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The Risk of Thiazide-Induced Metabolic Adverse Events in Older Adults

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Abstract

Objectives—To evaluate the risk and predictors of thiazide-induced adverse events (AEs) in multimorbid older adults in real-world clinical settings.

Design—Observational cohort study.

Setting—National Veterans Administration data from 2007–08.

Patients—Veterans 65 years or older newly prescribed a thiazide (N=1,060) compared to propensity matched non-users of anti-hypertensive medications (N=1,060).

Measurements—The primary outcome was a composite of metabolic AEs defined as sodium <135 mEq/L, potassium <3.5 mEq/L, or decrease in estimated GFR by more than 25%. Secondary outcomes included severe AEs (sodium <130 mEq/L, potassium <3.0 mEq/L, or decrease in estimated GFR by more than 50%).

Results—Over 9 months of follow-up, 14.3% of new thiazide users developed an AE compared to 6.0% of non-users (NNH 12, 95% CI, 9–17, $p < .001$), 1.8% developed a severe AE compared to 0.6% (NNH=82, $p < .01$), and 3.8% had an ED visit or hospitalization with an AE compared to 2.0% (NNH=56, $p = .02$). Risk of AEs did not vary by age, but having 5 or more comorbidities compared to 1 comorbidity (hypertension) was associated with 3.0 times the odds of developing an AE (95%

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CI, 1.4-6.2). Low-normal and unmeasured baseline sodium and potassium values were among the strongest predictors of hyponatremia and hypokalemia respectively. Only 42% of thiazide users had laboratory monitoring within 90 days after initiation.

Conclusion—Thiazide-induced AEs are common in older adults. Greater attention should be devoted to potential complications in prescribing thiazides to older adults, including closer laboratory monitoring before and after initiation of thiazides.

Keywords

Aged; adverse effects; sodium chloride symporter inhibitors; hypertension; outcome assessment (healthcare)

Introduction

The Seventh Report of the Joint National Committee recommends a thiazide diuretic as the preferred initial medication for the treatment of hypertension (HTN) in older adults.¹ Several randomized controlled trials (RCT) with highly selected participants have shown thiazides to be relatively safe in this population.^{2, 3} However, little is known about the risk of thiazide-induced adverse events in “real world” clinical practice, where older patients who are treated may have greater comorbidity burden, complicated medical regimens, and poorer compliance with follow-up.^{4, 5}

Hyponatremia, hypokalemia, and acute kidney injury are potential metabolic adverse events due to thiazides that are associated with increased morbidity, mortality, and costs.⁶⁻¹⁷ An observational study of patients prescribed a thiazide at one of two academic centers found that 3 in 10 adults developed hyponatremia over a 10-year interval, a 60% greater risk compared to alternative antihypertensive therapy.¹⁸ While this study highlights one important metabolic complication due to thiazides, a more comprehensive metabolic risk assessment of thiazides is needed, especially for older adults who are more likely to be at risk for medication-induced adverse events.^{19, 20}

Since other antihypertensive classes are as effective as thiazides at reducing cardiovascular events in older adults, a better understanding of the risk of thiazide-induced metabolic adverse events in this population, including defining subgroups of patients that may be at particularly high risk of complications, can help inform safer prescribing practices.^{21, 22} However, an RCT examining the metabolic risk of thiazides in this population is unlikely to be forthcoming. Therefore, we used national observational data using propensity scoring techniques to evaluate the risk of thiazide-induced metabolic adverse events in older adults, predictors of this risk, and laboratory surveillance patterns after thiazide initiation.

Methods

Data Sources and Study Population

We conducted an observational cohort study using merged national Veterans Affairs (VA) pharmacy, laboratory, administrative, and Medicare administrative data for fiscal years 2007

and 2008. We employed a new user design to minimize bias.²³ The study population included veterans aged 65 years or older with essential hypertension who were not prescribed a first-line antihypertensive medication during a 9-month baseline period before the index date. First-line antihypertensive medications were defined as a thiazide diuretic, angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), calcium channel blocker (CCB), or beta blocker (BB). Hypertension was defined as having two or more outpatient encounter *International Classification of Diseases, Ninth Revision* (ICD-9) codes 401-404. We followed individuals over a 6-month period between July and December 2007 to identify individuals who were either newly prescribed a thiazide diuretic or remained untreated with a first-line antihypertensive medication, hereafter referred to as “non-users.” The index date was the date of the initial outpatient prescription for a thiazide, or the date of a randomly selected outpatient visit during the same time period for non-users. Patients were stratified into two mutually exclusive groups, thiazide users and non-users, and were prospectively observed for 9 months after the index date for the occurrence of adverse events. We analyzed patients according to initial group stratification, allowing for crossover between group assignments and accrual of additional antihypertensive medications in both groups per usual care after the index date.

To allow for complete capture of medication use and laboratory test results, we restricted our analysis to patients who received all of their care within the VA health system, defined as having two or more outpatient encounters within the VA system with at least one encounter within seven days of the index date, one or more outpatient prescriptions for a non-antihypertensive medication from a VA pharmacy, and no encounters in Medicare inpatient or outpatient settings during the study period. Since our aim was to examine the risk of metabolic adverse events, we excluded individuals with abnormal baseline values for sodium (<135 mEq/L) and potassium (<3.5 mEq/L) and individuals with missing follow-up laboratory testing for sodium (Na), potassium (K), and estimated glomerular filtration rate (eGFR). Additionally, we excluded patients newly prescribed a CCB, BB, ACEi, ARB or two or more first-line antihypertensive medications on the index date.

Because our primary analysis focused on metabolic risks, we included only patients with laboratory follow-up data and normal Na and K values at baseline. To evaluate patterns of laboratory monitoring for thiazide users, we derived a broader cohort that included patients with abnormal baseline labs and missing follow-up laboratory testing, as well as patients who were prescribed a CCB, an alternative first-line antihypertensive medication.

Baseline Characteristics

We evaluated baseline characteristics for all subjects during the 9 months prior to, and inclusive of the index date. We measured comorbidity burden by a count of 23 of the most common chronic conditions in older adults as has been described elsewhere.²⁴ An individual was classified as having a condition of interest if he or she had one or more relevant ICD-9 codes during an inpatient or outpatient encounter. For patients with more than one baseline laboratory value for Na, K, or eGFR, we used the value nearest to the index date. The dose of initial thiazide prescription was dichotomized as low dose (less than the

equivalent of 25 mg of hydrochlorothiazide per day) and high dose (equal to or greater than the equivalent of 25 mg of hydrochlorothiazide daily).

Outcomes

The values of the first laboratory test results for Na, K, and eGFR after the index date were ascertained during the 9-month follow-up period. The primary outcome was a composite of three thiazide-related metabolic adverse events: hyponatremia ($\text{Na} < 135 \text{ mEq/L}$), hypokalemia ($\text{K} < 3.5 \text{ mEq/L}$), and risk for kidney injury (decrease in eGFR by greater than 25% as defined by the RIFLE criteria).²⁵ Secondary outcomes included each individual adverse event included in the primary outcome, a composite of severe metabolic adverse events ($\text{Na} < 130 \text{ mEq/L}$, $\text{K} < 3.0 \text{ mEq/L}$, decrease in eGFR by greater than 50%), and a composite of emergency department (ED) visits and hospitalizations with hyponatremia, hypokalemia, electrolyte imbalance, and acute kidney injury (ICD-9 codes 276.1, 276.8, 276.9, 584.5, 584.9, 586, and 593.9 for either a primary or secondary discharge diagnosis). We did not evaluate for hyperuricemia since the clinical severity and significance of this metabolic disturbance is uncertain.⁷

Statistical Analysis

Risk of Thiazide-Induced Adverse Events—To estimate the attributable risk of adverse events due to thiazides, we used propensity-score based approaches to balance observable differences between treatment and control groups. Predictors in our model of propensity to receive thiazide treatment included age, sex, race and ethnicity, comorbidity count, selected comorbidities, number of medications, use of non-thiazide diuretics, use of psychiatric medications, baseline laboratory values (Na, K, eGFR), healthcare utilization, and region. The Hosmer-Lemeshow goodness of fit test ($p = .26$) and the receiver-operator characteristic (c-statistic = 0.70) confirmed adequate model fit. We then matched thiazide users to nonusers with the closest propensity score using 1:1 nearest-neighbor matching.²⁶ Common support graphing and covariate imbalance testing showed excellent overlap with only 2 subjects dropped from the thiazide user group. We estimated the risk of each outcome using generalized estimating equations (GEE) with an independent working correlation structure to account for clustering of patients within medical centers.

We performed two sensitivity analyses to assess the validity of our inferences. First, we repeated the propensity score model, but instead of nearest-neighbor matching, we stratified patients by quintile of propensity. Second, we repeated our initial analysis using new users of CCB as the control group in lieu of non-users to account for potentially unmeasured confounding that may arise from the decision to treat or not treat patients with antihypertensive medications. We chose CCBs as the active comparison group because unlike other first-line antihypertensive medications (ACEi, ARB, BB), they do not themselves cause metabolic disturbances and are not used to treat heart failure and other conditions that may increase the risk of metabolic adverse events.

Predictors of Adverse Events in Thiazide Users—We examined predictors of increased risk of adverse events among thiazide users using GEE models with independent working correlation structures to account for clustering of patients within medical centers.

Our primary predictors of interest were age, comorbid burden, and baseline laboratory values. We developed separate models for the composite outcome and for each individual adverse event included. We assessed the functional form of continuous variables using cubic splines and polynomials. The Hosmer-Lemeshow goodness of fit test was used to confirm model fit.

Since unmeasured baseline laboratory tests may have important prognostic implications, we included unmeasured tests as indicator variables in the models. Due to collinearity between having unmeasured eGFR and having unmeasured sodium and potassium values at baseline, eGFR status ($\geq$ or < 60 mL/min/1.73m²) was treated as missing at random based on known covariates and estimated using multiple imputation for 142 patients (13.4%).

The data was analyzed using STATA statistical software, version 12.0 (Stata-Corp, College Station, Texas). This study was approved by the institutional review boards of the University of California, San Francisco and the San Francisco VA Medical Center.

Results

Of 35,865 veterans with hypertension who were untreated at baseline, 3,568 were newly prescribed a CCB, BB, ACEi, or ARB, 1,175 were prescribed two or more first-line antihypertensive medications on the index date, 1,246 had abnormal Na and K values at baseline, and 11,388 did not have laboratory testing during the follow-up period. Of the remaining, 1,062 were newly prescribed a thiazide diuretic and 18,816 remained untreated with a first-line antihypertensive ("non-users"). Propensity score matching resulted in 1,060 patients in each matched group (Figure 1).

Baseline characteristics were similar for the two propensity matched groups (Table 1). Patients were predominantly white and black males, had a mean age of 74 years, and a median of 3 comorbidities. Among thiazide users, 98% of the initial prescriptions were for hydrochlorothiazide.

Thiazide users had a 14.3% risk of developing an adverse event compared to 6.0% for matched non-users, yielding a number needed to harm (NNH) of 12 patients (95% CI, 9-17, $p < .001$; see Table 2). Likewise, thiazide users had an increased risk for each individual adverse event included in the composite outcome. The number needed to be prescribed a thiazide to result in one excess case of an incident severe adverse event was 82 patients (NNH 95% CI, 47-326, $p = .008$) and one excess case of an ED visit or hospitalization with an adverse event was 56 (NNH 95% CI, 31-323, $p = .019$). Findings from our sensitivity analyses using an alternative analytic technique and new users of CCBs as the comparison group were materially similar and are not reported here.

In multivariate analysis, a high comorbidity burden compared to a low comorbidity burden was associated with a threefold increase in the odds of developing a metabolic adverse event and 2.6 times the odds of developing hyponatremia (Table 3). Although age was not associated with a significant increase in the odds of the composite outcome, there was a trend for increasing age being associated with the risk of hyponatremia (OR 1.47 per each 10 years of age, $p = .06$).

Low-normal baseline Na and K values and unmeasured baseline testing for Na and K were among the strongest predictors of hyponatremia and hypokalemia respectively. Other than an association between race/ethnicity and risk of kidney injury (OR 2.32 for non-white compared to white individuals, 95% CI, 1.29-4.17, $p=.005$), we did not find a significant association between race/ethnicity, sex, or thiazide dose and any adverse event outcome.

Pattern of Laboratory Monitoring After Thiazide Initiation

Only 42% of thiazide users had laboratory monitoring for Na, K, and eGFR within 90 days after thiazide initiation and 76% within the entire follow-up period of 270 days (Figure 2). Thiazide users were more likely to have follow-up laboratory monitoring within 90 days after the index date compared to new users of CCB or non-users ($p<.001$ for both).

Discussion

In this national cohort study of older veterans with hypertension, we found that for every 12 veterans newly prescribed a thiazide diuretic, one additional patient developed a metabolic adverse event within a 9-month follow-up period that he or she would otherwise not have had. The number of patients needed to be prescribed a thiazide to result in one excess case of a severe adverse event was 82 and one excess case of an ED visit or hospitalization with a metabolic complication was 56. Comorbidity burden and baseline laboratory tests were important predictors of adverse events. Despite thiazide-induced adverse events being common, less than half of patients had laboratory monitoring within 90 days after thiazide initiation.

Several clinical trials have examined the metabolic risk of thiazides among older adults. Within the first-year of follow-up in the Systolic Hypertension in the Elderly Program (SHEP) trial, 1% of chlorthalidone users developed hypokalemia compared to 0.1% in the placebo group and 1.8% experienced hyponatremia compared to 0.4% in the placebo arm.² In the Hypertension in the Very Elderly Trial (HYVET) the mean change in potassium and creatinine values were similar between patients receiving indapamide and placebo with few serious adverse events attributed to the trial medication.³ While it is difficult to directly compare our findings to these trials given the differences in follow-up periods, number of laboratory measurements, and definitions of metabolic risks, based on our findings from initial laboratory testing, we believe the risk of thiazide-induced metabolic adverse events is underestimated in real-world clinical settings. Furthermore, these trials included highly selected participants without significant preexisting comorbidities (heart failure, renal insufficiency, and dementia), limiting generalizability. This underscores the importance of observational studies to estimate the metabolic risk in actual clinical settings, where older patients who are treated with a thiazide are more likely to be medically complex and frail.

Few studies have examined this risk in clinical practice. Leung et al followed thiazide users receiving care at one of two academic medical centers for 10-years with a median of 9.5 sodium measurements and found the cumulative incidence of hyponatremia to be 32.4% with a number needed to harm of 15.¹⁸ In a recent population-based study in Canada, the one-year cumulative incidence of hospitalization with hyponatremia and hypokalemia in older adults prescribed hydrochlorothiazide was approximately 0.3% and 0.6%

respectively.²⁷ Our analysis markedly extends upon these studies by providing a more comprehensive metabolic risk assessment of thiazides in older adults. Future research should evaluate longer term outcomes beyond 9 months after thiazide initiation, and include a broader range of potential adverse events, including acute gout, orthostatic hypotension, and falls.

Our results also build upon prior research on predictors of thiazide-induced adverse events. Notably, multimorbid older adults had a threefold greater odds of adverse events compared to individuals with a low comorbidity burden. Although not previously identified as a risk factor for thiazide-induced adverse events, a high comorbid burden has been shown to confer an elevated risk of adverse drug reactions in general among older adults.²⁸ This increased risk may be due to drug-drug and drug-disease interactions, as well as altered drug distribution and metabolism.²⁰ While the overall risk did not significantly vary by age, we identified a trend for advancing age and an increased risk of hyponatremia. In studies that included patients with a wider age range, advancing age has been shown to be a strong predictor of thiazide-induced hyponatremia.^{29, 30} Our inclusion of patients 65 years or older may reflect an age threshold effect blunting this risk. Also, our study better controlled for comorbidity burden, which may in part mediate the effect of aging on sodium homeostasis. In keeping with previous literature on average decrements in sodium and potassium concentrations after thiazide initiation, we noted that low-normal sodium and potassium values were significant predictors of hyponatremia and hypokalemia respectively.^{31, 32} These findings should be interpreted cautiously. The clinical importance of mild decrements in laboratory values is uncertain.³³

In this study, we reported the incidence of metabolic adverse events due to thiazides as a proxy of harm. Certainly, the severity of metabolic abnormalities dictates the degree and acuity of clinical symptoms. Less severe metabolic derangements may not be as alarming, but are hardly inconsequential. Mild hyponatremia and hypokalemia have been linked to increased mortality.^{10, 12, 16, 17} Furthermore, mild hyponatremia is associated with increased risk of falls, gait unsteadiness, and cognitive impairment, as well as greater healthcare utilization and costs;^{13, 16, 34} and mild hypokalemia with a greater burden of cardiovascular events.^{10, 11} In light of these consequences, the high observed incidence of adverse events in the setting of suboptimal monitoring is concerning. Combined with our findings that unmeasured baseline laboratory tests are significant predictors of metabolic adverse events, we should strive for closer laboratory monitoring before and after thiazide initiation. Further research is needed to help delineate the optimal surveillance strategies and to examine the impact of early surveillance on clinical outcomes.

At the present, without firm evidence of the benefits of early laboratory surveillance strategies, for patients at particularly higher risk, such as multimorbid older adults, it may be prudent to consider alternative therapy. Thiazide diuretics undoubtedly reduce cardiovascular morbidity and mortality in older adults with hypertension.^{21, 35} However, other classes of antihypertensive medications are equally effective in this population and are available at comparable costs in generic formulations^{21, 22}

Our study had certain limitations. First, we studied patients within the VA healthcare system, who are predominantly men. Since other studies have shown that women may be at higher risk of metabolic complications from thiazides than men, our results may underestimate the actual incidence.^{30, 36} Second, given the observational design of our study there may have been residual confounding between groups. However, unmatched non-users had greater comorbidity burden, number of medications, and healthcare utilization than thiazide users at baseline. If there were unmeasured differences between groups, we would expect a conservative bias attenuating the risk differences. Additionally, we used propensity score techniques with excellent covariate overlap to match patients between groups. Third, our study was designed as an intention-to-treat analysis based on the prescription status on the index date. As evidenced by considerable thiazide discontinuation rates from previous studies, we would expect potential crossover between group assignments to lead to a more conservative estimate.^{18, 22} Fourth, there was differential laboratory follow-up time between thiazide users and non-users. By design, all patients included in our risk analysis had laboratory tests resulted at least once and time to follow-up testing would not be expected to influence adverse events among non-users. Fifth, we did not have data on blood pressure. Differences in blood pressure due to thiazide treatment and potentially other antihypertensive medications accrued during the follow-up period may have confounded our results.

In conclusion, thiazide-induced metabolic adverse events are common among older adults with hypertension. Findings from this study imply a need for more vigilance in prescribing thiazides. At a minimum, closer laboratory monitoring is warranted before and after thiazide initiation. For patients at particularly high risk of developing adverse events, such as multimorbid older adults, it may be reasonable to consider alternative therapy, especially given the availability of other equally effective antihypertensive medications at comparable costs.

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Figure 1. Study flowchart

^aPatients may have met more than 1 exclusion criteria

Figure 2. Cumulative proportion of patients who had laboratory tests completed at least once within selected time intervals before and after the index date.^a

Abbreviations: CCB, calcium channel blocker

^a Laboratory tests included sodium, potassium, and estimated glomerular filtration rate

Table 1
Baseline Characteristics of Study Population

Characteristic	Matched Thiazide Users	Matched Non-Users	P-value
n	1,060	1,060	
Age, mean years (SD)	74 (6)	74 (6)	.38
Male, n (%)	1,030 (97)	1,022 (96)	.32
Ethnicity, n (%)			.87
White	843 (80)	858 (81)	
Black	156 (15)	147 (14)	
Other	61 (6)	55 (5)	
23 comorbidity count, median n (IQR)	3 (2-4)	3 (2-4)	.75
Selected comorbidities, n(%)			
Congestive heart failure	7 (0.7)	9 (0.9)	.80
Cirrhosis	4 (0.4)	9 (0.9)	.27
Dementia	36 (3)	37 (3)	.91
Diabetes	146 (14)	136 (13)	.52
Malignancy	142 (13)	116 (11)	.08
Psychosis	14 (1)	15 (1)	.85
Medications, median n (IQR)	5 (3-8)	5 (3-8)	< .001 ^a
Non-thiazide diuretic, ^b n (%)	11 (1)	13 (1)	.68
Psychiatric medication, n (%)	108 (10)	106 (10)	.89
Potassium supplementation, n (%)	38 (4)	21 (2)	.03
Dose of thiazide medication, n (%)			-
Low	603 (57)	-	
High	457 (43)	-	
Laboratory monitoring, n (%)	872 (82)	883 (83)	.53
Sodium, mean mEq/L (SD)	140 (2.2)	140 (2.3)	.50
Potassium, mean mEq/L (SD)	4.3 (0.4)	4.3 (0.4)	.46
eGFR, median mL/min/1.7 m ² (IQR)	71 (60-83)	71 (60-83)	.84
Outpatient visits, median n (IQR)	3 (2-4)	2 (2-4)	< .001
Any emergency department visit, n (%)	112 (11)	95 (9)	.21
Any hospitalizations, n (%)	46 (4)	49 (5)	.75

Abbreviations: eGFR, estimated glomerular filtration rate

^a non-user group more right-skewed than thiazide users

^b Defined as loop diuretics and potassium-sparing diuretics, including spironolactone

Table 2

Study Outcomes

	Matched Thiazide Users		Matched Non-users		NNH (95% CI)	RR (95% CI)	P
	N (%)		N (%)				
Adverse events ^a	152 (14.3)		64 (6.0)		12 (9-17)	2.61 (1.91-3.55)	<.001
Hyponatremia	68 (6.5)		21 (2.0)		22 (15-40)	3.40 (1.95-5.93)	<.001
Hypokalemia	47 (4.5)		15 (1.4)		33 (22-70)	3.21 (1.85-5.60)	<.001
Decrease in eGFR> 25%	50 (5.5)		29 (3.2)		43 (24-229)	1.76 (1.11-2.79)	.015
Severe adverse events ^b	19 (1.8)		6 (0.6)		82 (47-326)	3.21 (1.36-7.55)	.008
ED visit/hospitalization for AE	40 (3.8)		21 (2.0)		56 (31-323)	1.94 (1.11-3.39)	.02

Abbreviations: AE, adverse events; ED, emergency department; NNH, number needed to harm

^a Includes hyponatremia (Na < 135 mEq/L), hypokalemia (K < 3.5 mEq/L), and decrease in eGFR by > 25%

^b Includes Na < 130 mEq/L, K < 3.0 mEq/L, and decrease in eGFR by > 50%

Table 3
Predictors of Increased Risk of Metabolic Adverse Events among New Thiazide Users^a

Characteristics	Composite AEs (N=1,062)		Hyponatremia (N=1,041)		Hypokalemia (N=1,053)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Age, per 10 years [†]	1.30 (0.94-1.79)	1.28 (0.91-1.78)	1.53 (1.03-2.26) [‡]	1.47 (0.98-2.19)	1.02 (0.62-1.67)	1.03 (0.61-1.75)
Comorbidity Count						
1 (low)	Ref	Ref	Ref	Ref	Ref	Ref
2-4 (average)	1.24 (0.63-2.42)	1.42 (0.71-2.85)	0.90 (0.41-1.99)	1.13 (0.47-2.69)	1.17 (0.38-3.58)	1.27 (0.40-4.00)
5 (high)	2.59 (1.23-5.32) ^b	2.96 (1.41-6.21) ^c	2.21 (0.92-5.3)	2.63 (1.04-6.69) ^b	1.19 (0.34-4.15)	1.20 (0.31-4.61)
eGFR, mL/min/1.7 m ²						
60	Ref	Ref	Ref	Ref	Ref	Ref
< 60	1.08 (0.70-1.67)	0.94 (0.62-1.44)	1.16 (0.59-2.26)	0.95 (0.49-1.84)	1.64 (0.93-2.89)	1.56 (0.85-2.89)
Sodium, mEq/L						
140	Ref	Ref	Ref	Ref	-	-
135-139	1.73 (1.19-2.50) ^c	1.78 (1.23-2.58) ^c	3.50 (2.02-6.09) ^c	3.67 (2.13-6.33) ^c	-	-
Not tested	1.32 (0.80-2.17)	1.91 (0.56-6.55)	2.2 (1.02-4.93) ^b	2.54 (1.09-5.91) ^b	-	-
Potassium, mEq/L						
4.0	Ref	Ref	-	-	Ref	Ref
3.5-3.9	1.33 (0.85-2.08)	1.28 (0.82-2.01)	-	-	2.93 (1.31-6.52) ^c	3.13 (1.41-6.95) ^c
Not tested	1.09 (0.66-1.79)	0.81 (0.23-2.88)	-	-	2.38 (0.88-6.42)	2.56 (0.93-7.02)

Abbreviations: AEs, adverse events; eGFR, estimated glomerular filtration rate

^a Separate models were fitted for each outcome. All models were adjusted for the above covariates, plus sex, race/ethnicity, and dose of thiazide, accounting for clustering of patients within VA medical centers. Results shown are odds ratios with 95% confidence intervals

^b p-value < .05

^c p-value < .01