ORIGINAL ARTICLE

Intensive Ambulance-Delivered Blood-Pressure Reduction in Hyperacute Stroke

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ABSTRACT

BACKGROUND

Treatment of acute stroke, before a distinction can be made between ischemic and hemorrhagic types, is challenging. Whether very early blood-pressure control in the ambulance improves outcomes among patients with undifferentiated acute stroke is uncertain.

METHODS

We randomly assigned patients with suspected acute stroke that caused a motor deficit and with elevated systolic blood pressure (≥150 mm Hg), who were assessed in the ambulance within 2 hours after the onset of symptoms, to receive immediate treatment to lower the systolic blood pressure (target range, 130 to 140 mm Hg) (intervention group) or usual blood-pressure management (usual-care group). The primary efficacy outcome was functional status as assessed by the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at 90 days after randomization. The primary safety outcome was any serious adverse event.

RESULTS

A total of 2404 patients (mean age, 70 years) in China underwent randomization and provided consent for the trial: 1205 in the intervention group and 1199 in the usual-care group. The median time between symptom onset and randomization was 61 minutes (interquartile range, 41 to 93), and the mean blood pressure at randomization was 178/98 mm Hg. Stroke was subsequently confirmed by imaging in 2240 patients, of whom 1041 (46.5%) had a hemorrhagic stroke. At the time of patients' arrival at the hospital, the mean systolic blood pressure in the intervention group was 159 mm Hg, as compared with 170 mm Hg in the usual-care group. Overall, there was no difference in functional outcome between the two groups (common odds ratio, 1.00; 95% confidence interval [CI], 0.87 to 1.15), and the incidence of serious adverse events was similar in the two groups. Prehospital reduction of blood pressure was associated with a decrease in the odds of a poor functional outcome among patients with hemorrhagic stroke (common odds ratio, 0.75; 95% CI, 0.60 to 0.92) but an increase among patients with cerebral ischemia (common odds ratio, 1.30; 95% CI, 1.06 to 1.60).

CONCLUSIONS

In this trial, prehospital blood-pressure reduction did not improve functional outcomes in a cohort of patients with undifferentiated acute stroke, of whom 46.5% subsequently received a diagnosis of hemorrhagic stroke. (Funded by the National Health and Medical Research Council of Australia and others; INTERACT4 ClinicalTrials.gov number, NCT03790800; Chinese Trial Registry number, ChiCTR1900020534.)

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*A complete list of trial sites, investigators, and coordinators in the INTERACT4 trial is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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The optimal approach to blood-pressure control in patients with acute stroke is uncertain.[1,2] Bundled-care protocols incorporating intensive treatment to lower blood pressure have been shown to benefit patients with acute intracerebral hemorrhage,[3,4] but trials evaluating blood-pressure reduction alone have produced inconsistent results.[5,6] Differences in trial design, intervention, and population may explain these findings.[7-9] Because the important treatment goal of limiting hematoma expansion is time-dependent,[10] the effects of blood-pressure reduction might be enhanced if treatment to lower blood pressure is initiated as early as possible.[11-14] However, in patients with acute ischemic stroke, the role of early intensive blood-pressure reduction is an even more complicated issue.[15]

The safety and efficacy of prehospital blood-pressure reduction within several hours after acute stroke were investigated in two phase 3 multicenter trials that had similar designs and produced similar results. The Second Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT-2) showed no effect of a transdermal glyceryl trinitrate patch as compared with a sham patch in the intention-to-treat population, but in the subgroup of 142 patients with intracerebral hemorrhage, those who received the glyceryl trinitrate patch had worse outcomes than those who received the sham patch.[16,17] A trend toward higher mortality from intracerebral hemorrhage with the use of transdermal glyceryl trinitrate was noted in the Multicenter Randomized Trial of Acute Stroke Treatment in the Ambulance with a Nitroglycerin Patch (MR ASAP), which prompted the early termination of that trial after 380 patients were enrolled.[18]

We conducted the Fourth Intensive Ambulance-Delivered Blood Pressure Reduction in Hyper-Acute Stroke Trial (INTERACT4) to evaluate the safety and efficacy of initiating intravenous antihypertensive treatment in the ambulance within 2 hours after an acute stroke.

Methods

Study Design and Oversight

We conducted an open-label, randomized trial, with blinded outcome assessment, at 51 hospitals in China; 43 of the participating sites used hospital-based ambulance services, and 8 (6 in Shanghai Pudong, 1 in Xuzhou, and 1 in Yantai) used centralized ambulance services (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Details of the rationale of the trial, the trial design, and the analysis of trial data are provided in the protocol, available at NEJM.org.[19-21] The trial was sponsored in part by Takeda Pharmaceuticals China, the manufacturer of the principal medication (urapidil) used in the trial, but this sponsor had no role in the conduct of the trial. An international steering committee designed the trial. The trial was monitored by an independent data and safety monitoring board. Personnel at the George Institute for Global Health China performed the analyses and coordinated the trial with regional research centers in Shanghai and Chengdu.

The ethics committee at each participating site approved the use of a two-stage process for obtaining consent from participants or approved surrogates: initial use of either a brief written informed consent (one site) or a waiver of consent (all other sites) for the intervention to commence in the ambulance, followed by written consent obtained in the hospital for the use of medical data and for follow-up. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The fourth author wrote the first draft of the manuscript. All the other authors commented on drafts of the manuscript and agreed to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

Patients

Adult patients (≥18 years of age) were eligible for the trial if they had a presumed acute stroke, defined by a FAST score (face [facial droop]–arms [inability to lift arms]–speech [slurred speech]–time [time to call emergency services]) of 2 or higher (range, 0 to 4, with higher scores indicating more symptoms) that included an arm motor deficit; elevated systolic blood pressure (≥150 mm Hg); and the ability to start treatment within 2 hours after symptom onset or after they were last known to be well. Patients who were in a coma or who had severe coexisting disease, epilepsy, a recent head injury, or hypoglycemia were not eligible. A patient's eligibility was determined by ambulance staff who were doctors employed by the participating ambulance services. Details of the inclu-

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sion and exclusion criteria are provided in the Supplementary Appendix.

RANDOMIZATION AND PROCEDURES

After confirmation of eligibility, patients were randomly assigned, in a 1:1 ratio, to receive prehospital blood-pressure reduction (intervention group) or to receive usual blood-pressure management (i.e., commencement of blood-pressure management on arrival at the hospital) (usual-care group). Randomization was performed with the use of a central Web-based system that included a minimization algorithm to balance the stratification factors of region (eastern vs. western China), age (≥65 years vs. <65 years), and FAST score (≥3 vs. 2).

For patients assigned to the intervention group, the goal was to initiate treatment immediately after randomization to achieve a systolic blood pressure between 130 and 140 mm Hg within 30 minutes and to maintain this blood pressure until arrival at the hospital. For patients assigned to usual care, treatment to lower blood pressure was used in the ambulance only for systolic blood pressure of 220 mm Hg or higher or for diastolic blood pressure of 110 mm Hg or higher. Both groups received in-hospital blood-pressure management and other care according to established local guidelines. In China, the recommended targets for systolic blood pressure in the hospital setting are less than 140 mm Hg in patients with acute intracerebral hemorrhage[22] and 140 to 160 mm Hg in patients with acute ischemic stroke.[23]

The recommended treatment regimen to lower blood pressure in the ambulance was an intravenous bolus of 25 mg of urapidil administered over 1 minute, with the dose repeated only once after 5 minutes if the blood pressure remained elevated. Urapidil is an intravenous antihypertensive drug that is widely used in China, with α_1-adrenoceptor antagonist and 5-hydroxytryptamine type 1A (5-HT_{1A}) receptor agonist activity that results in an almost immediate effect on blood pressure that peaks within 5 minutes and subsides completely within 4 hours. Patients were kept in a horizontal position with their blood pressure monitored every 5 minutes in the ambulance while they were being transported. A systolic blood pressure of 130 mm Hg was considered to be the threshold for cessation of treatment. The ambulance staff notified the receiving hospital staff of the patients' assigned treatment group; treatment with urapidil or another agent as a bolus, infusion, or oral administration was to continue in the emergency department, stroke unit, or monitored facility.

Ambulance staff were trained to assess patients for trial eligibility, perform randomization, administer the assigned treatment, and collect key baseline data. Further data were collected at the hospital with the use of standard diagnostic criteria for transient ischemic attack and acute stroke caused by cerebral ischemia or acute stroke caused by intracerebral hemorrhage or subarachnoid hemorrhage. The level of neurologic impairment was assessed according to the National Institutes of Health Stroke Scale (NIHSS) (range, 0 to 42, with higher scores indicating greater neurologic deficits). Follow-up data (including NIHSS scores) were collected at 24 hours and at 7 days after randomization or at the time of hospital discharge if discharge occurred earlier than 7 days. Follow-up evaluations were undertaken at 90 days, either in person or by telephone, by trained, certified staff who were unaware of the assigned treatment group. All brain images were analyzed by expert assessors who were unaware of the assigned treatment group (procedures are outlined in the Supplementary Appendix); for this report, only the abnormalities noted by investigators are included.

OUTCOMES

The primary outcome was functional status, which was assessed by the distribution of scores on the modified Rankin scale at 90 days. The modified Rankin scale is a standard global 7-level measure of disability, in which a score of 0 or 1 indicates a favorable outcome without symptoms or with symptoms but no disability, scores of 2 through 5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death. Secondary efficacy outcomes were disability or death and were evaluated with the use of a conventional dichotomous analysis of scores on the modified Rankin scale at 90 days: 3 through 6 (moderate-to-severe disability or death) as compared with 0 through 2. The following outcomes were also assessed: death from any cause and cause-specific death within 90 days, neurologic impairment (as indicated by NIHSS scores) at 24 hours and 7 days, disability (scores of 3 through 5 on the modified Rankin scale) at 90 days, hospital discharge by day 7, living situation (residing at home or in an institution) at 90 days, and health-relat-

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ed quality of life as measured by the EuroQol 5-dimension 3-level (EQ-5D-3L) patient-reported questionnaire at 90 days. The EQ-5D-3L questionnaire combines scores from five domains of health-related quality of life to calculate an overall health utility score, with a score of 1 indicating perfect health, 0 indicating death, and negative scores indicating health states considered to be worse than death. For patients with intracerebral hemorrhage, investigators provided details regarding hematoma volumes on computed tomographic (CT) scans at baseline and at 24 hours. The prespecified safety outcome was any serious adverse event.

STATISTICAL ANALYSIS

We calculated that a sample size of 2320 patients would provide the trial with 90% power to detect 22% lower odds of a poor functional outcome in the intervention group than in the usual-care group (common odds ratio, 0.78), under the assumption that 6% of patients would have a condition mimicking a stroke and that an assessment of the primary outcome would be unavailable for 5% of patients.[16,18,20,24] The primary-outcome analysis was based on the intention-to-treat population. Sensitivity analysis of the primary outcome included additional adjustments for the covariates of prestroke function, sex, and time from symptom onset to randomization. The use of multiple imputation was planned but not undertaken, since the amount of missing data was below a prespecified threshold of 5%. A per-protocol analysis included patients who received the assigned treatment and had no clinically meaningful deviations from the protocol. We also conducted an analysis in the modified intention-to-treat population, which included patients with cerebral ischemia (ischemic stroke or transient ischemic attack) or a nonstructural cause of intracerebral hemorrhage and excluded patients with a condition that mimicked a stroke, those with a structural cause of intracerebral hemorrhage, and those with subarachnoid hemorrhage.

The primary analysis was performed with the use of ordinal logistic regression after confirmation that the proportional-odds assumption was not violated. The model included the group assignment and the stratification variables as fixed effects, with within-subject correlations accounted for as random or repeated effects. Given the use by the data and safety monitoring board of the conservative Haybittle–Peto stopping boundary and the negligible amount of type I error in a single interim analysis of the emerging data, a P value of less than 0.05 was used to indicate statistical significance. Secondary efficacy analyses were performed with the use of ordinal logistic regression. EQ-5D-3L health utility scores were calculated on the basis of a Chinese general population.[25,26] We analyzed 10 prespecified subgroups. Because the subgroup analysis was not part of a hierarchical plan with adjustment for multiple comparisons, we report only point estimates with 95% confidence intervals, from which causal inferences should not be made. SAS software (version 9.3 or above; SAS Institute) and R software (version 4.0.0 or above) were used in the analyses.

RESULTS

PATIENTS

Between March 20, 2020, and August 31, 2023, a total of 2425 patients underwent randomization and treatment in China: 1215 were assigned to undergo prehospital treatment for blood-pressure reduction, and 1210 to undergo usual care. Consent could not be obtained from 9 patients in the intervention group and 11 in the usual-care group, and consent was withdrawn by 1 patient in the intervention group. Thus, the intention-to-treat population included 1205 patients in the intervention group and 1199 in the usual-care group. Primary outcome data were available for 2362 patients (98.3%; 1185 in the intervention group and 1177 in the usual-care group); 41 patients (20 in the intervention group and 21 in the usual-care group) could not be contacted, and 1 patient in the usual-care group declined to participate. (Details regarding screening, randomization, and follow-up are provided in Figs. S2 and S3 and Tables S1 through S5.)

The two treatment groups were well balanced with regard to demographic and clinical characteristics; 99.0% of patients were of Han Chinese descent (Table 1 and Table S6). The mean (±SD) age was 70±13 years, and 61.7% were men. The median time from symptom onset to randomization was 61 minutes (interquartile range, 41 to 93), and the mean systolic blood pressure at randomization was 178±21 mm Hg. Among 2240 patients who received a diagnosis of stroke confirmed by imaging, 1041 (46.5%) had hemorrhagic stroke;

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Table 1. Characteristics of the Patients at Randomization and during Hospitalization.*

Characteristic	Intervention (N=1205)	Usual Care (N=1199)
Age — yr	70±12	70±13
Male sex — no. (%)	719 (59.7)	764 (63.7)
Prehospital FAST score — no. (%)†		
2	296 (24.6)	283 (23.6)
3	481 (39.9)	489 (40.8)
4	428 (35.5)	427 (35.6)
Median time from symptom onset to randomization (IQR) — min	63 (41–93)	59 (41–93)
Blood pressure at randomization — mm Hg		
Systolic	178±20	178±22
Diastolic	98±15	98±16
Median time from symptom onset to hospital arrival (IQR) — min	80 (54–114)	75 (55–115)
Blood pressure on arrival at hospital — mm Hg		
Systolic	159±26	170±27
Diastolic	89±16	94±17
Relevant medical history — no./total no. (%)‡		
Hypertension	862/1198 (72.0)	834/1195 (69.8)
Previous stroke	232/1198 (19.4)	238/1195 (19.9)
Coronary artery disease	158/1198 (13.2)	133/1195 (11.1)
Atrial fibrillation	109/1198 (9.1)	98/1195 (8.2)
Diabetes mellitus	220/1198 (18.4)	195/1195 (16.3)
Symptom-free function before stroke onset — no./total no. (%)‡§	807/1198 (67.4)	823/1195 (68.9)
Median NIHSS score on hospital arrival (IQR)¶	12 (6–18)	11 (6–17)
Median GCS score on hospital arrival (IQR)‖	13 (10–15)	13 (10–15)
Diagnosis — no. (%)		
Cerebral ischemia**	599 (49.7)	600 (50.0)
Hemorrhagic stroke††	522 (43.3)	519 (43.3)
Another condition mimicking a stroke‡‡	77 (6.4)	77 (6.4)
Uncertain	7 (0.6)	3 (0.3)

* Plus–minus values are means ±SD. Data are shown for the intention-to-treat population, which included all patients who underwent randomization and provided consent. IQR denotes interquartile range.
† The FAST score includes face (facial droop), arms (inability to lift arms), speech (slurred speech), and time (time to call emergency services). Scores range from 0 to 4, with higher scores indicating more symptoms.
‡ The total numbers are the numbers of patients for whom the data were available.
§ Symptom-free function was specified as a score of 0 (no symptoms) on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability or death.
¶ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater neurologic deficits.
‖ Scores on the Glasgow Coma Scale (GCS) range from 15 (normal) to 3 (deep coma).
** Included are 27 patients in the intervention group and 26 in the usual-care group who received a diagnosis of transient ischemic attack.
†† Included are 11 patients in the intervention group and 1 in the usual-care group who received a diagnosis of subarachnoid hemorrhage.
‡‡ Included are conditions such as migraine, seizure, functional weakness, and syncope (see Table S4).

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of these, 1029 (98.8%) had an intracerebral hemorrhage — with 872 (84.7%) having it in a deep location — and 12 (1.2%) had a subarachnoid hemorrhage. A total of 1199 patients (53.5%) had cerebral ischemia — of whom 907 (75.6%) had cerebral ischemia due to atheromatous occlusion of an extracranial or intracranial large vessel or cardioembolism — and 53 (4.4%) had a transient ischemic attack. The characteristics of patients with hemorrhagic stroke and of those with cerebral ischemia and the management of their treatment are summarized in Tables S7, S8, and S9. The representativeness of the patients is addressed in Table S10.

The percentage of patients who received any blood-pressure–lowering treatment in the ambulance was higher in the intervention group than in the usual-care group (89.5% [1078 patients] vs. 9.7% [116 patients]), and intravenous urapidil was used in 98.2% (1172) of those who received any blood-pressure–lowering treatment (Table S11). There were minimal between-group differences in blood-pressure–lowering therapy after arrival at the hospital and over days 2 through 7 (Table S12). At the time of arrival at the hospital, the mean systolic blood pressure was 159±26 mm Hg in the intervention group as compared with 170±27 mm Hg in the usual-care group; at 24 hours, it was 140±18 mm Hg as compared with 140±19 mm Hg; and at 7 days, it was 136±17 mm Hg as compared with 138±18 mm Hg. The estimated mean between-group difference in systolic blood pressure was –15 mm Hg (95% confidence interval [CI], –17 to –13) in the ambulance and –4 mm Hg (95% CI, –5 to –3) in the hospital (Table 1 and Table S13 and Figs. S4 through S7). Specific blood-pressure data for patients with hemorrhagic stroke and for those with cerebral ischemia are summarized in Figures S8 through S15. There were no major differences in other aspects of clinical management over the first 7 days after randomization, including the use of intravenous thrombolysis for patients with cerebral ischemia (Table S9).

PRIMARY OUTCOME

The distribution of scores on the modified Rankin scale at 90 days did not differ significantly between patients in the intervention group and those in the usual-care group (common odds ratio, 1.00; 95% CI, 0.87 to 1.15) (Fig. 1A, Table 2, and Table

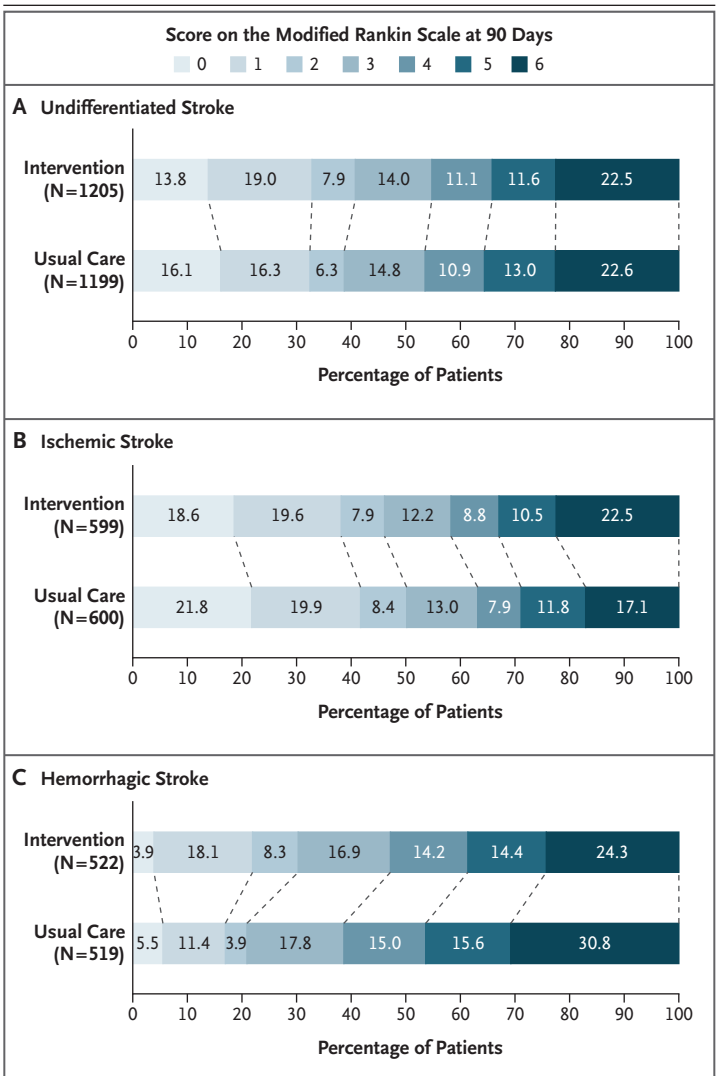

Figure 1. Functional Outcomes at 90 Days in the Two Groups, According to Scores on the Modified Rankin Scale (Primary Outcome).

Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderate-to-severe disability, 5 severe disability, and 6 death. For patients with undifferentiated stroke (Panel A), the distribution of scores did not differ significantly between the group that received immediate treatment to lower the systolic blood pressure (intervention group) and the group that received usual blood-pressure management (usual-care group); the common odds ratio was 1.00 (95% confidence interval [CI], 0.87 to 1.15) for a poor functional outcome after prehospital blood-pressure reduction. For patients with ischemic stroke (Panel B), including 53 with a transient ischemic attack, the distribution of scores indicates a significant increase in the odds of a poor functional outcome after prehospital blood-pressure reduction (common odds ratio, 1.30; 95% CI, 1.06 to 1.60), and for patients with hemorrhagic stroke (Panel C), including 12 with subarachnoid hemorrhage, the distribution of scores indicates a significant decrease in the odds of a poor functional outcome (common odds ratio, 0.75; 95% CI, 0.60 to 0.92).

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Table 2. Primary and Secondary Efficacy and Safety Outcomes at 90 Days.*

Outcome	Intervention (N=1205)	Usual Care (N=1199)	Odds Ratio (95% CI)†
Primary outcome			
Score on modified Rankin scale at 90 days — no./total no. (%)‡			
0: No symptoms	164/1185 (13.8)	190/1177 (16.1)	1.00 (0.87–1.15)§
1: No clinically significant disability despite symptoms	225/1185 (19.0)	192/1177 (16.3)	
2: Slight disability	94/1185 (7.9)	74/1177 (6.3)	
3: Moderate disability requiring some help	166/1185 (14.0)	174/1177 (14.8)	
4: Moderate-to-severe disability requiring assistance with daily living	131/1185 (11.1)	128/1177 (10.9)	
5: Severe disability; bed-bound and incontinent	138/1185 (11.6)	153/1177 (13.0)	
6: Death	267/1185 (22.5)	266/1177 (22.6)	
Secondary outcomes			
Score on modified Rankin scale at 90 days — no./total no. (%)			
3–6	702/1185 (59.2)	721/1177 (61.3)	0.92 (0.78–1.09)
3–5	435/918 (47.4)	455/911 (49.9)	0.90 (0.74–1.08)
Death within 90 days — no./total no. (%)	267/1185 (22.5)	266/1178 (22.6)	1.00 (0.82–1.22)
Median NIHSS score (IQR)			
At 24 hr	11.0 (4.0–19.0)	10.0 (4.0–18.0)	
At 7 days	8.0 (3.0–16.0)	9.0 (2.0–16.0)	
EQ-5D-3L overall health utility¶			
No. of patients	1182	1174	
Score	0.5±0.41	0.5±0.42	
Hospital discharge by day 7 — no./total no. (%)	333/1152 (28.9)	354/1149 (30.8)	0.92 (0.77–1.11)
Living in an institution at 90 days — no./total no. (%)	112/918 (12.2)	124/912 (13.6)	0.87 (0.66–1.16)
Safety			
Serious adverse events during follow-up — no. of events‖	350	351	
At least one serious adverse event — no. of patients (%)	331 (27.5)	344 (28.7)	

* Plus–minus values are means ±SD.

† For ordinal, continuous, and binary outcomes, generalized linear mixed models were used. The effect of the intervention is presented as an odds ratio (and 95% confidence interval [CI]) for a poor functional outcome, with the usual-care group as the reference group. The odds ratio for the primary outcome is an adjusted common odds ratio; the listed odds ratios for the other outcomes are adjusted odds ratios. The model includes a random effect of site and fixed effects of randomization group, region (eastern vs. western China), age (≥65 years vs. <65 years), and FAST score (≥3 vs. 2).

‡ The modified Rankin scale evaluates global disability, with scores ranging from 0 to 6.

§ P=0.16 for the test of the proportional-odds assumption.

¶ The EuroQol 5-dimension 3-level (EQ-5D-3L) patient-reported questionnaire covers 5 domains of health-related quality of life: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each domain has 3 graded levels of response: no problems, moderate problems, or extreme problems. Scores from these levels are combined to provide an overall health utility score that was calculated according to population norms in China. A score of 1 represents perfect health, a score of 0 represents death, and negative scores represent health states considered to be worse than death.

‖ Serious adverse events were prespecified to include events that may or may not be considered to be related to the treatment and that were life-threatening or resulted in hospitalization or prolongation of existing hospitalization, persistent or clinically significant disability or incapacity, medical or surgical intervention to prevent permanent impairment to bodily structure or function, or death. A patient could have more than one event.

S14). Sensitivity, per-protocol, and modified intention-to-treat analyses produced similar results (Tables S15, S16, and S17). There were differences in the effect of prehospital blood-pressure reduction according to stroke type, with a lower odds ratio for a poor functional outcome in patients with hemorrhagic stroke (common odds ratio, 0.75; 95% CI, 0.60 to 0.92) and a higher

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odds ratio in patients with cerebral ischemia (common odds ratio, 1.30; 95% CI, 1.06 to 1.60) (Figs. 1B and 1C and 2). However, because this subgroup analysis was not part of a hierarchical statistical plan, causal inferences about these associations cannot be drawn. The effect of the treatment group on the primary outcome was consistent across the other subgroups in the overall population and across the subgroups of patients with hemorrhagic stroke and those with cerebral ischemia (Fig. 2, Figs. S16 and S17, and Table S20).

OTHER EFFICACY OUTCOMES

Patients in the intervention group had degrees of neurologic impairment similar to those of patients in the usual-care group at 24 hours and at 7 days, and the groups were similar with regard to the incidence of death or disability (scores on the modified Rankin scale of 3 through 6) or disability alone at 90 days, EQ-5D-3L scores, the timing of hospital discharge, and living circumstances (living at home [the individual's own or that of a family member] or living at an institution [hospital, care facility, or other]) (Tables S21, S22, and S23). Data on secondary outcomes for patients with intracerebral hemorrhage and those with cerebral ischemia are provided in Tables S18 and S19.

SAFETY

Overall, the incidence of serious adverse events did not differ significantly between the intervention group and the usual-care group (27.5% vs. 28.7%). Tables S24 through S27 provide a complete list of serious adverse events and causes of death, overall and separately for patients with hemorrhagic stroke and for those with cerebral ischemia.

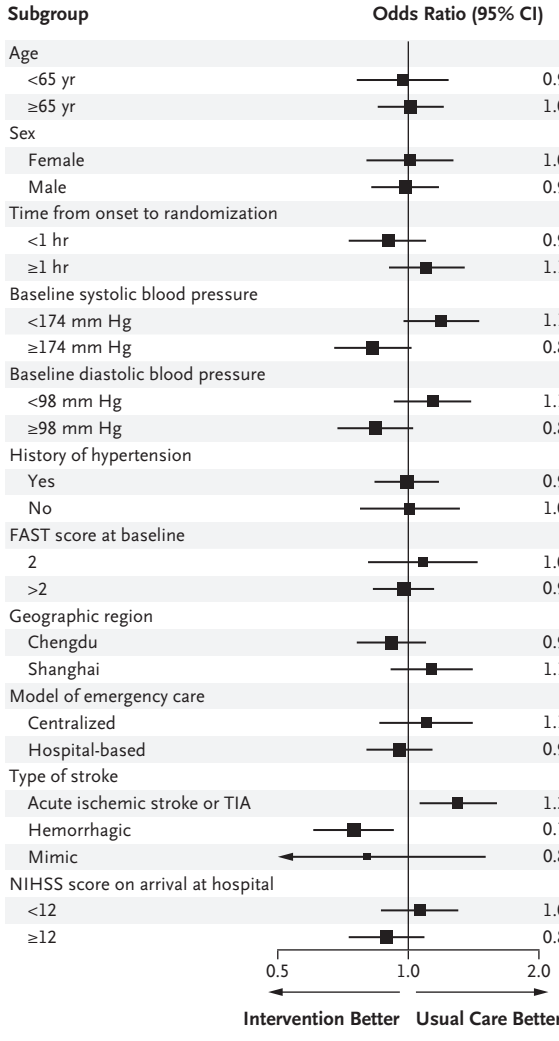

Figure 2. Subgroup Analysis of the Primary Outcome.

Shown are the common odds ratios for a poor functional outcome in prespecified subgroups. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. FAST (face–arm–speech–time) scores range from 0 to 4, with higher scores indicating more symptoms. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater neurologic deficits. Systolic and diastolic blood-pressure values and NIHSS scores are dichotomized as above or below the median value. TIA denotes transient ischemic attack.

DISCUSSION

In this randomized trial involving adults with acute stroke and elevated blood pressure who were identified by ambulance workers in China, the early initiation of intravenous antihypertensive treatment to reach a systolic blood-pressure target of 130 to 140 mm Hg had no overall effect on functional outcome at 90 days as compared with usual care (with commencement of blood-pressure management on arrival at the hospital). However, the prehospital initiation of intensive blood-pressure–lowering treatment within 2 hours after symptom onset was associated with lower odds of a poor functional outcome in patients with hemorrhagic stroke and higher odds in those with cerebral ischemia.

Although hypertension is common in patients with intracerebral hemorrhage and is strongly associated with poor outcomes, randomized, con-

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trolled trials of early intensive treatment to lower blood pressure in this patient group have shown inconsistent results,[5,6] which has led to only an intermediate-strength recommendation for this treatment in guidelines from health organizations.[27-29] The Third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT3)[3] showed that implementation of a goal-directed care bundle that included early intensive blood-pressure reduction in addition to other management strategies in hospital protocols improved outcomes of intracerebral hemorrhage; however, implementation of this intervention may be challenging.[30]

The role of intensive blood-pressure reduction in acute ischemic stroke is more complicated, especially since trials have shown that it can lead to adverse outcomes in patients after successful endovascular therapy.[31,32] The rationale for the inclusion of patients with hypertension who had an acute stroke that had produced a motor deficit was to reduce the number of patients enrolled with a condition that mimicked stroke and to improve efficiency. This approach may have led to the inclusion of a higher proportion of patients with an ischemic deficit due to large-vessel occlusion of the anterior circulation,[33,34] in whom early blood-pressure reduction may have compromised cerebral blood flow in the evolving ischemic penumbra.

Strengths of this trial include the involvement of doctors in emergency services, use of a waiver or a simple consent process, high rates of eligibility and adherence to the protocol, and the ability to lower blood pressure effectively with a simple, intravenous treatment regimen. However, involvement of trained doctors in emergency services limits the generalizability of our findings. In addition, this trial was conducted only in China, where the proportion of cases of acute ischemic stroke caused by intracranial atherosclerosis and cerebral small-vessel disease is higher than in North America and Europe and where the incidence of intracerebral hemorrhage is high.[33,34] Moreover, intravenous urapidil is not widely available outside China, and the mechanisms of action differ from those of comparable antihypertensive drugs in other countries. The results may also be less relevant to paramedic-run ambulance services and to patients presenting with possible stroke that has caused a minor neurologic deficit. The open-label design, the pragmatic approach with broad inclusion criteria, the variability of other medical care according to available resources, and the use of risk-based monitoring during quarantine restrictions in the coronavirus disease 2019 pandemic[20] may have compromised data quality and produced differences in management from that in other health settings. Even so, time performance metrics and the use of intravenous thrombolysis and other patterns of management in our trial population were similar to those in other studies.[35]

In patients with acute stroke and elevated blood pressure, the rapid initiation of intensive blood-pressure reduction to reach a target systolic blood pressure of 130 to 140 mm Hg in the ambulance within 2 hours after symptom onset had no benefit with regard to functional outcome in patients with undifferentiated stroke as compared with the standard approach of initiating blood-pressure management after arrival at the hospital. However, the intervention may have had divergent effects for patients with hemorrhagic stroke and those with cerebral ischemia.

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APPENDIX

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REFERENCES

1. Bath PM, Song L, Silva GS, et al. Blood pressure management for ischemic stroke in the first 24 hours. Stroke 2022;53:1074-84.
2. Minhas JS, Moullaali TJ, Rinkel GJE, Anderson CS. Blood pressure management after intracerebral and subarachnoid hemorrhage: the knowns and known unknowns. Stroke 2022;53:1065-73.
3. Ma L, Hu X, Song L, et al. The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial. Lancet 2023;402:27-40.
4. Parry-Jones AR, Sammut-Powell C, Paroutoglou K, et al. An intracerebral hemorrhage care bundle is associated with lower case fatality. Ann Neurol 2019;86:495-503.
5. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355-65.
6. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med 2016;375:1033-43.
7. Moullaali TJ, Wang X, Martin RH, et al. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. Lancet Neurol 2019;18:857-64.
8. Moullaali TJ, Wang X, Sandset EC, et al. Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. J Neurol Neurosurg Psychiatry 2022;93:6-13.
9. Wang X, Di Tanna GL, Moullaali TJ, et al. J-shape relation of blood pressure reduction and outcome in acute intracerebral hemorrhage: a pooled analysis of INTERACT2 and ATACH-II individual participant data. Int J Stroke 2022;17:1129-36.
10. Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. Lancet Neurol 2018;17:885-94.
11. Bowry R, Parker SA, Bratina P, et al. Hemorrhage enlargement is more frequent in the first 2 hours: a prehospital mobile stroke unit study. Stroke 2022;53:2352-60.
12. Li Q, Warren AD, Qureshi AI, et al. Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage. Ann Neurol 2020;88:388-95.
13. Li Q, Morotti A, Warren A, et al. Intensive blood pressure reduction is associated with reduced hematoma growth in fast bleeding intracerebral hemorrhage. Ann Neurol 2023 September 14 (Epub ahead of print).
14. Broderick JP, Hill MJ. Advances in stroke: treatments-acute. Stroke 2022;53:999-1003.
15. Anderson CS, Huang Y, Lindley RI, et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. Lancet 2019;393:877-88.
16. RIGHT-2 Investigators. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. Lancet 2019;393:1009-20.

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17. Bath PM, Woodhouse LJ, Krishnan K, et al. Prehospital transdermal glyceryl trinitrate for ultra-acute intracerebral hemorrhage: data from the RIGHT-2 trial. Stroke 2019;50:3064-71.
18. van den Berg SA, Uniken Venema SM, Reinink H, et al. Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (MR ASAP): an ambulance-based, multicentre, randomised, open-label, blinded endpoint, phase 3 trial. Lancet Neurol 2022;21:971-81.
19. Song L, Chen C, Chen X, et al. INTEnsive ambulance-delivered blood pressure Reduction in hyper-ACute stroke Trial (INTERACT4): study protocol for a randomized controlled trial. Trials 2021;22:885.
20. Chen C, Lin Y, Liu F, et al. Update on the INTEnsive ambulance-delivered blood pressure Reduction in hyper-ACute stroke Trial (INTERACT4): progress and baseline features in 2053 participants. Trials 2023;24:817.
21. Billot L, Chen C, Song L, et al. Statistical analysis plan for the INTEnsive ambulance-delivered blood pressure Reduction in hyper-Acute stroke Trial (INTERACT4). September 7, 2023 (https://doi.org/10.31219/osf.io/qj6u8). preprint.
22. Cao Y, Yu S, Zhang Q, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of intracerebral haemorrhage. Stroke Vasc Neurol 2020;5:396-402.
23. Liu L, Chen W, Zhou H, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. Stroke Vasc Neurol 2020;5:159-76.
24. Saver JL, Starkman S, Eckstein M, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. N Engl J Med 2015;372:528-36.
25. Liu GG, Wu H, Li M, Gao C, Luo N. Chinese time trade-off values for EQ-5D health states. Value Health 2014;17:597-604.
26. Zhang Y, Zhou Z, Gao J, et al. Health-related quality of life and its influencing factors for patients with hypertension: evidence from the urban and rural areas of Shaanxi Province, China. BMC Health Serv Res 2016;16:277.
27. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association / American Stroke Association. Stroke 2022;53(7):e282-e361.
28. Sandset EC, Anderson CS, Bath PM, et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. Eur Stroke J 2021;6:XLVIII-LXXXIX.
29. Stroke Foundation. Acute medical and surgical management. In: Clinical guidelines for stroke management. Rev. ed. 2023 (https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management).
30. Ouyang M, Anderson CS, Song L, et al. Implementing a goal-directed care bundle after acute intracerebral haemorrhage: process evaluation for Third INTEnsive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial study in China. Cerebrovasc Dis 2022;51:373-83.
31. Yang P, Song L, Zhang Y, et al. Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-endpoint, randomised controlled trial. Lancet 2022;400:1585-96.
32. Nam HS, Kim YD, Heo J, et al. Intensive vs conventional blood pressure lowering after successful endovascular thrombectomy in acute ischemic stroke: the OPTIMAL-BP randomized clinical trial. JAMA 2023;330:832-42.
33. Wang A, Jia B, Zhang X, et al. Efficacy and safety of butylphthalide in patients with acute ischemic stroke: a randomized clinical trial. JAMA Neurol 2023;80:851-9.
34. Chun M, Qin H, Turnbull I, et al. Heterogeneity in the diagnosis and prognosis of ischemic stroke subtypes: 9-year follow-up of 22,000 cases in Chinese adults. Int J Stroke 2023;18:847-55.
35. Wangqin R, Laskowitz DT, Wang Y, et al. International comparison of patient characteristics and quality of care for ischemic stroke: analysis of the China National Stroke Registry and the American Heart Association Get With The Guidelines — Stroke program. J Am Heart Assoc 2018;7(20):e010623.

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