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Thiazide Use and Cardiovascular Events in Type 2 Diabetic Patients With Well-Controlled Blood Pressure

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Abstract—Evidence regarding the efficacy and safety of thiazides in patients with well-controlled and relatively low blood pressure (BP) is lacking. This study aimed to assess whether thiazide use is effective and safe in type 2 diabetic patients with well-controlled BP and whether intensive BP control leads to decreased risk of cardiovascular events depending on thiazide use. We performed an observational cohort study using data from the ACCORD study (Action to Control Cardiovascular Risk in Diabetes). The primary outcome was major adverse cardiovascular events (MACE), which was a composite end point including cardiovascular death, myocardial infarction, and stroke. Hazard ratios for primary and secondary outcomes with 95% CIs were calculated using Cox proportional hazards models. We included 10 011 type 2 diabetic patients. The overall mean follow-up period was 7.7 years, and 1776 patients experienced MACE. Mean systolic BP at baseline in patients taking and not taking thiazides was 137.2 and 135.7 mm Hg, respectively. Thiazide use was associated with increased risk of MACE, particularly stroke (hazard ratio, 1.49 [95% CI, 1.18–1.88]). In addition, thiazide use was significantly associated with higher risks of MACE and stroke in patients receiving intensive BP control but not in those receiving standard BP control. Similar associations were observed in analyses using propensity score matching. Intensive BP control reduced the risks of MACE and stroke in patients not taking thiazides but not in patients taking thiazides. Thiazide use may be harmful in type 2 diabetic patients with relatively low BP. **(*Hypertension*. 2019;74:1541-1550. DOI: 10.1161/HYPERTENSIONAHA.119.13886.)** ● **Online Data Supplement**

Key Words: diabetes mellitus, type 2 ■ cardiovascular events ■ hypertension ■ stroke ■ thiazide

Hypertension is a highly prevalent public health concern worldwide.[1,2] It increases the risk of several cardiovascular diseases,[3,4] and lowering blood pressure (BP) results in significant benefits. Type 2 diabetic patients frequently have hypertension, and BP management is important in such patients.[5] Recent systematic reviews have concluded that available evidence supported the use of any major class of antihypertensive drugs, including thiazides, for the treatment of hypertensive patients with type 2 diabetes mellitus.[6–9] In fact, 2 or 3 decades ago, several studies demonstrated that the use of thiazides was beneficial, regardless of the presence of diabetes mellitus.[10,11] However, most of these studies were conducted in patients with moderate-to-severe high BP.[10–13] Overall, evidence regarding the efficacy and safety of thiazides in patients with well-controlled BP has been lacking. The present study aimed to assess whether the use of thiazides is effective and safe in type 2 diabetic patients with well-controlled and relatively low BP and whether intensive BP control leads to decreased risk of cardiovascular events compared with standard BP control depending on thiazide use.

Methods

The anonymized data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes)[14] and ACCORDION (Action to Control Cardiovascular Risk in Diabetes Follow-On)[15] studies have been made publicly available at the National Heart, Lung, and Blood Institute and can be accessed at https://biolincc.nhlbi.nih.gov/studies/accord/?q=ACCORD.

Study Design and Patients

We used data from the ACCORD[14] and ACCORDION[15] studies. The study protocol, design, and patient characteristics of the ACCORD and ACCORDION studies have been reported previously.[14–18] Briefly, the ACCORD study was supported by the National Heart, Lung, and Blood Institute and was conducted in 77 clinical centers across the United States and Canada.[14] A total of 10 251 high-risk type 2 diabetic patients were included. The patients were either 40 to 79 years old with cardiovascular disease or 55 to 79 years old with anatomic evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional cardiovascular disease risk factors (current smoking, obesity, hypertension, or dyslipidemia).[14,16,19] Exclusion criteria were body mass index (BMI; weight [kg]/height squared [m^2]) >45, frequent or recent serious hypoglycemia, refusal to receive home glucose monitoring or insulin injections, serum creatinine level >1.5 mg/dL, or any other serious illness. All ACCORD participants provided written informed consent. Patients were randomly assigned to an intensive glycemic control group with a target glycated hemoglobin level of <6.0% or a standard glycemic control group with a target glycated hemoglobin level of 7.0% to 7.9%.[14] Further, participants were randomly assigned (in a 2-by-2 factorial design) to either the ACCORD BP trial (intensive BP control targeting systolic BP <120 mm Hg or standard BP control targeting

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Table 1. Baseline Characteristics of Type 2 Diabetic Patients Taking and Not Taking Thiazides

	All Participants (n=10 011)			Standard BP Control (n=2315)			Intensive BP Control (n=2311)		
Characteristics	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value
n	7242	2769		1643	672		1659	652	
Age, y	62.5 (6.7)	63.4 (6.5)	<0.001	62.5 (6.8)	63.3 (6.6)	0.01	62.4 (6.6)	63.4 (6.5)	0.001
Female sex, %	36.3	44.4	<0.001	45.4	53.3	0.001	45.1	53.7	<0.001
Race and ethnicity, %			<0.001			<0.001			<0.001
White	64.4	57.7		59.8	53.1		62.9	53.1	
Black	15.6	27.4		21.3	31.6		18.8	33.6	
Hispanic	7.8	5.5		7.6	6.1		7.8	3.4	
Others	12.2	9.4		11.3	9.2		10.5	9.4	
Educational attainment, %			0.09			0.71			0.15
Less than high school	14.7	14.5		15.7	14.7		16.2	18.5	
High school	26.0	27.7		27.5	29.3		25.1	27.0	
Some college	32.6	33.3		32.3	30.7		33.0	32.7	
College degree or higher	26.7	24.5		24.5	25.3		25.7	21.8	
Current smoking, %	13.0	10.0	<0.001	11.7	10.3	0.32	13.4	8.1	<0.001
BMI, kg/m^2*	31.9 (5.4)	33.1 (5.3)	<0.001	31.8 (5.4)	32.9 (5.2)	<0.001	31.9 (5.6)	32.8 (5.4)	<0.001
Duration of diabetes mellitus, y	10.7 (7.6)	11.0 (7.7)	0.17	10.7 (7.8)	11.6 (8.1)	0.01	11.1 (7.8)	10.6 (7.7)	0.16
Hypertension, %	89.3	99.9	<0.001	92.6	100	<0.001	94.0	99.7	<0.001
Dyslipidemia, %	96.2	96.0	0.67	93.9	93.2	0.53	93.3	94.2	0.44
History of cardiovascular disease, %									
Coronary artery disease	31.5	25.7	<0.001	29.4	24.4	0.01	29.7	23.9	0.006
Stroke	5.7	7.0	0.02	5.7	6.3	0.58	6.8	7.8	0.36
Heart failure	5.4	3.0	<0.001	4.3	2.7	0.06	5.3	2.6	0.005
Medications, %									
Insulin	34.2	37.8	0.001	36.5	40.5	0.07	37.5	34.8	0.23
Sulfonylurea	53.4	53.4	0.99	48.2	52.4	0.06	52.0	52.0	0.98
Metformin	63.1	66.6	0.001	60.2	65.5	0.01	59.9	65.5	0.01
Thiazolidinedione	21.5	23.4	0.03	23.1	28.1	0.01	25.2	22.2	0.13
Other antihyperglycemic agents	4.4	3.8	0.18	4.8	2.5	0.01	4.4	4.8	0.71
ACE inhibitor/ARB	64.8	81.8	<0.001	67.6	81.3	<0.001	68.7	81.0	<0.001
CCB	10.0	15.9	<0.001	10.3	12.2	0.17	11.3	11.7	0.82
β-Blocker	28.4	34.9	<0.001	25.5	28.9	0.09	27.9	27.8	0.94
Loop diuretic	11.5	3.7	<0.001	11.1	4.3	<0.001	11.0	3.7	<0.001
Statin	62.9	65.8	0.006	64.4	69.5	0.01	64.0	64.9	0.69
Aspirin	53.8	57.2	0.002	49.7	55.1	0.02	53.5	54.9	0.54
Oral anticoagulant	3.1	3.0	0.87	3.2	2.7	0.48	3.1	2.5	0.42
Glycated hemoglobin (%)	8.3 (1.0)	8.2 (0.9)	<0.001	8.3 (1.0)	8.2 (1.0)	0.29	8.4 (1.1)	8.3 (1.0)	0.13
LDL cholesterol, mg/dL	105.2 (33.0)	103.0 (32.9)	0.002	109.3 (34.9)	106.5 (35.1)	0.08	110.1 (35.6)	111.7 (35.7)	0.30
HDL cholesterol, mg/dL	41.6 (11.2)	42.3 (11.2)	0.006	46.0 (13.2)	46.7 (12.8)	0.22	45.8 (12.9)	46.3 (12.5)	0.43
eGFR, mL/min per 1.73 m^2†	91.8 (22.6)	85.8 (22.0)	<0.001	92.1 (23.0)	86.8 (22.5)	<0.001	91.6 (22.9)	87.6 (23.8)	<0.001
Systolic BP, mm Hg	135.7 (16.3)	137.2 (16.9)	<0.001	139.0 (14.7)	139.3 (15.6)	0.70	138.7 (15.6)	138.8 (15.4)	0.85
Diastolic BP, mm Hg	74.6 (10.2)	74.8 (10.4)	0.42	76.0 (9.8)	75.5 (10.1)	0.28	75.6 (10.2)	75.9 (9.9)	0.47

(*Continued*)

Table 1. Continued

Characteristics	All Participants (n=10 011)			Standard BP Control (n=2315)			Intensive BP Control (n=2311)		
	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value
Glycemic control strategy									
Intensive glycemic treatment, %	50.1	49.9	0.89	50.9	48.5	0.28	49.7	49.9	0.93
BP control strategy									
Intensive BP treatment, %	22.9	23.6	0.49	…	…	…	…	…	…
Lipid control strategy									
Intensive lipid treatment, %	27.2	26.1	0.27	…	…	…	…	…	…

Data are presented as number of participants, percentage, or mean (SD). *P* value was calculated by comparing variables in thiazide users with those in thiazide nonusers. Glycated hemoglobin, 8.3%=67 mmoL/moL, 8.2%=66 mmoL/moL, 8.4%=68 mmoL/moL. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*BMI was calculated as weight in kilograms divided by square of height in meters.

†The eGFR was calculated using the following Modification of Diet in Renal Disease Study equation: eGFR (mL/min per 1.73 m^2)=175×(sem creatinine in mg/dL)$^{-1.154}$×(age in years)$^{-0.203}$×(0.742 for women)×(1.212 for blacks).

systolic BP <140 mm Hg) or the ACCORD lipid trial (intensive lipid control using fenofibrate 160 mg/d or standard lipid control using placebo).[14,19] Because of the increased risk of all-cause and cardiovascular mortality, intensive glycemic therapy was discontinued on February 6, 2008,[14] and the participants were switched to the standard regimen and followed up until December 31, 2010. From participating sites, all surviving ACCORD participants were subsequently offered the opportunity to participate in the ACCORDION study, during which cardiovascular and other health-related outcomes were recorded.[15] No active therapies were provided during this follow-up period. All participants provided written informed consent to participate in ACCORDION. In the present study, patients with missing information regarding thiazide use were excluded (n=27). In addition, patients with missing information regarding potential confounders were excluded from the main analyses (n=213), which resulted in a sample of 10 011. 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 ACCORD and ACCORDION data.

Primary and Secondary Outcomes

The primary outcome was major adverse cardiovascular events (MACE), which was a composite end point including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes were cardiovascular death, major coronary heart disease, and stroke. All-cause death and congestive heart failure were also evaluated. Cardiovascular death was defined as presumed cardiovascular death, unexpected death, or death from myocardial infarction, congestive heart failure, arrhythmia, stroke, or other cardiovascular diseases including pulmonary emboli and abdominal aortic aneurysm rupture.[16] Major coronary events were fatal coronary heart disease, nonfatal myocardial infarction, or unstable angina. Stroke comprised fatal and nonfatal stroke events. The outcome events were classified by a Working Group of the Morbidity and Mortality subcommittee. Consenting participants in ACCORDION were observed or contacted via telephone by 72 sites in the United States and Canada on ≤7 occasions between May 2011 and October 2014. Each outcome event was prespecified. The ACCORD participants were followed up at least every 4 months to monitor study outcomes[14] and were followed up for a maximum of 13 years in the present study. The occurrence of cardiovascular outcomes and deaths was ascertained during 4 telephone calls and 3 clinic visits.

Potential Confounders

Potential confounders included age, sex, race/ethnicity, educational attainment, smoking status, BMI, duration of diabetes mellitus, hypertension, dyslipidemia, history of cardiovascular disease (coronary artery disease, stroke, and congestive heart failure), use of medications (insulin, metformin, thiazolidinedione, other antihyperglycemic medications, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, β-blockers, loop diuretics, statins, aspirin, and oral anticoagulants), glycated hemoglobin, low- and high-density lipoprotein cholesterol, systolic and diastolic BP, estimated glomerular filtration rate, and the glycemic, BP, and lipid control strategy assigned in the ACCORD trial.

Statistical Analyses

Patients were divided into 2 groups depending on use of thiazides or no use of thiazides. Further, the patients were stratified into 3 subgroups: all patients, patients receiving standard BP control, and patients receiving intensive BP control. Demographic data were represented as proportions or means±SDs. Comparisons were performed between patients taking and not taking thiazides. Categorical variables were compared using χ^2 tests, and continuous variables were compared using *t* tests. Kaplan-Meier survival curves were constructed for primary and secondary outcomes, and the rate of each event was calculated in patients taking and not taking thiazides. Unadjusted and adjusted hazard ratios (HRs) for primary and secondary outcomes with 95% CIs were calculated using Cox proportional hazard models to compare time to occurrence of outcome events. We adjusted for potential confounders including age, sex, race/ethnicity, educational attainment, smoking status, BMI, duration of diabetes mellitus, hypertension, dyslipidemia, history of cardiovascular disease (coronary artery disease, stroke, and congestive heart failure), use of medications (insulin, metformin, thiazolidinedione, other antihyperglycemic medications, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, β-blockers, loop diuretics, statins, aspirin, and oral anticoagulants), glycated hemoglobin, low- and high-density lipoprotein cholesterol, systolic and diastolic BP, estimated glomerular filtration rate, and the glycemic, BP, and lipid control strategy assigned in the ACCORD trial (BP and lipid control strategy were excluded from the multivariable analyses for participants in the ACCORD BP trial). We performed an additional analysis, considering the use of thiazides as a time-varying variable in an extended Cox model.[20] To confirm the results, additional analyses using propensity score (PS) 1:1 nearest neighbor matching without replacement were performed[21] separately in all patients, patients receiving standard BP control, and patients receiving intensive BP control. The PS was calculated using a logistic regression model that included use of thiazides as the outcome variable and the potential confounders related to the indication of thiazides as predictors. Standardized differences of ≤0.1 were considered negligible.

The association between use of thiazides and cardiovascular events was also analyzed in the following subgroups: age (<65 or ≥65

years), sex (male or female), obesity (nonobese or obese), duration of diabetes mellitus (<10 or ≥10 years), history of cardiovascular disease (no history of cardiovascular disease or history of cardiovascular disease), systolic BP (<140 or ≥140 mm Hg), and diastolic BP (<80 or ≥80 mm Hg). Cardiovascular disease was defined as myocardial infarction, angina pectoris, coronary revascularization including coronary artery bypass grafting or percutaneous coronary intervention, stroke, or other revascularization procedures such as carotid artery revascularization and peripheral artery revascularization. We tested effect modification by evaluating interactions between thiazide use and the subgroups.

In addition, we assessed the visit-to-visit BP variability in patients taking and not taking thiazides. Visit-to-visit BP variability was defined as the coefficient of variation (calculated as SD/mean BP×100%) of systolic BP at 4, 8, and 12 months.[22]

Further, considering the effects of thiazides on cardiovascular events, we assessed the associations between BP control strategy and cardiovascular events separately in patients taking and not taking thiazides.

All statistical analyses were conducted using the software Stata (version 14.1; Stata Corp, College Station, TX). A P of <0.05 was considered statistically significant in all tests.

Results

Baseline Characteristics

The present study included 10 011 type 2 diabetic patients: 7242 patients not taking thiazides and 2769 patients taking thiazides. Patient characteristics are presented in Table 1. Among all the patients, thiazide use was associated with older age, higher proportion of women, lower proportion of white, lower current smoking rate, greater BMI, more complications due to hypertension and stroke, and fewer complications due to coronary artery disease and heart failure. In terms of antihypertensive medications, thiazide use in all patients was associated with more frequent use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, and β-blockers but less frequent use of loop diuretics. In patients receiving standard or intensive BP control, thiazide use was associated with more frequent use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers but less frequent use of loop diuretics. Mean (SD) systolic BP at baseline in patients taking and not taking thiazides was 137.2 (16.9) and 135.7 (16.3) mm Hg, respectively, and diastolic BP was 74.8 (10.4) and 74.6 (10.2) mm Hg, respectively. Similar baseline characteristics were observed in patients receiving standard (n=2315) or intensive (n=2311) BP control.

Primary and Secondary Outcomes

The overall mean (SD) follow-up period was 7.7 (3.3) years, and 1776 patients experienced MACE; specifically, in patients not taking and taking thiazides, respectively, the follow-up period was 7.7 (3.3) and 7.7 (3.1) years, and 1262 and 514 of them experienced MACE. Among all patients, the event rate (per 1000 person-years) for MACE in those taking and not taking thiazides was 24.2 and 22.5, respectively (Table 2). After multivariable adjustments, the risk of MACE was significantly higher in those taking thiazides than in those not taking thiazides (adjusted HR, 1.12 [95% CI, 1.01–1.25]; P=0.03; Table 2). The risk of MACE in patients receiving standard BP control did not differ significantly between those taking and not taking thiazides (adjusted HR, 1.09 [95% CI, 0.86–1.37]; P=0.47), whereas the risk of MACE in patients receiving intensive BP control was significantly higher in those taking thiazides than in those not taking thiazides (adjusted HR, 1.49 [95% CI, 1.18–1.88]; P<0.001). The risks of all-cause death, cardiovascular death, and major coronary events in all patients were not significantly different between those taking and not taking thiazides. However, the risk of stroke was significantly higher in patients taking thiazides than in those not taking thiazides (adjusted HR, 1.34 [95% CI, 1.10–1.63]; P=0.004). Among patients receiving standard BP control, the risks of all-cause death, cardiovascular death, major coronary events, and stroke did not differ significantly between those taking and not taking thiazides. Among patients receiving intensive BP control, the risks of all-cause death, cardiovascular death, and major coronary events were not significantly different between the 2 groups, whereas the risk of stroke was significantly higher in those taking thiazides than in those not taking thiazides (adjusted HR, 2.15 [95% CI, 1.47–3.32]; P<0.001). Analysis using a time-varying model showed significant associations between thiazide use and increased risk of stroke in patients receiving standard BP control (adjusted HR, 1.31 [95% CI, 1.03–1.67]; P=0.02) and in those receiving intensive BP control (adjusted HR, 1.73 [95% CI, 1.35–2.21]; P<0.001).

Figure S1 in the online-only Data Supplement shows the association of thiazide use with the risk of MACE or stroke in each subgroup. In terms of risk of MACE (Figure S1A), there were no significant interactions between thiazide use and age (<65 or ≥65 years), sex (male or female), obesity (BMI <30 or ≥30 kg/m^2), duration of diabetes mellitus (<10 or ≥10 years), history of cardiovascular disease (no history or history), glycated hemoglobin (<8% or ≥8%), systolic BP (<140 or ≥140 mm Hg), or diastolic BP (<80 or ≥80 mm Hg). Similarly, no significant interactions were detected in terms of stroke risk (Figure S1B).

The proportions of patients with systolic BP <100 mm Hg were not significantly different between patients taking and not taking thiazides at baseline (0.6% versus 0.8%; P=0.29) and on follow-up after 1 year (2.2% versus 2.2%; P=0.84) and 2 years (2.6% versus 2.5%; P=0.97). Patients taking and not taking thiazides had no significant differences in the mean (SD) coefficient of variation for standard BP control (5.7 [3.6]% and 5.7 [3.5]%, respectively; P=0.93) and intensive BP control (6.3 [4.0]% versus 6.0 [3.7]%, respectively; P=0.20).

PS-Matched Analyses

The baseline characteristics of PS-matched patients taking (n=2620) and not taking (n=2620) thiazides are shown in Table S1. The characteristics were well matched. Similarly, the characteristics of PS-matched patients receiving standard or intensive BP control were well matched between patients taking and not taking thiazides (Tables S2 and S3).

Kaplan-Meier survival curves for MACE, cardiovascular death, major coronary events, and stroke in the PS-matched patients are shown in Figure 1. The risk of MACE was significantly higher in PS-matched patients taking thiazides than in those not taking thiazides (HR, 1.14 [95% CI, 1.00–1.29]; P=0.04). In addition, the risk of stroke was significantly higher in those taking thiazides than in those not taking thiazides (HR, 1.40 [95% CI, 1.10–1.77];

Table 2. Cardiovascular Events and Death in Type 2 Diabetic Patients Taking and Not Taking Thiazides

	All			Standard BP Control			Intensive BP Control		
	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value
Event	n=7242	n=2769		n=1643	n=672		n=1659	n=652	
MACE*									
No. of events	1262	514		279	114		238	124	
Event rate (per 1000 person-years)	22.5	24.2		21.8	21.8		18.6	24.7	
Unadjusted HR (95% CI)	1.00 (ref)	1.08 (0.97–1.20)	0.14	1.00 (ref)	1.01 (0.81–1.25)	0.96	1.00 (ref)	1.34 (1.07–1.66)	0.009
Adjusted HR (95% CI)	1.00 (ref)	1.12 (1.01–1.25)	0.03	1.00 (ref)	1.09 (0.86–1.37)	0.47	1.00 (ref)	1.49 (1.18–1.88)	<0.001
All-cause death									
No. of events	1375	521		295	103		296	106	
Event rate (per 1000 person-years)	20.8	20.7		19.3	16.5		19.5	17.6	
Unadjusted HR (95% CI)	1.00 (ref)	1.01 (0.91–1.11)	0.91	1.00 (ref)	0.86 (0.69–1.08)	0.18	1.00 (ref)	0.90 (0.72–1.12)	0.35
Adjusted HR (95% CI)	1.00 (ref)	1.03 (0.93–1.15)	0.58	1.00 (ref)	0.91 (0.72–1.15)	0.42	1.00 (ref)	0.99 (0.78–1.26)	0.95
Cardiovascular death									
No. of events	470	174		93	29		85	33	
Event rate (per 1000 person-years)	7.1	6.9		6.1	4.6		5.6	5.5	
Unadjusted HR (95% CI)	1.00 (ref)	0.98 (0.82–1.17)	0.83	1.00 (ref)	0.77 (0.51–1.17)	0.22	1.00 (ref)	0.98 (0.66–1.47)	0.93
Adjusted HR (95% CI)	1.00 (ref)	1.07 (0.89–1.29)	0.45	1.00 (ref)	0.93 (0.60–1.46)	0.76	1.00 (ref)	1.11 (0.73–1.71)	0.61
Major coronary events‡									
No. of events	1333	477		295	105		276	98	
Event rate (per 1000 person-years)	24.0	22.6		23.3	20.1		22.0	19.5	
Unadjusted HR (95% CI)	1.00 (ref)	0.94 (0.84–1.04)	0.22	1.00 (ref)	0.87 (0.69–1.08)	0.20	1.00 (ref)	0.89 (0.71–1.12)	0.31
Adjusted HR (95% CI)	1.00 (ref)	0.97 (0.87–1.09)	0.64	1.00 (ref)	0.94 (0.74–1.19)	0.61	1.00 (ref)	0.98 (0.77–1.25)	0.89
Stroke									
No. of events	334	170		82	44		58	49	
Event rate (per 1000 person-years)	5.7	7.7		6.1	8.1		4.4	9.3	
Unadjusted HR (95% CI)	1.00 (ref)	1.35 (1.13–1.63)	0.001	1.00 (ref)	1.33 (0.92–1.91)	0.13	1.00 (ref)	2.15 (1.47–3.15)	<0.001
Adjusted HR (95% CI)	1.00 (ref)	1.34 (1.10–1.63)	0.004	1.00 (ref)	1.36 (0.91–2.02)	0.13	1.00 (ref)	2.21 (1.47–3.32)	<0.001

Data are presented as n or HR (95% CI). BP indicates blood pressure; HR, hazard ratio; and MACE, major adverse cardiovascular events.

*MACE were defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

‡Major coronary events were defined as fatal coronary events, nonfatal myocardial infarction, or unstable angina.

P=0.005). The risks of cardiovascular death and major coronary events were not significantly different between the 2 groups (HR for cardiovascular death, 1.11 [95% CI, 0.89–1.38]; *P*=0.34; and HR for major coronary events, 0.97 [95% CI, 0.85–1.10]; *P*=0.60). Among PS-matched patients receiving standard BP control, the risks of MACE, cardiovascular death, major coronary events, and stroke did not significantly differ between those taking and not taking thiazides (Figure S2). However, among PS-matched patients receiving intensive BP control, the risks of cardiovascular death and major coronary events were not significantly different, whereas the risks of MACE and stroke were significantly higher in those taking thiazides than in those not taking thiazides (HR for MACE, 1.63 [95% CI, 1.22–2.18]; *P*=0.001; and HR for stroke, 2.30 [95% CI, 1.36–3.89]; *P*=0.001; Figure 2).

The risks of all-cause death and congestive heart failure were not significantly higher in patients taking thiazides than in those not taking thiazides within each PS-matched patient group (Figures S3 through S5).

Effects of Intensive BP Control in Type 2 Diabetic Patients Taking Thiazides or Not Taking Thiazides

Changes in BP among patients receiving standard or intensive BP control are shown in Figure S6. In patients taking thiazides and in those not taking thiazides, systolic and diastolic

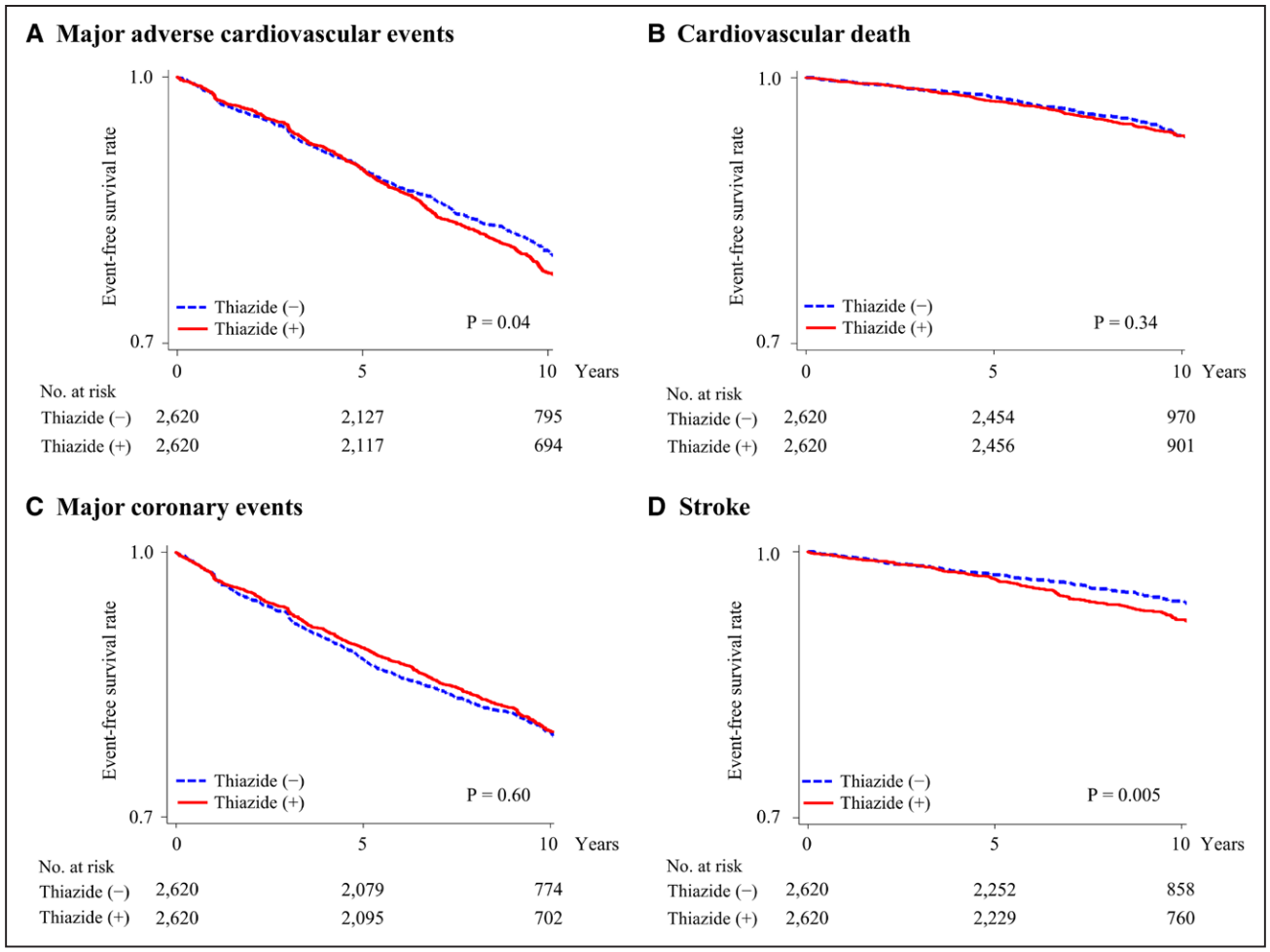

Figure 1. Kaplan-Meier survival curves for cardiovascular events in propensity score–matched patients taking and not taking thiazides. Kaplan-Meier survival curves for major adverse cardiovascular events (**A**), cardiovascular death (**B**), major coronary events (**C**), and stroke (**D**) in patients taking and not taking thiazides.

BP were significantly lower in patients receiving intensive BP control than in those receiving standard BP control. Although the difference between patients receiving standard and intensive BP control was reduced after the intervention in the ACCORD BP study was stopped, some difference remained. Kaplan-Meier survival curves for MACE and stroke in the standard or intensive BP control group in patients taking thiazides or not taking thiazides are shown in Figure 3. Among patients not taking thiazides, intensive BP control resulted in lower risk of MACE than standard BP control (HR, 0.84 [95% CI, 0.70–0.99]; *P*=0.03; Figure 3A). In contrast, among patients taking thiazides, the risk of MACE was not significantly lower in the intensive BP control group than in the standard BP control group (HR, 1.11 [95% CI, 0.86–1.42]; *P*=0.42; Figure 3B). Similarly, the risk of stroke in patients not taking thiazides was significantly lower in the intensive BP control group (HR, 0.69 [95% CI, 0.50–0.97]; *P*=0.03; Figure 3C), whereas that in patients taking thiazides did not differ significantly between the 2 groups (HR, 1.17 [95% CI, 0.78–1.75]; *P*=0.44; Figure 3D).

Discussion

The present study demonstrated that the use of thiazides was associated with increased risk of MACE, particularly stroke, in type 2 diabetic patients. The difference in the MACE risk was possibly due to the difference in the stroke risk between patients taking and not taking thiazides because the incidence of major coronary events and cardiovascular mortality was similar between the 2 groups. In addition, the risk of cardiovascular events in patients receiving standard BP control was not significantly different between those taking and not taking thiazides, whereas the risks of MACE and stroke in patients receiving intensive BP control were significantly higher in those taking thiazides than in those not taking thiazides. Similar associations were observed in the analyses using PS matching. There were no significant interactions between the use of thiazides and clinically important variables. Intensive BP control in patients taking thiazides did not reduce cardiovascular risk, whereas that in patients not taking thiazides resulted in decreased risks of MACE and stroke.

Thiazide use in hypertensive patients is recommended by many guidelines.[5,23,24] However, 2 or 3 decades ago, several studies reported that the use of thiazides in patients with diabetes mellitus lowers BP and is associated with reduced risk of cardiovascular events.[10–12] In addition, even in previous trials reporting associations between thiazide use and decreased risk of cardiovascular events, the cardiovascular benefits might have been derived from lowering BP.[6–9] Thus, there have been few studies assessing the effects of thiazides on cardiovascular events in patients with well-controlled BP. Several previous

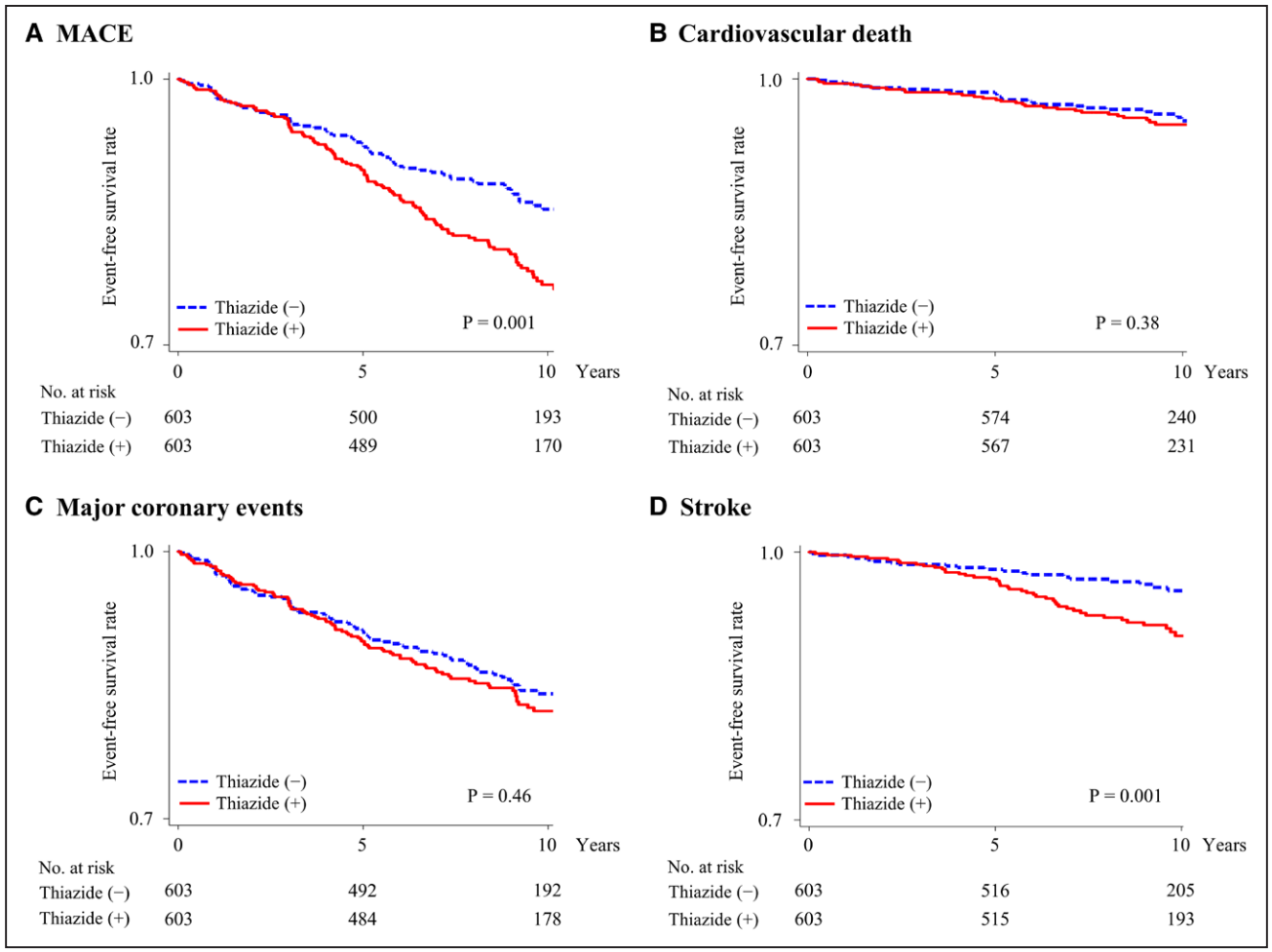

Figure 2. Kaplan-Meier survival curves for cardiovascular events in propensity score–matched patients receiving intensive blood pressure control taking and not taking thiazides. Kaplan-Meier survival curves for major adverse cardiovascular events (MACE; **A**), cardiovascular death (**B**), major coronary events (**C**), and stroke (**D**) in patients taking and not taking thiazides.

trials have shown that thiazides were potentially inferior, when compared with other antihypertensive classes.[25–27] The ANBP2 (Second Australian National Blood Pressure Study) demonstrated that angiotensin-converting enzyme inhibitors in older subjects, particularly men, appeared to improve the outcomes than treatment with diuretic agents, despite similar reductions of BP.[25] The ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) reported that compared with atenolol adding thiazide as required, the amlodipine adding perindopril as required prevented more major cardiovascular events and induced less diabetes mellitus.[26] The ACCOMPLISH trial (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) showed that combination treatment with benazepril plus amlodipine was superior to treatment with benazepril plus hydrochlorothiazide in reducing the risk of cardiovascular events and death among high-risk patients with hypertension.[27] Although thiazides inhibit sodium transport in the distal convoluted tubule, the mechanisms responsible for decline in BP remain unclear. The hypotensive response is partially mediated by a modest reduction in plasma volume and cardiac output.[28] The present study indicated that the use of thiazides in type 2 diabetic patients, particularly those receiving intensive BP control, was associated with increased risk of stroke. Considering that the present study included many type 2 diabetic patients with atherosclerosis, a possible explanation is that reduction in plasma volume and cardiac output due to thiazides in patients with atherosclerosis and low BP might result in cerebral blood hypoperfusion, leading to stroke events. Another possible explanation is that hypokalemia in patients with thiazides might induce arrhythmias such as atrial fibrillation.[29,30] Previous studies suggested that a relatively high visit-to-visit BP variability was associated with higher risk of stroke.[31,32] In the present study, although the visit-to-visit BP variability was not significantly different between patients taking and not taking thiazides, further analyses were required to determine the associations between thiazide use and visit-to-visit BP variations. Because the reason for the increased risk of stroke remains unclear, further studies are warranted to assess the efficacy and safety of thiazides in patients receiving intensive BP control.

The ACCORD BP study demonstrated that, compared with standard BP control, intensive BP control in high-risk patients with type 2 diabetes mellitus showed no significant reduction in the composite outcome of fatal and nonfatal major cardiovascular events.[33] Additionally, previous studies have suggested

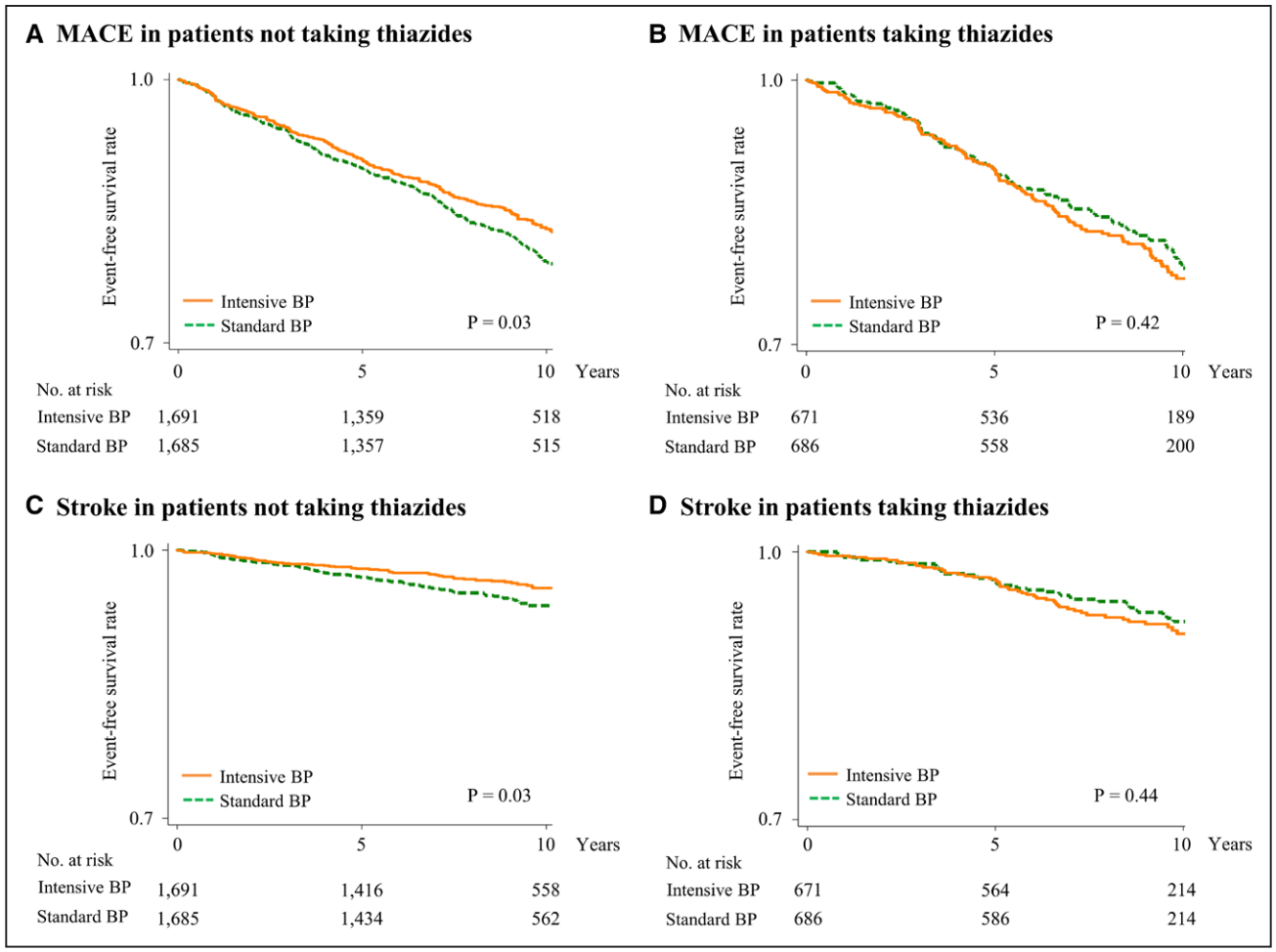

Figure 3. Blood pressure (BP) control strategy and major adverse cardiovascular events (MACE) or stroke in patients not taking or taking thiazides. Kaplan-Meier survival curves for MACE in patients not taking thiazides (**A**), MACE in those taking thiazides (**B**), stroke in those not taking thiazides (**C**), and stroke in those taking thiazides (**D**).

that low BP, especially low diastolic BP, in high-risk patients was associated with increased risks of cardiovascular events and renal failure.[34,35] In contrast, SPRINT (Systolic Blood Pressure Intervention Trial) reported that compared with standard BP control, intensive BP control decreased the incidence of cardiovascular events in high-risk patients without diabetes mellitus or a prior history of stroke.[36] These differing results between the ACCORD BP and the SPRINT studies might be attributed to the inclusion of different subjects, different BP measurements, and different composite outcomes of cardiovascular events. However, recent studies suggested that intensive BP control in type 2 diabetic patients may reduce incidence of cardiovascular events.[37–39] In the present study, although the BP was significantly lower in patients receiving intensive BP control than in those receiving standard BP control, regardless of thiazide use, the beneficial effects of intensive BP control were observed only in patients not taking thiazides. Considering the results of the present study using data from the ACCORD BP study, an intensive BP control strategy may be beneficial in type 2 diabetic patients under specific conditions.

The present study has several limitations. First, it was an observational study using data from the ACCORD and ACCORDION studies. Many baseline characteristics, including antihypertensive medications, were different between patients taking and not taking thiazides. Particularly, thiazide use was associated with older age, higher proportion of black race, and greater BMI, which might have affected the results of this study. Although the various analyses, including multivariable adjustment and PS matching, suggested the risks associated with thiazide use in type 2 diabetic patients with low BP, there might have been residual bias including unmeasured and unknown confounders, even after adjustment, due to the uncontrolled nature of observational studies. Second, it is unknown whether the patients took thiazides during follow-up. The various analyses, including the fixed covariate Cox model and the time-dependent Cox model that used thiazides as a time-varying variable, found similar associations between thiazide use and increased risk of stroke. However, the results of this study should be validated using other large-scale dataset with detailed information, such as the United Kingdom Clinical Practice Research Datalink dataset. Third, there was no information regarding the doses and types of thiazides, such as chlorthalidone, indapamide, and hydrochlorothiazide. Thiazides are a heterogeneous group of drugs, and different effects have been documented between thiazide-type and thiazide-like diuretics.[40] It would have been

important to identify the types of thiazides that were associated with increased risk of stroke. In addition, because of the lack of information regarding orthostatic hypotension and syncope, we could not assess these adverse events. Further studies about the association between thiazide use and stroke in patients with relatively low BP are required, using data with detailed information, including the doses and types of thiazides and adverse events. Moreover, the associations between other diuretics and stroke in patients with relatively low BP should be assessed in future studies. Fourth, the ACCORD and ACCORDION participants were high-risk type 2 diabetic patients. Therefore, it remains unclear whether similar results would be observed in low-risk type 2 diabetic patients or nondiabetic patients. Fifth, diabetes mellitus management strategies have changed since the ACCORD study was initiated. Therefore, new randomized controlled trials or more recent cohorts are needed to validate the results of the present study.

In conclusion, the present study demonstrated that the use of thiazides was associated with an increased risk of stroke in type 2 diabetic patients, specifically those receiving intensive BP control. Further studies are warranted to assess the association between thiazide use and stroke in type 2 diabetic patients with relatively low BP.

Perspectives

Recent systematic reviews have concluded that available evidence supports antihypertensive drug treatment in type 2 diabetic patients with hypertension, using any major classes including thiazides. In fact, 2 or 3 decades ago, several studies had demonstrated that the use of thiazides was beneficial in hypertensive patients. However, most of these studies were conducted in patients with moderate-to-severe high BP. In addition, because some study patients taking thiazides had a greater reduction in BP compared with those taking placebo or other antihypertensive agents, it remains unknown whether the benefits were derived from lowering BP or the use of thiazides. Overall, evidence regarding the efficacy and safety of thiazides in patients with well-controlled and relatively low BP is lacking. In the present study, thiazide use was associated with an increased risk of stroke in type 2 diabetic patients, specifically those receiving intensive BP control. Our findings indicate that thiazide use may increase the risk of stroke in type 2 diabetic patients with relatively low BP.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Evidence regarding the efficacy and safety of thiazides in patients with well-controlled and relatively low blood pressure (BP) is lacking. The present study revealed that thiazide use was associated with increased risk of major adverse cardiovascular events, particularly stroke. In addition, thiazide use was significantly associated with higher risks of major adverse cardiovascular events and stroke in patients receiving intensive BP control but not in those receiving standard BP control.

What Is Relevant?

- Thiazide use may be harmful in hypertensive patients with type 2 diabetes mellitus and relatively low BP.

Summary

The present study demonstrated that thiazide use was associated with an increased risk of stroke in type 2 diabetic patients with well-controlled BP, specifically those receiving intensive BP control.