3] It was reported that half of stroke-related mortality was attributed to ICH, and most of the survivors after ICH were left with severe disability.[4] Compared with the younger counterparts, the elderly patients presented with a higher incidence of ICH, more severe manifestations, more complications, and worse outcomes.[2,5–8] Despite the devastating outcomes in elderly patients with ICH, no proven effective treatment is available.[9]

Elevated blood pressure (BP), a common condition in the early stage of ICH, is associated with poor outcomes, and considered an important target of ameliorating consequences of ICH.[10–15] Guidelines for ICH suggested lowering the systolic BP (SBP) to 140 mmHg in patients with SBP between 150 and 220 mmHg.[11,16,17] However, none of the above guidelines were targeted at elderly patients with severe ICH. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) reported that intensive SBP reduction (with a target of SBP <140 mmHg) after ICH improved the functional outcomes of patients.[6,18] In contrast, analyses from the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2) showed that intensive SBP reduction (with a target of SBP between 110 to 139 mmHg) did not result in favorable effects and even had an excess of adverse events.[19] In a recent pooled analysis of INTERACT2 and ATACH-2, the results indicated that a target SBP of 120 to 130 mmHg was associated with favorable outcomes in ICH patients with mild-to-moderate severity.[20] Given most patients with mild to moderate ICH in above studies, the conclusion might not be suitable for severe ICH. As for the severe grade ICH, a post hoc analysis of ATACH-2 trial suggested that the intensive SBP reduction with a target of 110–139 mm Hg did not reduce the poor outcome in patients with moderate to severe ICH.[21] Results of Controlling Hypertension After Severe Cerebrovascular Event (CHASE) trial showed that individualized BP-lowering treatment (with a reduction of 10%–15% in SBP from baseline level) had the trend of improving functional outcome in patients with severe ICH.[22] Despite efforts by above researches, the optimal management of BP in elderly patients with severe ICH is still an ongoing dilemma.

In order to tailor decision making in the elderly with severe ICH, we designed this exploratory analysis of CHASE trial to determine whether the individualized BP-lowering treatment, a modest BP-lowering treatment, during the acute phase of ICH affect the functional outcomes of elderly patients.

Methods

Study design and subjects

The CHASE study was a multicenter randomized controlled trial of controlling hypertension in subjects with severe stroke (ClinicalTrials.gov Identifier: NCT02982655). The study enrolled patients with severe acute ischemic stroke (AIS) and severe ICH (defined as Glasgow Coma Scale [GCS] $\leq$ 12 or National Institutes of Health Stroke Scale [NIHSS] $\geq$ 11 on admission) aged 18 or older from 26 centers in the northwest of China who received individualized BP-lowering strategy or standard BP-lowering strategy.[22,23] The study was approved by each ethics committee at every hospital. The protocol of CHASE trial has been published in elsewhere and the details of the design were displayed in Supplement 1.[23] All participants or their legally authorized representatives provided written informed consent for enrollment. In this exploratory analysis, we included all subjects with ICH in CHASE study. The patients were further divided into two groups with the cutoff age of 65 years old.

Intervention

In the CHASE trial, the individualized BP-lowering treatment aimed at reducing SBP by 10% to 15% within the first 2 h after randomization, achieving the range of 130 to 180 mmHg within the following 7 days. For ICH patients assigned to the standard BP-lowering treatment, antihypertensive medications were administered when the ICH patients had an elevated SBP more than 180 mmHg, achieving a SBP less than 180 mmHg within 7 days after randomization. At the hospital discharge, ICH patients with elevated BP in both treatment groups were prescribed properly antihypertensive agents according to the guidelines.[11,16,17]

Measurements

The demographics, severity of stroke, medical history, and clinical characteristics were collected at the time of enrollment. Stroke severity was assessed using the NIHSS and GCS by trained neurologists at baseline. Outcomes at hospital discharge were evaluated using the GCS, NIHSS, Barthel Index (BI), and modified Rankin Scale (mRS). Scores of mRS and BI were assessed by telephone at 90-days follow-up by qualified investigators blinded to the protocol treatments.

Blood pressure was recorded at baseline, 12 times during the first day (every 2 h), 12 times during day 2 to day 3 (every 4 h), and 12 times during day 4 to day 7 (every 8 h). Eight measures of SBP features were calculated in acute phase (24 h after randomization): SBP reduction (2,

4, 6, 12, 24 h), mean, SD, functional successive variation (FSV).[24,25] The baseline SBP measurement was excluded in calculating the mean, SD, and FSV in the acute phase. Four measures of SBP features were calculated in the subacute phase (day 2 to day 7 after randomization): SBP reduction (day 2 to day 7), mean, SD, and FSV.[24,25]

Outcome measurements

For this analysis, the primary outcome was the percentage of patients with functional independence at day 90. Secondary outcomes were good outcome and death at day 90, as well as functional independence, good outcome, death, decrease in NIHSS (ΔNIHSS), and increase in GCS (ΔGCS) at discharge. Functional independence was defined as a score of 0 to 2 measured with mRS. Good outcome was defined as mRS score of 0 to 3. Then, we analyzed the effect of individualized BP-lowering strategy on the outcomes. The adverse events (AEs) and serious adverse events (SAEs) were also collected.

Statistical analysis

Continuous data were summarized with median (interquartile range [IQR]) or mean (standard deviation [SD]), and compared using the Student's t test or the Wilcoxon rank-sum test, respectively. Dichotomous data were expressed as number with rates and compared using the chi-square test or Fisher exact test. The generalized estimating equations (GEE) were used to compare the changes in SBP between groups. The effect of individualized BP-lowering strategy on the functional outcomes was assessed using logistic regression models, adjusting for age, sex, time from onset to randomization, baseline GCS, and presence of infratentorial hemorrhage. A two-sided P value < 0.05 was considered significant. Statistical analyses were performed using SPSS version 19 software (SPSS Inc., Chicago, IL, United States).

Results

Study population and clinical characteristics

Of the 483 patients randomized in CHASE trial, 242 patients with severe ICH were included in the final analysis, consisting of 142 patients aged <65 years and 100 patients aged ≥65 years (Fig. 1). In patients with age <65 years, there were 75 patients receiving individualized BP-lowering treatment and 67 patients receiving standard BP-lowering treatment. In patients with age ≥65 years, there were 51 patients receiving individualized BP-lowering treatment and 49 patients receiving standard BP-lowering treatment. Demographics, baseline severity, time from onset to randomization, medical history, imaging characteristics, baseline SBP and hospital stay are displayed in Table 1 and Table 2. Compared to the patients aged <65 years, those patients aged ≥65 years presented with higher proportion of medical history of coronary artery disease (17.0% vs. 7.7%, $P = 0.027$) and diabetes (17.0% vs. 8.5%, $P = 0.044$), lower incidence of infratentorial hemorrhage (10.0% vs. 21.1%, $P = 0.029$). Patients aged ≥65 years had significantly higher baseline NIHSS scores (17 [13-21] vs. 14 [11-18], $P = 0.004$), lower baseline GCS scores (11 [8-13] vs. 12 [9-14], $P = 0.015$), and shorter hospital stays (14 [10-23] vs. 17 [13-24], $P = 0.011$) as compared with patients aged <65 years. In patients aged <65 years, most of the baseline characteristics were similar in individualized BP-lowering group and standard BP-lowering group except for the history of ischemic stroke (4.0% vs. 13.4%, $P = 0.044$), hypertension

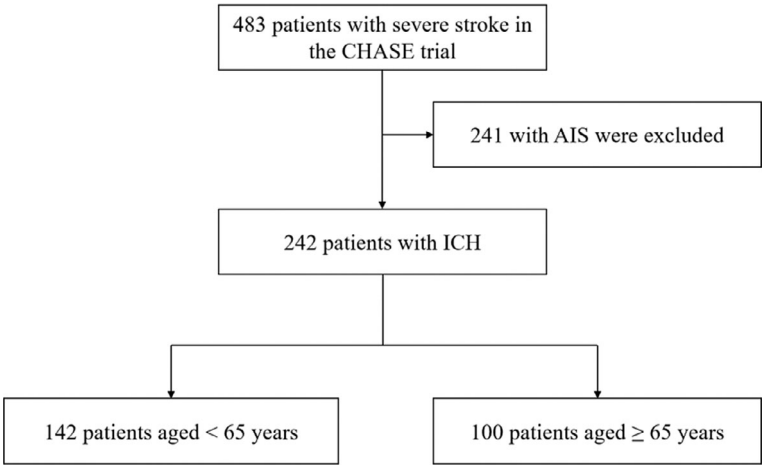

Figure 1. Flowchart. AIS, acute ischemic stroke, ICH, intracerebral hemorrhage.

Table 1. Baseline characteristics in patients aged <65 years and patients aged ≥65 years.

Characteristic	All (N = 242)	Age <65 years (N = 142)	Age ≥65 years (N = 100)	*P*-value
Demographics				
Age (years)	62 ± 12	53 ± 8	73 ± 6	<0.001
Male	149 (61.6%)	94 (66.2%)	55 (55.0%)	0.078
Severity				
Admission GCS	11 (8-14)	12 (9-14)	11 (8-13)	0.015
Admission NIHSS	15 (12-20)	14 (11-18)	17 (13-21)	0.004
Time from onset to randomization (h)	12 (4-28)	11 (4-26)	16 (5-33)	0.308
Medical history				
Ischemic stroke	26 (10.7%)	12 (8.5%)	14 (14.0%)	0.170
Hemorrhagic stroke	25 (10.3%)	12 (8.5%)	13 (13.0%)	0.252
Coronary artery disease	28 (11.6%)	11 (7.7%)	17 (17.0%)	0.027
Renal disease	2 (0.8%)	0 (0.0%)	2 (2.0%)	0.170
Diabetes	29 (12.0%)	12 (8.5%)	17 (17.0%)	0.044
Hypertension	197 (81.4%)	114 (80.3%)	83 (83.0%)	0.593
Imaging characteristics				
IVH (N = 221)	77 (34.8%)	42 (31.6%)	35 (39.8%)	0.211
Hematoma volume (mL)	13.0 (6.0-22.8)	12.0 (5.8-20.0)	15.0 (7.6-25.0)	0.135
Infratentorial hemorrhage (N = 223)	37 (16.6%)	28 (21.1%)	9 (10.0%)	0.029
Baseline SBP (mmHg)	176.6 ± 17.6	175.8 ± 17.9	177.9 ± 17.0	0.364
Hospital stays (d)	16 (12-23)	17 (13-24)	14 (10-23)	0.011

Abbreviations: GCS, glasgow coma scale; IVH, intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

Table 2. Baseline characteristics of ICH patients according to treatment in different age group.

	Age <65 years (N = 142)			Age ≥65 years (N = 100)		
Characteristic	Individualized BP-lowering (N = 75)	Standard BP-lowering (N = 67)	*P*-value	Individualized BP-lowering (N = 51)	Standard BP-lowering (N = 49)	*P*-value
Demographics						
Age (years)	54 ± 8	53 ± 8	0.605	74 ± 7	73 ± 6	0.606
Male	47 (62.7%)	47 (70.1%)	0.347	29 (56.9%)	26 (53.1%)	0.702
Severity						
Admission GCS	11 (8-14)	13 (9-15)	0.171	10 (8-13)	11 (8-14)	0.726
Admission NIHSS	14 (11-19)	14 (11-18)	0.861	17 (13-20)	16 (13-21)	0.614
Time from onset to randomization (h)	12 (5-33)	10 (3-24)	0.166	10 (3-24)	18 (5-35)	0.197
Medical History						
Ischemic stroke	3 (4.0%)	9 (13.4%)	0.044	9 (17.6%)	5 (10.2%)	0.284
Hemorrhagic stroke	6 (8.0%)	6 (9.0%)	0.838	6 (11.8%)	7 (14.3%)	0.708
Coronary artery disease	5 (6.7%)	6 (9.0%)	0.611	7 (13.7%)	10 (20.4%)	0.374
Renal disease	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	2 (4.1%)	0.145
Diabetes	5 (6.7%)	7 (10.7%)	0.419	9 (17.6%)	8 (16.3%)	0.860
Hypertension	55 (73.3%)	59 (88.1%)	0.028	45 (88.2%)	38 (77.6%)	0.155
Imaging Characteristics						
IVH (N = 221)	30 (40.5%)	12 (20.3%)	0.013	19 (37.3%)	16 (43.2%)	0.571
Hematoma volume (mL)	10.0 (5.0-20.0)	15.0 (6.0-21.0)	0.277	13.0 (7.0-27.3)	15.0 (8.3-25.0)	0.711
Infratentorial hemorrhage (N = 223)	17 (23.3%)	11 (18.3%)	0.486	4 (7.8%)	5 (12.8%)	0.493
Baseline SBP	176.6 ± 17.6	174.9 ± 18.4	0.576	178.9 ± 15.8	176.8 ± 18.2	0.542
Hospital stays (d)	16 (13-24)	17 (15-23)	0.463	14 (9-27)	14 (10-21)	0.908

Abbreviations: GCS, glasgow coma scale; IVH, intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

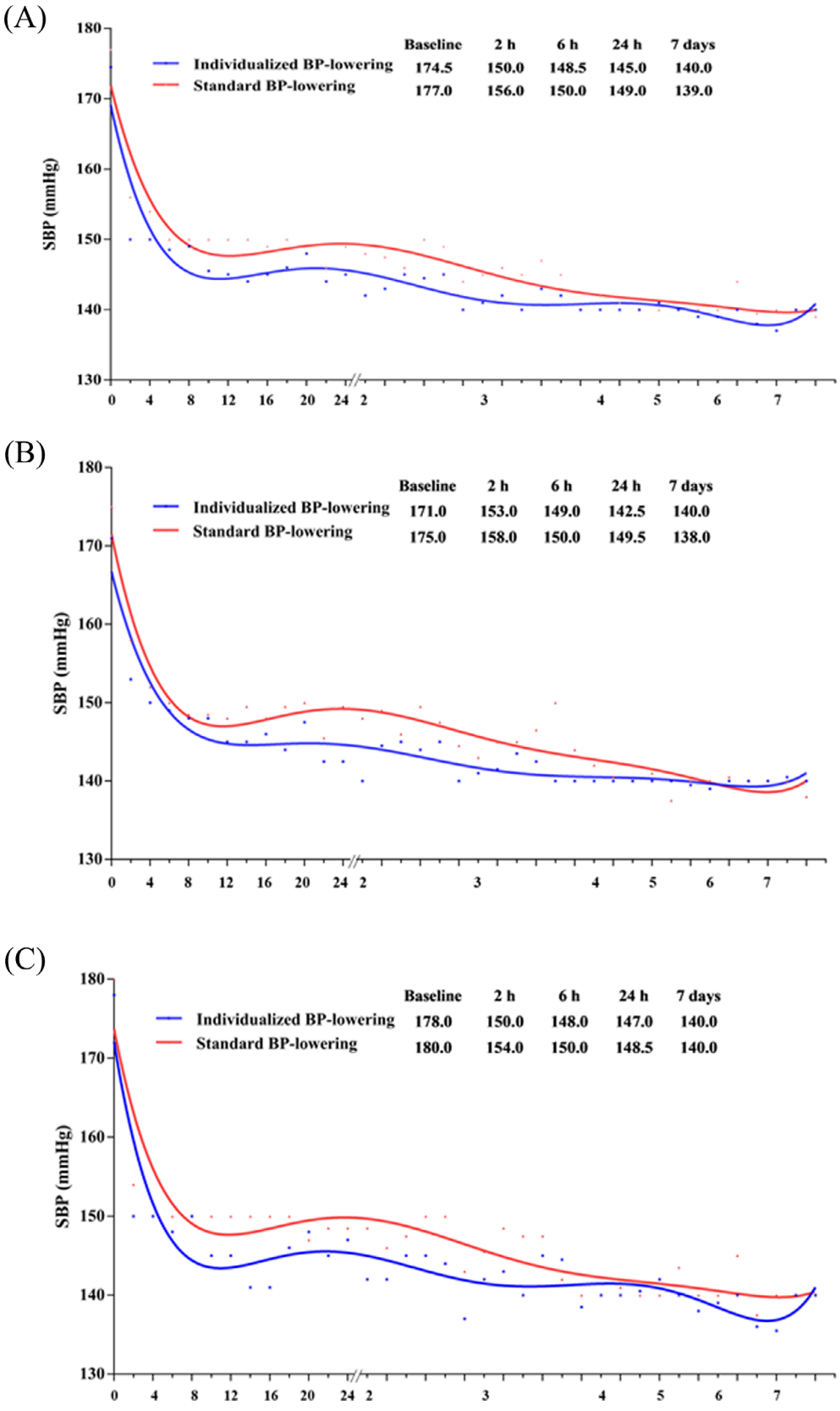

Figure 2. The derivative curve of mean systolic blood pressure during the first 7 days after enrollment. (A) All age group: The mean systolic blood pressure (SBP) was150.0, 148.5, 145.0, 140.0 mmHg in the individualized treatment group and 156.0, 150.0, 149.0, and 139.0 mmHg in the standard treatment group at the first 2 h, 6 h, 24 h, and 7 days after enrollment, respectively (mean difference from baseline to day 7: −4.536, 95% CI: −7.320 to −1.752, P = 0.001). (B) Age <65 years group: The mean SBP was153.0, 149.0, 142.5, and 140.0 mmHg in the individualized treatment group and 158.0, 150.0, 149.5, and 138.0 mmHg in the standard treatment group at the first 2 h, 6 h, 24 h, and 7 days after enrollment, respectively (mean difference from baseline to day 7: −3.025, 95% CI: −6.798 to 0.748, P = 0.116). (C) Age ≥65 years group: The mean SBP was 150.0, 148.0, 147.0, and 140.0 mmHg in the individualized treatment group and 154.0, 150.0, 148.5, and 140.0 mmHg in the standard treatment group at the first 2 h, 6 h, 24 h, and 7 days after enrollment, respectively (mean difference from baseline to day 7: −6.508, 95% CI: −10.514 to −2.502, *P* = 0.001).

Table 3. Systolic blood pressure features of patients.

	Age <65 years			Age ≥65 years		
	Individualized BP-lowering	Standard BP-lowering	*P*-value	Individualized BP-lowering	Standard BP-lowering	*P*-value
Acute (N = 225)						
SBP reduction (2 h, mmHg)	23.0 (10.0-31.0)	14.5 (1.0-26.0)	0.004	29.0 (17.0-47.0)	13.0 (0.0-27.0)	0.002
SBP reduction (4 h, mmHg)	26.0 (10.0-43.0)	16.5 (6.8-31.5)	0.083	30.0 (21.0-46.0)	16.0 (8.0-28.0)	< 0.001
SBP reduction (6 h, mmHg)	26.0 (15.0-39.0)	20.0 (8.8-34.3)	0.076	30.0 (18.0-48.0)	16.0 (8.0-40.0)	0.006
SBP reduction (12 h, mmHg)	29.5 (17.8-43.3)	22.5 (10.0-41.0)	0.133	36.0 (19.0-51.0)	22.0 (7.0-34.0)	0.022
SBP reduction (24 h, mmHg)	31.5 (19.0-42.5)	28.0 (10.0-41.0)	0.241	30.0 (19.0-46.0)	21.0 (10.0-43.3)	0.139
Mean (mmHg)	160.0 ± 12.0	163.9 ± 13.9	0.085	159.3 ± 10.3	165.2 ± 14.5	0.027
SD	11.1 ± 4.9	11.1 ± 4.3	0.968	11.0 ± 4.8	10.8 ± 4.4	0.795
FSV	19.0 ± 8.3	19.2 ± 7.8	0.887	19.6 ± 8.5	18.9 ± 7.9	0.677
Subacute (N = 205)						
SBP reduction (day 2 to day 7, mmHg)	7.0 (0.0-20.0)	9.5 (−2.5-22.8)	0.712	2.0 (−6.0-16.0)	3.5 (−4.5-18.3)	0.566
Mean (mmHg)	141.5 ± 10.8	142.7 ± 13.1	0.558	140.0 ± 8.7	143.9 ± 11.0	0.093
SD	11.0 ± 3.5	11.3 ± 3.5	0.562	10.4 ± 4.3	11.7 ± 4.6	0.197
FSV	11.6 ± 3.6	11.5 ± 3.5	0.964	10.8 ± 4.5	12.4 ± 5.3	0.187

Abbreviations: FSV, functional successive variation; SBP, Systolic blood pressure; SD, standard deviation.

(73.3% vs. 88.1%, *P* = 0.028) and intraventricular hemorrhage (IVH) (40.5% vs. 20.3%, *P* = 0.013). In patients aged ≥65 years, the baseline characteristics were all balanced between individualized BP-lowering group and standard BP-lowering group.

Blood pressure features

As shown in Table S1, more patients aged <65 years than aged ≥65 years received antihypertensive agents (84.5% vs. 74.0%, *P* = 0.044) and calcium channel blocker agents (66.9% vs. 53.0%, *P* = 0.029). There was no difference in the proportion of patients meeting their BP target as the protocol recommended between patients aged <65 years and ≥65 years at 2 h (77.4% vs. 83.3%, *P* = 0.274), 4 h (83.9% vs. 91.1%, *P* = 0.119), and 6 h (89.1% vs. 93.3%, *P* = 0.276). The median time from baseline to reaching BP target was similar between different age groups (age < 65 years: 2 [2-2] h vs. age ≥65 years: 2 [2-2] h, *P* = 0.247).

The blood pressure features are presented in Figure 2 and Table 3. The mean SBPs during the first 24 h and the following 6 days after randomization are displayed in Figure 2. Compared with the changes in SBP in standard BP-lowering group from baseline to day 7, the individualized BP-lowering group showed a statistically significant reduction in patients with all ages group (mean difference: −4.536, 95% CI: −7.320 to −1.752, *P* = 0.001) and age ≥65 years groups (mean difference: −6.508, 95% CI: −10.514 to −2.502, *P* = 0.001), rather than age <65 years group (mean difference: −3.025, 95% CI: −6.798 to 0.748, *P* = 0.116) (Fig. 2).

During the first 2 h after randomization, the median SBP reduction was significantly more in individualized BP-lowering group than standard BP-lowering group in both age groups (<65 years: 23.0 mmHg vs. 14.5 mmHg, *P* = 0.004; ≥65 years: 29.0 mmHg vs. 13.0 mmHg, *P* = 0.002). In patients aged ≥65 years old, the median SBP reduction during the first 4h, 6 h, and 12h were all significantly more in patients assigned to individualized BP-lowering group than patients assigned to standard BP-lowering group (all *P* < 0.05). The mean SBP was significantly lower in patients aged ≥ 65 years assigned to

Table 4. Outcomes of ICH patients.

Outcome	Age <65 years (N = 142)			Age ≥65 years (N = 100)		
	Individualized BP-lowering (N = 75)	Standard BP-lowering (N = 67)	*P*-value	Individualized BP-lowering (N = 51)	Standard BP-lowering (N = 49)	*P*-value
Day 90						
mRS	3 (2–3)	3 (1–4)	0.796	3 (3–5)	4 (3–5)	0.142
Barthel index	70 (50–90)	65 (40–90)	0.602	40 (5–80)	35 (4–60)	0.174
Functional independence (mRS 0-2)	35 (46.7%)	33 (49.3%)	0.758	11 (21.6%)	4 (8.2%)	0.061
Good outcome (mRS 0-3)	59 (78.7%)	46 (68.7%)	0.175	29 (56.9%)	21 (42.9%)	0.161
Death	5 (6.7%)	5 (7.5%)	1.000	11 (21.6%)	9 (18.4%)	0.689
Discharge						
NIHSS	9 (5–11)	9 (6–14)	0.630	10 (7–15)	14 (9–25)	0.026
GCS	15 (13–15)	15 (14–15)	0.049	15 (10–15)	14 (8–15)	0.766
mRS	4 (3–4)	4 (3–4)	0.585	4 (4–5)	4 (4–5)	0.175
Barthel index	40 (20–60)	35 (20–55)	0.602	20 (10–40)	20 (0–30)	0.331
Functional independence (mRS 0-2)	9 (12.0%)	12 (17.9%)	0.322	3 (5.9%)	2 (4.1%)	1.000
Good outcome (mRS 0-3)	27 (36.0%)	26 (38.8%)	0.730	9 (17.6%)	7 (14.3%)	0.647
Death	3 (4.0%)	3 (4.5%)	1.000	5 (9.8%)	3 (6.1%)	0.715
Δ NIHSS	6 (3–9)	5 (2–9)	0.149	6 (2–9)	2 (−1.5–5)	0.001
Δ NIHSS ≥4	53 (70.7%)	42 (62.7%)	0.313	33 (64.7%)	17 (34.7%)	0.003
Δ GCS	1 (0–4)	1 (0–4)	0.533	2 (0–4)	1 (0–3)	0.119

Abbreviations: Δ GCS, GCS increase from baseline to discharge; Δ NIHSS, NIHSS decrease from baseline to discharge; GCS, glasgow coma scale; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

individualized BP-lowering group than standard BP-lowering group (159.3 mmHg vs. 165.2 mmHg, $P = 0.027$). The SD and FSV were similar in patients receiving individualized BP-lowering treatment and standard BP-lowering treatment in both age groups (Table 3).

Differences in SBP reduction between different age group were further explored in patients receiving individualized BP-lowering treatment. Patients aged ≥65 years showed a significantly SBP reduction during the first 2 h after randomization than patients aged <65 years (29.0 mmHg vs. 23.0 mmHg, $P = 0.028$). However, no significant difference was observed in SBP reduction during the first 4 h, 6 h, 12 h, and 24 h after randomization between different age groups in patients receiving individualized BP-lowering treatment.

Clinical outcomes

There were significant differences between patients aged ≥65 years and patients aged < 65 years in the proportion of functional independence (47.9% vs. 15.0%, $P < 0.001$) and good outcome (73.9% vs. 50.0%, $P < 0.001$) at day 90. As displayed in Table S2, patients with age ≥65 years presented with higher percentage of renal failure and pneumonia after severe ICH than younger patients (renal failure: 4.0% vs. 0.0%, $P = 0.028$; pneumonia: 60.0% vs. 45.1%, $P = 0.022$). Other AEs and SAEs were similar in different age groups.

In patients aged <65 years, the outcomes at day 90 and discharge were all comparable in individualized BP-lowering group and standard BP-lowering group (Table 4). The distribution of mRS at day 90 in patients aged <65 years was similar in both treatment groups (Fig. 3A).

In patients with age ≥65 years, the outcomes at day 90 and discharge were better in those receiving individualized BP-lowering treatment than standard BP-lowering treatment (Table 4). At day 90, the proportion of functional independence was higher in patients assigned to individualized BP-lowering group than standard BP-lowering group (21.6% vs. 8.2%, $P = 0.061$). The distribution of 90-day mRS in patients aged ≥65 years is presented in Figure 3B. At hospital discharge, the NIHSS was significantly lower in patients assigned to individualized BP-lowering group than standard BP-lowering group (10 vs. 14, $P = 0.026$). The decrease in NIHSS from baseline level to discharge (ΔNIHSS) was 6 in the individualized BP-lowering group and was 2 in the standard BP-lowering group ($P = 0.001$). The percentage of ΔNIHSS ≥ 4 at discharge was significantly higher in individualized BP-lowering group than standard BP-lowering group (64.7% vs. 34.7%, $P = 0.003$).

After adjustment for factors including age, sex, time from onset to randomization, baseline GCS, and the presence of infratentorial hemorrhage or not, the effects of individualized BP-lowering treatment on clinical outcomes are presented in Figure 4. The individualized BP-lowering treatment had an unequivocal effect on improving the outcomes at both day 90 and discharge in patients

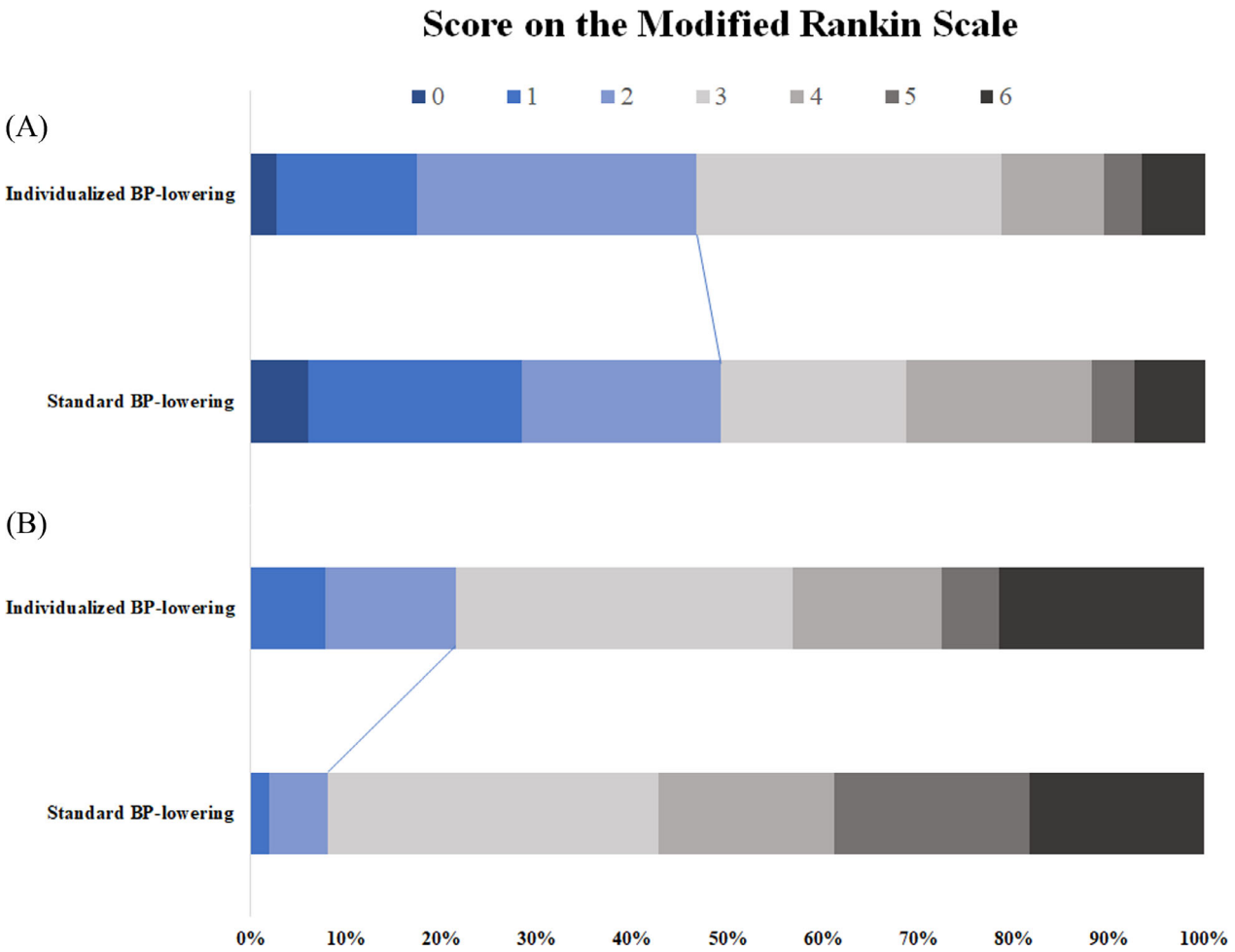

Figure 3. The distribution of the modified Rankin Scale at 90 days according to different age group. (A) Age <65 years; (B) Age ≥65 years. Scores range from 0 to 6 indicating no symptoms to death.

aged ≥65 years (functional independence at day 90: OR: 4.309, 95% CI: 1.040-17.859, $P = 0.044$; Δ NIHSS ≥ 4 at discharge: OR: 4.300, 95% CI: 1.599-11.563, $P = 0.004$).

Discussion

The current exploratory analysis of the CHASE trial evaluated the impact of an individualized BP-lowering treatment with a target of 10%-15% reduction in SBP from baseline level, on outcomes of ICH patients in different age groups. In patients with younger age (<65 years old), the individualized BP-lowering treatment was not associated with outcomes at either discharge or 90 days. On the other hand, the individualized BP-lowering treatment had a significant effect on increasing the proportion of favorable outcome at both discharge and 90 days in patients with older age. These findings suggest that the individualized BP-lowering treatment could be regarded as an optimal management of elevated BP in elderly patients with severe ICH.

It has been indicated that elevated levels of SBP after ICH were associated with poor functional outcomes.[12–15] With the increasing of age and the consequent decline of BP regulation capacity, elderly's BP level could be easily affected by various factors, resulting in frequently abnormal BP fluctuation, which would make things worse.[2,6–8,26] In this exploratory analysis, we confirmed that the elderly patients aged ≥65 years with ICH experienced more severe manifestations, lower incidence of infratentorial hemorrhage, and more comorbidities, as well as poor outcomes, which were in accordance with previous studies.[6,8]

Despite the serious condition in elderly patients with severe ICH, no definite evidence for the management of elevated BP in those patients is available. The INTERACT2 (with mean age of 63.5 years) and ATACH-II (with mean age of 61.9 years) trial compared the early intensive

Outcomes	Individualized BP-lowering (N, %)	Standard BP-lowering (N, %)	OR (95%CI)	P value
Day 90				
Functional independence				
Age < 65 yr	35 (46.7%)	33 (49.3%)	1.004 (0.461-2.189)	0.992
Age ≥ 65 yr	11 (21.6%)	4 (8.2%)	4.309 (1.040-17.859)	0.044
Good outcome				
Age < 65 yr	59 (78.7%)	46 (68.7%)	2.405 (0.896-6.454)	0.081
Age ≥ 65 yr	29 (56.9%)	21 (42.9%)	2.154 (0.801-5.793)	0.129
Death				
Age < 65 yr	5 (6.7%)	5 (7.5%)	0.700 (0.119-4.127)	0.694
Age ≥ 65 yr	11 (21.6%)	9 (18.4%)	1.130 (0.258-4.938)	0.871
Discharge				
Functional independence				
Age < 65 yr	9 (12.0%)	12 (17.9%)	0.723 (0.268-1.948)	0.521
Age ≥ 65 yr	3 (5.9%)	2 (4.1%)	2.360 (0.207-26.972)	0.49
Good outcome				
Age < 65 yr	27 (36.0%)	26 (38.8%)	1.024 (0.481-2.177)	0.951
Age ≥ 65 yr	9 (17.6%)	7 (14.3%)	1.346 (0.435-4.782)	0.617
Death				
Age < 65 yr	3 (4.0%)	3 (4.5%)	1.672 (0.132-21.199)	0.692
Age ≥ 65 yr	5 (9.8%)	3 (6.1%)	4.473 (0.341-58.717)	0.254
Δ NIHSS ≥4				
Age < 65 yr	53 (70.7%)	42 (62.7%)	1.250 (0.588-2.658)	0.562
Age ≥ 65 yr	33 (64.7%)	17 (34.7%)	4.300 (1.599-11.563)	0.004

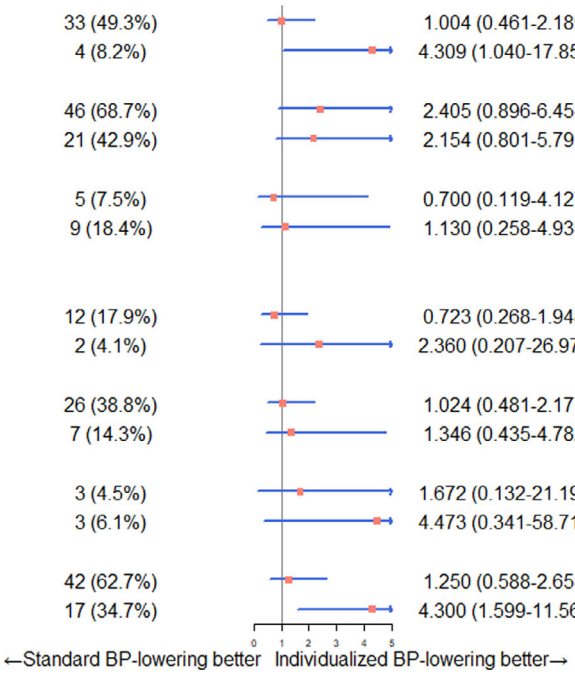

Figure 4. Effect of individualized BP-lowering treatment on the outcomes according to different age group. Adjusted by age, sex, time from onset to randomization, baseline GCS, infratentorial hemorrhage or not. Δ NIHSS, the decrease in NIHSS from baseline to discharge. NIHSS, National Institutes of Health Stroke Scale.

BP lowering with standard management in ICH patients with median NIHSS of 10 to 11.[18,19] However, the efficacy and safety of intensive BP lowering from above two studies had been a controversial topic and the conclusions might not be suitable for patients with severe ICH. An additional post hoc analysis of ATACH-2 trial suggested that the intensive SBP reduction did not reduce the poor outcome in patients with moderate to severe ICH.[21] Although the Guidelines for ICH suggested lowering the SBP to 140 mmHg in patients with SBP between 150 and 220 mmHg, none of them focused on elderly patients with severe ICH.[11,16,17]

In this analysis, we found that the percentage of favorable outcomes in elderly patients receiving individualized BP-lowering was significantly higher than those treated with standard BP-lowering at both discharge and 90 days. After adjusting the confounding factors in elderly patients, the use of individualized BP-lowering treatment after severe ICH was positively correlated to the favorable outcomes at both discharge and 90 days. As for the BP features, the SBP of elderly patients assigned to individualized BP-lowering group was reduced to <150 mmHg within 4 h, reached to about 145 mmHg within 8 h, and fluctuated around 140 mmHg during the following 6 days.

The current exploratory analysis included the elderly patients from the CHASE trial, which focused on the BP management after an acute severe stroke, with low loss of follow-up. However, some limitations should also be noted. Firstly, the sample size of the current analysis was relatively small, thus a further large-scale clinical trial is necessary to verify the findings. Secondly, the detailed imaging data of the patients were not collected, thus it's hard to know the effect of different BP-lowering treatment on the hematoma and edema after ICH. Thirdly, the data of discharge disposition was not collected, which may influence the outcome as well.

In conclusion, the individualized BP-lowering treatment in patients aged ≥65 years with acute severe ICH was positively associated with favorable outcomes at both discharge and 90 days. Elderly patients with acute severe ICH might benefit more from individualized BP-lowering treatment during the first seven days compared with the younger counterparts.

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Conflict of Interest

None.

Authors' Contributions

This study was conceived by F Yang and WJ. WJ was the chief investigator, and JJZ and F Yuan were sub-investigators. FF, YL, CHX, KJW, XJY, DAL, QWL, WZ, YJ, JBH, JZ, XCW, HL, KH, ZHL, BZ, CKW, and HZL were the principal investigators at each study site. XMW analyzed the data and conducted the statistical analysis. The manuscript was produced by JJZ and F Yang with advice from WJ. All the authors are responsible for this study and the final content of the paper.

Ethics Approval

The study was approved by the ethics committee of each hospital.

Consent to Participate

All participants or their legally authorized representatives provided written informed consent at enrollment.

Consent for Publication

All the authors have approved the publication of this manuscript.

Data Availability Statement

The detailed data will be available from the corresponding authors for reasonable request.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary 1. Protocol of CHASE trial.
Supplementary 2. Supplemental tables.
Table S1. Blood pressure treatment for patients aged <65 years and ≥65 years.
Table S2. AEs and SAEs in patients aged <65 years and patients aged ≥65 years.

