Annals of Internal Medicine | ORIGINAL RESEARCH

Chlorthalidone Versus Hydrochlorothiazide for the Treatment of Hypertension in Older Adults

A Population-Based Cohort Study

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Background: Some evidence suggests that chlorthalidone may be superior to hydrochlorothiazide for the treatment of hypertension.

Objective: To compare the effectiveness and safety of chlorthalidone and hydrochlorothiazide in older adults.

Design: Propensity score–matched observational cohort study with up to 5 years of follow-up.

Setting: Ontario, Canada.

Patients: All individuals aged 66 years or older who were newly treated with chlorthalidone or hydrochlorothiazide and were not hospitalized for heart failure, stroke, or myocardial infarction in the prior year were eligible for inclusion. Each chlorthalidone recipient was matched to up to 2 hydrochlorothiazide recipients on the basis of age, sex, year of treatment initiation, and propensity score.

Measurements: The primary outcome was a composite of death or hospitalization for heart failure, stroke, or myocardial infarction. Safety outcomes included hospitalization with hypokalemia or hyponatremia.

Results: A total of 29 873 patients were studied. During follow-up, chlorthalidone recipients (n = 10 384) experienced the primary outcome at a rate of 3.2 events per 100 person-years of follow-up, and hydrochlorothiazide recipients experienced 3.4 events per 100 person-years of follow-up (adjusted hazard ratio, 0.93 [95% CI, 0.81 to 1.06]). Patients treated with chlorthalidone were more likely to be hospitalized with hypokalemia (adjusted hazard ratio, 3.06 [CI, 2.04 to 4.58]) or hyponatremia (adjusted hazard ratio, 1.68 [CI, 1.24 to 2.28]). In 9 post hoc analyses comparing patients initially prescribed 12.5, 25, or 50 mg of chlorthalidone per day with those prescribed 12.5, 25, or 50 mg of hydrochlorothiazide per day, the former were more likely to be hospitalized with hypokalemia for all 6 comparisons in which a statistically significant association was found. The results of other effectiveness and safety outcomes were also consistent with those of the main analysis.

Limitation: Unmeasured differences in baseline characteristics or physician treatment approaches or an insufficiently large sample may have limited the ability to detect small differences in the comparative effectiveness of the drugs.

Conclusion: As typically prescribed, chlorthalidone in older adults was not associated with fewer adverse cardiovascular events or deaths than hydrochlorothiazide. However, it was associated with a greater incidence of electrolyte abnormalities, particularly hypokalemia.

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Hypertension affects approximately 1 of every 3 adults in the United States (1) and is responsible for more than 1 of every 8 premature deaths worldwide (2). The pharmacologic treatment of hypertension, one of the great successes of modern medicine, substantially reduces the risk for stroke, myocardial infarction, heart failure, and death.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure strongly recommends thiazide diuretics and other inhibitors of the Na^+-Cl^- cotransporter in the distal nephron as first-line treatment of hypertension but does not distinguish among available agents (3). Although hydrochlorothiazide is by far the most commonly prescribed diuretic in North America (4), limited evidence suggests that chlorthalidone may be superior (5–7). As a result, some experts have argued that clinicians should favor it over hydrochlorothiazide (8–13), whereas others have argued that the drugs are largely interchangeable (14). One network meta-analysis that indirectly compared chlorthalidone with other diuretics supports the latter view (15), but a more recently published network meta-analysis supports the view that chlorthalidone may be superior to hydrochlorothiazide (16).

Given the widespread use of chlorthalidone and hydrochlorothiazide for the treatment of hypertension; the discrepancy between prescribing patterns and expert opinion; and the absence of a large randomized, controlled trial comparing the 2 drugs, we conducted a large population-based cohort study comparing the relative safety and effectiveness of these drugs in clinical practice.

Methods

Setting

We conducted a retrospective population-based cohort study of residents of Ontario, Canada, aged 66 years or older, who initiated chlorthalidone or hydrochlorothiazide therapy between 1 January 1993 and 31 March 2010. Ontario is a large, ethnically diverse province with a population of more than 13 million persons, all of whom have

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Web-Only
Supplement

Context

There is conflicting evidence about whether clinicians should treat uncomplicated hypertension with hydrochlorothiazide or chlorthalidone.

Contribution

This study of elderly patients found little difference in a composite outcome that included death and hospitalization with heart failure, stroke, or myocardial infarction, but patients treated with hydrochlorothiazide had fewer hospitalizations for hypokalemia or hyponatremia than those treated with chlorthalidone.

Caution

The results could not be adjusted for unmeasured differences in baseline clinical characteristics.

Implication

Hydrochlorothiazide may be superior to chlorthalidone for treating uncomplicated hypertension because it is associated with less hypokalemia and hyponatremia, at least in commonly prescribed doses.

—The Editors

coverage for physician and hospital services. Those older than 65 years also receive public insurance for prescription drugs. This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Data Sources

We used the following linked health care databases to complete this study: the Ontario Drug Benefit database (records of prescription medications dispensed to Ontarians aged 65 years or older), the Registered Persons Database (demographic information, including date of death, for all Ontario residents), the Canadian Institute for Health Information Discharge Abstract Database (data from all hospitalizations), the National Ambulatory Care Reporting System (data from all emergency department visits), the Institute for Clinical Evaluative Sciences Physicians Database (demographic and specialty data for all physicians practicing in Ontario), and the Ontario Health Insurance Plan database (data from all inpatient and outpatient physician services). These databases were anonymously linked using encrypted identifiers, have been shown to be complete and of high quality (17), and are routinely used to study the safety and effectiveness of prescription drugs (18–20).

Cohort Design and Propensity-Based Matching

We constructed a cohort of patients newly treated with chlorthalidone or hydrochlorothiazide as evidenced by no prescription for either drug in the 365 days before the index date, which was defined as the date of first prescription between 1 January 1993 and 1 March 2010. We excluded patients in the first year of eligibility for prescription drug coverage (age 65 years) to avoid incomplete medication records. To restrict the analysis to patients newly prescribed a diuretic for hypertension, we also excluded those who had received a thiazide other than chlorthalidone or hydrochlorothiazide in the 365 days before the index date. To mimic the clinical decision physicians face in treating uncomplicated hypertension, we excluded individuals who had been hospitalized for myocardial infarction, stroke, or heart failure in the previous year. Other exclusion criteria are listed in the **Appendix Figure** (available at www.annals.org). For both drugs, we defined "continuous use" as the receipt of a prescription at least every 180 days. Patients were censored if they switched study medications, discontinued treatment (in which case they were followed for 100 days from their last prescription to identify events that may have precipitated discontinuation), commenced treatment with a different thiazide, or reached the end of the study (31 March 2010). We followed patients for a maximum of 5 years.

Because patients treated with chlorthalidone may differ from those treated with hydrochlorothiazide, we used high-dimensional propensity score matching to compare patients with similar observed characteristics (21, 22). Each chlorthalidone recipient was matched with up to 2 hydrochlorothiazide recipients on the basis of age at index date (within 1 year), sex, calendar year of treatment initiation, receipt of a nonthiazide antihypertensive drug in the year before the index date, and propensity score (within 0.2 SD). When only 1 suitable match could be found, we retained the pair for analysis, but we did not include chlorthalidone recipients for whom no hydrochlorothiazide match could be found. Further details about the propensity score and matching methods are provided in the **Appendix** (available at www.annals.org).

Our primary objective was to study the comparative effectiveness of hydrochlorothiazide and chlorthalidone as they are used in clinical practice. After reviewing our initial data, however, we also performed 9 post hoc analyses comparing patients initially prescribed 12.5, 25, or 50 mg of chlorthalidone per day with those initially prescribed 12.5, 25, or 50 mg of hydrochlorothiazide per day to explore the relationship between initial dose and outcome in greater detail (14).

Outcomes

Our primary outcome was a composite of death or hospitalization with acute myocardial infarction, heart failure, or ischemic stroke, all of which are consequences of inadequately treated hypertension. Each individual component of this outcome was examined as a secondary outcome. We also examined hospitalization with hypokalemia or hyponatremia and all-cause hospitalization as safety outcomes.

Statistical Analysis

We used standardized differences to compare baseline characteristics between the groups; differences less than 0.1 generally indicate good balance. To account for incomplete

matching, we weighted all percentages calculated for hydrochlorothiazide recipients by the matching success rate and calculated standardized differences using these weighted proportions. We used Cox proportional hazards regression (PROC PHREG in SAS, version 9.2 [SAS Institute, Cary, North Carolina]) to compare outcomes of patients treated with chlorthalidone and those treated with hydrochlorothiazide. All models were stratified on the matched pairs and adjusted for any unbalanced baseline characteristics (standardized difference >0.1). We examined log–log survival curves to test the proportional hazards assumption and used the Breslow method to address ties. We also produced unadjusted Kaplan–Meier curves with 95% CIs to display the cumulative incidence of the primary outcome and the hypokalemia and hyponatremia safety outcomes. We conducted prespecified secondary analyses in several subgroups: patients older than the median age, women, patients with diabetes mellitus, and those who had not received antihypertensive medications in the previous year.

We also conducted a sensitivity analysis to account for clustering within physician practices by using a Cox proportional hazards model with a γ frailty distribution (coxph command with a frailty function using the survival package in R, version 2.12.2 [R Foundation for Statistical Computing, Vienna, Austria]), in which the association between failure times was modeled with a random-effect term (23, 24). All frailty models were also stratified on the matched pairs in our data.

All analyses were performed using SAS, version 9.2, except for the frailty models, which were run using R, version 2.12.2.

Role of the Funding Source

This study was funded by a grant from the Ontario Ministry of Health and Long-Term Care. The funding source had no involvement in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Cohort Creation and Follow-up

We identified 1 123 418 patients who began receiving chlorthalidone or hydrochlorothiazide between 1 January 1993 and 1 March 2010. After exclusion criteria and matching were applied, the final cohort contained 10 384 patients newly treated with chlorthalidone and 19 489 patients newly treated with hydrochlorothiazide (**Appendix Figure**). Median follow-up was 255 days (interquartile range, 100 to 873 days) in the chlorthalidone group and 398 days (interquartile range, 123 to 1307 days) in the hydrochlorothiazide group. The reasons patients ceased to be followed are described in **Table 1** of the **Supplement** (available at www.annals.org).

Baseline Characteristics

Before propensity score matching, chlorthalidone recipients were younger, had fewer hospitalizations in the 3 years before the index date, were less likely to live in a rural area, were more likely to be prescribed a β-blocker, and were less likely to be prescribed an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (**Table 2** of the **Supplement**). All of these factors, except for concomitant medication use, were equally distributed after propensity score matching (**Table 1**). In the matched cohort, the mean doses used to initiate treatment were 27.3 mg for chlorthalidone and 18.3 mg for hydrochlorothiazide. The percentages of patients in the matched cohort initially prescribed 12.5, 25, and 50 mg of chlorthalidone per day were 11%, 70%, and 10%, respectively, and the percentages of those initially prescribed the same doses of hydrochlorothiazide per day were 67%, 24%, and 5%, respectively. Of note, we were able to estimate starting doses of drugs only from 1 January 1997 onward because of the availability of richer information about prescription duration from that date.

Effectiveness Outcomes

The primary outcome, a composite of death or hospitalization with myocardial infarction, heart failure, or stroke, occurred in 510 chlorthalidone recipients (3.2 events per 100 person-years of follow-up) and 1265 hydrochlorothiazide recipients (3.4 events per 100 person-years of follow-up). After adjusting for baseline differences, we did not find that patients treated with chlorthalidone were at significantly lower risk for the primary outcome (adjusted hazard ratio, 0.93 [95% CI, 0.81 to 1.06]) (**Table 2**). The cumulative incidence of the primary outcome for the first 3 years of follow-up is presented in the top panel of the **Figure**. In addition, there were no statistically significant differences in any of the secondary efficacy outcomes (**Table 2**). The adjusted hazard ratio for the primary outcome in each of the prespecified subgroups was similar to that of the entire cohort (**Table 3**).

Safety Outcomes

Hospitalization with an admission diagnosis of an electrolyte abnormality was more likely to occur in patients treated with chlorthalidone (**Table 2**). Patients with hypokalemia were hospitalized at a rate of 0.69 events per 100 person-years of follow-up in the chlorthalidone group compared with 0.27 events per 100 person-years of follow-up in the hydrochlorothiazide group (adjusted hazard ratio, 3.06 [CI, 2.04 to 4.58]). Patients with hyponatremia were hospitalized at a rate of 0.69 events per 100 person-years of follow-up in the chlorthalidone group compared with 0.49 events per 100 person-years of follow-up in the hydrochlorothiazide group (adjusted hazard ratio, 1.67 [CI, 1.24 to 2.28]). The cumulative incidence of both of these outcomes for the first 3 years of follow-up is presented in the middle and bottom panels of

Table 1. **Baseline Characteristics of Patients in the Propensity Score–Matched Cohort**

Characteristic	Chlorthalidone Group (n = 10 384)	Hydrochlorothiazide Group (n = 19 489)	Standardized Difference	P Value
Demographic variables				
Mean age (SD), *y*	73 (6.0)	73 (5.9)	0.00	0.83
Female, *n (%)*	6160 (59.3)	11 505 (59.0)	0.00	1.00
Rural location, *n (%)*	1045 (10.1)	2513 (12.9)	0.10	<0.001
Health service utilization variables				
Median different prescription drugs in prior year (IQR), *n*	5 (2–9)	5 (3–9)	0.03	0.002
Mean outpatient physician visits in prior year (SD), *n*	10.6 (8.4)	10.6 (8.2)	0.01	0.56
Mean hospitalizations in prior 3 y (SD), *n*	0.37 (0.87)	0.36 (0.84)	0.01	0.48
Visit to cardiologist in prior year, *n (%)*	1162 (11.2)	2305 (11.8)	0.01	0.40
Medications, *n (%)**				
Oral antihyperglycemic	1125 (10.8)	2391 (12.3)	0.05	<0.001
Insulin	297 (2.9)	538 (2.8)	0.01	0.52
Digoxin	352 (3.4)	681 (3.5)	0.01	0.40
Statin	2558 (24.6)	5106 (26.2)	0.02	0.145
β-Blocker	3914 (37.7)	4198 (21.5)	0.39	<0.001
Calcium-channel blocker	2516 (24.2)	4808 (24.7)	0.01	0.38
ACE inhibitor or ARB	3562 (34.3)	9013 (46.2)	0.25	<0.001
Other antihypertensive	6763 (65.1)	12 746 (65.4)	0.00	1.00
Loop diuretic	706 (6.8)	1343 (6.9)	0.01	0.43
Potassium-sparing diuretic	85 (0.8)	162 (0.8)	0.00	0.80
Clopidogrel	108 (1.0)	210 (1.1)	0.00	0.88
Acetylsalicylic acid	1542 (14.8)	3017 (15.5)	0.03	0.023
Comorbid conditions, *n (%)*†				
Previous cancer	1082 (10.4)	1911 (9.8)	0.03	0.030
Heart failure	41 (0.4)	64 (0.3)	0.01	0.53
Stroke	17 (0.2)	17 (0.1)	0.02	0.088
Myocardial infarction	42 (0.4)	76 (0.4)	0.00	1.00
Chronic liver disease	12 (0.1)	32 (0.2)	0.01	0.37
Chronic obstructive pulmonary disease	48 (0.5)	84 (0.4)	0.01	0.64
Chronic kidney disease	22 (0.2)	42 (0.2)	0.00	0.80

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; IQR = interquartile range.
* Medication use in the year before cohort entry.
† Comorbid conditions documented in the 2 y before cohort entry.

the **Figure**. There was no difference in the risk for all-cause hospitalization between the groups.

Clustering of Patients Within Physician Practices

The results of a sensitivity analysis done to account for the clustering of patients within physician practices were consistent with those of the main analysis (**Tables 3** and **4** of the **Supplement**).

Post Hoc Analyses to Explore Relationships Between Initial Dosing and Outcome

In a series of post hoc analyses, we constructed 9 cohorts to compare patients initially prescribed 12.5, 25, or 50 mg of chlorthalidone per day with those initially prescribed 12.5, 25, or 50 mg of hydrochlorothiazide per day. In these analyses, we included only patients who began receiving chlorthalidone or hydrochlorothiazide between 1 January 1997 and 1 March 2010 because we did not have dose data from before this period.

Outcome data for the primary effectiveness outcome and the hypokalemia and hyponatremia safety outcomes for all 9 comparisons are presented in **Table 4**. Of note, we found that, compared with hydrochlorothiazide, chlorthalidone was consistently associated with an increased risk for hypokalemia. Other results from these post hoc analyses were also consistent with our main findings. Baseline characteristics for these cohorts, after application of exclusion criteria and matching, are presented in **Tables 5** to **13** of the **Supplement**. Detailed outcome data are presented in **Tables 14** to **22** of the **Supplement**.

Discussion

In this large population-based cohort study of older adults, we found no difference between chlorthalidone and hydrochlorothiazide, as typically prescribed, with respect to stroke, myocardial infarction, heart failure, or death. However, we did find that patients treated with chlorthalidone were approximately 3 times more likely to be hospitalized with hypokalemia and approximately 1.7 times more likely to be hospitalized with hyponatremia than those prescribed hydrochlorothiazide.

In 9 post hoc analyses comparing patients initially prescribed 12.5, 25, and 50 mg of chlorthalidone per day with patients initially prescribed 12.5, 25, and 50 mg of hydro-

chlorothiazide per day, we found that chlorthalidone was associated with an increased risk for hypokalemia for all 6 comparisons in which a statistically significant association was found. We found no convincing evidence in any of the 9 analyses that chlorthalidone was superior in preventing the clinical sequelae of hypertension.

Dorsch and colleagues (5) recently reported data from a post hoc comparison of patients treated with hydrochlorothiazide or chlorthalidone in MRFIT (Multiple Risk Factor Intervention Trial). In this trial, which began in 1973, men between the ages of 35 and 57 years who were at high risk for heart disease were randomly assigned to receive a "special intervention," including stepped treatment of hypertension, or usual care. The first medication used to treat hypertension in the special intervention group was chlorthalidone or hydrochlorothiazide. In 1980, after a review of preliminary data suggested that mortality was higher among hydrochlorothiazide-treated men and lower among chlorthalidone-treated men relative to usual care, the MRFIT steering committee decided that all patients in the special intervention group requiring antihypertensive treatment should receive chlorthalidone. In their secondary analysis of this trial, Dorsch and colleagues found that patients treated with chlorthalidone were less likely to have a cardiovascular event than those treated with hydrochlorothiazide (adjusted hazard ratio, 0.79 [CI, 0.68 to 0.92]). They did not report rates of hospitalization for hypokalemia or hyponatremia. The association between chlorthalidone treatment and fewer cardiovascular events detected in this retrospective analysis should be viewed cautiously, primarily because of the important differences between the patient groups. Most notably, those treated with chlorthalidone received higher doses and were almost twice as likely to have received the special intervention (84% vs. 45%). In the subgroup of patients who received this intervention, the difference in cardiovascular events between those treated with chlorthalidone and those treated with hydrochlorothiazide was not statistically significant.

Two studies that compared chlorthalidone and hydrochlorothiazide indirectly using network meta-analytic techniques had conflicting results. Psaty and colleagues (15) included 3 clinical trials that used chlorthalidone and 3 that used other low-dose diuretics. They examined cardiovascular disease and mortality end points and concluded that major health outcomes for chlorthalidone and other thiazide-like drugs are likely to be similar. In contrast, Roush and colleagues (16) included 6 clinical trials that used chlorthalidone and 3 that used hydrochlorothiazide and concluded that chlorthalidone is likely to be superior to hydrochlorothiazide. One possible reason these studies reached different conclusions is the inclusion of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (25) and the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) trial (26) in the more recently completed network meta-analysis. Of note, neither study reported the incidence of hyponatremia or hypokalemia.

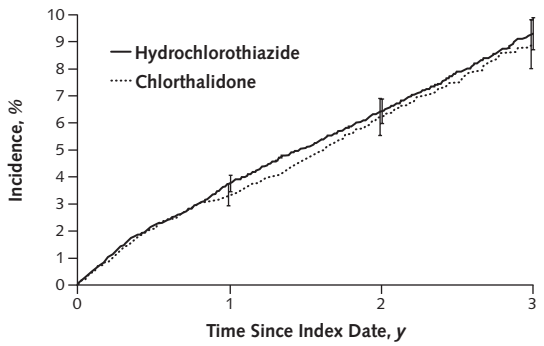
Lund and Ernst (7) also did not specifically report the incidence of hyponatremia or hypokalemia in their recent cohort study comparing chlorthalidone with hydrochlorothiazide, but they did note that patients treated with chlorthalidone were more likely to discontinue treatment (adjusted odds ratio, 1.49 [CI, 1.37 to 1.62]) than those treated with hydrochlorothiazide. Although there are many reasons why patients treated with chlorthalidone may be less likely to continue treatment, 1 possible reason is that chlorthalidone is more likely to cause electrolyte abnormal-

Table 2. **Effectiveness and Safety Outcomes Among Patients Treated With Chlorthalidone or Hydrochlorothiazide**

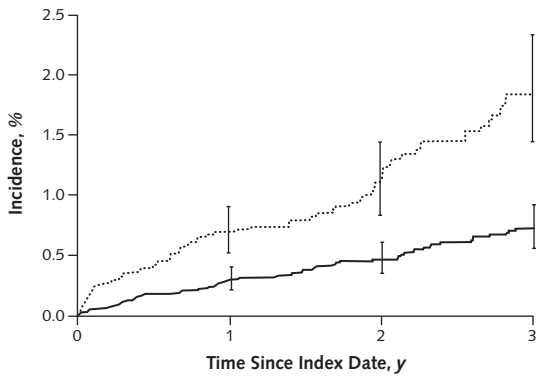
Outcome	Chlorthalidone Group (n = 10 384)		Hydrochlorothiazide Group (n = 19 489)		Unadjusted Hazard Ratio (95% CI)*	Adjusted Hazard Ratio (95% CI)†
	Patients, *n*	Events per 100 Person-Years, *n*	Patients, *n*	Events per 100 Person-Years, *n*		
Primary efficacy outcome‡	510	3.2	1265	3.4	0.94 (0.82–1.07)	0.93 (0.81–1.06)
Secondary efficacy outcomes						
Acute myocardial infarction	97	0.61	310	0.82	0.86 (0.65–1.15)	0.86 (0.65–1.16)
Heart failure	131	0.82	360	0.95	0.90 (0.70–1.15)	0.91 (0.71–1.18)
Stroke	73	0.46	174	0.46	0.85 (0.60–1.21)	0.79 (0.54–1.14)
Death	300	1.88	686	1.80	1.01 (0.85–1.21)	1.00 (0.83–1.20)
Safety outcomes						
Hypokalemia§	109	0.69	102	0.27	3.20 (2.21–4.63)	3.06 (2.04–4.58)
Hyponatremia§	109	0.69	184	0.49	1.67 (1.25–2.23)	1.68 (1.24–2.28)
All-cause hospitalization	1953	13.9	4475	13.8	1.02 (0.95–1.09)	1.00 (0.93–1.07)

* Patients treated with hydrochlorothiazide are the reference. The hazard ratio compares the risk among patients currently receiving chlorthalidone with that among patients currently receiving hydrochlorothiazide.
† Adjusted for differences in baseline use of β-blockers and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.
‡ A composite of death or hospitalization with acute myocardial infarction, heart failure, or ischemic stroke.
§ Hospitalization with hypokalemia or hyponatremia listed as an admission diagnosis.

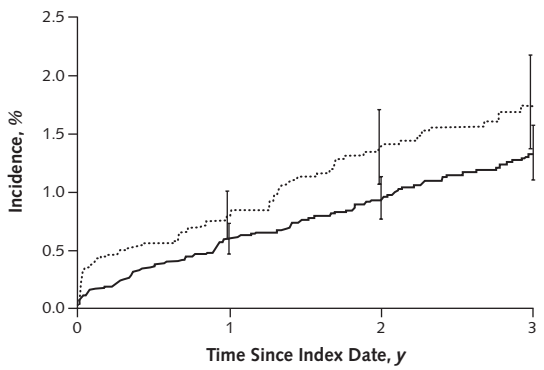
Figure. **Observed incidence of the primary outcome (*top*), hospitalization with hypokalemia (*middle*), and hospitalization with hyponatremia (*bottom*).**



Drug	Patients at Risk, *n*		
	End of Year 1	End of Year 2	End of Year 3
Chlorthalidone	4385	2940	2062
Hydrochlorothiazide	10 032	7361	5568



Drug	Patients at Risk, *n*		
	End of Year 1	End of Year 2	End of Year 3
Chlorthalidone	4406	2953	2078
Hydrochlorothiazide	10 115	7446	5641



Drug	Patients at Risk, *n*		
	End of Year 1	End of Year 2	End of Year 3
Chlorthalidone	4401	2957	2080
Hydrochlorothiazide	10 105	7440	5639

The error bars represent 95% CIs.

ities. This drug is a more potent and longer-lasting antihypertensive medication than hydrochlorothiazide at the most frequently prescribed doses, but it also reduces serum potassium level to a greater extent (27, 28). In their meta-analysis, for example, Peterzan and colleagues (28) estimated that the dose of chlorthalidone predicted to reduce serum potassium level by 0.4 mmol/L was 11.9 mg/d; in contrast, the dose of hydrochlorothiazide predicted to have the same effect was 40.5 mg/d. Despite the relative potency of both drugs, we and others have found that chlorthalidone is typically used at higher doses than hydrochlorothiazide (7). This is likely to partially explain why chlorthalidone is associated with a higher risk for electrolyte abnormalities in studies, like ours, that are based in a real-world practice setting.

However, in a series of exploratory post hoc analyses, we also found that treatment with chlorthalidone was associated with an increased risk for hospitalization with hypokalemia compared with hydrochlorothiazide across a wide range of initial doses. These findings support the notion that the drugs have different methods of action (10). Also, the shorter half-life of hydrochlorothiazide may be a disadvantage with respect to continuous blood pressure control but an advantage with respect to electrolyte balance. Furthermore, the effect of chlorthalidone on sodium and potassium concentrations may be exaggerated in elderly adults, which may also partially explain the difference in electrolyte abnormality–associated hospitalizations seen in our study.

Our study has several limitations. First, although the 2 groups in our main analysis were well-matched on most characteristics after propensity score matching, patients treated with chlorthalidone were more likely to also be treated with a β-blocker and less likely to also be treated with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, possibly because a chlorthalidone–atenolol combination is available in the public formulary in Ontario. It could be argued that, in our main analysis, we did not detect a benefit with chlorthalidone treatment because β-blockers may be less effective than other antihypertensive medications, particularly in elderly adults (29–32). To mitigate this possibility, we adjusted for the differences in concomitant medications in the Cox regression model. The unadjusted and adjusted hazard ratios were similar for all safety and efficacy outcomes, suggesting that the difference in concomitant medication use was not a significant factor. Second, despite our use of high-dimensional propensity score matching, the possibility remains that the 2 groups differed in unmeasured characteristics. Third, patients treated with chlorthalidone were more likely to be censored because they initiated treatment with a different thiazide or thiazide-like diuretic. It is difficult to predict the effect of this difference, which has been seen by others (7), on our observed findings. Fourth, although our study included more than 30 000 patients, we were unable to exclude a clinically important relative re-

Table 3. **Subgroup Analyses for Primary Outcome**

Characteristic	Chlorthalidone Group (n = 10 384)		Hydrochlorothiazide Group (n = 19 489)		Unadjusted Hazard Ratio (95% CI)*	Adjusted Hazard Ratio (95% CI)†
	Patients, *n* (%)	Events per 100 Person-Years, *n*	Patients, *n* (%)	Events per 100 Person-Years, *n*		
Age						
Older than median	4742 (46)	5.1	8907 (46)	5.1	0.99 (0.84–1.16)	0.98 (0.83–1.15)
Median or younger	5642 (54)	1.9	10 582 (54)	2.1	0.86 (0.69–1.08)	0.85 (0.68–1.06)
Sex						
Women	6160 (59)	2.8	11 505 (59)	3.0	1.01 (0.84–1.21)	1.01 (0.84–1.22)
Men	4224 (41)	3.8	7984 (41)	3.9	0.87 (0.72–1.06)	0.85 (0.70–1.04)
Diabetes						
Yes	1289 (12)	6.1	2691 (14)	5.2	0.97 (0.67–1.40)	0.95 (0.66–1.38)
No	9095 (88)	2.8	16 798 (86)	3.1	0.94 (0.81–1.09)	0.92 (0.78–1.07)
Received antihypertensive medications in previous year						
Yes	6763 (65)	3.4	12 746 (65)	3.6	0.93 (0.79–1.08)	0.91 (0.77–1.07)
No	3621 (35)	2.8	6743 (35)	2.9	0.98 (0.76–1.26)	0.98 (0.76–1.26)

* Patients treated with hydrochlorothiazide are the reference. The hazard ratio compares the risk among patients currently receiving chlorthalidone with that among patients currently receiving hydrochlorothiazide.
† Adjusted for differences in baseline use of β-blockers and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.

duction in the risk for death or hospitalization with myocardial infarction, heart failure, or stroke associated with chlorthalidone. Fifth, the administrative codes we used to identify electrolyte abnormalities are likely to be specific but insensitive (33). Although the true rates of clinically significant hyponatremia and hypokalemia in our study are unknown, we believe that they are probably greater than the rates we have reported. Of note, in a randomized trial of 24 patients treated with hydrochlorothiazide (up to 50 mg/d) or chlorthalidone (up to 25 mg/d), the incidence of hypokalemia (serum potassium level <3.5 mmol/L) was approximately 50% in both groups (6). Finally, our data did not allow us to examine physician characteristics associated with the choice of one drug over another. Although we conducted a sensitivity analysis to account for the clustering of patients within physician practices, unmeasured differences in physician-level characteristics or treatment approaches may have been an additional source of confounding in our study.

In the absence of convincing evidence for the superiority of either chlorthalidone or hydrochlorothiazide, we believe that clinicians who care for older adults should focus primarily on reaching patient-relevant blood pressure goals (34) while being mindful of the risk for electrolyte

Table 4. **Adjusted Hazard Ratios (95% CIs) for the Primary Efficacy Outcome, Hospitalization With Hypokalemia, and Hospitalization With Hyponatremia, at Various Initial Doses**

Chlorthalidone	Hydrochlorothiazide*			Comparison†
	12.5 mg/d	25 mg/d	50 mg/d	
12.5 mg/d	0.69 (0.40–1.22)	1.11 (0.54–2.27)	1.32 (0.24–7.26)	Primary efficacy outcome
25 mg/d	1.05 (0.86–1.29)	1.05 (0.83–1.33)	0.70 (0.50–0.97)	
50 mg/d	0.66 (0.38–1.17)	–‡	0.67 (0.39–1.16)	
12.5 mg/d	3.02 (0.74–12.4)	–‡	–‡	Hospitalization with hypokalemia
25 mg/d	3.41 (1.89–6.13)	2.15 (1.06–4.33)	2.99 (1.18–7.55)	
50 mg/d	9.29 (1.10–78.2)	6.72 (1.91–23.6)	5.46 (1.14–26.1)	
12.5 mg/d	2.36 (0.69–8.00)	1.01 (0.22–4.58)	–‡	Hospitalization with hyponatremia
25 mg/d	1.94 (1.24–3.02)	1.54 (0.96–2.47)	1.28 (0.64–2.57)	
50 mg/d	2.61 (0.67–10.2)	1.81 (0.75–4.37)	2.25 (0.70–7.18)	

* Patients treated with hydrochlorothiazide are the reference. The hazard ratio compares the risk among patients currently receiving chlorthalidone with that among patients currently receiving hydrochlorothiazide and was adjusted for baseline variables with a standardized difference >0.1.
† The number of patients included in each pairwise comparison was as follows: chlorthalidone, 12.5 mg/d vs. hydrochlorothiazide, 12.5 mg/d: n = 2055; chlorthalidone, 12.5 mg/d vs. hydrochlorothiazide, 25 mg/d: n = 1456; chlorthalidone, 12.5 mg/d vs. hydrochlorothiazide, 50 mg/d: n = 282; chlorthalidone, 25 mg/d vs. hydrochlorothiazide, 12.5 mg/d: n = 15 275; chlorthalidone, 25 mg/d vs. hydrochlorothiazide, 25 mg/d: n = 10 820; chlorthalidone, 25 mg/d vs. hydrochlorothiazide, 50 mg/d: n = 5101; chlorthalidone, 50 mg/d vs. hydrochlorothiazide, 12.5 mg/d: n = 2154; chlorthalidone, 50 mg/d vs. hydrochlorothiazide, 25 mg/d: n = 2160; chlorthalidone, 50 mg/d vs. hydrochlorothiazide, 50 mg/d: n = 1824.
‡ Proportional hazards assumption was violated, model failed to converge, or output was suppressed because of small number of outcomes.

abnormalities in patients treated with diuretics (35, 36). A large, well-designed, carefully conducted randomized trial would be necessary to definitively determine the comparative safety and effectiveness of hydrochlorothiazide and chlorthalidone. In the absence of such a trial, it may be reasonable to conclude that hydrochlorothiazide is safer than chlorthalidone in elderly patients at typically prescribed doses.

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Appendix: Details of the Propensity Score and Matching Methods

We used a high-dimensional propensity score method to control for confounding by baseline patient characteristics (21).

We specified the following 7 groups of covariates, or data dimensions, in the algorithm we used to calculate the propensity scores: prescription drug claims, physician services fee codes, physician services diagnosis codes, hospital diagnosis codes, hospital procedure codes, emergency department diagnosis codes, and emergency department procedure codes, all in the year before the index date. Within each dimension, empirical candidate covariates were identified by sorting codes in order of prevalence. We retained the 200 most prevalent codes in each dimension. For each identified code, we constructed 3 binary covariates using patient-level data. One represented whether the code appeared at least once for a given patient, the second represented whether the code appeared in a patient's records more frequently than the median frequency in the overall population, and the third represented whether the code appeared in a patient's records more frequently than the 75th percentile in the overall population.

All potential covariates were sorted in descending order by the magnitude of the log of the multiplicative bias term, as previously suggested (21). We kept only the top 500 covariates for inclusion in the propensity score model. In addition, all variables listed in **Table 1** (except for drug variables) were included in the propensity score estimation. This procedure was done using a freely available high-dimensional propensity score model macro (version 1) (37).

After propensity score matching, each chlorthalidone recipient was matched with up to 2 hydrochlorothiazide recipients on the basis of age at index date (within 1 year), sex, calendar year of treatment initiation, receipt of a nonthiazide antihypertensive drug in the year before the index date, and propensity score (within 0.2 SD). Each patient treated with hydrochlorothiazide could be matched to no more than 1 patient treated with chlorthalidone. At least 1 match was found for 91% of the patients treated with chlorthalidone. Some chlorthalidone recipients could be matched to only 1 hydrochlorothiazide recipient rather than 2. We retained these pairs but excluded chlorthalidone recipients for whom no hydrochlorothiazide match was found.

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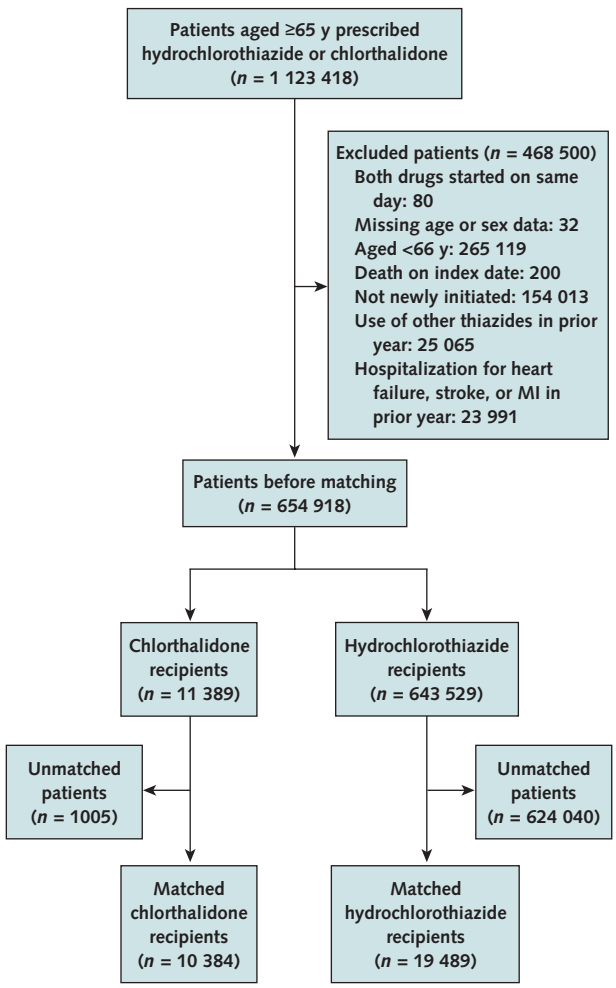
Appendix Figure. **Study flow diagram.**



MI = myocardial infarction.