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Intensive Blood Pressure Treatment for Resistant Hypertension

Secondary Analysis of a Randomized Controlled Trial

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See Editorial Commentary, pp 299–300

Abstract—Evidence about the target blood pressure (BP) in patients with resistant hypertension is limited. The present study aimed to assess the efficacy of intensive BP treatment (systolic BP target, <120 mm Hg) versus standard BP treatment (systolic BP target, <140 mm Hg) in patients with resistant hypertension. This is a secondary analysis using data from SPRINT (Systolic Blood Pressure Intervention Trial). This study included 1397 patients with resistant hypertension and 7698 without resistant hypertension. Using the Cox proportional hazards model, we compared time to first occurrence of a major adverse cardiovascular event (cardiovascular death, myocardial infarction, and stroke) between the intensive and standard BP treatment groups. Mean follow-up was 3.1 years; major adverse cardiovascular events was confirmed in 381 patients. Risk of major adverse cardiovascular events was significantly lower in the intensive treatment group than in the standard treatment group (hazard ratio, 0.62; 95% CI, 0.40–0.96; *P*=0.03). Risks of all-cause and cardiovascular death in patients with resistant hypertension were also significantly lower in the intensive treatment group than in the standard treatment group (hazard ratio for all-cause death: 0.60; 95% CI, 0.38–0.97; *P*=0.03; hazard ratio for cardiovascular death: 0.34; 95% CI, 0.15–0.81; *P*=0.01). Similar associations were observed in various subgroups. Intensive BP treatment was significantly associated with a decreased risk of major adverse cardiovascular events in patients with resistant hypertension. **(*Hypertension*. 2019;73:415-423. DOI: 10.1161/HYPERTENSIONAHA.118.12156.)** ● **Online Data Supplement**

Key Words: blood pressure ■ hypertension ■ mortality ■ myocardial infarction ■ resistant hypertension ■ SPRINT ■ stroke

Hypertension is a public health concern with high prevalence reported worldwide.[1,2] It increases the risk of several cardiovascular events, such as coronary heart disease, stroke, and heart failure,[3,4] and lowering blood pressure (BP) results in significantly decreased risk of developing such cardiovascular events.[5] Nonpharmacologic therapy, such as restriction of dietary salt restriction, exercise, and weight loss, and therapy with antihypertensive drugs are both effective in lowering BP in hypertensive patients.[6,7] However, the optimal BP target remains controversial. The SPRINT study (Systolic Blood Pressure Intervention Trial) reported that intensive treatment with a systolic BP target of 120 mm Hg was associated with decreased incidence of cardiovascular events and death in high-risk patients without diabetes mellitus or prior history of stroke, compared with a standard SBP target of 140 mm Hg.[5] In contrast, the ACCORD BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) demonstrated that, compared with the standard systolic BP target of <140 mm Hg, the intensive systolic BP target of <120 mm Hg in high-risk patients with type 2 diabetes mellitus did not reduce the composite outcome of fatal and nonfatal major cardiovascular events.[8] The discrepancy between the results of the SPRINT and ACCORD BP studies warrants further investigation on the applicability of intensive BP treatment.

Resistant hypertension is a common clinical problem faced by both specialists and primary care clinicians.[9,10] Although the exact prevalence of resistant hypertension is unclear, it is estimated to range from 10% to 30% of all hypertensive patients.[11] Therefore, the management of resistant hypertension is important. However, evidence about the BP target in patients with resistant hypertension is currently limited. The SPRINT study reported the overall benefits of intensive BP treatment in high-risk patients, but it remains unknown whether the impact of intensive BP treatment was

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equally observed in patients with resistant hypertension. The aim of the present study was to assess the efficacy of intensive BP treatment in patients with resistant hypertension and to investigate the possible association between resistant hypertension and increased risk of cardiovascular events among the participants in the SPRINT study.

Methods

The anonymized data from the SPRINT study have been made publicly available at the National Heart, Lung, and Blood Institute and can be accessed at https://biolincc.nhlbi.nih.gov/studies/sprint_pop/?q=SPRINT.

Study Design and Patients

Using data from the SPRINT study,[5] the benefits of intensive BP treatment in patients with resistant hypertension were assessed. The study design, protocol, and patient characteristics of the SPRINT study have been previously reported.[5,12] Briefly, SPRINT was a multicenter, randomized, controlled, open-label trial. Between November 2010 and August 2015, a total of 9361 patients enrolled at 102 clinical sites in the United States, including Puerto Rico, were randomly assigned to a systolic BP target of either <120 mm Hg (intensive BP treatment) or <140 mm Hg (standard BP treatment). The objective of the SPRINT study was to determine whether intensive BP treatment reduced the risk of cardiovascular events. The efficacy of specific medications was beyond the scope of the study. Consequently, the BP treatment protocol was flexible in terms of the selection and dosage of antihypertensive medications.[5,12] The dosage of medications was adjusted on the basis of the average of 3 BP measurements performed using an automated measurement system (Model 907, Omron Healthcare, Kyoto, Japan).[5,12] BP was measured during an office visit with the patient in a seated position after 5 minutes of quiet rest. Eligible participants of the SPRINT study were aged ≥50 years, with systolic BP of 130 to 180 mm Hg and had at least 1 cardiovascular risk (ref). Exclusion criteria included diabetes mellitus, history of stroke, or known secondary cause of hypertension.[5,12] Patients with missing data on potential confounders were also excluded from this study (n=266). The final sample size of this analysis was 9095 patients. The Institutional Review Board of the National Center for Global Health and Medicine approved the present study. The National Heart, Lung, and Blood Institute approved the use of data from the SPRINT study.

Resistant Hypertension and Study Outcomes

In accordance with the previous studies,[13–15] resistant hypertension was defined as a persistent BP of ≥140/90 mm Hg, despite the concurrent use of 3 antihypertensive agents or a controlled BP of <140/90 mm Hg requiring 4 or more antihypertensive agents. In addition, using the definitions of resistant hypertension given in the American Heart Association (AHA) Scientific Statements of 2008 and 2018, we assessed the effects on the primary outcome event of intensive BP treatment in patients with resistant hypertension.[9,10] Resistant hypertension was defined in the 2008 AHA Scientific Statement as a BP of ≥140/90 mm Hg or a BP of ≥130/80 mm Hg in patients with diabetes mellitus or chronic kidney disease, despite the concurrent use of 3 antihypertensive agents or a controlled BP requiring 4 or more antihypertensive agents.[9] Resistant hypertension was defined in the 2018 AHA Scientific Statement as a BP of ≥130/80 mm Hg, despite the concurrent use of 3 antihypertensive agents or a controlled BP requiring 4 or more antihypertensive agents.[10] Chronic kidney disease was defined as an estimated glomerular filtration rate (GFR) of <60 mL/min per 1.73 m^2. The primary outcome was a major adverse cardiovascular event (MACE), which included cardiovascular death, myocardial infarction, and stroke.[5] Secondary outcomes included all-cause and cardiovascular death, myocardial infarction, stroke, and heart failure. The outcome measurements have been previously reported in detail.[5,12] Patients were followed up for a maximum of 4 years. Similar to the SPRINT main study,[5] the relationship of serious adverse events to the intensive BP treatment was also assessed.

Potential Confounders

Potential confounders at baseline included age, sex, race and ethnicity (white, black, or other), smoking status (current smoker, former smoker, or never smoked), body mass index (BMI), history of cardiovascular disease, number of antihypertensive agents, aspirin use, statin use, fasting plasma glucose, fasting LDL (low-density lipoprotein) cholesterol, fasting HDL (high-density lipoprotein) cholesterol, estimated GFR, and systolic and diastolic BP. BMI was calculated as weight in kilograms divided by the square of the height in meters. BMI was categorized as <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2, with obesity defined as BMI of ≥30.0 kg/m^2. LDL cholesterol was calculated using the Friedewald equation (total cholesterol−HDL cholesterol−triglycerides/5) in fasting participants with triglyceride levels of ≤400 mg/dL (to convert mg/dL, to mmol/L, multiply by 0.0113).[16] History of cardiovascular disease included previous myocardial infarction; treatment with percutaneous coronary intervention or coronary artery bypass grafting; carotid stenting; peripheral artery disease with revascularization; acute coronary syndrome; at least 50% stenosis of a coronary, carotid, or lower extremity artery; or an abdominal aortic aneurysm of ≥5 cm with or without repair.[12]

Statistical Analysis

Patients were divided into those with and without resistant hypertension at baseline. Demographic data are presented as proportions or means±SDs. Categorical and continuous variables were compared using the χ^2 test and *t* test, respectively. We calculated the mean systolic BP from all values during the follow-up from 3 to 48 months, irrespective of the number of systolic BP per subject. Kaplan-Meier survival curves were constructed, and event rates of the primary and secondary outcomes were calculated in patients with and without resistant hypertension. Using the randomized design of the SPRINT study, the Cox proportional hazards model was used to compare the time to first occurrence of a primary or secondary outcome event in the intensive and standard treatment groups separately in patients with and without resistant hypertension. The lines in Figure 2, particularly Figure 2A, crossed slightly around 2 years. Therefore, we tested the proportional hazards assumption using graphical and scaled Schoenfeld residual methods. Because the proportional hazard assumptions might be violated, we performed an additional analysis considering BP treatment strategy as a time-varying variable in an extended Cox model.[17] Sensitivity analyses limited to patients with resistant hypertension whose BP was ≥140/90 mm Hg receiving treatment with 3 or more antihypertensive agents were performed. We have further analyzed the hazard ratios (HRs) for MACE separately in patients receiving intensive BP treatment, who achieved or did not achieve systolic BP <120 mm Hg at 1 year. To equalize the conditions in the intensive BP and standard BP treatment groups, the analyses excluded patients, who experienced MACE within 1 year and who were not followed for >1 year. In addition, using overall SPRINT data, a multivariable analysis, including treatment arm, resistant hypertension, and their interactions, was also performed.

The association between intensive BP treatment and primary outcome in patients with resistant hypertension was further analyzed according to the following subgroups: age (<70 or ≥70 years), sex (male or female), obesity (nonobese or obese), smoking status (never/former or current smoker), cardiovascular disease (no history of cardiovascular disease or prior history of cardiovascular disease), chronic kidney disease (estimated GFR <60 mL/min per 1.73 m^2 or an estimated GFR ≥60 mL/min per 1.73 m^2), and number of antihypertensive agents (3 or 4 or more). In addition, we tested for interactions between the BP treatment strategy and these subgroups.

Similar to the SPRINT main study,[5] the relationship between serious adverse events and intensive BP treatment was also assessed. In addition, to evaluate the dropout rate in patients with and without resistant hypertension, patients who did not have an outcome event (MACE/death) and were not followed for >1 year were assessed.

Moreover, irrespective of the assigned BP treatment group, further analyses were performed to determine the cardiovascular event rate in resistant hypertension as compared with nonresistant hypertension

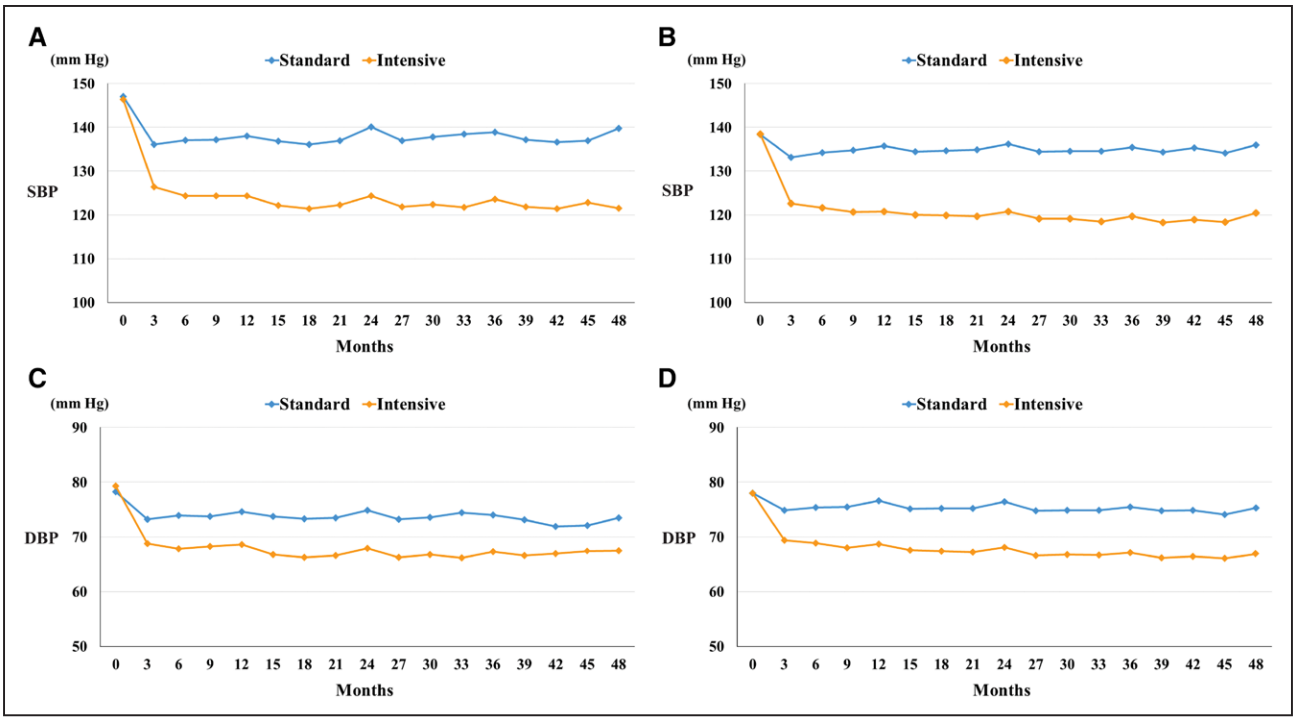

Figure 1. Mean systolic and diastolic blood pressure (SBP and DBP) during the follow-up in patients with and without resistant hypertension. Mean SBP and DBP during the follow-up in patients with (**A** and **C**) and without (**B** and **D**) resistant hypertension.

in the SPRINT study. Unadjusted and adjusted HRs for the primary and secondary outcomes with 95% CIs were calculated using the Cox proportional hazards model to compare patients with resistant hypertension and those without resistant hypertension. Two multivariable models were used. Age, sex, race and ethnicity, smoking status, BMI, history of cardiovascular disease, and randomization arm (intensive or standard BP treatment) were included in model 1. In addition to the variables in model 1, the number of antihypertensive agents, aspirin

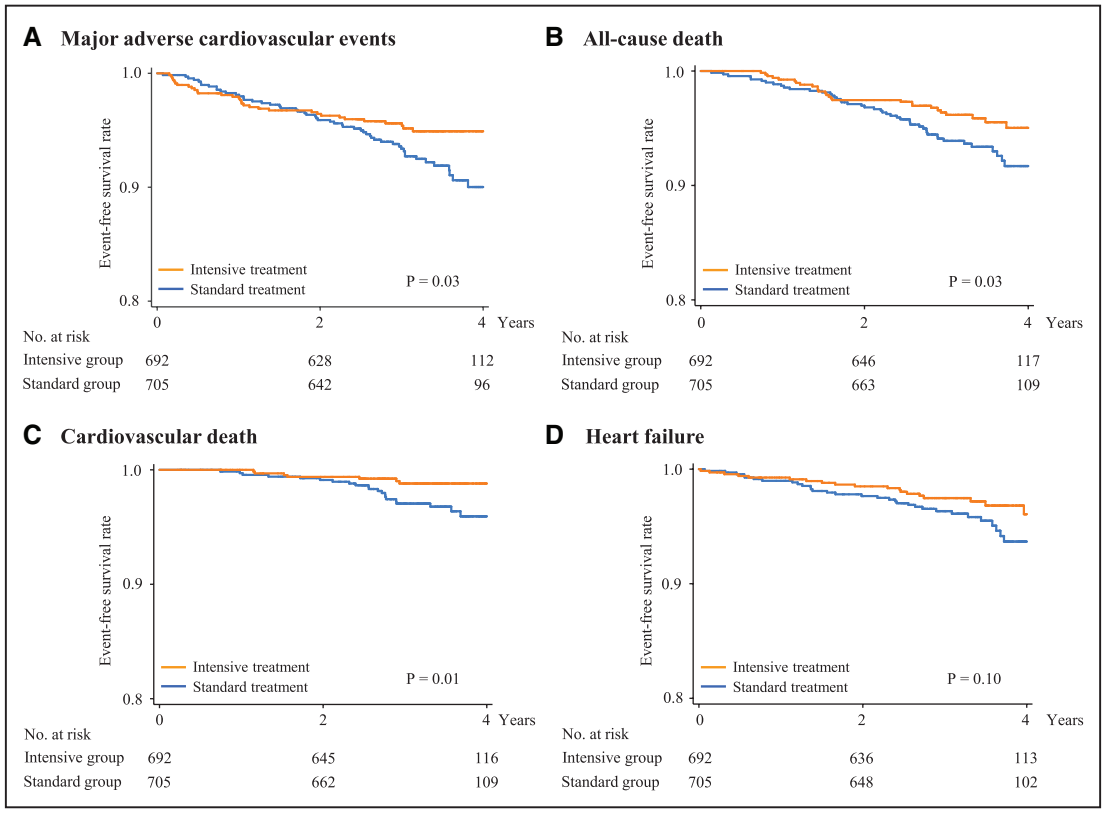

Figure 2. Kaplan-Meier survival curves for cardiovascular events and death in patients with resistant hypertension. Kaplan-Meier survival curves for major adverse cardiovascular events (**A**), all-cause death (**B**), cardiovascular death (**C**), and heart failure (**D**) in patients with resistant hypertension.

Table 1. Baseline Characteristics of Patients With and Without Resistant Hypertension*

	Resistant Hypertension (+)			Resistant Hypertension (–)		
	Standard, n=705	Intensive, n=692	*P* Value	Standard, n=3829	Intensive, n=3869	*P* Value
Age, y	69.3 (9.6)	68.7 (9.4)	0.27	67.6 (9.4)	67.8 (9.4)	0.47
Female sex, %	38.9	40.4	0.54	34.6	35.2	0.58
Race and ethnicity, %			0.35			0.35
White	54.8	53.9		57.9	58.3	
Black	37.4	36.1		29.4	28.2	
Others	7.8	10.0		12.7	13.5	
Smoking status, %			0.15			0.14
Never	44.1	41.9		44.4	44.4	
Former	43.3	47.8		42.7	41.3	
Current	12.6	10.3		12.9	14.3	
Body mass index (kg/m^2),† %			0.15			0.91
<18.5	0.1	0.0		0.5	0.6	
18.5–24.9	15.7	14.3		18.8	18.8	
25.0–29.9	37.6	35.7		39.3	39.1	
30.0–34.9	27.0	25.1		26.0	25.7	
≥35.0	19.6	24.9		15.4	15.8	
History of cardiovascular events, %	21.4	21.1	0.88	16.0	16.0	0.99
Antihypertensive agents (n)	3.4 (0.5)	3.4 (0.5)	0.46	1.5 (0.8)	1.6 (0.8)	0.19
Antihypertensive agents, %			0.40			0.62
0	…	…		11.4	10.9	
1	…	…		35.0	34.2	
2	…	…		41.3	41.9	
3	65.5	63.3		12.3	13.0	
4	33.1	35.7		…	…	
5 or more	1.4	1.0		…	…	
Aspirin use, %	60.4	57.7	0.29	48.6	50.6	0.08
Statin use, %	50.8	48.3	0.34	43.7	41.7	0.08
Fasting plasma glucose (mg/dL)	99.4 (12.5)	100.3 (13.5)	0.19	98.6 (13.4)	98.5 (13.8)	0.87
Fasting LDL cholesterol (mg/dL)	105.7 (32.8)	108.8 (34.7)	0.08	113.5 (35.1)	113.3 (35.4)	0.79
Fasting HDL cholesterol (mg/dL)	52.1 (13.5)	52.1 (14.3)	0.93	53.1 (14.7)	53.2 (14.3)	0.74
Estimated GFR (mL/min per 1.73 m^2)	66.5 (21.3)	67.8 (21.8)	0.23	72.8 (20.2)	72.4 (20.3)	0.41
Systolic blood pressure (mm Hg)	147.0 (14.4)	146.4 (14.6)	0.41	138.4 (15.2)	138.5 (15.7)	0.68
Diastolic blood pressure (mm Hg)	78.3 (13.1)	78.3 (13.0)	0.13	78.0 (11.8)	78.0 (11.8)	0.99
Framingham 10-year CVD risk score	21.3 (10.8)	20.5 (10.7)	0.17	19.7 (10.6)	19.9 (10.8)	0.67

CVD indicates cardiovascular disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.
*Data are presented as no. of participants, percentages, or means (SD).
†Body mass index was calculated as weight in kilograms divided by the square of height in meters.

use, statin use, fasting plasma glucose, fasting LDL cholesterol, fasting HDL cholesterol, estimated GFR, and systolic and diastolic BP were included in model 2. For a sensitivity analysis, the Framingham 10-year cardiovascular risk score was added to the variables in model 2 as an additional adjustment.

The statistical analysis was performed using the Stata software (version 14.1, Stata Corp, College Station, TX). *P* values of <0.05 were considered statistically significant in all tests.

Results

Patient Characteristics

Baseline characteristics are shown in Table 1. The present study included patients with (n=1397) and without (n=7698) resistant hypertension. In patients with and without resistant hypertension, the baseline characteristics did not

Table 2. Cardiovascular Events and Death in Patients With and Without Resistant Hypertension*

	Resistant Hypertension (+)			Resistant Hypertension (–)		
	Standard, n=705	Intensive, n=692	*P* Value	Standard, n=3829	Intensive, n=3869	*P* Value
Event						
Major adverse cardiovascular events						
No. of patients	53	32		163	133	
Event rate (per 1000 person-year)	24.2	15.0		13.3	10.7	
Hazard ratio (95% CI)	1.00 (ref)	0.62 (0.40–0.96)	0.03	1.00 (ref)	0.81 (0.64–1.01)	0.07
All-cause death						
No. of patients	46	27		152	120	
Event rate (per 1000 person-year)	20.4	12.3		12.5	9.7	
Hazard ratio (95% CI)	1.00 (ref)	0.60 (0.38–0.97)	0.03	1.00 (ref)	0.78 (0.61–0.98)	0.03
Cardiovascular death						
No. of patients	21	7		39	27	
Event rate (per 1000 person-year)	9.4	3.2		3.2	2.2	
Hazard ratio (95% CI)	1.00 (ref)	0.34 (0.15–0.81)	0.01	1.00 (ref)	0.68 (0.42–1.11)	0.12
Myocardial infarction						
No. of patients	25	19		89	75	
Event rate (per 1000 person-year)	11.3	8.8		7.4	6.2	
Hazard ratio (95% CI)	1.00 (ref)	0.78 (0.43–1.41)	0.41	1.00 (ref)	0.83 (0.61–1.13)	0.23
Stroke						
No. of patients	16	16		52	44	
Event rate (per 1000 person-year)	7.2	7.4		4.3	3.6	
Hazard ratio (95% CI)	1.00 (ref)	1.03 (0.51–2.05)	0.94	1.00 (ref)	0.83 (0.56–1.24)	0.36
Heart failure						
No. of patients	31	19		67	39	
Event rate (per 1000 person-year)	14.1	8.8		5.6	3.2	
Hazard ratio (95% CI)	1.00 (ref)	0.62 (0.35–1.10)	0.10	1.00 (ref)	0.57 (0.38–0.85)	0.005

*Data are presented as number or hazard ratio (95% CI).

significantly differ between the intensive and standard treatment groups. The characteristics between patients with and without resistant hypertension significantly differ (Table S1 in the online-only Data Supplement). The BP decreased rapidly with intensive BP treatment and were significantly lower in the intensive treatment group than that in the standard treatment group during the follow-up (*P* for all <0.001; Figure 1). In patients with and without resistant hypertension, the mean systolic BP during the follow-up in the intensive treatment groups was 122.9 and 119.9 mm Hg, respectively. For those in the standard treatment groups, the mean systolic BP was 137.6 and 134.8 mm Hg, respectively. The achievement rates of the target BP in patients with resistant hypertension were significantly lower than those reported in patients without resistant hypertension (achievement rates at 1, 2, and 3 years from randomization in the intensive treatment groups: 49.0% versus 57.1%, 49.8% versus 59.4%, and 50.7% versus 61.6%, respectively [*P* for all <0.001]; achievement rates at 1, 2, and 3 years in the standard treatment groups: 58.3% versus 65.6%, 55.0% versus 65.2%, and 58.2% versus 67.7%, respectively [*P* for all <0.001]).

Primary and Secondary Outcomes in Patients With and Without Resistant Hypertension

The overall mean (±SD) follow-up period was 3.1 (±0.9) years. MACE was confirmed in 381 patients. Kaplan-Meier survival curves and cumulative event rates for cardiovascular events and death in patients with resistant hypertension are shown in Figure 2 and Table 2, respectively. The risk of MACE was significantly lower in the intensive treatment group than in the standard treatment group (HR, 0.62; 95% CI, 0.40–0.96; *P*=0.03). In addition, analyses using different definitions of resistant hypertension showed similar results (2008 AHA Scientific Statement: HR, 0.62; 95% CI, 0.41–0.94; *P*=0.02 and 2018 AHA Scientific Statement: HR, 0.61; 95% CI, 0.41–0.90; *P*=0.01). The risks of all-cause and cardiovascular death in patients with resistant hypertension were significantly lower in the intensive treatment group than in the standard treatment group. Sensitivity analyses limited to

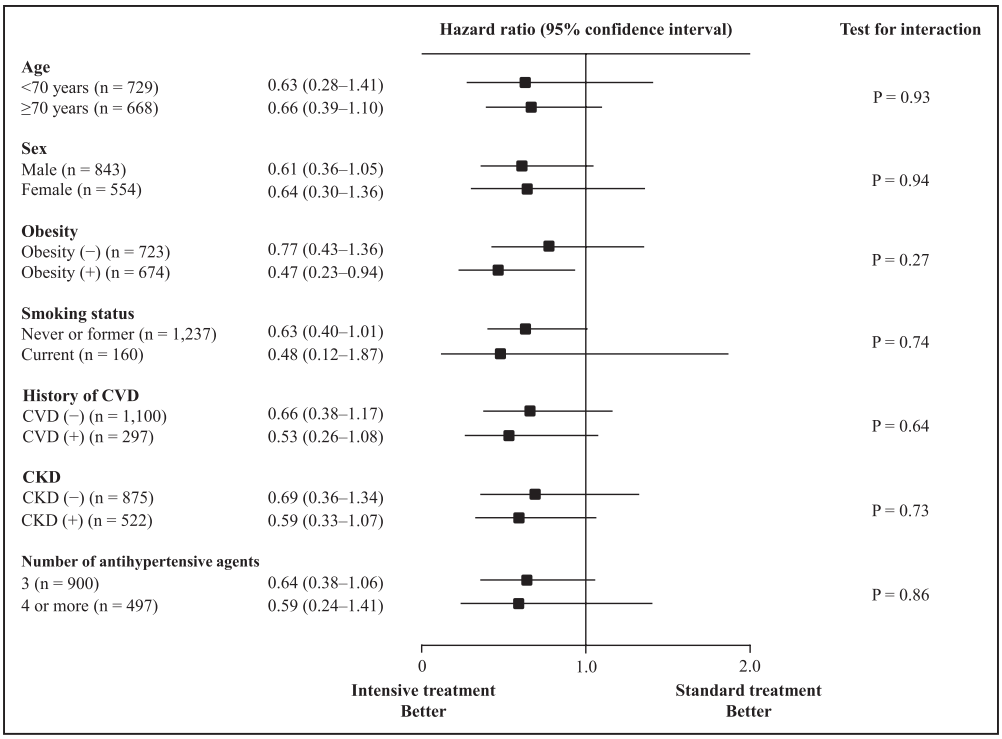

Figure 3. Association between blood pressure (BP) treatment and major adverse cardiovascular events in subgroups with resistant hypertension. Obesity was defined as body mass index ≥30 kg/m^2. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2. CVD indicates cardiovascular disease.

patients with resistant hypertension whose BP was ≥140/90 mm Hg on receiving 3 or more antihypertensive agents showed similar results (HR for MACE: 0.69; 95% CI, 0.43–1.09; HR for all-cause death: 0.67; 95% CI, 0.40–1.11; HR for cardiovascular death: 0.35; 95% CI, 0.14–0.89; and HR for heart failure: 0.67; 95% CI, 0.36–1.25). Furthermore, the additional analyses using definitions of resistant hypertension in the AHA Scientific Statements of 2008 and 2018 did not change the overall results (Figures S1 and S2). The analysis using a time-varying model showed similar results (HR for MACE: 0.66; 95% CI, 0.51–0.85; *P*=0.001; HR for all-cause death, 0.79; 95% CI, 0.63–0.98; *P*=0.03; HR for cardiovascular death, 0.60; 95% CI, 0.41–0.89; *P*=0.01; HR for heart failure, 0.81; 95% CI, 0.62–1.05; *P*=0.11). Kaplan-Meier survival curves for cardiovascular events and death in patients without resistant hypertension are shown in Figure S3. Although the event rates were lower in patients without resistant hypertension than in those with resistant hypertension, similar findings were observed. No significant interactions were observed between BP treatment strategy and resistant hypertension (*P* for interaction=0.29), which suggests that intensive BP treatment was associated with a decreased risk of MACE regardless of the presence or absence of resistant hypertension.

The risk of MACE was significantly lower in the intensive treatment group, and limited to patients who achieved systolic BP <120 mm Hg, than in the standard treatment group, irrespective of the presence or absence of resistant hypertension (Figure S4A and S4B). There was no significant interaction between BP treatment strategy and resistant hypertension (*P* for interaction=0.34). Similarly, the risk of MACE was nonsignificantly lower in the intensive treatment group limited to patients who did not achieve systolic BP <120 mm Hg than in the standard treatment group (Figure S4C and S4D). No significant interaction between BP treatment strategy and resistant hypertension was observed (*P* for interaction=0.24).

Additional analyses were performed to assess the risk of MACE in intensive BP treatment compared with standard BP treatment in various subgroups with resistant hypertension. The HRs for MACE in the intensive treatment group compared with the standard treatment group are plotted in Figure 3. The analyses showed that intensive BP treatment also tended to be better in each subgroup with resistant hypertension, and there were no significant interactions between the BP treatment strategy and age, sex, obesity, smoking status, chronic kidney disease, or a number of antihypertensive agents used.

Adverse Events

Serious adverse events, conditions of interest, and monitored clinical events are presented in Table S2. Consistent with the SPRINT main study, the risk of syncope and hyponatremia in patients with resistant hypertension was significantly higher in the intensive treatment group than in the standard treatment group. However, the risk of hypotension and acute kidney injury/acute renal failure in patients with resistant hypertension did not differ significantly between the groups.

There were 31 patients (2.2%) who did not have MACE/death and were not followed for >1 year with resistant hypertension and 189 patients (2.4%) without resistant hypertension. There was no significant difference between the 2 groups (*P*=0.27). The analysis was limited to patients receiving intensive or standard BP treatment and showed similar findings.

Associations Between Resistant Hypertension and Clinical Outcomes in the Participants of the SPRINT Study

Further analyses were performed to assess the HRs for cardiovascular events and death in patients with resistant hypertension compared with those without resistant hypertension in the SPRINT study (Table 3). After multivariable adjustment, the risk of MACE was significantly higher in patients with resistant hypertension. Multivariable adjustments for the confounders of model 2 and the Framingham 10-year cardiovascular risk score did not alter the results. The risks of cardiovascular death, stroke, and heart failure were significantly higher in patients with resistant hypertension than in those without resistant hypertension.

Discussion

The present study demonstrated that intensive BP treatment resulted in a decreased incidence of cardiovascular events and death in patients with resistant hypertension. Similar associations between intensive BP treatment and decreased risk of cardiovascular events and death were observed in the relevant subgroups with resistant hypertension. Resistant hypertension was associated with increased risk of cardiovascular events and death among the participants of the SPRINT study. Recently, the 2018 AHA Scientific Statement on resistant hypertension was updated with a definition of resistant hypertension different from that in the 2008 statement.[10] Based on the updated definition of resistant hypertension, the risk of cardiovascular events and death in patients with resistant hypertension was also significantly lower in the intensive BP treatment than in the standard BP treatment. The results of this study suggest that intensive BP treatment strategy may be beneficial even when the therapeutic goal of systolic BP <120 mm Hg is not achieved.

Cases of resistant hypertension are commonly encountered.[9] Resistant hypertension can be attributed to genetic predisposition, incorrect drug selection, several classes of pharmacological agents such as nonsteroidal anti-inflammatory agents, obstructive sleep apnea, or endocrine disorders, such as primary aldosteronism. Moreover, although dropout rates did not differ significantly between patients with and without resistant hypertension, those rates may be different in real-world settings and may be associated with hypertension resistant to therapy. Medication adherence is an important factor to control hypertension. The diagnosis of resistant hypertension in the 2018 AHA Scientific Statement requires the exclusion of medication nonadherence; assessing optimal medication adherence is an important step in the evaluation of patients with resistant hypertension.[10] The results of the present study are consistent with those of previous studies reporting that resistant hypertension was associated with poor prognosis.[15,18] A possible explanation is that resistant hypertension leads to cumulative organ damage from exposure to poorly controlled BP. However, there is currently limited evidence about resistant hypertension, and the treatment strategy, including the target BP for patients with resistant hypertension, remains unclear. The present study revealed that intensive BP treatment improved outcomes even in patients with resistant hypertension. Therefore, the target BP in patients

Table 3. HR for Cardiovascular Events and Death in Patients With Resistant Hypertension Compared With Those Without Resistant Hypertension*

	Resistant Hypertension (–) n=7698	Resistant Hypertension (+) n=1397	*P* Value
Major adverse cardiovascular events			
No. of patients	296	85	
Event rate (per 1000 person-year)	12.0	19.6	
Unadjusted HR (95% CI)	1.00 (ref)	1.64 (1.29–2.09)	<0.001
Adjusted HR, model 1 (95% CI)	1.00 (ref)	1.49 (1.17–1.91)	0.001
Adjusted HR, model 2 (95% CI)	1.00 (ref)	1.45 (1.13–1.86)	0.003
All-cause death			
No. of patients	272	73	
Event rate (per 1000 person-year)	11.1	16.4	
Unadjusted HR (95% CI)	1.00 (ref)	1.48 (1.14–1.92)	0.002
Adjusted HR, model 1 (95% CI)	1.00 (ref)	1.29 (0.99–1.68)	0.05
Adjusted HR, model 2 (95% CI)	1.00 (ref)	1.23 (0.95–1.61)	0.12
Cardiovascular death			
No. of patients	66	28	
Event rate (per 1000 person-year)	2.7	6.3	
Unadjusted HR (95% CI)	1.00 (ref)	2.34 (1.50–3.64)	<0.001
Adjusted HR, model 1 (95% CI)	1.00 (ref)	1.99 (1.27–3.12)	0.002
Adjusted HR, model 2 (95% CI)	1.00 (ref)	1.77 (1.12–2.80)	0.01
Myocardial infarction			
No. of patients	164	44	
Event rate (per 1000 person-year)	6.8	10.1	
Unadjusted HR (95% CI)	1.00 (ref)	1.48 (1.06–2.07)	0.02
Adjusted HR, model 1 (95% CI)	1.00 (ref)	1.36 (0.97–1.90)	0.07
Adjusted HR, model 2 (95% CI)	1.00 (ref)	1.33 (0.94–1.87)	0.10
Stroke			
No. of patients	96	32	
Event rate (per 1000 person-year)	4.0	7.3	
Unadjusted HR (95% CI)	1.00 (ref)	1.85 (1.24–2.76)	0.002
Adjusted HR, model 1 (95% CI)	1.00 (ref)	1.71 (1.14–2.56)	0.009
Adjusted HR, model 2 (95% CI)	1.00 (ref)	1.65 (1.09–2.48)	0.01
Heart failure			
No. of patients	106	50	
Event rate (per 1000 person-year)	4.4	11.4	
Unadjusted HR (95% CI)	1.00 (ref)	2.63 (1.88–3.68)	<0.001
Adjusted HR, model 1 (95% CI)	1.00 (ref)	2.14 (1.52–3.01)	<0.001
Adjusted HR, model 2 (95% CI)	1.00 (ref)	1.94 (1.37–2.74)	<0.001

DBP indicates diastolic blood pressure.
*Data are presented as number or HR (95% CI).

with resistant hypertension may be < 120 mm Hg. However, achieving the target BP may be difficult despite treatment with recommended antihypertensive agents such as thiazide/thiazide-like diuretics, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and calcium channel blockers.[9,19–21] Of note, the achievement rate of the target BP among patients with resistant hypertension in the SPRINT study was low. The SPRINT study did not test the efficacy of specific medications, and the study protocol was flexible in terms of the selection and dosages of antihypertensive medications.[5,12] Therefore, it did not determine the optimal antihypertensive drugs to be used in this subset of patients. A recent clinical trial demonstrated that spironolactone was the most effective add-on drug for the treatment of resistant hypertension.[22] Considering the pathogenesis of resistant hypertension associated with aldosterone and mineralocorticoid receptor signaling, mineralocorticoid receptor antagonists, specifically spironolactone, may be a highly effective BP-lowering treatment option for patients with resistant hypertension.[13] In addition, achieving lower target BP requires a combination of treatment with antihypertensive drugs and lifestyle adjustments, such as restriction of dietary salt restriction, exercise, and weight loss. Moreover, improving adherence to BP treatment and detecting treatable causes of resistant hypertension, such as obstructive sleep apnea and primary aldosteronism, are important.[13,23] Further long-term follow-up studies are required to investigate the effective management of BP in patients with resistant hypertension.

The present study had several limitations that should be noted. First, this was a secondary analysis of data obtained in a randomized controlled trial. These results require corroboration by primary investigations. In addition, the number of patients with resistant hypertension was relatively small. A post hoc power analysis using an alpha error rate of 5% showed low statistical power, calculated to be 23.5% for MACE, 22.1% for all-cause death, and 30.8% for cardiovascular death. This low statistical power might have reduced our ability to detect significant differences. Therefore, future large-scale studies are needed to verify our findings. Second, the participants of the SPRINT study were high-risk patients for cardiovascular disease and did not include patients with diabetes mellitus or history of stroke. Therefore, the effect of intensive BP treatment in other subsets of patients with resistant hypertension remains unknown. Third, although intensive BP treatment led to a greater reduction in BP than standard BP treatment, the achievement rates of target BP were insufficient. However, intensive BP treatment may be associated with a decreased risk of cardiovascular events even when the goal of systolic BP <120 mm Hg is not achieved. Moreover, BP measurements differed between studies. Thus, an optimal target BP and a method for BP measurement have not yet been established. Fourth, detailed information on antihypertensive medications actually used in the intensive and standard BP treatment groups was not available, and thus we could not assess whether specific medications, such as diuretics, spironolactone, or other K^+ sparing diuretics, are potentially effective in controlling BP or reducing the risk of cardiovascular events in patients with resistant hypertension. Further information is required to determine the appropriate management of resistant hypertension. Finally, undetermined confounders may be involved in the association between resistant hypertension and the risk of cardiovascular events and death observed among the participants of the SPRINT study. However, because the results of the present study are consistent with those of previous studies, resistant hypertension should be treated as an important cardiovascular risk factor.

In conclusion, the present study demonstrated that intensive BP treatment was significantly associated with a decreased risk of cardiovascular events and death in patients with resistant hypertension. Moreover, the association between intensive BP treatment and decreased cardiovascular events was observed in the clinically important subgroups with resistant hypertension. However, syncope and hyponatremia significantly occurred more frequently in patients with resistant hypertension receiving intensive BP treatment. Therefore, those risks should be observed more closely. Consistent with the results of previous studies, resistant hypertension was associated with increased risks of cardiovascular events and death among the participants of the SPRINT study. Further studies are required to confirm the safety and efficacy of intensive BP treatment in patients with resistant hypertension.

Perspectives

Resistant hypertension is a common clinical problem faced by both specialists and primary care clinicians. Although the management of resistant hypertension is important, evidence about the BP target in patients with resistant hypertension is currently limited. The present study demonstrated that intensive BP treatment resulted in a decreased incidence of cardiovascular events and death in patients with resistant hypertension. Similar associations between intensive BP treatment and decreased risk of cardiovascular events and death were observed in the relevant subgroups with resistant hypertension. Considering the pathogenesis of resistant hypertension associated with aldosterone and mineralocorticoid receptor signaling, mineralocorticoid receptor antagonists, specifically spironolactone, may be a highly effective BP-lowering treatment option for patients with resistant hypertension. In addition, achieving lower target BP requires a combination of treatment with antihypertensive drugs and lifestyle adjustments, such as restriction of dietary salt restriction, exercise, and weight loss. Moreover, improving adherence to BP treatment and detecting treatable causes of resistant hypertension, such as obstructive sleep apnea and primary aldosteronism, are important. Further long-term follow-up studies are required to investigate the effective management of BP in patients with resistant hypertension.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Although resistant hypertension is a common clinical problem, evidence about the blood pressure (BP) target in patients with resistant hypertension is currently limited. In the present study, we demonstrated that intensive BP treatment was significantly associated with a decreased risk of cardiovascular events and death in patients with resistant hypertension.

What Is Relevant?

- Intensive BP treatment resulted in a decreased incidence of cardiovascular events and death in patients with resistant hypertension.

Summary

The present study demonstrated that intensive BP treatment was significantly associated with a decreased risk of cardiovascular events and death in patients with resistant hypertension. The association between intensive BP treatment and decreased cardiovascular events was observed in the clinically important subgroups with resistant hypertension.