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Tolerability of bedtime diuretics: A prospective cohort analysis

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ABSTRACT

OBJECTIVES

We sought to validate, or refute, the common belief that bedtime diuretics are poorly tolerated due to nocturia.

DESIGN

Prespecified prospective cohort analysis embedded within the randomized BedMed trial, in which hypertensive participants are randomized to morning vs. bedtime antihypertensive administration.

SETTING

352 community family practices across 4 Canadian provinces between March 2017 and September 2020.

PARTICIPANTS

552 hypertensive patients (65.6 years old, 57.4% female) already established on a single once-daily morning antihypertensive and randomized to switch that antihypertensive to bedtime. Of these, 203 used diuretics (27.1% thiazide alone, 70.0% thiazide/non-diuretic combinations) and 349 used non-diuretics.

INTERVENTION

Switching the established antihypertensive from morning to bedtime, and comparing the experience of diuretic and non-diuretic users.

PRIMARY AND SECONDARY OUTCOME MEASURES

PRIMARY OUTCOME: Adherence to bedtime allocation time at 6-months (defined as the willingness to continue with bedtime use, not an assessment of missed doses). SECONDARY 6-

MONTH OUTCOMES: 1) Nocturia considered to be a major burden, 2) Increase in overnight urinations/week. All outcomes were self-reported, and additionally collected at 6-weeks.

RESULTS

At 6-months: Adherence to bedtime allocation time was lower in diuretic users than non-diuretic users [77.3% vs 89.8%; difference 12.6%; 95%CI 5.8% to 19.8%; p<0.0001; NNH 8.0], and more diuretic users considered nocturia a major burden [15.6% vs 1.3%; difference 14.2%; 95%CI 8.9% to 20.6%; p < 0.0001; NNH 7.0]. Compared to baseline, diuretic users experienced 1.0 more overnight urinations/week [95%CI 0.0 to 1.75; p = 0.01]. Results did not differ between sexes.

CONCLUSIONS

Switching diuretics to bedtime did promote nocturia, but only 15.6% found nocturia a major burden. At 6-months, 77.3% of diuretic users were adherent to bedtime dosing. Bedtime diuretic use is viable for most hypertensive patients, if indicated.

TRIAL REGISTRATION

NCT02990663

Key Words: Hypertension, diuretics, nocturia, chronotherapy, bedtime

STENGTHS AND LIMITATIONS OF THIS STUDY

- Our study question arises directly from members of the public who participated in the design of the BedMed trial.

- Intervention and comparison groups were randomly selected from the same clinical trial population.
- Our data represent the first prospective evaluation of the tolerability of bedtime diuretics.
- Limitation: All participants were well established on morning antihypertensives at baseline. Those who previously tried and failed morning diuretics due to nocturia would be absent from the diuretic cohort. This could bias towards better bedtime diuretic tolerance.

INTRODUCTION

Although consensus is lacking,[1-3] two randomized trials by the same principal investigator suggest large reductions in major adverse cardiovascular events occur if blood pressure medications are taken at bedtime, as compared to conventional morning use.[4, 5] This finding, however, may be difficult to implement for those using diuretics - common first-line therapeutics, with a unique and important role in volume control and natriuresis.[6, 7] This is because diuretics are widely believed to promote nocturia, and typically recommended for morning use only as a result.[8, 9]

Nocturia occurs in roughly 2/3 of men and women over the age of 70 years[10] and is believed to disrupt sleep, impair quality of life, and increase the risk of nighttime falls and fractures. [11, 12] However, there are no randomized trials examining diuretic timing and adverse

effects. The concern that bedtime diuretics could produce troublesome nocturia, being based on opinion and observational data, could be incorrect. Morning diuretics (typically thiazides) are generally well tolerated, and cross-sectional analysis of diuretic-using populations, without accounting for administration time, does not support a strong association between diuretic use and nocturia. [13, 14] Whether clinicians can recommend diuretics for bedtime use is therefore unclear.

To determine how well diuretics are tolerated at bedtime we conducted a pre-specified prospective cohort study embedded within the ongoing BedMed trial. BedMed randomizes Canadian primary care patients with hypertension to take their existing antihypertensive medications either in the morning, or at bedtime, and examines mortality and morbidity outcomes.[15] Recruitment started in March 2017 and the trial is ongoing, with follow-up continuing until late 2023. This paper examines those participants with a single morning antihypertensive at baseline who were randomized to switch that antihypertensive to bedtime. Our goal was to compare adherence with bedtime allocation, and self-reported nocturia burden, between those switching a diuretic to bedtime, and those switching other types of blood pressure lowering medication to bedtime. Note, our definition of adherence to allocation time differs from the conventional notion. When we refer to adherence to bedtime allocation, we are talking about the participant's *intention* to use their antihypertensive at bedtime. This study is NOT evaluating the extent to which individual doses are missed. As such, we did not compare bedtime diuretic use to morning diuretic use because morning medication use was already well established for all participants. As we have defined it, we would expect virtually

everyone allocated to morning antihypertensives to be adherent to their administration time, as a morning allocation meant no change of any kind was needed.

METHODS

Study Design and Sample Size

BedMed is an ongoing prospective, randomized, open, blinded-endpoint (PROBE)[16] trial. Recruitment is registry-like, with participating family physicians using their usual-care electronic medical records to identify their eligible patients, and then mailing those patients information about the study. Interested patients call the study team and, if eligible and consenting, are randomized to take all their regular blood pressure medication (as tolerated) either in the morning, or at bedtime. Participants received their allocation, using the REDCap[17] server's central randomization module, directly from a research assistant with no prior clinical interactions, achieving irreversible, independent, and concealed allocation.

The prospective cohort study reported in this manuscript is a prespecified interim analysis of BedMed data, carried out as part of an adaptive trial design. The analysis was triggered upon the allocation to bedtime dosing of 203 participants whose only baseline antihypertensive included a morning diuretic (whether a diuretic only, or a diuretic/non-diuretic combination pill). If adherence with bedtime diuretic use had been poor, the BedMed trial's inclusion criteria would have been altered to exclude future such individuals from enrolling. This sample size gave a 90% chance of detecting a 20% relative reduction in adherence to bedtime allocation if 1) morning adherence was 75%, and 2) there were an equal

number of participants switching a non-diuretic antihypertensive to bedtime with whom to compare.

Setting and Participants

In Canada's publicly funded healthcare system, residents are not billed directly for physician services, but medication costs are either paid for privately, or partially or completely covered by either employer-sponsored health insurance, or government subsidized programs (including coverage for seniors). The vast majority of Canadians have family physicians, who are normally the sole prescriber of their patient's hypertension medications.

BedMed recruitment began in March 2017, with the final participant included in this analysis enrolling in September 2020. Over this period, participants were being recruited by 352 family physicians (typical practice panel ~ 1,500 patients, with 20% hypertension prevalence amongst adults) in the Canadian provinces of Alberta, Manitoba, British Columbia, and Saskatchewan. Some BedMed participants (22% of those randomized) also learned about the study through social media, or other sources, and were enrolled with their family physician's consent, but without their family physician actively recruiting them. To be eligible for BedMed, participants needed to be community dwelling (including assisted living), and to have a physician diagnosis of hypertension for which they used one or more blood pressure-lowering medications. BedMed excluded anyone with a personal history of glaucoma because of an association between nocturnal hypotension and ischemic optic neuropathy in such individuals.[18-21] For this sub-study we intentionally kept our eligibility criteria as broad as possible (including participants with potentially nocturia-modifying conditions like diabetes,

sleep apnea, and congestive heart failure) so as to most closely resemble, and be generalizable to, a hypertensive primary care population.

For this sub-study, the following inclusion and exclusion criteria defined the study cohort.

Inclusion Criteria

1. Physician diagnosis of hypertension
2. Only one antihypertensive pill in use at baseline (combination antihypertensive pills permitted)
3. That single baseline antihypertensive pill was used in the morning at baseline, and only once a day
4. The participant was randomized to switch that morning antihypertensive pill to bedtime

Exclusion Criteria

1. Participant did not attempt a medication timing change*
2. Physician changed the type of antihypertensive prior to the timing change*

*We made both these exclusions since, for the diuretic group, including patients who were not actually attempting to switch a diuretic to bedtime would have lessened any potential nocturia, and biased the groups towards looking more similar. When looking at adverse effects of an intervention, such a "modified intention-to-treat" analysis is the more conservative analytic option, given a full intention-to-treat analysis, for the reason described above, is more likely to underestimate nocturia-related problems.

Procedures

Assistance Changing Antihypertensive Medication to Bedtime

Participants had their choice of being assisted in making their timing change by their family physician, who applied their own judgement as to how to make the change or, if they described no heart disease, by the research assistant with whom they were dialoging. Exceptions included those whose BP-lowering medication was Tiazac XC or Diltiazem XC (which have delayed-release kinetics), and furosemide, isosorbide mononitrate/dinitrate, or alpha blockers (medications whose timing decision may be more complicated). Such participants had their family physician guide their timing change. Advice from research assistants was to delay the next morning dose until bedtime, and to continue all future doses at bedtime. If bedtime use was problematic, switching to dinnertime was suggested. As a memory aid, participants were advised to place pill bottles near objects they use when getting ready for bed (e.g., toothbrush, denture case, alarm clock), or to use an AM/PM dosette.

Follow-up Interviews

Baseline characteristics were collected directly from participants through telephone interview prior to randomization. The first follow-up with a research assistant occurred by telephone 7-days post timing change to encourage adhering to the timing change, and to troubleshoot participant concerns. Another telephone follow-up took place at 6-weeks to obtain self-reported adherence to bedtime antihypertensive use (“Are you taking your blood pressure medication at bedtime?”; and if “no” - the reason for not doing so), and to assess nocturia. Participants could report nocturia as “no”, “minor”, or “major” burden (subjective overall

assessment, no itemized criteria), and they were asked to quantify the number of overnight urinations per week by estimating the number of nights they rose to urinate, and the number of times per night they urinated on those evenings. The same follow-up questions were asked again at 6-months, either by telephone or by e-mail questionnaire (participant's choice), and again every 6-months thereafter.

Note: this study was not designed to explore whether or not individual medication doses were missed, something which could be better assessed with electronic devices, or pill counting. We were instead assessing each participant's willingness to persist with bedtime antihypertensive use. As such, self-report more accurately reflects the patient feedback prescribers could expect, were they to recommend diuretics be administered at bedtime.

Administrative Health Claims Data

Comorbidities were also collected as baseline characteristics (coronary artery disease, diabetes, sleep apnea, chronic kidney disease, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and stroke). For non-Alberta residents, these comorbidities were self-reported. For Alberta residents, the vast majority of participants (83%), these comorbidities were derived from physician diagnoses submitted to Alberta Health in the normal course of care, specifically, by extracting comorbidities from linked governmental databases recording community physician billings and hospital separations. Access and analysis of this administrative data was performed by Alberta Health Services, the governmental data steward. These data, and this linking process, have been widely used in other studies and have been identified as valid.[22-25] Most comorbidities were considered present if there were two

community visits with that diagnosis, or one hospital diagnosis, from any physician. However only one such diagnosis was required for stroke (since the diagnosis might not repeat outside of the acute event), and for chronic kidney disease (which, in our experience, is infrequently recorded by primary care providers).

Outcomes (as self-reported by participants)

Primary

1. Adherence to bedtime allocation at 6-months (nonadherence = changing back to morning, stopping altogether, or switching antihypertensives)

Secondary

1. Adherence to bedtime allocation at 6-weeks
2. Nocturia considered to be a "major burden" at 6-weeks, and at 6-months (includes those who report a major burden, and those who failed the timing change because of nocturia)
3. Number of overnight urinations per week at 6-weeks, and at 6-months

Statistical Analysis

Our inclusion and exclusion criteria created one prospective cohort with two exposures, 1) an established morning diuretic medication being switched to bedtime, and 2) an established morning non-diuretic medication being switched to bedtime. Participants using a combination pill with two or more antihypertensive components were considered diuretic users if at least one of those components was a diuretic. The analysis was by modified intention-to-treat and consisted of descriptive statistics, comparing proportions using Fisher's Exact Test (primary

outcome analysis), comparing the number of overnight urinations/week using Mann-Whitney, and using Hodges-Lehmann estimation for difference in medians. All analyses utilized GraphPad Prism version 9.1.2.

Modified Intention-to-treat Assumptions

1. Missing data: Missing variables were imputed using the value from the subsequent follow-up interview. For example, if 6-week data were missing, adherence and nocturia burden were assigned the 6-month value. If no subsequent data were available for imputation (i.e., loss to follow-up or study drop-out) participants were excluded from analysis. We did not impute missing values for lost or dropped-out participants because we were looking to demonstrate potential harm (harm constituting a difference in nonadherence or major nocturia burden) and imputing missing values, being reasonably balanced between groups, would have biased the groups towards looking more similar. Baseline characteristics of those excluded from the primary analysis were compared to assess whether analysis exclusion appeared random.
2. Medication changes: If nocturia resulted in participants switching medications, or medication timing, we considered them non-adherent and to have a "major nocturia burden", even if a lesser degree of nocturia burden was reported at their follow-up interview. Data from these non-adherent individuals was not used for assessment of nocturia frequency. If medication or timing changes were made for reasons other than nocturia, participants were excluded from analysis. We made this exclusion because

including such individuals would have biased the groups towards appearing more similar, and could have led us to underestimate the nocturia burden in diuretic users.

Patient and Public Involvement

Patient working group

BedMed has a 10-member patient working group which began meeting in 2016 prior to the recruitment of any participants. Working group members have participated in 1) the construction of all participant facing materials, 2) the wording of research assistant follow-up scripts, 3) decisions as to what data to collect, and 3) the hiring of research assistants.

Patient-driven question

The draft BedMed protocol was presented to a group of ~25 seniors in 2015, prior to grant application and study registration. The question pursued in this manuscript derived directly from this group's feedback, where concern was expressed that bedtime diuretics would be poorly tolerated due to nocturia.

RESULTS

Of 579 eligible participants, 552 (95.3%) had analyzable data at 6-weeks, and 533 (92.1%) had analyzable data at 6-months. This included, for our 6-month adherence primary outcome, 198/210 (94.3%) of the eligible diuretic users and 335/369 (90.8%) of the eligible non-diuretic users. Individual reasons for exclusion are shown in Figure 1. A comparison of baseline

characteristics (eTable 1 of the online supplement), shows no notable differences between those excluded from the primary outcome analysis, and those analyzed.

Baseline

Overall, most participants were from Alberta (83.0%), 94.7% identified as white, and they were a mean 65.6 (STD 10.0) years of age. Baseline characteristics were comparable between groups (Table 1) although slightly more diuretic users were female (65.5% vs 52.7%). They were largely non-smokers (92.4%), exercised a median 3 (IQR 0-5) days/week, and had a median BMI of 28.3 (IQR 25.5-32.3). The most common comorbidities were coronary artery disease (19.2%), sleep apnea (18.3%), and diabetes (17.2%). The cohort-defining medications used are broken down in Figure 2. Of the diuretic users, 142 (70.0%) used a thiazide containing combination pill, and 42 (20.7%) used hydrochlorothiazide alone. Although BedMed does not collect information on drug dosage, it would be unusual for Canadians to be prescribed hydrochlorothiazide outside a range of 12.5 – 25 mg/day. Of the non-diuretic cohort, 150 (43.0%) used angiotensin receptor blockers (ARB), 148 (42.4%) used angiotensin-converting enzyme inhibitors (ACEI), 38 (10.9%) used calcium channel blockers (CCB), 4 (1.1%) used beta-blockers (BB), and 9 (2.6%) used combination pills that did not include diuretics. Baseline nocturia was similar between diuretic vs non-diuretic users, in terms of the number of overnight urinations per week (median 5.5 vs 6.0), and the percentage of participants perceiving nocturia to be a major burden (1.5% vs 2.3%). However slightly more diuretic users felt nocturia was a minor burden (30.5% vs 23.5%). Overall, 3/4 of participants did experience nocturia at least once per week. Of these, 62.8% considered it “not a problem”, 34.5% considered it “a minor problem”, and 2.6% considered it “a major problem”.

Table 1. Baseline Characteristics			
Characteristics	Diuretic (n=203) No. (%)	Non-Diuretic (n=349) No. (%)	p-value
Sex, female	133 (65.5)	184 (52.7)	0.004
Age, mean (STD), y	65.4 (8.9)	65.6 (10.6)	0.81
Province			
Alberta	169 (83.3)	289 (82.8)	0.99
British Columbia	14 (6.9)	37 (10.6)	0.17
Manitoba	16 (7.9)	19 (5.4)	0.23
Saskatchewan	4 (2.0)	4 (1.1)	0.47
Ethnicity			
White	195 (96.1)	328 (94.0)	0.33
South east asian	2 (1.0)	10 (2.9)	0.23
Asian	0	3 (0.8)	0.30
First nation	0	6 (1.7)	0.09
Black	0	0	0.99
Other	5 (2.5)	2 (0.6)	0.11
Decline to answer	1 (0.5)	0	0.37
Comorbidities[a]			
Coronary artery disease	39 (19.2)	67 (19.2)	0.99
Diabetes	31 (15.3)	64 (18.3)	0.41
Sleep apnea	38 (18.7)	63 (18.1)	0.91
Chronic kidney disease	14 (6.9)	39 (11.2)	0.13
COPD	16 (7.9)	35 (10.0)	0.45
Stroke	11 (5.4)	18 (5.2)	0.99
Heart failure	4 (2.0)	6 (1.7)	0.99
Cigarette smoker (current)	14 (6.9)	28 (8.0)	0.74
Physical exercise, median (IQR), days per week[b]	3 (1-5)	3 (0-5)	0.14
BMI, median (IQR), Kg/M^2	28.9 (26-33)	28.0 (25-32)	0.15
Underweight (< 18.5)	1 (0.5)	2 (0.6)	0.99
Normal weight (18.5 - 24.9)	35 (17.2)	74 (21.2)	0.27
Overweight (25 - 29.9)	84 (41.4)	143 (41.0)	0.93

Obese (≥ 30)	83 (40.9)	130 (37.2)	0.42
Nocturia, median (IQR), nocturnal urinations/wk	5.5 (1-10.5)	6.0 (1-10.5)	0.91
Does not experience nocturia	49 (24.1)	86 (24.6)	0.92
Nocturia occurs but "not a problem"	89 (43.8)	173 (49.6)	0.22
Nocturia "a minor problem"	62 (30.5)	82 (23.5)	0.07
Nocturia "a major problem"	3 (1.5)	8 (2.3)	0.75

[a] Derived from Alberta provincial health claims data for 454 participants, and self-reported for 98.

[b] "How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"

6-Weeks

Adherence with bedtime medication use was lower in diuretic users (88.7% vs 94.6%), but still high in both cohorts [difference 5.8%; 95%CI, 1.0% to 11.6%; p = 0.02; NNH 17.0] (Table 2). Change in the number of overnight urinations per week could be calculated for 180 diuretic users, and 330 non-diuretic users (Figure 3). Compared to baseline, there were a median 1.0 more overnight urinations per week in diuretic users [95%CI, 0.0 to 1.5; p < 0.0001], and 9.9% more diuretic users perceived nocturia to be a major burden as compared with those who did not use diuretics [11.3% vs 1.4%; 95%CI Diff, 5.5% to 15.4%; p < 0.0001; Number Needed to Harm (NNH) 10.1] (Table 3).

6-Months

At 6-month, adherence to bedtime medication use (our primary outcome) had fallen somewhat in both groups (77.3% vs 89.8%), and the difference in adherence had widened [difference 12.6%; 95%CI Diff, 5.8% to 19.8%; p < 0.0001; NNH 8.0]. However most diuretic users were still adherent to bedtime medication use. Nocturia was given as the reason for nonadherence by 25/45 (55.6%) diuretic users, compared to 0/34 (0%) non-diuretic users, whose main reasons

for nonadherence were forgetting to take their pill (10/34, 29.4%), worsening of BP control (8/34, 23.5%), and non-symptom driven medication changes (6/34, 17.6%). Of those still adherent to allocation (153 diuretic users and 301 non-diuretic users), the median difference in overnight urinations compared to baseline remained 1.0 urinations per week higher in diuretic users, compared to non-diuretic users [95%CI, 0.0 to 1.75; p=0.012]. Including those who had stopped adhering because of nocturia, 14.2% more diuretic users had perceived nocturia to be a major burden [15.6% vs 1.3%; 95%CI Diff, 8.9% to 20.6%; p < 0.0001; NNH 7.0].

Sex Differences

Given slightly more diuretic users were female, we conducted a post-hoc analysis to determine whether nocturia burden or adherence differed between sexes. Using the Mann-Whitney test there was no difference, male vs female, in the number of overnight urinations at 6-weeks for the diuretic group [median difference 0.0; 95%CI Diff, -1.0 to 1.0; p = 0.96], nor for the non-diuretic group [median difference 0.0; 95%CI Diff, 0.0 to 0.0; p = 0.98]. Adherence with bedtime antihypertensive use, diuretic vs non-diuretic users, was also similar between males and females at 6-months [male: 76.5% vs 90.5%; female: 77.7% vs 89.3%; p = 0.86 for the difference in adherence between male and female diuretic users]. The same was true for major nocturia burden at 6-months, which was no different between sexes [male: 14.8% vs 0%; female: 16.0% vs 2.5%; p > 0.99 for the difference in major nocturia burden between male and female diuretic users].

Table 2. Non-adherence to Bedtime Allocation and Major Nocturia Burden, No. (%)

	Diuretic	Non-diuretic	Attributable Risk[c] (%) (95%CI)	p-value
6-weeks				
Major burden[a]	23/198 (11.6)	5/330 (1.5)	10.1 (5.6-15.7)	<0.0001
Nonadherence[b]	23/203 (11.3)	19/349 (5.4)	5.9 (1.0-11.6)	0.02
6-months				
Major burden[a]	28/180 (15.6)	4/301 (1.3)	14.2 (8.9-20.6)	<0.0001
Nonadherence[b]	45/198 (22.7)	34/335 (10.2)	12.6 (5.8-19.8)	<0.0001

[a]Includes those reporting major burden while using a bedtime diuretic, and those nonadherent due to nocturia. Data are number (%).

[b]Nonadherent for any reason. Data are number (%)

[c]Excess risk of the outcome (noncompliance or major burden) for those in the diuretic group, compared to the non-diuretic group.

Table 3. Change in Number of Overnight Urinations per Week, median (IQR)

	Number of Overnight Urinations per Week		Median Change from Baseline		Between Group Difference Median (95%CI)	p-value
	Diuretic	Non-diuretic	Diuretic	Non-diuretic		
Baseline	5.5 (1.0-10.5)	6.0 (1.0-10.5)	-	-	0.0[a,b] (0.0-0.0)	0.92
6-weeks	7.0 (2.6-11.6)	7.0 (1.5-10.5)	0.0 (0.0-3.5)	0.0 (-1.0-1.0)	1.0[a,c] (0.0-1.5)	<0.0001
6-months	6.2 (0.0-10.5)	5.0 (0.0-10.5)	0.5 (-1.5-4.0)	0.0 (-2.0-2.0)	1.0[a,d] (0.0-1.8)	0.01

[a] The between group difference in medians is by Hodges–Lehmann estimation, hence this value differs from a simple subtraction of the diuretic and non-diuretic group medians provided

[b] Between group difference for the median number of urinations per week at baseline

[c] Between group difference for the median change from baseline at 6-weeks

[d] Between group difference for the median change from baseline at 6-months

DISCUSSION

In this prospective cohort of hypertensive primary care patients, 1.5% of morning diuretic users experienced nocturia as a major burden at baseline. When these morning diuretic users switched their diuretic to bedtime, nocturia was more frequent, becoming a major burden for 15.6% of participants over a period of 6 months. Similar primary care patients simultaneously

switching other types of antihypertensives from morning to bedtime experienced no increase in nocturia, but they still failed to adhere to bedtime use 10.2% of the time. Due to the extra burden of nocturia, nonadherence in diuretic users was higher, at 22.7%. Hence 1 in 8 diuretic users, compared to non-diuretic users, will fail the switch to bedtime, with 1 in 4 diuretic users failing the switch overall.

Our findings are limited by the potential for selection bias, given some BedMed participants may have previously tried diuretics (morning or evening) and, if they experienced troublesome nocturia, may have stopped using diuretics altogether prior to enrolling. Morning diuretic users may also have avoided enrolling in BedMed if they were concerned about the possibility of needing to switch their diuretics to bedtime. The subjective nature of our outcomes might also be considered a limitation, in that nocturia burden could be interpreted differently by different people. However, self-reporting of nocturia burden integrates the patient's perceptions and values, and our use of it prioritizes the individual's own assessment of their experience. Our findings are simultaneously strengthened by the prospective nature of the design, and by the cohort selection process, which ensured diuretic and non-diuretic users were all recruited from the same practices, using the same approach, and meeting the same inclusion and exclusion criteria.

To our knowledge, our study is the first to prospectively evaluate the link between bedtime diuretic use and nocturia. Our finding the majority of diuretic users able to adhere to bedtime use is consistent with the generally weak and variable association of diuretics and nocturia in cross-sectional studies,[11, 13] and the inability of baseline diuretics to predict future nocturia (2-year incidence) in 1,289 community dwelling MESA study respondents 60 years and

older.[26] Although bedtime antihypertensive use might offer an advantage so far as cardiovascular risk reduction,[4, 5] our clinical experience is that most BP-lowering medication is still administered in the morning. In a 2017 survey of hypertensive primary care patients (single center in Ohio, 139 respondents), 75.5% used all of their antihypertensive medication in the morning.[27] Of the same population, 21 of 22 thiazide-diuretic users (95.5%) took that thiazide in the morning.

Although roughly 14% of hypertensive primary care patients will newly experience nocturia as a major burden after switching a thiazide diuretic from morning to bedtime, the vast majority of morning diuretic users can successfully make the switch to bedtime should it become clinically indicated to do so. The key remaining question is whether or not an attempt to switch diuretics to bedtime is clinically indicated for cardiovascular risk reduction, as the MAPEC and Hygia trials suggest.[4, 5] Three confirmatory trials, of which BedMed is one, are currently underway,[28-30] with one, the TIME trial,[28] recently reporting neither benefit, nor harm, to bedtime prescribing at the Aug 2022 European Society of Cardiology Congress. Detailed publication of the TIME findings are anticipated later this year, with BedMed expected to report in mid 2024.

CONTRIBUTORS

SRG conceptualized the study. SRG, CSK, MRK, GMA, JAB, AGS, AK, FAM, RSP, RL, MDH, KM, DPM, STW, JPM, LAG designed the study and obtained grant funding. SRG, CSK, MRK, GMA, AGS, BGON, MGDPM, DAM, JEMK, JPMA recruited physicians for the study. SRG supervised the conduct of the trial. MDK and JMSY prepared the study data. SRG and MDK analyzed the data.

SRG and MDK wrote the draft manuscript. All authors contributed to critical revision of the manuscript, and all authors approved the final manuscript. SRG is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: SRG is the nominated principal applicant of two grants from governmental sources that are funding the BedMed trial (from Alberta Innovates, and the Canadian Institutes of Health Research); RSP is CEO of "mmHg Inc", a digital health company and maker of software solutions for BP monitoring; MDH is the recipient of several grants from pharmaceutical and device companies related to interventions geared at stroke treatment. He holds two device patents related to stroke imaging, has chaired or sat on the Data Safety Monitoring Boards of 5 other cardiovascular trials, is the President of the Canadian Neurological Sciences Federation, a member of the board of the Canadian Stroke Consortium, and has private stock ownership in two companies targeting imaging interventions (Circle Inc, and PureWeb Inc).

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DATA SHARING

De-identified patient level data upon which this analysis is based will be freely available for download at www.PragmaticTrials.ca following publication.

ETHICAL APPROVAL

All procedures and methods were approved by the clinical research ethics boards of the Universities of Alberta (Pro00045958), Calgary (REB17-1887), British Columbia (H21-00523), Saskatchewan (1421), and Manitoba (HS20852:B2017:08).

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FIGURE LEGENDS

Figure 1:

Figure 1 Study flow diagram for analysis of adherence

Figure 2:

Figure 2 Medication frequency at baseline. HCTZ = hydrochlorothiazide

Figure 3:

Figure 3 6-week change in overnight urinations per week. Figure is the change in the number of overnight urinations per week experienced by hypertensive primary care patients 6-weeks after being randomly allocated to switch their only blood pressure lowering pill from morning to bedtime. Grouped by those whose pill contained a diuretic (90.7% of which were thiazides), and those who used a different class of blood pressure lowering medication.

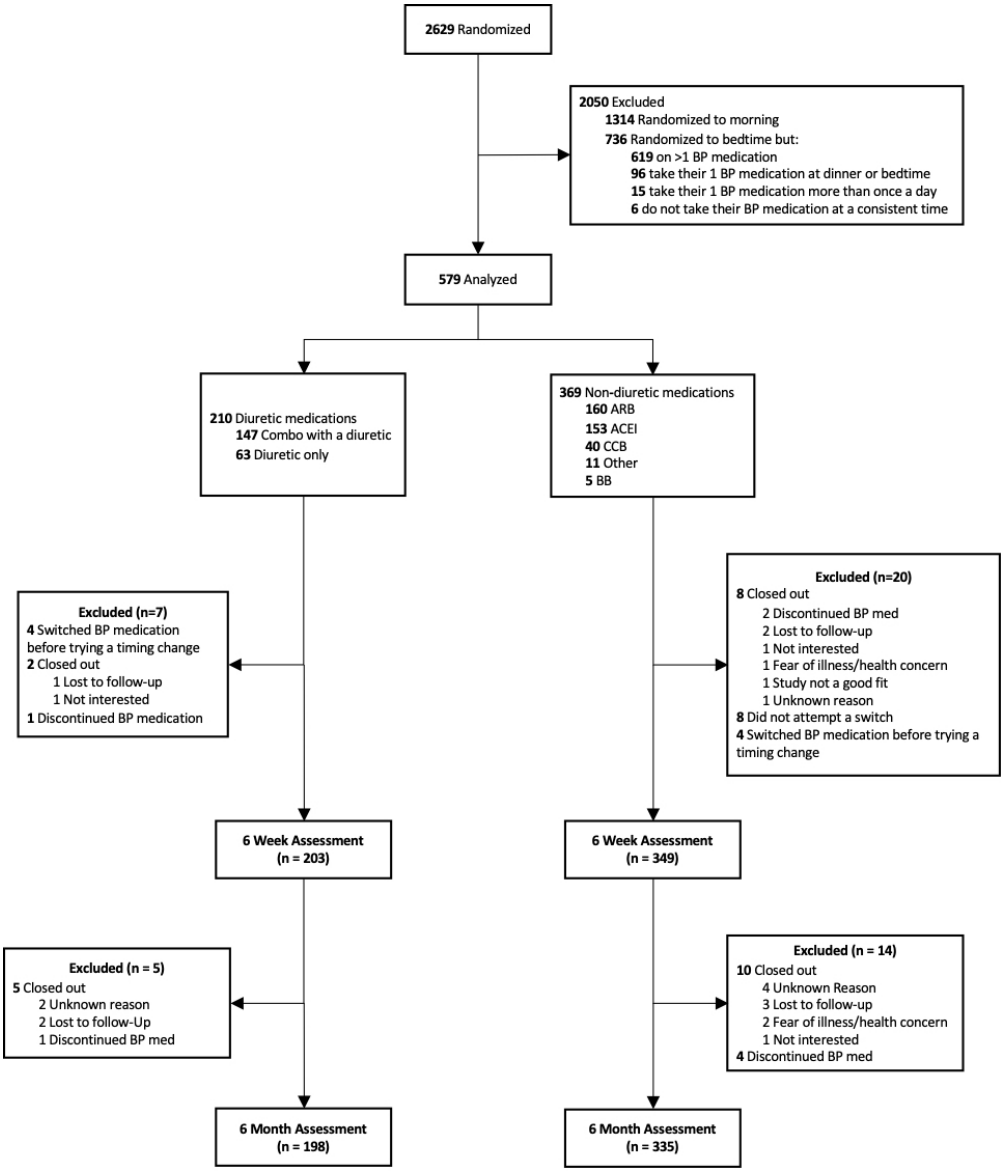


Figure 1 Study flow diagram for analysis of adherence

163x190mm (150 x 150 DPI)

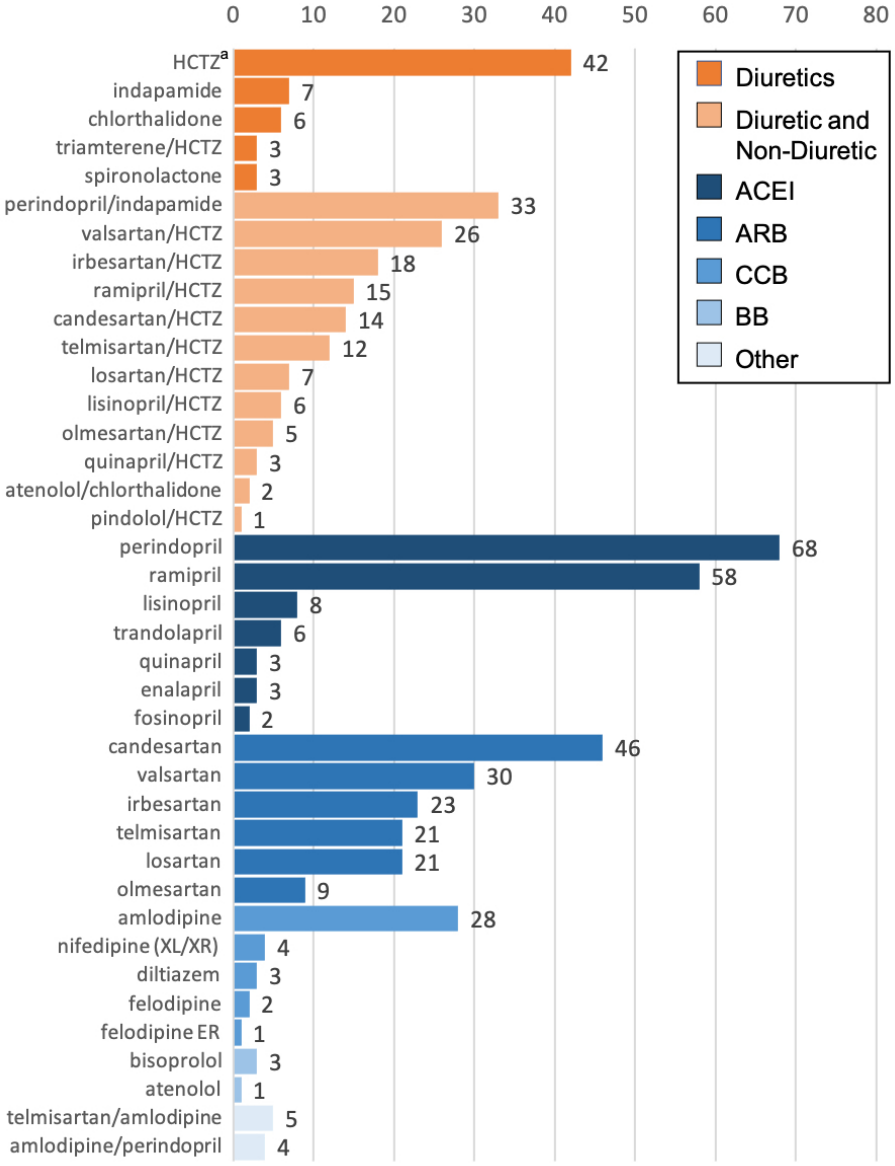
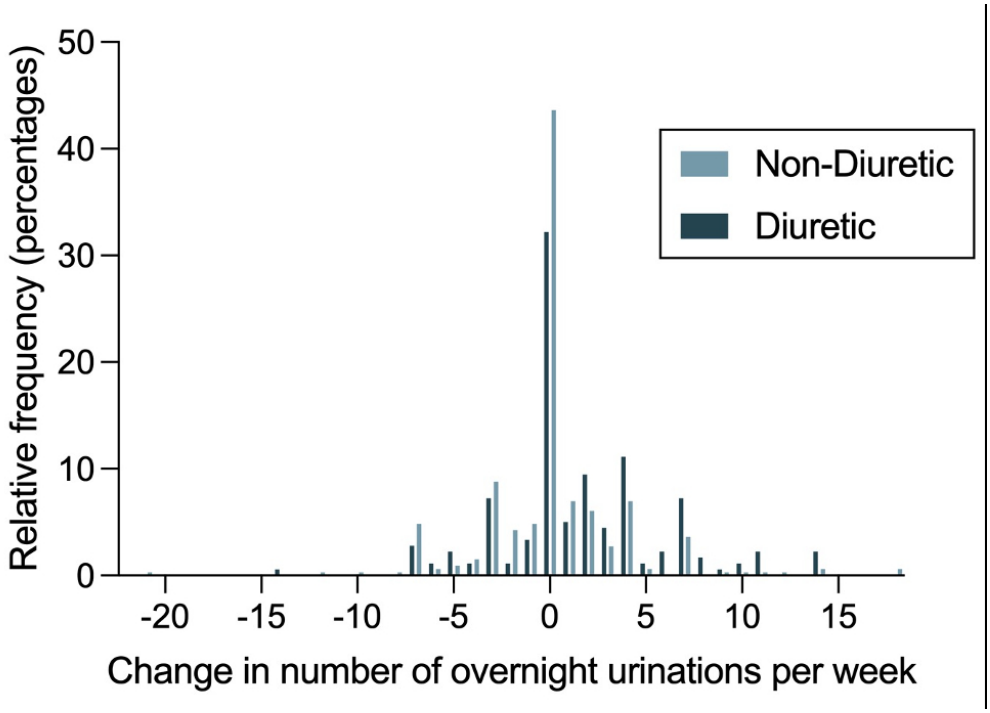


Figure 2 Medication frequency at baseline. HCTZ = hydrochlorothiazide

154x200mm (150 x 150 DPI)



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165x116mm (150 x 150 DPI)

Tolerability of Bedtime Diuretics:
A Prospective Cohort Analysis
(Supplementary Information)

eTable 1. Comparison of baseline characteristics for participants that were excluded vs. included in the primary outcome analysis

Characteristics	Excluded (n=46) No. (%)	Included (n=533) No. (%)	p-value
Sex, female	27 (58.7)	308 (57.8)	0.99
Province			
Alberta	39 (84.8)	442 (82.9)	0.84
British Columbia	4 (8.7)	48 (9.0)	0.99
Manitoba	2 (4.4)	35 (6.6)	0.76
Saskatchewan	1 (2.2)	8 (1.5)	0.53
Rural resident	4 (8.7)	71 (13.3)	0.49
Age, mean (STD), y	64.6 (10.6)	65.5 (10.0)	0.55
≤ 29	0	1 (0.2)	0.99
30 - 39	0	2 (0.4)	0.99
40 - 49	3 (6.5)	24 (4.5)	0.46
50 - 59	9 (19.6)	116 (21.8)	0.85
60 - 69	18 (39.1)	202 (37.9)	0.87
70 - 79	11 (23.9)	146 (27.4)	0.73
80 - 89	5 (10.9)	39 (7.3)	0.38
≥ 90	0	3 (0.6)	0.99
Ethnicity			
White	43 (93.5)	504 (94.6)	0.73
South east asian	0	12 (2.3)	0.61
Asian	1 (2.2)	3 (0.6)	0.28
First nation	0	6 (1.1)	0.99
Black	0	0	0.99
Other	1 (2.2)	7 (1.3)	0.49
Decline to answer	1 (2.2)	1 (0.2)	0.15

Education level			
Less than high school	4 (8.7)	21 (3.9)	0.13
High school diploma	19 (41.3)	147 (27.6)	0.06
Technical or trade college diploma	9 (19.6)	146 (27.4)	0.30
University degree	13 (28.3)	219 (41.1)	0.12
Decline to answer	1 (2.2)	0	0.08
Annual household income, CAD$			
< 25,000	4 (8.7)	25 (4.7)	0.28
25,000 to 100,000	20 (43.5)	287 (53.8)	0.22
> 100,000	20 (43.5)	189 (35.5)	0.34
Decline to answer	2 (4.4)	32 (6.0)	0.99
Comorbidities[a]			
Coronary artery disease	9 (19.6)	100 (18.8)	0.85
Diabetes	6 (13)	92 (17.3)	0.54
Sleep apnea	11 (23.9)	99 (18.6)	0.43
Chronic kidney disease	7 (15.2)	48 (9.0)	0.19
COPD	6 (13.0)	50 (9.4)	0.43
Stroke	1 (2.2)	28 (5.3)	0.72
Heart failure	0	10 (1.9)	0.99
Hip fracture	1 (2.2)	2 (0.4)	0.22
Cigarette smoker (current)	2 (4.4)	42 (7.9)	0.56
Nocturia, median (IQR), nocturnal urinations/wk	7 (0-14.0)	6 (1-10.5)	0.61
Does not experience nocturia	12 (26.1)	129 (24.2)	0.72
Nocturia occurs but "not a problem"	21 (45.6)	255 (47.8)	0.88
Nocturia "a minor problem"	12 (26.1)	139 (26.1)	0.99
Nocturia "a major problem"	1 (2.2)	10 (1.9)	0.60
Physical exercise, median (IQR), days per week[b]	3 (0-5.0)	3 (0.5-5.0)	0.42
0	15 (32.6)	133 (25.0)	0.29
1	6 (13.0)	43 (8.1)	0.26
2	1 (2.2)	68 (12.8)	0.03
3	6 (13.0)	75 (14.1)	0.99
4	6 (13.0)	54 (10.1)	0.46
5	2 (4.4)	49 (9.2)	0.41

6	1 (2.2)	15 (2.8)	0.99
7	9 (19.6)	96 (18.0)	0.84
BMI, median (IQR), Kg/M^2	27.7 (26.1-33.4)	28.3 (25.5-32.3)	0.80
Underweight (< 18.5)	0	3 (0.6)	0.99
Normal weight (18.5 - 24.9)	9 (19.6)	105 (19.7)	0.99
Overweight (25 - 29.9)	21 (45.7)	220 (41.3)	0.64
Obese (≥ 30)	16 (34.8)	205 (38.5)	0.75
EQ-5D-5L overall health score, median (IQR)[c]	80 (75-90)	80 (75-90)	0.88
Physically frail[d]	7 (15.2)	73 (13.7)	0.82
Cognition[e]			
Normal	41 (89.1)	496 (93.1)	0.37
Questionable impairment	3 (6.5)	36 (6.8)	0.99
Impairment consistent with dementia	2 (4.4)	1 (0.2)	0.02

[a] Derived from Alberta provincial health claims data and self-report.
[b] "How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"
[c] Self-rating of overall health on a scale of 0 (worst) to 100 (best).
[d] As per Tilburg Frailty Indicator's physical sub-scale (sub-scale score ≥3 defines physically frail).
[e] As per Short Blessed screening test score. Considered to be normal (0-4), questionable impairment (5-9), or impairment consistent with dementia (>9).

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Tolerability of bedtime diuretics: A prospective cohort analysis

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Primary Subject	Cardiovascular medicine

Heading:	
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice, Urology
Keywords:	Hypertension < CARDIOLOGY, CLINICAL PHARMACOLOGY, PRIMARY CARE, Cardiology < INTERNAL MEDICINE

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Tolerability of bedtime diuretics: A prospective cohort analysis

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ABSTRACT

OBJECTIVES

We sought to validate, or refute, the common belief that bedtime diuretics are poorly tolerated due to nocturia.

DESIGN

Prespecified prospective cohort analysis embedded within the randomized BedMed trial, in which hypertensive participants are randomized to morning vs. bedtime antihypertensive administration.

SETTING

352 community family practices across 4 Canadian provinces between March 2017 and September 2020.

PARTICIPANTS

552 hypertensive patients (65.6 years old, 57.4% female) already established on a single once-daily morning antihypertensive and randomized to switch that antihypertensive to bedtime. Of these, 203 used diuretics (27.1% thiazide alone, 70.0% thiazide/non-diuretic combinations) and 349 used non-diuretics.

INTERVENTION

Switching the established antihypertensive from morning to bedtime, and comparing the experience of diuretic and non-diuretic users.

PRIMARY AND SECONDARY OUTCOME MEASURES

PRIMARY OUTCOME: Adherence to bedtime allocation time at 6-months (defined as the willingness to continue with bedtime use, not an assessment of missed doses). SECONDARY 6-

MONTH OUTCOMES: 1) Nocturia considered to be a major burden, 2) Increase in overnight urinations/week. All outcomes were self-reported, and additionally collected at 6-weeks.

RESULTS

At 6-months: Adherence to bedtime allocation time was lower in diuretic users than non-diuretic users [77.3% vs 89.8%; difference 12.6%; 95%CI 5.8% to 19.8%; p<0.0001; NNH 8.0], and more diuretic users considered nocturia a major burden [15.6% vs 1.3%; difference 14.2%; 95%CI 8.9% to 20.6%; p < 0.0001; NNH 7.0]. Compared to baseline, diuretic users experienced 1.0 more overnight urinations/week [95%CI 0.0 to 1.75; p = 0.01]. Results did not differ between sexes.

CONCLUSIONS

Switching diuretics to bedtime did promote nocturia, but only 15.6% found nocturia a major burden. At 6-months, 77.3% of diuretic users were adherent to bedtime dosing. Bedtime diuretic use is viable for many hypertensive patients, should it ever become clinically indicated.

TRIAL REGISTRATION

NCT02990663

Key Words: Hypertension, diuretics, nocturia, chronotherapy, bedtime

STENGTHS AND LIMITATIONS OF THIS STUDY

- Our study question arises directly from members of the public who participated in the design of the BedMed trial.

- Intervention and comparison groups were randomly selected from the same clinical trial population.
- Our data represent the first prospective evaluation of the tolerability of bedtime diuretics.
- Limitation: Those who previously tried and failed morning diuretics due to nocturia would be absent from the diuretic cohort, which could bias towards better bedtime diuretic tolerance.

INTRODUCTION

Although consensus is lacking,[1-3] two randomized trials by the same principal investigator suggest large reductions in major adverse cardiovascular events occur if blood pressure medications are taken at bedtime, as compared to conventional morning use.[4, 5] This finding, however, may be difficult to implement for those using diuretics - common first-line therapeutics, with a unique and important role in volume control and natriuresis.[6, 7] This is because diuretics are widely believed to promote nocturia, and typically recommended for morning use only as a result.[8, 9]

Nocturia occurs in roughly 2/3 of men and women over the age of 70 years[10] and is believed to disrupt sleep, impair quality of life, and increase the risk of nighttime falls and fractures. [11, 12] However, there are no randomized trials examining diuretic timing and adverse effects. The concern that bedtime diuretics could produce troublesome nocturia, being based

on opinion and observational data, could be incorrect. Morning diuretics (typically thiazides) are generally well tolerated, and cross-sectional analysis of diuretic-using populations, without accounting for administration time, does not support a strong association between diuretic use and nocturia. [13, 14] Whether clinicians can recommend diuretics for bedtime use is therefore unclear.

To determine how well diuretics are tolerated at bedtime we conducted a pre-specified prospective cohort study embedded within the ongoing BedMed trial. BedMed randomizes Canadian primary care patients with hypertension to take their existing antihypertensive medications either in the morning, or at bedtime, and examines mortality and morbidity outcomes.[15] Recruitment started in March 2017 and the trial is ongoing, with follow-up continuing until late 2023. This paper examines those participants with a single morning antihypertensive at baseline who were randomized to switch that antihypertensive to bedtime. Our goal was to compare adherence with bedtime allocation, and self-reported nocturia burden, between those switching a diuretic to bedtime, and those switching other types of blood pressure lowering medication to bedtime. Note, our definition of adherence to allocation time differs from the conventional notion. When we refer to adherence to bedtime allocation, we are talking about the participant's *intention* to use their antihypertensive at bedtime. This study is NOT evaluating the extent to which individual doses are missed. As such, we did not compare bedtime diuretic use to morning diuretic use because morning medication use was already well established for all participants. As we have defined it, we would expect virtually everyone allocated to morning antihypertensives to be adherent to their administration time, as a morning allocation meant no change of any kind was needed.

METHODS

Study Design and Sample Size

BedMed is an ongoing prospective, randomized, open, blinded-endpoint (PROBE)[16] trial. Recruitment is registry-like, with participating family physicians using their usual-care electronic medical records to identify their eligible patients, and then mailing those patients information about the study. Interested patients call the study team and, if eligible and consenting, are randomized to take all their regular blood pressure medication (as tolerated) either in the morning, or at bedtime. Participants received their allocation, using the REDCap[17] server's central randomization module, directly from a research assistant with no prior clinical interactions, achieving irreversible, independent, and concealed allocation.

The prospective cohort study reported in this manuscript is a prespecified interim analysis of BedMed data, carried out as part of an adaptive trial design. The analysis was triggered upon the allocation to bedtime dosing of 203 participants whose only baseline antihypertensive included a morning diuretic (whether a diuretic only, or a diuretic/non-diuretic combination pill). If adherence with bedtime diuretic use had been poor, the BedMed trial's inclusion criteria would have been altered to exclude future such individuals from enrolling. This sample size gave a 90% chance of detecting a 20% relative reduction in adherence to bedtime allocation if 1) morning adherence was 75%, and 2) there were an equal number of participants switching a non-diuretic antihypertensive to bedtime with whom to compare.

Setting and Participants

In Canada's publicly funded healthcare system, residents are not billed directly for physician services, but medication costs are either paid for privately, or partially or completely covered by either employer-sponsored health insurance, or government subsidized programs (including coverage for seniors). The vast majority of Canadians have family physicians, who are normally the sole prescriber of their patient's hypertension medications.

BedMed recruitment began in March 2017, with the final participant included in this analysis enrolling in September 2020. Over this period, participants were being recruited by 352 family physicians (typical practice panel ~ 1,500 patients, with 20% hypertension prevalence amongst adults) in the Canadian provinces of Alberta, Manitoba, British Columbia, and Saskatchewan. Some BedMed participants (22% of those randomized) also learned about the study through social media, or other sources, and were enrolled with their family physician's consent, but without their family physician actively recruiting them. To be eligible for BedMed, participants needed to be community dwelling (including assisted living), and to have a physician diagnosis of hypertension for which they used one or more blood pressure-lowering medications. BedMed excluded anyone with a personal history of glaucoma because of an association between nocturnal hypotension and ischemic optic neuropathy in such individuals.[18-21] For this sub-study we intentionally kept our eligibility criteria as broad as possible (including participants with potentially nocturia-modifying conditions like diabetes, sleep apnea, and congestive heart failure) so as to most closely resemble, and be generalizable to, a hypertensive primary care population.

For this sub-study, the following inclusion and exclusion criteria defined the study cohort.

Inclusion Criteria

1. Physician diagnosis of hypertension
2. Only one antihypertensive pill in use at baseline (combination antihypertensive pills permitted)
3. That single baseline antihypertensive pill was used in the morning at baseline, and only once a day
4. The participant was randomized to switch that morning antihypertensive pill to bedtime

Exclusion Criteria

1. Participant did not attempt a medication timing change*
2. Physician changed the type of antihypertensive prior to the timing change*

*We made both these exclusions since, for the diuretic group, including patients who were not actually attempting to switch a diuretic to bedtime would have lessened any potential nocturia, and biased the groups towards looking more similar. When looking at adverse effects of an intervention, such a "modified intention-to-treat" analysis is the more conservative analytic option, given a full intention-to-treat analysis, for the reason described above, is more likely to underestimate nocturia-related problems.

Procedures

Assistance Changing Antihypertensive Medication to Bedtime

Participants had their choice of being assisted in making their timing change by their family physician, who applied their own judgement as to how to make the change or, if they described no heart disease, by the research assistant with whom they were dialoging. Exceptions included those whose BP-lowering medication was Tiazac XC or Diltiazem XC (which have delayed-release kinetics), and furosemide, isosorbide mononitrate/dinitrate, or alpha blockers (medications whose timing decision may be more complicated). Such participants had their family physician guide their timing change. Advice from research assistants was to delay the next morning dose until bedtime, and to continue all future doses at bedtime. If bedtime use proved problematic, and there was concern participants would switch back to morning, switching to dinnertime was suggested. As a memory aid, participants were advised to place pill bottles near objects they use when getting ready for bed (e.g., toothbrush, denture case, alarm clock), or to use an AM/PM dosette.

Follow-up Interviews

Baseline characteristics were collected directly from participants through telephone interview prior to randomization. The first follow-up with a research assistant occurred by telephone 7-days post timing change to encourage adhering to the timing change, and to troubleshoot participant concerns. Another telephone follow-up took place at 6-weeks to obtain self-reported adherence to bedtime antihypertensive use ("Are you taking your blood pressure medication at bedtime?"; and if "no" - the reason for not doing so), and to assess nocturia. Participants could report nocturia as "no", "minor", or "major" burden (subjective overall assessment, no itemized criteria), and they were asked to quantify the number of overnight

urinations per week by estimating the number of nights they rose to urinate, and the number of times per night they urinated on those evenings. The same follow-up questions were asked again at 6-months, either by telephone or by e-mail questionnaire (participant's choice), and again every 6-months thereafter.

Note: this study was not designed to explore whether or not individual medication doses were missed, something which could be better assessed with electronic devices, or pill counting. We were instead assessing each participant's willingness to persist with bedtime antihypertensive use. As such, self-report more accurately reflects the patient feedback prescribers could expect, were they to recommend diuretics be administered at bedtime.

Administrative Health Claims Data

Comorbidities were also collected as baseline characteristics (coronary artery disease, diabetes, sleep apnea, chronic kidney disease, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and stroke). For non-Alberta residents, these comorbidities were self-reported. For Alberta residents, the vast majority of participants (83%), these comorbidities were derived from physician diagnoses submitted to Alberta Health in the normal course of care, specifically, by extracting comorbidities from linked governmental databases recording community physician billings and hospital separations. Access and analysis of this administrative data was performed by Alberta Health Services, the governmental data steward. These data, and this linking process, have been widely used in other studies and have been identified as valid.[22-25] Most comorbidities were considered present if there were two community visits with that diagnosis, or one hospital diagnosis, from any physician. However

only one such diagnosis was required for stroke (since the diagnosis might not repeat outside of the acute event), and for chronic kidney disease (which, in our experience, is infrequently recorded by primary care providers).

Outcomes (as self-reported by participants)

Primary

1. Adherence to bedtime allocation at 6-months (nonadherence = changing back to morning, stopping altogether, or switching antihypertensives)

Secondary

1. Adherence to bedtime allocation at 6-weeks
2. Nocturia considered to be a "major burden" at 6-weeks, and at 6-months (includes those who report a major burden, and those who failed the timing change because of nocturia)
3. Number of overnight urinations per week at 6-weeks, and at 6-months

Statistical Analysis

Our inclusion and exclusion criteria created one prospective cohort with two exposures, 1) an established morning diuretic medication being switched to bedtime, and 2) an established morning non-diuretic medication being switched to bedtime. Participants using a combination pill with two or more antihypertensive components were considered diuretic users if at least one of those components was a diuretic. The analysis was by modified intention-to-treat and consisted of descriptive statistics, comparing proportions using Fisher's Exact Test (primary outcome analysis), comparing the number of overnight urinations/week using Mann-Whitney,

and using Hodges-Lehmann estimation for difference in medians. All analyses utilized GraphPad Prism version 9.1.2.

Modified Intention-to-treat Assumptions

1. Missing data: Missing variables were imputed using the value from the subsequent follow-up interview. For example, if 6-week data were missing, adherence and nocturia burden were assigned the 6-month value. If no subsequent data were available for imputation (i.e., loss to follow-up or study drop-out) participants were excluded from analysis. We did not impute missing values for lost or dropped-out participants because we were looking to demonstrate potential harm (harm constituting a difference in nonadherence or major nocturia burden) and imputing missing values, being reasonably balanced between groups, would have biased the groups towards looking more similar. Baseline characteristics of those excluded from the primary analysis were compared to assess whether analysis exclusion appeared random.
2. Medication changes: If nocturia resulted in participants switching medications, or medication timing, we considered them non-adherent and to have a "major nocturia burden", even if a lesser degree of nocturia burden was reported at their follow-up interview. Data from these non-adherent individuals was not used for assessment of nocturia frequency. If medication or timing changes were made for reasons other than nocturia, participants were excluded from analysis. We made this exclusion because including such individuals would have biased the groups towards appearing more similar, and could have led us to underestimate the nocturia burden in diuretic users. If physicians

changed the participant's medication to twice daily (with the second dose at bedtime or dinnertime) we considered them to still experience the effects of a bedtime dose, and included them in the analysis.

Patient and Public Involvement

Patient working group

BedMed has a 10-member patient working group which began meeting in 2016 prior to the recruitment of any participants. Working group members have participated in 1) the construction of all participant facing materials, 2) the wording of research assistant follow-up scripts, 3) decisions as to what data to collect, and 3) the hiring of research assistants.

Patient-driven question

The draft BedMed protocol was presented to a group of ~25 seniors in 2015, prior to grant application and study registration. The question pursued in this manuscript derived directly from this group's feedback, where concern was expressed that bedtime diuretics would be poorly tolerated due to nocturia.

RESULTS

Of 579 eligible participants, 552 (95.3%) had analyzable data at 6-weeks, and 533 (92.1%) had analyzable data at 6-months. This included, for our 6-month adherence primary outcome, 198/210 (94.3%) of the eligible diuretic users and 335/369 (90.8%) of the eligible non-diuretic

users. Individual reasons for exclusion are shown in Figure 1. A comparison of baseline characteristics (eTable 1 of the online supplement), shows no notable differences between those excluded from the primary outcome analysis, and those analyzed. At 6-months, of those considered compliant with allocation in the diuretic group, 147/153 (96.1%) took their medication at bedtime, 5/153 (3.3%) took it at dinner, and 1/153 (0.7%) had their diuretic split into twice daily dosing. This compares to the non-diuretic group, of whom 282/301 (93.7%) took their medication at bedtime, 12/301 (4.0%) took it at dinner, and 7/301 (2.3%) had been split into twice daily dosing.

Baseline

Overall, most participants were from Alberta (83.0%), 94.7% identified as white, and they were a mean 65.6 (STD 10.0) years of age. Baseline characteristics were comparable between groups (Table 1) although slightly more diuretic users were female (65.5% vs 52.7%). They were largely non-smokers (92.4%), exercised a median 3 (IQR 0-5) days/week, and had a median BMI of 28.3 (IQR 25.5-32.3). The most common comorbidities were coronary artery disease (19.2%), sleep apnea (18.3%), and diabetes (17.2%). The cohort-defining medications used are broken down in Figure 2. Of the diuretic users, 142 (70.0%) used a thiazide containing combination pill, and 42 (20.7%) used hydrochlorothiazide alone. Although BedMed does not collect information on drug dosage, it would be unusual for Canadians to be prescribed hydrochlorothiazide outside a range of 12.5 – 25 mg/day. Of the non-diuretic cohort, 150 (43.0%) used angiotensin receptor blockers (ARB), 148 (42.4%) used angiotensin-converting enzyme inhibitors (ACEI), 38 (10.9%) used calcium channel blockers (CCB), 4 (1.1%) used beta-blockers (BB), and 9 (2.6%) used combination pills that did not include diuretics. Baseline nocturia was similar between diuretic

vs non-diuretic users, in terms of the number of overnight urinations per week (median 5.5 vs 6.0), and the percentage of participants perceiving nocturia to be a major burden (1.5% vs 2.3%). However slightly more diuretic users felt nocturia was a minor burden (30.5% vs 23.5%). Overall, 3/4 of participants did experience nocturia at least once per week. Of these, 62.8% considered it "not a problem", 34.5% considered it "a minor problem", and 2.6% considered it "a major problem".

Table 1. Baseline Characteristics

Characteristics	Diuretic (n=203) No. (%)	Non-Diuretic (n=349) No. (%)	p-value
Sex, female	133 (65.5)	184 (52.7)	0.004
Age, mean (STD), y	65.4 (8.9)	65.6 (10.6)	0.81
Province			
Alberta	169 (83.3)	289 (82.8)	0.99
British Columbia	14 (6.9)	37 (10.6)	0.17
Manitoba	16 (7.9)	19 (5.4)	0.23
Saskatchewan	4 (2.0)	4 (1.1)	0.47
Ethnicity			
White	195 (96.1)	328 (94.0)	0.33
South east asian	2 (1.0)	10 (2.9)	0.23
Asian	0	3 (0.8)	0.30
First nation	0	6 (1.7)	0.09
Black	0	0	0.99
Other	5 (2.5)	2 (0.6)	0.11
Decline to answer	1 (0.5)	0	0.37
Comorbidities[a]			
Coronary artery disease	39 (19.2)	67 (19.2)	0.99
Diabetes	31 (15.3)	64 (18.3)	0.41
Sleep apnea	38 (18.7)	63 (18.1)	0.91
Chronic kidney disease	14 (6.9)	39 (11.2)	0.13

COPD	16 (7.9)	35 (10.0)	0.45
Stroke	11 (5.4)	18 (5.2)	0.99
Heart failure	4 (2.0)	6 (1.7)	0.99
Cigarette smoker (current)	14 (6.9)	28 (8.0)	0.74
Physical exercise, median (IQR), days per week[b]	3 (1-5)	3 (0-5)	0.14
BMI, median (IQR), Kg/M^2	28.9 (26-33)	28.0 (25-32)	0.15
Underweight (< 18.5)	1 (0.5)	2 (0.6)	0.99
Normal weight (18.5 - 24.9)	35 (17.2)	74 (21.2)	0.27
Overweight (25 - 29.9)	84 (41.4)	143 (41.0)	0.93
Obese (≥ 30)	83 (40.9)	130 (37.2)	0.42
Nocturia, median (IQR), nocturnal urinations/wk	5.5 (1-10.5)	6.0 (1-10.5)	0.91
Does not experience nocturia	49 (24.1)	86 (24.6)	0.92
Nocturia occurs but "not a problem"	89 (43.8)	173 (49.6)	0.22
Nocturia "a minor problem"	62 (30.5)	82 (23.5)	0.07
Nocturia "a major problem"	3 (1.5)	8 (2.3)	0.75

[a] Derived from Alberta provincial health claims data for 454 participants, and self-reported for 98.
[b] "How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"

6-Weeks

Adherence with bedtime medication use was lower in diuretic users (88.7% vs 94.6%), but still high in both cohorts [difference 5.8%; 95%CI, 1.0% to 11.6%; p = 0.02; NNH 17.0] (Table 2). Change in the number of overnight urinations per week could be calculated for 180 diuretic users, and 330 non-diuretic users (Figure 3). Compared to baseline, there were a median 1.0 more overnight urinations per week in diuretic users [95%CI, 0.0 to 1.5; p < 0.0001], and 9.9% more diuretic users perceived nocturia to be a major burden as compared with those who did not use diuretics [11.3% vs 1.4%; 95%CI Diff, 5.5% to 15.4%; p < 0.0001; Number Needed to Harm (NNH) 10.1] (Table 3).

6-Months

At 6-month, adherence to bedtime medication use (our primary outcome) had fallen somewhat in both groups (77.3% vs 89.8%), and the difference in adherence had widened [difference 12.6%; 95%CI Diff, 5.8% to 19.8%; p < 0.0001; NNH 8.0]. However most diuretic users were still adherent to bedtime medication use. Nocturia was given as the reason for nonadherence by 25/45 (55.6%) diuretic users, compared to 0/34 (0%) non-diuretic users, whose main reasons for nonadherence were forgetting to take their pill (10/34, 29.4%), worsening of BP control (8/34, 23.5%), and non-symptom driven medication changes (6/34, 17.6%). Of those still adherent to allocation (153 diuretic users and 301 non-diuretic users), the median difference in overnight urinations compared to baseline remained 1.0 urinations per week higher in diuretic users, compared to non-diuretic users [95%CI, 0.0 to 1.75; p=0.012]. Including those who had stopped adhering because of nocturia, 14.2% more diuretic users had perceived nocturia to be a major burden [15.6% vs 1.3%; 95%CI Diff, 8.9% to 20.6%; p < 0.0001; NNH 7.0].

Sex Differences

Given slightly more diuretic users were female, we conducted a post-hoc analysis to determine whether nocturia burden or adherence differed between sexes. Using the Mann-Whitney test there was no difference, male vs female, in the number of overnight urinations at 6-weeks for the diuretic group [median difference 0.0; 95%CI Diff, -1.0 to 1.0; p = 0.96], nor for the non-diuretic group [median difference 0.0; 95%CI Diff, 0.0 to 0.0; p = 0.98]. Adherence with bedtime antihypertensive use, diuretic vs non-diuretic users, was also similar between males and females at 6-months [male: 76.5% vs 90.5%; female: 77.7% vs 89.3%; p = 0.86 for the difference

in adherence between male and female diuretic users]. The same was true for major nocturia burden at 6-months, which was no different between sexes [male: 14.8% vs 0%; female: 16.0% vs 2.5%; p > 0.99 for the difference in major nocturia burden between male and female diuretic users].

Table 2. Non-adherence to Bedtime Allocation and Major Nocturia Burden, No. (%)

	Diuretic	Non-diuretic	Attributable Risk[c] (%) (95%CI)	p-value
6-weeks				
Major burden[a]	23/198 (11.6)	5/330 (1.5)	10.1 (5.6-15.7)	<0.0001
Nonadherence[b]	23/203 (11.3)	19/349 (5.4)	5.9 (1.0-11.6)	0.02
6-months				
Major burden[a]	28/180 (15.6)	4/301 (1.3)	14.2 (8.9-20.6)	<0.0001
Nonadherence[b]	45/198 (22.7)	34/335 (10.2)	12.6 (5.8-19.8)	<0.0001

[a]Includes those reporting major burden while using a bedtime diuretic, and those nonadherent due to nocturia. Data are number (%).

[b]Nonadherent for any reason. Data are number (%)

[c]Excess risk of the outcome (noncompliance or major burden) for those in the diuretic group, compared to the non-diuretic group.

Table 3. Change in Number of Overnight Urinations per Week, median (IQR)

	Number of Overnight Urinations per Week		Median Change from Baseline		Between Group Difference Median (95%CI)	p-value
	Diuretic	Non-diuretic	Diuretic	Non-diuretic		
Baseline	5.5 (1.0-10.5)	6.0 (1.0-10.5)	-	-	0.0[a,b] (0.0-0.0)	0.92
6-weeks	7.0 (2.6-11.6)	7.0 (1.5-10.5)	0.0 (0.0-3.5)	0.0 (-1.0-1.0)	1.0[a,c] (0.0-1.5)	<0.0001
6-months	6.2 (0.0-10.5)	5.0 (0.0-10.5)	0.5 (-1.5-4.0)	0.0 (-2.0-2.0)	1.0[a,d] (0.0-1.8)	0.01

[a] The between group difference in medians is by Hodges–Lehmann estimation, hence this value differs from a simple subtraction of the diuretic and non-diuretic group medians provided

[b] Between group difference for the median number of urinations per week at baseline

[c] Between group difference for the median change from baseline at 6-weeks

[d] Between group difference for the median change from baseline at 6-months

DISCUSSION

In this prospective cohort of hypertensive primary care patients, 1.5% of morning diuretic users experienced nocturia as a major burden at baseline. When these morning diuretic users switched their diuretic to bedtime, nocturia was more frequent, becoming a major burden for 15.6% of participants over a period of 6 months. Similar primary care patients simultaneously switching other types of antihypertensives from morning to bedtime experienced no increase in nocturia, but they still failed to adhere to bedtime use 10.2% of the time. Due to the extra burden of nocturia, nonadherence in diuretic users was higher, at 22.7%. Hence 1 in 8 diuretic users, compared to non-diuretic users, will fail the switch to bedtime, with 1 in 4 diuretic users failing the switch overall.

Our findings are limited by the potential for selection bias, given some BedMed participants may have previously tried diuretics (morning or evening) and, if they experienced troublesome nocturia, may have stopped using diuretics altogether prior to enrolling. Morning diuretic users may also have avoided enrolling in BedMed if they were concerned about the possibility of needing to switch their diuretics to bedtime. The subjective nature of our outcomes might also be considered a limitation, in that nocturia burden could be interpreted differently by different people. However, self-reporting of nocturia burden integrates the patient's perceptions and values, and our use of it prioritizes the individual's own assessment of their experience. Similarly, while our allowing patients struggling with bedtime use to switch their diuretic to dinnertime might lessen nocturia, this would likely reflect real world practice. Our findings are simultaneously strengthened by the prospective nature of the design, and by the cohort selection process, which ensured diuretic and non-diuretic users were all recruited

from the same practices, using the same approach, and meeting the same inclusion and exclusion criteria.

To our knowledge, our study is the first to prospectively evaluate the link between bedtime diuretic use and nocturia. Our finding the majority of diuretic users able to adhere to bedtime use is consistent with the generally weak and variable association of diuretics and nocturia in cross-sectional studies,[11, 13] the inability of baseline diuretics to predict future nocturia (2-year incidence) in 1,289 community dwelling MESA study respondents 60 years and older,[26] and the number of participants changing the timing of a diuretic in the TIME antihypertensive timing trial.[27] While 22.5% of TIME subjects used a diuretic at baseline, post-randomization diuretic timing changes were made by 5.2% of the evening group vs 0.7% of the morning group ($p<0.0001$), suggesting 5.2% / 22.5% = ¼ of diuretic users chose not to continue bedtime use. Although bedtime antihypertensive use might offer an advantage so far as cardiovascular risk reduction,[4, 5] our clinical experience is that most BP-lowering medication is still administered in the morning. In a 2017 survey of hypertensive primary care patients (single center in Ohio, 139 respondents), 75.5% used all of their antihypertensive medication in the morning.[28] Of the same population, 21 of 22 thiazide-diuretic users (95.5%) took that thiazide in the morning.

Although roughly 14% of hypertensive primary care patients will newly experience nocturia as a major burden after switching a thiazide diuretic from morning to bedtime, the vast majority of morning diuretic users can successfully make the switch to bedtime should it become clinically indicated to do so. The key remaining question is whether or not an attempt to switch diuretics to bedtime is clinically indicated for cardiovascular risk reduction, as the

MAPEC and Hygia trials suggest.[4, 5] Three confirmatory trials, of which BedMed is one, are looking to evaluate this,[15, 27, 29] with the first of these, the TIME trial,[27] recently reporting neither benefit, nor harm, to bedtime prescribing. Final results of the remaining two trials, BedMed,[15] and BedMed-Frail,[29] are expected in mid 2024.

CONTRIBUTORS

SRG conceptualized the study. SRG, TK, MRK, GMA, JAB, AGS, AK, FAM, RSP, RL, MDH, KM, DPM, STW, JPM, LAG designed the study and obtained grant funding. SRG, TK, MRK, GMA, AGS, BGON, MG, DPM, DAM, JEMK, JPMA recruited physicians for the study. SRG supervised the conduct of the trial. MDK and JMSY prepared the study data. SRG and MDK analyzed the data. SRG and MDK wrote the draft manuscript. All authors contributed to critical revision of the manuscript, and all authors approved the final manuscript. SRG is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: SRG is the nominated principal applicant of two grants from governmental sources that are funding the BedMed trial (from Alberta Innovates, and the Canadian Institutes of Health Research); RSP is CEO of “mmHg Inc”, a digital health company and maker of software solutions for BP monitoring; MDH is the recipient of several grants from pharmaceutical and device companies related to interventions

geared at stroke treatment. He holds two device patents related to stroke imaging, has chaired or sat on the Data Safety Monitoring Boards of 5 other cardiovascular trials, is the President of the Canadian Neurological Sciences Federation, a member of the board of the Canadian Stroke Consortium, and has private stock ownership in two companies targeting imaging interventions (Circle Inc, and PureWeb Inc).

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DATA SHARING

Coincident with publication, de-identified patient-level data upon which this manuscript's analyses are based will be freely available for download on the Pragmatic Trials Collaborative's website (www.PragmaticTrials.ca).[30] Downloadable data will include age at study entry, sex, specific BP medication used, corresponding cohort assignment (i.e. diuretic / non-diuretic), baseline nocturia measures, and all primary and secondary outcomes.

ETHICAL APPROVAL

All procedures and methods were approved by the clinical research ethics boards of the Universities of Alberta (Pro00045958), Calgary (REB17-1887), British Columbia (H21-00523), Saskatchewan (1421), and Manitoba (HS20852:B2017:08).

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FIGURE LEGENDS

Figure 1:

Figure 1 Study flow diagram for analysis of adherence

Figure 2:

Figure 2 Medication frequency at baseline. HCTZ = hydrochlorothiazide

Figure 3:

Figure 3 6-week change in overnight urinations per week. Figure is the change in the number of overnight urinations per week experienced by hypertensive primary care patients 6-weeks after being randomly allocated to switch their only blood pressure lowering pill from morning to bedtime. Grouped by those whose pill contained a diuretic (90.7% of which were thiazides), and those who used a different class of blood pressure lowering medication.

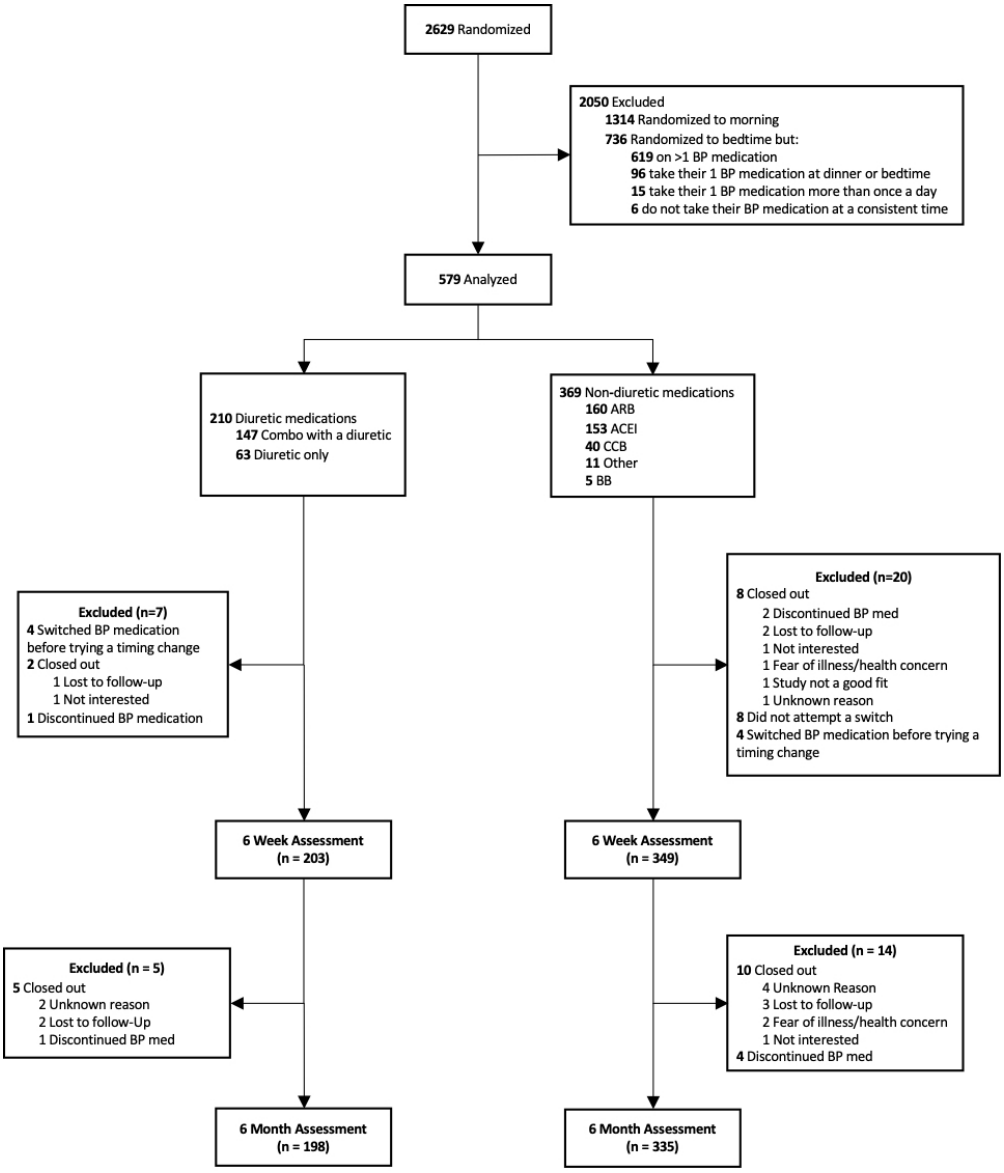

Figure 1 Study flow diagram for analysis of adherence

163x190mm (150 x 150 DPI)

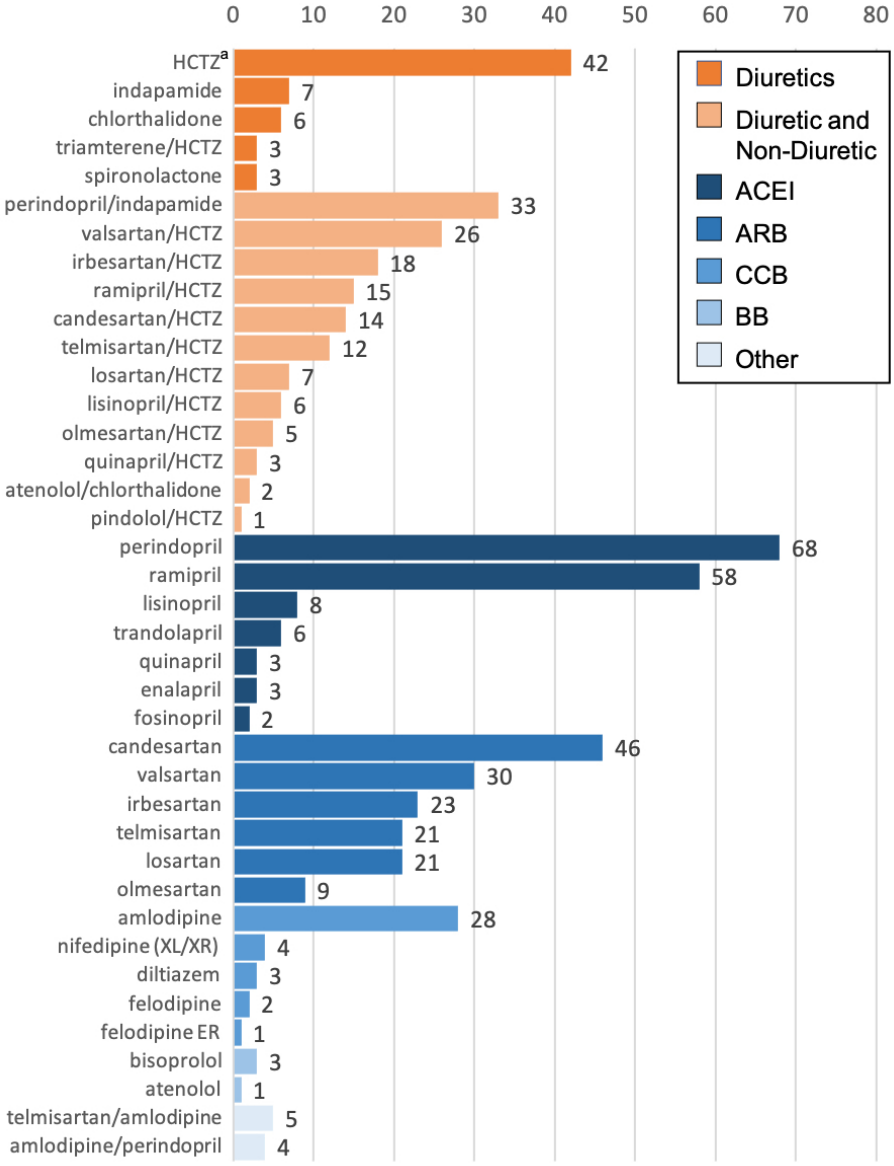

Figure 2 Medication frequency at baseline. HCTZ = hydrochlorothiazide

154x200mm (150 x 150 DPI)

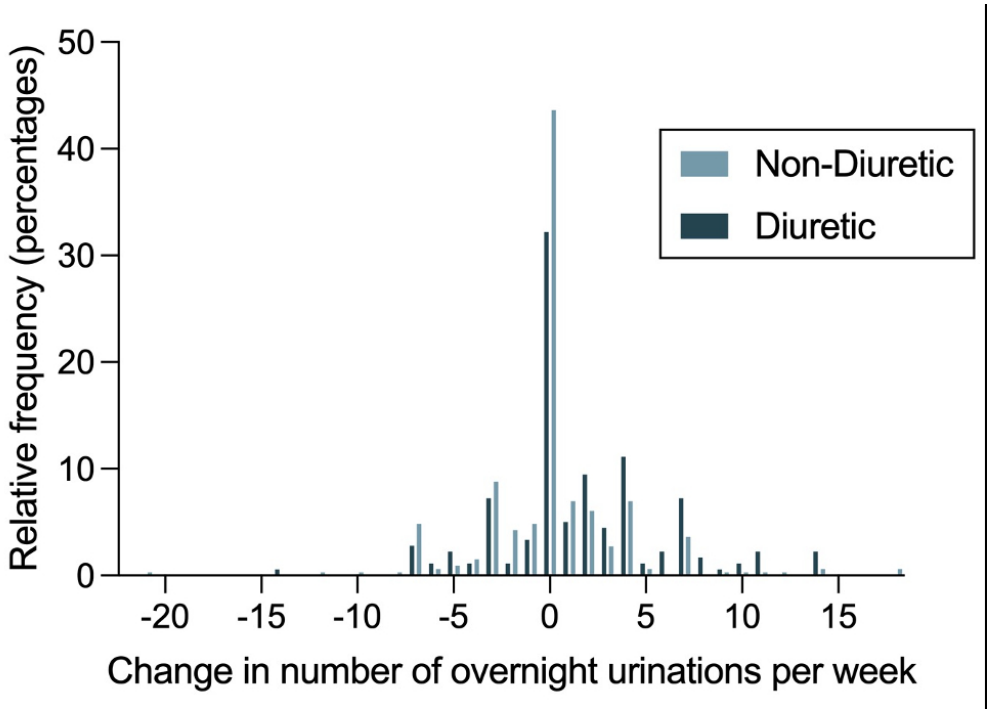

Figure 3 6-week change in overnight urinations per week. Figure is the change in the number of overnight urinations per week experienced by hypertensive primary care patients 6-weeks after being randomly allocated to switch their only blood pressure lowering pill from morning to bedtime. Grouped by those whose pill contained a diuretic (90.7% of which were thiazides), and those who used a different class of blood pressure lowering medication.

165x116mm (150 x 150 DPI)

Tolerability of Bedtime Diuretics:
A Prospective Cohort Analysis
(Supplementary Information)

eTable 1. Comparison of baseline characteristics for participants that were excluded vs. included in the primary outcome analysis			
Characteristics	Excluded (n=46) No. (%)	Included (n=533) No. (%)	p-value
Sex, female	27 (58.7)	308 (57.8)	0.99
Province			
Alberta	39 (84.8)	442 (82.9)	0.84
British Columbia	4 (8.7)	48 (9.0)	0.99
Manitoba	2 (4.4)	35 (6.6)	0.76
Saskatchewan	1 (2.2)	8 (1.5)	0.53
Rural resident	4 (8.7)	71 (13.3)	0.49
Age, mean (STD), y	64.6 (10.6)	65.5 (10.0)	0.55
≤ 29	0	1 (0.2)	0.99
30 - 39	0	2 (0.4)	0.99
40 - 49	3 (6.5)	24 (4.5)	0.46
50 - 59	9 (19.6)	116 (21.8)	0.85
60 - 69	18 (39.1)	202 (37.9)	0.87
70 - 79	11 (23.9)	146 (27.4)	0.73
80 - 89	5 (10.9)	39 (7.3)	0.38
≥ 90	0	3 (0.6)	0.99
Ethnicity			
White	43 (93.5)	504 (94.6)	0.73
South east asian	0	12 (2.3)	0.61
Asian	1 (2.2)	3 (0.6)	0.28
First nation	0	6 (1.1)	0.99
Black	0	0	0.99
Other	1 (2.2)	7 (1.3)	0.49
Decline to answer	1 (2.2)	1 (0.2)	0.15

Education level			
Less than high school	4 (8.7)	21 (3.9)	0.13
High school diploma	19 (41.3)	147 (27.6)	0.06
Technical or trade college diploma	9 (19.6)	146 (27.4)	0.30
University degree	13 (28.3)	219 (41.1)	0.12
Decline to answer	1 (2.2)	0	0.08
Annual household income, CAD$			
< 25,000	4 (8.7)	25 (4.7)	0.28
25,000 to 100,000	20 (43.5)	287 (53.8)	0.22
> 100,000	20 (43.5)	189 (35.5)	0.34
Decline to answer	2 (4.4)	32 (6.0)	0.99
Comorbidities[a]			
Coronary artery disease	9 (19.6)	100 (18.8)	0.85
Diabetes	6 (13)	92 (17.3)	0.54
Sleep apnea	11 (23.9)	99 (18.6)	0.43
Chronic kidney disease	7 (15.2)	48 (9.0)	0.19
COPD	6 (13.0)	50 (9.4)	0.43
Stroke	1 (2.2)	28 (5.3)	0.72
Heart failure	0	10 (1.9)	0.99
Hip fracture	1 (2.2)	2 (0.4)	0.22
Cigarette smoker (current)	2 (4.4)	42 (7.9)	0.56
Nocturia, median (IQR), nocturnal urinations/wk	7 (0-14.0)	6 (1-10.5)	0.61
Does not experience nocturia	12 (26.1)	129 (24.2)	0.72
Nocturia occurs but "not a problem"	21 (45.6)	255 (47.8)	0.88
Nocturia "a minor problem"	12 (26.1)	139 (26.1)	0.99
Nocturia "a major problem"	1 (2.2)	10 (1.9)	0.60
Physical exercise, median (IQR), days per week[b]	3 (0-5.0)	3 (0.5-5.0)	0.42
0	15 (32.6)	133 (25.0)	0.29
1	6 (13.0)	43 (8.1)	0.26
2	1 (2.2)	68 (12.8)	0.03
3	6 (13.0)	75 (14.1)	0.99
4	6 (13.0)	54 (10.1)	0.46
5	2 (4.4)	49 (9.2)	0.41

6	1 (2.2)	15 (2.8)	0.99
7	9 (19.6)	96 (18.0)	0.84
BMI, median (IQR), Kg/M^2	27.7 (26.1-33.4)	28.3 (25.5-32.3)	0.80
Underweight (< 18.5)	0	3 (0.6)	0.99
Normal weight (18.5 - 24.9)	9 (19.6)	105 (19.7)	0.99
Overweight (25 - 29.9)	21 (45.7)	220 (41.3)	0.64
Obese (≥ 30)	16 (34.8)	205 (38.5)	0.75
EQ-5D-5L overall health score, median (IQR)[c]	80 (75-90)	80 (75-90)	0.88
Physically frail[d]	7 (15.2)	73 (13.7)	0.82
Cognition[e]			
Normal	41 (89.1)	496 (93.1)	0.37
Questionable impairment	3 (6.5)	36 (6.8)	0.99
Impairment consistent with dementia	2 (4.4)	1 (0.2)	0.02

[a] Derived from Alberta provincial health claims data and self-report.

[b] "How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"

[c] Self-rating of overall health on a scale of 0 (worst) to 100 (best).

[d] As per Tilburg Frailty Indicator's physical sub-scale (sub-scale score ≥3 defines physically frail).

[e] As per Short Blessed screening test score. Considered to be normal (0-4), questionable impairment (5-9), or impairment consistent with dementia (>9).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-13
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-11
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11-13
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	14-18
Outcome data	15*	Report numbers of outcome events or summary measures over time	16-18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-18
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14, 17-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Tolerability of bedtime diuretics: A prospective cohort analysis

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Primary Subject	Cardiovascular medicine

Heading:	
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice, Urology
Keywords:	Hypertension < CARDIOLOGY, CLINICAL PHARMACOLOGY, PRIMARY CARE, Cardiology < INTERNAL MEDICINE

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Tolerability of bedtime diuretics: A prospective cohort analysis

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ABSTRACT

OBJECTIVES

We sought to validate, or refute, the common belief that bedtime diuretics are poorly tolerated due to nocturia.

DESIGN

Prespecified prospective cohort analysis embedded within the randomized BedMed trial, in which hypertensive participants are randomized to morning vs. bedtime antihypertensive administration.

SETTING

352 community family practices across 4 Canadian provinces between March 2017 and September 2020.

PARTICIPANTS

552 hypertensive patients (65.6 years old, 57.4% female) already established on a single once-daily morning antihypertensive and randomized to switch that antihypertensive to bedtime. Of these, 203 used diuretics (27.1% thiazide alone, 70.0% thiazide/non-diuretic combinations) and 349 used non-diuretics.

INTERVENTION

Switching the established antihypertensive from morning to bedtime, and comparing the experience of diuretic and non-diuretic users.

PRIMARY AND SECONDARY OUTCOME MEASURES

PRIMARY OUTCOME: Adherence to bedtime allocation time at 6-months (defined as the willingness to continue with bedtime use, not an assessment of missed doses). SECONDARY 6-

MONTH OUTCOMES: 1) Nocturia considered to be a major burden, 2) Increase in overnight urinations/week. All outcomes were self-reported, and additionally collected at 6-weeks.

RESULTS

At 6-months: Adherence to bedtime allocation time was lower in diuretic users than non-diuretic users [77.3% vs 89.8%; difference 12.6%; 95%CI 5.8% to 19.8%; p<0.0001; NNH 8.0], and more diuretic users considered nocturia a major burden [15.6% vs 1.3%; difference 14.2%; 95%CI 8.9% to 20.6%; p < 0.0001; NNH 7.0]. Compared to baseline, diuretic users experienced 1.0 more overnight urinations/week [95%CI 0.0 to 1.75; p = 0.01]. Results did not differ between sexes.

CONCLUSIONS

Switching diuretics to bedtime did promote nocturia, but only 15.6% found nocturia a major burden. At 6-months, 77.3% of diuretic users were adherent to bedtime dosing. Bedtime diuretic use is viable for many hypertensive patients, should it ever become clinically indicated.

TRIAL REGISTRATION

NCT02990663

Key Words: Hypertension, diuretics, nocturia, chronotherapy, bedtime

STENGTHS AND LIMITATIONS OF THIS STUDY

- Our study question arises directly from members of the public who participated in the design of the BedMed trial.

- Intervention and comparison groups were randomly selected from the same clinical trial population.
- Our data represent the first prospective evaluation of the tolerability of bedtime diuretics.
- Limitation: Those who previously tried and failed morning diuretics due to nocturia would be absent from the diuretic cohort, which could bias towards better bedtime diuretic tolerance.

INTRODUCTION

Although consensus is lacking,[1-3] two randomized trials by the same principal investigator suggest large reductions in major adverse cardiovascular events occur if blood pressure medications are taken at bedtime, as compared to conventional morning use.[4, 5] This finding, however, may be difficult to implement for those using diuretics - common first-line therapeutics, with a unique and important role in volume control and natriuresis.[6, 7] This is because diuretics are widely believed to promote nocturia, and typically recommended for morning use only as a result.[8, 9]

Nocturia occurs in roughly 2/3 of men and women over the age of 70 years[10] and is believed to disrupt sleep, impair quality of life, and increase the risk of nighttime falls and fractures. [11, 12] However, there are no randomized trials examining diuretic timing and adverse effects. The concern that bedtime diuretics could produce troublesome nocturia, being based

on opinion and observational data, could be incorrect. Morning diuretics (typically thiazides) are generally well tolerated, and cross-sectional analysis of diuretic-using populations, without accounting for administration time, does not support a strong association between diuretic use and nocturia. [13, 14] Whether clinicians can recommend diuretics for bedtime use is therefore unclear.

To determine how well diuretics are tolerated at bedtime we conducted a pre-specified prospective cohort study embedded within the ongoing BedMed trial. BedMed randomizes Canadian primary care patients with hypertension to take their existing antihypertensive medications either in the morning, or at bedtime, and examines mortality and morbidity outcomes.[15] Recruitment started in March 2017 and the trial is ongoing, with follow-up continuing until late 2023. This paper examines those participants with a single morning antihypertensive at baseline who were randomized to switch that antihypertensive to bedtime. Our goal was to compare adherence with bedtime allocation, and self-reported nocturia burden, between those switching a diuretic to bedtime, and those switching other types of blood pressure lowering medication to bedtime. Note, our definition of adherence to allocation time differs from the conventional notion. When we refer to adherence to bedtime allocation, we are talking about the participant's *intention* to use their antihypertensive at bedtime. This study is NOT evaluating the extent to which individual doses are missed. As such, we did not compare bedtime diuretic use to morning diuretic use because morning medication use was already well established for all participants. As we have defined it, we would expect virtually everyone allocated to morning antihypertensives to be adherent to their administration time, as a morning allocation meant no change of any kind was needed.

METHODS

Study Design and Sample Size

BedMed is an ongoing prospective, randomized, open, blinded-endpoint (PROBE)[16] trial. Recruitment is registry-like, with participating family physicians using their usual-care electronic medical records to identify their eligible patients, and then mailing those patients information about the study. Interested patients call the study team and, if eligible and consenting, are randomized to take all their regular blood pressure medication (as tolerated) either in the morning, or at bedtime. Participants received their allocation, using the REDCap[17] server's central randomization module, directly from a research assistant with no prior clinical interactions, achieving irreversible, independent, and concealed allocation.

The prospective cohort study reported in this manuscript is a prespecified interim analysis of BedMed data, carried out as part of an adaptive trial design. The analysis was triggered upon the allocation to bedtime dosing of 203 participants whose only baseline antihypertensive included a morning diuretic (whether a diuretic only, or a diuretic/non-diuretic combination pill). If adherence with bedtime diuretic use had been poor, the BedMed trial's inclusion criteria would have been altered to exclude future such individuals from enrolling. This sample size gave a 90% chance of detecting a 20% relative reduction in adherence to bedtime allocation if 1) morning adherence was 75%, and 2) there were an equal number of participants switching a non-diuretic antihypertensive to bedtime with whom to compare.

Setting and Participants

In Canada's publicly funded healthcare system, residents are not billed directly for physician services, but medication costs are either paid for privately, or partially or completely covered by either employer-sponsored health insurance, or government subsidized programs (including coverage for seniors). The vast majority of Canadians have family physicians, who are normally the sole prescriber of their patient's hypertension medications.

BedMed recruitment began in March 2017, with the final participant included in this analysis enrolling in September 2020. Over this period, participants were being recruited by 352 family physicians (typical practice panel ~ 1,500 patients, with 20% hypertension prevalence amongst adults) in the Canadian provinces of Alberta, Manitoba, British Columbia, and Saskatchewan. Some BedMed participants (22% of those randomized) also learned about the study through social media, or other sources, and were enrolled with their family physician's consent, but without their family physician actively recruiting them. To be eligible for BedMed, participants needed to be community dwelling (including assisted living), and to have a physician diagnosis of hypertension for which they used one or more blood pressure-lowering medications. BedMed excluded anyone with a personal history of glaucoma because of an association between nocturnal hypotension and ischemic optic neuropathy in such individuals.[18-21] For this sub-study we intentionally kept our eligibility criteria as broad as possible (including participants with potentially nocturia-modifying conditions like diabetes, sleep apnea, and congestive heart failure) so as to most closely resemble, and be generalizable to, a hypertensive primary care population.

For this sub-study, the following inclusion and exclusion criteria defined the study cohort.

Inclusion Criteria

1. Physician diagnosis of hypertension
2. Only one antihypertensive pill in use at baseline (combination antihypertensive pills permitted)
3. That single baseline antihypertensive pill was used in the morning at baseline, and only once a day
4. The participant was randomized to switch that morning antihypertensive pill to bedtime

Exclusion Criteria

1. Participant did not attempt a medication timing change*
2. Physician changed the type of antihypertensive prior to the timing change*

*We made both these exclusions since, for the diuretic group, including patients who were not actually attempting to switch a diuretic to bedtime would have lessened any potential nocturia, and biased the groups towards looking more similar. When looking at adverse effects of an intervention, such a "modified intention-to-treat" analysis is the more conservative analytic option, given a full intention-to-treat analysis, for the reason described above, is more likely to underestimate nocturia-related problems.

Procedures

Assistance Changing Antihypertensive Medication to Bedtime

Participants had their choice of being assisted in making their timing change by their family physician, who applied their own judgement as to how to make the change or, if they described no heart disease, by the research assistant with whom they were dialoging. Exceptions included those whose BP-lowering medication was Tiazac XC or Diltiazem XC (which have delayed-release kinetics), and furosemide, isosorbide mononitrate/dinitrate, or alpha blockers (medications whose timing decision may be more complicated). Such participants had their family physician guide their timing change. Advice from research assistants was to delay the next morning dose until bedtime, and to continue all future doses at bedtime. If bedtime use proved problematic, and there was concern participants would switch back to morning, switching to dinnertime was suggested. As a memory aid, participants were advised to place pill bottles near objects they use when getting ready for bed (e.g., toothbrush, denture case, alarm clock), or to use an AM/PM dosette. If medication type, dosage, or timing needed to be changed, for any reason, those decisions were at the sole discretion of the prescribing physician.

Follow-up Interviews

Baseline characteristics were collected directly from participants through telephone interview prior to randomization. The first follow-up with a research assistant occurred by telephone 7-days post timing change to encourage adhering to the timing change, and to troubleshoot participant concerns. Another telephone follow-up took place at 6-weeks to obtain self-reported adherence to bedtime antihypertensive use ("Are you taking your blood pressure

medication at bedtime?"; and if "no" - the reason for not doing so), and to assess nocturia. Participants could report nocturia as "no", "minor", or "major" burden (subjective overall assessment, no itemized criteria), and they were asked to quantify the number of overnight urinations per week by estimating the number of nights they rose to urinate, and the number of times per night they urinated on those evenings. The same follow-up questions were asked again at 6-months, either by telephone or by e-mail questionnaire (participant's choice), and again every 6-months thereafter.

Note: this study was not designed to explore whether or not individual medication doses were missed, something which could be better assessed with electronic devices, or pill counting. We were instead assessing each participant's willingness to persist with bedtime antihypertensive use. As such, self-report more accurately reflects the patient feedback prescribers could expect, were they to recommend diuretics be administered at bedtime.

Administrative Health Claims Data

Comorbidities were also collected as baseline characteristics (coronary artery disease, diabetes, sleep apnea, chronic kidney disease, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and stroke). For non-Alberta residents, these comorbidities were self-reported. For Alberta residents, the vast majority of participants (83%), these comorbidities were derived from physician diagnoses submitted to Alberta Health in the normal course of care, specifically, by extracting comorbidities from linked governmental databases recording community physician billings and hospital separations. Access and analysis of this administrative data was performed by Alberta Health Services, the governmental data steward.

These data, and this linking process, have been widely used in other studies and have been identified as valid.[22-25] Most comorbidities were considered present if there were two community visits with that diagnosis, or one hospital diagnosis, from any physician. However only one such diagnosis was required for stroke (since the diagnosis might not repeat outside of the acute event), and for chronic kidney disease (which, in our experience, is infrequently recorded by primary care providers).

Outcomes (as self-reported by participants)

Primary

1. Adherence to bedtime allocation at 6-months (nonadherence = changing back to morning, stopping altogether, or switching antihypertensives)

Secondary

1. Adherence to bedtime allocation at 6-weeks
2. Nocturia considered to be a "major burden" at 6-weeks, and at 6-months (includes those who report a major burden, and those who failed the timing change because of nocturia)
3. Number of overnight urinations per week at 6-weeks, and at 6-months

Statistical Analysis

Our inclusion and exclusion criteria created one prospective cohort with two exposures, 1) an established morning diuretic medication being switched to bedtime, and 2) an established morning non-diuretic medication being switched to bedtime. Participants using a combination pill with two or more antihypertensive components were considered diuretic users if at least

one of those components was a diuretic. The analysis was by modified intention-to-treat and consisted of descriptive statistics, comparing proportions using Fisher's Exact Test (primary outcome analysis), comparing the number of overnight urinations/week using Mann-Whitney, and using Hodges-Lehmann estimation for difference in medians. All analyses utilized GraphPad Prism version 9.1.2.

Modified Intention-to-treat Assumptions

1. Missing data: Missing variables were imputed using the value from the subsequent follow-up interview. For example, if 6-week data were missing, adherence and nocturia burden were assigned the 6-month value. If no subsequent data were available for imputation (i.e., loss to follow-up or study drop-out) participants were excluded from analysis. We did not impute missing values for lost or dropped-out participants because we were looking to demonstrate potential harm (harm constituting a difference in nonadherence or major nocturia burden) and imputing missing values, being reasonably balanced between groups, would have biased the groups towards looking more similar. Baseline characteristics of those excluded from the primary analysis were compared to assess whether analysis exclusion appeared random.
2. Medication changes: If nocturia resulted in participants switching medications, or medication timing, we considered them non-adherent and to have a "major nocturia burden", even if a lesser degree of nocturia burden was reported at their follow-up interview. Data from these non-adherent individuals was not used for assessment of nocturia frequency. If medication or timing changes were made for reasons other than

nocturia, participants were excluded from analysis. We made this exclusion because including such individuals would have biased the groups towards appearing more similar, and could have led us to underestimate the nocturia burden in diuretic users. If physicians changed the participant's medication to twice daily (with the second dose at bedtime or dinnertime) we considered them to still experience the effects of a bedtime dose, and included them in the analysis.

Patient and Public Involvement

Patient working group

BedMed has a 10-member patient working group which began meeting in 2016 prior to the recruitment of any participants. Working group members have participated in 1) the construction of all participant facing materials, 2) the wording of research assistant follow-up scripts, 3) decisions as to what data to collect, and 3) the hiring of research assistants.

Patient-driven question

The draft BedMed protocol was presented to a group of ~25 seniors in 2015, prior to grant application and study registration. The question pursued in this manuscript derived directly from this group's feedback, where concern was expressed that bedtime diuretics would be poorly tolerated due to nocturia.

RESULTS

De-identified patient-level outcome data are available for download on the Pragmatic Trials Collaborative's website (www.PragmaticTrials.ca).[26] Of 579 eligible participants, 552 (95.3%) had analyzable data at 6-weeks, and 533 (92.1%) had analyzable data at 6-months. This included, for our 6-month adherence primary outcome, 198/210 (94.3%) of the eligible diuretic users and 335/369 (90.8%) of the eligible non-diuretic users. Individual reasons for exclusion are shown in Figure 1. A comparison of baseline characteristics (Supplemental Table 1), shows no notable differences between those excluded from the primary outcome analysis, and those analyzed. At 6-months, of those considered compliant with allocation in the diuretic group, 147/153 (96.1%) took their medication at bedtime, 5/153 (3.3%) took it at dinner, and 1/153 (0.7%) had their diuretic split into twice daily dosing. This compares to the non-diuretic group, of whom 282/301 (93.7%) took their medication at bedtime, 12/301 (4.0%) took it at dinner, and 7/301 (2.3%) had been split into twice daily dosing.

Baseline

Overall, most participants were from Alberta (83.0%), 94.7% identified as white, and they were a mean 65.6 (STD 10.0) years of age. Baseline characteristics were comparable between groups (Table 1) although slightly more diuretic users were female (65.5% vs 52.7%). They were largely non-smokers (92.4%), exercised a median 3 (IQR 0-5) days/week, and had a median BMI of 28.3 (IQR 25.5-32.3). The most common comorbidities were coronary artery disease (19.2%), sleep apnea (18.3%), and diabetes (17.2%). The cohort-defining medications used are broken down in Figure 2. Of the diuretic users, 142 (70.0%) used a thiazide containing combination pill, and 42 (20.7%) used hydrochlorothiazide alone. Although BedMed does not collect information on drug dosage, it would be unusual for Canadians to be prescribed hydrochlorothiazide outside a

range of 12.5 – 25 mg/day. Of the non-diuretic cohort, 150 (43.0%) used angiotensin receptor blockers (ARB), 148 (42.4%) used angiotensin-converting enzyme inhibitors (ACEI), 38 (10.9%) used calcium channel blockers (CCB), 4 (1.1%) used beta-blockers (BB), and 9 (2.6%) used combination pills that did not include diuretics. Baseline nocturia was similar between diuretic vs non-diuretic users, in terms of the number of overnight urinations per week (median 5.5 vs 6.0), and the percentage of participants perceiving nocturia to be a major burden (1.5% vs 2.3%). However slightly more diuretic users felt nocturia was a minor burden (30.5% vs 23.5%). Overall, 3/4 of participants did experience nocturia at least once per week. Of these, 62.8% considered it "not a problem", 34.5% considered it "a minor problem", and 2.6% considered it "a major problem".

Table 1. Baseline Characteristics

Characteristics	Diuretic (n=203) No. (%)	Non-Diuretic (n=349) No. (%)	p-value
Sex, female	133 (65.5)	184 (52.7)	0.004
Age, mean (STD), y	65.4 (8.9)	65.6 (10.6)	0.81
Province			
Alberta	169 (83.3)	289 (82.8)	0.99
British Columbia	14 (6.9)	37 (10.6)	0.17
Manitoba	16 (7.9)	19 (5.4)	0.23
Saskatchewan	4 (2.0)	4 (1.1)	0.47
Ethnicity			
White	195 (96.1)	328 (94.0)	0.33
South east asian	2 (1.0)	10 (2.9)	0.23
Asian	0	3 (0.8)	0.30
First nation	0	6 (1.7)	0.09
Black	0	0	0.99
Other	5 (2.5)	2 (0.6)	0.11

Decline to answer	1 (0.5)	0	0.37
Comorbidities[a]			
Coronary artery disease	39 (19.2)	67 (19.2)	0.99
Diabetes	31 (15.3)	64 (18.3)	0.41
Sleep apnea	38 (18.7)	63 (18.1)	0.91
Chronic kidney disease	14 (6.9)	39 (11.2)	0.13
COPD	16 (7.9)	35 (10.0)	0.45
Stroke	11 (5.4)	18 (5.2)	0.99
Heart failure	4 (2.0)	6 (1.7)	0.99
Cigarette smoker (current)	14 (6.9)	28 (8.0)	0.74
Physical exercise, median (IQR), days per week[b]	3 (1-5)	3 (0-5)	0.14
BMI, median (IQR), Kg/M^2	28.9 (26-33)	28.0 (25-32)	0.15
Underweight (< 18.5)	1 (0.5)	2 (0.6)	0.99
Normal weight (18.5 - 24.9)	35 (17.2)	74 (21.2)	0.27
Overweight (25 - 29.9)	84 (41.4)	143 (41.0)	0.93
Obese (≥ 30)	83 (40.9)	130 (37.2)	0.42
Nocturia, median (IQR), nocturnal urinations/wk	5.5 (1-10.5)	6.0 (1-10.5)	0.91
Does not experience nocturia	49 (24.1)	86 (24.6)	0.92
Nocturia occurs but "not a problem"	89 (43.8)	173 (49.6)	0.22
Nocturia "a minor problem"	62 (30.5)	82 (23.5)	0.07
Nocturia "a major problem"	3 (1.5)	8 (2.3)	0.75

[a] Derived from Alberta provincial health claims data for 454 participants, and self-reported for 98.

[b] "How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"

6-Weeks

Adherence with bedtime medication use was lower in diuretic users (88.7% vs 94.6%), but still high in both cohorts [difference 5.8%; 95%CI, 1.0% to 11.6%; p = 0.02; NNH 17.0] (Table 2). Change in the number of overnight urinations per week could be calculated for 180 diuretic users, and 330 non-diuretic users (Supplemental Figure 1). Compared to baseline, there were a

median 1.0 more overnight urinations per week in diuretic users [95%CI, 0.0 to 1.5; p < 0.0001], and 9.9% more diuretic users perceived nocturia to be a major burden as compared with those who did not use diuretics [11.3% vs 1.4%; 95%CI Diff, 5.5% to 15.4%; p < 0.0001; Number Needed to Harm (NNH) 10.1] (Table 3).

6-Months

At 6-month, adherence to bedtime medication use (our primary outcome) had fallen somewhat in both groups (77.3% vs 89.8%), and the difference in adherence had widened [difference 12.6%; 95%CI Diff, 5.8% to 19.8%; p < 0.0001; NNH 8.0]. However most diuretic users were still adherent to bedtime medication use. Nocturia was given as the reason for nonadherence by 25/45 (55.6%) diuretic users, compared to 0/34 (0%) non-diuretic users, whose main reasons for nonadherence were forgetting to take their pill (10/34, 29.4%), worsening of BP control (8/34, 23.5%), and non-symptom driven medication changes (6/34, 17.6%). Of those still adherent to allocation (153 diuretic users and 301 non-diuretic users), the median difference in overnight urinations compared to baseline remained 1.0 urinations per week higher in diuretic users, compared to non-diuretic users [95%CI, 0.0 to 1.75; p=0.012]. Including those who had stopped adhering because of nocturia, 14.2% more diuretic users had perceived nocturia to be a major burden [15.6% vs 1.3%; 95%CI Diff, 8.9% to 20.6%; p < 0.0001; NNH 7.0].

Sex Differences

Given slightly more diuretic users were female, we conducted a post-hoc analysis to determine whether nocturia burden or adherence differed between sexes. Using the Mann-Whitney test there was no difference, male vs female, in the number of overnight urinations at 6-weeks for

the diuretic group [median difference 0.0; 95%CI Diff, -1.0 to 1.0; p = 0.96], nor for the non-diuretic group [median difference 0.0; 95%CI Diff, 0.0 to 0.0; p = 0.98]. Adherence with bedtime antihypertensive use, diuretic vs non-diuretic users, was also similar between males and females at 6-months [male: 76.5% vs 90.5%; female: 77.7% vs 89.3%; p = 0.86 for the difference in adherence between male and female diuretic users]. The same was true for major nocturia burden at 6-months, which was no different between sexes [male: 14.8% vs 0%; female: 16.0% vs 2.5%; p > 0.99 for the difference in major nocturia burden between male and female diuretic users].

Table 2. Non-adherence to Bedtime Allocation and Major Nocturia Burden, No. (%)

	Diuretic	Non-diuretic	Attributable Risk[c] (%) (95%CI)	p-value
6-weeks				
Major burden[a]	23/198 (11.6)	5/330 (1.5)	10.1 (5.6-15.7)	<0.0001
Nonadherence[b]	23/203 (11.3)	19/349 (5.4)	5.9 (1.0-11.6)	0.02
6-months				
Major burden[a]	28/180 (15.6)	4/301 (1.3)	14.2 (8.9-20.6)	<0.0001
Nonadherence[b]	45/198 (22.7)	34/335 (10.2)	12.6 (5.8-19.8)	<0.0001

[a]Includes those reporting major burden while using a bedtime diuretic, and those nonadherent due to nocturia. Data are number (%).

[b]Nonadherent for any reason. Data are number (%)

[c]Excess risk of the outcome (noncompliance or major burden) for those in the diuretic group, compared to the non-diuretic group.

Table 3. Change in Number of Overnight Urinations per Week, median (IQR)

	Number of Overnight Urinations per Week		Median Change from Baseline		Between Group Difference Median (95%CI)	p-value
	Diuretic	Non-diuretic	Diuretic	Non-diuretic		
Baseline	5.5 (1.0-10.5)	6.0 (1.0-10.5)	-	-	0.0[a,b] (0.0-0.0)	0.92
6-weeks	7.0 (2.6-11.6)	7.0 (1.5-10.5)	0.0 (0.0-3.5)	0.0 (-1.0-1.0)	1.0[a,c] (0.0-1.5)	<0.0001
6-months	6.2 (0.0-10.5)	5.0 (0.0-10.5)	0.5 (-1.5-4.0)	0.0 (-2.0-2.0)	1.0[a,d] (0.0-1.8)	0.01

[a] The between group difference in medians is by Hodges–Lehmann estimation, hence this value differs from a simple subtraction of the diuretic and non-diuretic group medians provided
[b] Between group difference for the median number of urinations per week at baseline
[c] Between group difference for the median change from baseline at 6-weeks
[d] Between group difference for the median change from baseline at 6-months

DISCUSSION

In this prospective cohort of hypertensive primary care patients, 1.5% of morning diuretic users experienced nocturia as a major burden at baseline. When these morning diuretic users switched their diuretic to bedtime, nocturia was more frequent, becoming a major burden for 15.6% of participants over a period of 6 months. Similar primary care patients simultaneously switching other types of antihypertensives from morning to bedtime experienced no increase in nocturia, but they still failed to adhere to bedtime use 10.2% of the time. Due to the extra burden of nocturia, nonadherence in diuretic users was higher, at 22.7%. Hence 1 in 8 diuretic users, compared to non-diuretic users, will fail the switch to bedtime, with 1 in 4 diuretic users failing the switch overall.

Our findings are limited by the potential for selection bias, given some BedMed participants may have previously tried diuretics (morning or evening) and, if they experienced troublesome nocturia, may have stopped using diuretics altogether prior to enrolling. Morning diuretic users may also have avoided enrolling in BedMed if they were concerned about the possibility of needing to switch their diuretics to bedtime. The subjective nature of our outcomes might also be considered a limitation, in that nocturia burden could be interpreted differently by different people. However, self-reporting of nocturia burden integrates the patient's perceptions and values, and our use of it prioritizes the individual's own assessment of

their experience. Similarly, while our allowing patients struggling with bedtime use to switch their diuretic to dinnertime might lessen nocturia, this would likely reflect real world practice. Our findings are simultaneously strengthened by the prospective nature of the design, and by the cohort selection process, which ensured diuretic and non-diuretic users were all recruited from the same practices, using the same approach, and meeting the same inclusion and exclusion criteria.

To our knowledge, our study is the first to prospectively evaluate the link between bedtime diuretic use and nocturia. Our finding the majority of diuretic users able to adhere to bedtime use is consistent with the generally weak and variable association of diuretics and nocturia in cross-sectional studies,[11, 13] the inability of baseline diuretics to predict future nocturia (2-year incidence) in 1,289 community dwelling MESA study respondents 60 years and older,[27] and the number of participants changing the timing of a diuretic in the TIME antihypertensive timing trial.[28] While 22.5% of TIME subjects used a diuretic at baseline, post-randomization diuretic timing changes were made by 5.2% of the evening group vs 0.7% of the morning group ($p<0.0001$), suggesting 5.2% / 22.5% = ¼ of diuretic users chose not to continue bedtime use. Although bedtime antihypertensive use might offer an advantage so far as cardiovascular risk reduction,[4, 5] our clinical experience is that most BP-lowering medication is still administered in the morning. In a 2017 survey of hypertensive primary care patients (single center in Ohio, 139 respondents), 75.5% used all of their antihypertensive medication in the morning.[29] Of the same population, 21 of 22 thiazide-diuretic users (95.5%) took that thiazide in the morning.

Although roughly 14% of hypertensive primary care patients will newly experience nocturia as a major burden after switching a thiazide diuretic from morning to bedtime, the vast majority of morning diuretic users can successfully make the switch to bedtime should it become clinically indicated to do so. The key remaining question is whether or not an attempt to switch diuretics to bedtime is clinically indicated for cardiovascular risk reduction, as the MAPEC and Hygia trials suggest.[4, 5] Three confirmatory trials, of which BedMed is one, are looking to evaluate this,[15, 28, 30] with the first of these, the TIME trial,[28] recently reporting neither benefit, nor harm, to bedtime prescribing. Final results of the remaining two trials, BedMed,[15] and BedMed-Frail,[30] are expected in mid 2024.

CONTRIBUTORS

SRG conceptualized the study. SRG, TK, MRK, GMA, JAB, AGS, AK, FAM, RSP, RL, MDH, KM, DPM, STW, JPM, LAG designed the study and obtained grant funding. SRG, TK, MRK, GMA, AGS, BGON, MG, DPM, DAM, JEMK, JPMA recruited physicians for the study. SRG supervised the conduct of the trial. MDK and JMSY prepared the study data. SRG and MDK analyzed the data. SRG and MDK wrote the draft manuscript. All authors contributed to critical revision of the manuscript, and all authors approved the final manuscript. SRG is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: SRG is the nominated principal applicant of two grants from governmental sources that are funding the BedMed trial (from Alberta Innovates, and the Canadian Institutes of Health Research); RSP is CEO of "mmHg Inc", a digital health company and maker of software solutions for BP monitoring; MDH is the recipient of several grants from pharmaceutical and device companies related to interventions geared at stroke treatment. He holds two device patents related to stroke imaging, has chaired or sat on the Data Safety Monitoring Boards of 5 other cardiovascular trials, is the President of the Canadian Neurological Sciences Federation, a member of the board of the Canadian Stroke Consortium, and has private stock ownership in two companies targeting imaging interventions (Circle Inc, and PureWeb Inc).

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DATA SHARING

Coincident with publication, de-identified patient-level data upon which this manuscript's analyses are based will be freely available for download on the Pragmatic Trials Collaborative's website (www.PragmaticTrials.ca). Downloadable data will include age at study entry, sex, specific BP medication used, corresponding cohort assignment (i.e. diuretic / non-diuretic), baseline nocturia measures, and all primary and secondary outcomes.

ETHICAL APPROVAL

All procedures and methods were approved by the clinical research ethics boards of the Universities of Alberta (Pro00045958), Calgary (REB17-1887), British Columbia (H21-00523), Saskatchewan (1421), and Manitoba (HS20852:B2017:08).

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FIGURE LEGENDS

Figure 1:

Figure 1 Study flow diagram for analysis of adherence

Figure 2:

Figure 2 Medication frequency at baseline. HCTZ = hydrochlorothiazide

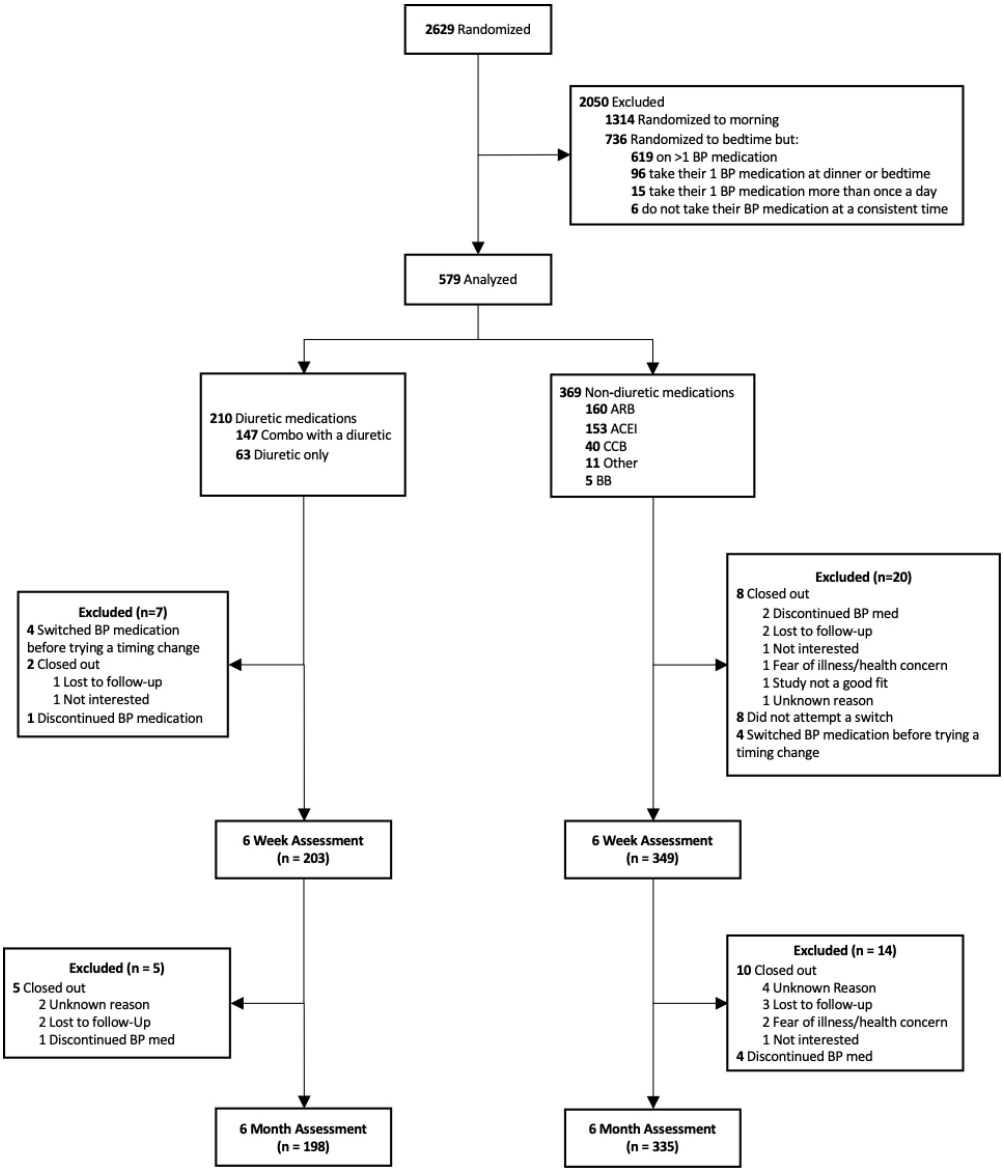

Figure 1 Study flow diagram for analysis of adherence

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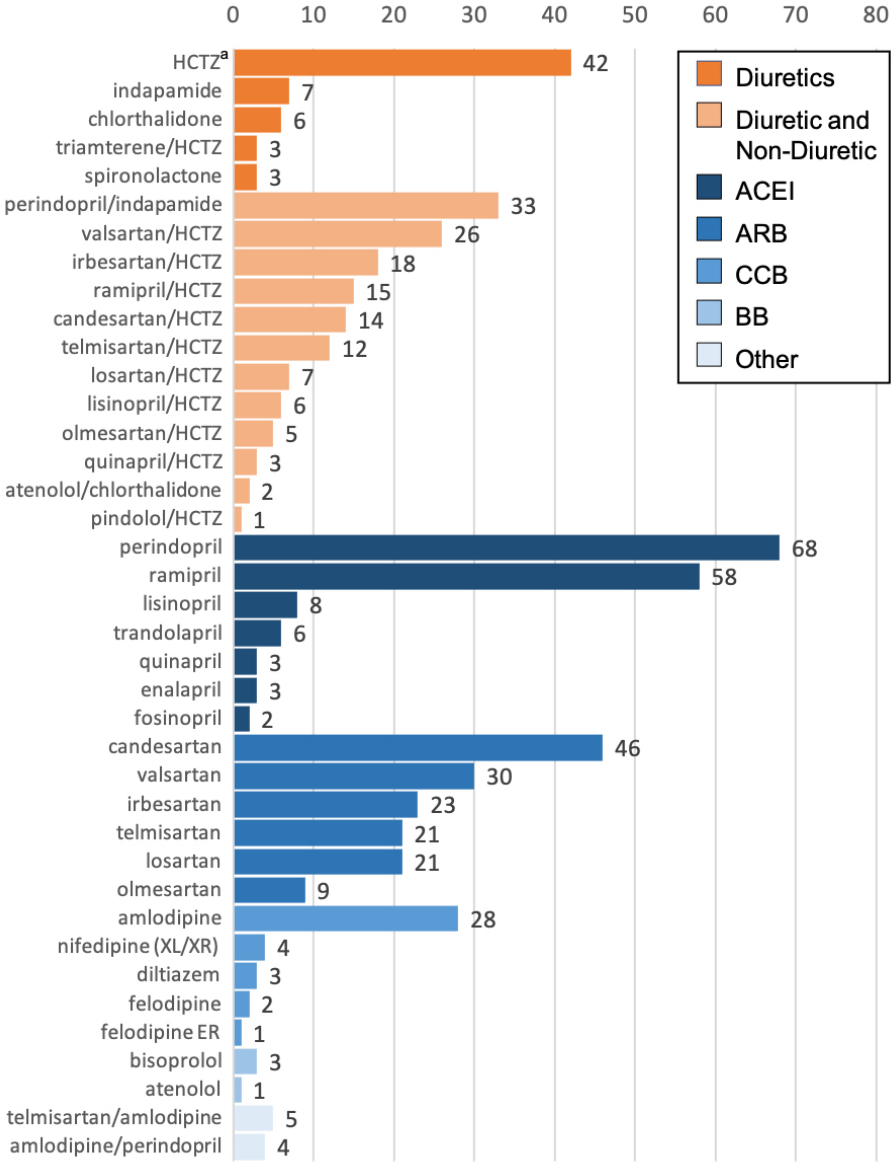

Figure 2 Medication frequency at baseline. HCTZ = hydrochlorothiazide

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Tolerability of Bedtime Diuretics:
A Prospective Cohort Analysis
(Supplemental Information)

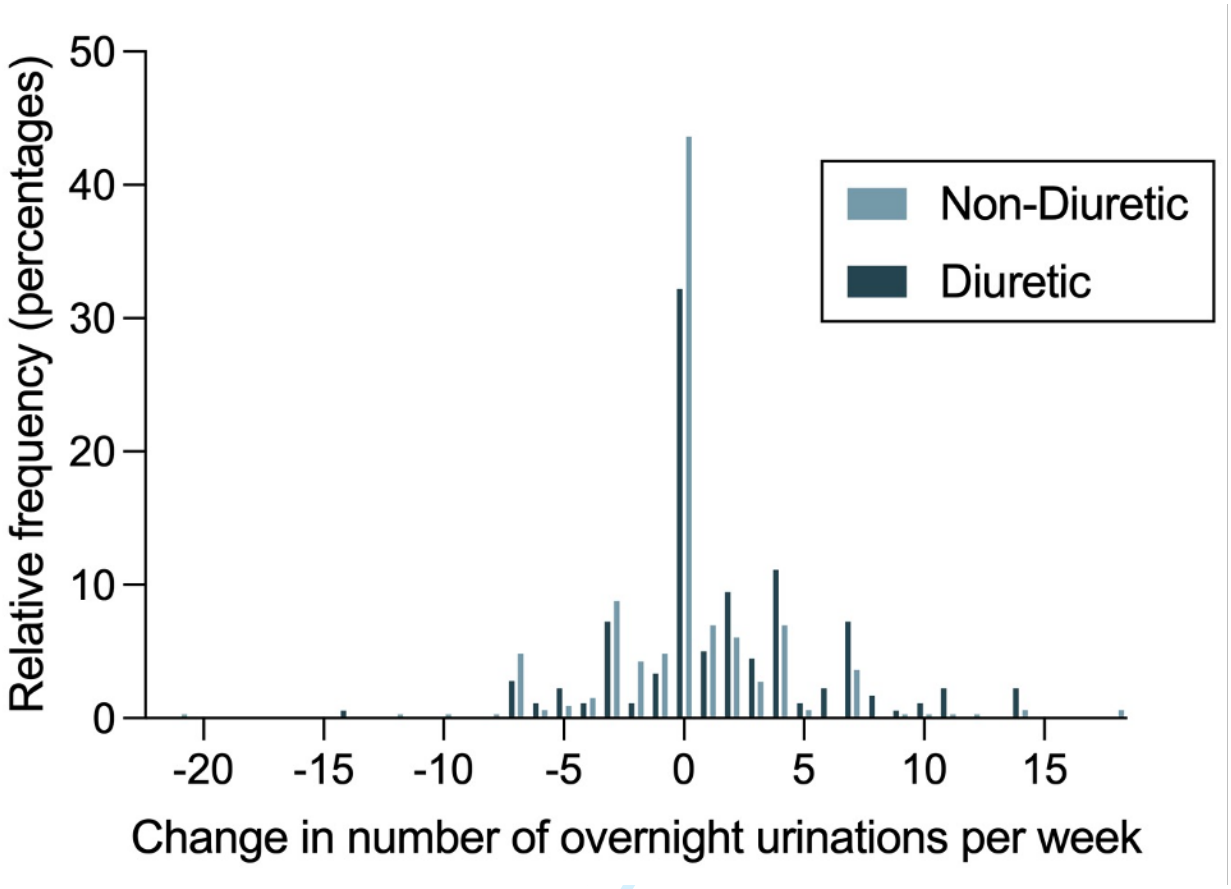
Supplemental Table 1. Comparison of baseline characteristics for participants that were excluded vs. included in the primary outcome analysis

Characteristics	Excluded (n=46) No. (%)	Included (n=533) No. (%)	p-value
Sex, female	27 (58.7)	308 (57.8)	0.99
Province			
Alberta	39 (84.8)	442 (82.9)	0.84
British Columbia	4 (8.7)	48 (9.0)	0.99
Manitoba	2 (4.4)	35 (6.6)	0.76
Saskatchewan	1 (2.2)	8 (1.5)	0.53
Rural resident	4 (8.7)	71 (13.3)	0.49
Age, mean (STD), y	64.6 (10.6)	65.5 (10.0)	0.55
≤ 29	0	1 (0.2)	0.99
30 - 39	0	2 (0.4)	0.99
40 - 49	3 (6.5)	24 (4.5)	0.46
50 - 59	9 (19.6)	116 (21.8)	0.85
60 - 69	18 (39.1)	202 (37.9)	0.87
70 - 79	11 (23.9)	146 (27.4)	0.73
80 - 89	5 (10.9)	39 (7.3)	0.38
≥ 90	0	3 (0.6)	0.99
Ethnicity			
White	43 (93.5)	504 (94.6)	0.73
South east asian	0	12 (2.3)	0.61
Asian	1 (2.2)	3 (0.6)	0.28
First nation	0	6 (1.1)	0.99
Black	0	0	0.99
Other	1 (2.2)	7 (1.3)	0.49
Decline to answer	1 (2.2)	1 (0.2)	0.15

Education level			
Less than high school	4 (8.7)	21 (3.9)	0.13
High school diploma	19 (41.3)	147 (27.6)	0.06
Technical or trade college diploma	9 (19.6)	146 (27.4)	0.30
University degree	13 (28.3)	219 (41.1)	0.12
Decline to answer	1 (2.2)	0	0.08
Annual household income, CAD$			
< 25,000	4 (8.7)	25 (4.7)	0.28
25,000 to 100,000	20 (43.5)	287 (53.8)	0.22
> 100,000	20 (43.5)	189 (35.5)	0.34
Decline to answer	2 (4.4)	32 (6.0)	0.99
Comorbidities[a]			
Coronary artery disease	9 (19.6)	100 (18.8)	0.85
Diabetes	6 (13)	92 (17.3)	0.54
Sleep apnea	11 (23.9)	99 (18.6)	0.43
Chronic kidney disease	7 (15.2)	48 (9.0)	0.19
COPD	6 (13.0)	50 (9.4)	0.43
Stroke	1 (2.2)	28 (5.3)	0.72
Heart failure	0	10 (1.9)	0.99
Hip fracture	1 (2.2)	2 (0.4)	0.22
Cigarette smoker (current)	2 (4.4)	42 (7.9)	0.56
Nocturia, median (IQR), nocturnal urinations/wk	7 (0-14.0)	6 (1-10.5)	0.61
Does not experience nocturia	12 (26.1)	129 (24.2)	0.72
Nocturia occurs but "not a problem"	21 (45.6)	255 (47.8)	0.88
Nocturia "a minor problem"	12 (26.1)	139 (26.1)	0.99
Nocturia "a major problem"	1 (2.2)	10 (1.9)	0.60
Physical exercise, median (IQR), days per week[b]	3 (0-5.0)	3 (0.5-5.0)	0.42
0	15 (32.6)	133 (25.0)	0.29
1	6 (13.0)	43 (8.1)	0.26
2	1 (2.2)	68 (12.8)	0.03
3	6 (13.0)	75 (14.1)	0.99
4	6 (13.0)	54 (10.1)	0.46
5	2 (4.4)	49 (9.2)	0.41

6	1 (2.2)	15 (2.8)	0.99
7	9 (19.6)	96 (18.0)	0.84
BMI, median (IQR), Kg/M^2	27.7 (26.1-33.4)	28.3 (25.5-32.3)	0.80
Underweight (< 18.5)	0	3 (0.6)	0.99
Normal weight (18.5 - 24.9)	9 (19.6)	105 (19.7)	0.99
Overweight (25 - 29.9)	21 (45.7)	220 (41.3)	0.64
Obese (≥ 30)	16 (34.8)	205 (38.5)	0.75
EQ-5D-5L overall health score, median (IQR)[c]	80 (75-90)	80 (75-90)	0.88
Physically frail[d]	7 (15.2)	73 (13.7)	0.82
Cognition[e]			
Normal	41 (89.1)	496 (93.1)	0.37
Questionable impairment	3 (6.5)	36 (6.8)	0.99
Impairment consistent with dementia	2 (4.4)	1 (0.2)	0.02

[a] Derived from Alberta provincial health claims data and self-report.
[b] "How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"
[c] Self-rating of overall health on a scale of 0 (worst) to 100 (best).
[d] As per Tilburg Frailty Indicator's physical sub-scale (sub-scale score ≥3 defines physically frail).
[e] As per Short Blessed screening test score. Considered to be normal (0-4), questionable impairment (5-9), or impairment consistent with dementia (>9).



Supplemental Figure 1. 6-week change in overnight urinations per week.

Figure is the change in the number of overnight urinations per week experienced by hypertensive primary care patients 6-weeks after being randomly allocated to switch their only blood pressure lowering pill from morning to bedtime. Grouped by those whose pill contained a diuretic (90.7% of which were thiazides), and those who used a different class of blood pressure lowering medication.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-13
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-11
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11-13
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	14-18
Outcome data	15*	Report numbers of outcome events or summary measures over time	16-18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-18
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14, 17-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.