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ORIGINAL ARTICLE

The renin-angiotensin aldosterone system and osteoporosis: findings from the Women's Health Initiative

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Abstract

Summary New users of RAAS inhibitors, including ACE inhibitors and ARBs, have a small increased risk for fracture in the first 3 years of use, with a reduced risk of fracture with longer duration of use.

Introduction Pharmacological inhibitors of the renin-angiotensin aldosterone system (RAAS) are used to treat hypertension. However, the relationship of these medications to osteoporosis is inconsistent, and no study has included simultaneous measurements of both incident fractures and bone mineral density (BMD).

Methods The association of RAAS inhibitor use ($n = 131{,}793$) with incident fractures in new users of these medications in women in the Women's Health Initiative over a minimum median follow-up of 6.5 years was assessed by Cox proportional hazard models. The association of incident fractures by a cumulative duration of use of these medications ($\leq$ 3 years.) and (> 3 years.) was also estimated. Subgroup analysis of fracture risk by RAAS inhibitor use confined to women with hypertension was also performed ($n = 33{,}820$). The association of RAAS inhibitor use with changes in BMD of the hip was estimated by linear regression in 8940 women with dual energy X-ray absorptiometry measurements.

Results There was no significant association between RAAS inhibitor use and all fractures in the final adjusted multivariable models including hip BMD (HR 0.86 (0.59, 1.24)). However, among users of RAAS inhibitors, including ACE inhibitors and angiotensin receptor blockers (ARBs), hazard ratios for all incident fracture sites in final multivariable models including hip BMD showed dramatic differences by duration of use, with short duration of use (3 years or less) associated with a marked increased risk for fracture (HR 3.28 (1.66, 6.48)) to (HR 6.23 (3.11, 12.46)) and use for more than 3 years associated with a reduced fracture risk (HR 0.40 (0.24, 0.68) to (HR 0.44 (0.20, 0.97)) . Findings were similar in the subgroup of women with a history of hypertension. There was no significant change in BMD of the hip by RAAS inhibitor use.

Conclusions In postmenopausal women, use of RAAS inhibitors, including ACE inhibitors and ARBs, is associated with an increased risk for fracture among new users of these medications in the first 3 years of use. However, long-term use (> 3 years) is associated with a reduced risk. Consideration for fracture risk may be part of the decision-making process for initiation of these medications for other disease states.

Keywords Aging · Fracture · Medication · Postmenopausal

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Osteoporosis and cardiovascular disease (CVD) are serious problems for postmenopausal women. One-third of postmenopausal women will sustain an osteoporotic fracture [1, 2], 25% of persons dying in the first year following a hip fracture [3, 4]. CVD is the leading cause of death for women in the USA and worldwide [5]. Our work [6], and that of others [7], has demonstrated a fundamental but as yet undefined link between these two conditions.

The renin-angiotensin aldosterone system (RAAS) plays a key role in hypertension [8]. Experimental studies have also implicated a role for the RAAS in osteoporosis. Osteoclasts have components of the RAAS including the angiotensin 1 receptor (AT1R), and angiotensin 2 receptor (AT2R) and aldosterone receptors. In experimental studies, activation of RAAS or chronic infusion of angiotensin II (Ang II) increases bone resorption, while absence of AT1R is associated with increased bone strength [9, 10]. Ang II can also induce mitochondrial oxidative stress and damage in mesenchymal-derived osteoblasts by reducing sirtuin 1 (SIRT1) expression [11]. In experimental models, SIRT1 is positively associated with bone mass [12].

However, the relationship of pharmacological inhibition of the RAAS system to osteoporosis is controversial [13–33]. Prior reports are limited by study design (case-control studies) [25, 26], failure to include important potential confounders including calcium and vitamin D supplements [18, 22–27, 30], did not include women without hypertension [13, 18, 21, 23, 29, 32] or multiethnic cohorts [14, 16, 23, 24, 26, 27, 30]. To date, no study has simultaneously examined the relationship of pharmacological inhibition of the RAAS system to both incident fractures over more than 5 years of follow-up and areal bone mineral density (BMD) in a well-characterized, multiethnic population of postmenopausal women.

The Women's Health Initiative (WHI), with its detailed assessments of medication use, fractures, and BMD, provides an important opportunity to determine the impact of RAAS inhibition to incident fractures and changes in BMD of the hip.

Participants and methods

The study population included women in the WHI observational study (OS) and clinical trials (CT) (hormone therapy, dietary modification, and calcium and vitamin D trials). The WHI included postmenopausal women aged 50 to 79 years recruited between October 1, 1993, and December 31, 1998, at 40 clinical centers in the USA. Details of the original WHI recruitment, after which participants were followed for outcomes between 1993 and 2005, have been previously described [34]. Between 2005 and 2010, consenting original study, participants were enrolled in the WHI extension study for an additional 5 years of follow-up. All extension study participants completed annual data collection forms primarily by mail, using procedures similar to those used to collect follow-up data from the OS. Protocols were approved by the institutional review board (IRB) at each participating center. Women provided written informed consent for their participation in the original WHI study and the extension study.

There were 161,808 women enrolled in WHI. Among these, women missing a medication history at baseline ($n = 3800$), those who reported extremes of kilocalorie intake (< 600 or > 5000 kcal/day) ($n = 9732$), had a history of a hip fracture at baseline ($n = 1731$), or had a discrepancy in their medication inventory date ($n = 9$) were excluded. The baseline Food Frequency Questionnaire (FFQ) was used to determine eligibility in the WHI-dietary modification (DM) cohort; hence, the values from year 1 were used as "baseline" values for the WHI-DM participants. All participants who reported at the baseline visit of WHI use of at least one of the following medication classes: ACE inhibitors, ARBs, direct renin inhibitors, selective aldosterone receptor antagonists (SARAs), or RAAS fixed-dose combination drugs (ACE, ARB, direct renin inhibitor or selective aldosterone receptor antagonist (SARAs)) in combination with another antihypertensive medication other than a RAAS inhibitor were excluded, as all analyses were conducted only in "new users" of these medications who started the use during WHI. Duration of use of the medication at any follow-up time was reported on periodic medication inventories with follow-up censored at 3.5 years following the most recent inventory. We further excluded 1 participant with uncertain follow-up time and 346 OS participants who had medication inventories at unscheduled time periods. The final users of RAAS inhibitors cohort included 131,793 women (Fig. 1).

In post hoc, subgroup analyses, only women with a history of hypertension at study baseline, defined in WHI as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or use of a medication for hypertension were included in the analyses ($N = 33,820$).

Outcomes

Incident fractures

Specific outcomes and hospitalizations were assessed by questionnaires collected semi-annually for CT and annually in the OS through the end of the main WHI study and annually in the CT and OS participants in the extension study. Fracture history was collected in all by self-report. Hip fractures were also verified by a review of

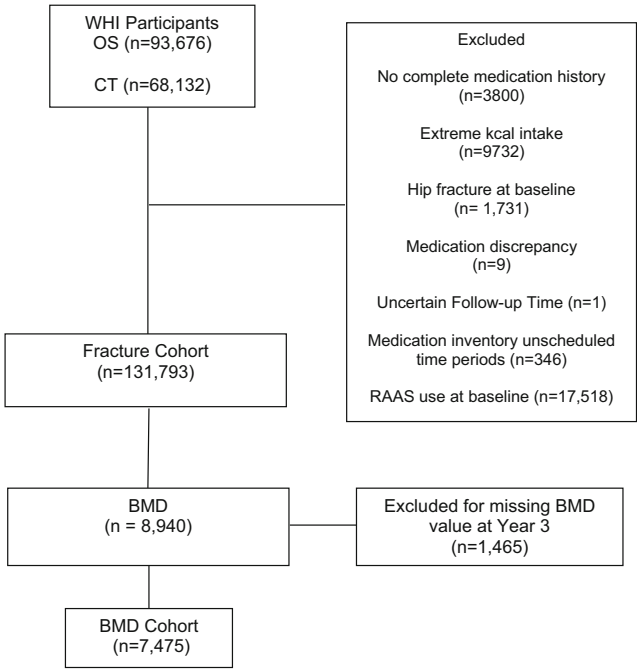

Fig. 1 Derivation of WHI analytic entire cohort

medical records with central blinded adjudication [35]. Fractures other than hip fractures were locally adjudicated for the CT and a subset of the OS (BMD participants) from 1993 to 2005. For the OS participants who did not have BMD measured and all OS and CT participants during 2005–2010 (extension study), fracture information (other than hip fractures) was only obtained by self-report with no adjudication.

Categories of fractures examined included: (1) hip fractures, (2) upper limb fractures (humerus, radius/ulna, hand (excluding fingers), carpal, clavicle, scapula), (3) lower limb fractures (femur (not hip), patella, tibia or fibula, tibia plateau, foot (tarsal or metatarsal), ankle), (4) central body fractures (hip, pelvis, spine) (5) any fracture excluding fingers or coccyx [36]. The median length of follow-up was 6.56 years for hip and central body fractures, 6.55 years for upper and lower limb fractures and 6.53 years for the category of all fractures.

BMD measurements

BMD of the hip (total, femoral neck) was done in participants at three of the forty clinical centers of the WHI (Pittsburgh, Pennsylvania, Birmingham, Alabama, and Phoenix/Tucson, Arizona) were obtained by DXA using a Hologic QDR densitometer Model 2000, 2000+ or 4500 Fan-beam technology (Hologic, Inc., Waltham, MA). Only measurements on the same side and on the same machine (except where calibrated scanner upgrades occurred) were used. Technologists were trained and certified by the University of California, San Francisco, and Bone Density Coordinating Center. Standard protocols were used for positioning and analysis. Site-specific spine phantoms were used. Calibration phantoms were scanned across instruments and clinical sites with inter-scanner variability of < 4.8% for the hip [37, 38]. For these analyses, BMD measurements at 3 and 6 years were included.

Predictors

Pharmacological inhibition of the RAAS

Participants were asked about current prescription and over-the-counter medications taken in the past 2 weeks at the baseline, year 1, 3, 6, 9 and year 4 of the extension study for CT participants and baseline and year 3 of the main WHI study and year 4 of the extension study for OS participants. Interviewers entered each medication into the database, which assigned drug codes using Medi-Span software (First Data Bank, Inc., San Bruno, California). Information on the

Table 1 Use of RAAS medications by Women in WHI

	Baseline *N* (%)	Year 3 *N* (%)	Year 6 *N* (%)	Extension study year 4 *N* (%)
Total number with a medication claim[a]	149,658 (100)	131,908 (88.1)	53,270 (35.6)	92,527 (85.2)
Any RAAS inhibitor use	13,738 (9.2)	18,732 (14.2)	12,112 (22.7)	34,558 (37.4)
ACE	11,287 (7.5)	12,295 (9.3)	6760 (12.7)	15,715 (17.0)
ARB	1053 (0.7)	3637 (2.8)	3013 (5.7)	10,178 (11.0)
Direct renin inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	13 (0.0)
Selective aldosterone receptor antagonists (SARAs)	0 (0.0)	0 (0.0)	0 (0.0)	21 (0.0)
RAAS combination drug	1465 (1.0)	2967 (2.3)	2543 (4.8)	9207 (10.0)

[a] The % in this row represents the proportion of participants with a medication claims in that year divided by total number of eligible participant at WHI enrollment ($N = 149,658$) (for Baseline, year 1 and 3) and at extension study enrollment ($N = 108,630$) for year 4 of extension study. The % in all other rows represents the proportion of people using that drug among those who have a medication claim in that year

Table 2 Baseline characteristics of study population by anytime use of RAAS inhibitors (ACE, ARB, direct renin inhibitor, selective aldosterone receptor antagonists, RAAS fixed-dose combination drug). Total $N = 131,793$

Characteristics	RAAS inhibitor use *N* (%)	No RAAS inhibitor use *N* (%)	*P* value
Total	33,441 (25.37)	98,352 (74.63)	
Baseline age ± SD	64.69(6.84)	64.10(7.30)	< .0001
Baseline BMI (kg/m^2) ± SD	28.83(5.98)	27.07(5.65)	< .0001
Race/ethnicity			< .0001
White	28,281(85.60)	82,905(85.49)	
Black	2847(8.62)	7232(7.46)	
Hispanic	1028(3.11)	3799(3.92)	
American Indian	129(0.39)	394(0.41)	
Asian/Pacific Islander	754(2.28)	2647(2.73)	
Current smokers at baseline	2031(6.13)	7000(7.20)	< .0001
History of fracture on/after age 55 at baseline			< .0001
Fracture,≥ 55 years of age	4270(13.55)	11,893(12.68)	
Fracture, < 55 years of age	6793(21.55)	20,646(22.02)	
No fracture	19,167(60.82)	57,700(61.53)	
Fracture, unknown age	1285(4.08)	3531(3.77)	
Parents with a hip fracture after age 40 at baseline	4177(13.79)	13,011(14.65)	0.0002
Self-reported health status			< .0001
Excellent	4865(14.60)	19,479(19.90)	
Very good	14,063(42.21)	42,225(43.15)	
Good	11,612(34.86)	28,649(29.28)	
Fair	2601(7.81)	6843(6.99)	
Poor	172(0.52)	664(0.68)	
History of treated diabetes at baseline	1963(5.88)	2369(2.41)	< .0001
History of cardiovascular disease[a] at baseline	6666(19.93)	16,836(17.12)	< .0001
History of hypertension (treated/untreated) at baseline	13,883(43.95)	19,937(21.28)	< .0001
Physical function construct at baseline, ± SD	80.67(19.71)	82.57(19.56)	< .0001
Alcohol use at baseline			< .0001
Non/past drinker	13,976(41.85)	39,337 (40.07)	
Current drinker, < 7 drinks/week	15,384 (46.07)	46,867 (47.74)	
Current drinker, 7+ drinks/week	4034 (12.08)	11,963 (12.19)	
Clinical trial (CT) vs. observation (OS) study enrollment			< .0001
CT	15,919 (47.60)	36,364 (36.97)	
OS	17,522 (52.40)	61,988 (63.03)	
Dietary modification trial enrollment			< .0001
Not randomized to DM	22,347 (66.83)	73,127 (74.35)	
Intervention	4443 (13.29)	10,376 (10.55)	
Control	6651 (19.89)	14,849 (15.10)	
HT trial enrollment arm			< .0001
Not randomized to HRT	26,660 (79.72)	83,307 (84.70)	
Intervention (E-only trial)	1411 (4.22)	2660 (2.70)	
Control (E-only trial)	1383 (4.14)	2790 (2.84)	
Intervention (E+P trial)	2083 (6.23)	4848 (4.93)	
Control (E+P trial)	1904 (5.69)	4747 (4.83)	
CAD trail enrollment			< .0001
Not randomized to CAD	24,215 (72.41)	78,222 (79.53)	
Intervention	4653 (13.91)	10,049 (10.22)	
Control	4573 (13.67)	10,081 (10.25)	

Table 2 (continued)

Characteristics	RAAS inhibitor use *N* (%)	No RAAS inhibitor use *N* (%)	*P* value
Geographic study site			< .0001
Northeast	7895 (23.61)	22,285 (22.66)	
South	8662 (25.90)	24,505 (24.92)	
Midwest	7443 (22.26)	22,116 (22.49)	
West	9441 (28.23)	29,446 (29.94)	
Log transformed total calcium intake (in mg/day)	6.92 (0.60)	6.92 (0.61)	0.7887
Log transformed total vitamin D intake (in IU/day)	5.62 (0.88)	5.61 (0.90)	0.0129
Medication use (antihypertensives) at baseline			
Thiazides	2088 (6.24)	2898 (2.95)	< .0001
Loop diuretics	804 (2.40)	1509 (1.53)	< .0001
Other diuretics (other than thiazide or loop)	134 (0.40)	374 (0.38)	0.6023
Alpha-beta blockers	111 (0.33)	143 (0.15)	< .0001
Central agonists	306 (0.92)	420 (0.43)	< .0001
Vasodilators	40 (0.12)	95 (0.10)	0.2556
Peripheral adrenergic inhibitors	447 (1.34)	496 (0.50)	< .0001
Beta blockers	3530 (10.56)	6235 (6.34)	< .0001
Calcium channel blockers	4611 (13.79)	6870 (6.99)	< .0001
Other fixed-dose combination antihypertensive[b]	2890 (8.64)	4707 (4.79)	< .0001
Other medication use			
Hormone replacement therapy/estrogen			0.1992
Never used	14,412 (43.13)	42,680 (43.43)	
Past user	5464 (16.35)	15,665 (15.94)	
Current user	13,537 (40.51)	39,922 (40.63)	
Bisphosphonates	665 (1.99)	2293 (2.33)	0.0003
SERMs	24 (0.07)	80 (0.08)	0.5902
Calcitonin	89 (0.27)	327 (0.33)	0.0617
Proton pump inhibitors	887 (2.65)	1941 (1.97)	< .0001
Thiazolidinedione	56(0.17)	39 (0.04)	< .0001
Thyroid medications	4656 (13.92)	13,206 (13.43)	0.0221
Psychoactive medications[c]	4377 (13.09)	12,295 (12.50)	0.0052
Oral corticosteroids	200 (0.60)	783 (0.80)	0.0003

For non-DM participants baseline is considered the time of WHI enrolment whereas for DM participants (both intervention and control arm), baseline is considered 1 year after WHI enrolment

[a] Heart failure, ischemic heart disease, (MI/angina, stroke, and/or CABC/PTCA)

[b] Combination antihypertensive drug that does not contain a RAAS inhibitor

[c] Anticonvulsants, antipsychotics/mania, antianxiety, antidepressants, hypnotics/sleep/sedatives

duration of use was recorded. No information was collected on dose. For this study, we defined the use of a RAAS inhibitor as any use of at least one of the following medication classes: ACE inhibitor, ARB, direct renin inhibitor, selective aldosterone receptor antagonist (SARA), or RAAS fixed-dose combination drug (ACE, ARB, direct renin inhibitor or selective aldosterone receptor antagonist (SARA) in combination with another antihypertensive medication other than a RAAS inhibitor). The association of the individual classes of ACE inhibitors and ARBs with each outcome was also examined. Baseline users of RAAS inhibitors as a whole, ACE inhibitors and ARBs were excluded as we were only including new users of these medications in all analyses.

Falls

Fall history was considered as a potential mediator of observed fracture associations and was obtained by self-report of the number of times a participant fell and landed on the floor or ground in the preceding 12 months (participants were instructed not to include falls due to sports activities such as snow or water skiing or horseback riding).

Table 3 Association of RAAS inhibitor use with incident osteoporotic fractures (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted model[b]	Final model: fully adjusted plus baseline Hip BMD[c]
	HR (95% CI)	HR (95% CI)	HR (95% CI)
All fractures[d]	1.23 (1.15, 1.32)	1.20 (1.11, 1.30)	0.86 (0.59, 1.24)
Upper limb fractures[e]	1.20 (1.08, 1.33)	1.22 (1.08, 1.38)	0.61 (0.34, 1.09)
Lower limb fractures[f]	1.28 (1.15, 1.42)	1.20 (1.06, 1.37)	0.84 (0.46, 1.57)
Central body fractures[g]	1.26 (1.11, 1.43)	1.17 (1.01, 1.36)	1.04 (0.56, 1.93)
Hip Fracture	1.20 (0.99, 1.46)	1.08 (0.87, 1.35)	0.92 (0.29, 2.94)

Fractures (adjudicated or self-report) reported until the end of extension study of WHI

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for age at baseline, BMI and race/ethnicity

[b] Adjusted for age at baseline, BMI, physical function, log transformed total calcium and vitamin-D, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

[d] First type of fracture (if multiple types occurred) was captured and time to that first fracture was modeled (excludes, fingers, toes and tailbone fracture)

[e] Defined as the first occurrence of the elbow, hand (not finger), lower arm or wrist, upper arm, or shoulder fracture

[f] Defined as the first occurrence of the lower leg or ankle, upper leg (not hip), knee, foot (not toe)

[g] Defined as the first occurrence of the hip, pelvis, or spine fracture

Covariates

Height and weight at the baseline visit were measured in WHI as previously described [39] and used to calculate body mass index (BMI). Questionnaires obtained at the baseline visit were used to collect demographic and clinical information. Enrollment in the OS or CT (and particular CT) was recorded. Indicators were created for participation in each arm (treatment and control) of each clinical trial. Geographic study site was categorized by region (northeast, south, midwest, and west) [40]. Food frequency questionnaires (FFQ) were used to collect information on calcium and vitamin D intakes [41]. Dietary and supplemental calcium and vitamin D were summed to derive total calcium and vitamin D intake. Antihypertensive medications (other than RAAS inhibitors), medications for osteoporosis, and other medications that might affect bone metabolism including proton pump inhibitors, thiazolidinediones, thyroid medications, psychoactive medications, and oral corticosteroids were included.

Statistical analyses

Descriptive statistics were reported by RAAS use. The mean and standard deviation is presented for continuous variables and the frequencies and percentages for categorical variables. For continuous variables, two sample *t*-tests were used to

Table 4 Association of ACE inhibitor use with incident osteoporotic fractures (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted model[b]	Final model: fully adjusted plus baseline hip BMD[c]
	HR	HR	HR
	(95% CI)	(95% CI)	(95% CI)
All fractures[d]	1.19	1.16	0.78
	(1.09, 1.30)	(1.05, 1.29)	(0.47, 1.29)
Upper limb fractures[e]	1.16	1.17	0.41
	(1.01, 1.33)	(1.00, 1.37)	(0.16, 1.03)
Lower limb fractures[f]	1.23	1.16	1.23
	(1.07, 1.41)	(0.99, 1.36)	(0.62, 2.43)
Central body fractures[g]	1.21	1.15	0.77
	(1.02, 1.42)	(0.96, 1.38)	(0.32, 1.85)
Hip fracture	1.25	1.12	1.23
	(0.98, 1.60)	(0.86, 1.48)	(0.33, 4.59)

Fractures (adjudicated or self-report) reported until end of extension study of WHI

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for age at baseline, BMI and Race/Ethnicity

[b] Adjusted for Age at baseline, BMI, Physical Function, Log transformed Total Calcium & Vitamin-D, Race/Ethnicity, Smoking Status at baseline, parental history of hip fracture, History of fracture after age 55, Self-reported health status, history of diabetes, CVD, hypertension, Alcohol use at baseline, region, Medication Use at baseline (Thiazides, Loop diuretics, Other Diuretics, Central agonists, Peripheral adrenergic inhibitors, Beta blockers, Calcium channel blockers, Other fixed-dose combination antihypertensives, Hormone replacement therapy, Bisphosphonates, Proton pump inhibitors, Thyroid medications, Psychoactive medications, Oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have Hip BMD value at baseline

[d] First type of fracture (if multiple types occurred) was captured and time to that first fracture was modeled (excludes, fingers, toes and tailbone fracture)

[e] Defined as the first occurrence of the elbow, hand (not finger), lower arm or wrist, upper arm, or shoulder fracture

[f] Defined as the first occurrence of the lower leg or ankle, upper leg (not hip), knee, foot (not toe)

[g] Defined as the first occurrence of hip, pelvis, or spine fracture

compare RAAS users to non-users while for categorical variables; the chi-squared test was used to assess differences.

Cox proportional hazards model, stratified by baseline age (10-year intervals), study participation (CT or OS enrollment, DM trial randomization arms, CAD trail randomization arms (time-dependent), hormone therapy trial randomization arms), and WHI extension study participation (time-dependent) were used to determine associations between any RAAS use and fracture outcome. Results are reported as hazard ratios and 95% CI. Change in any RAAS use over time was evaluated by entering current RAAS use as a time-dependent exposure. The fracture hazard rate at any follow-up time was modeled as a function of the most recent medication use. Women contributed to follow-up until the occurrence of the outcome, death, or end of follow-up, whichever came first. Women who did not enroll in the extension study and did not have an outcome were censored at their date of last data collection prior to the closeout of the main WHI study. To account for out-of-date medication use, women were censored at the first time they did not have a medication inventory report within 3.5 years of their previous report.

We also refined the time of initiation of the said medication from the duration of use variable reported at their medication inventory. This addresses the change

Table 5 Association of ARB Use with incident osteoporotic fractures (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted model[b]	Final model: fully adjusted plus baseline hip BMD[c]
	HR (95% CI)	HR (95% CI)	HR (95% CI)
All fractures[d]	1.22 (1.10, 1.36)	1.17 (1.03, 1.32)	1.16 (0.69, 1.95)
Upper limb fractures[e]	1.16 (0.98, 1.37)	1.15 (0.95, 1.40)	0.60 (0.22, 1.67)
Lower limb fractures[f]	1.22 (1.03, 1.46)	1.08 (0.88, 1.33)	0.70 (0.27, 1.85)
Central body fractures[g]	1.35 (1.11, 1.63)	1.27 (1.02, 1.57)	2.53 (1.21, 5.31)
Hip fracture	1.31 (0.98, 1.76)	1.25 (0.91, 1.72)	0.52 (0.06, 4.30)

Fractures (adjudicated or self-report) reported until end of extension study of WHI

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for age at baseline, BMI and race/ethnicity

[b] Adjusted for age at baseline, BMI, physical function, log transformed total calcium and vitamin-D, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

[d] First type of fracture (if multiple types occurred) was captured and time to that first fracture was modeled (excludes, fingers, toes, and tailbone fracture)

[e] Defined as the first occurrence of the elbow, hand (not finger), lower arm or wrist, upper arm, or shoulder fracture

[f] Defined as the first occurrence of the lower leg or ankle, upper leg (not hip), knee, foot (not toe)

[g] Defined as the first occurrence of the hip, pelvis, or spine fracture

in drug use between medication inventory collections and extends the participants recall of medication use to at most 1 or 2 years and consequently does not supersede the preceding collection [42, 43]. In addition to defining an indicator variable for medication use (yes/no), we also assessed the medication use by defining a cumulative duration of medication use. In this alternate definition, we represented medication use up to a particular follow-up time as the duration a participant was taking the medication up to that time. We defined short-term use as use for 3 years or less [44]. The fracture hazard rate at any particular time was modeled as a function of cumulative duration of medication use up to that particular time.

Three models were fit for each outcome: A minimally adjusted model adjusted for baseline age, BMI, and race/ethnicity; a fully adjusted multivariable model including baseline age, BMI, race/ethnicity, physical function, log-transformed total calcium and vitamin D intake, smoking status, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, alcohol use, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers,

Table 6 Association of cumulative duration of RAAS inhibitor use with incident osteoporotic fractures (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted[b]	Final model: fully adjusted plus baseline hip BMD[c]
	HR (95%CI)	HR (95%CI)	HR (95%CI)
All fracture[d]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.02 (3.67, 4.41)	3.98 (3.59, 4.41)	3.97 (2.48, 6.36)
> 3 years	0.66 (0.60, 0.73)	0.64 (0.57, 0.71)	0.40 (0.24, 0.68)
Upper limb fracture[e]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.00 (3.47, 4.60)	4.27 (3.64, 5.00)	2.36 (1.15, 4.84)
> 3 years	0.63 (0.55, 0.74)	0.62 (0.53, 0.74)	0.23 (0.08, 0.62)
Lower limb fracture[f]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.52 (3.91, 5.22)	4.39 (3.70, 5.19)	4.52 (2.01, 10.16)
> 3 years	0.67 (0.58, 0.78)	0.65 (0.55, 0.78)	0.40 (0.17, 0.96)
Central body fracture[g]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.67 (3.91, 5.57)	4.14 (3.39, 5.04)	5.17 (2.19, 12.19)
> 3 years	0.72 (0.61, 0.85)	0.65 (0.54, 0.79)	0.49 (0.21, 1.13)
Hip fracture			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.18 (3.16, 5.53)	3.91 (2.87, 5.33)	1.58 (0.27, 9.37)
> 3 years	0.74 (0.58, 0.95)	0.62 (0.46, 0.83)	0.71 (0.19, 2.70)

Fractures (adjudicated or self-report) reported until end of extension study of WHI

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for age at baseline, BMI and race/ethnicity

[b] Adjusted for age at baseline, BMI, physical function, log transformed total calcium and vitamin-D, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, Self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

[d] First type of fracture (if multiple types occurred) was captured and time to that first fracture was modeled (excludes, fingers, toes and tailbone fracture)

[e] Defined as the first occurrence of the elbow, hand (not finger), lower arm or wrist, upper arm or shoulder fracture

[f] Defined as the first occurrence of lower leg or ankle, upper leg (not hip), knee, foot (not toe)

[g] Defined as the first occurrence of hip, pelvis, or spine fracture

Table 7 Association of cumulative duration of ACE inhibitor use with incident osteoporotic fractures (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted[b]	Final model: fully adjusted plus baseline hip BMD[c]
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Any fracture[d]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	3.98 (3.55, 4.47)	3.98 (3.50, 4.53)	3.28 (1.66, 6.48)
> 3 years	0.62 (0.54, 0.70)	0.58 (0.50, 0.67)	0.43 (0.22, 0.83)
Upper limb fracture[e]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.18 (3.51, 4.98)	4.40 (3.61, 5.37)	1.27 (0.36, 4.48)
> 3 years	0.58 (0.48, 0.70)	0.57 (0.46, 0.72)	0.32 (0.11, 0.91)
Lower limb fracture[f]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.55 (3.80, 5.45)	4.47 (3.63, 5.50)	5.88 (2.31, 14.94)
> 3 years	0.63 (0.52, 0.77)	0.59 (0.47, 0.75)	0.69 (0.29, 1.64)
Central body fracture[g]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.22 (3.38, 5.27)	3.78 (2.96, 4.83)	2.43 (0.68, 8.61)
> 3 years	0.66 (0.53, 0.82)	0.61 (0.47, 0.78)	0.33 (0.10, 1.11)
Hip fracture			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.42 (3.17, 6.16)	3.94 (2.71, 5.70)	0.96 (0.10, 9.45)
> 3 years	0.71 (0.52, 0.98)	0.63 (0.44, 0.91)	0.86 (0.18, 4.15)

Fractures (adjudicated or self-report) reported until end of extension study of WHI

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were allowed to re-enter back in to the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for age at baseline, BMI and race/ethnicity

[b] Adjusted for age at baseline, BMI, physical function, log-transformed total calcium and vitamin-D, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

[d] First type of fracture (if multiple types occurred) was captured, and time to that first fracture was modeled (excludes, fingers, toes, and tailbone fracture)

[e] Defined as the first occurrence of the elbow, hand (not finger), lower arm or wrist, upper arm or shoulder fracture

[f] Defined as the first occurrence of the lower leg or ankle, upper leg (not hip), knee, foot (not toe)

[g] Defined as the first occurrence of the hip, pelvis, or spine fracture

Table 8 Association of cumulative duration of ARB use with incident osteoporotic fractures (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted[b]	Final model: fully adjusted plus baseline hip BMD[c]
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Any fracture[d]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.39 (3.83, 5.05)	4.08 (3.48, 4.78)	6.23 (3.11, 12.46)
> 3 years	0.62 (0.53, 0.73)	0.61 (0.51, 0.73)	0.44 (0.20, 0.97)
Upper limb fracture[e]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.14 (3.33, 5.16)	4.01 (3.12, 5.14)	5.93 (1.63, 21.58)
> 3 years	0.58 (0.45, 0.75)	0.57 (0.43, 0.76)	0.15 (0.02, 1.09)
Lower limb fracture[f]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.87 (3.90, 6.09)	4.19 (3.21, 5.47)	1.81 (0.45, 7.36)
> 3 years	0.61 (0.48, 0.79)	0.59 (0.44, 0.79)	0.30 (0.07, 1.31)
Central body fracture[g]			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	5.48 (4.24, 7.08)	5.14 (3.87, 6.82)	32.73 (12.58, 85.17)
> 3 years	0.79 (0.61, 1.02)	0.73 (0.55, 0.97)	0.90 (0.29, 2.80)
Hip fracture			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	4.56 (3.00, 6.95)	4.43 (2.83, 6.92)	9.03 (0.52, 156.35)
> 3 years	0.87 (0.61, 1.26)	0.76 (0.50, 1.16)	0 (0)

Fractures (adjudicated or self-report) reported until end of extension study of WHI

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] adjusted for age at baseline, BMI and race/ethnicity

[b] Adjusted for age at baseline, BMI, physical function, log-transformed total calcium & vitamin-d, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

[d] First type of fracture (if multiple types occurred) was captured and time to that first fracture was modeled (excludes, fingers, toes and tailbone fracture)

[e] Defined as the first occurrence of the elbow, hand (not finger), lower arm or wrist, upper arm, or shoulder fracture

[f] Defined as the first occurrence of the lower leg or ankle, upper leg (not hip), knee, foot (not toe)

[g] Defined as the first occurrence of the hip, pelvis, or spine fracture

Table 9 Association of cumulative duration of RAAS inhibitor use with incident falls (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted[b]	Fully adjusted plus baseline hip BMD[c] (among those with a BMD value)
	HR (95%CI)	HR (95%CI)	HR (95%CI)
≥ 1 Fall			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	2.07 (1.98, 2.15)	1.97 (1.88, 2.06)	1.92 (1.58, 2.32)
> 3 years	0.33 (0.30, 0.36)	0.32 (0.29, 0.35)	0.23 (0.15, 0.36)
≥ 2 Fall			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	2.31 (2.21, 2.41)	2.14 (2.03, 2.24)	2.12 (1.72, 2.61)
> 3 years	0.37 (0.34, 0.41)	0.35 (0.32, 0.38)	0.35 (0.24, 0.51)

Defined as time to 1 or more (or 2 or more) fall during a period within 6 years from baseline. For DM participants, baseline for capturing falls started 365 (+ 90) days from WHI enrollment, and falls were captured for 6 years after. For Non-DM participants, baseline was at WHI enrollment, and falls were captured for a period of 6 years (+ 90) days. A window of 90 days was given to account for late arrival of self-report form

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for age at baseline, BMI and race/ethnicity

[b] Adjusted for age at baseline, BMI, physical function, log-transformed total calcium & vitamin-D, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

calcium channel blockers, other fixed-dose combination antihypertensive, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids); and a final model that included total hip BMD at baseline plus all the covariates from the fully adjusted multivariable model using the reduced sample of participants with BMD measurements.

We assessed the association baseline RAAS use had on percentage change in BMD from 3 to 6 years using minimally and fully adjusted linear regression models. The minimally adjusted model was adjusted for baseline age, BMI, and race/ethnicity. The corresponding baseline BMD value was added to the fully adjusted model in addition to all the covariates listed in Table 2.

Two post hoc analyses were performed: (1) including only women who had a history of hypertension, (2) the relationship of RAAS inhibitor use to one and two or more falls.

Results

Use of RAAS inhibitors increased over time, such that by the extension study; 37.4% of the women reported use of a RAAS inhibitor. ACE inhibitors followed by ARBs were the most common class of RAAS inhibitor used at all-time points. Thirteen women who used both a direct renin inhibitor and an ARB at year 4 of the extension study were considered in the direct renin inhibitor category (Table 1).

Table 10 Association of cumulative duration of ACE inhibitor use with incident falls (HR and 95% CI)

	Minimally A\adjusted[a] HR (95%CI)	Fully adjusted[b] HR (95%CI)	Final model: fully adjusted plus baseline hip BMD[c] HR (95%CI)
≥ 1 Fall			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	2.13 (2.02, 2.24)	2.05 (1.93, 2.17)	1.94 (1.50, 2.50)
> 3 years	0.33 (0.30, 0.37)	0.32 (0.28, 0.36)	0.23 (0.13, 0.40)
≥ 2 Fall			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	2.37 (2.24, 2.50)	2.22 (2.09, 2.37)	2.39 (1.83, 3.13)
> 3 years	0.37 (0.33, 0.41)	0.35 (0.31, 0.39)	0.22 (0.12, 0.40)

Defined as time to 1 or more (or 2 or more) fall during a period within 6 years from baseline. For DM participants, baseline for capturing falls started 365 (+ 90) days from WHI enrollment, and falls were captured for 6 years after. For Non-DM participants, baseline was at WHI enrollment, and falls were captured for a period of 6 years (+ 90) days. A window of 90 days was given to account for late arrival of self-report form

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for ge at baseline, BMI and race/ethnicity

[b] Adjusted for Age at baseline, BMI, physical function, log-transformed total calcium and vitamin-D, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

Baseline characteristics of the entire cohort by the use of RAAS inhibitors are shown in Table 2. Baseline use of calcitonin, thiazolidinedione, vasodilators, alpha-beta blockers, and SERMS was very infrequent (< 1%), and these medications were not included in subsequent models.

In fully adjusted models (not including hip BMD), there was a significant association of RAAS inhibitor (HR 1.20 (1.11, 1.30)), ACE u (HR 1.16 (1.05, 1.29)), and ARB use (HR 1.17 (1.03, 1.32)) for all fractures. However, in final models, in the smaller subset of women who also had hip BMD measurements, this relationship was attenuated and no longer significant for all fractures for RAAS inhibitor, ACE, and ARB use and any site-specific fracture except for central body fractures with ARB use (HR 2.53, 95% CI 1.21, 5.31) (Tables 3, 4, 5).

There was a striking differential association of duration of use of RAAS and ACE inhibitors and ARBs with fractures in final models that included hip BMD. Short duration use of RAAS and ACE inhibitors and ARBs (≤ 3 years.) was associated with a significantly increased risk for all fractures, whereas long-term use (> 3 years.) was associated with a reduced risk for all fractures (Tables 6, 7, 8). Short duration use of RAAS and ACE inhibitors and ARBs (≤ 3 years.) was associated with a significantly increased risk for one and two more falls, whereas long-term use (> 3 years.) was associated with a reduced risk fall risk (Tables 9, 10, 11). In subgroup analysis confined to women with hypertension, in final models including hip BMD, there was no significant association of RAAS inhibitor use with all fractures (HR 1.1 (95% CI 0.65, 1.79)). Similarly, in these women with hypertension, short duration of use of RAAS inhibitors (≤ 3 years.) was associated with an increased risk for falls (HR 2.38 (95% CI

Table 11 Association of cumulative duration of ARB use with Incident Falls (HR and 95% CI)

	Minimally adjusted[a]	Fully adjusted[b]	Final model: fully adjusted plus baseline hip BMD[c] (among those with a BMD value)
	HR (95%CI)	HR (95%CI)	HR (95%CI)
≥ 1 Fall			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	2.01 (1.88, 2.15)	1.91 (1.78, 2.06)	1.94 (1.36, 2.77)
> 3 years	0.33 (0.28, 0.38)	0.32 (0.27, 0.37)	0.24 (0.12, 0.51)
≥ 2 Fall			
Cumulative duration of use			
0 years	Ref	Ref	Ref
≤ 3 years	2.20 (2.05, 2.36)	2.06 (1.91, 2.23)	2.08 (1.44, 2.98)
> 3 years	0.38 (0.33, 0.43)	0.35 (0.30, 0.41)	0.49 (0.27, 0.86)

Defined as time to 1 or more (or 2 or more) fall during a period within 6 years from baseline. For DM participants, baseline for capturing falls started 365 (+ 90) days from WHI enrollment, and falls were captured for 6 years after. For Non-DM participants, baseline was at WHI enrollment, and falls were captured for a period of 6 years (+ 90) days. A window of 90 days was given to account for late arrival of self-report form

All proportional hazards models are stratified by age at baseline (10-year interval), study participation (CT or OS enrollment, DM trial enrollment, CAD trail enrollment (time-dependent), hormone therapy trial randomization arms), WHI extension 1 participation (time-dependent). Medication use was entered in the model as a time-dependent indicator variable. Medication use at a particular follow-up time was defined based on what was indicated in the participant's most recent medication inventory. The hazard rate was modeled as a function of most recent medication use. Excluded women who reported medication use at baseline. To account for out of date medication use, women were censored if they did not have a medication inventory 3.5 years from their prior inventory and were not allowed to re-enter back into the risk set if a future medication inventory was found. To account for duration of use, we refined the time of initiation of said medication based on what they reported at their medication inventory. This extends the participants recall of medication use to at most one or 2 years and consequently does not supersede the preceding collection

[a] Adjusted for age at baseline, BMI and race/ethnicity

[b] Adjusted for age at baseline, bmi, physical function, log-transformed total calcium and vitamin-D, race/ethnicity, smoking status at baseline, parental history of hip fracture, history of fracture after age 55, self-reported health status, history of diabetes, CVD, hypertension, alcohol use at baseline, region, medication use at baseline (thiazides, loop diuretics, other diuretics, central agonists, peripheral adrenergic inhibitors, beta blockers, calcium channel blockers, other fixed-dose combination antihypertensives, hormone replacement therapy, bisphosphonates, proton pump inhibitors, thyroid medications, psychoactive medications, oral corticosteroids)

[c] Adjusted for all the variables listed above and total hip BMD at baseline. This model was run only among those who have hip BMD value at baseline

1.83, 3.10)), and long-term use (> 3 years.) was associated with a reduced risk for falls (HR 0.22 (95% CI 0.13, 0.37)).

BMD at the total hip and femoral neck was significantly higher in RAAS users compared with nonusers at baseline and at 3 and 6 years ($p < 0.0001$ for all). However, in fully adjusted multivariable models, there was no significant difference in percentage changes in BMD at the total hip from 3 to 6 years by use of RAAS inhibitors, ACE inhibitors, or ARBs (data not shown).

Discussion

In postmenopausal women in the WHI, the use of RAAS inhibitors including ACE inhibitors and ARBs was associated with a small but significant risk of fractures which was no longer present when hip BMD was considered in the models. However, there was a striking difference in risk for fractures by the duration of use of RAAS inhibitors, ACE inhibitors, and ARBs, with short duration of use (3 years or less) associated with a significant increased risk for fractures, and longer duration of use (> 3 years) associated with reduced fracture risk. Findings were similar in the subgroup of women with hypertension. There was no significant relationship between the use of RAAS or ACE inhibitors or ARBs with changes in BMD of the hip.

To our knowledge, there are no prior studies examining risk of incident fractures in the overall class of RAAS inhibitors. There are, however, reports of the association of ACE inhibitor and ARB use with incident fractures. Our findings in WHI of a small increased risk for all fractures in users of RAAS inhibitors, ACE inhibitors, and ARBS in models that did not

include BMD measurements are in accordance with one meta-analysis in which a small but significant increased risk of all fractures was reported in ACE users, particularly those over age 65 [28]. In contrast with our findings, a population-based cohort that included both ACE inhibitors and ARBs reported no increased risk for all fractures [24]. In Medicare recipients in two reports, the use of ARBs were associated with fewer fractures [18], [22]. However, notably, in WHI, when hip BMD was included in the final models, there was no significant association between use of RAAS inhibitors, ACE inhibitors, or ARBs with fractures. Further, in WHI, the use of RAAS inhibitors including ACE inhibitors and ARBs was associated with an increased risk of falls with short-term use and a decreased risk with long-term use. It is possible that the differences in the literature relative to the association of fracture risk with RAAS inhibitors may at least in part be because studies did not uniformly include baseline BMD measurements [18, 22] or did not examine fracture incidence by time periods since drug initiation [24, 28]. It is well known that potential side effects from antihypertensive medications include orthostatic hypotension and syncope [45] which may increase fall risk at least in the short term. The reduced risk for falls over longer-term use of RAAs inhibitors may be because lower extremity muscle weakness [46] is a major risk factor for falls in older adults, and some reports suggest decreased age-related declines in muscle strength [47, 48], improved exercise capacity [49–51], and physical function [48, 52] with use of RAAS inhibitors.

In WHI, after consideration of hip BMD, there was no increased risk for any site-specific fractures except for central body fractures in ARB users. Prior studies of the association of ACE inhibitor and ARB use with hip fractures are inconsistent, but again, did not include measurements of BMD [18, 24, 53]. In agreement with these findings in WHI, one study of Medicare beneficiaries found no association between any use of ACE inhibitors and hip fractures [18]. In contrast with WHI, however, this study did report a reduced risk for hip fractures in new users of ARBs [18], and others have reported a reduced risk for hip fractures in ACE and ARB users [24]. Conversely, one claims database study confined to Norwegian men and women reported an increased risk of hip fractures with ACE use, in particular in persons younger than 80 [53]. To our knowledge, no prior studies have examined the risk of upper and lower limb and central body fractures by ACE and ARB use. In WHI, wrist and humerus fractures were included among upper extremity fractures. Our findings of no significant association of upper limb fractures in RAAS and ACE inhibitors and ARB users are in contrast with a prior study confined to new users of ACE inhibitors and ARBs, which reported a decreased risk of wrist fractures with ACE inhibitor use, although not with humerus fractures [18]. In contrast with women in WHI, in whom there was a significant positive relationship between ARB use and central body fractures, one study [18] reported no association of ARB use with one central body fracture site (pelvis). However, it is possible that these findings of a significant relationship between ARB use and central body fractures in WHI are simply due to chance as the sample size was small and multiple testing was done.

Our findings that the use of RAAS inhibitors was not related to changes in BMD of the hip is, to our knowledge, the first time that this has been reported including all classes of RAAS inhibitors. Prior studies of individual classes of RAAS inhibitors and association with BMD changes in postmenopausal women are limited to reports of ACE inhibitors. In accordance with our findings, in the Study of Women's Health Across the Nation, the use of ACE inhibitors was not associated with differences in BMD at the femoral neck [33]. Other, smaller studies have reported discordant results with respect to the use of ACE inhibitors and changes in BMD. In one study including fifty women, the ACE inhibitor fosinopril was associated with a decreased loss of BMD at the lumbar spine and femoral neck compared with untreated controls [54], whereas other prospective cohort studies confined to Asians reported significant losses in BMD at the hip in women taking ACE inhibitors [16, 17]. Our results may differ from these [16, 17] as less than 6% of our study population were of Asian descent.

This study has a number of strengths. It is the first to include both incident fractures that was able to account for BMD. Further, the WHI is a large, well-characterized multiethnic population of postmenopausal women and as such, we were able to include a number of important covariates for these analyses. We included all classes of RAAS inhibitors as well as individual classes of sufficient frequency (ACE and ARBs). Further, it is recommended that pharmacoepidemiological studies include new-user designs to mitigate two types of bias; first, the idea that prevalent users are actually (survivors) of early periods of pharmacotherapy and, second, that covariates for drug users at study entry may be affected by the drug itself [55]. Thus, all analyses were restricted to new users. In addition, we were able to examine the relationship of duration of use of these medications to incident fractures and, in additional analyses, included the population of women who had an underlying indication for these medications, i.e., hypertensive women. However, there are also some limitations. To start, this was an observational study. Although we adjusted for known covariates of importance, residual confounding remains a possibility. Our findings were from a population of postmenopausal women enrolled in WHI, and the results may not be generalizable to other populations. We lacked measurements of renal function and serum vitamin D levels. Use of direct renin inhibitors and SARAs was uncommon (< 1%). We did not have information on the doses of medications used, or in fact, whether the medications were taken as directed. Confidence intervals relative to the association of specific fracture sites with ACE and ARB

use in the BMD sub-cohort by duration of use were wide. Poor recall of falls is of concern [56], and the current gold standard for reporting falls is prospective recording of falls using techniques including calendars [57], diaries [58, 59] or postcards [60] which was not done in WHI. Moreover, it was not possible to determine whether the falls caused the fractures using observational data from WHI. However, the annual self-report assessment of falls done in WHI was standardized and has been used in a number of previous studies [61, 62].

In conclusion, in postmenopausal women, the use of RAAS inhibitors including ACE inhibitors and ARBs is associated with a significant risk for fractures in new users of these medications, over short term (3 years or less). However, long-term use is associated with a reduced risk for fractures. Consideration for fracture risk may be part of the decision-making process for the initiation of these medications for other disease states.

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Additional information A full list of all the investigators who have contributed to Women's Health Initiative science appears at https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

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Compliance with ethical standards

Conflicts of interest None.

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