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ORIGINAL ARTICLE

Antihypertensive medications and the risk of kidney stones in older adults: a retrospective cohort study

R Todd Alexander[1,2], Eric McArthur[3], Racquel Jandoc[3], Blayne Welk[3,4,5], Jade S Hayward[3], Arsh K Jain[3,6], Branko Braam[7], Veit Flockerzi[8], Amit X Garg[3,5,6] and Robert Ross Quinn[9,10]

Antihypertensives are widely prescribed and could influence kidney stone risk by altering urinary calcium excretion. However, the impact of different classes of antihypertensives on kidney stone risk is unknown. To assess this impact, we conducted a retrospective, population-based cohort study using linked health administrative databases. Individuals aged >65 years who initiated one of the four antihypertensive classes (that is, angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers or thiazide diuretics) were included. The participants were followed for the occurrence of a kidney stone event while maintaining continuous usage on their drug class. The association between antihypertensive class and outcome was estimated by Cox regression. Of the 542 581 people included, we observed 4533 kidney stone events (0.83%) over a median follow-up of 368 days (365–729). Compared with beta-blockers, thiazides were associated with a lower risk of kidney stones (hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.68–0.84), ACEis/ARBs with a borderline decreased risk (HR 0.90; 95% CI 0.83–0.98) and calcium channel blockers with a comparable risk (HR 1.02; 95% CI 0.92–1.13). When the risk of requiring an intervention for a kidney stone was examined, the results were consistent with the primary analysis; however, the protective effect of ACEis/ARBs was eliminated (HR 0.96; 95% CI 0.87–1.06). In conclusion, relative to beta-blockers, thiazide diuretics were associated with a decreased risk of kidney stone formation in adults aged >65 years, whereas ACEis/ARBs and calcium channel blockers had a comparable risk of presenting with a kidney stone.
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INTRODUCTION

Kidney stones are common, affecting 1 in 10 men and 1 in 20 women,[1] and co-occur with many other common conditions, including chronic kidney disease, cardiovascular disease, diabetes and hypertension.[2–5] Antihypertensive medications are commonly prescribed to individuals with these conditions and may independently influence the risk of developing kidney stones by affecting urinary calcium excretion.

Most kidney stones are composed of calcium; consequently, hypercalciuria is the greatest risk factor for kidney stone formation.[6] Several classes of antihypertensive medications can affect renal calcium handling. Thiazide diuretics reduce urinary calcium excretion and are protective against kidney stone formation.[7] By contrast, calcium channel blockers increase urinary calcium excretion and may lead to a higher risk of stones.[8–10] The effects of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are less clear, but these antihypertensives may increase urinary calcium excretion by blocking the action of angiotensin II.[8–12] We are unaware of an effect of beta blockade on urinary calcium excretion. Whether the modification of urinary calcium excretion by different antihypertensive classes translates into a significantly increased risk of developing kidney stones is unknown.

The primary objective of our study was to determine whether initiating treatment with different classes of antihypertensive agents influences the likelihood of presenting with a kidney stone.

METHODS

Population/data sources

We used linked, administrative health databases housed at the Institute for Clinical Evaluative Sciences in Ontario, Canada to conduct a retrospective, population-based cohort study. Ontario has a population of approximately 13.7 million people, including 2 million individuals aged >65 years who have access to a universal health-care system and provincially funded prescription drug coverage.

[1]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; [2]Department of Physiology, University of Alberta, Edmonton, Alberta, Canada; [3]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; [4]Department of Surgery, Western University, London, Ontario, Canada; [5]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada; [6]Department of Medicine, Western University, London, Ontario, Canada; [7]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [8]Department of Pharmacology and Toxicology, Saarland University School of Medicine, Homburg, Germany; [9]Department of Medicine, University of Calgary, Calgary, Alberta, Canada and [10]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada
Correspondence: Dr RT Alexander, Department of Pediatrics, University of Alberta, 4-585 Edmonton Clinic Health Academy, 11405-87 Ave, Edmonton, Alberta, Canada T6G 2R7.
E-mail: todd2@ualberta.ca
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The data sets were linked using unique, encoded identifiers derived from health card numbers, and patient-level data were analyzed at the Institute for Clinical Evaluative Sciences. The vital statistics data were obtained from the Registered Persons Database. The Ontario Drug Benefits database provided prescription drug data.[13] The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) was used to identify hospital admissions, baseline comorbidity data and emergency department visits. The reasons for the visits were captured in the CIHI National Ambulatory Care Reporting System database. Finally, physician billing claims were used to identify visits for kidney stone episodes, and other relevant episodes of care were captured from the Ontario Health Insurance Plan database. The reporting of this study followed the guidelines for observational studies (Supplementary Table S1).[14]

Cohort entry criteria

We identified a cohort of individuals aged ⩾66 years (to avoid an incomplete medication history), who filled a new prescription for any of the following four drug classes between 1 April 2003 and 31 March 2014: calcium channel blockers, ACEis/ARBs, beta-blockers, or thiazide diuretics. Supplementary Table S3 includes a detailed list of the drug identification numbers used. Individuals with invalid data regarding the health-care number, age, sex or death were excluded. The date of the antihypertensive prescription served as the index date. To capture new users, we excluded individuals, who received a prescription for any of these drugs in the 180 days prior to the index date. For all analyses, individuals prescribed a beta-blocker were treated as the referent category because beta-blockers are not thought to alter urinary calcium excretion. All individuals who had filled a prescription for drugs that might alter kidney stone risk in the preceding 180 days, including loop diuretics, potassium-sparing diuretics, alpha adrenergic blocking agents, centrally acting anti-adrenergics, vasodilator antihypertensive drugs, adrenergic neuron blockers, direct renin inhibitors, indinavir, topiramate, prednisone or any non-oral formulation or a combination therapy of the study drugs, were excluded. Patients with end-stage renal disease (defined as being on chronic dialysis or having received a kidney transplant) and those who had a hospital admission in the previous 90 days prior to the index date were also excluded.

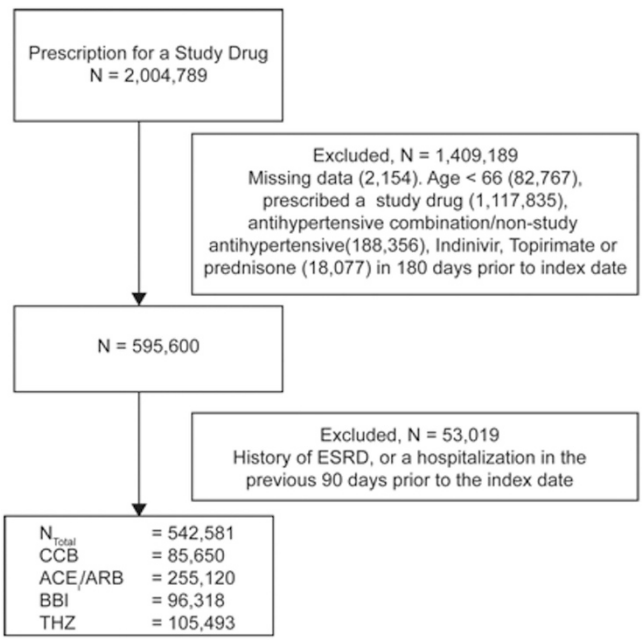

Figure 1 Cohort selection. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BBI, beta-blocker; CCB, calcium channel blocker; ESRD, end-stage renal disease; THZ, thiazide diuretic.

Baseline covariates

Demographic information, including age and sex, was obtained from the Registered Persons Database, and socioeconomic status was determined based on the neighborhood income quintile according to Statistics Canada. We used a 5-year look-back window to identify important baseline comorbidities, including alcoholism, chronic liver disease, dementia, heart failure, history of kidney stones, human immunodeficiency virus, hypercalcemia, hyperparathyroidism, hypertension, inflammatory bowel disease, leukemia, peripheral vascular disease and stroke/transient ischemic attack. We used 3 years of prior CIHI-DAD hospitalization data to calculate the Charlson comorbidity index. The Charlson comorbidity index was calculated based on the adaptation by Quan *et al.*[15] Codes were used to ascertain exposures, and the covariates are detailed in Supplementary Tables S3 and S4. The baseline demographic, comorbidity and treatment information was reported according to the first class of antihypertensive agent prescribed.

Identification of kidney stone events

Our primary outcome was the first presentation with a kidney stone to a primary care physician or emergency department or an admission to a hospital following the index antihypertensive prescription. These outcomes were captured using the Ontario Health Insurance Plan, CIHI-DAD and National Ambulatory Care Reporting System databases via a validated algorithm[2,3,16] based on the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes and the Tenth Revision (ICD-10-CA) diagnostic codes. A more specific outcome definition of kidney stones requiring surgery was evaluated in a secondary analysis. Refer to Supplementary Table S2 for a complete list of the diagnostic codes used to identify our primary outcome of interest.

Statistical analysis

Variables were complete with no missing values except for income quintile (0.3% missing) and rural residence (<0.1% missing). Standardized differences were used to assess the balance in baseline variables between the groups, with a standardized difference of >10% being considered potentially important.[17]

Patients were followed up from the time of the index prescription until the occurrence of the primary outcome, death, a prescription for a different study antihypertensive (that is, switch to prevent a carry-over effect), no subsequent prescription refill (stop) or the end of the study follow-up period (31 March 2015). To be defined as continually using the study drug, an individual was required to have a subsequent prescription refill for the same index drug class within 1.5 times the days supplied of their previous prescription.[18] Individuals were censored 365 days after their last prescription refill in order to allow time for a stone formed to become clinically apparent.

We used Cox proportional hazards regression with beta-blockers as the referent group to model the unadjusted hazard ratio (HR) and 95% confidence limits of a kidney stone event according to the class of antihypertensive prescribed. The models were adjusted for the following factors defined *a priori*: age (per 1 year), sex (male referent), number of primary care provider visits in the prior year (per one visit), and Charlson comorbidity score (per one unit increase) as well as history of stroke, diabetes, hypertension, hypercalcemia, hyperparathyroidism, kidney stones and inflammatory bowel disease. Please refer to Supplementary Table S4 for the specific codes.

Several sensitivity analyses were performed. First, we restricted the outcome definition to a kidney stone requiring surgical intervention. Second, calcium channel blockers were classified as either dihydropyridine or non-dihydropyridine calcium channel blockers based on their mechanism of action and their potential effect on urinary calcium excretion and were analyzed as two separate groups in an additional analysis. Finally, in subgroup analyses using interaction terms, we evaluated whether the presence or absence of a history of kidney stones, diabetes or hypertension in the preceding 5 years modified the relationship between the antihypertensive class and the risk of kidney stones.

We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, NC, USA, 2011) according to a prespecified protocol that was approved by the Institutional Review Board at Sunnybrook Health Sciences Centre

Table 1 Baseline characteristics

	Total		*Beta-blockers*		*ACEi/ARB*		*Calcium channel blockers (CCB)*		*Thiazide diuretics (THZ)*		*Standardized differences[a] (%) (relative to beta-blockers)*		
Characteristics	N	%	N	%	N	%	N	%	N	%	*ACEi/ARB*	*CCB*	*THZ*
Total patients	542 581	100.0	96 318	17.8	255 120	47.0	85 650	15.8	105 493	19.4	—	—	—
Demographics													
Age (mean ± s.d.)	73.64 ± 6.59		73.82 ± 6.60		73.11 ± 6.31		74.42 ± 6.92		74.14 ± 6.84		11	9	5
Female	300 253	55.3	50 368	52.3	127 938	50.1	50 276	58.7	71 671	67.9	4	13	32
Rural location[b,c]	73 576	13.6	13 747	14.3	32 804	12.9	9934	11.6	17 091	16.2	4	8	5
Prior urologist consult	51 601	9.5	10 299	10.7	25 640	10.1	7687	9.0	7975	7.6	2	6	11
Comorbidities													
Alcoholism	2657	0.5	625	0.6	1178	0.5	493	0.6	361	0.3	1	0	4
Chronic liver disease	15 920	2.9	3214	3.3	7443	2.9	2704	3.2	2559	2.4	2	1	5
Dementia	32 590	6.0	6312	6.6	14 260	5.6	5569	6.5	6449	6.1	4	0	2
Diabetes	54 415	10.0	5312	5.5	41 868	16.4	4078	4.8	3157	3.0	35	3	12
Heart failure	21 851	4.0	6107	6.3	9353	3.7	3371	3.9	3020	2.9	12	11	16
History of kidney stone	5086	0.9	992	1.0	2516	1.0	751	0.9	827	0.8	0	1	2
HIV	383	0.1	74	0.1	173	0.1	69	0.1	67	0.1	0	0	0
Hypercalcemia	358	0.1	102	0.1	132	0.1	65	0.1	59	0.1	0	0	0
Hyperpara-thyroidism	261	0.0	44	0.0	113	0.0	55	0.1	49	0.0	0	4	0
Hypertension	355 589	65.5	54 750	56.8	170 201	66.7	59 827	69.9	70 811	67.1	20	27	21
Inflammatory bowel disease	2150	0.4	443	0.5	951	0.4	317	0.4	439	0.4	1	1	1
Leukemia	5373	1.0	1154	1.2	2302	0.9	894	1.0	1023	1.0	3	2	2
Peripheral vascular disease	4020	70.0	951	1.0	1969	0.8	649	0.8	451	0.4	2	2	7
Stroke/TIA	7819	1.4	1548	1.6	4080	1.6	1178	1.4	1013	1.0	0	2	5
Charlson comorbidity index[d] (mean ± s.d.)	0.16 ± 0.69		0.20 ± 0.79		0.17 ± 0.69		0.16 ± 0.72		0.11 ± 0.58		4	5	13
Primary care physician visits (mean ± s.d.)	6.92 ± 7.92		7.70 ± 9.19		6.80 ± 7.54		6.90 ± 8.31		6.52 ± 7.19		11	9	14
Number of medications[e] (mean ± s.d.)	3.14 ± 3.30		3.33 ± 3.43		3.19 ± 3.29		3.00 ± 3.40		2.93 ± 3.12		4	10	12

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; TIA, transient ischemic attack.
[a]Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled s.d.; a value >10% is interpreted as a meaningful difference between the groups.[17]
[b]Rural residence was defined as a population <10 000 people.
[c]Location was missing for <0.1% of the cohort.
[d]Charlson comorbidity index[15] was calculated using 3 years of hospitalization data. 'No hospitalizations' received a score of 0.
[e]Baseline medication use in the 180 days preceding the index date was considered.

Table 2 Association between antihypertensive prescription and kidney stones

Drug group	*Number of individuals*	*Number with an event*	*Percentage with an event (%)*	*Incidence rate per 1000 person-years*	*Unadjusted HR (95% CI)*	*Adjusted HR (95% CI)*	*Adjusted P-value*
Beta-blockers (referent)	96 318	795	0.83	5.3	1.00	1.00	—
ACEi/ARB	255 120	2500	0.98	4.8	0.95 (0.88, 1.03)	0.90 (0.83, 0.98)	0.01
CCB	85 650	699	0.82	4.8	0.92 (0.83, 1.02)	1.02 (0.92, 1.13)	0.76
THZ	105 493	539	0.51	3.3	0.63 (0.56, 0.70)	0.76 (0.68, 0.84)	<0.01

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CI, confidence interval; HR, hazard ratio; THZ, thiazide diuretics.

(Toronto, Ontario, Canada). Participant informed consent was not required for this study. Two-sided *P*-values <0.05 were considered significant.

RESULTS

Characteristics of the cohort

A total of 2 004 789 patients filled a prescription for an antihypertensive drug during the accrual period. After the exclusions were applied, 542 581 patients met our criteria for cohort entry (Figure 1). A total of 255 120 (47%) patients had a prescription for an ACEi or an ARB; 85 650 (16%) patients received a calcium channel blocker; 105 493 (19%) patients received a thiazide diuretic; and 96 318 (18%) patients received a beta-blocker. The median follow-up time for the entire cohort was 368 days (365–729). The median follow-up time was 401 days (interquartile range (IQR): 365–888) for patients who were prescribed an ACEi or an ARB and 365 days for patients who received a beta-blocker (IQR: 349–576), calcium channel blocker (IQR: 260–685) or thiazide diuretic (IQR: 248–570). The baseline characteristics are presented in Table 1 according to the antihypertensive drug

Table 3 Association between antihypertensive prescription and kidney stone surgery

Drug group	*Number of individuals*	*Number with an event*	*Percentage with an event (%)*	*Unadjusted HR (95% CI)*	*Adjusted HR (95% CI)*	*Adjusted P-value*
Beta-blockers (referent)	96 318	515	0.53	1.00	1.00	—
ACEi/ARB	255 120	1693	0.66	1.00 (0.90, 1.10)	0.96 (0.87, 1.06)	0.42
CCB	85 650	495	0.58	1.01 (0.89, 1.14)	1.10 (0.97, 1.25)	0.12
THZ	105 493	353	0.33	0.64 (0.55, 0.73)	0.76 (0.67, 0.88)	<0.01

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CI, confidence interval; HR, hazard ratio; THZ, thiazide diuretics.

Table 4 Subgroup analysis

Drug group	*Number of individuals*	*Number with an event*	*Percentage with an event (%)*	*Adjusted HR (95% CI)*	*Interaction P-value*
Prior kidney stone					0.30
Beta-blockers (referent)	992	91	9.17	1.00	
ACEi/ARB	2516	286	11.37	1.01 (0.80, 1.29)	
CCB	751	81	10.79	1.17 (0.87, 1.58)	
THZ	827	64	7.74	0.86 (0.62, 1.19)	
No prior kidney stone					
Beta-blockers (referent)	95 326	704	0.74	1.00	
ACEi/ARB	252 604	2214	0.88	0.89 (0.81, 0.97)	
CCB	84 899	618	0.73	1.00 (0.90, 1.11)	
THZ	104 666	475	0.45	0.74 (0.66, 0.84)	
Diabetes					0.66
Beta-blockers (referent)	5312	67	1.26	1.00	
ACEi/ARB	41 868	591	1.41	0.80 (0.62, 1.04)	
CCB	4078	39	0.96	0.91 (0.61, 1.35)	
THZ	3157	25	0.79	0.85 (0.53, 1.34)	
No diabetes					
Beta-blockers (referent)	91 006	728	0.80	1.00	
ACEi/ARB	213 252	1909	0.90	0.91 (0.84, 0.99)	
CCB	81 572	660	0.81	1.03 (0.92, 1.14)	
THZ	102 336	514	0.50	0.76 (0.68, 0.85)	
Hypertension					0.27
Beta-blockers (referent)	54 750	461	0.84	1.00	
ACEi/ARB	170 201	1632	0.96	0.88 (0.79, 0.98)	
CCB	59 827	483	0.81	0.97 (0.85, 1.10)	
THZ	70 811	350	0.49	0.70 (0.61, 0.81)	
No hypertension					
Beta-blockers (referent)	41 568	334	0.80	1.00	
ACEi/ARB	84 919	868	1.02	0.93 (0.82, 1.06)	
CCB	25 823	216	0.84	1.10 (0.93, 1.31)	
THZ	34 682	189	0.54	0.87 (0.72, 1.04)	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CI, confidence interval; HR, hazard ratio; THZ, thiazide diuretics.

class. The groups were well balanced. Individuals prescribed a beta-blocker had a history of more visits to their primary care physicians, and those prescribed thiazide diuretics tended to have lower Charlson comorbidity scores and fewer baseline medications relative to those prescribed beta-blockers. There were more females prescribed a thiazide, and more individuals with diabetes mellitus received an ACEi/ARB relative to beta-blockers. The reasons for censoring are shown in Supplementary Table S5.

Relationship between the type of antihypertensive prescribed and kidney stone events

Overall, 0.83% of the cohort (4533 patients) experienced a kidney stone episode following a new antihypertensive prescription. The median time to event was 375 days (IQR: 147–910) for patients prescribed an ACEi or an ARB, 307 days (IQR; 136–714) for patients prescribed a beta-blocker, 300 days (IQR: 100–710) for patients prescribed a calcium channel blocker and 281 days

(IQR: 107–606) for patients prescribed a thiazide diuretic. Using beta-blockers as the referent group, we examined the risk of a kidney stone event based on the antihypertensive drug class (Table 2). Of those prescribed a beta-blocker, 795 (5.3 per 1000 person-years) experienced a kidney stone episode. Of those prescribed an ACEi or an ARB, 2500 (4.8 per 1000 person-years) had an event ($HR_{adjusted}$ 0.90; 95% confidence interval (CI): 0.83–0.98, $P=0.01$). Of those prescribed a calcium channel blocker, 699 (4.8 per 1000 person-years) had a stone episode ($HR_{adjusted}$ 1.02; 95% CI: 0.92–1.13, $P=0.76$) and 539 (3.3 per thousand person-years) of those receiving a thiazide had an event ($HR_{adjusted}$ 0.76; 95% CI: 0.68–0.84, $P<0.01$) (Table 2).

Sensitivity analyses

The lack of an altered risk in the calcium channel blocker group persisted in a sensitivity analysis examining the risk of presenting with a kidney stone requiring surgical intervention ($HR_{adjusted}$ 1.10; 95% CI: 0.97–1.25, $P=0.12$). This stricter, more specific definition attenuated the significantly decreased risk of kidney stones in patients receiving an ACEi/ARB ($HR_{adjusted}$ 0.96; 95% CI: 0.87–1.06, $P=0.42$). However, the protective association of thiazides was retained ($HR_{adjusted}$ 0.76; 95% CI: 0.67–0.88, $P<0.01$) (Table 3).

The risk of a kidney stone event did not vary according to the subclass of calcium channel blocker prescribed (Supplementary Table S6). A history of a prior kidney stone did not modify the effect of antihypertensive class on the occurrence of a subsequent stone (P-value for interaction = 0.30, Table 4) and neither did diabetes (P-value for interaction = 0.66) or hypertension (P-value for interaction = 0.27). Finally, the exclusion of patients with hypercalcemia and hyperparathyroidism did not significantly alter the results.

DISCUSSION

We examined the risk of presenting with a kidney stone in elderly patients treated with different classes of antihypertensive agents. New thiazide diuretic prescriptions were associated with a decreased risk relative to beta-blockers. Although ACEi/ARBs had a slight protective effect in the primary analysis, this effect did not persist when the stricter outcome of kidney stone surgery was used. Calcium channel blockers did not confer an altered risk of developing kidneys stones relative to beta-blockers in either analysis. Given the widespread long-term use of antihypertensive medications, these results are reassuring.

Kidney stones and hypertension are both common, and individuals who experience a kidney stone are more likely to have hypertension.[3,4] Furthermore, the administration of calcium channel blockers causes both natriuresis and calciuria.[8–10] Although the chronic administration of either Quinapril or Enalapril did not cause hypercalciruia,[19] angiotensin induces hypocalciuria,[11,12] suggesting that this inhibition could raise urinary calcium excretion. It is therefore biologically plausible that the increased urinary calcium excretion induced by the calcium channel blockers or ACEi/ARBs could confer an increased risk of kidney stone formation in persons receiving these drugs. Moreover, ACE signaling has been implicated in bone remodeling after injury.[20] These associations led us to examine the relative risk of stone formation by antihypertensive drug class prescription. In this large cohort of older persons (>65 years of age), we were unable to find an increased risk of kidney stones in those receiving a new prescription for either ACEi/ARBs or calcium channel blockers. We are unaware of any other studies examining kidney stone risk in persons receiving these classes of drugs.

Thiazide diuretics induce hypocalciuria, and multiple studies, including a large meta-analysis, support their clinical utility in reducing the risk of kidney stone formation.[21] Most kidney stones are composed of calcium (calcium oxalate or calcium phosphate), and drugs that reduce urinary calcium excretion decrease the risk of kidney stone formation. It should also be considered that renal calculi can take significant time to form.[22] Given our relatively short follow-up of approximately 1 year, we must consider the possibility that thiazides have a stabilizing effect, preventing stones from passing and, therefore, becoming clinically significant. Overall, our results support this notion and the utility of thiazides in preventing kidney stones.

Our results have potential implications for the delivery of health care and, in particular, the choice of antihypertensive agents. First, our study is consistent with previous studies suggesting that the use of thiazide diuretics is associated with a reduced risk of kidney stones.[7] However, the other classes of antihypertensives, despite their potential effects on urinary calcium excretion, do not appear to confer an altered risk of kidney stone formation. Thus the choice of antihypertensive should consider the potential cardiovascular or renal benefits of these therapies rather than the kidney stone risk when tailoring therapy to an individual patient.

Our study has several limitations. Our outcome relied on patients presenting to physicians for care of a kidney stone; therefore, asymptomatic kidney stones were not detected. Although we adjusted for multiple potential confounders, we were not able to adjust for some factors potentially affecting kidney stone formation, such as dietary factors, the occurrence of primary or secondary hypertension, the degree of blood pressure lowering, over-the-counter medications such as calcium and vitamin D and body mass index. Furthermore, individuals were not randomly assigned to the treatment groups. Thus the risk of residual confounding remains. In addition, as our cohort only included individuals aged >65 years, a confirmation of our results in younger patients is required. The need to censor when another study drug was administered to prevent contamination is also a limitation because the study drug may induce the development of a kidney stone, which may not present clinically for years to come. Despite these limitations, with the strict restriction of the outcomes to patients receiving a single study drug, we were still able to observe differences in the risk conferred by thiazide diuretics.

In conclusion, we found a decreased risk of kidney stones in adults aged >65 years who were prescribed a thiazide diuretic relative to beta-blockers. However, the new prescription of a calcium channel blocker or ACEi/ARB was not associated with an altered risk of kidney stone formation relative to beta-blockers. Given the number of individuals with kidney stones and hypertension, the lack of an increased risk of a clinically significant kidney stone episode in persons receiving a new prescription for ACEi/ARBs or calcium channel blockers is reassuring.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)