ORIGINAL ARTICLE

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

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ABSTRACT

BACKGROUND

The appropriate target for systolic blood pressure to reduce cardiovascular risk in older patients with hypertension remains unclear.

METHODS

In this multicenter, randomized, controlled trial, we assigned Chinese patients 60 to 80 years of age with hypertension to a systolic blood-pressure target of 110 to less than 130 mm Hg (intensive treatment) or a target of 130 to less than 150 mm Hg (standard treatment). The primary outcome was a composite of stroke, acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

RESULTS

Of the 9624 patients screened for eligibility, 8511 were enrolled in the trial; 4243 were randomly assigned to the intensive-treatment group and 4268 to the standard-treatment group. At 1 year of follow-up, the mean systolic blood pressure was 127.5 mm Hg in the intensive-treatment group and 135.3 mm Hg in the standard-treatment group. During a median follow-up period of 3.34 years, primary-outcome events occurred in 147 patients (3.5%) in the intensive-treatment group, as compared with 196 patients (4.6%) in the standard-treatment group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.92; P=0.007). The results for most of the individual components of the primary outcome also favored intensive treatment: the hazard ratio for stroke was 0.67 (95% CI, 0.47 to 0.97), acute coronary syndrome 0.67 (95% CI, 0.47 to 0.94), acute decompensated heart failure 0.27 (95% CI, 0.08 to 0.98), coronary revascularization 0.69 (95% CI, 0.40 to 1.18), atrial fibrillation 0.96 (95% CI, 0.55 to 1.68), and death from cardiovascular causes 0.72 (95% CI, 0.39 to 1.32). The results for safety and renal outcomes did not differ significantly between the two groups, except for the incidence of hypotension, which was higher in the intensive-treatment group.

CONCLUSIONS

In older patients with hypertension, intensive treatment with a systolic blood-pressure target of 110 to less than 130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment with a target of 130 to less than 150 mm Hg. (Funded by the Chinese Academy of Medical Sciences and others; STEP ClinicalTrials.gov number, NCT03015311.)

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Hypertension is a common risk factor for death from cardiovascular causes worldwide and in China.[1,2] With aging of the population, determination of the treatment target for systolic blood pressure in older patients with hypertension has become a focus of research.[3] Current guideline-based recommendations for the systolic blood-pressure target in older patients remain inconsistent.[4-6] The target is less than 150 mm Hg in the American College of Physicians–American Academy of Family Physicians guideline,[4] 130 to 139 mm Hg in the European guideline,[5] and less than 130 mm Hg in the American College of Cardiology–American Heart Association guideline.[6]

Impressive cardiovascular benefits were observed with intensive blood-pressure control (systolic blood-pressure target, <120 mm Hg), as compared with standard blood-pressure control (target, <140 mm Hg), in the Systolic Blood Pressure Intervention Trial (SPRINT), even in patients 75 years of age or older.[7,8] A meta-analysis showed that a systolic blood-pressure target of less than 130 mm Hg was associated with a decreased risk of cardiovascular events and death, especially in high-risk patients.[9] However, recent large-scale observational studies have suggested that a reduction in the systolic blood pressure to less than 130 mm Hg in older patients should be applied with caution.[10,11] In addition, decreased adherence to treatment and subsequent adverse effects related to lower systolic blood-pressure targets should be considered.[12]

Of note, an evaluation of cardiovascular risk that relies solely on blood-pressure measurements obtained during office visits (office blood pressure) is insufficient, because blood pressure varies both in short-term and long-term paradigms.[13,14] Recent guidelines have highlighted the importance of blood-pressure measurements obtained at home (home blood pressure) in the management of hypertension.[5,6,15,16]

Therefore, we conducted the STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) trial to assess whether intensive treatment (systolic blood-pressure target, 110 to <130 mm Hg) would reduce cardiovascular risk to a greater extent than standard treatment (target, 130 to <150 mm Hg) in Chinese patients 60 to 80 years of age with hypertension. Moreover, we used a smartphone-based application (app) to examine home blood pressure as an adjunct to office blood pressure during the follow-up period.

Methods

Trial Design

The STEP trial was a prospective, multicenter, randomized, controlled trial performed at 42 clinical centers throughout China (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The planned follow-up period was 4 years. Details regarding the trial design and rationale have been published previously.[17]

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The trial was sponsored by FuWai Hospital and the Chinese Academy of Medical Sciences. The trial was approved by the ethics committees of FuWai Hospital and collaborating centers. The members of the data and safety monitoring committee and the STEP Study Group are listed in the Supplementary Appendix. The steering committee was responsible for the design of the trial, and the executive committee (in collaboration with investigators at the clinics) was responsible for the conduct of the trial and the collection, analysis, and interpretation of the data. The first draft of the manuscript was written by the first and second authors. All the authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol, available at NEJM.org.

Olmesartan medoxomil tablets were donated by Nanjing Chia Tai Tianqing Pharmaceutical Company (Nanjing, China), and amlodipine besylate tablets were donated by China Resources Saike Pharmaceutical Company (Beijing, China). Blood-pressure monitors were donated by Omron Healthcare. The companies that donated the drugs and devices had no role in the design of the trial or in the analysis of the data.

Patient Population

From January 10 to December 31, 2017, patients were recruited and screened for eligibility. All eligible patients were required to be 60 to 80 years of age and to have hypertension with a systolic blood pressure of 140 to 190 mm Hg during three screening visits or to be taking antihypertensive medication. Patients with a history of ischemic or hemorrhagic stroke were excluded. A full list of inclusion and exclusion criteria is provided in the Supplementary Appendix. All the patients provided written informed consent.

Randomization

At each center, eligible patients were randomly assigned in a 1:1 ratio to a systolic blood-pressure

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target of 110 to less than 130 mm Hg (intensive treatment) or a target of 130 to less than 150 mm Hg (standard treatment). Investigators and patients were aware of the trial-group assignments. Randomization was performed with the use of a central computerized randomization program on a Web-based interface, with stratification according to clinical center.

TRIAL PROCEDURE

After randomization, all patients were scheduled for follow-up visits at 1, 2, and 3 months and every 3 months thereafter until 48 months. The patients were provided with antihypertensive drugs, including olmesartan (an angiotensin-receptor blocker), amlodipine (a calcium-channel blocker), and hydrochlorothiazide (a diuretic). The treatment algorithms are shown in Figure S2. Adjustment of the medications to reach the systolic blood-pressure target was based on office blood-pressure measurements obtained during the screening phase and the entire follow-up period.

For home blood-pressure monitoring, every patient was provided with a validated automated home blood-pressure monitor (Omron Healthcare). The blood-pressure monitor was paired to the smartphone-based app with a Bluetooth function. The app was used to collect home blood-pressure readings obtained by the patient and then to upload the readings to a data-recording center. All the patients were required to obtain home blood-pressure readings at least 1 day per week during follow-up. Details regarding home blood-pressure monitoring are provided in the Supplementary Appendix.

To examine the effects of app management on blood-pressure control, the 42 participating clinical centers were randomly assigned, in a 1:1 ratio at the center level, to be either an app-management center or a usual-care center. The app had a patient portal and a doctor portal. Through the patient portal, patients could receive alerts about blood-pressure control and reminders about adherence and could communicate with doctors; these options were available to patients at app-management centers but not to patients at usual-care centers. Through the doctor portal, doctors could receive monthly reports regarding patients' home blood pressure; the plan had been to send these reports only to doctors at app-management centers, but a decision was made to send the reports also to doctors at usual-care centers to monitor home blood pressure in the entire trial population. Patients were not enrolled in the trial unless they could use the app or had a family member who could use it on their behalf. The effects of app management on blood-pressure control will be further studied and are not presented here. Details regarding app management are provided in the Supplementary Appendix.

TRIAL ASSESSMENTS

At the time of recruitment, baseline data were collected by physicians at face-to-face visits with the use of a standardized questionnaire. The 10-year risk of cardiovascular disease was estimated with the use of the Framingham Risk Score.[18] At each follow-up visit, the office blood pressure and heart rate were measured and information was collected regarding concomitant medication use, antihypertensive-drug adherence, adverse events, and trial outcomes (with outcomes data ascertained by trained investigators). Laboratory data were obtained at baseline and every year thereafter.

Measurement of the office blood pressure was performed by a trained trial staff member (physician or nurse). Patients were required to rest for at least 5 minutes in a seated position, and then the blood pressure was measured by trial staff (observed) three times at 1-minute intervals. This process was standardized and the same validated office blood-pressure monitor (Omron Healthcare) was used at all participating centers during all baseline and follow-up clinic visits.

TRIAL OUTCOMES

Definitions and ascertainment criteria for the trial outcomes are provided in Table S1. Members of the adjudication committee were unaware of the trial-group assignments. The primary outcome was a composite of stroke (ischemic or hemorrhagic), acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

The following secondary outcomes were prespecified: the individual components of the primary outcome, death from any cause, major adverse cardiac events (a composite of the individual components of the primary outcome except for

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stroke), and renal outcomes (a decrease in renal function or the development of end-stage renal disease). To monitor for renal outcomes, the estimated glomerular filtration rate and serum creatinine level were obtained. Safety outcomes, which were assessed during the trial, included adverse events (hypotension and dizziness) and serious adverse events (syncope and fracture). Definitions of the safety outcomes and details regarding quality control are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

In the STEP trial, we planned to conduct 4 years of follow-up through December 31, 2021. We estimated that a sample of 8000 patients (4000 in each trial group) would provide the trial with 90% power to detect a 20% lower risk of a primary-outcome event in the intensive-treatment group than in the standard-treatment group. The estimated annual event rate was 2.5% for primary-outcome events in patients 60 years of age or older with hypertension in China.[19] The anticipated rate of loss to follow-up was 0.5% per year. A two-sided alpha level of 0.05 was used.

Cumulative incidence curves are shown for the two trial groups. In the analyses of the primary outcome and secondary outcomes except for death from any cause, the Fine–Gray subdistribution hazard model was used to account for the competing risk of death.[20] For death from any cause, the Cox regression model was used. All analyses were based on the intention-to-treat approach, and all models were adjusted for clinical center. The follow-up time was censored on the date of the last event. Although patients could have had multiple events, only one event of any type per patient (the event that occurred first) was used in the analysis. Patients who were lost to follow-up were included in the final analysis, with data censored at the time of the last follow-up visit. Mean imputation was used for missing data.

Prespecified subgroup analyses were performed for the primary outcome, according to age (<70 years vs. ≥70 years), sex, systolic blood pressure at baseline (distribution in thirds), history of diabetes mellitus at baseline (yes vs. no), 10-year cardiovascular risk on the basis of the Framingham Risk Score (<15% [low or moderate risk] vs. ≥15% [high risk]), and random assignment to app management (yes vs. no). Results for safety outcomes were compared between the two groups with the use of a logistic-regression model.

Hazard ratios are reported. A two-sided P value of less than 0.05 was considered to indicate significance. There was no prespecified plan to adjust for multiple comparisons. Therefore, only 95% confidence intervals are reported for secondary outcomes, and definitive treatment effects cannot be inferred. Analyses were performed with R software, version 3.6.3 (R Foundation for Statistical Computing).

Prespecified interim analyses were performed by the data and safety monitoring committee at the end of each year. The O'Brien–Fleming alpha-spending function was used to maintain the overall type I error rate of 0.05 across these repeated analyses.[21,22] The complete statistical analysis plan is included in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

Of the 9624 patients screened at 42 clinical centers throughout China, 1113 (11.6%) were excluded. A total of 8511 patients 60 to 80 years of age were randomly assigned to the intensive-treatment group (4243 patients) or the standard-treatment group (4268 patients) (Fig. 1). A total of 234 patients (2.7%) were lost to follow-up before the end of the trial; the censoring time is shown in Table S2.

Baseline characteristics were well balanced between the two trial groups (Table 1 and Table S3). The mean age of the patients was 66.2 years, and 46.5% were men. A total of 19.1% of the patients had a history of diabetes mellitus, 6.3% had a history of cardiovascular disease, and 64.8% had a Framingham Risk Score of 15% or higher, which indicated a high 10-year cardiovascular risk. All enrolled patients downloaded the app. The percentage of patients who used the app to transmit home blood-pressure readings was 95.8%; the remaining patients did not use the app during the follow-up period.

At the third interim analysis, performed on December 22, 2019, after 272 primary-outcome events had been reported, the intensive-treatment group had a significantly lower incidence of primary-outcome events than the standard-treatment group (hazard ratio, 0.71; 95% confidence

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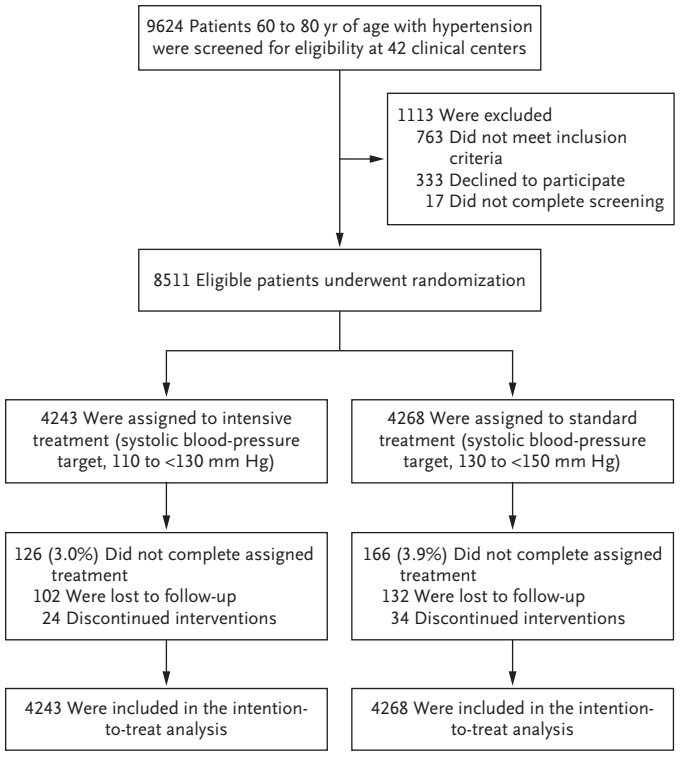

Figure 1. Screening, Randomization, and Follow-up.

In patients who discontinued interventions, the trial interventions were discontinued because of adverse effects related to the systolic blood-pressure target or to antihypertensive drugs, but follow-up visits were still attended. In patients who were lost to follow-up, contact was lost and data regarding the primary outcome were not ascertained from a certain follow-up visit until the end of the trial. Analysis of the data was based on the intention-to-treat approach. Patients who were lost to follow-up were included in the analysis, with data censored at the time of the last follow-up visit.

interval [CI], 0.56 to 0.91; P=0.007). At the fourth interim analysis, performed on December 31, 2020, after 343 primary-outcome events had been reported, the intensive-treatment group still had a significantly lower incidence of primary-outcome events (hazard ratio, 0.75; 95% CI, 0.61 to 0.93; P=0.008). The data and safety monitoring committee recommended that the trial be stopped early on the basis of a clear cardiovascular benefit in the intensive-treatment group at two consecutive time points (Fig. S3). The principal investigators adopted this recommendation, and the trial was stopped on December 31, 2020, with a median follow-up of 3.34 years (interquartile range, 3.22 to 3.51).

BLOOD PRESSURE

The two treatment strategies led to a rapid and sustained between-group difference in the systolic blood pressure in older patients with hypertension (Fig. 2). At 1 year of follow-up, the mean systolic blood pressure was 127.5 mm Hg in the intensive-treatment group and 135.3 mm Hg in the standard-treatment group. During the median follow-up period of 3.34 years, the mean decrease in systolic blood pressure from baseline was 19.4 mm Hg in the intensive-treatment group and 10.1 mm Hg in the standard-treatment group. Throughout follow-up, the mean systolic blood pressure was 126.7 mm Hg in the intensive-treatment group and 135.9 mm Hg in the standard-treatment group; the mean diastolic blood pressure was 76.4 mm Hg and 79.2 mm Hg, respectively (Fig. S4). Similar differences were observed in home blood pressure (Fig. S5). In the intensive-treatment group, the percentage of patients who reached the systolic blood-pressure target (110 to <130 mm Hg) was 67.2% at 1 year of follow-up, 70.4% at 2 years, and 77.2% at 3 years (Table S2). At 42 months, the mean number of antihypertensive medications administered per patient was 1.9 in the intensive-treatment group and 1.5 in the standard-treatment group (Fig. 2). Data regarding the medication classes (angiotensin-receptor blocker, calcium-channel blocker, and diuretic) used in each group are shown in Table S4.

CLINICAL OUTCOMES

During the median follow-up period of 3.34 years, primary-outcome events occurred in 147 of 4243 patients (3.5% [1.0% per year]) in the intensive-treatment group, as compared with 196 of 4268 patients (4.6% [1.4% per year]) in the standard-treatment group (hazard ratio, 0.74; 95% CI, 0.60 to 0.92; P=0.007). The incidence of primary-outcome events was significantly lower in the intensive-treatment group than in the standard-treatment group, with an absolute difference of 1.1 percentage points (Table 2 and Fig. 3). The results for most of the secondary outcomes also favored intensive treatment (Table 2 and Fig. S6). Analyses of the effects of intensive treatment on the primary outcome in prespecified subgroups are shown in Figure S7. In a sensitivity analysis involving patients who had a diastolic blood pressure of less than 60 mm Hg or a pulse pressure of more than 60 mm Hg (or both) within 3 months

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intensive Treatment (N=4243)	Standard Treatment (N=4268)
Age — yr	66.2±4.8	66.3±4.8
Distribution of age — no. (%)		
60–69 yr	3220 (75.9)	3236 (75.8)
70–80 yr	1023 (24.1)	1032 (24.2)
Male sex — no. (%)	1990 (46.9)	1969 (46.1)
Body-mass index†	25.5±3.2	25.6±3.2
Blood pressure — mm Hg		
Systolic	146.1±16.8	146.0±16.5
Diastolic	82.7±10.6	82.3±10.5
Distribution of systolic blood pressure — no. (%)‡		
≤138 mm Hg	1416 (33.4)	1442 (33.8)
139–151 mm Hg	1406 (33.1)	1445 (33.9)
≥152 mm Hg	1421 (33.5)	1381 (32.4)
Renal dysfunction — no. (%)§	99/4180 (2.4)	97/4214 (2.3)
Fasting serum glucose — mmol/liter	6.2±1.8	6.2±1.7
Lipid profile — mmol/liter		
Total cholesterol	4.9±1.2	4.9±1.1
Median triglycerides (IQR)	1.3 (1.0–2.0)	1.4 (1.0–1.9)
High-density lipoprotein cholesterol	1.3±0.3	1.3±0.3
Low-density lipoprotein cholesterol	2.7±0.9	2.7±0.9
Medical history — no. (%)		
Diabetes mellitus	800 (18.9)	827 (19.4)
Hyperlipidemia	1591 (37.5)	1541 (36.1)
Cardiovascular disease	268 (6.3)	272 (6.4)
Framingham Risk Score ≥15% — no./total no. (%)¶	2588/3975 (65.1)	2576/3996 (64.5)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. To convert the values for fasting serum glucose to milligrams per deciliter, divide by 0.05551. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The ranges for systolic blood pressure are based on the distribution in thirds at baseline.
§ Renal dysfunction was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2.
¶ A Framingham Risk Score of 15% or higher indicates a high 10-year risk of cardiovascular disease.

after randomization, results were similar to the results of the primary analysis, which suggests that intensive treatment did not adversely affect these patients (Table S5).

SAFETY AND RENAL OUTCOMES

The incidences of dizziness, syncope, and fracture and the results for renal outcomes did not differ significantly between the two trial groups (Table 3), nor did the incidences of angioedema, headache, cough, and hives (Table S6). However, the incidence of hypotension was significantly higher in the intensive-treatment group than in the standard-treatment group (3.4% vs. 2.6%, P=0.03).

DISCUSSION

The STEP trial showed that in patients 60 to 80 years of age with hypertension in China, reduction of the systolic blood pressure to a target of

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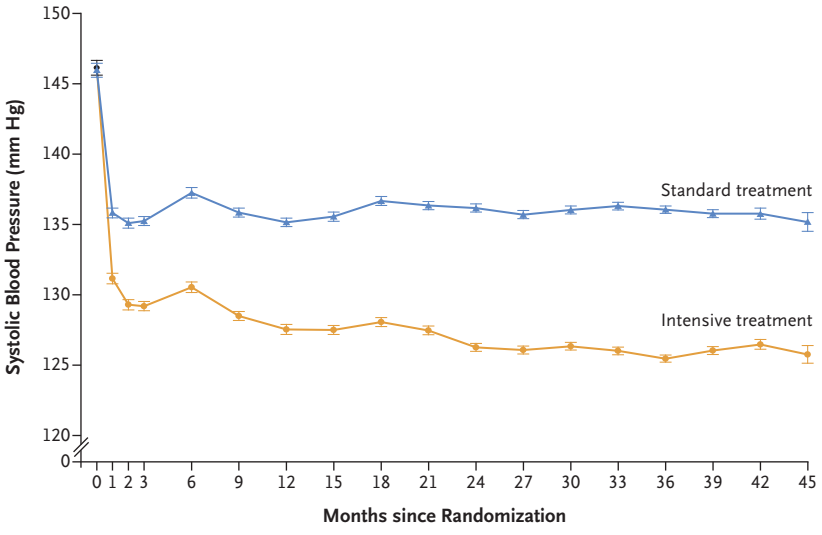

No. with Data								
Standard treatment	4268	4139	4086	4092	4072	3954	3857	1885
Intensive treatment	4243	4128	4086	4049	4050	3969	3894	1850
Mean No. of Medications								
Standard treatment	1.4	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Intensive treatment	1.5	1.7	1.8	1.8	1.9	1.9	1.9	1.9

Figure 2. Office Systolic Blood-Pressure Measurements.

The systolic blood-pressure target was 110 to less than 130 mm Hg in the intensive-treatment group and 130 to less than 150 mm Hg in the standard-treatment group. The mean number of medications is based on the number of blood-pressure medications administered at each visit per patient. I bars indicate 95% confidence intervals.

110 to less than 130 mm Hg (intensive treatment) resulted in a significantly lower incidence of cardiovascular events than reduction to a target of 130 to less than 150 mm Hg (standard treatment). During a median follow-up period of 3.34 years, primary-outcome events occurred in 3.5% of the patients in the intensive-treatment group, as compared with 4.6% of the patients in the standard-treatment group (absolute difference, 1.1 percentage points). The results for most of the secondary outcomes were also more favorable in the intensive-treatment group than in the standard-treatment group. The risk of death from any cause did not differ significantly between the two trial groups. Hypotension occurred more frequently in the intensive-treatment group than in the standard-treatment group, but the incidences of other intervention-related safety outcomes (dizziness, syncope, and fracture) and the results for renal outcomes did not differ significantly between the two groups.

Several large trials have shown a beneficial effect of intensive blood-pressure control on cardiovascular outcomes in older patients,[7,23-25] but the appropriate systolic blood-pressure target remains unclear. Our large trial provides important evidence, showing that a reduction in the systolic blood pressure to less than 130 mm Hg resulted in cardiovascular benefits in older patients with hypertension in China.

Comparison of the STEP trial with SPRINT is interesting; intensive blood-pressure control resulted in cardiovascular benefits in both trials.[7] Several major differences between the trials should be noted. In SPRINT, office blood pressure was measured with the use of an automated system, and trial staff were not present during the rest period, when the measurement was taken, or throughout the entire process. In the STEP trial, office blood pressure was measured by trained trial staff with the use of an oscillometric electronic sphygmomanometer; with this blood-pressure monitor, only the inflating procedure is automated. SPRINT excluded persons with dia-

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Table 2. Hazard Ratios for the Primary and Secondary Outcomes.*

Outcome	Intensive Treatment (N=4243)		Standard Treatment (N=4268)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% with event per year*	*no. of patients (%)*	*% with event per year*		
Primary outcome†	147 (3.5)	1.0	196 (4.6)	1.4	0.74 (0.60–0.92)	0.007
Secondary outcomes						
Components of primary outcome						
Stroke	48 (1.1)	0.3	71 (1.7)	0.5	0.67 (0.47–0.97)	—
Acute coronary syndrome	55 (1.3)	0.4	82 (1.9)	0.6	0.67 (0.47–0.94)	—
Acute decompensated heart failure	3 (0.1)	0.03	11 (0.3)	0.09	0.27 (0.08–0.98)	—
Coronary revascularization	22 (0.5)	0.1	32 (0.7)	0.2	0.69 (0.40–1.18)	—
Atrial fibrillation	24 (0.6)	0.2	25 (0.6)	0.2	0.96 (0.55–1.68)	—
Death from cardiovascular causes	18 (0.4)	0.1	25 (0.6)	0.2	0.72 (0.39–1.32)	—
Death from any cause	67 (1.6)	0.5	64 (1.5)	0.5	1.11 (0.78–1.56)	—
Major adverse cardiac events‡	100 (2.4)	0.7	138 (3.2)	1.0	0.72 (0.56–0.93)	—

* For the primary outcome and secondary outcomes except for death from any cause, the hazard ratios, 95% confidence intervals, and P value were calculated with the use of the Fine–Gray subdistribution hazard model for the competing risk of death. For death from any cause, the Cox regression model was used. All models were adjusted for clinical center.

† The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

‡ The secondary outcome of major adverse cardiac events was a composite of the individual components of the primary outcome except for stroke.

betes mellitus, whereas the STEP trial did not. Both trials excluded persons with a history of stroke; further trials could assess the cardiovascular benefits of intensive blood-pressure treatment in persons with a history of stroke, given the high burden of hypertension and stroke worldwide and in China.[26,27]

Although SPRINT showed that a systolic blood-pressure target of less than 120 mm Hg was associated with cardiovascular benefits, practical issues have been raised with regard to this treatment strategy.[7] Such a low systolic blood-pressure target is challenging to reach and can result in higher medication costs and more frequent clinic visits. In addition, a significantly increased incidence of kidney injury was observed with a systolic blood-pressure target of less than 120 mm Hg among participants without chronic kidney disease in SPRINT; an increased incidence of kidney injury was not observed with a systolic blood-pressure target of 110 to less than 130 mm Hg in the STEP trial. Of note, the incidence of hypotension increased significantly with intensive blood-pressure control in both trials. Previous studies have shown that, among older people with a pulse pressure of more than 60 mm Hg or a diastolic blood pressure of less than 60 mm Hg (or both), a very low systolic blood pressure might increase the risk of subclinical myocardial ischemia[28] and recurrent stroke.[29] Caution is warranted when aiming for lower systolic blood-pressure targets among older patients, particularly those who have stiff arteries.[30]

The STEP trial showed that a systolic blood-pressure target of 110 to less than 130 mm Hg was associated with reduced risks of stroke and acute coronary syndrome in older patients with hypertension, but similar results were not observed in SPRINT. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[31] showed that a systolic blood-pressure target of less than 120 mm Hg was associated with a reduced risk of stroke. In the STEP trial, intensive treatment did not have a significant effect on the risk of death from cardiovascular causes (hazard ratio, 0.72; 95% CI, 0.39 to 1.32) or the risk of death from any cause (hazard ratio, 1.11; 95% CI, 0.78 to 1.56); in SPRINT, intensive treatment led to significantly reduced risks of death from cardiovascular causes (hazard ratio, 0.58; 95% CI, 0.39

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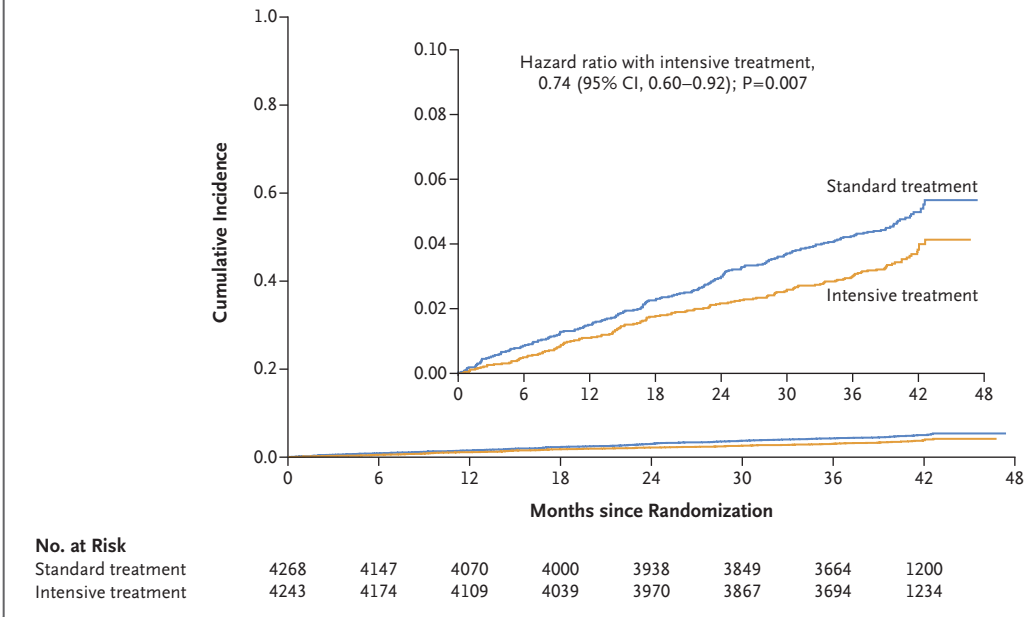

Figure 3. Cumulative Incidence for the Primary Outcome.

The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes. The hazard ratio, 95% confidence interval, and P value for the primary outcome were calculated with the use of the Fine–Gray subdistribution hazard model for the competing risk of death, with adjustment for clinical center. The inset shows the same data on an enlarged y axis.

to 0.84) and death from any cause (hazard ratio, 0.75; 95% CI, 0.61 to 0.92). In addition, the annual event rates for the primary outcome in the intensive-treatment group and the standard-treatment group observed in the STEP trial (1.0% per year and 1.4% per year, respectively) were lower than those observed in SPRINT (1.77% per year and 2.40% per year, respectively), a finding consistent with lower cardiovascular risk in Asian populations than in U.S. and European populations.[10,32] The difference between the STEP trial and SPRINT in the risks of death from any cause and death from cardiovascular causes might be partially explained by differences in the trial design and eligibility criteria, the systolic blood-pressure targets, or the geographic location along with the racial and ethnic background of the trial population.

Strengths of the STEP trial include the large sample size, the diverse patient population (ranging from 60 to 80 years of age) with coexisting chronic diseases, the high rate of follow-up, and the use of home blood-pressure monitoring. Given the large population of patients 60 to 80 years of age with hypertension, the trial results could be generalized to and benefit more than 100 million persons in China.[2] The between-group differences in systolic blood pressure were significant, persistent, and consistent across office and home blood-pressure measurements. Home blood-pressure monitoring more accurately reflects the long-term fluctuations in blood pressure than office blood-pressure monitoring and facilitates hypertension management for older patients.[33,34]

A limitation of our trial is the inclusion of only Han Chinese persons, which account for more than 90% of the Chinese population. Our scientific rationale for this inclusion criterion was the variation in diet, lifestyle, and genetic background and in the prevalence of hypertension across Chinese ethnic groups.[35,36] In addition, most ethnic minorities live in remote mountain areas, which would have made trial follow-up challenging. However, this factor limits the generalizability of our findings. An alternative approach to address these issues that might be considered when designing future trials would be to stratify randomization according to ethnic

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Table 3. Safety and Renal Outcomes Related to the Blood-Pressure Intervention.*

Outcome	Intensive Treatment (N=4243)	Standard Treatment (N=4268)	Relative Risk (95% CI)	P Value
Safety outcomes — no. of patients (%)				
Adverse events				
Hypotension†	146 (3.4)	113 (2.6)	1.31 (1.02–1.68)	0.03
Dizziness‡	45 (1.1)	49 (1.1)	0.92 (0.61–1.39)	0.70
Serious adverse events				
Syncope§	6 (0.1)	2 (<0.1)	3.02 (0.61–14.97)	0.18
Fracture¶	15 (0.4)	19 (0.4)	0.79 (0.40–1.56)	0.50
Renal outcomes — no. of patients/total no. (%)‖				
Reduction in eGFR				
≥50% reduction in patients with chronic kidney disease at baseline	1/99 (1.0)	1/97 (1.0)	1.01 (0.06–16.09)	0.99
≥30% reduction to <60 ml/min/1.73 m^2 in patients without chronic kidney disease at baseline	55/4081 (1.3)	61/4117 (1.5)	0.90 (0.63–1.30)	0.58
Elevation in serum creatinine level				
>1.5 mg/dl elevation in men	70/1953 (3.6)	70/1938 (3.6)	0.99 (0.71–1.39)	0.95
>1.3 mg/dl elevation in women	43/2227 (1.9)	48/2276 (2.1)	0.91 (0.60–1.38)	0.67
eGFR <30 ml/min/1.73 m^2	12/4243 (0.3)	13/4268 (0.3)	0.93 (0.42–2.04)	0.85

* The relative risks, 95% confidence intervals, and P values were calculated with the use of a logistic-regression model, with the standard-treatment group used as the reference. The investigator determined whether the event was related to the intervention.
† Hypotension was defined as a systolic blood pressure of less than 110 mm Hg or a diastolic blood pressure of less than 50 mm Hg.
‡ Dizziness was defined as a false sense that you or your surroundings are spinning or moving.
§ Syncope was defined as a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.
¶ Fracture was defined as destruction of bone integrity or continuity.
‖ The specified reductions in the estimated glomerular filtration rate (eGFR) and elevations in the serum creatinine level indicate a decrease in renal function; an eGFR of less than 30 ml per minute per 1.73 m^2 indicates the development of end-stage renal disease.

group to ensure balance between the trial groups and to include or exclude patients on the basis of the distance of their home from a study center. Another limitation is that the Framingham Risk Score was formulated primarily in White populations[18] and may overestimate the risk of cardiovascular disease in Chinese adults.[37,38] Several other issues — such as the effects of intensive blood-pressure control on quality of life, cost effectiveness, and long-term clinical outcomes — could be addressed in future research.

In the STEP trial, intensive treatment to reach a systolic blood-pressure target of 110 to less than 130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment to reach a target of 130 to less than 150 mm Hg in patients 60 to 80 years of age with hypertension. However, caution is advised when generalizing the results to populations that were not included in the trial, including patients with a history of stroke.

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APPENDIX

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