Original Article

Patterns and Correlates of Baseline Thiazide-Type Diuretic Prescription in the Systolic Blood Pressure Intervention Trial

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Abstract—Thiazides and thiazide-type diuretics are recommended as first-line agents for the treatment of hypertension, but contemporary information on their use in clinical practice is lacking. We examined patterns and correlates of thiazide prescription in a cross-sectional analysis of baseline data from participants enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT). We examined baseline prescription of thiazides in 7582 participants receiving at least 1 antihypertensive medication by subgroup, and used log-binomial regression to calculate adjusted prevalence ratios for thiazide prescription (versus no thiazide). Forty-three percent of all participants were prescribed a thiazide at baseline, but among participants prescribed a single agent, the proportion was only 16%. The prevalence of thiazide prescription differed significantly by demographic factors, with younger participants, women, and blacks all having higher adjusted prevalence of thiazide prescription than other corresponding subgroups. Participants in the lowest category of kidney function (estimated glomerular filtration rate <30 mL/min per 1.73 m2) were half as likely to be prescribed a thiazide as participants with preserved kidney function. In conclusion, among persons with hypertension and heightened cardiovascular risk, we found that thiazide prescription varied significantly by demographics and kidney disease status, despite limited evidence about relative differences in effectiveness. **(*Hypertension*. 2016;67:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.06851.)** ● **Online Data Supplement**

Key Words: antihypertensive agents ■ blood pressure ■ hypertension ■ risk factors ■ thiazides

Thiazide-type diuretics are among the first-line agents recommended for use in the treatment of hypertension by multiple clinical practice guidelines published during the past decade.[1–3] The Seventh Report of the Joint National Committee (JNC 7), published in 2003, gave one of the strongest endorsements for thiazide prescription, recommending that they be given as initial therapy for most patients with hypertension.[2] These recommendations were based in large part on the lower incidence of several cardiovascular disease outcomes after treatment with chlorthalidone compared with other antihypertensive agents (ie, the angiotensin-converting enzyme inhibitors [ACEI] lisinopril, the α-blocker doxazosin, or the calcium channel blocker amlodipine) reported in the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[4,5]

An increase in thiazide prescription was observed after publication of ALLHAT and JNC 7, but the magnitude and duration of this effect was relatively modest and short lived.[6,7] Moreover, reported rates of thiazide prescription remained lower than for other antihypertensive medication classes.[8–10] However, even the most recent of these studies only included patients through 2010, and so may not represent the most up-to-date information on the use of thiazides in clinical practice.

We therefore sought to examine patterns and correlates of thiazide prescription in a contemporary cohort of patients with hypertension. We conducted a cross-sectional analysis of baseline data from the Systolic Blood Pressure Intervention Trial (SPRINT), a randomized clinical trial that enrolled persons with hypertension and other cardiovascular risk factors

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between November 2010 and March 2013.[11] We hypothesized that a minority of the overall cohort would have evidence of thiazide prescription, and that older patients and patients with chronic kidney disease (CKD) would have lower prevalence of prescription than other subgroups.

Methods

Study Participants

SPRINT is a multicenter clinical trial sponsored by the National Institutes of Health comparing 2 strategies for control of systolic blood pressure (SBP) and effects on cardiovascular, brain, and renal outcomes.[11,12] Briefly, between November 2010 and March 2013, participants with a history of hypertension (treated or untreated SBP≥130 mm Hg) and aged >75 years or ≥50 years with at least one of the following cardiovascular risk factors were enrolled: history of cardiovascular disease, Framingham risk score for 10-year cardiovascular disease event ≥15%, or CKD, defined as an estimated glomerular filtration rate (eGFR) of 20 to 59 mL/min per 1.73 m2 using the 4-variable modification of diet in renal disease equation.[13] Participants with a history of stroke, diabetes mellitus, polycystic kidney disease, dementia, nonadherence, eGFR <20 mL/min per 1.73 m2, or ≥1 g of proteinuria/d (or the equivalent) were not eligible for participation. Participants were randomly assigned to a standard SBP target (<140 mm Hg) or to a lower SBP target (<120 mm Hg).

For this analysis, we restricted the cohort to participants prescribed at least 1 antihypertensive medication at baseline, before any changes in medications by the SPRINT investigators. All participants provided written informed consent for participation in the trial. The trial was approved by the Institutional Review Board at each site, and it is registered with ClinicalTrials.gov (NCT01206062).

Baseline Characteristics and Antihypertensive Medications

Trained study personnel ascertained information about participant baseline characteristics during the screening or randomization visit. Fasting blood and urine samples were collected at that time. All antihypertensive medications prescribed before the time of the screening visit (ie, baseline antihypertensive medications) were documented and classified into the following categories: thiazides (eg, hydrochlorothiazide, chlorthalidone, and metolazone), ACEIs, angiotensin II receptor blockers, β-blockers, calcium channel blockers, loop diuretics, mineralocorticoid receptor antagonists, direct renin inhibitors, α-blockers, centrally acting agents, and direct vasodilators.

Statistical Analysis

Our main outcome variable was evidence of baseline thiazide prescription. We examined thiazide prescription by subgroups based on sociodemographic variables, history of cardiovascular conditions, and kidney function, and plotted the unadjusted results. We used log-binomial regression to calculate prevalence ratios (95% confidence intervals) for thiazide prescription versus no thiazide prescription, and included the following variables in the model: age, sex, race, insurance status, cardiovascular comorbid conditions, eGFR, and presence of albuminuria (defined as a spot albumin/creatinine ratio ≥30 mg/g). For common outcomes, prevalence ratios are a more consistent approximation of relative risks than odds ratios derived from logistic regression.[14] We defined statistical significance based on 2-sided *P* values <0.05. All analyses were conducted using SAS 9.4 (Cary, NC).

Results

Of the 9361 participants enrolled in SPRINT, 8426 (90% of total cohort) were taking at least 1 antihypertensive medication at baseline; 7582 had complete data needed for this analysis (90% of treated participants), forming the present cohort.

Table. Baseline Characteristics of Systolic Blood Pressure Intervention Trial (SPRINT) Participants Prescribed At Least 1 Antihypertensive Medication

Variable	Overall, n=7582	Thiazide, n=3275	No Thiazide, n=4307
Age, y, mean (SD)	68.2 (9.4)	67.3 (9.2)	68.8 (9.5)
Age categories, y			
50–59	20.2	22.4	18.5
60–69	36.2	37.9	34.9
70–79	30.7	29.1	31.9
80+	12.8	10.6	14.6
Female sex	36.7	40.2	34.0
Race/Ethnicity			
White	57.0	53.5	59.7
Black	30.2	36.3	25.5
Hispanic	11.1	8.9	12.8
Other	1.8	1.3	2.1
Insurance status			
Private	42.2	42.1	42.3
Medicare	26.3	24.7	27.5
Medicaid	7.0	6.2	7.7
Veterans affairs	14.6	15.0	14.4
None	9.8	12.0	8.1
No insurance for drugs	19.3	21.4	17.8
History of cardiovascular disease			
Coronary artery disease	13.9	9.5	17.3
Myocardial infarction	8.5	5.6	10.7
Heart failure	3.7	2.3	4.8
Atrial fibrillation	8.4	5.9	10.3
Arrhythmia	17.6	14.8	19.7
Body mass index, kg/m², mean (SD)	30 (5.8)	30.5 (5.8)	29.6 (5.8)
Systolic blood pressure, mm Hg, mean (SD)	139.1 (15.5)	137.8 (15.2)	140.2 (15.8)
Diastolic blood pressure, mm Hg, mean (SD)	77.5 (11.8)	77.7 (11.6)	77.3 (12)
Heart rate, bpm, mean (SD)	66.0 (12)	66.7 (11.5)	65.3 (11.5)
Baseline laboratory values			
Estimated glomerular filtration rate category (mL/min per 1.73 m2)			
≥60	69.7	71.9	68.1
45–59	19.8	19.9	19.8
30–44	8.6	7.4	9.4
20–30	1.9	0.8	2.7
Albuminuria mg/g			
<30	80.1	83.8	77.3
30–300	16.9	14.2	19.0
>300	3.0	2.0	3.7

All values are % unless otherwise noted.

The 43% of participants prescribed a thiazide at baseline were generally younger, with a larger proportion of women, nonwhite race and uninsured status. They also had a lower prevalence of cardiovascular disease than participants not prescribed a thiazide at baseline (Table).

Large proportions of the cohort were prescribed ACEIs or angiotensin II receptor blockers (65%), β-blockers (40%) or dihydropyridine calcium channel blockers (33%) at baseline (Table S1 in the online-only Data Supplement). For the 2436 participants (32% of the cohort) prescribed a single antihypertensive agent at baseline, only 16% received a thiazide, whereas 43% received either an ACEI or an angiotensin II receptor blocker (Figure 1A). Of the 2967 participants prescribed 2 antihypertensive medications at baseline, fewer than half received a thiazide (Figure 1B). Of the 2179 participants prescribed ≥3 antihypertensive medications at baseline, 62% received a thiazide.

In unadjusted analyses, we saw a stepwise difference in the prevalence of thiazide prescription with older age, from 48% in participants aged 50 to 59 years down to 36% in participants aged ≥80 years (Figure S1). In multivariable-adjusted models, there was a 14% (confidence intervals, 5%–23%) lower adjusted prevalence of thiazide prescription among participants aged ≥80 years compared with participants aged 50 to 59 years (Figure 2). Women were more likely than men to have thiazides prescribed, and thiazide prescription also varied by race/ethnicity, with blacks having the highest and Hispanics the lowest prevalence of thiazide prescription (Figure S1; Figure 2). Although participants who lacked health insurance or drug benefits had higher unadjusted prevalence of thiazide prescription, the results were not statistically different after adjusting for other baseline variables (Figure S1; Figure 2).

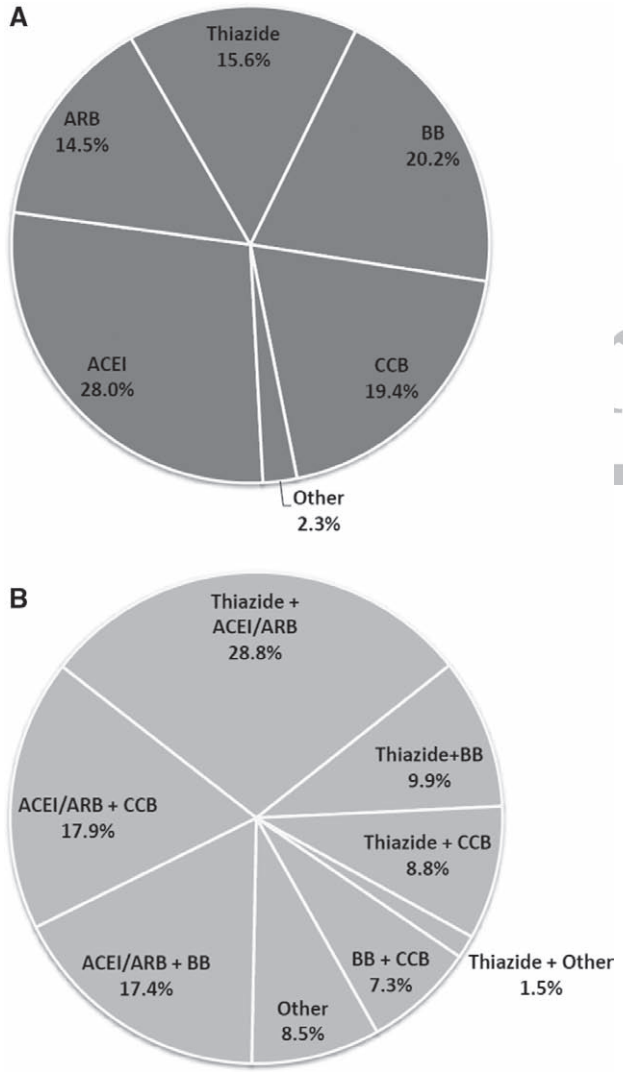

Figure 1. Distribution of antihypertensive medication class prescription among Systolic Blood Pressure Intervention Trial (SPRINT) participants prescribed (**A**) a single agent at baseline (n=2436); and (**B**) 2 agents at baseline (n=2967). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; and CCB, calcium channel blocker.

Participants with a history of coronary disease, myocardial infarction, heart failure, atrial fibrillation, or cardiac arrhythmias were less likely to have thiazides prescribed at baseline than participants without these comorbid conditions in unadjusted and adjusted models (Figure S2; Figure 2). We saw a stepwise difference in the prevalence of thiazide prescription in participants with lower eGFR, from 45% in participants with preserved eGFR to 19% in participants with an eGFR<30 mL/min per 1.73 m2 (Figure S2). In adjusted models, there was a 51% (confidence intervals, 31%–65%) lower prevalence of thiazide prescription for participants with an eGFR<30 mL/min per 1.73 m2 compared with participants with an eGFR≥60 mL/min per 1.73 m2 (Figure 2).

Discussion

We conducted a cross-sectional analysis of baseline data from SPRINT, a diverse cohort of persons with hypertension and other cardiovascular risk factors enrolled between November 2010 and March 2013. We found that 43% of the overall cohort was prescribed a thiazide at baseline, but that the prevalence of thiazide prescription was only 16% among participants treated with a single agent. Over half of patients prescribed 2 antihypertensive medications at baseline, and over one third of patients taking ≥3 agents did not receive a thiazide. Our results show that thiazide prescription continues to be suboptimal, and they are consistent with previous studies. For example, a study of managed care patients initiating antihypertensive medications in 2004 to 2005[8] showed that 37% of all patients had a regimen that included a thiazide, and only 21% of patients receiving a single drug used a thiazide. Similarly, only 18% of Medicare beneficiaries initiating antihypertensive medications in 2010 started treatment with a thiazide,[9] despite recommendations published as part of broadly endorsed clinical practice guidelines.[2]

In our study, thiazide prescription differed significantly by certain participant demographics, with participants in older age categories having a lower prevalence of thiazide prescription compared with the younger participants (50–59 years). The Hypertension in the Very Elderly Trial (HYVET),[15] which randomized patients ≥80 years of age to receive the thiazide-type diuretic indapamide (with or without an ACEI) or placebo, showed fewer adverse events in the active treatment group. However, fears about higher risks of adverse events associated with thiazides may persist in a nontrial, clinical setting. In an observational analysis of older veterans,[16] initiation with a thiazide was associated with a 2- to 3-fold higher risk of an adverse event, such as hypokalemia, hyponatremia, or acute kidney injury, compared with propensity score–matched

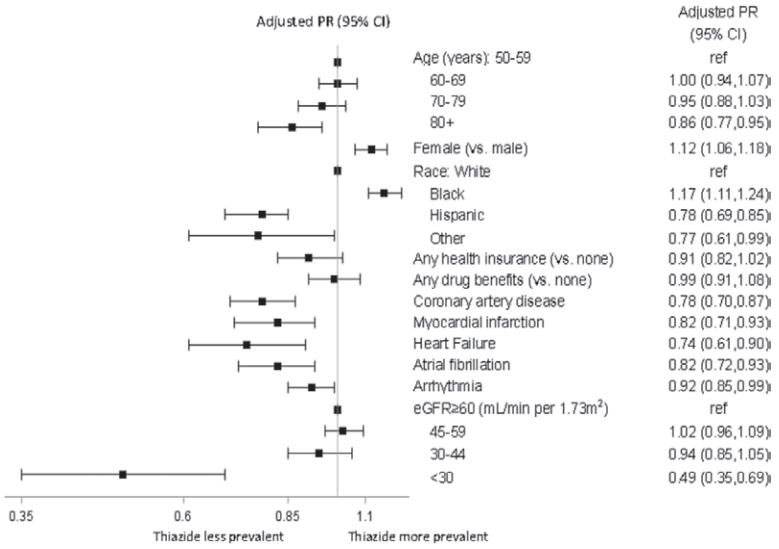

Figure 2. Adjusted prevalence ratios (PRs) and 95% confidence intervals (CI) of thiazide prescription in Systolic Blood Pressure Intervention Trial (SPRINT) participants receiving at least 1 antihypertensive medication at baseline. eGFR indicates estimated glomerular filtration rate.

nonusers (P<0.001). However, caveats of that study included its atypical patient population (hypertension treated for at least 9 months with second-line agents only), and other methodological issues.[17]

We also found that women had a 12% higher adjusted prevalence of thiazide prescription compared with men, a phenomenon observed in several other studies[10,18–20] despite the lack of evidence to indicate differences in thiazide effectiveness by sex.[21,22] Potential explanations for the difference may relate to concerns of adverse effects of thiazides on sexual function and metabolic syndrome in men. In women, thiazides may be used preferentially to treat more frequent complaints of edema. There may also be heightened concerns for osteoporosis in women, and thiazides inhibit calcium excretion, preserve bone mineral density and may lower the risk of hip fracture.[23]

Racial and ethnic differences in thiazide prescription were observed in our study: blacks were 17% more likely, but Hispanics were 22% less likely than non-Hispanic whites to receive thiazides, consistent with previous studies.[8,12] Current guidelines recommend preferential prescription of thiazides (or calcium channel blockers) in blacks, based in part on results from ALLHAT, which, in a prespecified subgroup analysis, showed a larger SBP reduction and improved cardiovascular outcomes with chlorthalidone versus lisinopril[24] (even in those with the metabolic syndrome[25]). Reasons for the lower prevalence of thiazide prescription in Hispanics are unclear, as Hispanic ALLHAT participants had better blood pressure control than non-Hispanics prescribed chlorthalidone.[26]

Participants in the lowest eGFR category had an adjusted 51% lower prevalence of thiazide prescription compared with participants without CKD. The guidelines from the National Kidney Foundation, published in 2002, recommend changing from a thiazide to a loop diuretic when the estimated GFR falls <30 mL/min per 1.73 m2 (with the exception of the thiazide metolazone),[27] citing lower effectiveness of thiazides with impaired kidney function. However, recent studies provide evidence to the contrary. A study of 60 patients with CKD (mean eGFR, 38 mL/min per 1.73 m2) versus 60 non-CKD controls (mean eGFR, 76 mL/min per 1.73 m2) showed a similar decrease of ≈20 mm Hg in SBP in both groups after 8 weeks of taking chlorthalidone in addition to other nondiuretic antihypertensive medications.[28] A pilot study of 14 participants with CKD (eGFR, 20–45 mL/min per 1.73 m2) and poorly controlled hypertension showed that home SBP fell by 10, 13, and 9 mm Hg after 4, 8, and 12 weeks and 24-hour SBP was reduced by 10.5 mm Hg after 12 weeks of treatment with chlorthalidone added to other antihypertensive medications.[29] Interestingly, albuminuria was also reduced by 40% in that study. Larger, controlled studies are needed to confirm these findings, but they challenge the conventional wisdom that thiazides are not effective in advanced CKD. Clinical practice guidelines may need updating to incorporate newer evidence.

Although our analysis has several strengths, such as its large sample size, diverse participant population including a significant proportion of participants >75 years of age or with CKD, there are also several limitations that should be considered. First, we did not have information on medication prescriptions before enrollment in SPRINT. Thus, we are unable to determine whether some participants may have previously been initiated on a thiazide but then discontinued the drug because of adverse side effects, allergies, or other intolerances. Second, we relied on participant reporting to collect information about baseline medication prescriptions, and did not have more objective information (ie, pharmacy fill data and electronic health records) to verify the participants' reports. We also could not determine whether lack of baseline thiazide prescription was because of indications for other drugs, physician preference, or participant nonadherence. Finally, results from persons recruited into a randomized clinical trial such as SPRINT may not be fully generalizable to the overall population of persons with hypertension. However, a recent study using data from the National Health and Nutrition Examination Survey found that a substantial proportion of US adults would meet SPRINT eligibility criteria.[30]

Perspectives

In a contemporary, diverse cohort with hypertension and other cardiovascular risk factors, we show that thiazides prescription remains suboptimal. Thiazides are prescribed less often than

other classes of antihypertensive medications among participants on monotherapy, and thiazides were not prescribed for over half of patients on 2 antihypertensive medications and for over one third of patients on ≥3 antihypertensive medications at baseline. Moreover, thiazide prescription varied significantly by demographics and CKD status, despite limited evidence about differences in effectiveness in any particular subgroup. At the time of SPRINT enrollment (2010–2013), JNC 7 and most other guidelines recommended thiazides as at least one of the first-line agents,[2] suggesting that contemporary prescribing practices are not consistent with US hypertension guidelines. Our results suggest the need for focused interventions so that clinical practice patterns more closely reflect practice guidelines, which may improve global clinical outcomes.

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Disclosures

Dr Cushman reports serving as an uncompensated consultant to Takeda Pharmaceuticals. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- We report on patterns and correlates of thiazides and thiazide-type prescriptions in a large, contemporary cohort of participants enrolled between November 2010 and March 2013 in the Systolic Blood Pressure Intervention Trial (SPRINT), a multicenter trial of 2 different blood pressure targets in the United States.

What Is Relevant?

- Among participants receiving 1, 2, or 3+ blood pressure medication, 16%, 49%, and 62% were prescribed a thiazide, respectively.
- Certain demographic subgroups, such as older participants, men, and nonblacks, were less likely to have a thiazide prescription, even though there is little evidence that other antihypertensive classes are as or more effective in reducing cardiovascular events than thiazides in any given population.
- Participants with more advanced kidney disease had lower prevalence of thiazide prescription, but recent studies suggest thiazides may still work well in this subgroup.

Summary

In the 7582 SPRINT participants included in our analysis, thiazide prescription remained suboptimal at baseline. Thiazide prescription varied significantly by demographics and kidney disease status, despite limited evidence about differences in effectiveness in any particular subgroup. Our results suggest the need for focused interventions so that clinical practice patterns more closely reflect guidelines, which may improve global clinical outcomes.