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Intensive Blood-Pressure Control in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Effective targets for systolic blood-pressure control in patients with type 2 diabetes are unclear.

METHODS

We enrolled patients 50 years of age or older with type 2 diabetes, elevated systolic blood pressure, and an increased risk of cardiovascular disease at 145 clinical sites across China. Patients were randomly assigned to receive intensive treatment that targeted a systolic blood pressure of less than 120 mm Hg or standard treatment that targeted a systolic blood pressure of less than 140 mm Hg for up to 5 years. The primary outcome was a composite of nonfatal stroke, nonfatal myocardial infarction, treatment or hospitalization for heart failure, or death from cardiovascular causes. Multiple imputation was used for missing outcome data, with an assumption that the data were missing at random.

RESULTS

Of 12,821 patients (6414 patients in the intensive-treatment group and 6407 in the standard-treatment group) enrolled from February 2019 through December 2021, 5803 (45.3%) were women; the mean (±SD) age of the patients was 63.8±7.5 years. At 1 year of follow-up, the mean systolic blood pressure was 121.6 mm Hg (median, 118.3 mm Hg) in the intensive-treatment group and 133.2 mm Hg (median, 135.0 mm Hg) in the standard-treatment group. During a median follow-up of 4.2 years, primary-outcome events occurred in 393 patients (1.65 events per 100 person-years) in the intensive-treatment group and 492 patients (2.09 events per 100 person-years) in the standard-treatment group (hazard ratio, 0.79; 95% confidence interval, 0.69 to 0.90; P<0.001). The incidence of serious adverse events was similar in the treatment groups. However, symptomatic hypotension and hyperkalemia occurred more frequently in the intensive-treatment group than in the standard-treatment group.

CONCLUSIONS

Among patients with type 2 diabetes, the incidence of major cardiovascular events was significantly lower with intensive treatment targeting a systolic blood pressure of less than 120 mm Hg than with standard treatment targeting a systolic blood pressure of less than 140 mm Hg. (Funded by the National Key Research and Development Program of the Ministry of Science and Technology of China and others; BPROAD ClinicalTrials.gov number, NCT03808311.)

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Elevated systolic blood pressure is the most common coexisting condition among patients with diabetes.[1] It increases the risk of cardiovascular disease among patients with diabetes, and it constitutes the most modifiable risk factor for cardiovascular disease in these patients.[2-4] Because blood-pressure reduction has unequivocal benefits with respect to decreasing the risk of cardiovascular disease, current clinical guidelines recommend decreasing blood pressure in patients with type 2 diabetes; however, the effective systolic blood-pressure reduction targets in this population are unclear.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a randomized trial that compared an intensive treatment targeting a systolic blood pressure of less than 120 mm Hg with a standard treatment that targeted a systolic blood pressure of less than 140 mm Hg in patients with type 2 diabetes.[5] That trial did not find a significant benefit of intensive treatment in the prevention of cardiovascular disease. However, the ACCORD trial was underpowered for blood-pressure intervention, and results may have been biased by the factorial design of the glucose intervention used in the trial.[6,7] The Systolic Blood Pressure Intervention Trial (SPRINT) tested systolic blood-pressure reduction targets similar to those of the ACCORD trial but in patients without diabetes. In the SPRINT trial, the risk of major cardiovascular disease events was significantly lower in the intensive-treatment group than in the standard-treatment group.[8,9] Subgroup analyses in recent clinical trials have suggested consistent benefits of more-intensive systolic blood-pressure targets for preventing major cardiovascular disease events regardless of diabetes status,[10,11] although a lack of efficacy of intensive lowering of systolic blood pressure in persons with and in those without diabetes has also been reported.[12]

Thus, current evidence is inconclusive concerning effective systolic blood-pressure treatment targets in patients with type 2 diabetes. We conducted the Blood Pressure Control Target in Diabetes (BPROAD) trial to investigate whether intensive treatment targeting a systolic blood pressure of less than 120 mm Hg would be more effective than standard treatment targeting a systolic blood pressure of less than 140 mm Hg in reducing the risk of major cardiovascular disease events among patients with type 2 diabetes.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted a parallel-design, randomized clinical trial at 145 clinical sites located in seven geographic regions across China (for a complete list of participating sites, see Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Assessment of outcomes was conducted in a blinded fashion. Patients with type 2 diabetes were enrolled and were randomly assigned to receive either intensive or standard blood-pressure treatment for up to 5 years. Details regarding the rationale and trial design have been published previously[13] and are provided in the BPROAD trial protocol, available at NEJM.org.

The primary trial sponsor was the National Key Research and Development Program from the Ministry of Science and Technology of China. The protocol was approved by the ethics committee at Ruijin Hospital and at each participating site. An executive committee (Section S1) designed the trial and made major decisions regarding factors such as the trial timeline, trial-data quality assurance and quality control, and responses to the coronavirus disease 19 (Covid-19) pandemic during conduct of the trial. An independent, international data and safety monitoring board monitored the design, data quality, and patient safety throughout the trial. Trial and data coordinating center personnel coordinated the local sites of the trial and performed data analyses. The first two authors and the last two authors wrote the first draft of the manuscript. All the authors commented on drafts of the manuscript and agreed to submit the manuscript for publication. The first and second authors, fourth to last author, and last two authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Members of the BPROAD research group are listed in Section S1.

PATIENTS

Patients with type 2 diabetes were eligible if they were 50 years of age or older, had an elevated systolic blood pressure, and were deemed to have an increased risk of cardiovascular disease. Elevated systolic blood pressure was defined as 130 to 180 mm Hg in patients taking antihypertensive medications or at least 140 mm Hg in patients not

taking medications. Increased risk of cardiovascular disease was defined as the meeting of one or more of the following criteria: a history of clinical cardiovascular disease at least 3 months before enrollment in the trial, subclinical cardiovascular disease within 3 years before enrollment, two or more cardiovascular disease risk factors, and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) of 30 to less than 60 ml per minute per 1.73 m^2 of body-surface area. Detailed inclusion and exclusion criteria are listed in Section S2. Written informed consent was obtained from each patient.

RANDOMIZATION AND INTERVENTIONS

Eligible patients were randomly assigned to receive intensive treatment that targeted a systolic blood pressure of less than 120 mm Hg or standard treatment that targeted a systolic blood pressure of less than 140 mm Hg. Randomization was stratified according to clinical site, and within each site a block randomization with randomly selected block sizes of two, four, and six was performed with the use of a Web-based central randomization system. Patients and trial physicians were aware of group assignments, but outcome assessors, adjudicators, and statisticians were not.

After randomization, the antihypertensive regimens of the patients were adjusted on the basis of their blood-pressure levels and assigned treatment group in order to achieve systolic blood-pressure targets as described above. Patients were seen monthly for the first 3 months and every 3 months thereafter if systolic blood-pressure targets were achieved or no more drug adjustment was planned. Otherwise, monthly visits would continue. Trial physicians followed blood-pressure treatment algorithms (Figs. S1 and S2 in the Supplementary Appendix) similar to those used in the SPRINT trial in order to manage patients' blood pressure. Details of blood-pressure measurement and treatment are provided in Section S3. Standard management of other risk factors such as glucose and lipid levels was based on current clinical guidelines, and the delivery of these therapies was decided by each patient's clinician.

TRIAL MEASUREMENTS

Data were collected locally with the use of an electronic data-capturing system according to a standard protocol and standardized procedures to ensure uniformity of data quality across sites. Demographic data, lifestyle data, and disease history were obtained at baseline. Antihypertensive and concomitant medications were recorded at each visit. The collection of clinical-outcome data started 3 months after randomization and continued every 3 months thereafter for both treatment groups and was performed by clinical staff who were unaware of the treatment assignment. Clinical documents, including admission and discharge summaries, laboratory measurements, imaging, and procedure documents, were collected for central and standardized assessment and for adjudication of trial outcomes. Adverse events were reported at all trial visits, regardless of whether the visit was part of the trial protocol. Blood and urine samples were obtained at baseline and at annual visits and were assayed at the central laboratory to assess kidney outcomes and glucose and lipid levels. Laboratory measurements for safety were conducted at specified time points at local sites (see the protocol).

During the Covid-19 pandemic, telephone interviews were recommended for the collection of trial data, and blood pressure was measured at home. Patients were provided an automated blood-pressure measurement device and a blood-pressure diary chart and had access to a training video made by the trial coordinating center that showed how to obtain and record a standard blood-pressure measurement at home (Section S3). The numbers and percentages of telephone interviews conducted throughout the trial are shown in Figure S3 and Table S1.

TRIAL OUTCOMES

The primary outcome was a composite of the first occurrence of nonfatal stroke, nonfatal myocardial infarction, treatment or hospitalization for heart failure, or death from cardiovascular causes. Secondary outcomes included fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, treatment or hospitalization for heart failure, death from cardiovascular causes, death from any cause, and an expanded composite of the primary outcome or death from any cause. CKD outcomes included progression of CKD (a composite of end-stage renal disease, an eGFR of <15 ml per minute per 1.73 m^2, or a >50% decrease in eGFR from baseline) in patients with

CKD at baseline, development of CKD (an eGFR of <60 ml per minute per 1.73 m^2 and a >30% decrease from baseline) in patients without CKD at baseline, and incident albuminuria (a doubling of the urinary albumin-to-creatinine ratio from a value of <10 to a value of ≥10, with albumin measured in milligrams and creatinine measured in grams) in all patients with or without CKD. Definitions and adjudication criteria for each outcome are listed in Section S4.

In addition to serious adverse events, a selected list of other important adverse events that led to emergency department visits was also reported. Clinical safety alerts with respect to low or high concentrations of serum sodium or potassium during treatment were recorded.

STATISTICAL ANALYSIS

We calculated the sample size by assuming a primary cardiovascular disease event rate of 2.0% per year in the standard-treatment group, a 20% effect size with respect to the difference between the intensive treatment and the standard treatment, a 2-year uniform recruitment period and a total trial duration of 5 years, and an anticipated loss to follow-up of 2.0% per year. We estimated that a sample of 12,702 patients (6351 in each treatment group) would provide the trial with 90% statistical power at a two-sided significance level of 0.05.

All analyses in the current trial followed the intention-to-treat principle by including all patients who had been randomly assigned to a treatment group. We tested and confirmed the proportional-hazards assumption for the primary analysis by calculating the Schoenfeld residuals (Fig. S4). Cox proportional-hazards regression was used to compare the treatment groups with respect to the time from randomization to the first primary cardiovascular disease event. The model included indicators for the intervention and for the regions where the clinical sites were located (North, Northeast, East, South, Middle, Southwest, and Northwest China). Follow-up time was censored on the date of the last ascertainment of an event. Effect estimates were reported as hazard ratios with 95% confidence intervals. Because one interim analysis was conducted when 54.5% of adjudicated primary cardiovascular disease events had accrued (Section S5), the two-sided nominal significance level calculated with the Lan–DeMets alpha-spending function was updated to 0.045 for the primary outcome. Effect estimates of secondary outcomes were obtained with models similar to those used for the primary outcome, without adjustments for multiple comparisons. Subgroups that were defined according to age, sex, previous cardiovascular disease, previous CKD, systolic blood pressure, glycated hemoglobin, duration of diabetes, and duration of high blood pressure were prespecified for the primary outcome.

We used multiple imputation for missing outcomes in the primary analysis, assuming the data were missing at random. A total of 50 imputed data sets were generated, and estimates were combined across data sets with the use of Rubin's rule. We also conducted several sensitivity analyses that censored missing outcome data or that assumed that outcome data were not missing at random (Section S6). In addition, we used the Fine and Gray hazard model to account for competing risk.[14] Details of the statistical analysis are available in the statistical analysis plan in the protocol. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute), or R software, version 4.3.3 (R Foundation for Statistical Computing).

RESULTS

PATIENTS

A total of 12,821 patients were enrolled from February 2019 through December 2021. Of these patients, 6414 were randomly assigned to the intensive-treatment group and 6407 were assigned to the standard-treatment group. Baseline characteristics of the patients appeared to be balanced between the two groups (Table 1 and Table S2). The mean (±SD) age of the patients was 63.8±7.5 years, and 5803 patients (45.3%) were women; 2888 patients (22.5%) had a history of clinical cardiovascular disease at baseline. The trial patients were broadly representative of the relevant population (Table S3). During a median follow-up of 4.2 years (interquartile range, 2.9 to 4.6 years), 152 patients (1.2%) discontinued the trial intervention, 605 patients (4.7%) were lost to follow-up, and 423 patients (3.3%) withdrew consent (Fig. S5).

BLOOD PRESSURE

The mean systolic blood pressure at baseline was 140.0±10.2 mm Hg in the intensive-treatment

group and 140.4±10.2 mm Hg in the standard-treatment group. Systolic blood pressure decreased rapidly in both groups after the intervention, and the between-group difference in systolic blood pressure was sustained throughout the trial (Fig. 1 and Fig. S6). At 1 year, the mean systolic blood pressure was 121.6 mm Hg (median, 118.3 mm Hg) in the intensive-treatment group and 133.2 mm Hg (median, 135.0 mm Hg) in the standard-treatment group. After 1 year, approximately 60% of patients in the intensive-treatment group met the systolic blood pressure target (Table S4). Diastolic blood pressure and systolic and diastolic blood pressures that were obtained in clinic showed similar trends (Figs. S7 and S8). More antihypertensive drugs were used in the intensive-treatment group than in the standard-treatment group (Fig. 1). Use of hypoglycemic drugs and glycated hemoglobin level (mean 7.6% in both groups), body-mass index, waist circumference, and lipid levels, which are considered cardiovascular disease risk factors, were similar in the two groups during follow-up (Tables S5 and S6).

CLINICAL OUTCOMES

During a median follow-up of 4.2 years, primary-outcome events occurred in 393 patients (1.65 events per 100 person-years) in the intensive-treatment group as compared with 492 patients (2.09 events per 100 person-years) in the standard-treatment group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001) (Table 2). The separation of Kaplan–Meier curves between the intensive-treatment group and the standard-treatment group became apparent after 1 year of intervention (Fig. 2). Fatal or nonfatal stroke occurred in 284 patients (1.19 events per 100 person-years) in the intensive-treatment group and in 356 patients (1.50 events per 100 person-years) in the standard-treatment group (hazard ratio, 0.79; 95% CI, 0.67 to 0.92). Findings with respect to fatal or nonfatal myocardial infarction, treatment or hospitalization for heart failure, and death from cardiovascular causes were similar in the treatment groups. Death from any cause occurred in 169 patients (0.69 events per 100 person-years) in the intensive-treatment group and in 179 patients (0.73 events per 100 person-years) in the standard-treatment group (hazard ratio, 0.95; 95% CI, 0.77 to 1.17) (Table 2 and Table S7). The effects of the interventions on the primary outcome were consistent across the prespecified subgroups (Fig. 3).

Similar incidences of CKD progression and CKD development were observed in the two groups (Table 2, Table S8, and Fig. S9). Incident albuminuria occurred in 554 patients (11.29 events per 100 person-years) in the intensive-treatment group and in 648 patients (13.84 events per 100 person-years) in the standard-treatment group (hazard ratio, 0.87; 95% CI, 0.77 to 0.97). Sensitivity analyses showed similar results for the reported outcomes under different assumptions for missing outcomes and when competing risk was considered (Tables S9, S10, and S11).

ADVERSE EVENTS

Serious adverse events occurred in 2340 patients (36.5%) in the intensive-treatment group and in 2328 patients (36.3%) in the standard-treatment group. There was no significant between-group difference in the incidence of serious adverse events (hazard ratio, 1.00; 95% CI, 0.94 to 1.06; P=0.96) (Table 3 and Table S12). The incidence of most conditions of interest was similar in the two treatment groups. However, symptomatic hypotension occurred more frequently in the intensive-treatment group than in the standard-treatment group (in 8 of 6414 patients [0.1%] vs. 1 of 6407 patients [<0.1%], P=0.05). In addition, high serum potassium concentration (>5.5 mmol per liter) was more common in the intensive-treatment group than in the standard-treatment group (in 177 of 6230 patients [2.8%] vs. 125 of 6220 patients [2.0%], P=0.003).

DISCUSSION

We found that among patients with type 2 diabetes and an elevated systolic blood pressure, the incidence of major cardiovascular disease events for up to 5 years of follow-up was significantly lower with an intensive treatment strategy to lower systolic blood pressure to less than 120 mm Hg than with a standard treatment strategy to lower systolic blood pressure to less than 140 mm Hg, with a hazard ratio of 0.79 (95% CI, 0.69 to 0.90). The benefits of intensive treatment were consistent across all prespecified subgroups.

The earlier ACCORD trial compared an intensive blood-pressure treatment target with a standard blood-pressure treatment target in patients with type 2 diabetes and showed no significant

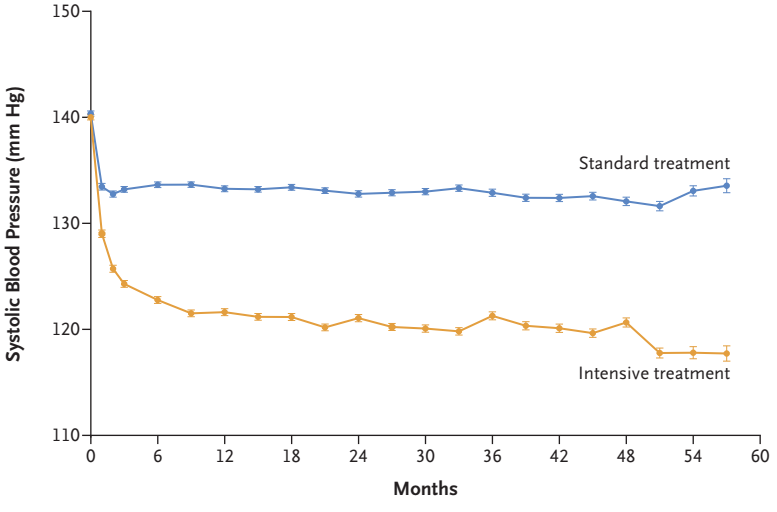
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Intensive Treatment (N=6414)	Standard Treatment (N=6407)
Female sex — no. (%)	2923 (45.6)	2880 (45.0)
Age — yr	63.7±7.4	63.9±7.5
Age group — no. (%)		
<65 yr	3607 (56.2)	3500 (54.6)
≥65 yr	2807 (43.8)	2907 (45.4)
Systolic blood pressure — mm Hg	140.0±10.2	140.4±10.2
Diastolic blood pressure — mm Hg	76.3±9.2	76.3±9.1
Duration of hypertension — yr	11.8±9.4	11.6±9.4
Duration of diabetes — yr	10.3±7.6	10.3±7.7
History of clinical cardiovascular disease — no. (%)	1480 (23.1)	1408 (22.0)
History of subclinical cardiovascular disease — no. (%)	2173 (33.9)	2251 (35.1)
Educational level: high school diploma or greater — no./total no. (%)	3090/6401 (48.3)	3045/6396 (47.6)
Current smoker — no./total no. (%)	1580/6401 (24.7)	1636/6392 (25.6)
Body-mass index†	26.7±3.2	26.7±3.3
Waist circumference — cm	95.2±8.2	95.2±8.1
Fasting plasma glucose — mg/dl	148.7±48.1	148.4±48.0
Glycated hemoglobin — %	7.6±1.4	7.6±1.4
Total cholesterol — mg/dl	157.8±48.1	157.2±47.8
LDL cholesterol — mg/dl	84.3±34.6	83.7±34.1
HDL cholesterol — mg/dl	40.2±12.7	40.1±11.8
Median triglycerides (IQR) — mg/dl	130.2 (92.1–192.2)	131.1 (92.1–194.0)
eGFR — ml/min/1.73 m^2‡	88.6±17.8	88.7±18.0
eGFR of <60 ml/min/1.73 m^2 — no. (%)‡	501 (7.8)	469 (7.3)
Median urinary albumin-to-creatinine ratio (IQR)§	20.5 (9.6–61.4)	19.3 (9.5–56.9)
Urinary albumin-to-creatinine ratio of ≥30 — no./total no. (%)§	2528/6378 (39.6)	2452/6378 (38.4)
Medications at baseline		
Any antihypertensive drug — no. (%)	6356 (99.1)	6338 (98.9)
No. of antihypertensive drugs per participant	1.4±0.6	1.4±0.6
Antihypertensive drugs — no./total no. (%)		
ACE inhibitor	904/6395 (14.1)	885/6386 (13.9)
Angiotensin-receptor blocker	2790/6395 (43.6)	2814/6386 (44.1)
Calcium-channel blocker	3774/6395 (59.0)	3780/6386 (59.2)
Diuretic	471/6395 (7.4)	447/6386 (7.0)
α-Receptor blocker	45/6395 (0.7)	46/6386 (0.7)
β-Receptor blocker	960/6395 (15.0)	906/6386 (14.2)
Other	206/6395 (3.2)	198/6386 (3.1)
Any hypoglycemic drug — no. (%)	6321 (98.6)	6294 (98.2)
Hypoglycemic drugs — no./total no. (%)		
Insulin	3114/6394 (48.7)	3069/6385 (48.1)

Table 1. (Continued.)

Characteristic	Intensive Treatment (N=6414)	Standard Treatment (N=6407)
Metformin	4228/6395 (66.1)	4287/6385 (67.1)
Thiazolidinedione	164/6395 (2.6)	178/6385 (2.8)
Sulfonylurea	961/6395 (15.0)	949/6385 (14.9)
α-Glucosidase inhibitor	2170/6395 (33.9)	1976/6385 (30.9)
GLP-1 receptor agonist	283/6395 (4.4)	277/6385 (4.3)
DPP-4 inhibitor	642/6395 (10.0)	641/6385 (10.0)
SGLT2 inhibitor	674/6395 (10.5)	658/6385 (10.3)
Statin — no. (%)	4192 (65.4)	4159 (64.9)
Aspirin — no. (%)	3225 (50.3)	3200 (49.9)

* Plus–minus values are means ±SD. To convert plasma glucose values to millimoles per liter, multiply by 0.0555. To convert total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol values to millimoles per liter, multiply by 0.0259. To convert triglyceride values to millimoles per liter, multiply by 0.0113. ACE denotes angiotensin-converting enzyme, DPP-4 dipeptidyl peptidase 4, GLP-1 glucagon-like peptide-1, IQR interquartile range, and SGLT2 sodium–glucose cotransporter 2.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The estimated glomerular filtration rate (eGFR) was based on the serum creatinine level and was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation.
§ The albumin-to-creatinine ratio was calculated as the ratio of urinary albumin (in milligrams) to urinary creatinine (in grams).



No. with Data										
Standard treatment	6407	5885	5663	5555	5257	4535	4091	3550	3187	1597
Intensive treatment	6414	5858	5612	5474	5244	4541	4119	3573	3198	1622
Mean No. of Medications Prescribed										
Standard treatment	1.6	1.5	1.5	1.5	1.5	1.4	1.4	1.4	1.4	1.3
Intensive treatment	1.7	2.0	2.1	2.1	2.2	2.2	2.2	2.2	2.2	2.1

Figure 1. Systolic Blood Pressure throughout the Trial.

Shown are the mean systolic blood-pressure values among patients who received intensive treatment that targeted a systolic blood pressure of less than 120 mm Hg and among patients who received standard treatment that targeted a systolic blood pressure of less than 140 mm Hg. I bars represent 95% confidence intervals.

Table 2. Primary Outcome and Main Secondary Outcomes.*

Outcome	Intensive Treatment (N=6414)		Standard Treatment (N=6407)		Hazard Ratio (95% CI)†	P Value†
	No. of Events	Incidence Rate	No. of Events	Incidence Rate		
		no. of events/100 person-yr		*no. of events/100 person-yr*		
Primary outcome: nonfatal stroke, nonfatal MI, treatment or hospitalization for heart failure, or death from cardiovascular causes	393	1.65 (1.50–1.82)	492	2.09 (1.91–2.28)	0.79 (0.69–0.90)	<0.001
Secondary outcomes						
Fatal or nonfatal MI	68	0.28 (0.22–0.35)	81	0.33 (0.27–0.41)	0.84 (0.60–1.16)	—
Fatal or nonfatal stroke	284	1.19 (1.06–1.33)	356	1.50 (1.35–1.66)	0.79 (0.67–0.92)	—
Treatment or hospitalization for heart failure	31	0.13 (0.09–0.18)	46	0.19 (0.14–0.25)	0.66 (0.41–1.04)	—
Death from cardiovascular causes	60	0.24 (0.19–0.31)	79	0.32 (0.26–0.40)	0.76 (0.55–1.06)	—
Death from any cause	169	0.69 (0.59–0.80)	179	0.73 (0.63–0.84)	0.95 (0.77–1.17)	—
Primary-outcome event or death from any cause	493	2.07 (1.90–2.26)	584	2.48 (2.28–2.69)	0.83 (0.74–0.94)	—
CKD outcomes						
CKD progression	24	1.61 (1.08–2.41)	16	1.11 (0.68–1.80)	1.36 (0.71–2.59)	—
CKD development	232	1.14 (1.00–1.29)	214	1.05 (0.92–1.20)	1.11 (0.92–1.34)	—
Incident albuminuria	554	11.29 (10.39–12.27)	648	13.84 (12.81–14.95)	0.87 (0.77–0.97)	—

* Patients were counted only once for each outcome. Confidence intervals for outcomes other than the primary outcome have not been adjusted for multiplicity and may not be used for hypothesis testing. CKD denotes chronic kidney disease, and MI myocardial infarction.

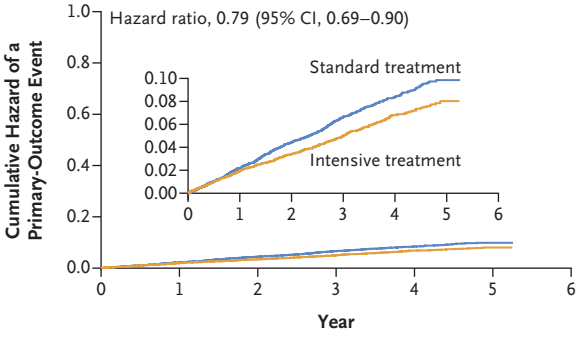
† Multiple imputation for missing outcomes, under an assumption that data were missing at random, was used for the analyses of clinical outcomes.

difference in the risk of cardiovascular events (hazard ratio, 0.88; 95% CI, 0.73 to 1.06) or death from any cause (hazard ratio, 1.07; 95% CI, 0.85 to 1.35) between the two treatment groups.[5] However, the incidence rate of the primary outcome in the standard-treatment group in the ACCORD trial was only half the incidence rate used for the calculation of sample size (2.09% vs. 4% per year), which led to a reduced statistical power to detect a true difference between treatment groups. In our trial, we assumed a major cardiovascular disease event rate of 2.0% per year in the standard-treatment group and enrolled a sufficient number of patients to achieve 90% statistical power. In the present trial, the actual incidence rate of the primary outcome in the standard-treatment group (2.09 events per 100 person-years) was very close to the estimated rate.

In addition, interaction between glucose control and blood-pressure control may have occurred in the ACCORD trial because a subgroup analysis suggested a substantial reduction in cardiovascular risk with intensive blood-pressure lowering among patients assigned to the standard glycemic control group, whereas no reduction occurred with intensive blood-pressure lowering among patients assigned to the intensive glycemic control group (P=0.08 for interaction).[5,7] Our trial used an algorithm of standard glucose control in accordance with current clinical guidelines, and the mean glycated hemoglobin level was 7.6% in both treatment groups at the 48-month visit (Table S6), a level similar to the median achieved glycated hemoglobin level (7.5%) in the standard glycemic control group in the ACCORD trial.[6]

Our trial provided convincing evidence of the benefits of lowering systolic blood pressure to a target of less than 120 mm Hg in patients with type 2 diabetes. This finding is consistent with findings of two other trials that tested the same intensive and standard systolic blood-pressure treatment targets in patients with hypertension.[8,9,11] The SPRINT trial showed a significant 27% lower risk of major cardiovascular disease events among patients without diabetes who received intensive treatment (hazard ratio, 0.73; 95% CI, 0.63 to 0.86).[9] The Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular Events (ESPRIT) trial recently showed a 12% lower risk of major vascular events among patients with and those without diabetes who received intensive treatment (hazard ratio, 0.88; 95% CI, 0.78 to 0.99).[11] A subgroup analysis in the ESPRIT trial suggested that the effects with intensive treatment were similar among patients with and those without diabetes. In addition, among 4359 patients with diabetes, those who received intensive treatment had a nonsignificant lower risk of major vascular events than those who received standard treatment (hazard ratio, 0.91; 95% CI, 0.77 to 1.08).

In our trial, among secondary outcomes, stroke occurred less frequently in the intensive-treatment group (1.19 events per 100 person-years) than in the standard-treatment group (1.50 events per 100 person-years). Stroke is the most common type of cardiovascular disease among Chinese persons, and hypertension is the leading contributor to stroke and stroke-related death.[15] The risk of stroke as a secondary outcome was lower with intensive treatment than with standard treatment in the ACCORD trial, although the incidence rate was much lower than that in our trial. Unlike the SPRINT trial, we did not observe a between-group difference with regard to death from any cause, for which the incidence rate was lower in our trial than in the SPRINT trial; however, the incidence rate in our trial was similar to that in other



No. at Risk

Standard treatment	6407	6087	5814	4626	3674	132
Intensive treatment	6414	6092	5871	4692	3738	112

Figure 2. Kaplan–Meier Curves for the Primary Outcome.

The primary outcome was a composite of nonfatal stroke, nonfatal myocardial infarction, treatment or hospitalization for heart failure, or death from cardiovascular causes. Shown is the cumulative hazard of a primary-outcome event among patients who received intensive treatment and among patients who received standard treatment. The hazard ratio and 95% confidence interval for the intensive treatment were calculated by Cox proportional-hazards regression with adjustment for the regions where the clinical sites were located. The numbers listed below the graph are the numbers of patients who were undergoing follow-up and were still at risk. The inset shows the same data on an expanded y axis.

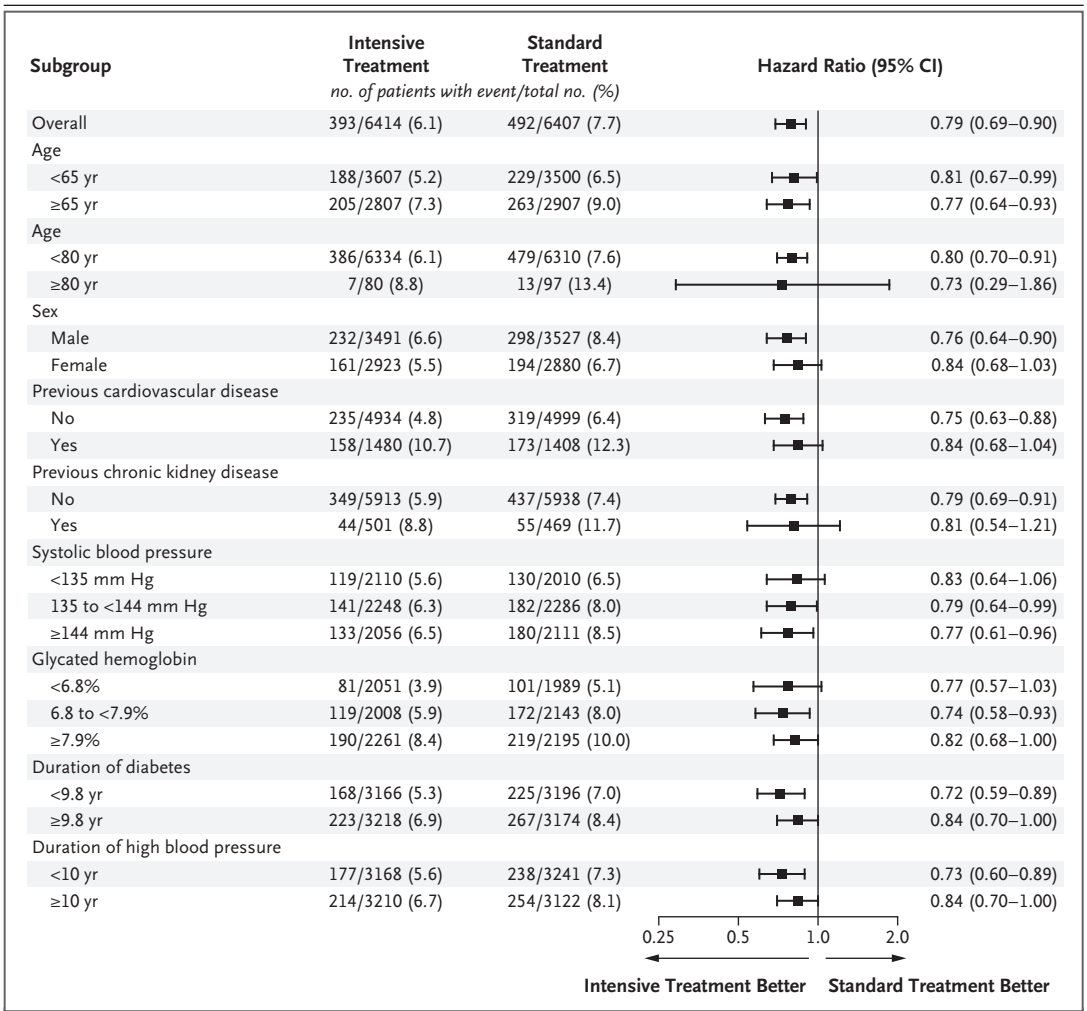


Figure 3. Prespecified Subgroup Analysis.

Shown are the effects of the interventions on the primary composite outcome across prespecified subgroups. Data on the glycated hemoglobin level were missing for 94 patients in the intensive-treatment group and for 80 patients in the standard-treatment group; on the duration of diabetes for 30 and 37, respectively; and on the duration of high blood pressure for 36 and 44, respectively. Confidence intervals for estimates in the prespecified subgroups have not been adjusted for multiplicity and may not be used for hypothesis testing.

trials that tested systolic blood-pressure treatment targets in the Chinese population.[10,11] Differences in patient characteristics, such as age and sex, may account for these differences between our trial and the SPRINT trial. However, secondary outcomes in our trial were not used for hypothesis testing.

Our trial has important implications for blood-pressure management in clinical practice. Although the Eighth Joint National Committee recommended a systolic blood pressure of less than 140 mm Hg in patients with type 2 diabetes on the basis of findings from the ACCORD trial,[16] most current guidelines recommend a systolic blood pressure of less than 130 mm Hg in patients with diabetes.[17-20] However, evidence supporting this recommendation is lacking. Our results with respect to the primary outcome provide support for more-intensive systolic blood-pressure control in patients with diabetes for the prevention of major cardiovascular disease events. However, with intensive blood-pressure targets, patients need to be monitored for hypotension, especially during the start of intensive blood-pressure reduction. Furthermore, hyperkalemia after the use of multiple antihypertensive drugs must be monitored during treatment.[21]

Table 3. Adverse Events.*

Outcome	Intensive Treatment (N=6414)		Standard Treatment (N=6407)		Hazard Ratio (95% CI)	P Value
	No. of Events	Percentage of Participants	No. of Events	Percentage of Participants		
Serious adverse event†	2340	36.5	2328	36.3	1.00 (0.94–1.06)	0.96
Conditions of interest‡						
Arrhythmia	69	1.1	68	1.1	1.01 (0.72–1.41)	0.95
Electrolyte abnormality	36	0.6	35	0.6	1.03 (0.65–1.64)	0.91
Injurious fall	65	1.0	61	1.0	1.06 (0.75–1.51)	0.74
Symptomatic hypotension	8	0.1	1	<0.1	7.92 (0.99–63.34)	0.05
Syncope	10	0.2	10	0.2	1.00 (0.41–2.39)	0.99
Acute renal failure	4	0.1	5	0.1	0.79 (0.21–2.95)	0.73
Clinical safety alerts§						
Serum sodium <130 mmol/liter	46	0.7	47	0.8	0.97 (0.65–1.46)	0.89
Serum sodium >150 mmol/liter	22	0.4	25	0.4	0.88 (0.49–1.56)	0.65
Serum potassium <3.0 mmol/liter	32	0.5	33	0.5	0.97 (0.60–1.58)	0.90
Serum potassium >5.5 mmol/liter	177	2.8	125	2.0	1.41 (1.12–1.77)	0.003

* Patients were counted only once for each adverse event.
† Serious adverse events were events that were fatal or life-threatening, resulted in substantial or persistent disability, resulted in or prolonged hospitalization, or were important medical events that investigators judged to represent substantial hazards or harm to research participants.
‡ Conditions of interest were a selected list of events that were serious adverse events or led to an emergency department visit.
§ Data were missing for 184 patients in the intensive-treatment group and 187 patients in the standard-treatment group.

Our trial has several limitations. First, patients and trial physicians were aware of treatment group assignments. However, outcome assessors were unaware of the assigned treatment group, and cardiovascular disease risk factors, such as levels of glycated hemoglobin and lipids, were similar in the treatment groups during follow-up. Second, telephone interviews were used to collect data, especially during lockdowns due to the Covid-19 pandemic, when standard blood-pressure monitoring at home was encouraged, although the percentage of telephone interviews for each protocol visit was similar in the treatment groups. Third, only approximately 60% of patients in the intensive-treatment group met the target systolic blood pressure after 1 year. Fourth, the diastolic blood pressure differed markedly between the treatment groups; therefore, an independent effect of systolic blood pressure on trial outcomes may not have been shown. Finally, the generalizability of our findings to other ethnic populations or to populations with different characteristics may be limited.

Among patients with type 2 diabetes and an increased risk of cardiovascular disease, the incidence of major cardiovascular events was lower with intensive treatment targeting a systolic blood pressure of less than 120 mm Hg than with standard treatment targeting a systolic blood pressure of less than 140 mm Hg.

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