Published in final edited form as:

BJU Int. 2012 June ; 109(11): 1676–1684. doi:10.1111/j.1464-410X.2011.10593.x.

Commonly-used antihypertensives and lower urinary tract symptoms: Results from the Boston Area Community Health (BACH) Survey

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Abstract

Objective—To examine differences in the prevalence of lower urinary tract symptom (LUTS) among users of five common antihypertensive (AHT) classes compared to non-users, adjusted for LUTS risk factors in a large, representative sample.

Subjects and Methods—Data were from the Boston Area Community Health Survey, a population-based study of community-dwelling male and female (30–79y) residents of Boston, MA for whom prescription drug information was collected (2002–2005). The urologic symptoms of storage, voiding, and nocturia were assessed using interviewer-administered questionnaires and the American Urologic Association Symptom Index. This analysis was conducted among 1,865 participants with an AHT indication. Associations of angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers (CCBs), loop and thiazide diuretics with the three groups of LUTS were estimated using odds ratios (ORs) and 95% confidence intervals (CIs) from multivariate logistic regression (referent group=untreated hypertension). Overlap in use was accounted for using monotherapy and combination therapy exposure categories.

Results—Among women, monotherapy with CCBs was associated with increased prevalence of nocturia (OR=2.65, 95% CI: 1.04–6.74) and voiding symptoms (OR=3.84, 95% CI: 1.24–11.87); these results were confined to women aged <55. Among men of all ages, positive associations were observed for thiazides and voiding symptoms (monotherapy OR=2.90, 95% CI: 1.17–7.19), and loop diuretics and nocturia (combination therapy OR=2.55, 95% CI: 1.26–5.14).

Conclusion—Results are consistent with the hypothesis that certain AHTs may aggravate LUTS. The presence of new or worsening LUTS among AHT users suggests review of medications and consideration of a change in AHT class.

MESH Keywords

urination disorders; antihypertensive agents; epidemiology

Introduction

Lower urinary tract symptoms (LUTS) are common, bothersome and associated with decrements on quality-of-life scales.[1] In past cross-sectional studies, LUTS have been associated with chronic medical illness including heart disease[2, 3] and hypertension.[3–5] Certain antihypertensives, particularly diuretics and calcium channel blockers (CCBs), are known to be associated with increased risk of LUTS including nocturia[6–8] but little is known about sex-specific effects. Given the commonality of both hypertension, antihypertensive (AHT) use and LUTS, the objectives of this analysis were to examine whether frequently-used classes of AHTs had consistent associations with LUTS (specifically, voiding symptoms, storage symptoms, and nocturia). This is the first epidemiologic study that compares the prevalence of urologic symptoms among male and female users of a wide variety of common AHTs in a community-based sample.

Materials and Methods

Study design and data collection

The BACH Survey is a population-based epidemiologic study conducted among 5,503 persons aged 30 to 79 years residing in Boston, Massachusetts, USA. A multistage, stratified cluster sampling design was used to recruit approximately equal numbers of participants in pre-specified groups defined by age (30–39, 40–49, 50–59, 60–79), race/ethnicity and gender. The present analysis was of baseline, cross-sectional data collected 2002–2005 during an in-person interview conducted by a trained, bilingual interviewer after acquisition of written informed consent. Interviews for 63.3% of eligible persons were completed, with a resulting study population of 2301 men and 3202 women (1767 black, 1877 Hispanic, and 1859 white). All protocols and procedures were approved by the Institutional Review Board of New England Research Institutes. Further details of the study design and procedures are available.[9]

Urologic symptoms—voiding, storage and nocturia

We defined the presence of LUTS as a score of 8+ on the American Urologic Association Symptom Index (AUA-SI) (equivalent to the International Prostate Symptom Scale) that measures seven urologic symptoms (score range 0–35, higher=more symptomatic),[10] with further stratification by voiding (obstructive) symptoms and storage (irritative) symptoms. The AUA-SI was interviewer-administered, and is a widely-used instrument with excellent test-retest reliability, with a validated and reliable Spanish version.[10] [11] While the scale was originally developed to measure symptoms due to benign prostatic hyperplasia (BPH), its captured symptoms are not specific to the prostate (e.g., frequency, nocturia) and the scale has been validated among both men and women.[10, 12, 13] Higher scores indicate more symptoms (range 0–35). Consistent with a prior study,[3] our operational definition for storage symptoms was a score of 4+ (possible range 0–15) for the three relevant questions (frequency, urgency, nocturia). Similarly, a cutpoint of 5+ on a subscale of voiding symptoms created from four related questions (possible range 0–20) regarding incomplete emptying, intermittency, weak stream, and hesitancy was used to define the presence of voiding symptoms. These cutpoints correspond with the convention of using 8+ on the full LUTS scale to indicate “moderate and higher” symptoms.

Due to its common occurrence and impact on quality of life,[5, 14] the storage symptom of nocturia was considered separately. It was determined using responses to two questions: “During last month how often have you had to get up to urinate more than once during the night” and “In the last 7 days on average how many times have you had to go to the bathroom to empty your bladder during the night after falling asleep?” Those who reported

getting up ‘fairly often’ or more frequently to urinate 2+ times nightly after falling asleep (considering the past month) and/or those who reported on average urinating 2+ times nightly after falling asleep (considering the last 7 days) were defined as having nocturia.

Medications

Use of prescription medications were captured using self-report and direct observation/recording of medication labels by the interviewer. In the first process, participants were asked if they had taken any prescription drugs in the last four weeks for 14 indications (e.g., “In the last four weeks, have you been taking blood pressure or fluid pills?”) In the second process, participants were asked to gather containers for all medications used in the past four weeks. Medication labels and/or responses were coded using the Slone Drug Dictionary,[15] which classifies medications using a modification of the American Hospital Formulary Service Drug Pharmacologic Therapeutic Classification System. We considered the six classes of AHTs most commonly used in our population: beta blockers, angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, calcium channel blockers (CCBs), loop diuretics, and angiotensin receptor blockers (ARBs).[16] Because of substantial overlap in use, we created a four-level variable of mutually-exclusive exposure groups for use in statistical models representing: 1) the drug class of interest in monotherapy; 2) the class of interest used with other AHT(s); 3) use of any *other* AHT class(es); and 4) no AHT use (referent). Persons using two or more drugs in only one class were considered monotherapy for that class. Numbers were insufficient to consider ARBs, or loop diuretics in monotherapy in multivariate analyses.

Covariates

The mean of two interviewer-measured blood pressure values were used to define a case of measured hypertension using the cutpoints in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[17] (i.e., high systolic pressure: 140 mm Hg or high diastolic pressure: 90 mm Hg). Other comorbidities were based self-report of health care provider diagnosis. Body mass index (BMI) was calculated from interviewer-measured weight and height (normal <25, overweight 25–29.9, and obese >30 kg/m²). Socioeconomic status (SES) was constructed as a function of standardized income and education variables for the Northeastern U.S.[18] Physical activity was measured using the Physical Activity Scale for the Elderly and was categorized as low (<100), medium (100–250), and high (>250).[19]

Analytic sample

In previous analyses, we observed that self-reported hypertension was associated with overall LUTS among women[2] and that diuretic use was an independent risk factor for nocturia among women and men.[14] Given the importance of separating the underlying influence of hypertension with the potential influence of its treatment, a recommended strategy to control for ‘confounding by indication’ among AHT users was used.[20] Analyses were restricted to those with evidence of AHT indications, defined in our data as any of: measured hypertension, a self-report of ‘ever’ diagnosis of high blood pressure with current treatment or no treatment (i.e., persons treated in the past were assumed to have resolved hypertension and excluded), history of myocardial infarction, angina, congestive heart failure, or current AHT use. This left an analysis sample of 1,865 (33.8% of the original BACH sample). This proportion is comparable to the National Health Examination and Nutrition Survey for the prevalence of untreated or treated hypertension for 2001–2002 and 2003–2004 (26.0% and 29.3%, respectively), among a slightly younger study population (mean 44y) than BACH (mean 48y).[21]

Our analytic goal was to understand the association between AHT use and urologic symptoms, without confounding by established urologic disease. Therefore, we excluded those who reported surgical treatment for incontinence, had bladder or prostate surgery, had use of a catheter recommended to them, were current users of urologic medications, who had a history of genitourinary cancers, self-reported prolapsed bladder or neurogenic bladder. Persons who reported the significant neurologic disease states of Parkinson's disease and multiple sclerosis were also excluded. Thirty-six subjects taking only AHTs that were not among the six most popular classes were removed in order to accurately define "no AHT use".

Statistical Analysis

Analyses were unweighted and conducted using SAS version 9.2 and SUDAAN 10.0.1. Missing data were replaced by plausible values using multiple imputation; [22] less than 1% of data were missing for most variables. Multiple logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the AHT class of interest adjusted for relevant covariates. Due to gender differences in voiding and storage symptoms, [23] analyses were run separately among men and women, for five AHT exposures and three urologic symptom outcomes (30 models total). Potential confounders evaluated included age, race/ethnicity, diabetes, cardiac and vascular disease, stroke, BMI, physical activity, SES, health insurance status, smoking, arthritis, and use of statins. To determine the structure of the confounder-adjusted model, a full model was fit and backwards-selected to include only those covariates that induced 15% change in the drug-outcome OR in the final model (except that race/ethnicity and age were always retained, as design variables). [24]

Results

The characteristics of the analysis sample by AHT treatment status, and prevalence of LUTS are displayed in Table 1. Nocturia occurred in 40.8% of our sample and was the most common of the three symptom groups, followed by storage (35.6%) and voiding (11.3%). Persons on AHTs were on average nearly 10 years older than persons not using AHTs and were more often female, while race/ethnic differences between the two groups were not substantial. Persons using AHTs were less likely to report having no health insurance compared to users (10.0% vs. 22.4%) and less likely to be current smokers (24.6% vs. 34.6%, respectively). There were strong differences among AHT users vs. non-users by comorbidity status, especially for diabetes, where 31.7% of AHT users reported type I or II diabetes compared to 8.3% of non-users.

Table 2 displays the demographic characteristics of users of each class, and the substantial overlap in use among the AHT classes. Persons on loop and thiazide diuretics had the oldest and youngest mean ages (62.6y vs. 57.6y, respectively). Persons using ACE inhibitors were most likely to report using that drug class in monotherapy (36.8%), while users of loop diuretics were the least likely (13.5%). There was substantial overlap in use of beta blockers and other classes—approximately one-third to one-half of users of the five other classes also used a beta blocker. Results were similar for ACE inhibitors (except that only 7% of ARB users also used an ACE inhibitor) and thiazide diuretics (except that there was little overlap between use of loop and thiazide diuretics). Between 21.9% and 35.0% of users of other drug classes also reported the use of a CCB.

Considering fully-adjusted logistic regression models, there were more associations of drug exposure and urologic symptom outcomes observed among women (Table 3) than men (Table 5). Among women, only CCBs showed a significant association with a urologic symptom (nocturia) in monotherapy, while both CCBs and loop diuretics were significantly and consistently associated with voiding and nocturia symptoms when used with other

AHTs. We further explored whether there was any difference in association of CCBs with urologic symptoms by age (Table 4). CCB associations were confined to women aged <55, with no associations observed among women aged 55+. In monotherapy, associations with voiding and nocturia symptoms among women <55 became of stronger magnitude and were statistically significant, although confidence intervals for these estimates were imprecise (nocturia: OR=2.65, 95% CI: 1.04, 6.74; voiding: OR=3.84, 95% CI: 1.24, 11.87). There were insufficient numbers to separately analyze monotherapy with loop diuretics, but we observed significant associations of any use of loop diuretics with nocturia (OR=1.94, 95% CI: 1.12, 3.36) and voiding symptoms (OR=2.30, 95% CI: 1.08, 4.89), considering women of all ages. Because of the observed associations of CCBs with voiding symptoms and nocturia, we examined the loop diuretic associations when CCB users were removed from the analysis. The odds ratios were attenuated and no longer significant for nocturia (OR=1.53, 95% CI: 0.81, 2.90) and were slightly attenuated for voiding symptoms becoming non-significant (OR=2.19, 95% CI: 0.90, 5.34), suggesting that at least part of the association of loop diuretics when used with other AHTs was due to exposure to CCBs.

Among men, only the diuretic classes had significant associations with urologic symptoms in fully-adjusted models (Table 5). Monotherapy with thiazide diuretics was significantly associated with voiding symptoms (OR=2.90, 95% CI: 1.17, 7.19), although the imprecise confidence interval reflects the small number of observations in monotherapy (n=32). Use of loop diuretics with or without other AHTs was associated with nocturia symptoms (OR=2.55, 95% CI: 1.26, 5.14). We again hypothesized that some of the association observed for loop diuretics and nocturia may be due to interactions with CCBs, but removing men on CCBs from the loop diuretics analysis did not attenuate the loop diuretic estimate (OR=2.57, 95% CI: 1.06, 6.21). There was insufficient sample size to consider whether associations varied by subgroups of age for these diuretic associations.

Discussion

Our large, population-based study of urologic symptoms that also captured comorbidities, prescription drug exposures, and risk factors for urologic symptoms provided a unique opportunity to examine whether commonly-used AHT agents were associated with symptoms of voiding, storage, and nocturia. Our analysis strategy enabled consideration of the drug classes as monotherapy or used with other AHTs, so that associations could be identified in the absence of interactions with other AHTs. We believe this analysis is the broadest in scope on this topic to date, considering the number of urologic symptoms and AHT agents examined, as well as the first to try to account for overlap in use of AHTs.

Our confounder-adjusted models showed a significant association of CCBs with nocturia and voiding symptoms among younger women, but not men. In a past analysis of the BACH data, we found that CCBs were also significantly and substantially (more than 4-fold) associated with symptoms of painful bladder syndrome among women.[25] The L-type calcium channel receptor is expressed in the smooth muscle of the urinary bladder and, at least in the murine bladder, mediates spontaneous and cholinergic-induced contraction. Transgenic mice deficient in this receptor in smooth muscle have severely reduced micturition.[26] A direct relationship between estrogens and the regulation of L-type Ca²⁺ channels has been reported in neurons[27] and the urinary bladder.[28] Taken together these data provide a potential biological explanation, not only for observed effects of CCBs on LUTS, but also for the restriction of effects to younger women, and sex-related differences.

Among women, associations for loop diuretics with voiding and especially nocturia symptoms appeared to be at least partially explained by concomitant use of CCBs, while no associations with our three symptom groups were seen for thiazide diuretics. A past analysis

of the BACH Survey found that any diuretic use was a risk factor for nocturia, but it was restricted to broad comparisons and did not consider subgroups of common diuretics and the effect of underlying hypertension on nocturia.[14] Our findings are in agreement with most published studies on this topic that used multivariate methods. A study of diuretics and urologic symptoms among a primarily female clinic population aged 65+ found that diuretics (both loop and non-loop) were not associated with symptoms of nocturia after accounting for risk factors, although loop diuretics were found to be associated with overactive bladder, a storage-related condition, in contrast to our findings.[29] Two additional studies of older (60+) European community-dwelling populations found no persistent associations with any type of diuretics and nocturia but results were not presented by gender, permitting further comparison to our results.[30, 31] A study based on a younger Danish population of women (40–60) found an association with diuretics for the voiding symptoms of hesitancy and incomplete emptying, but not nighttime frequency.[32] Finally, a community-based study among those aged 60+ in Michigan found that use of any diuretics was an independent risk factor for nocturia, but results were not presented separately by gender; this may explain the differences compared to our results.[33]

Among men in the present analysis, there were associations for loop diuretics and nocturia, and thiazide diuretics and voiding symptoms not explained by concomitant use of CCBs. Our findings related to thiazide diuretics and voiding symptoms among men should be interpreted with caution as they were based on small numbers, but given the commonality of thiazide use, this would be a useful association to evaluate in future studies. A multivariate analysis of men in the Beaver Dam Eye Study found that diuretics (type not specified) were associated with overall LUTS, but only among men who did not have enlarged prostates. [34] Although we adjusted for comorbidities, our findings on loop diuretics among both genders may be confounded by severity of underlying disease. Loop diuretics were least likely to be used on their own in our population, and they are prescribed in preference over other diuretics for heart failure indications including acute decompensated heart failure.[35] The proportion of persons with congestive heart failure among users of loop diuretics in our data was 24%, by far the highest prevalence among the AHTs classes considered in our analysis; the next highest prevalence was 7% among users of ARBs (data not shown).

A recent analysis of a community-based study conducted in the Netherlands examined certain AHT medications in relation to incident LUTS among men in a longitudinal design. While thiazide diuretics and beta blockers were not significantly related to LUTS, CCBs were inversely related with risk of LUTS (hazard ratio=0.39, 95% CI: 0.15, 0.98).[36] The CCB amlodipine has recently been investigated for voiding symptom relief among men,[37] but we did not observe an inverse association for voiding symptoms among male CCB users in our analysis. It is possible that any protective effect of CCBs on voiding symptoms in men may take time to accumulate; duration of use was not captured in our study.

As a cross-sectional analysis of associations, our study cannot be used to make conclusions about cause and effect. Strengths of our study include the age, gender race/ethnic and socioeconomic diversity of our study population, the ability to examine overlap in use of common AHTs, and the community-based nature of our study with simultaneous capture of AHT use and urologic symptoms. The inclusion of persons outside of medical care also allows comparison of self-reported urologic symptoms among those with treated hypertension to those with untreated hypertension. The estimate of the proportion of our population with treated and untreated hypertension was similar to national estimates, suggesting our subpopulation of the BACH Survey is generalizable.[21] Other limitations of our study include a small number of events in some analyses, lack of information on dose or duration of use or compliance (i.e, it is not known if reported drugs were actually taken), and potential confounding by severity of underlying hypertension or other indications for AHTs.

The primary clinical implication from our analysis is that the CCB use among women under age 55 appears to be associated with approximately twice the odds of voiding and storage symptoms compared to women with untreated hypertension. However, users of most other commonly-used AHTs did not have more symptoms compared to non-users with hypertension, except for some diuretic classes among men. This may indicate that the potential for urologic symptoms from hypertension treatment may be less of a problem than is commonly believed. The presence of new, or worsening LUTS with hypertension treatment with CCBs among women should prompt review of medications and consideration of a change in class of AHT agent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

This work was supported by Award Number R21DK082652 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (NIH). Funding for the BACH Survey was provided by NIDDK DK 56842. The funder had no role in study design, data collection, data analysis, manuscript preparation and/or publication decisions. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIDDK or the NIH.

References

1. Litman HJ, McKinlay JB. The future magnitude of urological symptoms in the USA: projections using the Boston Area Community Health survey. *BJU Int.* 2007 Oct;100:820–825. Erratum in: *BJU Int.* 2007 Oct;100(4):971. [PubMed: 17550412]
2. Kupelian V, Rosen RC, Link CL, et al. Association of urological symptoms and chronic illness in men and women: contributions of symptom severity and duration--results from the BACH Survey. *J Urol.* 2009 Feb;181:694–700. [PubMed: 19091335]
3. Joseph MA, Harlow SD, Wei JT, et al. Risk factors for lower urinary tract symptoms in a population-based sample of African-American men. *Am J Epidemiol.* 2003 May 15;157:906–914. [PubMed: 12746243]
4. Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). *Int J Obes (Lond).* 2005 Mar;29:310–316. [PubMed: 15672112]
5. Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. *BJU Int.* 2003 Dec;92:948–954. [PubMed: 14632853]
6. Kujubu DA, Aboseif SR. An overview of nocturia and the syndrome of nocturnal polyuria in the elderly. *Nature clinical practice.* 2008 Aug;4:426–435.
7. Rosenberg MT, Newman DK, Tallman CT, Page SA. Overactive bladder: recognition requires vigilance for symptoms. *Cleveland Clinic journal of medicine.* 2007 May; 74(Suppl 3):S21–S29. [PubMed: 17546830]
8. Rosenberg MT, Staskin DR, Kaplan SA, MacDiarmid SA, Newman DK, Ohl DA. A practical guide to the evaluation and treatment of male lower urinary tract symptoms in the primary care setting. *Int J Clin Pract.* 2007 Sep;61:1535–1546. [PubMed: 17627768]
9. McKinlay JB, Link CL. Measuring the Urologic Iceberg: Design and Implementation of the Boston Area Community Health (BACH) Survey. *Eur Urol.* 2007 Aug;52:389–396. [PubMed: 17383808]
10. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol.* 1992 Nov;148:1549–1557. discussion 64. [PubMed: 1279218]

11. Badia X, Garcia-Losa M, Dal-Re R, Carballido J, Serra M. Validation of a harmonized Spanish version of the IPSS: evidence of equivalence with the original American scale. *International Prostate Symptom Score*. *Urology*. 1998 Oct;52:614–620. [PubMed: 9763080]
12. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK. Correlation of the American Urological Association symptom index with self-administered versions of the Madsen-Iversen, Boyarsky and Maine Medical Assessment Program symptom indexes. Measurement Committee of the American Urological Association. *J Urol*. 1992 Nov;148:1558–1563. discussion 64. [PubMed: 1279219]
13. Okamura K, Nojiri Y, Osuga Y, Tange C. Psychometric analysis of international prostate symptom score for female lower urinary tract symptoms. *Urology*. 2009 Jun;73:1199–1202. [PubMed: 19371926]
14. Fitzgerald MP, Litman HJ, Link CL, McKinlay JB. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. *J Urol*. 2007 Apr;177:1385–1389. [PubMed: 17382738]
15. Kelley KE, Kelley TP, Kaufman DW, Mitchell AA. The Slone Drug Dictionary: A research driven pharmacoepidemiology tool. *Pharmacoepidemiol Drug Safety*. 2003; 12:168–169.
16. Hall SA, Chiu GR, Kaufman DW, et al. General exposures to prescription medications by race/ethnicity in a population-based sample: results from the Boston Area Community Health Survey. *Pharmacoepidemiol Drug Saf*. 2010 Apr;19:384–392. [PubMed: 20140890]
17. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama*. 2003 May 21;289:2560–2572. [PubMed: 12748199]
18. Green LW. Manual for scoring socioeconomic status for research on health behavior. *Public Health Rep*. 1970 Sep;85:815–827. [PubMed: 4989476]
19. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993 Feb;46:153–162. [PubMed: 8437031]
20. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. *Bmj*. 1997 Nov 1;315:1151–1154. [PubMed: 9374894]
21. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension*. 2007 Jan;49:69–75. [PubMed: 17159087]
22. Schafer, JL. Analysis of incomplete multivariate data. New York: Chapman & Hall; 1997.
23. Kupelian V, Wei JT, O'Leary MP, et al. Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample: the Boston Area Community Health (BACH) Survey. *Arch Intern Med*. 2006 Nov 27;166:2381–2387. [PubMed: 17130393]
24. Rothman, KJ.; Greenland, S. *Modern Epidemiology*. Second Edition. Philadelphia: Lippincott-Raven Publishers; 1998.
25. Hall SA, Link CL, Pulliam SJ, et al. The relationship of common medical conditions and medication use with symptoms of painful bladder syndrome: results from the Boston Area Community Health Survey. *J Urol*. 2008 Aug;180:593–598. [PubMed: 18554659]
26. Wegener JW, Schulla V, Lee TS, et al. An essential role of Cav1.2 L-type calcium channel for urinary bladder function. *Faseb J*. 2004 Jul;18:1159–1161. [PubMed: 15132976]
27. Sarkar SN, Huang RQ, Logan SM, Yi KD, Dillon GH, Simpkins JW. Estrogens directly potentiate neuronal L-type Ca²⁺ channels. *Proceedings of the National Academy of Sciences of the United States of America*. 2008 Sep 30;105:15148–15153. [PubMed: 18815371]
28. Batra S. Interaction of antiestrogens with binding sites for muscarinic cholinergic drugs and calcium channel blockers in cell membranes. *Cancer chemotherapy and pharmacology*. 1990; 26:310–312. [PubMed: 2369797]
29. Ekundayo OJ, Markland A, Lefante C, et al. Association of diuretic use and overactive bladder syndrome in older adults: a propensity score analysis. *Arch Gerontol Geriatr*. 2009 Jul-Aug;49:64–68. [PubMed: 18752858]
30. Rembratt A, Norgaard JP, Andersson KE. Nocturia and associated morbidity in a community-dwelling elderly population. *BJU Int*. 2003 Nov;92:726–730. [PubMed: 14616455]

31. Bing MH, Moller LA, Jennum P, Mortensen S, Lose G. Nocturia and associated morbidity in a Danish population of men and women aged 60–80 years. *BJU Int.* 2008 Sep.102:808–814. discussion 14–5. [PubMed: 18564133]
32. Alling Moller L, Lose G, Jorgensen T. Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. *Obstet Gynecol.* 2000 Sep.96:446–451. [PubMed: 10960640]
33. Johnson TM 2nd, Sattin RW, Parmelee P, Fultz NH, Ouslander JG. Evaluating potentially modifiable risk factors for prevalent and incident nocturia in older adults. *J Am Geriatr Soc.* 2005 Jun.53:1011–1016. [PubMed: 15935026]
34. Klein BE, Klein R, Lee KE, Bruskewitz RC. Correlates of urinary symptom scores in men. *Am J Public Health.* 1999 Nov.89:1745–1748. [PubMed: 10553401]
35. Felker GM, O'Connor CM, Braunwald E. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? *Circ Heart Fail.* 2009 Jan.2:56–62. [PubMed: 19750134]
36. Kok ET, Schouten BW, Bohnen AM, Groeneveld FP, Thomas S, Bosch JL. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: the Krimpen Study. *J Urol.* 2009 Feb.181:710–716. [PubMed: 19091352]
37. Liu H, Liu P, Mao G, et al. Efficacy of combined amlodipine/terazosin therapy in male hypertensive patients with lower urinary tract symptoms: a randomized, double-blind clinical trial. *Urology.* 2009 Jul.74:130–136. [PubMed: 19371934]

Table 1

Characteristics of antihypertensives users and non-users among those with indications for antihypertensives, N=1865.

Covariates*	Using any antihypertensive (n=1204)	Not using any antihypertensive (n=661)	TOTAL (n=1865)
Age (Mean and SE)	58.4 (0.3)	49.3 (0.4)	55.2 (0.3)
Median	58.5	48.6	55.1
Female (%)	63.2	42.8	56.0
Age 65+ (%)	30.4	10.6	23.4
Socioeconomic status (%)			
Low	56.0	45.0	52.1
Middle	35.3	43.3	38.1
High	8.7	11.7	9.8
Race/ethnicity (%)			
Black	41.0	38.5	40.1
Hispanic	30.1	32.0	30.8
White	29.0	29.5	29.2
Health insurance (%)			
Private	41.5	43.9	42.3
Public	48.5	33.8	43.3
None	10.0	22.4	14.4
Current smoker (%)			
Never	44.1	41.8	43.3
Former	31.4	23.6	28.6
Current	24.6	34.6	28.1
Body mass index categories (%)			
<25.0	13.6	19.4	15.6
25.0–29.9	31.4	33.1	32.0
30.0+	55.1	47.5	52.4
Physical activity level (%)			
Low	49.3	29.4	42.3
Medium	40.5	49.9	43.8
High	10.1	20.7	13.9
LUTS (%)	22.9	17.8	21.1
Voiding symptoms (%)	12.3	9.6	11.3
Storage symptoms (%)	37.5	32.0	35.6
Weekly urinary incontinence (%)	8.1	4.0	6.6
Nocturia (%)	44.9	33.5	40.8
Urgency (%)	16.1	11.8	14.6
Frequency (%)	34.1	28.6	32.1
Type I or Type II diabetes (%)	31.7	8.3	23.4
Cardiac disease (%)	20.8	15.5	18.9

Covariates[*]	Using any antihypertensive (n=1204)	Not using any antihypertensive (n=661)	TOTAL (n=1865)
Vascular disease (%)	13.8	6.4	11.2
Stroke (%)	3.2	0.5	2.2
Hypertension (self-report) (%)	86.4	40.7	70.2
Hypertension (measured) (%)	34.8	71.0	47.6
Arthritis (%)	42.6	22.5	35.5
Statin use (%)	35.3	8.0	25.6

* Percents shown are column percents and may not sum to 100.0 due to rounding. SE: Standard error

Table 2

Characteristics of users by antihypertensive class, and overlap among classes.

	Beta blockers (N=504)	ACE inhibitors (N=547)	Calcium channel blockers (N=330)	Angiotensin receptor blockers (N=100)	Thiazide diuretics (N=451)	Loop diuretics (N=126)
Mean age (SE)	59.7 (0.5)	58.4 (0.5)	59.4 (0.6)	62.2 (1.0)	57.6 (0.5)	62.6 (0.9)
% 65+	35.5	29.3	36.4	40.0	28.4	44.4
% women	60.5	59.1	62.7	64.0	71.6	67.5
% using beta blockers	100.0	32.4	36.1	40.0	33.0	54.8
% using ACE inhibitors	35.1	100.0	36.4	7.0	35.7	51.6
% using CCBs	23.6	21.9	100.0	35.0	25.1	34.1
% using ARBs	7.9	1.3	10.6	100.0	10.6	13.5
% using thiazide diuretics	29.6	29.4	34.2	48.0	100.0	6.4
% using loop diuretics	13.7	11.9	13.0	17.0	1.8	100.0
% using only this class	31.6	36.8	27.6	19.0	27.5	13.5
% using 2 classes	36.5	36.6	29.7	37.0	45.7	31.0
% using 3+ classes	31.9	26.7	42.7	44.0	26.8	55.6

* Percents shown are column percents and may not sum to 100.0 due to rounding.

ACE=angiotensin-converting enzyme, CCB=calcium channel blocker, ARB=angiotensin receptor blocker.

Table 3

Odds ratios and 95% confidence intervals from confounder-adjusted logistic regression models of the association between antihypertensive classes and 3 LUTS outcomes among **WOMEN** (N=1044). ^a

		STORAGE			VOIDING			NOCTURIA		
N with outcome		425			119			481		
		OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Beta blockers				0.64 ^b			0.01 ^b			0.03 ^b
	No AHT use	283	referent	--	referent	--	referent	referent	--	--
	Using other AHT	456	1.07 (0.77, 1.47)		1.28 (0.76, 2.17)			1.60 (1.16, 2.21)		
	Using beta blockers and other AHTs	211	1.19 (0.81, 1.76)		2.06 (1.17, 3.62)			1.28 (0.87, 1.89)		
	Using beta blockers only	94	0.87 (0.53, 1.42)		0.58 (0.21, 1.59) ^c			1.18 (0.71, 1.95)		
ACE inhibitors				0.63 ^d			0.53 ^b			0.04 ^d
	No AHT use	283	referent	--	referent	--	referent	referent	--	--
	Using other AHT	438	0.99 (0.72, 1.38)		1.26 (0.75, 2.11)			1.39 (1.00, 1.94)		
	Using ACE inhibitors and other AHTs	211	1.02 (0.68, 1.52)		1.47 (0.81, 2.67)			1.38 (0.92, 2.06)		
	Using ACE inhibitors only	112	0.75 (0.46, 1.23)		1.57 (0.78, 3.16)			0.84 (0.52, 1.36)		
CCBs				0.09 ^d			0.04 ^e			<0.01 ^d
	No AHT use	283	referent	--	referent	--	referent	referent	--	--
	Using other AHT	554	0.87 (0.63, 1.19)		1.19 (0.71, 2.01)			1.13 (0.82, 1.55)		
	Using CCBs and other AHTs	153	1.34 (0.87, 2.05)		2.04 (1.10, 3.80)			1.93 (1.24, 2.98)		
	Using CCBs only	54	1.26 (0.69, 2.29)		2.29 (0.99, 5.30) ^c			2.11 (1.14, 3.89)		
Thiazide diuretics				0.21 ^b			0.09 ^b			0.35 ^d
	No AHT use	283	referent	--	referent	--	referent	referent	--	--
	Using other AHT	438	1.20 (0.87, 1.66)		1.59 (0.94, 2.68)			1.29 (0.92, 1.82)		
	Using thiazide diuretics and other AHTs	231	1.00 (0.69, 1.46)		1.40 (0.77, 2.54)			1.23 (0.84, 1.81)		
	Using thiazide diuretics only	92	0.73 (0.44, 1.22)		0.54 (0.20, 1.46) ^c			1.48 (0.90, 2.41)		
Loop diuretics ^f				0.12 ^d			<0.01 ^e			<0.01 ^d

N with outcome	STORAGE				VOIDING				NOCTURIA			
	OR	95% CI	p		OR	95% CI	p		OR	95% CI	p	
No AHT use	283	referent	--		referent	--			referent	--		
Using other AHT	676	0.93 (0.68, 1.27)			1.33 (0.81, 2.20)				1.26 (0.93, 1.73)			
Using loop and other AHTs	85	1.51 (0.89, 2.55)			2.30 (1.08, 4.89)				1.94 (1.12, 3.36)			

^aNumber of AHTs are limited to these 6 groups. Categories are mutually exclusive and the referent group is “not using any AHT”. Estimates in bold are have confidence intervals that exclude 1.00. OR=odds ratio, CI=confidence interval, AHT=antihypertensive, ACE=angiotensin-converting enzyme, CCB=calcium channel blocker.

^bModel adjusted for age and race/ethnicity. Model is fully-adjusted for confounders: no additional confounders identified after further consideration of diabetes, cardiac disease, stroke, body mass index, physical activity, socioeconomic status, health insurance status, smoking, arthritis, and use of statins (considered for all models in Table 3–5).

^cCell sizes of <10 in these comparisons.

^dConfounder-adjusted model contains age, race/ethnicity, and diabetes.

^eConfounder-adjusted model contains age, race/ethnicity, and cardiac disease.

^fThere were inadequate numbers to consider loop diuretics in monotherapy.

Table 4

Odds ratios and 95% confidence intervals from confounder-adjusted logistic regression models of the association between calcium channel blockers (CCBs) and 3 LUTS outcomes among **WOMEN** aged <55 (N=458) vs. aged 55+ (N=586).^a

	STORAGE				VOIDING				NOCTURIA			
	OR	95% CI	p		OR	95% CI	p		OR	95% CI	p	
CCBs <55 years												
N with outcome		193				60				196		
No AHT use	185	referent	--	0.33 ^b	referent	--	0.05 ^c	referent	--	--	0.03 ^e	
Using other AHT	206	(0.50, 1.23)			1.76	(0.89, 3.48)			1.36	(0.87, 2.11)		
Using CCBs and other AHTs	46	(0.64, 2.51)			2.59	(1.05, 6.40)^d			2.50	(1.22, 5.11)		
Using CCBs only	21	(0.57, 3.57)			3.84	(1.24, 11.87)^d			2.65	(1.04, 6.74)^d		
CCBs 55+ years												
N with outcome		232				59				285		
No AHT use	98	referent	--	0.25 ^f	referent	--	0.16 ^g	referent	--	--	0.08 ^e	
Using other AHT	348	(0.56, 1.46)			0.59	(0.27, 1.30)			0.87	(0.54, 1.41)		
Using CCBs and other AHTs	107	(0.81, 2.51)			1.19	(0.49, 2.87)			1.47	(0.82, 2.66)		
Using CCBs only	33	(0.51, 2.61)			0.99	(0.27, 3.66) ^d			1.60	(0.71, 3.60)		

^aCategories are mutually exclusive and the referent group is "not using any AHT". Estimates in bold are have confidence intervals that exclude 1.00. . OR=odds ratio, AHT=antihypertensive, ACE=angiotensin-converting enzyme, CI=confidence interval, CCB=calcium channel blocker. The following confounders were considered for all models: age, race/ethnicity, diabetes, cardiac disease, vascular disease, stroke, body mass index, physical activity, socioeconomic status, health insurance status, smoking, arthritis, and use of statins.

^bConfounder-adjusted model contains age, race/ethnicity, arthritis, and diabetes.

^cConfounder-adjusted model contains age, race/ethnicity, and cardiac disease.

^dCell sizes of <10 in these comparisons.

^eConfounder-adjusted model contains age, race/ethnicity, and diabetes.

^fConfounder-adjusted model contains age, and race/ethnicity.

^gConfounder-adjusted model contains age, race/ethnicity, and statin use.

Table 5

Odds ratios and 95% confidence intervals from confounder-adjusted logistic regression models of the association between antihypertensive classes (AHTs) and 3 LUTS among **MEN** (N=821).^a

	STORAGE				VOIDING				NOCTURIA			
	OR	95% CI	p		OR	95% CI	p		OR	95% CI	p	
N with outcome	239				93				281			
Beta blockers				0.10 ^b				0.32 ^c				0.84 ^e
No AHT use	378	referent	--	referent	referent	--	referent	--	referent	--	referent	--
Using other AHT	244	1.39 (0.95, 2.03)			1.12 (0.62, 2.03)				1.04 (0.72, 1.49)			
Using beta blockers and other AHTs	134	0.88 (0.53, 1.44)			0.61 (0.29, 1.24)				1.22 (0.79, 1.88)			
Using beta blockers only	65	0.75 (0.39, 1.45)			0.91 (0.38, 2.19) ^d				1.03 (0.57, 1.85)			
ACE inhibitors				0.33 ^b				0.53 ^c				0.52 ^f
No AHT use	378	referent	--	referent	referent	--	referent	--	referent	--	referent	--
Using other AHT	219	0.98 (0.65, 1.47)			0.99 (0.53, 1.84)				1.06 (0.73, 1.55)			
Using ACE inhibitors and other AHTs	135	1.11 (0.69, 1.80)			0.68 (0.34, 1.37)				1.01 (0.65, 1.57)			
Using ACE inhibitors only	89	1.58 (0.94, 2.65)			1.21 (0.55, 2.67)				0.70 (0.40, 1.22)			
CCBs				0.55 ^e				0.23 ^c				0.25 ^e
No AHT use	378	referent	--	referent	referent	--	referent	--	referent	--	referent	--
Using other AHT	320	1.12 (0.78, 1.62)			0.94 (0.53, 1.67)				0.97 (0.69, 1.37)			
Using CCBs and other AHTs	86	1.29 (0.76, 2.20)			0.53 (0.21, 1.31) ^d				1.59 (0.96, 2.63)			
Using CCBs only	37	1.60 (0.78, 3.30)			1.87 (0.68, 5.13) ^d				1.12 (0.56, 2.25)			
Thiazide diuretics				0.31 ^f				0.04 ^f				0.83 ^e
No AHT use	378	referent	--	referent	referent	--	referent	--	referent	--	referent	--
Using other AHT	315	1.15 (0.78, 1.69)			0.94 (0.53, 1.67)				1.14 (0.81, 1.61)			
Using thiazide diuretics and other AHTs	96	0.77 (0.45, 1.33)			0.55 (0.23, 1.34) ^d				0.98 (0.60, 1.60)			
Using thiazide diuretics only	32	1.59 (0.73, 3.47)			2.90 (1.17, 7.19)^d				0.91 (0.41, 1.99)			
Loop diuretics ^g				0.20 ^b				0.96 ^c				0.02 ^h

	STORAGE				VOIDING				NOCTURIA			
	OR	95% CI	p		OR	95% CI	p		OR	95% CI	p	
N with outcome		239				93				281		
No AHT use	378	referent	--		referent	--			referent	--		
Using other AHT	402	1.09 (0.77, 1.55)			0.93 (0.53, 1.61)				0.98 (0.70, 1.36)			
Combining monotherapy & loop + other AHT cats	41	1.89 (0.94, 3.77)			0.96 (0.38, 2.46) ^d				2.55 (1.26, 5.14)			

^aCategories are mutually exclusive and the referent group is “not using any AHT”. Estimates in bold are have confidence intervals that exclude 1.00. OR=odds ratio, CI=confidence interval, AHT=antihypertensive, ACE=angiotensin-converting enzyme, CCB=calcium channel blocker. The following confounders were considered for all models: age, race/ethnicity, diabetes, cardiac disease, vascular disease, stroke, body mass index, physical activity, socioeconomic status, health insurance status, smoking, arthritis, and use of statins.

^bModel adjusted for age, race/ethnicity, and cardiac disease.

^cModel adjusted for age, race/ethnicity, diabetes and cardiac disease.

^dCell sizes of <10 in these comparisons.

^eConfounder-adjusted model contains age and race/ethnicity.

^fConfounder-adjusted model contains age, race/ethnicity, and diabetes.

^gThere were inadequate numbers to consider loop diuretics in monotherapy.

^hConfounder-adjusted model contains age, race/ethnicity, and health insurance status.