

Loop Diuretic Use and Fracture in Postmenopausal Women

Findings From the Women's Health Initiative

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Background: The relationship of loop diuretics to bone mineral density (BMD), falls, and fractures in postmenopausal women has not been established.

Methods: We examined whether loop diuretics are associated with changes in BMD, falls, and fractures in women enrolled in the Women's Health Initiative. We included the 133 855 women (3411 users and 130 444 nonusers of loop diuretics) who were enrolled in the WHI from October 29, 1993 to December 31, 1998 and determined incident falls and fractures for a mean of 7.7 years. Women who had BMD measurements at baseline and at year 3 (300 users and 9124 nonusers of loop diuretics) were also examined.

Results: After adjustment for covariates, no significant association was found between ever use of loop diuretics and total (hazard ratio [HR], 1.09; 95% confidence interval [CI],

1.00-1.19), hip (HR, 1.21; 95% CI, 0.91-1.60), and clinical vertebral fractures (HR, 1.17; 95% CI, 0.92-1.48) and falls (1.02; 0.96-1.08). An increased risk was found for other clinical fractures (1.16; 1.01-1.33) and total fractures (1.16; 1.03-1.31) with more than 3 years' use of loop diuretics. The BMD changes were not associated with loop diuretic use.

Conclusions: After adjustment for confounding variables, no significant association was found between ever use of loop diuretics and changes in BMD, falls, and fractures. Loop diuretics were used by women in poor health who were already at risk for fractures. However, prolonged use of loop diuretics was associated with higher fracture risk in postmenopausal women.

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OSTEOPOROSIS AND HEART failure are particular health concerns for women.¹⁻³ Half of all postmenopausal women will experience an osteoporosis-related fracture in their lifetime.^{1,2} By the age of 40 years, the lifetime risk for women of developing heart failure is 1 in 5.³

In 2007, in the United States, loop diuretics were among the top 200 prescribed medications, with 37 094 000 prescriptions for furosemide, 1 907 000 prescriptions for torsemide, and 1 741 000 prescriptions for bumetanide.⁴ Loop diuretics increase calcium excretion⁵ and, in some studies, hypercalciuria is associated with low bone mineral density (BMD),^{6,7} a risk factor for fractures.⁸ Loop diuretics may also cause orthostatic hypotension,⁹ which has been associated with falls in some,¹⁰ albeit not all,¹¹ studies. However, data are conflicted with regard to the association between loop diuretics and BMD, falls, and fractures. In a cross-sectional study of 140 postmenopausal women, no association was found between loop diuretic use and BMD¹²; in con-

trast, in a randomized clinical trial that included 84 postmenopausal women and was performed by the same investigators, the loop diuretic bumetanide decreased BMD.¹³ Similarly, findings are inconsistent with respect to the association of loop diuretics with falls—1 meta-analysis suggested that loop diuretics are weakly associated with falls,¹⁴ although cross-sectionally, in the British Women's Heart and Health Study, cardiovascular drugs were not independently associated with falls.¹⁵ Relative to fractures, a positive association of loop diuretic use with osteoporotic fractures was reported in a prospective cohort study that included more than 300 postmenopausal women¹⁶ and in a large population-based pharmacoepidemiologic case-control study of more than 44 000 users of loop diuretics.¹⁷ However, in another case-control study published in 1986, a small inverse association of loop diuretic use with femoral neck fractures was noted, although the confidence interval (CI) included 1.¹⁸

To our knowledge, no study to date has examined the relationship between loop

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diuretic use and BMD, falls, and fractures within the context of a large prospective study that uniformly collected medication exposure, BMD, fall, and fracture outcomes. In addition, the relationship between loop diuretics and fractures in women with congestive heart failure (CHF) has not been studied. The purpose of this article is to examine the association between loop diuretic use and changes in BMD, falls, and fractures in patients enrolled in the Women's Health Initiative (WHI), including women with and without CHF.

We hypothesized that, compared with loop diuretic nonusers, loop diuretic users would have greater loss of BMD, more falls, and more fractures and that these results would be a function of duration of use of this type of drug. Moreover, in experimental studies, aldosteronism, which accompanies heart failure, is associated with impairments in bone strength, which are accentuated by administration of a loop diuretic,¹⁹ and hip fractures are increased with CHF.²⁰ For this reason, we predicted that use of loop diuretics would be a particular risk for loss of BMD, falls, and fractures in the setting of CHF.

METHODS

STUDY SETTING AND PARTICIPANTS

We conducted a prospective study of loop diuretic use and subsequent changes in BMD (mean follow-up of 3 years), falls (mean follow-up of 7.7 years), and fractures (mean follow-up of 7.7 years) in women aged 50 to 79 years enrolled at 40 clinical centers in the WHI from October 29, 1993 to December 31, 1998 and who were subsequently observed for an average of 7.7 years. The study population for the fracture and fall outcomes (3411 loop diuretic users and 130 444 nonusers) included all women in the WHI observational study and the WHI clinical trials who were not in the active arms of the hormone or calcium and vitamin D trials. The BMD was available in a subset (300 loop diuretic users and 91 244 nonusers). Details of the WHI methods have been described elsewhere.²¹ All protocols were reviewed and approved by the institutional review board at each participating center.

ASCERTAINMENT OF CHF

There were 3820 women with CHF in these analyses, including 993 women with self-reported prevalent CHF (388 loop diuretic users and 605 nonusers) and 2827 with physician-adjudicated incident CHF (454 loop diuretic users and 2373 nonusers).

MEDICATION USE

Current medication use was ascertained by having the participants bring all the containers for medications taken for the 2 weeks prior to the baseline visit and the year 3 visit. Interviewers entered each medication into the database, which assigned drug codes using Medi-Span software (Wolters Kluwer Health; Conshohocken, Pennsylvania). Information on duration of use but not dose was recorded. For this study, we defined hormone therapy as use of an estrogen with or without progesterone (oral or patch formulations) and current loop diuretic use as any use at the baseline and/or at the time of the year 3 visit. Duration of use of loop diuretics was examined in 3 categories (<1 year, 1-3 years, or >3 years).

DIETARY SUPPLEMENTS

Dietary intake of calcium and vitamin D was measured with a semiquantitative food frequency questionnaire. Vitamin D intake was defined as the sum of vitamin D from supplements and diet, whereas calcium intake included all calcium from medications, supplements, and diet.

OTHER COVARIATES

Questionnaires were used to collect information on age, ethnicity, smoking, parental history of hip fractures, prevalent fractures on or after the age of 55 years, age at menopause, health status, history of CHF, and history of coronary heart disease (myocardial infarction, angina, and/or coronary artery bypass graft or percutaneous coronary angioplasty). Alcohol consumption was estimated from the food frequency questionnaire. A construct of chronic conditions, including treated diabetes mellitus, stroke, any cancer, cardiovascular disease, arthritis, hypertension, 2 or more falls, emphysema, and hip fractures after the age of 55 years, was calculated in the WHI enrollees and included as the number of chronic conditions (n=0-4). Energy expenditure from recreational physical activity was used to determine physical activity levels. The Rand 36-Item Short Form Health Survey was used to calculate a physical function construct, with higher scores indicating better physical function. Height and weight were measured in the WHI enrollees²¹ and used to calculate body mass index (BMI) as weight in kilograms divided by height in meters squared. Geographic study sites and trial enrollment were adjusted for in the statistical analyses. All covariates used were from the baseline visit.

OUTCOMES AND FOLLOW-UP

Measurement of BMD

The BMD of the total hip, anterior-posterior lumbar spine, and total body was measured at baseline and at year 3 in participants at 3 of the 40 clinical centers of the WHI (Pittsburgh, Pennsylvania; Birmingham, Alabama; and Phoenix/Tucson, Arizona) by using a Hologic QDR densitometer Model 2000, 2000+, or 4500 Fan-beam (Hologic Inc, Waltham, Massachusetts). We determined change in BMD by loop diuretic use at these sites from baseline to year 3.

Fracture Ascertainment

In the WHI clinical trials, total fractures were defined as all reported clinical fractures other than those of the ribs, sternum, skull or face, fingers, toes, and cervical vertebrae. Hip fractures were verified by review of radiologic reports or medical records by centrally trained and masked physician adjudicators at each clinical center. All fractures, including hip fractures, were adjudicated; however, all other fractures were ascertained by self-report.

Fall Ascertainment

A participant was identified as having a history of falls if she reported 2 or more falls in the year before baseline. Fall history was obtained by semiannual self-report questionnaires that asked the number of times the participant fell or landed on the ground (excluding falls due to sports participation). In epidemiologic studies, a recurrent faller has been defined as someone who has fallen twice or more during a defined period²²; for our study, we also defined a faller as a person who reported 2 or more falls in a year and determined during a mean follow-up of 7.7 years the number of times this event occurred in loop diuretic users compared with nonusers.

Table 1. Baseline Characteristics of the Study Population^a

Characteristic	Loop Diuretic Users (n=3411)		Nonusers (n=130 444)		P Value
	No.	Mean (SE) or %	No.	Mean (SE) or %	
Age at screening, y	3411	66.2 (0.12)	130 444	63.3 (0.02)	<.001
50-59	675	19.8	43 110	33.0	<.001
60-69	1485	43.5	58 400	44.8	
70-79	1251	36.7	28 934	22.2	
Ethnicity					
White	2593	76.0	108 081	82.9	<.001
Black	648	19.0	11 298	8.7	
Hispanic	70	2.1	5089	3.9	
American Indian	25	0.7	567	0.4	
Asian/Pacific Islander	24	0.7	3589	2.8	
Unknown	51	1.5	1820	1.4	
Smoking					
Never smoked	1629	47.8	65 627	50.3	<.001
Past smoker	1539	45.1	54 527	41.8	
Current smoker	193	5.7	8509	6.5	
History of fracture on or after the age of 55 years					
No	2500	73.3	101 318	77.7	<.001
Yes	543	15.9	16 491	12.6	
Parent with hip fracture after the age of 40 years					
No	2221	65.1	85 911	65.9	.46
Yes	22	0.6	686	0.5	
Self-reported health status					
Excellent	92	2.7	22 705	17.4	<.001
Very good	606	17.8	53 258	40.8	
Good	1475	43.2	42 242	32.4	
Fair	1040	30.5	10 453	8.0	
Poor	165	4.8	937	0.7	
Physical function construct (SF-36)	3307	58.8 (0.45)	127 981	81.5 (0.06)	<.001
CHF at baseline					
No	2954	86.6	129 713	99.4	<.001
Yes	457	13.4	724	0.6	
CHD (myocardial infarction, angina, CABG, or PTCA)					
No	2304	67.5	119 760	91.8	<.001
Yes	1025	30.0	8406	6.4	
No. of chronic conditions ^b					
0	147	4.3	35 133	26.9	<.001
1	672	19.7	48 896	37.5	
2	1014	29.7	31 653	24.3	
3	851	24.9	11 176	8.9	
≥4	727	21.3	3586	2.7	
Alcohol use					
Nondrinker	1688	49.5	37 901	29.1	<.001
Current drinker, <7 drinks per week	1463	42.9	76 088	58.3	
Current drinker, ≥7 drinks per week	224	6.6	15 564	11.9	
Clinical trial vs observational study enrollment					
Observational study	2450	71.8	91 226	69.9	.02
Clinical trial	961	28.2	39 218	30.1	
Hormone therapy trial enrollment (placebo only)					
No	3188	93.5	121 151	92.9	.19
Yes	223	6.5	9293	7.1	
Dietary modification trial enrollment					
No	2614	76.6	97 825	75.0	.03
Yes	797	23.4	32 619	25.0	
Calcium and vitamin D trial enrollment (placebo only)					
No	3089	90.6	116 738	89.5	.045
Yes	322	9.4	13 706	10.5	
Height, cm	3392	161.0 (0.11)	129 574	161.8 (0.02)	<.001
Weight, kg	3396	85.3 (0.36)	129 954	72.7 (0.05)	<.001
BMI	3379	32.8 (0.13)	129 172	27.6 (0.02)	<.001
Age at menopause, y	3157	46.4 (0.14)	123 874	48.1 (0.02)	<.001
Baseline total body bone density ^c	299	1.02 (0.006)	9090	1.01 (0.001)	.23
Baseline total body bone density (adjusted) ^{c,d}	296	1.01 (0.007)	9024	1.02 (0.004)	.72
Baseline lumbar spine bone density ^c	286	1.03 (0.010)	8823	0.98 (0.002)	<.001
Baseline lumbar spine bone density (adjusted) ^{c,d}	283	1.00 (0.011)	8757	0.98 (0.007)	.046
Baseline total hip bone density ^c	294	0.88 (0.008)	9094	0.85 (0.001)	<.001
Baseline total hip bone density (adjusted) ^{c,d}	291	0.85 (0.008)	9026	0.85 (0.005)	.59
Total MET hours per week of recreational activity	3304	8.3 (11.0)	125 640	12.9 (13.9)	<.001
Baseline total vitamin D intake, U/d	3407	350.6 (286.4)	130 232	374.6 (282.1)	<.001
Baseline total calcium intake, mg/d	3407	1083.5 (751.9)	130 232	1195.6 (753.9)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; CHD, chronic heart disease; CHF, congestive heart failure; MET, metabolic equivalent task; PTCA, percutaneous coronary angioplasty; SF-36, 36-Item Short Form Health Survey.

^aFrequencies of missing data for individual covariates not presented.

^bIncludes treated diabetes mellitus, stroke, any cancer, CHD, arthritis, hypertension, 2 or more falls, emphysema, and hip fracture after the age of 55 years.

^cFrom subset.

^dAdjusted for age, ethnicity, and BMI.

STATISTICAL ANALYSIS

Descriptive analyses (**Table 1** and **Table 2**) were stratified by loop diuretic use at baseline and are presented with the number of participants, means, and standard errors in each group for continuous variables and frequencies and percentages for categorical covariates. For continuous covariates, *P* values were taken from a loop diuretic term of an unadjusted linear model that modeled the continuous covariate as a function of baseline loop diuretic use, whereas for categorical variables, a χ^2 test was used. Modeling was performed with Cox proportional hazards models and includes results with both minimal adjustment (age, ethnicity, and BMI) and full adjustment (age; ethnicity; BMI; smoking status; alcohol intake; calcium and vitamin D intake; prevalent fracture at the age of 55 years or older; history of falls; number of chronic conditions; history of chronic heart disease; prevalent CHF; time-dependent incident CHF (to account for the presence or absence of the covariate, depending on the time in the model); physical function construct (36-Item Short Form Health Survey); β -blockers, thiazides, or bisphosphonates; past or current use of estrogen, corticosteroids, anticonvulsants, selective estrogen receptor modulators, angiotensin-converting enzyme inhibitors, statins, calcitonin, or heparin or warfarin sodium; age of menopause; physical activity levels; parental history of hip fractures; study site region; and self-reported health. All models were stratified within the models for enrollment in the WHI study arms (hormone therapy, Dietary Modification Trial, Calcium with Vitamin D Supplementation Trial, and observational study). The specified a priori analysis plan selected a stratified analysis to determine whether associations between loop diuretic use and falls and fractures were a function of CHF status. We, therefore, created a time-dependent variable for CHF and loop diuretic use. We did not determine the association between loop diuretic use and changes in BMD as a function of CHF status because of the small number of women with CHF who had these measurements taken.

Results for each outcome are presented with event totals, annualized percentages, and hazard ratios (HRs), with their corresponding 95% CIs. Fracture and fall outcomes were individually modeled first by any loop diuretic use at baseline and then by duration of loop diuretic use at baseline. Results are presented for both sets of models, with duration of loop diuretic use stratified into groups of less than 1 year, 1 to 3 years, and more than 3 years. Missing data for the covariates of parental history of hip fractures (33.6%), prevalent fractures after the age of 55 years (9.5%), and prevalent falls (3.3%) were set to 0 for all proportional hazards models. For the covariate of number of chronic conditions, if a participant had more than 4 of these chronic conditions at baseline, her value was set to 4.

In all fracture- and fall-adjusted analyses, data on 11.3% of the total sample of 133 855 women were not included because of missing data on covariates. The data analyses for fractures and falls were censored at the date of last follow-up, first fracture, or death, whichever came first.

The mean BMDs by loop diuretic use are presented with sample sizes and standard errors. Comparisons between means in the loop diuretic user and nonuser groups were performed in both minimally and fully adjusted linear models using the baseline covariates described herein. All analyses were conducted with SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Our data set included 3411 loop diuretic users; 88.9% of these were users of furosemide, 7.8% bumetanide, 2.9% torsemide, and 0.4% ethacrynic acid. Compared

with nonusers, loop diuretic users were older, more likely to have had a fracture on or before the age of 55 years, more likely to have a lower physical function construct, more likely to have CHF or chronic heart disease, and more likely to be in the observational study rather than the clinical trial arms of the WHI. Significant differences were found in the WHI enrollees between the loop diuretic users and nonusers with respect to ethnicity ($P < .001$), smoking status ($P < .001$), self-reported health ($P < .001$), number of chronic health conditions ($P < .001$), and alcohol use ($P < .001$). Among the clinical trial arms, loop diuretic users were less likely to be enrolled in the Dietary Modification Trial or the Calcium with Vitamin D Supplementation Trial ($P \leq .045$) (Table 1). Loop diuretic users were shorter and heavier on average and had a higher BMI, a younger age at menopause, a higher unadjusted BMD of the lumbar spine and total hip, lower levels of physical activity, and lower intakes of vitamin D and calcium than did nonusers ($P < .001$ for all; Table 1). No significant differences were found in parental history of hip fractures ($P = .46$) or unadjusted whole-body BMD ($P = .23$) at baseline between loop diuretic users and nonusers (Table 1). Baseline characteristic patterns similar to those of the whole population were present in women with CHF who were loop diuretic users compared with women with CHF who were nonusers, except that no significant differences were found in personal history of fracture on or after the age of 55 years, baseline vitamin D intake, or trial enrollments (other than the hormone therapy trial). However, there were significant differences in the whole-body bone mineral density between women with CHF who were loop diuretic users compared with women with CHF who were nonusers of loop diuretics (Table 2). Compared with nonusers of loop diuretics, users were significantly more likely to use β -blockers, calcitonin, anticonvulsants, corticosteroids, heparin or warfarin sodium, angiotensin-converting enzyme inhibitors, and statins ($P < .001$ for all) and significantly less likely to use thiazides ($P < .001$). Use of hormone therapy also differed significantly between the loop diuretic users and nonusers ($P < .001$). No significant differences were found between the groups with respect to use of bisphosphonate ($P = .38$) or selective estrogen receptor modulators ($P = .95$) (Table 3). Among women with CHF, users of loop diuretics were significantly more likely to use β -blockers, corticosteroids, heparin or warfarin sodium, angiotensin-converting enzyme inhibitors, and statins ($P \leq .03$) and significantly less likely to use thiazides ($P < .001$). No significant differences were found for loop diuretic use in women with CHF with respect to use of hormone replacement therapy ($P = .15$), bisphosphonates ($P = .52$), selective estrogen receptor modulators ($P = .63$), calcitonin ($P = .65$), or anticonvulsants ($P = .23$) (Table 4).

In models adjusted for age, ethnicity, and BMI, a significant association was found between loop diuretic use and total fractures (HR, 1.31; 95% CI, 1.20-1.42), hip fractures (1.75; 1.34-2.28), clinical vertebral fractures (1.68; 1.35-2.10), other fractures (1.27; 1.15-1.41), and 2 or

Table 2. Baseline Characteristics of the Congestive Heart Failure Population^a

Characteristic	Loop Diuretic Users (n=3411)		Nonusers (n=130 444)		P Value
	No.	Mean (SE) or %	No.	Mean (SE) or %	
Age at screening, y	821	67.1 (0.12)	3445	67.9 (0.24)	.01
50-59	128	15.6	442	12.8	<.001
60-69	356	43.4	1403	40.7	
70-79	337	41.0	1600	46.4	
Ethnicity					
White	605	73.7	2831	82.2	<.001
Black	169	20.6	395	11.5	
Hispanic	21	2.6	108	3.1	
American Indian	7	0.9	23	0.7	
Asian/Pacific Islander	4	0.5	39	1.1	
Unknown	15	1.8	49	1.4	
Smoking					
Never smoked	337	41.0	1544	44.8	<.001
Past smoker	413	50.3	1496	43.4	
Current smoker	52	63.0	325	9.4	
History of fracture on or after the age of 55 years					
No	579	70.5	2361	68.5	.41
Yes	149	18.1	639	18.5	
Parent with hip fracture after the age of 40 years					
No	538	65.5	2262	65.7	.96
Yes	5	0.6	24	0.7	
Self-reported health status					
Excellent	9	1.1	209	6.1	<.001
Very good	77	9.4	876	25.4	
Good	303	36.9	1459	42.4	
Fair	354	43.1	774	22.5	
Poor	72	8.8	99	2.9	
Physical function construct (SF-36)	801	50.72 (0.91)	3359	64.9 (0.44)	<.001
CHD (myocardial infarction, angina, CABG, or PTCA)					
No	576	70.2	2941	85.4	<.001
Yes	243	29.6	499	14.5	
No. of chronic conditions ^b					
0	9	1.1	231	6.7	<.001
1	68	8.3	744	21.6	
2	171	20.8	1007	29.2	
3	212	25.8	814	23.6	
≥4	361	44.0	649	18.8	
Alcohol use					
Nondrinker	488	59.4	1436	41.7	<.001
Current drinker, <7 drinks per week	282	34.3	1656	48.1	
Current drinker, ≥7 drinks per week	43	5.2	321	9.3	
Clinical trial vs observational study enrollment					
Observational study	225	27.4	1055	30.6	.07
Clinical trial	225	27.4	1055	30.6	
Hormone therapy trial enrollment (placebo only)					
No	770	93.8	3128	90.8	.006
Yes	51	6.2	317	9.2	
Dietary modification trial enrollment					
No	636	77.5	2616	75.0	.36
Yes	797	23.4	829	24.1	
Calcium and vitamin D trial enrollment (placebo only)					
No	751	91.5	3142	91.2	.81
Yes	70	8.5	303	8.8	
Height, cm	813	160.6 (0.24)	3418	160.8 (0.11)	.38
Weight, kg	815	84.0 (0.76)	3430	77.5 (0.33)	<.001
BMI	809	32.4 (0.28)	3408	29.8 (0.12)	<.001
Age at menopause, y	757	46 (0.29)	3161	47.3 (0.13)	<.001
Baseline total body bone density ^c	69	1.03 (0.014)	384	0.99 (0.006)	.02
Baseline total body bone density (adjusted) ^{c,d}	69	1.03 (0.019)	381	1.02 (0.015)	.39
Baseline lumbar spine bone density ^c	62	1.05 (0.021)	364	0.98 (0.010)	.006
Baseline lumbar spine bone density (adjusted) ^{c,d}	62	1.04 (0.032)	361	1.01 (0.024)	.17
Baseline total hip bone density ^c	67	0.89 (0.019)	383	0.83 (0.008)	.006
Baseline total hip bone density (adjusted) ^{c,d}	67	0.85 (0.022)	380	0.83 (0.017)	.31
Total MET hours per week of recreational activity	794	7.66 (0.37)	3285	9.71 (0.21)	<.001
Baseline total vitamin D intake, U/d	821	355 (10)	3440	356.3 (4.8)	.91
Baseline total calcium intake, mg/d	821	1067.7 (25.6)	3440	1137.1 (12.61)	.02

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; CHD, chronic heart disease; MET, metabolic equivalent task; PTCA, percutaneous coronary angioplasty; SF-36, 36-Item Short Form Health Survey.

^aFrequencies of missing data for individual covariates not presented.

^bIncludes treated diabetes mellitus, stroke, any cancer, CHD, arthritis, hypertension, 2 or more falls, emphysema, and hip fracture after the age of 55 years.

^cFrom subset.

^dAdjusted for age, ethnicity, and BMI.

Table 3. Baseline Medication Use in the Study Population by Loop Diuretic Use or Nonuse

Medication	Loop Diuretic Users, No. (%) (n=3411)	Nonusers, No. (%) (n=130 444)	P Value
β-Blockers	668 (19.6)	10 213 (7.8)	<.001
Thiazides	102 (3.0)	6180 (4.7)	<.001
Hormone therapy at baseline			
Never used	1605 (47.1)	54 229 (41.6)	<.001
Past user	589 (17.3)	19 633 (15.1)	
Current user	1217 (35.7)	56 582 (43.4)	
Bisphosphonates	66 (1.9)	2810 (2.2)	.38
SERMs	1 (0.0)	41 (0.0)	.95
Calcitonin	25 (0.7)	427 (0.3)	<.001
Corticosteroids	121 (3.5)	1248 (1.0)	<.001
Anticonvulsants	78 (2.3)	1335 (1.0)	<.001
Heparin or warfarin sodium	321 (9.4)	1086 (0.8)	<.001
ACE inhibitors	928 (27.2)	9121 (7.0)	<.001
Statins	590 (17.3)	9776 (7.5)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; SERMs, selective estrogen receptor modulators.

more falls (1.37; 1.30-1.45), and no statistically significant association was found between loop diuretic use and lower arm or wrist fractures (1.17; 0.97-1.41) (**Table 5**). However, in fully adjusted models, the association between loop diuretic use (ever) and total fractures (HR, 1.09; 95% CI, 1.00-1.19; $P=.052$), hip fractures (1.21; 0.91-1.60), clinical vertebral fractures (1.17; 0.92-1.48; $P=.20$), and falls (1.01; 0.96-1.08; $P=.62$) was no longer statistically significant (Table 5). Although the trends for duration of use of loop diuretics and falls and fractures were not statistically significant, we observed modest increased risks for other clinical fractures (1.16; 1.01-1.33) and total fractures (HR, 1.16; 95% CI, 1.03-1.31) in women who had used loop diuretics for more than 3 years.

In minimally adjusted models in the 2827 women with incident CHF, loop diuretic use was significantly inversely associated with clinical vertebral fractures but not hip fractures (HR, 0.69; 95% CI, 0.35-1.37). In fully adjusted models in women with CHF, loop diuretic use was also significantly inversely associated with both hip (HR, 0.44; 95% CI, 0.21-0.94) and clinical vertebral (0.46; 0.21-0.97) fractures although there were only 16 hip-fracture cases (3 in loop diuretic users and 13 in nonusers) and only 23 clinical vertebral fractures (3 in loop diuretic users and 20 in nonusers). In fully adjusted models, in a subgroup analysis of 1146 of these women with adjudicated incident CHF who, in addition to a clinical diagnosis of CHF, had imaging procedures that documented impaired systolic or diastolic function, there was similar directionality of findings (hip fractures: HR, 0.27; 95% CI, 0.06-1.23; $P=.09$; clinical vertebral fractures: HR, 0.39; 95% CI, 0.10-1.50; $P=.17$), although the results were not statistically significant.

The change in BMD analysis included 300 loop diuretic users and 9124 nonusers. In this subset, in the fully adjusted models, no significant differences were found between loop diuretic users and nonusers in baseline BMD

Table 4. Baseline Medication Use in Women With Congestive Heart Failure by Loop Diuretic Use or Nonuse

Medication	Loop Diuretic Users, No. (%) (n=821)	Nonusers, No. (%) (n=3445)	P Value
β-Blockers	161 (19.6)	566 (16.4)	≤.03
Thiazides	29 (3.5)	314 (9.1)	<.001
Hormone therapy at baseline			
Never used	444 (54.1)	1816 (52.7)	.15
Past user	161 (19.6)	613 (17.8)	
Current user	216 (26.3)	1016 (29.5)	
Bisphosphonates	18 (2.2)	89 (2.6)	.52
SERMs	0	1 (0.0)	.63
Calcitonin	4 (0.5)	13 (0.4)	.65
Corticosteroids	36 (4.4)	84 (2.4)	.002
Anticonvulsants	20 (2.4)	62 (1.8)	.23
Heparin or warfarin sodium	184 (22.4)	205 (6.0)	<.001
ACE inhibitors	357 (43.5)	553 (16.1)	<.001
Statins	187 (22.8)	466 (13.5)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; SERMs, selective estrogen receptor modulators.

of the total hip ($P=.45$), lumbar spine ($P=.31$), total body ($P=.29$), year 3 BMD of the total hip ($P=.34$), lumbar spine ($P=.05$), total body ($P=.05$), or change in BMD measurements from baseline to year 3 (**Table 6**).

COMMENT

In this large, prospective, population-based study of postmenopausal women, after adjustment for potential confounding variables, no significant association was found between ever use of loop diuretics and total or site-specific fractures, including hip, clinical vertebral, lower arm or wrist, and other clinical fractures. A small positive association was found between prolonged duration of use (>3 years) of loop diuretics and other clinical and total fractures. After adjustment for potential confounding variables, no significant association was found between loop diuretics and falls or change in BMD at multiple skeletal sites.

A small positive relationship between ever use of loop diuretics and hip fractures¹⁷ and total fractures^{17,23} has been reported. In the WHI, large differences in health status were found between users and nonusers of loop diuretics. Loop diuretic users were at high risk of fracture, independent of frequency of use; after controlling for confounding by indication,²⁴ we found no statistically significant association between ever use of loop diuretics and fractures. In support of this concept, it has been suggested that the relationship between thiazides and fractures may reflect selection bias, rather than being an independent association of the drug with fracture.²⁵ Indeed, in a small case-control study, in which, similar to our results, no significant association was found between ever use of loop diuretics and femoral neck fractures, the authors postulated that health status itself, rather than medication use, was the critically important factor.¹⁸ However, in the WHI, women who had used loop diuretics

Table 5. Fracture Incidence and Fall Frequency by Use or Nonuse of Loop Diuretics at Baseline

Fracture or Fall Type	No.	Annualized, %	HR (95% CI)	
			Model 1 ^a	Model 2 ^b
Hip fractures				
Nonuser	1309	0.15	1 [Reference]	1 [Reference]
User	59	0.29	1.75 (1.34-2.28)	1.21 (0.91-1.60)
<1 y	14	0.35	2.13 (1.26-3.62)	1.33 (0.76-2.31)
1-3 y	13	0.20	1.25 (0.72-2.16)	0.90 (0.51-1.57)
≥3 y	32	0.33	1.91 (1.34-2.72)	1.35 (0.93-1.94)
Clinical vertebral fractures				
Nonuser	2047	0.23	1 [Reference]	1 [Reference]
User	85	0.42	1.68 (1.35-2.10)	1.17 (0.92-1.48)
<1 y	13	0.32	1.35 (0.78-2.33)	0.95 (0.55-1.64)
1-3 y	29	0.44	1.82 (1.26-2.64)	1.26 (0.86-1.85)
>3 y	43	0.44	1.72 (1.27-2.34)	1.22 (0.89-1.67)
Lower arm or wrist				
Nonuser	4227	0.48	1 [Reference]	1 [Reference]
User	115	0.56	1.17 (0.97-1.41)	1.06 (0.87-1.29)
<1 y	20	0.50	1.06 (0.68-1.65)	1.00 (0.64-1.56)
1-3 y	37	0.56	1.19 (0.86-1.65)	1.10 (0.79-1.55)
>3 y	58	0.59	1.19 (0.92-1.55)	1.06 (0.81-1.40)
Other clinical fractures				
Nonuser	13 503	1.52	1 [Reference]	1 [Reference]
User	415	2.02	1.27 (1.15-1.41)	1.06 (0.96-1.18)
<1 y	78	1.94	1.23 (0.99-1.54)	1.02 (0.81-1.28)
1-3 y	119	1.79	1.13 (0.94-1.35)	0.95 (0.79-1.14)
>3 y	218	2.22	1.38 (1.21-1.58)	1.16 (1.01-1.33)
Total fractures				
Nonuser	18 721	2.11	1 [Reference]	1 [Reference]
User	581	2.83	1.31 (1.20-1.42)	1.09 (1.00-1.19)
<1 y	106	2.64	1.23 (1.01-1.48)	1.01 (0.83-1.23)
1-3 y	175	2.63	1.23 (1.06-1.43)	1.04 (0.89-1.21)
>3 y	300	3.05	1.39 (1.24-1.56)	1.16 (1.03-1.31)
≥2 Falls				
Nonuser	37 489	4.23	1 [Reference]	1 [Reference]
User	1283	6.26	1.37 (1.30-1.45)	1.02 (0.96-1.08)
<1 y	245	6.09	1.38 (1.22-1.57)	1.00 (0.88-1.14)
1-3 y	430	6.47	1.42 (1.29-1.56)	1.09 (0.98-1.20)
>3 y	608	6.18	1.34 (1.24-1.45)	0.98 (0.90-1.07)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; SERMs, selective estrogen receptor modulators.

^aModel 1 adjusted for age, ethnicity, and BMI.

^bModel 2 adjusted for age, ethnicity, BMI, smoking, alcohol, calcium and vitamin D intake, prevalent fractures (fracture at the age of 55 years or older), prevalent falls (≥2 in year before enrollment), comorbidity, history of CHD, prevalent CHF, time-dependent incident CHF, physical function construct, use of β-blockers, thiazides, bisphosphonates, present and past use of hormone therapy or estrogen, ACE inhibitors, statins, corticosteroids, anticonvulsants, SERMs, calcitonin, heparin or warfarin sodium, age of menopause, physical activity levels, parental history of hip fractures, study site region, and self-reported health.

for a prolonged period had a modest increased risk for other clinical and total fractures, even after controlling for other covariates, including health status. Therefore, it may be important to consider fracture prevention measures in women who receive loop diuretic therapy.

Conversely, in women with CHF in the WHI, a small inverse association was found between loop diuretics and hip and clinical vertebral fractures. Interestingly, loop diuretics have been reported to improve functional capacity²⁶ and reduce oxidative stress.²⁷ Oxidative stress has been linked with osteoporosis²⁸ and CHF.²⁷ However, only 3.2% of our study population had CHF and, of these, only 19.3% were loop diuretic users. In contrast, national data suggest that 6% to 10% of elderly persons have CHF,²⁹ and most are prescribed loop diuretics.³⁰ Although it is likely that these findings in women with CHF, which were based on small numbers, were simply attributable to

chance, additional studies of the relationship between loop diuretic use in women with CHF and osteoporosis are needed.

The relationship of falls to medication use is complex. We hypothesized that loop diuretics might be positively associated with falls because they may cause orthostatic hypotension. However, in a large meta-analysis,¹¹ gait and balance problems and prior falls were the principal risk factors for future falls; no independent relationship was found between orthostatic hypotension and falls. In support of our lack of association between loop diuretic use and falls, another study¹⁵ states that cardiovascular drugs are not independently associated with falls.

Cross-sectionally, in our study, in agreement with what has been previously published,^{12,31} unadjusted BMD was higher at the total hip site in users of loop diuretics com-

Table 6. Mean Bone Mineral Density (BMD) and Changes in Mean BMD by Current Loop Diuretic Use

	Loop Diuretic User		Loop Diuretic Nonuser		P Value	P Value (Adjusted) ^a
	No.	Mean (SE)	No.	Mean (SE)		
Total hip						
Initial, g/cm ²	294	0.88 (0.008)	9094	0.85 (0.001)	<.001	.45
Final, g/cm ²	202	0.88 (0.010)	7483	0.85 (0.002)	.002	.34
Change, %	196	-0.44 (0.295)	7395	0.40 (0.048)	.005	.77
Total spine						
Initial, g/cm ²	286	1.03 (0.010)	8823	0.98 (0.002)	<.001	.31
Final, g/cm ²	194	1.05 (0.013)	7263	0.99 (0.002)	<.001	.05
Change, %	192	1.85 (0.371)	7203	1.76 (0.061)	.82	.90
Total body						
Initial, g/cm ²	299	1.02 (0.006)	9090	1.01 (0.001)	.23	.29
Final, g/cm ²	203	1.04 (0.008)	7456	1.02 (0.001)	.02	.05
Change, %	200	1.56 (0.263)	7380	1.00 (0.043)	.03	.37

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CHF, congestive heart failure; SERMs, selective estrogen receptor modulators.

^aAdjusted for age, ethnicity, BMI, smoking, alcohol, calcium intake and vitamin D intake, prevalent fractures (fracture at the age of 55 years or older), prevalent falls (2 or more in year before enrollment), comorbidity, history of CHD, prevalent CHF, physical function construct, use of β -blockers, thiazides, bisphosphonates, present and past or current use of hormone therapy or estrogen, ACE inhibitors, statins, corticosteroids, anticonvulsants, SERMs, calcitonin, heparin or warfarin sodium, age of menopause, physical activity levels, parental history of hip fractures, study site region, and self-reported health.

pared with nonusers; these differences in BMD disappeared in adjusted models. Longitudinally, after adjustments, no significant differences were found in the changes in BMD at any skeletal site measured between loop diuretic users and nonusers in the WHI. In contrast, in a randomized clinical trial, significant losses in BMD were reported in loop diuretic users¹³ and, in men in the Osteoporotic Fractures in Men Study, loop diuretic use was associated with increased rates of hip bone loss.³²

Our study has a number of limitations. Prefracture health, which may change in older populations, is a predictor of fracture,^{33,34} and we only included baseline levels of prefracture health. Low levels of 25-hydroxyvitamin D may be associated with BMD,³⁵ falls,³⁶ and fractures³⁷; however, we could not adjust for this. A particularly important limitation of our study is the lack of information on doses of loop diuretics used; dose effects of loop diuretics on calcium homeostasis³⁸ and fracture risk have been reported.¹⁷ We could not determine whether there was a residual risk for changes in bone health after use of diuretics had been stopped because we did not have the exact date that use of these drugs was discontinued. There were few users of loop diuretics other than furosemide. Our fall history was from self-report, which may be inaccurate.³⁹ There were few hip and vertebral fractures in those with CHF. The mean calcium intake was 1083 mg/d in the total loop diuretic population and 1139 mg/d in those with incident CHF. Our results may not be applicable to populations with lower calcium intakes, those primarily being treated with loop diuretics, or men. Finally, this study is not applicable to thiazide-type diuretics, which have been associated with increases in BMD⁴⁰ and lower forearm and hip fracture risk.⁴¹

In conclusion, no significant association was found between ever use of loop diuretics and changes in BMD, falls, or fractures in postmenopausal women in the WHI. However, prolonged use of loop diuretics was associated with higher fracture risk in postmenopausal women.

Loop diuretics are most commonly used by women in poor health who are already at risk for falls, fractures, and loss of BMD.

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