

## A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group\*

### ABSTRACT

#### BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

#### METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

#### RESULTS

At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89;  $P < 0.001$ ). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90;  $P = 0.003$ ). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.

#### CONCLUSIONS

Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062.)

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N., B.S.N., M.A., Kaycee M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Reboussin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C.ushman, M.D., Alfred K. Cheung, M.D., and Walter T. Ambrosius, Ph.D.) assume responsibility for the overall content and integrity of the article. The affiliations of the members of the writing group are listed in the Appendix. Address reprint requests to Dr. Wright at the Division of Nephrology and Hypertension, University Hospitals Case Medical Center, Case Western Reserve University, 1100 Euclid Ave. Cleveland, OH 44106-6053, or at [jackson.wright@case.edu](mailto:jackson.wright@case.edu).

\*A complete list of the members of the Systolic Blood Pressure Intervention Trial (SPRINT) Research Group is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article was published on November 9, 2015, at [NEJM.org](http://NEJM.org).

*N Engl J Med* 2015;373:2103-16.

DOI: 10.1056/NEJMoa1511939

Copyright © 2015 Massachusetts Medical Society.

**H**YPERTENSION IS HIGHLY PREVALENT in the adult population in the United States, especially among persons older than 60 years of age, and affects approximately 1 billion adults worldwide.<sup>1,2</sup> Among persons 50 years of age or older, isolated systolic hypertension is the most common form of hypertension,<sup>3,4</sup> and systolic blood pressure becomes more important than diastolic blood pressure as an independent risk predictor for coronary events, stroke, heart failure, and end-stage renal disease (ESRD).<sup>5-13</sup> The Global Burden of Disease Study identified elevated blood pressure as the leading risk factor, among 67 studied, for death and disability-adjusted life-years lost during 2010.<sup>14</sup>

Clinical trials have shown that treatment of hypertension reduces the risk of cardiovascular disease outcomes, including incident stroke (by 35 to 40%), myocardial infarction (by 15 to 25%), and heart failure (by up to 64%).<sup>5,15,16</sup> However, the target for systolic blood-pressure lowering is uncertain. Observational studies have shown a progressive increase in cardiovascular risk as systolic blood pressure rises above 115 mm Hg,<sup>10</sup> but the available evidence from randomized, controlled trials in the general population of patients with hypertension only documents the benefit of treatment to achieve a systolic blood-pressure target of less than 150 mm Hg, with limited data concerning lower blood-pressure targets.<sup>11,17-21</sup> In a trial involving patients with type 2 diabetes mellitus, the rate of major cardiovascular events was similar with a systolic blood-pressure target of less than 120 mm Hg and the commonly recommended target of less than 140 mm Hg, though the rate of stroke was lower with the target of less than 120 mm Hg.<sup>22</sup> A recent trial involving patients who had had a stroke compared treatment to lower systolic blood pressure to less than 130 mm Hg with treatment to lower it to less than 150 mm Hg and showed no significant benefit of the lower target with respect to the overall risk of another stroke but a significant benefit with respect to the risk of hemorrhagic stroke.<sup>23</sup>

The hypothesis that a lower systolic blood-pressure goal (e.g., <120 mm Hg) would reduce clinical events more than a standard goal was designated by a National Heart, Lung, and Blood Institute (NHLBI) expert panel in 2007 as the most important hypothesis to test regarding the prevention of hypertension-related complications

among patients without diabetes.<sup>24</sup> The current article describes the primary results of the Systolic Blood Pressure Intervention Trial (SPRINT), which compared the benefit of treatment of systolic blood pressure to a target of less than 120 mm Hg with treatment to a target of less than 140 mm Hg.

## METHODS

### STUDY DESIGN AND OVERSIGHT

SPRINT was a randomized, controlled, open-label trial that was conducted at 102 clinical sites (organized into 5 clinical center networks) in the United States, including Puerto Rico (see the Supplementary Appendix, available with the full text of this article at NEJM.org). A trial coordinating center served as a data and biostatistical core center and supervised the central laboratory, the electrocardiography reading center, the magnetic resonance imaging reading center, and the drug-distribution center. The rationale and protocol for the trial are publicly available,<sup>25,26</sup> and the protocol is available at NEJM.org.

SPRINT was sponsored by the NHLBI, with cosponsorship by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging. An independent data and safety monitoring board monitored unblinded trial results and safety events. The study was approved by the institutional review board at each participating study site. The steering committee designed the study, gathered the data (in collaboration with investigators at the clinics and other study units), made the decision to submit the manuscript for publication, and vouches for the fidelity of the study to the protocol. The writing committee wrote the manuscript and vouches for the completeness and accuracy of the data and analysis. The coordinating center was responsible for analyzing the data. Scientists at the National Institutes of Health participated in the design of the study and as a group had one vote on the steering committee of the trial.

### STUDY POPULATION

Participants were required to meet all the following criteria: an age of at least 50 years, a systolic blood pressure of 130 to 180 mm Hg (see the Supplementary Appendix), and an increased risk

 A Quick Take is available at NEJM.org

of cardiovascular events. Increased cardiovascular risk was defined by one or more of the following: clinical or subclinical cardiovascular disease other than stroke; chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) of 20 to less than 60 ml per minute per 1.73 m<sup>2</sup> of body-surface area, calculated with the use of the four-variable Modification of Diet in Renal Disease equation; a 10-year risk of cardiovascular disease of 15% or greater on the basis of the Framingham risk score; or an age of 75 years or older. Patients with diabetes mellitus or prior stroke were excluded. Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix. All participants provided written informed consent.

#### RANDOMIZATION AND INTERVENTIONS

Eligible participants were assigned to a systolic blood-pressure target of either less than 140 mm Hg (the standard-treatment group) or less than 120 mm Hg (the intensive-treatment group). Randomization was stratified according to clinical site. Participants and study personnel were aware of the study-group assignments, but outcome adjudicators were not.

After the participants underwent randomization, their baseline antihypertensive regimens were adjusted on the basis of the study-group assignment. The treatment algorithms were similar to those used in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.<sup>22</sup> These algorithms and our formulary are listed in Figures S1 and S2 and Table S1 in the Supplementary Appendix. All major classes of antihypertensive agents were included in the formulary and were provided at no cost to the participants. SPRINT investigators could also prescribe other antihypertensive medications (not provided by the study). The protocol encouraged, but did not mandate, the use of drug classes with the strongest evidence for reduction in cardiovascular outcomes, including thiazide-type diuretics (encouraged as the first-line agent), loop diuretics (for participants with advanced chronic kidney disease), and beta-adrenergic blockers (for those with coronary artery disease).<sup>5,27</sup> Chlorthalidone was encouraged as the primary thiazide-type diuretic, and amlodipine as the preferred calcium-channel blocker.<sup>28,29</sup> Azilsartan and azilsartan combined with chlorthalidone were donated by

Takeda Pharmaceuticals International and Arbor Pharmaceuticals; neither company had any other role in the study.

Participants were seen monthly for the first 3 months and every 3 months thereafter. Medications for participants in the intensive-treatment group were adjusted on a monthly basis to target a systolic blood pressure of less than 120 mm Hg. For participants in the standard-treatment group, medications were adjusted to target a systolic blood pressure of 135 to 139 mm Hg, and the dose was reduced if systolic blood pressure was less than 130 mm Hg on a single visit or less than 135 mm Hg on two consecutive visits. Dose adjustment was based on a mean of three blood-pressure measurements at an office visit while the patient was seated and after 5 minutes of quiet rest; the measurements were made with the use of an automated measurement system (Model 907, Omron Healthcare). Lifestyle modification was encouraged as part of the management strategy. Retention in the study and adherence to treatment were monitored prospectively and routinely throughout the trial.<sup>26</sup>

#### STUDY MEASUREMENTS

Demographic data were collected at baseline. Clinical and laboratory data were obtained at baseline and every 3 months thereafter. A structured interview was used in both groups every 3 months to obtain self-reported cardiovascular disease outcomes. Although the interviewers were aware of the study-group assignments, they used the same format for interviews in the two groups to minimize ascertainment bias. Medical records and electrocardiograms were obtained for documentation of events. Whenever clinical-site staff became aware of a death, a standard protocol was used to obtain information on the event.

Serious adverse events were defined as events that were fatal or life-threatening, that resulted in clinically significant or persistent disability, that required or prolonged a hospitalization, or that were judged by the investigator to represent a clinically significant hazard or harm to the participant that might require medical or surgical intervention to prevent one of the other events listed above.<sup>30,31</sup> A short list of monitored conditions were reported as adverse events if they were evaluated in an emergency department:

hypotension, syncope, injurious falls, electrolyte abnormalities, and bradycardia. We also monitored occurrences of acute kidney injury or acute renal failure if they were noted on admission or occurred during a hospitalization and were reported in the hospital discharge summary as a primary or main secondary diagnosis. The *Medical Dictionary for Regulatory Activities* was used to classify the safety events. Coding was performed at the coordinating center, and up to three codes were assigned to each safety event. The relationship of serious adverse events to the intervention was assessed by the trial safety officer and reviewed monthly by the safety committee.

#### STUDY OUTCOMES

Definitions of study outcomes are outlined in the Supplementary Appendix. A committee whose members were unaware of the study-group assignments adjudicated the clinical outcomes specified in the protocol. The primary hypothesis was that treatment to reach a systolic blood-pressure target of less than 120 mm Hg, as compared with a target of less than 140 mm Hg, would result in a lower rate of the composite outcome of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Secondary outcomes included the individual components of the primary composite outcome, death from any cause, and the composite of the primary outcome or death from any cause.

We also assessed renal outcomes, using a different definition for patients with chronic kidney disease (eGFR <60 ml per minute per 1.73 m<sup>2</sup>) at baseline and those without it. The renal outcome in participants with chronic kidney disease at baseline was a composite of a decrease in the eGFR of 50% or more (confirmed by a subsequent laboratory test) or the development of ESRD requiring long-term dialysis or kidney transplantation. In participants without chronic kidney disease at baseline, the renal outcome was defined by a decrease in the eGFR of 30% or more to a value of less than 60 ml per minute per 1.73 m<sup>2</sup>. Incident albuminuria, defined for all study participants by a doubling of the ratio of urinary albumin (in milligrams) to creatinine (in grams) from less than 10 at baseline to greater than 10 during follow-up, was also a prespecified renal outcome.

Prespecified subgroups of interest for all outcomes were defined according to status with respect to cardiovascular disease at baseline (yes vs. no), status with respect to chronic kidney disease at baseline (yes vs. no), sex, race (black vs. non-black), age (<75 vs. ≥75 years), and baseline systolic blood pressure in three levels (≤132 mm Hg, >132 to <145 mm Hg, and ≥145 mm Hg). We also planned a comparison of the effects of systolic blood-pressure targets on incident dementia, changes in cognitive function, and cerebral small-vessel ischemic disease; these results are not presented here.

#### STATISTICAL ANALYSIS

We planned a 2-year recruitment period, with a maximum follow-up of 6 years, and anticipated a loss to follow-up of 2% per year. With an enrollment target of 9250 participants, we estimated that the trial would have 88.7% power to detect a 20% effect with respect to the primary outcome, assuming an event rate of 2.2% per year in the standard-treatment group.

Our primary analysis compared the time to the first occurrence of a primary outcome event between the two study groups with the use of the intention-to-treat approach for all randomly assigned participants; for this analysis, we used Cox proportional-hazards regression with two-sided tests at the 5% level of significance, with stratification according to clinic. Follow-up time was censored on the date of last event ascertainment. Interactions between treatment effect and prespecified subgroups were assessed with a likelihood-ratio test for the interaction with the use of Hommel-adjusted P values.<sup>32</sup> Interim analyses were performed for each meeting of the data and safety monitoring board, with group-sequential stopping boundaries defined with the use of the Lan–DeMets method with an O’Brien–Fleming–type spending function.<sup>33</sup> The Fine–Gray model for the competing risk of death was used as a sensitivity analysis.<sup>34</sup>

## RESULTS

#### STUDY PARTICIPANTS

A total of 9361 participants were enrolled between November 2010 and March 2013 (Fig. 1). Descriptive baseline statistics are presented in Table 1. On August 20, 2015, the NHLBI director accepted a recommendation from the data and

safety monitoring board of the trial to inform the investigators and participants of the cardiovascular-outcome results after analyses of the primary outcome exceeded the monitoring boundary at two consecutive time points (Fig. S3 in the Supplementary Appendix), thus initiating the process to end the blood-pressure intervention early. The median follow-up on August 20, 2015, was 3.26 years of the planned average of 5 years.

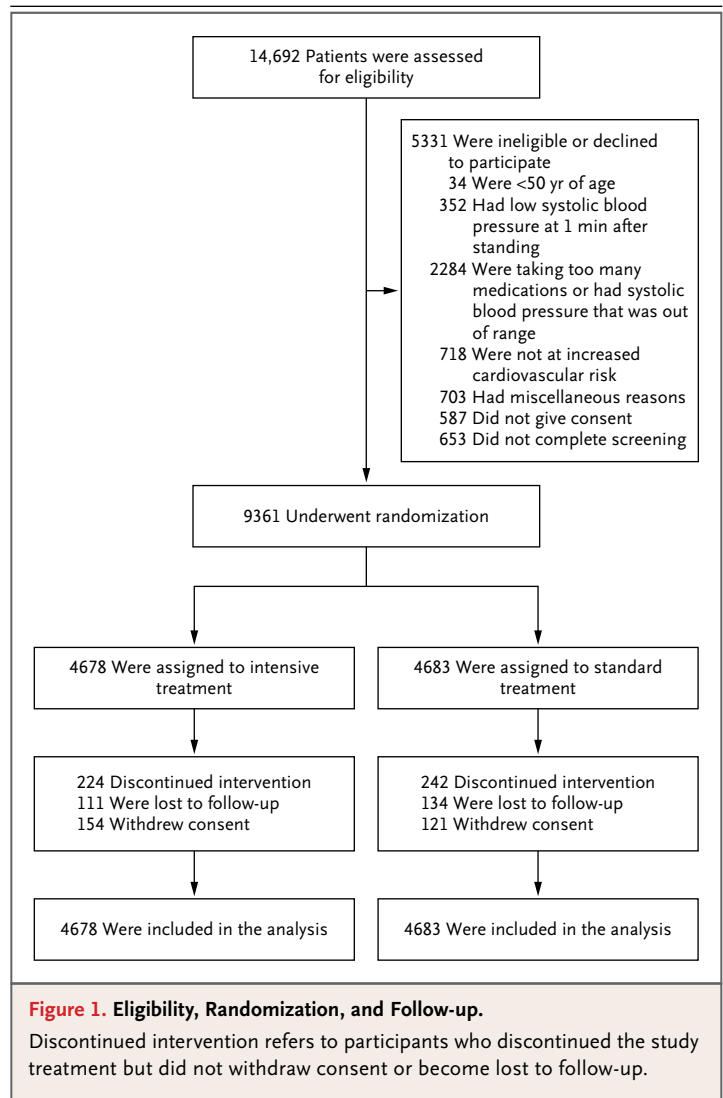
### BLOOD PRESSURE

The two treatment strategies resulted in a rapid and sustained between-group difference in systolic blood pressure (Fig. 2). At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group, for an average difference of 14.8 mm Hg. The mean diastolic blood pressure at 1 year was 68.7 mm Hg in the intensive-treatment group and 76.3 mm Hg in the standard-treatment group (Fig. S4 in the Supplementary Appendix). Throughout the 3.26 years of follow-up, the mean systolic blood pressure was 121.5 mm Hg in the intensive-treatment group and 134.6 mm Hg in the standard-treatment group, and the mean number of blood-pressure medications was 2.8 and 1.8, respectively. The relative distribution of antihypertensive medication classes used was similar in the two groups, though the use of each class was greater in the intensive-treatment group (Table S2 in the Supplementary Appendix).

### CLINICAL OUTCOMES

A primary outcome event was confirmed in 562 participants — 243 (1.65% per year) in the intensive-treatment group and 319 (2.19% per year) in the standard-treatment group (hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89;  $P < 0.001$ ) (Table 2). Separation in the primary outcome between the groups was apparent at 1 year (Fig. 3A). The between-group differences were consistent across the components of the primary outcome and other prespecified secondary outcomes (Table 2).

A total of 365 deaths occurred — 155 in the intensive-treatment group and 210 in the standard-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90;  $P = 0.003$ ). Separation in mortality between the groups became apparent at approximately 2 years (Fig. 3B). Causes of death are provided in Table S3 in the Supplementary Ap-



pendix. The relative risk of death from cardiovascular causes was 43% lower with the intensive intervention than with the standard treatment ( $P = 0.005$ ) (Table 2).

The numbers needed to treat to prevent a primary outcome event, death from any cause, and death from cardiovascular causes during the median 3.26 years of the trial were 61, 90, and 172, respectively. The effects of the intervention on the rate of the primary outcome and on the rate of death from any cause were consistent across the prespecified subgroups (Fig. 4, and Fig. S5 in the Supplementary Appendix). There were no significant interactions between treatment and subgroup with respect to the primary outcome or death from any cause. When death

<b>Table 1. Baseline Characteristics of the Study Participants.*</b>		
<b>Characteristic</b>	<b>Intensive Treatment (N = 4678)</b>	<b>Standard Treatment (N = 4683)</b>
Criterion for increased cardiovascular risk — no. (%) <sup>†</sup>		
Age ≥75 yr	1317 (28.2)	1319 (28.2)
Chronic kidney disease <sup>‡</sup>	1330 (28.4)	1316 (28.1)
Cardiovascular disease	940 (20.1)	937 (20.0)
Clinical	779 (16.7)	783 (16.7)
Subclinical	247 (5.3)	246 (5.3)
Framingham 10-yr cardiovascular disease risk score ≥15%	2870 (61.4)	2867 (61.2)
Female sex — no. (%)	1684 (36.0)	1648 (35.2)
Age — yr		
Overall	67.9±9.4	67.9±9.5
Among those ≥75 yr of age	79.8±3.9	79.9±4.1
Race or ethnic group — no. (%) <sup>§</sup>		
Non-Hispanic black	1379 (29.5)	1423 (30.4)
Hispanic	503 (10.8)	481 (10.3)
Non-Hispanic white	2698 (57.7)	2701 (57.7)
Other	98 (2.1)	78 (1.7)
Black race <sup>¶</sup>	1454 (31.1)	1493 (31.9)
Baseline blood pressure — mm Hg		
Systolic	139.7±15.8	139.7±15.4
Diastolic	78.2±11.9	78.0±12.0
Distribution of systolic blood pressure — no. (%)		
≤132 mm Hg	1583 (33.8)	1553 (33.2)
>132 mm Hg to <145 mm Hg	1489 (31.8)	1549 (33.1)
≥145 mm Hg	1606 (34.3)	1581 (33.8)
Serum creatinine — mg/dl	1.07±0.34	1.08±0.34
Estimated GFR — ml/min/1.73 m <sup>2</sup>		
Among all participants	71.8±20.7	71.7±20.5
Among those with estimated GFR ≥60 ml/min/1.73 m <sup>2</sup>	81.3±15.5	81.1±15.5
Among those with estimated GFR <60 ml/min/1.73 m <sup>2</sup>	47.8±9.5	47.9±9.5
Ratio of urinary albumin (mg) to creatinine (g)	44.1±178.7	41.1±152.9
Fasting total cholesterol — mg/dl	190.2±41.4	190.0±40.9
Fasting HDL cholesterol — mg/dl	52.9±14.3	52.8±14.6
Fasting total triglycerides — mg/dl	124.8±85.8	127.1±95.0
Fasting plasma glucose — mg/dl	98.8±13.7	98.8±13.4
Statin use — no./total no. (%)	1978/4645 (42.6)	2076/4640 (44.7)
Aspirin use — no./total no. (%)	2406/4661 (51.6)	2350/4666 (50.4)
Smoking status — no. (%)		
Never smoked	2050 (43.8)	2072 (44.2)
Former smoker	1977 (42.3)	1996 (42.6)
Current smoker	639 (13.7)	601 (12.8)
Missing data	12 (0.3)	14 (0.3)
Framingham 10-yr cardiovascular disease risk score — %	20.1±10.9	20.1±10.8

Table 1. (Continued.)

Characteristic	Intensive Treatment (N=4678)	Standard Treatment (N=4683)
Body-mass index <sup>  </sup>	29.9±5.8	29.8±5.7
Antihypertensive agents — no./patient	1.8±1.0	1.8±1.0
Not using antihypertensive agents — no. (%)	432 (9.2)	450 (9.6)

\* Plus-minus values are means ±SD. There were no significant differences ( $P<0.05$ ) between the two groups except for statin use ( $P=0.04$ ). To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. GFR denotes glomerular filtration rate, and HDL high-density lipoprotein.

† Increased cardiovascular risk was one of the inclusion criteria.

‡ Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m<sup>2</sup> of body-surface area.

§ Race and ethnic group were self-reported.

¶ Black race includes Hispanic black and black as part of a multiracial identification.

|| The body-mass index is the weight in kilograms divided by the square of the height in meters.

was treated as a competing risk in a Fine–Gray model, the results with respect to the primary outcome were virtually unchanged (hazard ratio, 0.76; 95% CI, 0.64 to 0.89).

Among participants who had chronic kidney disease at baseline, no significant between-group difference in the composite outcome of a decrease in the eGFR of 50% or more or the development of ESRD was noted, though the number of events was small (Table 2). Among participants who did not have chronic kidney disease at baseline, the incidence of the outcome defined by a decrease in the eGFR of 30% or more to a value of less than 60 ml per minute per 1.73 m<sup>2</sup> was higher in the intensive-treatment group than in the standard-treatment group (1.21% per year vs. 0.35% per year; hazard ratio, 3.49; 95% CI, 2.44 to 5.10;  $P<0.001$ ).

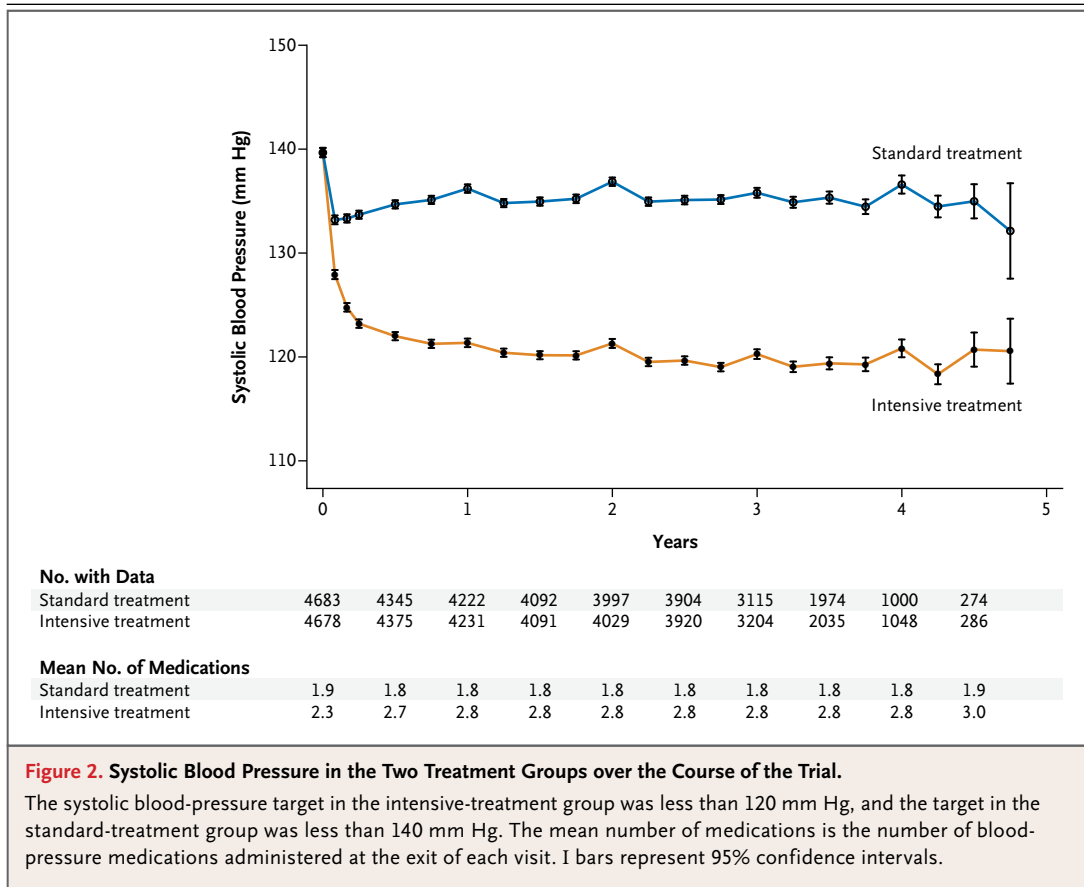
#### SERIOUS ADVERSE EVENTS

Serious adverse events occurred in 1793 participants in the intensive-treatment group (38.3%) and in 1736 participants in the standard-treatment group (37.1%) (hazard ratio with intensive treatment, 1.04;  $P=0.25$ ) (Table 3, and Table S4 in the Supplementary Appendix). Serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure, but not injurious falls or bradycardia, occurred more frequently in the intensive-treatment group than in the standard-treatment group. Orthostatic hypotension as assessed during a clinic visit was significantly less common in the intensive-treatment group. A total of 220

participants in the intensive-treatment group (4.7%) and 118 participants in the standard-treatment group (2.5%) had serious adverse events that were classified as possibly or definitely related to the intervention (hazard ratio, 1.88;  $P<0.001$ ) (Table S5 in the Supplementary Appendix). The magnitude and pattern of differences in adverse events according to treatment assignment among participants 75 years of age or older were similar to those in the overall cohort (Table S6 in the Supplementary Appendix).

#### DISCUSSION

SPRINT showed that among adults with hypertension but without diabetes, lowering systolic blood pressure to a target goal of less than 120 mm Hg, as compared with the standard goal of less than 140 mm Hg, resulted in significantly lower rates of fatal and nonfatal cardiovascular events and death from any cause. Trial participants assigned to the lower systolic blood-pressure target (intensive-treatment group), as compared with those assigned to the higher target (standard-treatment group), had a 25% lower relative risk of the primary outcome; in addition, the intensive-treatment group had lower rates of several other important outcomes, including heart failure (38% lower relative risk), death from cardiovascular causes (43% lower relative risk), and death from any cause (27% lower relative risk). During the follow-up period of the trial (median, 3.26 years), the number needed to treat with a strategy of intensive blood-pressure control to



prevent one primary outcome event was 61, and the number needed to treat to prevent one death from any cause was 90. These benefits with respect to both the primary outcome and death were consistent across all prespecified subgroups, including participants 75 years of age or older.

Owing in part to a lower-than-expected decline in the eGFR and to the early termination of the trial, the number of renal events was small. Among participants who had chronic kidney disease at baseline, the number of participants with a decrease in the eGFR of 50% or more or reaching ESRD over the course of the trial did not differ significantly between the two intervention groups. Among participants who did not have chronic kidney disease at baseline, a decrease in the eGFR of 30% or more to a value of less than 60 ml per minute per 1.73 m<sup>2</sup> occurred more frequently in the intensive-treatment group than in the standard-treatment group (1.21% per year vs. 0.35% per year). Among all participants, acute kidney injury or acute renal failure occurred

more frequently in the intensive-treatment group than in the standard-treatment group (Table 3, and Table S5 in the Supplementary Appendix). The differences in adverse renal outcomes may be related to a reversible intrarenal hemodynamic effect of the greater reduction in blood pressure and greater use of diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers in the intensive-treatment group.<sup>35,36</sup> With the currently available data, there is no evidence of substantial permanent kidney injury associated with the lower systolic blood-pressure goal; however, the possibility of a long-term adverse renal outcome cannot be excluded. These observations and hypotheses need to be explored further in analyses that incorporate more clinical outcomes and longer follow-up.

The results of SPRINT add substantially to the evidence of benefits of lowering systolic blood pressure, especially in older patients with hypertension. Trials such as the Systolic Hypertension in the Elderly Program trial,<sup>17</sup> the Sys-



**Table 2. Primary and Secondary Outcomes and Renal Outcomes.\***

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per year	no. of patients (%)	% per year		
<b>All participants</b>	<b>(N = 4678)</b>		<b>(N = 4683)</b>			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
<b>Participants with CKD at baseline</b>	<b>(N = 1330)</b>		<b>(N = 1316)</b>			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
<b>Participants without CKD at baseline  </b>	<b>(N = 3332)</b>		<b>(N = 3345)</b>			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m <sup>2</sup> §	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	110/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

\* CI denotes confidence interval, and CKD chronic kidney disease.

† The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.

‡ The composite renal outcome for participants with CKD at baseline was the first occurrence of a reduction in the estimated GFR of 50% or more, long-term dialysis, or kidney transplantation.

§ Reductions in the estimated GFR were confirmed by a second laboratory test at least 90 days later.

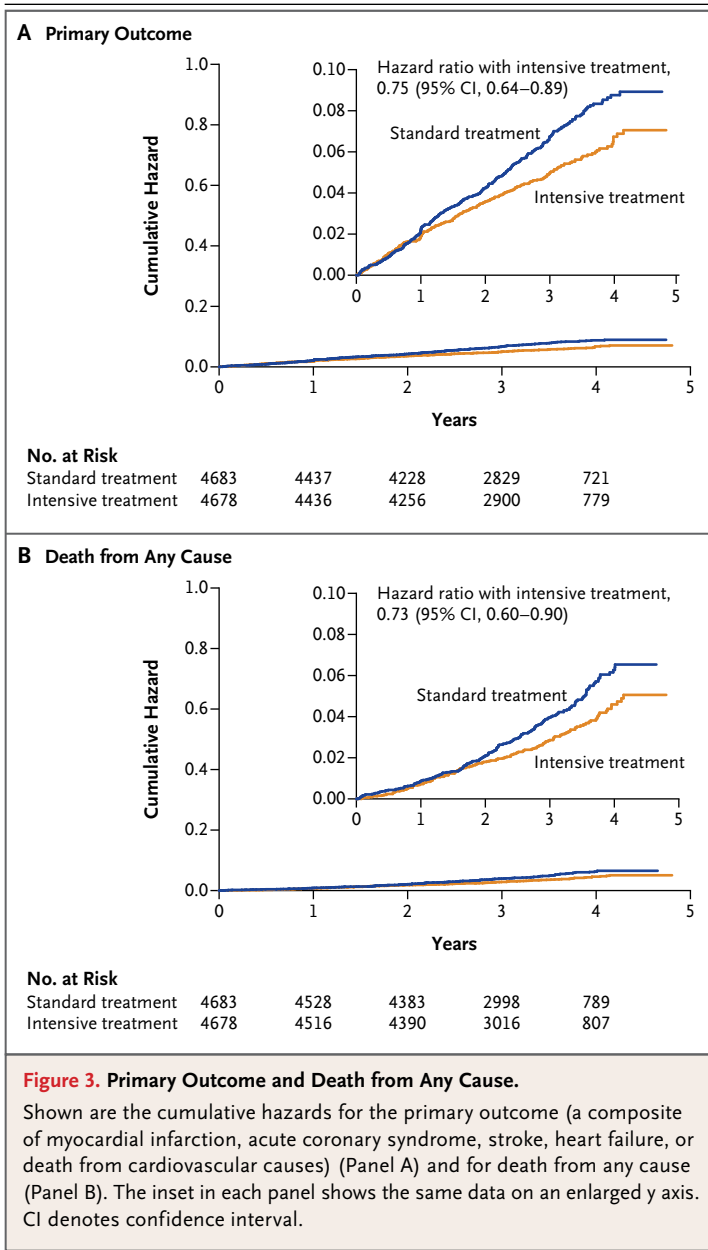
¶ Incident albuminuria was defined by a doubling of the ratio of urinary albumin (in milligrams) to creatinine (in grams) from less than 10 at baseline to greater than 10 during follow-up. The denominators for number of patients represent those without albuminuria at baseline.

|| No long-term dialysis or kidney transplantation was reported among participants without CKD at baseline.

tolic Hypertension in Europe trial,<sup>11</sup> and the Hypertension in the Very Elderly Trial<sup>18</sup> showed the benefits of lowering systolic blood pressure below 150 mm Hg. However, trials evaluating systolic blood-pressure levels lower than those studied in these trials have been either underpowered<sup>19-21</sup> or performed without specific systolic blood-pressure targets.<sup>37</sup> A major component of the controversy regarding the selection of the systolic blood-pressure goal in this population has resulted from inadequate data on the risks versus benefits of systolic blood-pressure targets below 150 mm Hg.<sup>11,17-21,37</sup> SPRINT now provides evidence of benefits for an even lower systolic

blood-pressure target than that currently recommended in most patients with hypertension.

Comparisons between SPRINT and the ACCORD trial<sup>22</sup> are inevitable, because the trials examined identical systolic blood-pressure targets (<120 mm Hg vs. <140 mm Hg). In contrast to the findings of SPRINT, the cardiovascular and mortality benefits observed in the ACCORD trial were not statistically significant and were of a lesser magnitude. Several important differences between these trials should be noted. The ACCORD trial enrolled participants with diabetes exclusively, whereas SPRINT excluded participants with diabetes; in addition, the sample

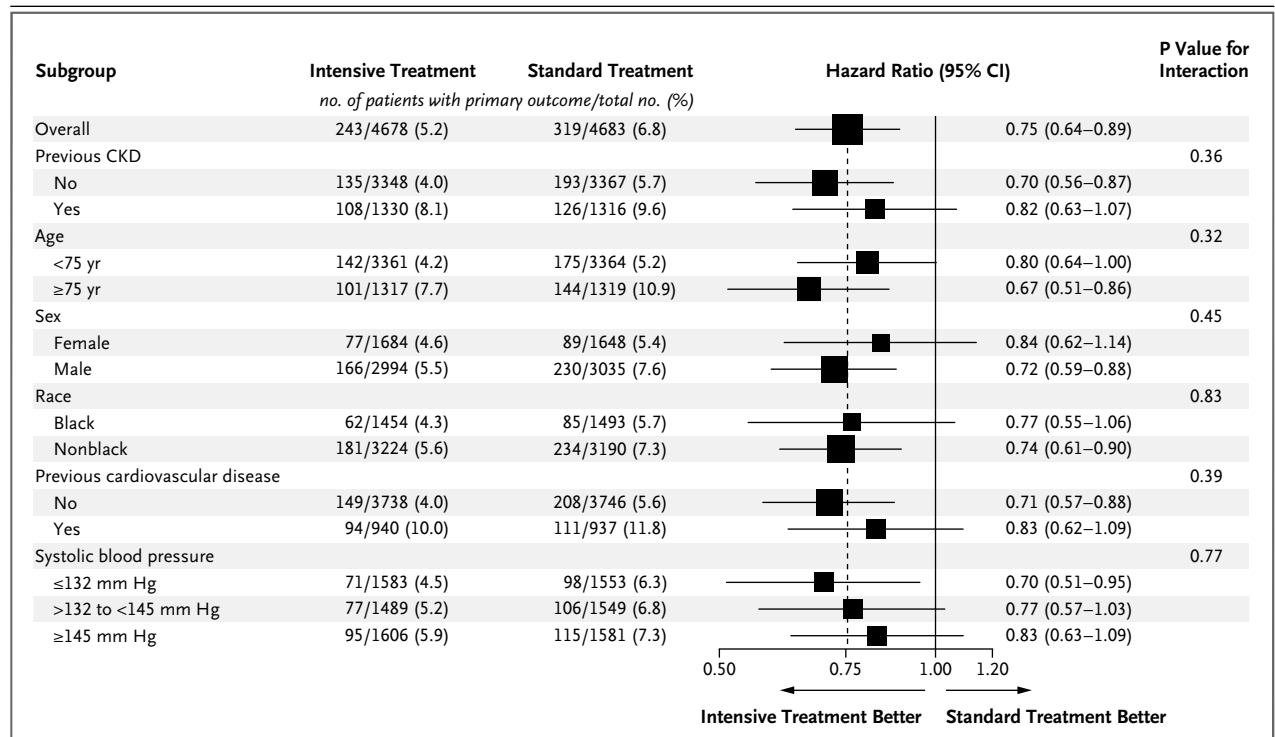


size of the ACCORD trial was only half that of SPRINT (4733 vs. 9361). SPRINT enrolled an older cohort (mean age, 68 years, vs. 62 years in the ACCORD trial), with 28% of participants 75 years of age or older, and also included participants with chronic kidney disease. The ACCORD trial showed a (nonsignificant) 12% lower risk of its primary composite cardiovascular outcome, with a 95% confidence interval that included the possibility of a 27% lower risk, which is consistent with the cardiovascular benefit

observed in SPRINT. The ACCORD trial also used a factorial design that included comparisons of standard and intensive glycemic and lipid treatment targets in the same trial. A secondary analysis of the ACCORD results showed that, as compared with the combined standard glycemia and blood-pressure treatments, intensive blood-pressure treatment alone reduced major cardiovascular outcomes by 26% without additional benefit from combining the two intensive treatments.<sup>38</sup> Thus, the difference in results between the trials could be due to differences in study design, treatment interactions, or the play of chance. An inherent difference in the cardiovascular benefits of systolic blood-pressure lowering between the population with diabetes and the population without diabetes seems unlikely but cannot be ruled out.

In the Secondary Prevention of Small Subcortical Strokes trial (intensive systolic blood-pressure goal <130 mm Hg)<sup>23</sup> and in the ACCORD trial (intensive systolic blood-pressure goal <120 mm Hg), the lower blood-pressure target was associated with a nonsignificant 19% lower incidence of stroke ( $P=0.08$ ) and a significant 41% lower incidence of stroke, respectively, than the incidence with higher targets. The intensive-treatment group in SPRINT had a nonsignificant 11% lower incidence of stroke, though SPRINT also excluded persons with prevalent stroke or transient ischemic attack at baseline.

In SPRINT, significant between-group differences were noted in some adverse effects that were attributed to the intervention (Table S5 in the Supplementary Appendix). Orthostatic hypotension as assessed during a clinic visit (Table 3) was observed less frequently in the intensive-treatment group than in the standard-treatment group ( $P=0.01$ ), but syncope was more common among participants in the intensive-treatment group than among those in the standard-treatment group (3.5% vs. 2.4%,  $P=0.003$ ), as was hypotension (3.4% vs. 2.0%,  $P<0.001$ ). There was no between-group difference in injurious falls (hazard ratio, 1.00;  $P=0.97$ ). There was a higher rate of acute kidney injury or acute renal failure in the intensive-treatment group, as noted above. These adverse events need to be weighed against the benefits with respect to cardiovascular events and death that are associated with intensive control of systolic blood pressure.



**Figure 4. Forest Plot of Primary Outcome According to Subgroups.**

The dashed vertical line represents the hazard ratio for the overall study population. The box sizes are proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision). The subgroup of no previous chronic kidney disease (CKD) includes some participants with unknown CKD status at baseline. Black race includes Hispanic black and black as part of a multiracial identification.

The strengths of SPRINT include a large sample size, the diversity of the population (including a large proportion of patients 75 years of age or older), and its success in achieving the intended separation in systolic blood pressure between the two intervention groups throughout the trial. The lack of generalizability to populations not included in the study — such as persons with diabetes, those with prior stroke, and those younger than 50 years of age — is a limitation. It is also worth noting that we did not enroll older adults residing in nursing homes or assisted-living facilities. In addition, the effects of the lower blood pressure on the central nervous system and kidney cannot be reasonably interpreted until analysis of these end points has been completed.

The SPRINT results raise important practical issues. Hypertension control to a blood pressure of less than 140/90 mm Hg is achieved in only about 50% of the general population in the

United States, which suggests that control to even that level is challenging.<sup>39</sup> We excluded patients with more severe hypertension, and control of systolic blood pressure to less than 120 mm Hg required, on average, one additional antihypertensive drug. In addition, the median systolic blood pressure in the intensive-treatment group was just above 120 mm Hg, which indicates that more than half the participants had a systolic blood pressure above the 120 mm Hg target. These observations suggest that achieving a systolic blood-pressure goal of less than 120 mm Hg in the overall population of patients with hypertension would be more demanding and time-consuming for both providers and patients than achieving a goal of 140 mm Hg, and would necessitate increased medication costs and clinic visits.

In conclusion, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, in patients at high risk for

**Table 3. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.**

Variable	Intensive Treatment (N=4678)	Standard Treatment (N=4683)	Hazard Ratio	P Value
	<i>no. of patients (%)</i>			
Serious adverse event*	1793 (38.3)	1736 (37.1)	1.04	0.25
Conditions of interest				
Serious adverse event only				
Hypotension	110 (2.4)	66 (1.4)	1.67	0.001
Syncope	107 (2.3)	80 (1.7)	1.33	0.05
Bradycardia	87 (1.9)	73 (1.6)	1.19	0.28
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35	0.02
Injurious fall†	105 (2.2)	110 (2.3)	0.95	0.71
Acute kidney injury or acute renal failure‡	193 (4.1)	117 (2.5)	1.66	<0.001
Emergency department visit or serious adverse event				
Hypotension	158 (3.4)	93 (2.0)	1.70	<0.001
Syncope	163 (3.5)	113 (2.4)	1.44	0.003
Bradycardia	104 (2.2)	83 (1.8)	1.25	0.13
Electrolyte abnormality	177 (3.8)	129 (2.8)	1.38	0.006
Injurious fall†	334 (7.1)	332 (7.1)	1.00	0.97
Acute kidney injury or acute renal failure‡	204 (4.4)	120 (2.6)	1.71	<0.001
Monitored clinical events				
Adverse laboratory measure§				
Serum sodium <130 mmol/liter	180 (3.8)	100 (2.1)	1.76	<0.001
Serum sodium >150 mmol/liter	6 (0.1)	0		0.02
Serum potassium <3.0 mmol/liter	114 (2.4)	74 (1.6)	1.50	0.006
Serum potassium >5.5 mmol/liter	176 (3.8)	171 (3.7)	1.00	0.97
Orthostatic hypotension¶				
Alone	777 (16.6)	857 (18.3)	0.88	0.01
With dizziness	62 (1.3)	71 (1.5)	0.85	0.35

\* A serious adverse event was defined as an event that was fatal or life-threatening, that resulted in clinically significant or persistent disability, that required or prolonged a hospitalization, or that was judged by the investigator to represent a clinically significant hazard or harm to the participant that might require medical or surgical intervention to prevent one of the other events listed above.

† An injurious fall was defined as a fall that resulted in evaluation in an emergency department or that resulted in hospitalization.

‡ Acute kidney injury or acute renal failure were coded if the diagnosis was listed in the hospital discharge summary and was believed by the safety officer to be one of the top three reasons for admission or continued hospitalization. A few cases of acute kidney injury were noted in an emergency department if the participant presented for one of the other conditions of interest.

§ Adverse laboratory measures were detected on routine or unscheduled tests; routine laboratory tests were performed at 1 month, then quarterly during the first year, then every 6 months.

¶ Orthostatic hypertension was defined as a drop in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of at least 10 mm Hg at 1 minute after the participant stood up, as compared with the value obtained when the participant was seated. Standing blood pressures were measured at screening, baseline, 1 month, 6 months, 12 months, and yearly thereafter. Participants were asked if they felt dizzy at the time the orthostatic measure was taken.

cardiovascular events but without diabetes resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause. However, some adverse events occurred significantly more frequently with the lower target.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH), the Department of Veterans Affairs, or the U.S. Government.

Supported by contracts (HHSN268200900040C, HHSN268200900046C, HHSN268200900047C,

HHSN268200900048C, and HHSN268200900049C) and an interagency agreement (A-HL-13-002-001) from the NIH, including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke. Several study sites were supported by Clinical and Translational Science Awards funded by the National Center for Advancing Translational Sciences of the NIH (Case Western Reserve University: UL1TR000439; Ohio State University: UL1RR025755; University of Pennsylvania: UL1RR024134 and UL1TR000003; Boston University: UL1RR025771; Stanford University: UL1TR000093; Tufts University: UL1RR025752, UL1TR000073, and UL1TR001064; University

of Illinois: UL1TR000050; University of Pittsburgh: UL1TR000005; University of Texas Southwestern: 9U54TR000017-06; University of Utah: UL1TR000105-05; Vanderbilt University: UL1TR000445; George Washington University: UL1TR000075; University of California, Davis: UL1TR000002; University of Florida: UL1TR000064; University of Michigan: UL1TR000433; and Tulane University: P30GM103337 COBRE Award NIGMS). The trial was also supported in part with respect to resources and the use of facilities by the Department of Veterans Affairs.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the study participants, without whom this trial would not have been possible.

#### APPENDIX

The affiliations of the members of the writing group are as follows: the Division of Nephrology and Hypertension, University Hospitals Case Medical Center, Case Western Reserve University (J.T.W., M.R.), and Division of Nephrology and Hypertension, Louis Stokes Cleveland Veterans Affairs (VA) Medical Center (M.R.), Cleveland; Sticht Center on Aging (J.D.W., K.M.S.), Section on Nephrology (M.V.R.), and Department of Biostatistical Sciences (D.M.R., W.T.A.), Wake Forest School of Medicine, Winston-Salem, NC; Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans (P.K.W.); Clinical Applications and Prevention Branch, National Heart, Lung, and Blood Institute (J.K.S., L.J.F., J.A.C.), and Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (P.L.K.), Bethesda, MD; Divisions of Cardiovascular Diseases (S.O.) and Preventive Medicine (C.E.L.), University of Alabama at Birmingham, Birmingham; Department of Preventive Medicine, University of Tennessee Health Science Center (K.C.J.), and the Preventive Medicine Section, VA Medical Center (W.C.C.), Memphis; School of Public Health, University of Colorado, Aurora (D.C.G.); and Division of Nephrology and Hypertension, University of Utah, Salt Lake City (A.K.C.).

#### REFERENCES

- Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217-23.
- Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics — 2014 update: a report from the American Heart Association. *Circulation* 2014;129(3):e28-292.
- Franklin SS. Cardiovascular risks related to increased diastolic, systolic and pulse pressure: an epidemiologist's point of view. *Pathol Biol (Paris)* 1999;47:594-603.
- Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension* 2001;37:869-74.
- Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 2003;289:2560-72.
- Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. 2. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827-38.
- Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Intern Med* 2005;165:923-8.
- Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557-62.
- MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
- Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757-64.
- Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291-7.
- Sundström J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. *Ann Intern Med* 2015;162:184-91.
- Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224-60.
- Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000;356:1955-64.
- Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: asystematic review and meta-analysis. *JAMA* 1997;277:739-45.
- SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-64.
- Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887-98.
- JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008;31:2115-27.
- Ogihara T, Saruta T, Rakugi H, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: Valsartan in Elderly Isolated Systolic Hypertension study. *Hypertension* 2010;56:196-202.
- Verdecchia P, Staessen JA, Angeli F, et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet* 2009;374:525-33.
- Cushman WC, Evans GW, Byington

- RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85.
23. Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomized trial. *Lancet* 2013;382:507-15.
24. Working group report: Expert Panel on a Hypertension Treatment Trial Initiative meeting summary, 2007. Bethesda, MD, National Heart Lung and Blood Institute (<http://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/hypertensionsion-full.pdf>).
25. Systolic Blood Pressure Intervention Trial (SPRINT) protocol. November 1, 2012 ([https://www.sprintrial.org/public/Protocol\\_Current.pdf](https://www.sprintrial.org/public/Protocol_Current.pdf)).
26. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials* 2014;11:532-46.
27. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005;366:1545-53.
28. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
29. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;47:352-8.
30. Office for Human Research Protections. OHRP guidance on unanticipated problems and adverse events. 2007 (<http://www.hhs.gov/ohrp/policy/advevtguid.html>).
31. Food and Drug Administration. Code of Federal Regulations. Title 21CFR312.32a, 2013 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32>).
32. Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* 1988;75:383-86.
33. Proschan MA, Lan KKG, Wittes JT. Statistical monitoring of clinical trials: a unified approach. New York: Springer, 2006.
34. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
35. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160:685-93.
36. Apperloo AJ, de Zeeuw D, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. *Kidney Int* 1997;51:793-7.
37. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens* 2005;23:2157-72.
38. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. *Diabetes Care* 2014;37:1721-8.
39. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011–2012. *NCHS Data Brief* 2013;133:1-8.

Copyright © 2015 Massachusetts Medical Society.

RECEIVE IMMEDIATE NOTIFICATION WHEN AN ARTICLE  
IS PUBLISHED ONLINE FIRST

To be notified by e-mail when *Journal* articles  
are published Online First, sign up at [NEJM.org](http://NEJM.org).