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Bone Mineral Density Changes Among Women Initiating Blood Pressure Lowering Drugs: A SWAN Cohort Study

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Abstract

Purpose—Several blood pressure lowering drugs may affect bone mineral density (BMD), leading to altered fracture risk. We examined the effect of blood pressure lowering drugs on BMD using data from the Study of Women's Health Across the Nation.

Methods—We conducted a propensity score matched cohort study. Women were initiators of ACE inhibitors (ACEi), beta-blockers (BB), or thiazide diuretics (THZD). Their annualized BMD changes during the 14-years of observation were compared with non-users.

Results—Among the 2312 eligible women, we found 69 ACEi, 71 BB, and 74 THZD users who were matched by a propensity score with the same number of non-users. THZD users had a slower annual percent decline in BMD compared to nonusers at the femoral neck (FN) (−0.28% vs −0.88%; p = 0.008) and the spine (−0.74% vs −1.0%; p = 0.34), albeit not statistically significant. Annual percent changes in BMD among ACEi and BB users were similar to rates in non-users. In comparison with BB, THZD use was associated with a trend toward less annualized BMD loss at the spine (−0.35% vs −0.60%; p = 0.08) and a similar trend at the FN (−0.39% vs −0.64%; p = 0.08); in comparisons with ACEi, THZD was also associated with less loss at the FN (−0.48% vs −0.82%; p = 0.02), but not at the spine (−0.40% vs −0.56%; p = 0.23).

Conclusions—Neither ACEi nor BB were associated with improvements in BMD. THZD use was associated with less annualized loss of BMD compared with non-users, as well as compared with ACEi and BB.

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Keywords

Osteoporosis; Hypertension; Epidemiology; Cohort

INTRODUCTION

Hypertension is the leading cause of stroke in the US and a major risk factor for coronary heart disease. (1) Many drugs lower blood pressure and selecting optimal therapy requires balancing potential benefits with risks in a given patient. The Joint National Committee (JNC) on Hypertension publishes recommendations for optimizing blood pressure lowering treatments; in the 2003 treatment recommendations, thiazide diuretics (THZD) were identified as a category of agents that was associated with improvement in bone mineral density (BMD).(2)

Since hypertension and osteoporosis are common morbidities in older adults, defining the BMD effects of drugs that lower blood pressure would be valuable to patients and providers when selecting treatments. Several randomized controlled trials demonstrate that THZDs improve BMD compared with placebo. (3, 4) As well, there are data, albeit less robust, suggesting that ACEi's and beta blockers (BBs) may improve BMD. ACEi's have been shown in animal models to diminish osteoporotic bone loss in a hypertensive rat model through their inhibition of the renin angiotensin system. (5) At least one cross-sectional study in humans demonstrates higher BMD among women using ACEi. (6) Similar to ACEi's, there have been mouse models demonstrating enhanced BMD from BBs through a leptin-dependent effect on osteoblasts. (7) There have been numerous studies in humans examining the effect of BBs on BMD, and they have produced conflicting results. Four cross-sectional studies found higher BMD among BB users;(8–11) but, two of the three longitudinal studies found no difference in BMD among BB users. (12, 13)

While large randomized controlled trials comparing multiple blood pressure lowering agents with bone fractures as the outcome would definitively put this question to rest, such trials would be large, expensive, and time-consuming. Longitudinal cohort studies with multiple assessments of blood pressure lowering medications and BMD could provide important insight into the plausibility of these associations. Furthermore, the fact that THZDs are known to improve BMD compared with placebo gives one a natural "positive control" to test the validity of a given study design. We examined annualized BMD changes among new users of ACEi's, BBs, and THZDs, compared with non-users and compared with each other.

METHODS

Study Design

Participants in the current analysis were participants in the Study of Women Across the Nation (SWAN), a community-based, multi-ethnic longitudinal observational cohort study of the menopause transition. Overall, SWAN enrolled 3,302 pre- or early peri-menopausal women at 7 clinical sites in the US who were between 42 and 52 years of age; five of the seven sites conducted a bone health study, with bone mineral density as one of its main

outcomes. After enrollment, women were seen approximately every year to monitor a variety of measures, with the 5 bone sub-study sites measuring BMD at all follow-up visits. Information on medication use is collected prospectively at all sites. Women are instructed to bring in all medication containers, and trained interviewers transcribe all preparations onto study forms. A detailed description of the study design has been published previously. (14)

The current study examined whether use of blood pressure lowering agents was associated with changes in BMD. To address this question, two separate analyses were conducted. First, we compared the annualized rate of change in BMD among women who initiated an ACEi, BB, or THZD, with non-users of any blood pressure lowering agents. The visit before the first visit with participants reporting use of one of these agents was considered baseline for the user group. For participants not reporting use of these medications (non-users), we randomly selected a frequency-matched visit to establish a comparable baseline, ensuring that the distribution of baseline visits is similar across the two groups. Three separate matched cohorts were then created using propensity scores (see below): ACEi versus non-users, BB versus non-users, and THZD versus non-users. Second, we directly compared annualized changes in BMD among ACEi and BB users to THZD users. These analyses were carried out using conventional regression as well as propensity score matched regression.

Study Sample

From the SWAN cohort, several selection criteria were applied. First, we identified new users of any blood pressure lowering agent, including ACEi, alpha agonists, angiotensin receptor blockers, calcium channel blockers, non-thiazide diuretics, THZDs, and other agents. Some of these groups had too few participants to analyze, so we focused on ACEi, BB, and THZDs. Participants who reported use of any blood pressure lowering agents at the first SWAN visit were excluded. Additionally, participants were required to have undergone at least 2 BMD measurements after the study baseline (see section above for definition of baseline for drug users and non-users). New users who discontinued use of each of the three blood pressure lowering agents of interest were censored at the last annual visit at which usage of the drug was reported. Women who became pregnant were also censored at the visit prior to reporting pregnancy.

All study participants gave written informed consent. The study protocol was approved by each SWAN site Institutional Review Boards.

Assessment of Medication Use

At each visit, interviewers administered questionnaires to ascertain all medication use since the last study visit; for the last two study visits, the questionnaire asks about the last three months. Use was verified by inspection of medication containers. If medication containers were not available, medication lists were reviewed. Each medication was classified from product brand or generic names using a computerized medication dictionary (Iowa Drug Information Service (IDIS) Drug Vocabulary, College of Pharmacy, University of Iowa,

Iowa City, IA). All blood pressure lowering agents were assessed at each visit to determine ongoing use. Dosage of the agents was not available.

Measurement of Bone Mineral Density

The BMD of the lumbar spine and femoral neck (g/cm^2) were measured annually using Hologic instruments (Hologic Inc, Waltham, Massachusetts). Three sites used Hologic 4500A models at baseline; two of these sites later upgraded to Discovery models, one at follow-up visit 12 and one at follow-up visit 13. Two sites started with 2000 models at baseline and both of upgraded to 4500A models at follow-up visit 8. Each site that upgraded its hardware scanned 40 volunteers on both old and new machines to develop cross-calibration regression equations, which were applied by the SWAN Coordinating Center. A standard quality control (QC) program was conducted in collaboration with QC centers at Synarc Inc (San Francisco, CA) from baseline to follow-up visit 10 and with the USCF DXA Quality Assurance Center (San Francisco, CA) thereafter. QC included daily phantom measurements, quarterly review of the daily QC plots by the QC centers with correction factors applied for drift if needed, local site review of all scans, and review of problem scans by a member of the SWAN Bone Committee. Short-term in vivo measurement variability was 0.014 g/cm^2 (1.4%) for the LS and 0.016 g/cm^2 (2.2%) for the FN.

The outcome of interest for this study was the annualized change in BMD, calculated as the annual percent change in a linear regression model, facilitating comparison of results across study groups. The change was calculated from a baseline BMD value determined at the visit prior to the first use of an ACEi, BB or THZD for the three user groups. For the non-user group, the visit before baseline was chosen. There was incomplete BMD data at visit 11, which was excluded; otherwise, BMD measurements were available through the 12th annual SWAN visit for this study.

Osteoporosis Risk Factors (Covariates)

SWAN participants underwent measurement of height and weight for calculation of body mass index (BMI, weight in kilograms divided by the square of height in meters). Participants completed interviewer-administered or self-administered questionnaires that assessed demographic characteristics (age, race, ethnicity, income, education, and marital status), lifestyle factors (alcohol intake and tobacco use), self-assessed health status, social support (items from the 20 item Medical Outcomes Study Social Support Survey),(15) vasomotor symptoms, and self-reported comorbid conditions (osteoporosis, thyroid disease, any cancer, diabetes mellitus). Bone active medications were considered as covariates, such as bisphosphonates, hormone therapy, oral glucocorticoids, calcium and vitamin D. In addition, physical activity was measured using a modified version of the Baecke Physical Activity Questionnaire (range 3–15).(16, 17) Menopause transition stage was assessed in SWAN based on bleeding criteria. Categories were: pre-menopause (no decreased regularity in menstrual bleeding during the last year), early peri-menopause (decreased menstrual regularity in the past year but the occurrence of menstrual bleeding in the past 3 months), late peri-menopause (no menses for 3–11 months), and post-menopause (no menses for 12 or more months). Women reporting oophorectomy or hysterectomy were classified as “other” menopausal status. Menopause transition stage was updated at every study visit.

Once a woman had advanced to a later transition stage she could not be reclassified to an earlier transition stage.

Statistical Analysis

The primary analyses compared the three user groups to non-users. Before choosing to use a propensity score matched approach, baseline characteristics across the four groups (ACEi, BB, THZD, and non-user) were examined and found to have considerable imbalance. We thus chose to improve the comparability of the groups by propensity score matching. A propensity score is the probability of use of an intervention compared with non-use. (18) We calculated three different propensity scores in multivariable logistic regression, estimating the probability of using an ACEi compared with non-use, a BB compared with non-use, and a THZD compared with non-use. Baseline variables comprising the three logistic regression models were the same and included: site, race/ethnicity, BMI, smoking, fracture (either traumatic or minimal trauma, excluding digits and face), marital status, proton pump inhibitor use, blood pressure, and osteoarthritis. The propensity score was then used to match a woman in the user group with a non-user. (19) All variables listed in Table 1 were considered for the propensity score. A greedy matching algorithm was used to find the best possible match and the matching caliper was set at 0.2 of the standard deviation of the logit of the PS. (20) This was repeated for each of the three user groups.

We described the baseline participant characteristics in each of the three matched exposure groups using descriptive statistics (mean, median and range). Continuous variables were analyzed using ANOVA and Kruskal-Wallis tests, whereas categorical variables were analyzed using Chi-Square tests. The relationship between medication use and annual change in BMD (change between two subsequent annual BMD measurements) was analyzed using a mixed-effects regression modeling strategy, allowing for a random intercept and slope. Factors selected *a priori* for inclusion in the base models included years from the baseline visit as a continuous linear covariate and several covariates known to be possible correlates of BMD: study site, race/ethnicity (Caucasian, African American, Chinese, Japanese), age, BMI, bisphosphonate and hormone replacement use, and total number comorbid conditions (anemia, stroke, osteoporosis, thyroid disease, any cancer, diabetes, cardiovascular disease, osteoarthritis, hypertension, migraine, and hyperlipidemia). Menopause transition stage was also included in all models. Other covariates of interest that we tested for inclusion in multivariable models were CES-D, calcium supplement use (yes/no), vitamin D supplement use (yes/no), current smoking (yes/no), annual income level, educational attainment, marital status, social support (continuous; range, 0–16), hot flashes (yes/no), and physical activity (continuous; range, 3–14). All covariates are treated as time-varying in the mixed models except for race and study site. Only those covariates with P values < 0.10 were entered into the models with the a priori variables. For consistency, if a covariate was found to be significant at one anatomical site (i.e., femoral neck), that covariate was forced into the other two models. Thus, all final models for each comparison group contain the same covariates.

We found differences in the comparisons of blood pressure lowering drugs compared with non-users. To explore these differences in secondary analyses, we made two separate two-

way comparisons: ACEi versus THZD and BB versus THZD. Because the characteristics of users of each of these blood pressure lowering agents were similar and there were relatively few users, we did not attempt to match these groups. Mixed model regression was again used employing similar modeling strategies as previously mentioned. Finally, in a sensitivity analysis, we ran a propensity-score matched regression comparing ACEi versus THZD and BB versus THZD. The propensity score matched analysis was run in the same fashion as it was for the primary analyses.

SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for the analyses.

RESULTS

The cohort assembly is described in Figure 1. The propensity score matched cohort was used in the comparisons between blood pressure lowering drug groups and non-users. These three different two-way analyses used: 69 ACEi users, 71 BB users, and 74 THZD users. The median number of annual visits observed for users in all groups was 4. The participants used for the analyses comparing amongst the different blood pressure lowering agents is described as the conventional regression cohort; a slightly higher number of blood pressure lowering drug users were included since no propensity score matching was required.

Table 1 shows the baseline characteristics of the propensity score matched cohort. The three non-user groups varied, but each of the three matched cohorts demonstrates good balance of baseline characteristics. The mean age across the cohorts was between 50–53 years of age, the majority were Caucasian except in the THZD user group. The majority of women were early or late peri-menopausal and reported good to excellent overall health. Mean BMIs were between 28–30kg/m^2 and comorbidities were very similar. The baseline BMD measurements at the lumbar spine and femoral neck were nearly identical across cohorts.

Figure 2 illustrates the annual percent change in BMD at the three anatomic regions for the three propensity score matched analyses. In Figure 2a, we see that the change in BMD associated with ACEi use did not differ from non-users at any of the anatomic regions. The same held true for BB use (see Figure 2b). However, THZD use was associated with significantly less bone loss (−0.29% vs −0.88%, p = 0.008) at the femoral neck compared with non-users (see Figure 2c). At the spine, there was a trend toward less bone loss (−0.74% vs −1.0%, p = 0.34), but this was not statistically significant.

We directly compared THZDs to both BB and ACEi using conventional mixed model analyses (see Figure 3a and 3b). THZD showed a trend toward less bone loss, albeit not statistically significant, than BB: spine (−0.35% vs −0.60%; p = 0.08) and the femoral neck (−0.39% vs −0.64%; p = 0.08). Compared with ACEi users, THZD users had less bone loss at the femoral neck (−0.48% vs −0.82%, p=0.02) and a trend at the spine (−0.4% vs −0.56%; p = 0.23). The propensity score sensitivity analyses show similar results, but no differences were statistically significant (data not shown).

DISCUSSION

We studied a longitudinal cohort of well characterized women transitioning through the menopause to determine the association between blood pressure lowering drugs and changes in BMD. We found similar data compared to prior findings that THZD use was associated with lower rates of BMD loss as measured at the lumbar spine and femoral neck BMD compared to non-use. However, relative to the longitudinal change in BMD at these sites in women who did not use any blood pressure lowering drugs, we found no evidence of enhanced BMD associated with either ACEi or BB use.

At least two prior randomized controlled trials have also demonstrated improved BMD with THZD use compared to placebo. (3, 4) The similarity of our THZD finding with the previously published studies suggests that this method for longitudinal assessment is likely valid and provides a useful “positive control”. In prior work using very similar methods, we demonstrated no effect of tricyclic anti-depressants on BMD, a negative control. (21) Such positive and negative controls are routine in laboratory science and have been strongly recommended for epidemiologic studies as well. (22)

The lack of an association between ACEi’s and improved BMD or BB’s and improved BMD requires further examination. ACEi’s have been found in an ovariectomized rat model to enhance the bone-forming potential of osteoblasts. (23) Supporting a potential positive impact of ACEi’s on BMD, one RCT suggested that women with a specific ACE polymorphism improved their BMD after treatment with quinapril. (24) However, two longitudinal studies found no improvement in BMD among women or men using ACEi’s. A longitudinal study of older Japanese adults using ACEi’s compared with those not using them found a reduction in BMD over 4 years of follow-up. (25) A second longitudinal study in a large cohort of men followed for 4 years found a very small reduction in BMD at the hip among ACEi users. (26) These prior human studies of ACEi’s and BMD agree with our results. This suggests that animal models of bone metabolism have important differences compared with human studies of ACEi’s.

There has been substantial investigation into the potential benefits of BBs on BMD. As noted above, there is a rich basic science literature suggesting the possibility that BB’s might improve BMD through a central effect on adipokines. (7) While several human studies agree with these animal findings,(8–11) several do not. (12, 13) Prior epidemiologic studies that support a positive association of BB on BMD were primarily cross-sectional or had relatively few measurements of drug utilization and BMD. It is interesting to note that baseline BMD assessment at the femoral neck suggested small differences at the time blood pressure lowering drugs were started. This is a reason that a new user longitudinal design is so important. As well, none excluded prevalent users of BBs. Without a good understanding of the duration of prior drug use, any relationship with BMD is conjecture.

Interpretation of prior studies of blood pressure lowering agents and BMD is hindered by a number of methodological limitations. Most prior studies conducted infrequent assessments of drug use and BMD making it difficult to estimate the duration of exposure. New user designs were rarely used, except in the prior RCTs. New user design, the preferred method

in drug epidemiology, mimics the randomized controlled trial where prior use would be an exclusion. (27) However, new user designs do not create balanced comparison groups the same way that a large RCT would. Without extensive information about BMI, menopausal status, overall health, or use of known bone-active agents, confounding control in prior work has been relatively weak. Finally, we included use of a positive control, THZD, providing important evidence that our study design yields valid results. (22)

Our study has potential limitations. Some of our exposure groups were relatively small, limiting the statistical power. We recognized this a priori but decided to limit bias through excluding potential subjects who could not be matched, trading-off statistical power for internal validity, which we deemed more important. There may be misclassification of exposure, i.e. participants who mistakenly reported use or non-use of blood pressure lowering agents. Participants did bring in medication containers at the majority of visits, which should limit misclassification error. However, we did not have daily medication use diaries and assumed continuous use if participants reported the same drugs at consecutive visits. It is also possible that some participants who had used these agents prior to SWAN were misclassified as “new users.” Unmeasured confounding bias is possible; that is where the use of a blood pressure lowering drug is associated with another variable that may affect BMD. We benefited from inclusion of a robust set of covariates to limit this possibility; such practice is supported by the literature that suggests only 2 subjects per variable are required for adequate power in multivariate linear regression models. (28) The positive control results with THZDs suggest that there was minimal confounding. As well, the propensity score matched cohorts were very well balanced in the measured covariates. We did not assess the association between blood pressure lowering agents and fractures, and prior literature suggests potential associations. (8, 9) Some of these agents may be associated with fractures independent of any effect on BMD by way of increasing the risk of falls; falls secondary to orthostasis is a very real phenomenon associated with BB and possibly other blood pressure lowering drugs. (29) We did not know the indication for the blood pressure lowering drugs, but most of them in this age group would be used for hypertension; as well, it’s unclear that use for other clinical purposes would meaningfully change the interpretation of the results. Finally, the current study only included middle-aged women going through the menopause transition and the results may not generalize to other populations.

In conclusion, we found similar results as to the previously observed benefit of THZD on BMD but found no effect of ACEi’s or BB on BMD. Based on our methods and the use of a positive control, we strongly believe that these findings represent valid results. They suggest that THZD may be a good choice for blood pressure lowering in older adults with, or at risk of, osteoporosis. This agrees with prior JNC recommendations. (2) Furthermore, these findings highlight the difficulty in applying observations made in animals to humans regarding drug effects on bone metabolism.

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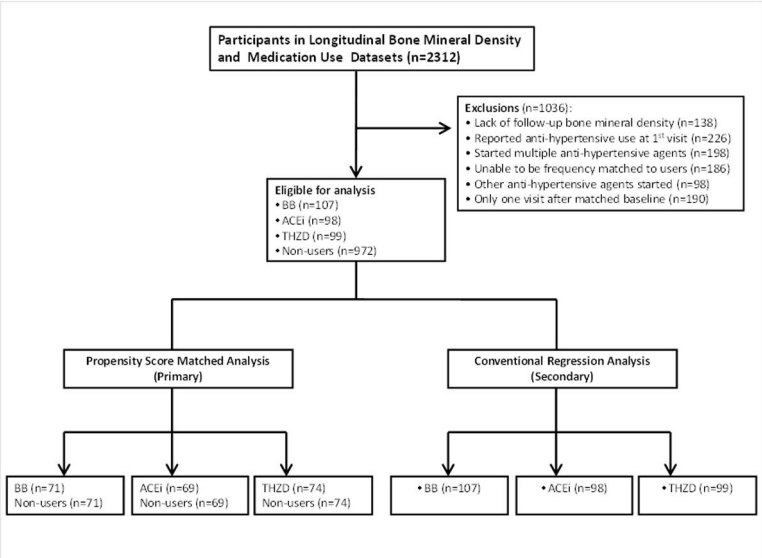
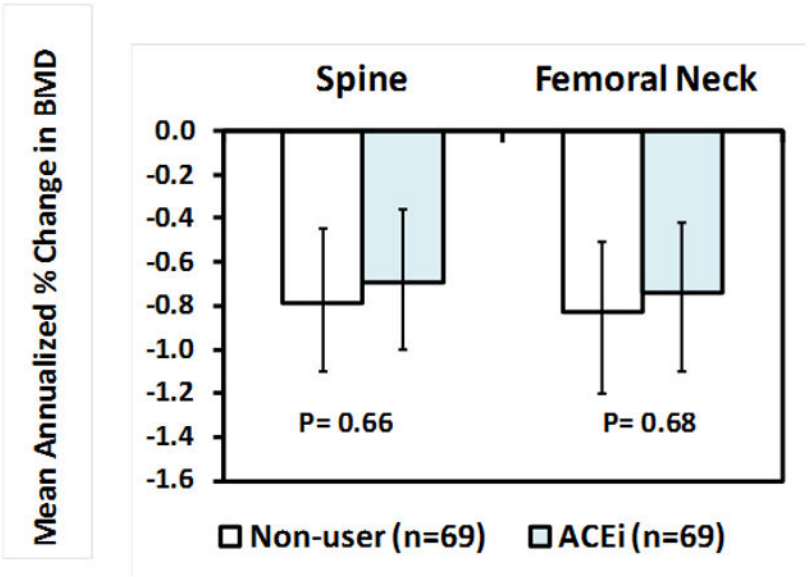


Figure 1. Flowchart of the study sample assembly

This figure demonstrates the assembly of the primary and secondary analytic cohorts. The primary cohort used propensity scores to match initiators of a blood pressure lowering drug with a non-user. The secondary cohort was not restricted to propensity score matched participants and has a larger number of blood pressure lowering drug initiators. Abbreviations: BB, beta-blocker; ACEi, ACE inhibitor; and THZD, thiazide diuretic.

Panel A:



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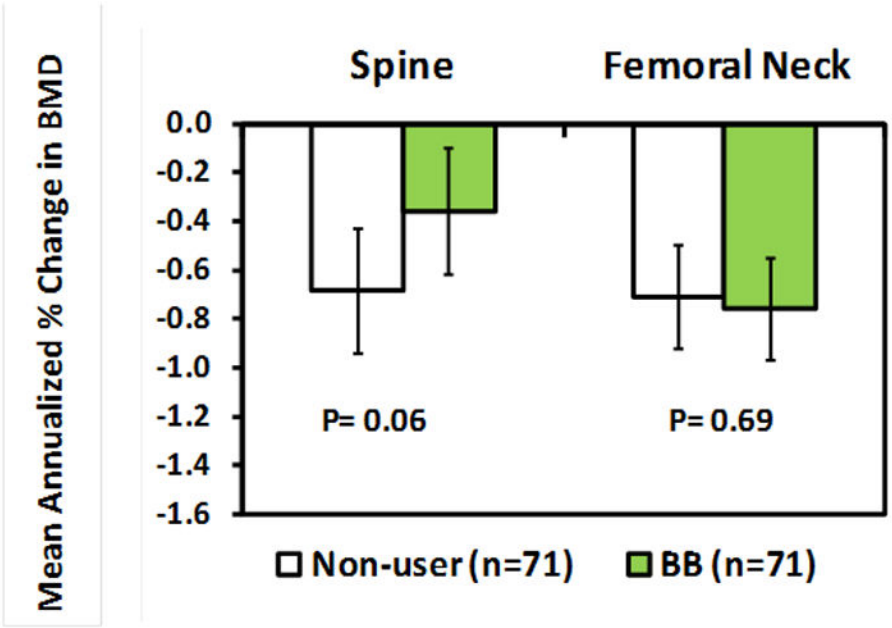

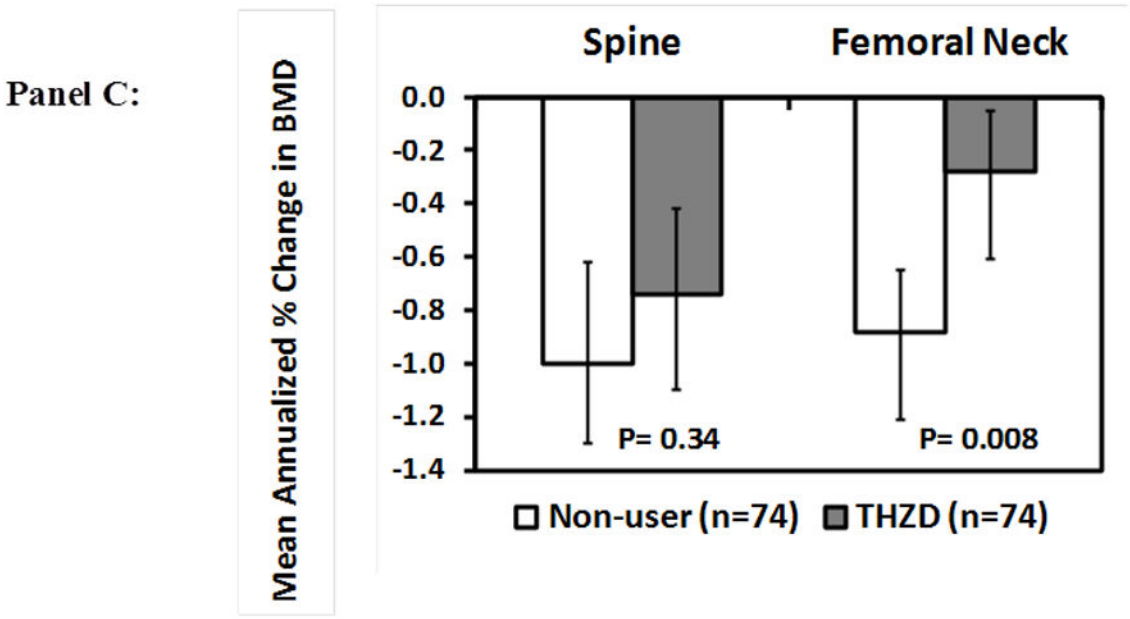

Figure 2. Bone Mineral Density Changes Comparing New Users of Selected Anti-Hypertensive Agents with Matched Non-Users

This figure demonstrates the bone mineral density change (95% confidence intervals) associated with initiation of an ACE inhibitor (Panel A), beta blocker (Panel B), or thiazide diuretic (Panel C). Each of these blood pressure lowering agents is compared with non-users of any such agent after propensity score matching in mixed-effects regression, allowing for a random intercept and slope.

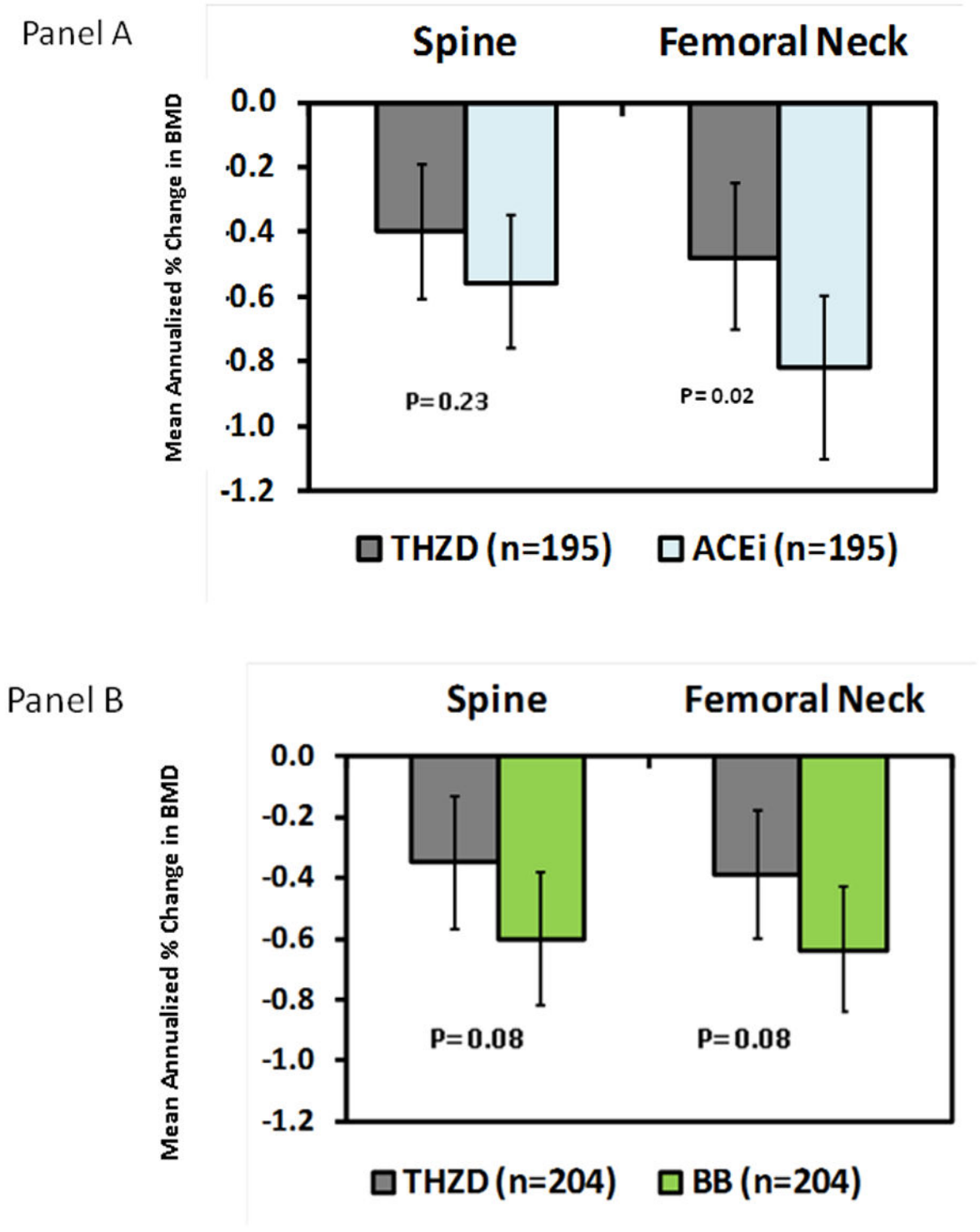

Figure 3. Bone Mineral Density Changes Comparing New Users of Selected Anti-Hypertensive Agents with Thiazide Initiators

This figure demonstrates the bone mineral density change (95% confidence intervals) associated with initiation of an ACE inhibitor (Panel A) or beta blocker (Panel B) compared

with a thiazide diuretic. These comparisons are made using mixed-effects regression, allowing for a random intercept and slope. P-values > 0.05 unless indicated.

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Table 1

Baseline Characteristics of Propensity Matched Study Cohorts

	ACE inhibitor (n = 69)	**Non-user (n = 69)**	**Beta blocker (n = 71)**	**Non-user (n = 71)**	**Thiazide diuretic (n = 74)**	**Non-user (n = 74)**
			Mean (SD) or %			
Age, years	54 (4)	53 (4)	52 (4)	52 (5)	53 (5)	52 (4)
BMI, kg/m2	**30.7 (6.4)**	**33.0 (6.8)**	27.9 (6.8)	28.9 (6.2)	30.2 (6.3)	31.4 (6.2)
Bone mineral density, g/cm2						
Femoral neck	0.81 (0.12)	0.81 (0.14)	**0.78 (0.12)**	**0.84 (0.14)**	0.85 (0.14)	0.86 (0.15)
Spine	1.07 (0.14)	1.05 (0.15)	1.02 (0.14)	1.04 (0.17)	1.07 (0.15)	1.07 (0.17)
Blood pressure, mmHg						
Systolic	**129 (15)**	**123 (14)**	122 (17)	118 (14)	**128 (14)**	**121 (14)**
Diastolic	**80 (10)**	**77 (10)**	77 (10)	76 (10)	**80 (9)**	**77 (9)**
Race						
White	55	51	52	28	45	34
Black	28	41	23	35	47	57
Asian	17	9	25	37	8	10
Menopausal status						
Early perimenopause*	30	35	41	56	38	42
Late perimenopause	7	4	10	3	8	7
Post menopausal	52	45	35	31	31	39
Unknown	10	16	14	10	23	12
Educational attainment						
≤ High School	3	2	6	1	1	0
> High School	61	59	41	48	54	58
College graduate	10	20	23	25	17	23
Post-college	26	19	31	25	28	19
CES-D	10 (10)	9 (10)	10 (10)	9 (9)	11 (10)	9 (10)

	ACE inhibitor (n = 69)	Non-user (n = 69)	Beta blocker (n = 71)	Non-user (n = 71)	Thiazide diuretic (n = 74)	Non-user (n = 74)
# comorbid conditions	**2.2 (1.4)**	**1.6 (1.2)**	**1.9 (1.2)**	**1.4 (1.0)**	**1.8 (1.0)**	**1.4 (1.1)**
Physical Activity	7 (2)	8 (2)	8 (1)	8 (2)	8 (2)	8 (2)
Social support	13 (3)	13 (3)	13 (3)	13 (3)	13 (3)	13 (3)
Follow up, years	6.8 (4.1)	7.2 (3.5)	7.7 (3.8)	7.4 (3.7)	7.0 (3.9)	7.3 (3.4)
Marital status						
Single	10	30	16	16	14	20
Married	65	54	68	66	61	61
Other	**25**	**16**	17	18	26	19
Annual household income, US$						
< 20,000	6	15	13	4	7	13
20– <50,000	9	12	12	16	13	21
50– <100,000	23	18	17	11	13	16
100– <150,000	18	27	16	24	20	27
≥ 150,000	44	27	41	44	46	24
Medication use						
Bisphosphonates	0	0	3	0	1	0
Proton pump inhibitor	6	4	10	7	5	4
Vitamin D	9	6	4	16	7	10
Calcium supplements	40	27	27	35	43	29
Hormone replacement	18	21	20	10	19	18

Notes: Bolded values represent significantly different values with $p < 0.05$.

*Includes pre-menopausal. CES-D, Center for Epidemiologic Studies Depression scale (higher score suggests greater likelihood of depression). Physical activity was measured using a modified version of the Baecke Physical Activity Questionnaire (range 3 – 15). Comorbid conditions were self-reported and included anemia, stroke, osteoporosis, thyroid disease, any cancer, diabetes mellitus, cardiovascular disease, osteoarthritis, hypertension, migraine, and hyperlipidemia.