CLINICAL RESEARCH STUDY

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Risk of Thiazide-induced Hyponatremia in Patients with Hypertension

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ABSTRACT

BACKGROUND: Although hyponatremia is a well-recognized complication of treatment with thiazide diuretics, the risk of thiazide-induced hyponatremia remains uncertain in routine care.

METHODS: We conducted a retrospective cohort study using a multicenter clinical research registry to identify 2613 adult outpatients that were newly treated for hypertension between January 1, 2000 and December 31, 2005 at 2 teaching hospitals in Boston, Massachusetts, and followed them for up to 10 years.

RESULTS: Two hundred twenty patients exposed to ongoing thiazide therapy were compared with 2393 patients who were not exposed. In the exposed group, 66 (30%) developed hyponatremia (sodium ≤130 mmol/L). The adjusted incidence rate of hyponatremia was 140 cases per 1000 person-years for patients treated with thiazides, compared with 87 cases per 1000 person-years in those without thiazides. Patients exposed to thiazides were more likely to develop hyponatremia (adjusted incidence rate ratio, 1.61; 95% confidence interval [CI], 1.15-2.25). There was no significant difference in the risk of hospitalizations associated with hyponatremia (adjusted rate ratio, 1.04; 95% CI, 0.46-2.32) or mortality (adjusted rate ratio, 0.41; 95% CI, 0.12-1.42). The number needed to harm (to result in one excess case of incident hyponatremia in 5 years) was 15.02 (95% CI, 7.88-160.30).

CONCLUSIONS: Approximately 3 in 10 patients exposed to thiazides who continue to take them develop hyponatremia.

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KEYWORDS: Hypertension; Hyponatremia; Incidence; Thiazide diuretics

One of the most important treatment decisions for hypertension is selecting a drug class for initial therapy. Thiazide and thiazide-like diuretics (hereafter collectively referred to as "thiazide diuretics") are widely recommended as first-line therapy for uncomplicated hypertension.[1-3] However, even with the global adoption of thiazide diuretics into practice and over half a century of experience with these medications, our knowledge of some of the common side effects of thiazides remains limited.[4]

Hyponatremia represents a well-recognized potential complication of thiazides that is linked to increased morbidity, and may have costly implications.[5-9] However, previous observational studies have not been designed to estimate the incidence of hyponatremia in unselected patients.[10,11] Furthermore, clinical trial data may underestimate significantly the risk of adverse drug events encountered in routine care.[12-14] As such, current literature offers limited guidance on the comparative risks between thiazides and other antihypertensive drugs in everyday practice.

Guidelines have called for more research about the adverse effects of commonly prescribed antihypertensive drugs.[5] Therefore, we performed this study to characterize the risk of hyponatremia and associated hospitalizations in patients treated with thiazides compared with those receiving alternative antihypertensive therapy. We focused on adult patients in the outpatient setting because this group accounts for the majority of patients receiving thiazides.

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METHODS

This study was approved by the Institutional Review Board at Partners Healthcare.

Study Design and Population

We designed a retrospective cohort study to evaluate the occurrence of hyponatremia in patients newly treated for hypertension through the Research Patient Data Registry—a database specifically designed for research and quality improvement purposes that serves as a central warehouse of clinical data of over 1.8 million patients. The database contains information on patient demographics, diagnoses, procedures, prescriptions, inpatient and outpatient encounters, health care providers, and laboratory results. Using this registry, we identified all adult outpatients with a diagnosis of hypertension between the dates January 1, 2000 and December 31, 2005 encountered at 2 academic hospitals and their affiliated clinics: the Brigham and Women's Hospital and Massachusetts General Hospital. These centers provide primary and tertiary care to an ethnically and socioeconomically diverse population within eastern Massachusetts.

CLINICAL SIGNIFICANCE

- The relative risk of hyponatremia among patients treated with thiazide diuretics is approximately 60% higher than patients on alternative antihypertensive therapy.
- The risk of thiazide-induced hyponatremia persists even up to 10 years of treatment.
- The number needed to harm to result in one excess case of hyponatremia in 5 years is approximately 15.

We defined the first date that a prescription was issued for an antihypertensive medication during the study interval to be the index date. We employed a new user design,[15] and excluded all patients that received any antihypertensive medication prescription in the 3 years before the index date from the study, reasoning that the remaining patients were treatment-naïve. We further excluded patients with hyponatremia before the index date (using laboratory data extending from August 1, 1988 onward), or if they died within the first 30 days of enrollment. Of those remaining, patients were defined as "thiazide-exposed" if their initial prescription was for hydrochlorothiazide, chlorthalidone, indapamide, bendroflumethiazide, metolazone, methyclothiazide, chlorothiazide, trichlormethiazide, or a combination pill containing any of these; "non-thiazide-exposed" patients were those that received an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, beta-adrenergic blocker, or calcium channel blocker as initial antihypertensive therapy. Patients receiving another agent as first-line therapy (eg, clonidine, hydralazine) were not considered for cohort inclusion.

Subjects were followed from their index date until first occurrence of hyponatremia, death, or December 31, 2009 (whichever came first), providing for a maximum follow-up of 10 years. To focus on specific treatment effects in our final cohort, patients were included only if they continued to receive antihypertensive prescriptions throughout the follow-up period. Among those in the "thiazide-exposed" group, only patients that had evidence of active treatment with thiazides up to and including the final 90 days of follow-up (ie, "current" users) were included. Likewise, a similar restriction was placed on the patients in the "non-thiazide-exposed" group. Additionally, "non-thiazide-exposed" patients were included only if they never received any prescription for a thiazide during the entire study period.

Outcomes

The primary outcome was the first occurrence of hyponatremia, defined as the first sodium $\leq$130 mmol/L from either an inpatient or outpatient blood collection. This threshold was chosen so that we would classify most biochemically significant cases of hyponatremia but also include fewer cases of mild (and probably clinically insignificant) hyponatremia. We used laboratory data for outcome ascertainment because diagnostic billing codes greatly underestimate the occurrence of hyponatremia.[16,17] We further classified the severity of hyponatremia according to the following categories: moderate (125-130 mmol/L), severe (120-124 mmol/L), and very severe ($<$120 mmol/L).[18] Secondary outcomes of interest were total number of hospitalizations associated with hyponatremia, total number of hospitalizations from any cause, and mortality. Hospitalizations were defined as any inpatient admission lasting at least 48 hours. Admissions associated with hyponatremia were hospitalizations with concurrent laboratory evidence of hyponatremia on the same day as admission. Mortality was determined from the Social Security Death Index.

Baseline Characteristics

The following baseline data were retrieved for each patient: sex, age, ethnicity, comorbidities (identified through International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes), and prescriptions. Active treatment for nonantihypertensive medications was defined as a prescription within 120 days before the index date. The Charlson comorbidity index was calculated using the enhanced ICD-9-CM method.[19]

Analyses

Baseline characteristics between treatment groups were compared using Fisher's exact test or chi-squared test for discrete variables, and the Student's *t* test or Wilcoxon rank-sum test for continuous variables where appropriate. The occurrence of each outcome was determined according to exposure

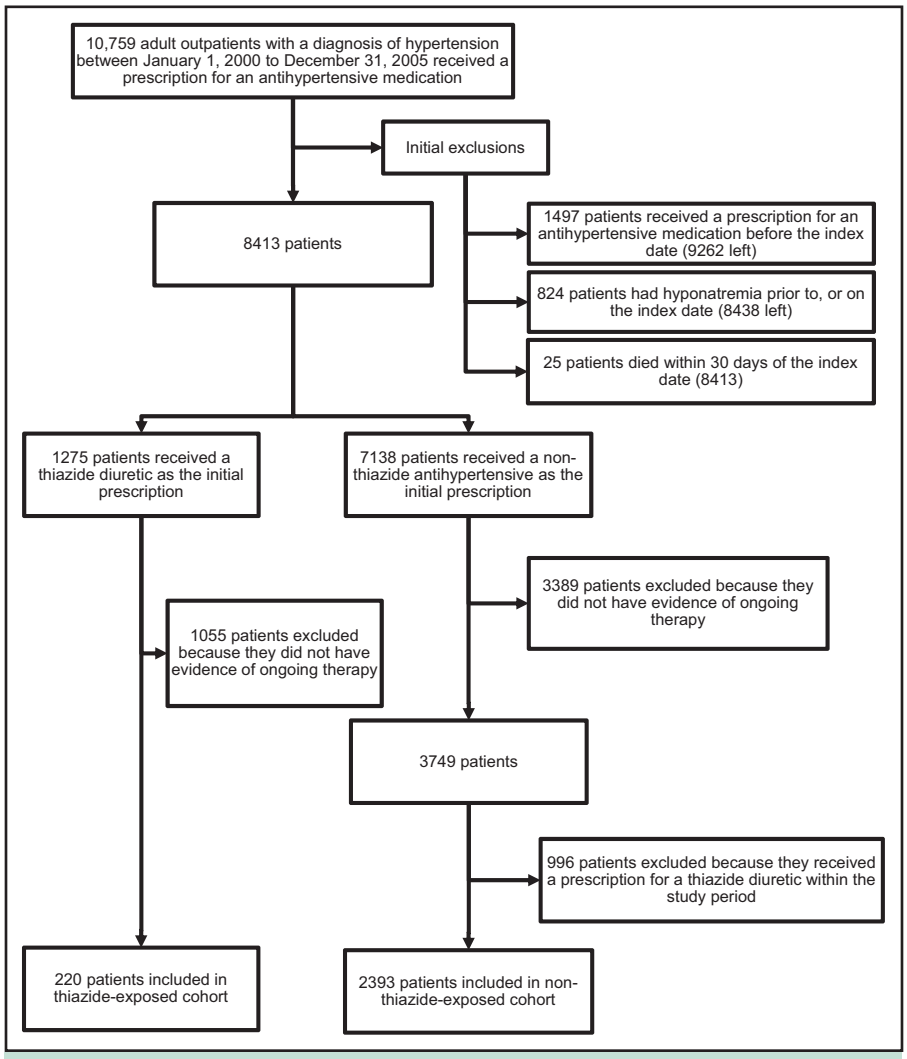

Figure 1 Flow diagram of cohort assembly for primary analysis.

group and reported as rates. The denominator was the total person-years of follow-up. For the secondary outcomes of interest, follow-up extended from the index date until death or December 31, 2009. To facilitate comparison between groups, adjusted incidence rates and incidence rate ratios (RRs) with 95% confidence intervals (CIs) were calculated using Poisson regression. Covariates were chosen based on clinical reasoning and baseline characteristics, and included age, sex, ethnicity, history of congestive heart failure, history of chronic kidney disease, history of malignancy, the Charlson comorbidity index, and exposure to nonsteroidal anti-inflammatory drugs (NSAIDs). Data were aggregated into subgroups according to covariate profiles, and a Poisson model was fitted by modeling the log of the number of events in each subgroup against the covariates, using total person-years of follow-up as the offset. Finally, the cumulative incidence of hyponatremia according to thiazide exposure was plotted against time in an unadjusted time-to-event analysis (accounting for competing risks), and differences were tested with the method of Pepe and Mori.[20] Accounting for varying lengths of follow-up, an estimate of the number needed to harm was calculated based on cumulative incidence estimates.[21,22]

RESULTS

A total of 10,759 hypertensive adult outpatients were identified during the study enrollment period. After exclusion of patients with previous antihypertensive treatment, prior hyponatremia, and early death following treatment, 8413 patients remained. Among the thiazide-exposed patients, 1055 did not have evidence of ongoing treatment and were excluded. An additional 4385 patients were excluded from the non-thiazide-exposed group because they did not have ongoing antihypertensive treatment, or because they received a prescription for a thiazide diuretic during the study interval. A final cohort of 2613 patients was assembled (Figure 1).

Of the 2613 patients enrolled in the cohort, 220 were exposed to thiazides compared with 2393 in the nonexposed

Table 1 Baseline Characteristics of Newly Treated Hypertensive Patients According to Thiazide Exposure

Variables at Baseline	Thiazide-exposed (n = 220)	Non-thiazide-exposed (n = 2393)	*P* Value
Male – number (%)	73 (33.2%)	1263 (52.8%)	<.01
Age – mean (SD), years	59.2 (13.2)	62.2 (15.0)	<.01
Ethnicity – n (%)			
White	99 (45.0%)	1736 (72.5%)	
Black	72 (32.7%)	303 (12.7%)	<.01*
Other or unknown	49 (22.3%)	354 (14.8%)	
Comorbidities – n (%)			
Diabetes mellitus	62 (28.2%)	797 (33.3%)	.13
Chronic liver disease or cirrhosis	7 (3.2%)	113 (4.7%)	.40
Congestive heart failure	17 (7.7%)	568 (23.7%)	<.01
Chronic kidney disease	8 (3.6%)	365 (15.3%)	<.01
Hypothyroidism	1 (0.5%)	9 (0.4%)	.59
Adrenal insufficiency	1 (0.5%)	14 (0.6%)	1.00
Polydipsia	1 (0.1%)	3 (0.1%)	1.00
Malignancy	35 (15.9%)	591 (24.7%)	<.01
SIADH	0 (0%)	2 (0.1%)	1.00
Charlson comorbidity index – median (IQR)	3.0 (2.0)	4.0 (3.0)	<.01
Initial thiazide prescription – n (%)			
Hydrochlorothiazide	211 (95.9%)	—	—
Other thiazide diuretic	9 (4.1%)	—	—
Other prescriptions – n (%)			
Anti-epileptic drugs	5 (2.3%)	75 (3.1%)	.68
SSRIs	7 (3.2%)	108 (4.5%)	.49
NSAIDs	23 (10.5%)	151 (6.3%)	.02

IQR = interquartile range; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation; SIADH = syndrome of inappropriate antidiuretic hormone release; SSRI = selective serotonin reuptake inhibitor.
*Chi-squared *P* value for 3-category ethnicity variable.

group. Patients exposed to thiazides were more likely to be younger, female, and black, but less likely to have congestive heart failure, chronic kidney disease, or cancer. Patients treated with thiazides tended to have a lower Charlson comorbidity index and also were more likely to receive prescriptions for NSAIDs. Otherwise, the 2 treatment groups were similar. Among the initial prescription for thiazides, 211 (95.9%) were for hydrochlorothiazide; other diuretics included chlorthalidone, indapamide, and metolazone (Table 1).

A total of 66 patients experienced hyponatremia among "current" thiazide users during the study, resulting in a crude incidence rate of 50 cases per 1000 person-years. In contrast, 422 cases of hyponatremia were observed in the non-thiazide-exposed group, with a crude incidence rate of 42 cases per 1000 person-years. Patients treated with thiazide diuretics were more likely to develop hyponatremia compared with those without thiazide therapy (adjusted incidence RR, 1.61; 95% CI, 1.15-2.25). The adjusted incidence rates increased with age in both treatment groups, and were greatest among the male subjects. The effect estimates for the relative risks were consistent across all ages and between both sexes (Table 2). However, at the extremes of age, there were relatively few patients, resulting in wide confidence intervals, therefore not meeting statistical significance.

Thiazide users had a median of 9.5 sodium measurements over the course of the follow-up period, compared with 6 in the non-thiazide-exposed group. Forty thiazide users (18.2%) and 611 non-thiazide users (25.5%) never received laboratory testing during the study interval. Among those that received laboratory testing, thiazide users were monitored for a median of 4.4 years (1624 days), and non-thiazide users for 3.7 years (1333.5 days). From the date of enrollment, the median time to first sodium measurement for patients treated with thiazides was 3.7 months (114 days), and 3 months (91 days) for non-thiazide users.

Among the "current" thiazide users that developed hyponatremia, the median time to event was 1.75 years (639.5 days). At the time of detection, the majority of patients (87.9%) experienced moderate incident hyponatremia (125-130 mmol/L), and a significant minority (10.6%) developed severe hyponatremia (120-124 mmol/L). Very severe cases of hyponatremia (<120 mmol/L) were rare (1.5%). Patients exposed to thiazide diuretics were more likely to develop hyponatremia of any severity (Figure 2).

A total of 22 hospitalizations associated with hyponatremia occurred in those currently treated with thiazides, compared with 229 in those without thiazide therapy, with an adjusted RR of 1.04 (95% CI, 0.46-2.32). Mortality was very uncommon, with no significant difference in risk (adjusted incidence RR, 0.41; 95% CI, 0.12-1.42) (Table 3).

Table 2 Risk of Incident Hyponatremia Associated with Thiazide Diuretic Exposure

Population	Thiazide Exposure Group	No. of Cases/Total no. of People in Category	Person-years of Follow-up*	Crude Incidence Rate per 1000 Person-years	Adjusted Incidence Rate per 1000 Person-years (95% CI)†	Adjusted Incidence Rate Ratio (95% CI)‡
All patients	None	422/2393	9938	42	87 (25-307)	1.61 (1.15-2.25)
	Current	66/220	1311	50	140 (38-518)	
Ages <40 years	None	36/155	765	47	9 (3-25)	1.53 (0.33-7.09)
	Current	3/11	61	50	13 (3-71)	
Ages 40-59 years	None	148/884	4464	33	59 (5-688)	1.74 (0.97-3.13)
	Current	24/103	656	37	102 (8-1282)	
Ages 60-79 years	None	182/1037	4009	45	67 (13-347)	1.65 (1.02-2.68)
	Current	29/88	521	56	111 (20-614)	
Ages ≥80 years	None	56/317	700	80	956 (100-9169)	1.73 (0.78-3.85)
	Current	10/18	73	136	1652 (154-17,775)	
Males	None	217/1263	4899	44	209 (46-953)	1.89 (1.12-3.17)
	Current	25/73	382	65	395 (79-1974)	
Females	None	205/1130	5039	41	36 (3-389)	1.53 (1.01-2.34)
	Current	41/147	929	44	55 (5-624)	

CI = confidence interval.

*Cohort followed from enrollment until first occurrence of hyponatremia, death, or December 31, 2009.

†Total population adjusted for age, sex, ethnicity, congestive heart failure, chronic kidney disease, malignancy, Charlson comorbidity index, and nonsteroidal anti-inflammatory drugs. Individual age bands adjusted for sex, ethnicity, congestive heart failure, chronic kidney disease, malignancy, Charlson comorbidity index, and nonsteroidal anti-inflammatory drugs. Male and female groups adjusted for age, ethnicity, congestive heart failure, chronic kidney disease, malignancy, Charlson comorbidity index, and nonsteroidal anti-inflammatory drugs.

‡Non-thiazide-exposed group is the reference group.

We further explored the relationship between the duration of treatment and the occurrence of hyponatremia (Figure 3). Over the 10-year study period, there were large differences in the cumulative incidence of hyponatremia between the thiazide-exposed and non-thiazide-exposed patients (32.4% vs 27.3%; $P = .02$ over the entire length of follow-up). An early increase in events was seen in the first quarter year, followed by a steady increase in incident hyponatremia thereafter for the entire study period. In clinical terms, we found that the number needed to harm (NNH) for one excess case of hyponatremia in 5 years was 15.02 (95% CI, 7.88-160.30).

DISCUSSION

In this study of adult outpatients newly treated for hypertension over a 10-year interval, we found that over 3 in 10

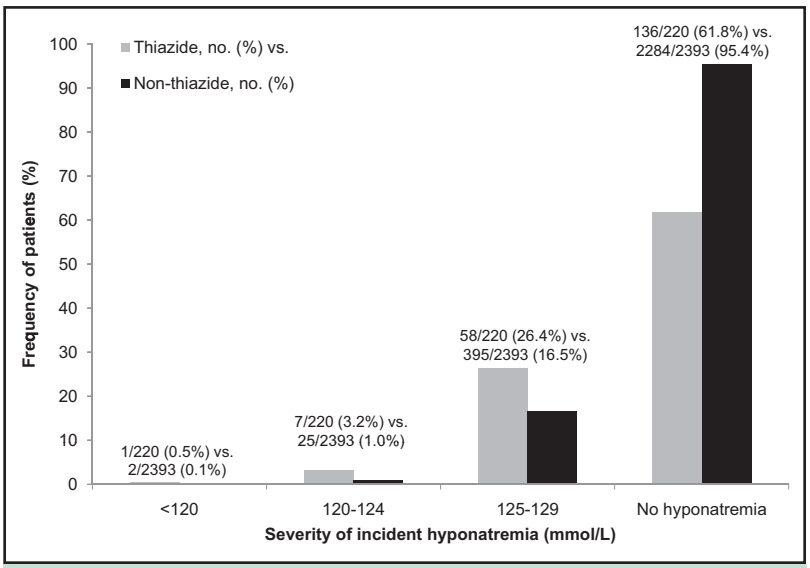

Figure 2 Distribution of severity of hyponatremia according to thiazide diuretic exposure.

Table 3 Secondary Outcomes of Interest According to Thiazide Diuretic Exposure

Outcome	Thiazide Exposure Group	No. of Events/ Total No. of People in Category	Person-years of Follow-up*	Crude Incidence Rate per 1000 Person-years	Adjusted Incidence Rate per 1000 Person-years (95% CI)†	Adjusted Rate Ratio (95% CI)‡
Hospitalizations associated with hyponatremia	None	229/2393	10,990	21	161 (33, 800)	1.04 (0.46, 2.32)
	Current	22/220	1416	16	167 (27, 1022)	
All-cause mortality	None	193/2393	10,990	18	6 (0, 191)	0.41 (0.12, 1.42)
	Current	7/220	1416	5	2 (0, 97)	

*Cohort followed from enrollment until death or December 31, 2009.

†Adjusted for age, sex, ethnicity, congestive heart failure, chronic kidney disease, malignancy, Charlson comorbidity index, and nonsteroidal anti-inflammatory drugs.

‡Non-thiazide-exposed group is the reference group.

patients developed hyponatremia among those receiving thiazide diuretics. The overall relative risk of hyponatremia was approximately 60% higher in patients exposed to thiazide diuretics compared with alternative therapy, and appeared to be similar regardless of patient age or sex. Further, we demonstrated that the increased risk of hyponatremia began early after starting treatment and persisted for at least a decade.

Not much is known about the epidemiology of thiazide-induced hyponatremia. An early review of 129 case reports found that most patients that developed hyponatremia from thiazides did so within 14 days of treatment.[23] In contrast, a more recent case-control study of patients hospitalized with symptomatic hyponatremia reported that the median duration of thiazide use in cases was 105 days. While we confirmed an early risk of thiazide-induced hyponatremia

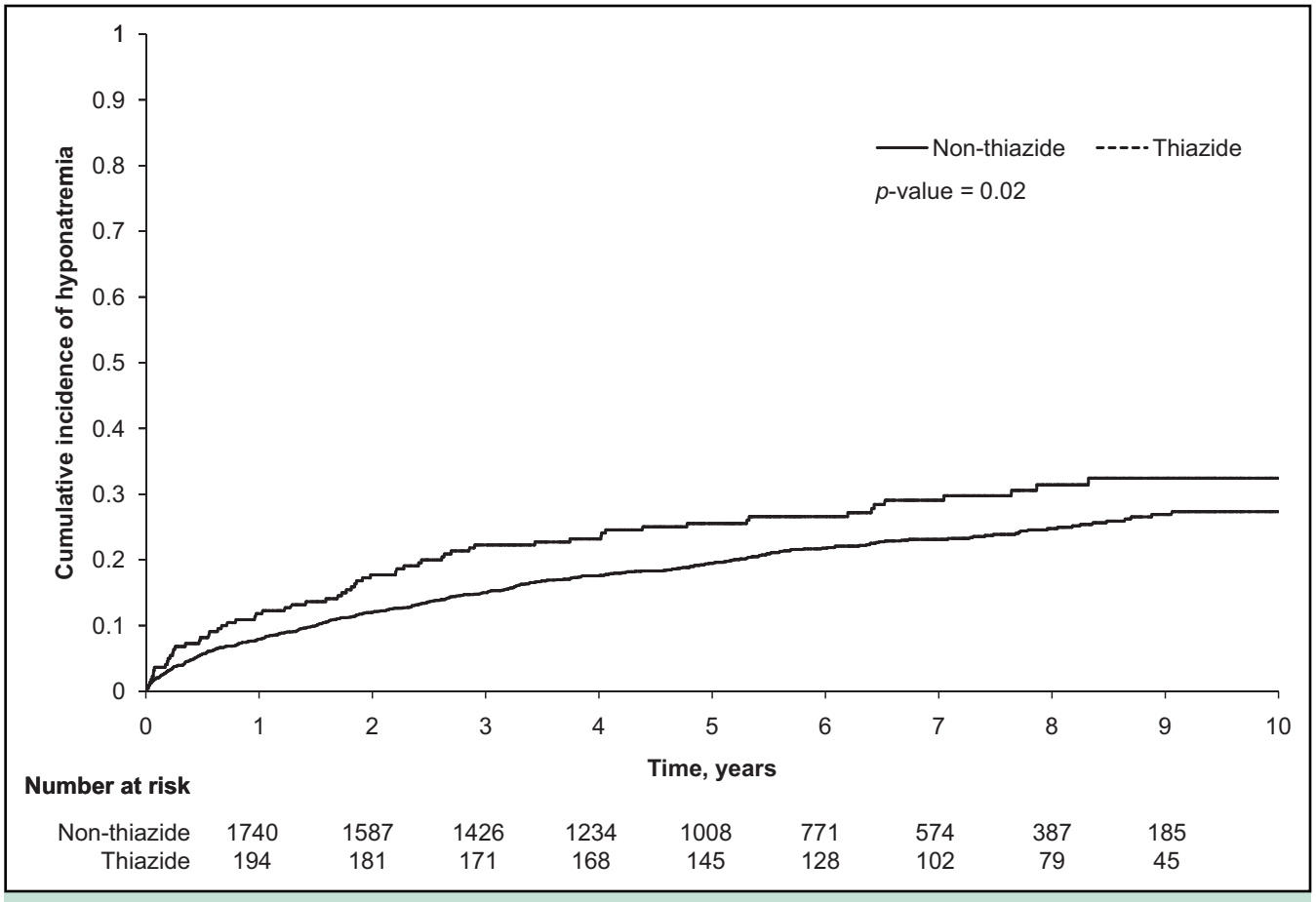

Figure 3 Cumulative incidence of hyponatremia according to thiazide diuretic exposure.

within the first quarter year of treatment, we further found that the risk of hyponatremia continued for even up to 10 years. In our study, among those that developed hyponatremia with thiazides, the median time to event was 1.75 years, suggesting that insufficient follow-up after treatment initiation may lead to underestimation of late events. Notably, a substantial number of patients in our non-thiazide-exposed comparator group experienced hyponatremia over time as well. Although the incidence rate of hyponatremia in the general population has not been previously studied, our data are consistent with the available evidence that suggests that the prevalence of hyponatremia is 7%-21% in unselected outpatients.[24]

In the Systolic Hypertension in the Elderly Program (SHEP) trial, 4.1% of patients treated with chlorthalidone eventually developed hyponatremia, versus 1.3% in the placebo group, with an average follow-up of 4.5 years (NNH, 35.71).[12] In contrast, we described a cumulative incidence of 32.4% and 27.3% for the thiazide- and non-thiazide-exposed groups, respectively, over 10 years of follow-up (NNH for 5 years = 15.02). The differences in reported rates and risks may relate to differences in diuretic choice, patient population, and frequency of laboratory monitoring between studies. Furthermore, SHEP participants were highly selected (ie, excluding patients with pre-existing cardiovascular diseases, cancer, liver disease, and renal dysfunction). However, many subjects observed in our study had known significant comorbidities, and more closely reflect patients routinely encountered in real-world clinical practice.

There is robust and convincing evidence from randomized trials demonstrating the benefits of thiazides in reducing mortality and cardiovascular morbidity.[25,26] In head-to-head studies, the benefits of thiazides appear to be broadly similar to other antihypertensive drug classes,[25-29] with no significant differences in mortality when comparing diuretics against beta-blockers,[5,30-32] ACE inhibitors,[1,5,33,34] or calcium channel blockers.[5,35-38] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial further suggested no mortality differences when comparing a thiazide against an ACE inhibitor or calcium channel blocker regardless of patient age, sex, ethnicity, or diabetes.[1] Accordingly, in our study, we found no detectable difference in mortality rates between groups. However, our study was not designed to be powered to detect a mortality difference.

Thiazide diuretics have many well-documented metabolic side effects that have been extensively reported.[1] However, characterization of hyponatremia risk has been limited. The only cost-effectiveness study performed on this topic concluded that both thiazide diuretics and calcium channel blockers should be offered as equal alternatives as first-line treatment of hypertension.[5] Yet, the authors believed that a major limitation of their study was lack of data on adverse drug events. Clearly, hyponatremia is neither insignificant nor inconsequential, as it is linked to excess morbidity.[18,39-41] Admittedly, symptoms related to hyponatremia are often subtle and may easily be overlooked. However, even mild chronic hyponatremia in so-called "asymptomatic" outpatients is associated with poorer performance on attention tests, unstable posture, gait disturbance, more falls, and greater risk of bone fractures.[42,43] An early conservative study[16,17,40] reported the direct annual costs of hyponatremia in the US to be between $1.6 billion and $3.6 billion.[6] Others have estimated that the medical costs may be as high as $19,215 per patient per year, resulting from clinical complications, prolonged lengths of stay, and readmission.[7-9] Further, with the recent introduction of generic medications from other antihypertensive drug classes, the cost-benefit ratio may no longer be as favorable towards thiazides. The choice of drug for the initial treatment of hypertension is undeniably complicated when considering factors such as affordability for patients, incurred costs to the medical system, and medication-related side effects. Importantly, we report the risk of thiazide-associated hyponatremia to help providers weigh the benefits and harms of treatment.

Our findings must be interpreted in the context of the study design. The most important limitation is that this is not a randomized trial, and consequently is subject to confounding. However, we identified the most important clinical predictors for hyponatremia and accounted for differences in our multivariable model. Moreover, the higher prevalence of congestive heart failure and chronic kidney disease in the non-thiazide-exposed group would likely attenuate our ability to detect the risk of thiazide-induced hyponatremia, and thus lead to an even more conservative estimate of true risk. A second limitation is that records used for outcome ascertainment were available only for patient encounters involving the Partners Healthcare system. Indeed, we may have underestimated the rates of hyponatremia and hospitalizations. However, we presume that this measurement bias would occur equally between both treatment groups. Therefore, the overall estimates of relative risk would remain similar. A third limitation is that hospitalizations associated with hyponatremia were defined using laboratory data. As a result, it is possible that some of the cases we reported may have been "incidental" laboratory findings unrelated to the primary admission diagnosis. We chose not to incorporate administrative records because these may underestimate cases of hyponatremia.[16] Even with extreme values of $\leq$115 mmol/L, the sensitivity of ICD-9 codes for detecting hyponatremia may be as low as 30%.[16] A final limitation is that our database was limited to prescription data, and we were unable to confirm medication dispensation. Addressing this, we included in our study only patients that had evidence of ongoing prescriptions for antihypertensive therapy, as they were most likely to receive active treatment. However, inherent to our study design and cohort assembly, there is a potential for selection bias. Therefore, our results apply only to patients that receive treatment with thiazides and continue to take them until the development of hyponatremia or death.

CONCLUSION

Hyponatremia is common among outpatients treated with thiazide diuretics and who continue to receive them. The associated risks appear to be 60% higher than similar patients treated with alternative therapy. In clinical terms, it appears that 15 patients need to be treated with thiazides to result in one excess case of incident hyponatremia over 5 years. The implication of our research is that both the short- and long-term consequences of thiazides should be thoroughly considered when prescribing therapy. Priorities to minimize harm to patients may include increasing awareness that hyponatremia commonly develops even after the first quarter year of treatment, monitoring of patients at high risk for metabolic complications, and individualizing care when considering whether alternative medications may be more suitable for certain patients.

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