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Thiazide Use and Decreased Risk of Heart Failure in Nondiabetic Patients Receiving Intensive Blood Pressure Treatment

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Abstract**—**The SPRINT (Systolic Blood Pressure Intervention Trial) study reported that intensive blood pressure (BP) treatment with a systolic BP target of <120 mm Hg decreased the risks of cardiovascular events. However, it remains unknown whether specific medications can further improve cardiovascular outcome in patients receiving intensive BP treatment. This study examined whether thiazide use improves cardiovascular outcome in patients receiving intensive BP treatment. We used data of nondiabetic patients receiving intensive BP treatment in the SPRINT study. The primary outcome was a composite end point of myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death. We analyzed hazard ratios for outcomes with 95% CIs in patients taking thiazides compared with those not taking thiazides using Cox proportional hazard models. This study included 2847 patients and the mean follow-up period was 3.3 years. The risk of primary outcome events was significantly lower in patients taking thiazides than in those not taking thiazides in both entire and propensity score-matched cohorts. Particularly, heart failure risk was significantly lower in those taking thiazides. These associations were also observed in various subgroups. In addition, thiazide use was associated with decreased risk of all-cause mortality. Hypokalemia occurred more frequently in patients taking thiazides than in those not taking thiazides. Thiazide use decreased risk of cardiovascular events, particularly heart failure, in nondiabetic high-risk patients receiving intensive BP treatment. **(*Hypertension*. 2020;76:432-441. DOI: 10.1161/HYPERTENSIONAHA.120.15154.)** • **Data Supplement**

Key Words: heart failure ■ hypertension ■ hypokalemia ■ myocardial infarction ■ stroke ■ thiazide

Hypertension is a worldwide health concern[1,2] as it increases the risks of cardiovascular events such as coronary artery disease, stroke, and heart failure,[3,4] while lowering blood pressure decreases these risks.[5] In addition to nonpharmacological therapy such as exercise, weight loss, and dietary salt restriction, use of antihypertensive medications are important to achieve target levels of blood pressure.[6,7] Recently, the SPRINT (Systolic Blood Pressure Intervention Trial) study reported that intensive blood pressure treatment with a systolic blood pressure target of <120 mm Hg decreased the risks of cardiovascular events and death in high-risk patients without diabetes mellitus or prior history of stroke compared with a standard systolic blood pressure target of <140 mm Hg.[5] However, this study allowed multiple antihypertensive drug regimens, and it remains unknown whether specific medications can further improve outcome. Although some studies have found that thiazide use is effective for reducing cardiovascular disease risk, these studies were conducted 2 or 3 decades ago in patients with moderate to severe hypertension.[8–11] Thus, there is little evidence regarding the clinical efficacy of thiazides in patients currently receiving intensive blood pressure treatment. The present study aimed to assess whether thiazide use provides additional health benefits in patients receiving intensive blood pressure treatment.

Methods

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

Study Design and Patients

We used data from the SPRINT study[5] to assess the associations between thiazide use and cardiovascular events in patients receiving intensive blood pressure treatment. The study protocol, study design, and patient characteristics were described in previous reports.[5,12] Briefly, the SPRINT study was a multicenter, open-label, randomized, controlled trial. At 102 clinical sites in the United States, including Puerto Rico, a total of 9361 patients were randomly assigned to a systolic blood pressure target of either <120 mm Hg (intensive blood pressure treatment strategy) or <140 mm Hg (standard blood pressure treatment strategy). The primary aim was to determine whether intensive blood pressure treatment decreased the risk of

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cardiovascular events. However, the study did not examine the efficacy of specific antihypertensive medications. Although the blood pressure treatment protocol of the SPRINT study allowed for a variety of antihypertensive medications and doses,[5,12] all regimens were recommended to use one or more drug classes with strong cardiovascular outcomes documented in large randomized controlled hypertension trials, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, thiazides, and calcium channel blockers.[8,11,13,14] Medication dosages were adjusted based on the average of 3 blood pressure measurements performed using an automated measurement system (Model 907, Omron Healthcare, Kyoto, Japan).[5,12] All blood pressure measures were conducted in a seated position after 5 minute of quiet rest during an office visit. Eligible criteria included age of ≥50 years, baseline systolic blood pressure of 130–180 mm Hg, and at least one of the following cardiovascular risk factors: age of ≥75 years, clinical or subclinical cardiovascular disease other than stroke, chronic kidney disease with an estimated glomerular filtration rate (eGFR) of 20 to 60 mL/minute per 1.73 m^2 but excluding polycystic kidney disease, and a Framingham score for 10-year risk of cardiovascular disease of ≥15%. Patients were excluded for any one of the following: diabetes mellitus, history of stroke, indications for specific antihypertensive medications, known secondary causes of hypertension, systolic blood pressure of <110 mm Hg after 1 minute of standing, arm circumference too large or too small for accurate blood pressure measurement, end-stage renal disease, glomerulonephritis treated with immunosuppressive therapy, proteinuria ≥1 g/day, left ventricular ejection fraction <35%, organ transplantation, pregnancy, unintentional weight loss >10% of body weight in last 6 months, active alcohol or substance abuse within the last 12 months, diagnosis and treatment of cancer within the previous 2 years, or a medical condition likely to limit survival to <3 years.[5,12] In the present study, analyses included only patients assigned to the intensive blood pressure treatment strategy (n=4678) and receiving at least one of the following antihypertensive medications at baseline: thiazides (eg, chlorthalidone, hydrochlorothiazide, or metolazone), angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, alpha-blockers, or loop diuretics (n=33). In addition, considering intensive blood pressure strategy and the adjustment of the antihypertensive medications during follow-up, particularly within 12 months,[5] we excluded patients who took thiazides at baseline but did not take thiazides at 12 months post-enrollment and patients who did not take thiazides at baseline but took thiazides at 12 months post-enrollment (n=1569). Patients with missing information about potential confounders were also excluded (n=229), which resulted in a sample size of 2847 patients. Among these patients, we performed multivariable analyses in the entire cohort and in the propensity score-matched cohort. In addition, we similarly investigated the association between thiazide use and cardiovascular events in patients receiving standard blood pressure treatment (n=2845). The Institutional Review Board of the National Center for Global Health and Medicine approved the present study, and The National Heart, Lung, and Blood Institute approved use of the SPRINT study data.

Study Outcomes and Potential Confounders

Similar to the SPRINT study,[5] the primary outcome was a composite end point of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or cardiovascular death.[5] Secondary outcomes included a major adverse cardiovascular event, myocardial infarction, stroke, and heart failure. Major adverse cardiovascular event was defined as myocardial infarction, stroke, or cardiovascular death. All-cause, cardiovascular, and noncardiovascular mortality were also assessed. Detailed definitions of the outcome measurements were provided in previous reports.[5,12] A committee blinded to the study group assignments adjudicated the outcomes described in the study protocol.[5,12] Patients were evaluated at months 1, 2, 3, and 6 post-enrollment, and then every 3 months thereafter.[12]

Trained personnel ascertained information about participant baseline characteristics including antihypertensive medications.[5,12] Potential confounders included age, sex, race/ethnicity (white, black, Hispanic, or other), smoking status (current smoker, former smoker, or never smoked), body mass index, history of cardiovascular disease (coronary artery disease, peripheral artery disease, atrial fibrillation, and heart failure), history of cancer, use of medications (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, alpha-blockers, loop diuretics, statin, and aspirin), fasting plasma glucose, fasting low-density lipoprotein cholesterol, fasting high-density lipoprotein cholesterol, eGFR, albumin-to-creatinine ratio, and systolic and diastolic blood pressure at baseline and at 12 months post-enrollment. Body mass index was calculated as weight in kilograms divided by the square of height in meters and was categorized as <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2. Low-density lipoprotein cholesterol was calculated using the Friedewald equation (total cholesterol−high-density lipoprotein cholesterol−triglycerides/5) in fasting participants with triglyceride levels of ≤400 mg/dL (to convert mg/dL to mmol/L, multiply by 0.0113).[15]

Statistical Analysis

Demographic data are presented as mean±SDs or proportions. Continuous variables were compared using *t*-test and categorical variables were compared using the χ^2 test. Kaplan–Meier survival curves were constructed for primary and secondary outcomes. Hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazard models to compare the time to first occurrence of a primary or secondary outcome event in patients taking and not taking thiazides. First, multivariable Cox proportional hazard analyses were conducted using the entire cohort as follows: (1) model 1 included age, sex, race/ethnicity, smoking status, body mass index, history of cardiovascular disease (coronary artery disease, peripheral artery disease, atrial fibrillation, and heart failure), history of cancer, use of statin and aspirin, fasting low-density lipoprotein cholesterol, fasting high-density lipoprotein cholesterol, and eGFR; (2) model 2 included the potential confounders of model 1 plus use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, alpha-blockers, and loop diuretics, fasting plasma glucose, albumin-to-creatinine ratio, and systolic and diastolic blood pressure at baseline and at 12 months post-enrollment. For a sensitivity analysis, the Framingham 10-year cardiovascular risk score was added to the variables in model 2 as an additional adjustment.

To minimize the differences between patients taking and not taking thiazides, we further performed propensity score matching on patient characteristics.[16] The propensity score was derived using a logistic regression model that included thiazide use as the outcome variable and all potential confounders as explanatory variables. We used 1:1 nearest-neighbor matching without replacement, and standardized differences of <0.10 between propensity score-matched patients were considered negligible.[16] The associations between thiazide use and outcome events in patients receiving intensive blood pressure treatment were further analyzed in the following subgroups stratified by age (<70 or ≥70 years), sex (male or female), race/ethnicity (nonwhite or white), obesity (nonobese or obese), cardiovascular disease history (no history or prior history), chronic kidney disease (eGFR <60 mL/minute per 1.73 m^2 or an eGFR ≥60 mL/minute per 1.73 m^2), albuminuria (albumin-to-creatinine ratio <30 mg/gCre or ≥30 mg/gCre), and baseline systolic blood pressure (<140 or ≥140 mm Hg). Obesity was defined as body mass index of ≥30.0 kg/m^2. History of cardiovascular disease included previous myocardial infarction, 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] We also tested for interactions between thiazide use and these subgroups. Adverse events were also assessed, including hypotension, syncope, bradycardia, acute kidney injury or acute renal failure, abnormal laboratory measures such as hyperkalemia and hypokalemia, and orthostatic hypotension. Detailed definitions of these adverse events were reported previously.[5,12]

Table 1. Baseline Characteristics of Patients Taking and Not Taking Thiazides for Intensive Blood Pressure Treatment*

Characteristics	Entire Cohort			Propensity Score-Matched Cohort			
	Thiazides (–) n=1037	Thiazides (+) n=1810	*P*-Value	Thiazides (–) n=825	Thiazides (+) n=825	Standardized Difference	*P*-Value
Age, y	69.2 (9.5)	67.3 (9.1)	<0.001	68.7 (9.5)	69.0 (9.2)	0.02	0.59
Female sex (%)	35.3	37.8	0.18	33.8	35.9	0.04	0.38
Race and ethnicity (%)			<0.001				0.84
White	62.6	54.9		64.5	64.4	0.02	
Black	22.7	32.8		20.5	18.9	0.03	
Hispanic	12.3	10.2		12.7	13.0	0.007	
Others	2.4	2.1		2.3	2.7	0.02	
Smoking status (%)			0.07				0.89
Never	47.0	43.0		46.9	46.5	0.007	
Former	41.8	43.6		40.7	41.7	0.02	
Current	11.2	13.4		12.4	11.8	0.01	
Body mass index, kg/m^2† (%)			<0.001				0.71
<18.5	1.2	0.2		0.5	0.5	<0.001	
18.5–24.9	21.7	15.3		21.6	21.3	0.006	
25.0–29.9	38.1	37.3		39.7	42.3	0.05	
30.0–34.9	23.9	27.6		25.2	25.0	0.005	
≥35.0	15.1	19.6		13.0	10.9	0.06	
History of cardiovascular events (%)							
Coronary artery disease (%)	17.5	11.6	<0.001	17.2	16.7	0.01	0.79
Peripheral artery disease (%)	6.2	4.6	0.06	5.5	5.6	0.005	0.91
Atrial fibrillation (%)	10.6	6.6	<0.001	9.3	9.8	0.01	0.73
Heart failure (%)	5.6	2.2	<0.001	3.0	2.2	0.05	0.27
History of cancer	24.9	21.4	0.03	24.4	25.1	0.01	0.73
Medications (%)							
ACE-I	50.5	42.2	<0.001	49.5	49.8	0.007	0.88
ARB	25.8	26.4	0.74	25.6	27.0	0.03	0.50
Calcium channel blockers	50.3	37.4	<0.001	47.4	47.3	0.002	0.96
β-Blockers	46.9	33.4	<0.001	42.8	44.5	0.03	0.48
Alpha-blockers	9.6	5.7	<0.001	8.7	7.9	0.03	0.53
Loop diuretics	16.0	0.4	<0.001	1.0	0.9	0.01	0.79
Statin	47.1	41.9	0.008	46.3	46.4	0.002	0.96
Aspirin	55.7	51.7	0.03	55.8	55.0	0.01	0.76
Fasting plasma glucose, mg/dL	97.9 (12.7)	99.6 (14.5)	0.002	98.2 (12.6)	98.2 (11.8)	0.003	0.94
Fasting LDL cholesterol, mg/dL	108.8 (35.4)	114.7 (35.2)	<0.001	109.8 (34.5)	111.4 (34.6)	0.04	0.33
Fasting HDL cholesterol, mg/dL	53.1 (15.2)	52.9 (13.8)	0.62	52.8 (14.1)	53.0 (13.7)	0.01	0.81
Estimated GFR, mL/min per 1.73 m^2	68.2 (22.6)	72.6 (19.1)	<0.001	71.5 (21.5)	70.8 (19.0)	0.03	0.48
Albumin-to-creatinine ratio, mg/gCre (%)							
≥30.0	21.3	17.0	0.004	17.6	17.5	0.003	0.94
Systolic blood pressure, mm Hg	137.3 (15.1)	140.4 (16.0)	<0.001	137.3 (15.0)	136.9 (14.2)	0.02	0.62
Diastolic blood pressure, mm Hg	76.1 (11.2)	79.3 (11.9)	<0.001	76.7 (10.9)	76.4 (10.9)	0.02	0.62

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Data are presented as number of participants, percentage, or mean (SD).

†Body mass index was calculated as weight in kilograms divided by the square of height in meters.

In the same manner as the analyses in patients receiving intensive blood pressure treatment, the associations between thiazide use and outcome events in patients receiving standard blood pressure treatment were analyzed.

All statistical analyses were performed using Stata software (version 14.1, Stata Corp, College Station, TX) and a *P*-value of <0.05 was considered statistically significant.

Table 2. Cardiovascular Events and Death for Patients Receiving Intensive Blood Pressure Treatment in the Entire Cohort*

Event	Thiazides (–), n=1037	Thiazides (+), n=1810	*P*-Value
Primary outcome events			
No. of patients	78	59	
Event rate (per 1000 person-year)	23.7	9.8	
Unadjusted HR	1.00 (ref)	0.41 (0.29–0.58)	<0.001
Multivariable-adjusted HR, model 1	1.00 (ref)	0.51 (0.36–0.72)	<0.001
Multivariable-adjusted HR, model 2	1.00 (ref)	0.56 (0.38–0.83)	0.004
Major adverse cardiovascular events			
No. of patients	46	48	
Event rate (per 1000 person-year)	13.7	7.9	
Unadjusted HR	1.00 (ref)	0.58 (0.39–0.87)	0.008
Multivariable-adjusted HR, model 1	1.00 (ref)	0.68 (0.45–1.04)	0.07
Multivariable-adjusted HR, model 2	1.00 (ref)	0.67 (0.43–1.06)	0.08
Myocardial infarction			
No. of patients	29	26	
Event rate (per 1000 person-year)	8.6	4.3	
Unadjusted HR	1.00 (ref)	0.50 (0.29–0.85)	0.01
Multivariable-adjusted HR, model 1	1.00 (ref)	0.56 (0.32–0.96)	0.03
Multivariable-adjusted HR, model 2	1.00 (ref)	0.48 (0.27–0.88)	0.01
Stroke			
No. of patients	15	18	
Event rate (per 1000 person-year)	4.4	3.0	
Unadjusted HR	1.00 (ref)	0.67 (0.34–1.33)	0.25
Multivariable-adjusted HR, model 1	1.00 (ref)	0.84 (0.41–1.72)	0.63
Multivariable-adjusted HR, model 2	1.00 (ref)	0.91 (0.42–1.95)	0.80
Heart failure			
No. of patients	29	5	
Event rate (per 1000 person-year)	8.6	0.8	
Unadjusted HR	1.00 (ref)	0.09 (0.04–0.24)	<0.001
Multivariable-adjusted HR, model 1	1.00 (ref)	0.13 (0.05–0.36)	<0.001
Multivariable-adjusted HR, model 2	1.00 (ref)	0.22 (0.07–0.69)	0.009
All-cause mortality			
No. of patients	42	23	
Event rate (per 1000 person-year)	12.3	3.7	
Unadjusted HR	1.00 (ref)	0.30 (0.18–0.50)	<0.001
Multivariable-adjusted HR, model 1	1.00 (ref)	0.36 (0.21–0.62)	0.002
Multivariable-adjusted HR, model 2	1.00 (ref)	0.39 (0.22–0.69)	0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; GFR, glomerular filtration rate; and HR, hazard ratio.

*Data are presented as number or hazard ratio (95% CI). *P* values were calculated using multivariable Cox proportional hazards models. Model 1 included age, sex, race/ethnicity, smoking status, BMI, history of cardiovascular disease (coronary artery disease, peripheral artery disease, atrial fibrillation, and heart failure), history of cancer, use of statin and aspirin, fasting low-density lipoprotein cholesterol, fasting high-density lipoprotein cholesterol, and estimated GFR. Model 2 included the potential confounders of model 1 plus use of ACE-Is, ARBs, calcium channel blockers, beta-blockers, alpha-blockers, and loop diuretics, fasting plasma glucose, albumin-to-creatinine ratio, and systolic and diastolic blood pressure at baseline and at 12 mo post-enrollment.

Results

Baseline Characteristics of Patients Before and After Propensity Score-Matching

Table 1 shows the baseline characteristics of patients receiving intensive blood pressure treatment before and after propensity score-matching. In the entire cohort, patient characteristics differed between patients taking and not taking thiazides. After propensity score-matching, the baseline characteristics were well-matched between the 2 groups. In addition, systolic and diastolic blood pressure decreased rapidly within 1 year (Figure S1 in the Data Supplement) and did not differ significantly between the 2 groups at baseline or after 1, 2, 3, and 4 years of follow-up. Mean (SD) systolic and diastolic blood pressure during the follow-up also did not differ between patients taking thiazides and not taking (121.3 [9.0] mm Hg versus 119.5 [8.4] mm Hg and 68.3 [8.1] mm Hg versus 67.8 [7.5] mm Hg, respectively).

Primary and Secondary Outcomes

We performed multivariable Cox proportional hazard analyses using the entire cohort (n=2847: patients taking thiazides [n=1810] and those not taking thiazides [n=1037]). The overall mean (SD) follow-up period was 3.3 (0.8) years, and primary outcome events were confirmed in 137 patients. The risk of primary outcome events was significantly lower in patients taking thiazides (model 1: HR 0.51 [95% CI, 0.36–0.72]; *P*=0.0002; model 2: HR 0.56 [95% CI, 0.38–0.83]; *P*=0.004; Table 2). The HR for primary outcome events did not change after adjustment for variables in model 2 and the Framingham 10-year cardiovascular risk score (HR 0.57 [95% CI, 0.38–0.84]; *P*=0.004). The risks of myocardial infarction and heart failure were significantly lower in patients taking thiazides (Model 1: HR for myocardial infarction, 0.56 [95% CI, 0.32–0.96]; *P*=0.03; HR for heart failure, 0.13 [95% CI, 0.05–0.36]; *P*<0.0001. Model 2: HR for myocardial infarction, 0.48 [95% CI, 0.27–0.88]; *P*=0.01; HR for heart failure, 0.22 [95% CI, 0.07–0.69]; *P*=0.009). The HRs for myocardial infarction and heart failure did not change after adjustment for the variables in model 2 and the Framingham 10-year cardiovascular risk score (HR for myocardial infarction, 0.48 [95% CI, 0.27–0.88]; *P*=0.01; HR for heart failure, 0.23 [95% CI, 0.07–0.73]; *P*=0.01). The risk of all-cause mortality was significantly lower in patients taking thiazides (model 1: HR for all-cause mortality 0.36 [95% CI, 0.21–0.62]; *P*<0.001; model 2: HR for all-cause mortality, 0.39 [95% CI, 0.22–0.69]; *P*=0.001). The HR for all-cause mortality did not change after adjustment for the variables in model 2 and the Framingham

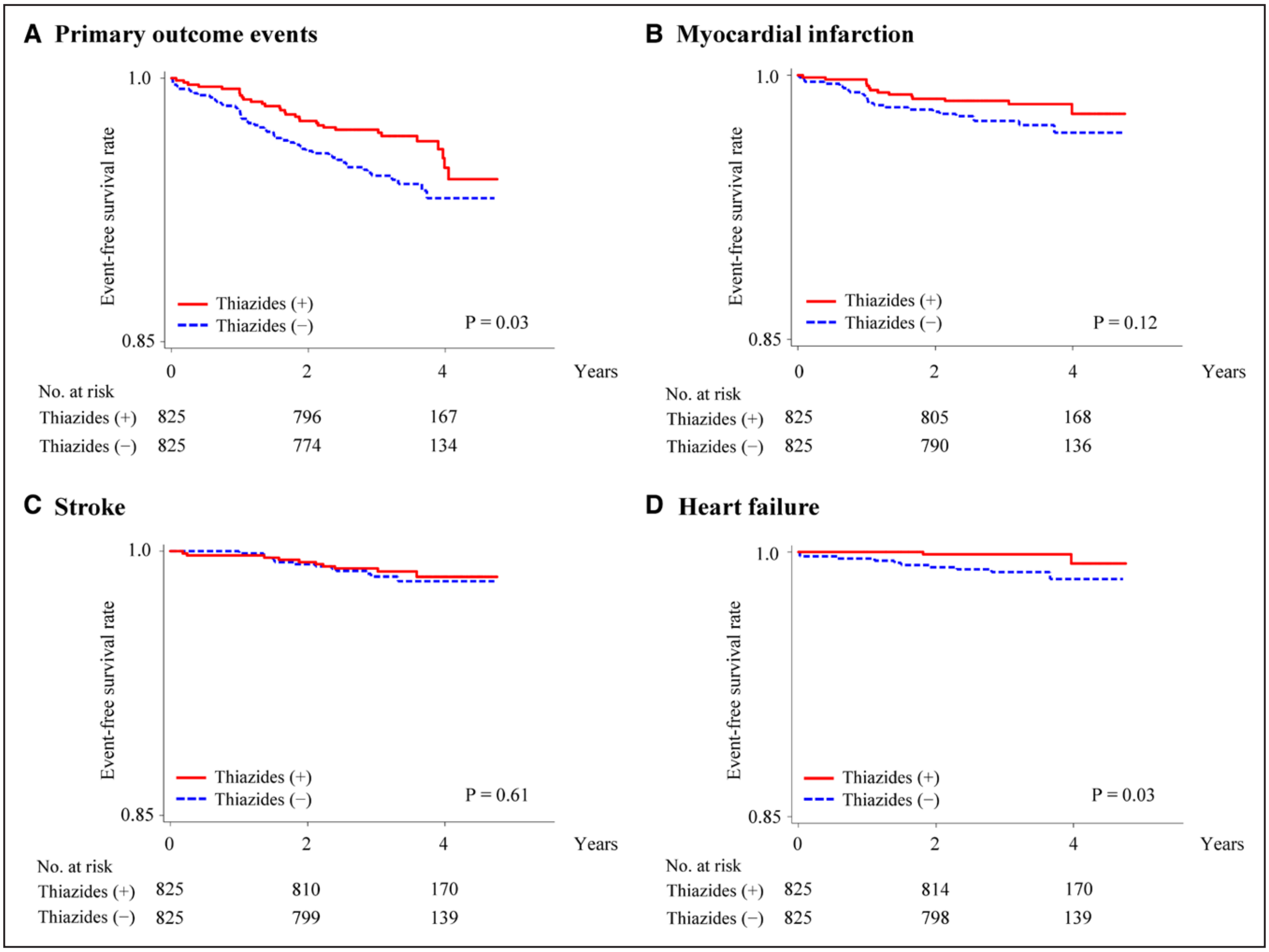

Figure 1. Kaplan-Meier survival curves for cardiovascular events in propensity score-matched patients taking and not taking thiazides for intensive blood pressure treatment. Primary outcome events (**A**), myocardial infarction (**B**), stroke (**C**), and heart failure (**D**). *P* values were calculated using univariate Cox proportional hazards models.

10-year cardiovascular risk score (HR for all-cause mortality, 0.39 [95% CI, 0.22–0.69]; *P*=0.001).

To confirm the robustness of the study results, Cox proportional hazard analyses were performed in the propensity score-matched cohort. The overall mean (SD) follow-up period was 3.3 (0.8) years. Kaplan-Meier survival curves and cumulative event rates for primary outcome events, myocardial infarction, stroke, and heart failure in the propensity score-matched patients are presented in Figure 1 and Table 3. The risk of primary outcome events was significantly lower in patients taking thiazides compared with those not taking thiazides (HR, 0.62 [95% CI, 0.48–0.81]; *P*=0.03). The risk of major adverse cardiovascular event, myocardial infarction, and stroke did not differ significantly between groups (HR for major adverse cardiovascular event, 0.72 [95% CI, 0.43–1.19]; *P*=0.19; HR for myocardial infarction 0.59 [95% CI, 0.30–1.15]; *P*=0.12; HR for stroke 0.79 [95% CI, 0.47–1.32]; *P*=0.61), whereas the risk of heart failure was significantly lower in patients taking thiazides (HR, 0.19 [95% CI, 0.04–0.87]; *P*=0.03). In addition, the risk of all-cause death was significantly lower in patients taking thiazides (HR, 0.48 [95% CI, 0.24–0.95]; *P*=0.03). According to subgroup analysis, there were no significant interactions between thiazide use and age, sex, race/ethnicity, obesity, history of cardiovascular disease, chronic kidney disease, albuminuria, or systolic blood pressure at baseline (Figure 2).

Adverse Events

Adverse events of propensity score-matched patients taking and not taking thiazides are summarized in Table 4. The rates of hypotension, syncope, bradycardia, injurious fall, acute kidney injury or acute renal failure, and orthostatic hypotension did not differ significantly between groups. Hypokalemia (defined as serum potassium <3.0 mmol/L) occurred more frequently in patients taking thiazides than in those not taking thiazides, whereas hyperkalemia (defined as serum potassium >5.5 mmol/L) occurred less frequently in patients taking thiazides than in those not taking thiazides.

Baseline Characteristics and Outcomes in Patients Receiving Standard Blood Pressure Treatment

Table S1 shows the baseline characteristics of patients receiving standard blood pressure treatment before and after propensity score-matching. In patients receiving standard blood pressure treatment, the risks of cardiovascular outcomes

Table 3. Cardiovascular Events and Death for Patients Receiving Intensive Blood Pressure Treatment in the Propensity Score-Matched Cohort*

Event	Thiazides (–), n=825	Thiazides (+), n=825	*P*-Value
Primary outcome events			
No. of patients	48	31	
Event rate (per 1000 person-year)	18.2	11.2	
HR, propensity score-matched	1.00 (ref)	0.62 (0.48–0.81)	0.03
Major adverse cardiovascular events			
No. of patients	35	26	
Event rate (per 1000 person-year)	13.1	9.4	
HR, propensity score-matched	1.00 (ref)	0.72 (0.43–1.19)	0.19
Myocardial infarction			
No. of patients	23	14	
Event rate (per 1000 person-year)	8.6	5.0	
HR, propensity score-matched	1.00 (ref)	0.59 (0.30–1.15)	0.12
Stroke			
No. of patients	12	10	
Event rate (per 1000 person-year)	4.4	3.6	
HR, propensity score-matched	1.00 (ref)	0.79 (0.47–1.32)	0.61
Heart failure			
No. of patients	10	2	
Event rate (per 1000 person-year)	3.7	0.7	
HR, propensity score-matched	1.00 (ref)	0.19 (0.04–0.87)	0.03
All-cause mortality			
No. of patients	24	12	
Event rate (per 1000 person-year)	8.8	4.2	
HR, propensity score-matched	1.00 (ref)	0.48 (0.24–0.95)	0.03

HR indicates hazard ratio.

*Data are presented as number or hazard ratio (95% CI). *P* values were calculated using univariate Cox proportional hazards models.

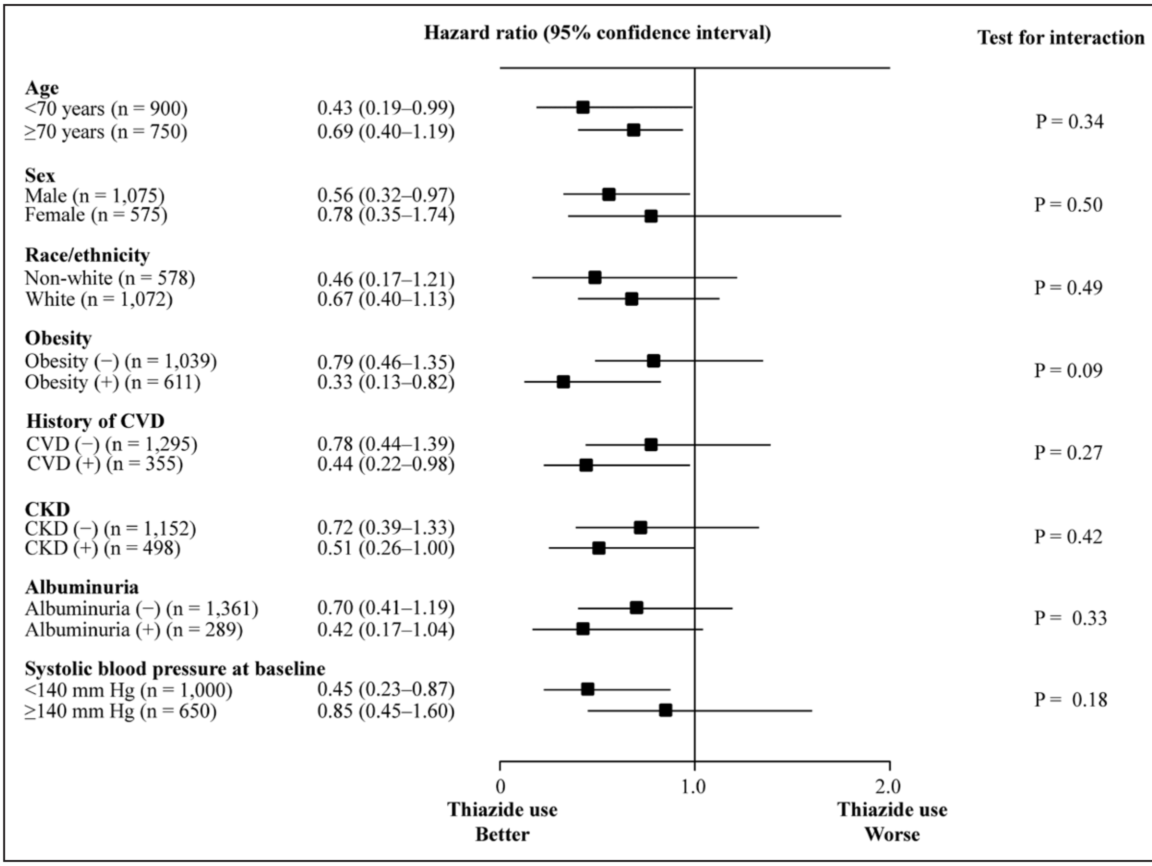

Figure 2. Associations between thiazide use and primary outcome events in various subgroups. Obesity was defined as body mass index ≥30 kg/m². Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate of <60 mL/min per 1.73 m². Albuminuria was defined as albumin-to-creatinine ratio of ≥30 mg/gCre. CVD indicates cardiovascular disease.

in those taking and not taking thiazides were analyzed in the entire cohort (Table S2) and in the propensity score-matched cohort (Table S3). In the entire cohort, the risks of primary outcome events and heart failure were lower in patients taking thiazides than in those not taking thiazides; however, there was no statistically significant difference (Model 1: HR for primary outcome events, 0.76 [95% CI, 0.56–1.04]; *P*=0.09; HR for heart failure, 0.72 [95% CI, 0.40–1.31]; *P*=0.14. Model 2: HR for primary outcome events, 0.78 [95% CI, 0.56–1.09]; *P*=0.14; HR for heart failure, 0.72 [95% CI, 0.37–1.38]; *P*=0.31). In the propensity score-matched cohort, similar findings were observed, and there was no significant difference between the 2 groups.

Discussion

The present study demonstrated that thiazide use was associated with decreased risks of cardiovascular events, particularly heart failure, in patients receiving intensive blood pressure treatment. Further, these findings were observed in both entire and propensity score-matched cohorts. In addition, thiazide use was also associated with decreased risk of all-cause mortality. Decreased risks of cardiovascular events were also observed in various subgroups. Hypokalemia occurred more frequently in patients taking thiazides, but hyperkalemia occurred less frequently. In patients receiving standard blood pressure treatment, the risk of cardiovascular events was not significantly different between patients taking and not taking thiazides. To the best of our knowledge, this is the first report to reveal the additional clinical benefits of thiazides in non-diabetic patients receiving intensive blood pressure treatment.

Many guidelines recommend thiazides for hypertension.[17,18] In fact, 2 or 3 decades ago, some studies had reported the association between thiazide use and cardiovascular events in patients with moderate to severe high blood pressure. Consistent with the results of the present study using data from the SPRINT study,[5] previous studies had suggested that thiazide use was associated with improved cardiovascular outcomes in patients with hypertension.[8,11,19] The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) reported that thiazides were superior in preventing cardiovascular events.[8] However, it was unclear whether these beneficial effects of thiazides result from lowering blood pressure or other factors. Thiazides lower blood pressure by inhibiting sodium transport in the distal convoluted tubule, thereby modestly reducing plasma volume.[20] Such a volume reduction can decrease the risk of heart failure, which is increasing in prevalence worldwide.[21,22] Therefore, thiazides may be particularly advantageous for reversing this trend, although hypokalemia induced by thiazides should be avoided. On the other hand, several studies have shown that thiazides were potentially inferior compared with other antihypertensive classes.[23,24] The ACCOMPLISH trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial showed that

Table 4. Adverse Events in Patients Taking and Not Taking Thiazides for Intensive Blood Pressure Treatment*

Event	Thiazides (–) n=825	Thiazides (+) n=825	*P*-Value
Conditions of interest			
Hypotension	24 (2.9)	15 (1.8)	0.14
Syncope	19 (2.3)	20 (2.4)	0.87
Bradycardia	19 (2.3)	8 (1.0)	0.05
Injurious fall†	24 (2.9)	18 (2.2)	0.34
Acute kidney injury or acute renal failure‡	34 (4.1)	24 (2.9)	0.18
Monitored clinical events			
Adverse laboratory measure§			
Hyponatremia (serum sodium <130 mmol/L)	29 (3.5)	24 (2.9)	0.48
Hypernatremia (serum sodium >150 mmol/L)	2 (0.2)	1 (0.1)	>0.99
Hypokalemia (serum potassium <3.0 mmol/L)	3 (0.4)	25 (3.0)	<0.001
Hyperkalemia (serum potassium >5.5 mmol/L)	49 (5.9)	19 (2.3)	<0.001
Orthostatic hypotension			
Alone	169 (20.5)	142 (17.2)	0.09
With dizziness	19 (2.3)	11 (1.3)	0.14

*Data are presented as number of participants (percentage).

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

‡Acute kidney injury and acute renal failure were coded if the diagnosis was listed in the hospital discharge summary and was judged to be one of the top 3 reasons for admission or continued hospitalization. A few cases of AKI were noted in the emergency department among participant presenting 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 mo post-enrollment, then quarterly during the first year and every 6 mo thereafter.

‖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 min after the participant stood up compared with the value obtained when seated. Standing blood pressures were measured at screening, baseline, 1, 6, and 12 mo post-enrollment, and then yearly. Participants were asked if they felt dizzy at the time of orthostatic measurement.

combination treatment with benazepril plus amlodipine was associated with reduced risk of cardiovascular events and death than treatment with benazepril plus hydrochlorothiazide in high-risk patients with hypertension.[23] The effects of thiazides in patients receiving intensive blood pressure treatment remain to be clarified.

This study has several limitations. First, this was a post hoc analysis of data from the SPRINT study. Unmeasured and unknown confounders can remain unadjusted. We performed various analyses, and results were consistent. However, residual confounders could still be present, even after multivariable adjustment in the entire cohort and in the propensity score-matched cohort. For instance, the doses of antihypertensive drugs, as well as knowing which drugs were used within the same drug class, remained unclear. In addition, geography or practice type might influence the choice of thiazides. Furthermore, the possibility of reverse causality with respect to thiazide use among enrolled patients before SPRINT initiation must be taken into account. Thus, compared with those not taking thiazides, patients taking thiazides could have lower cardiovascular risk despite their blood pressure levels without antihypertensive drug effect were high. Therefore, the results should be ideally confirmed by a large-scale, prospective, randomized controlled trial in which participants are randomly assigned to thiazide use and nonuse groups for intensive blood pressure treatment. However, randomized controlled trials may be difficult to perform. Even in those cases, extensive supporting evidence is needed to determine the effects of thiazides in patients receiving intensive blood pressure treatment. Second, the numbers of patients and events were relatively small, which might influence the results both in patients receiving intensive and standard blood pressure treatment. Third, thiazide use and nonuse were evaluated using data at baseline and 12 months post-enrollment, so it was unclear whether patients took thiazides during the entire follow-up period. However, overall fluctuations of blood pressure were not observed after 12 months, so changes in medication were likely minimal. Fourth, the SPRINT participants were high-risk patients without diabetes mellitus and prior history of stroke. Therefore, it remains unclear whether thiazides provide similar benefits to low-risk patients and patients with diabetes or stroke. Fifth, blood pressure in the SPRINT study was measured using a standardized method in both attended and unattended conditions.[25] The data used in the present study did not include the detailed information about attended or unattended conditions during blood pressure measurement. These conditions were important and could have influenced the results of the present study. Sixth, there was no information regarding the types of thiazides, such as chlorthalidone and hydrochlorothiazide. Thiazides are a heterogeneous group of drugs, and different effects have been documented between thiazide-type and thiazide-like diuretics.[26] A recent study has reported that chlorthalidone use was not associated with significant cardiovascular benefits when compared with hydrochlorothiazide, and its use was associated with greater risk of renal and electrolyte abnormalities.[27] It would have been important to identify which types of thiazides were associated with decreased risk of cardiovascular events and heart failure.

In conclusion, the present study demonstrated that thiazide use was significantly associated with decreased risks of cardiovascular events, particularly heart failure, in high-risk nondiabetic patients receiving intensive blood pressure treatment. The results of the present study could provide a potentially important perspective for thiazide use in patients receiving intensive blood pressure treatment.

Perspectives

Hypertension is a common clinical problem faced by both specialists and primary care clinicians. Recently, the SPRINT study demonstrated that intensive blood pressure treatment (systolic blood pressure target of <120 mm Hg) reduced the risk of cardiovascular events in patients without diabetes mellitus or prior history of stroke. Although many guidelines recommend thiazides for hypertension, it is unclear whether thiazides provide additional clinical benefits over other antihypertensive regimens in patients receiving intensive blood pressure treatment. The present study revealed that thiazides can reduce the risk of cardiovascular events, particularly heart failure, in patients receiving intensive blood pressure treatment. The global prevalence of heart failure continues to increase, and hypertension is a major risk factor. According to the present results, thiazide use could provide additional cardioprotective benefits in high-risk nondiabetic patients receiving intensive blood pressure treatment.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The SPRINT (Systolic Blood Pressure Intervention Trial) study reported that intensive blood pressure treatment decreased the risks of cardiovascular events. However, it remains unknown whether specific medications can further improve cardiovascular outcome in patients receiving intensive blood pressure treatment. The present study demonstrated that thiazide use resulted in decreased risks of cardiovascular events, particularly heart failure, in patients receiving intensive blood pressure treatment.

What Is Relevant?

- Thiazide use may provide additional cardioprotective benefits in high-risk nondiabetic patients receiving intensive blood pressure treatment.

Summary

Thiazide use decreased risk of cardiovascular events, particularly heart failure, in nondiabetic high-risk patients receiving intensive BP treatment.