JAMA Internal Medicine | Original Investigation

Association of 3 Different Antihypertensive Medications With Hip and Pelvic Fracture Risk in Older Adults
Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE On the basis of observational studies, the use of thiazide diuretics for the treatment of hypertension is associated with reduced fracture risk compared with nonuse. Data from randomized clinical trials are lacking.

OBJECTIVE To examine whether the use of thiazide diuretics for the treatment of hypertension is associated with reduced fracture risk compared with nonuse.

DESIGN, SETTING, AND PARTICIPANTS Using Veterans Affairs and Medicare claims data, this study examined hip and pelvic fracture hospitalizations in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial participants randomized to first-step therapy with a thiazide-type diuretic (chlorthalidone), a calcium channel blocker (amlodipine besylate), or an angiotensin-converting enzyme inhibitor (lisinopril). Recruitment was from February 1994 to January 1998; in-trial follow-up ended in March 2002. The mean follow-up was 4.9 years. Posttrial follow-up was conducted through the end of 2006, using passive surveillance via national databases. For this secondary analysis, which used an intention-to-treat approach, data were analyzed from February 1, 1994, through December 31, 2006.

MAIN OUTCOMES AND MEASURES Hip and pelvic fracture hospitalizations.

RESULTS A total of 22 180 participants (mean [SD] age, 70.4 [6.7] years; 43.0% female; and 49.9% white non-Hispanic, 31.2% African American, and 19.1% other ethnic groups) were followed for up to 8 years (mean [SD], 4.9 [1.5] years) during masked therapy. After trial completion, 16 622 participants for whom claims data were available were followed for up to 5 additional years (mean [SD] total follow-up, 7.8 [3.1] years). During the trial, 338 fractures occurred. Participants randomized to receive chlorthalidone vs amlodipine or lisinopril had a lower risk of fracture on adjusted analyses (hazards ratio [HR], 0.79; 95% CI, 0.63-0.98; $P = .04$). Risk of fracture was significantly lower in participants randomized to receive chlorthalidone vs lisinopril (HR, 0.75; 95% CI, 0.58-0.98; $P = .04$) but not significantly different compared with those randomized to receive amlodipine (HR, 0.82; 95% CI, 0.63-1.08; $P = .17$). During the entire trial and posttrial period of follow-up, the cumulative incidence of fractures was nonsignificantly lower in participants randomized to receive chlorthalidone vs lisinopril or amlodipine (HR, 0.87; 95% CI, 0.74-1.03; $P = .10$) and vs each medication separately. In sensitivity analyses, when 1 year after randomization was used as the baseline (to allow for the effects of medications on bone to take effect), similar results were obtained for in-trial and in-trial plus posttrial follow-up.

CONCLUSIONS AND RELEVANCE These findings from a large randomized clinical trial provide evidence of a beneficial effect of thiazide-type diuretic therapy in reducing hip and pelvic fracture risk compared with treatment with other antihypertensive medications.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00000542

JAMA Intern Med. 2017;177(1):67-76. doi:10.1001/jamainternmed.2016.6821
Published online November 21, 2016.

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Hypertension and osteoporotic fractures are age-related disorders whose incidences increase rapidly after the age of 65 years. The conditions are interrelated because people with hypertension have more osteoporotic fractures than people without hypertension.[1,2] A meta-analysis[3] revealed that many nonrandomized, observational studies suggest that therapy with thiazide-type diuretics improves bone strength and reduces fracture risk. A positive effect on calcium balance and a direct stimulatory effect on osteoblasts have been proposed as the biological basis for this putative beneficial effect.[4] β-Blockers may also reduce fracture risk[5] (possibly through β_2-adrenergic blockade of receptors present on osteoclasts[6]), although a review article[7] found that not all studies confirm this. Less is known regarding the effects of angiotensin-converting enzyme inhibitors (ACEis) and calcium channel blockers (CCBs) on fracture risk despite their ubiquitous use in older adults with hypertension. Studies[8,9] have found that ACEis exert a protective effect on bone strength through blockade of local angiotensin production, which stimulates osteoclast activity, and reduction of receptor activator nuclear factor-κβ ligand in osteoblasts, which activates osteoclasts. Several clinical studies suggest lower fracture risk with their use,[10,11] although not all studies agree.[12-15] Another study[16] found that CCBs decrease bone resorption through reduced osteoclast function owing to lower cytosolic calcium. Little information is available regarding their clinical effect on bone health.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large randomized clinical trial that compared the effect of first-step therapy with different classes of antihypertensive drug therapy in preventing fatal coronary heart disease (CHD) or nonfatal myocardial infarction (primary outcome) and other cardiovascular disease (CVD) events. The CCB amlodipine, the ACEi lisinopril, and the α-receptor blocker doxazosin mesylate were not superior to the diuretic chlorthalidone in preventing the primary CHD outcome or any other major CVD or renal outcomes.[17] Chlorthalidone was superior to amlodipine, lisinopril, and doxazosin in preventing heart failure and to lisinopril (blacks only) and doxazosin in preventing stroke. The large sample size, long follow-up, and randomized therapy provide a unique opportunity to examine post hoc the effects of the major classes of blood pressure–lowering medications on the incidence of hospitalizations for hip and pelvic fractures. These fracture types are well captured in administrative data sets and are serious fracture types that can be associated with mortality. We asked 3 questions: Are hip and pelvic fractures less common during treatment with a thiazide-type diuretic compared with CCBs or ACEis? Does the addition of a β-blocker to chlorthalidone further lower the risk of fracture? Assuming a beneficial effect in the chlorthalidone group during the trial, would this pattern continue during the posttrial period (ie, is there a legacy effect)?

To answer these questions, we used 2 approaches. First, we examined the cohort from the time of randomization until the time of event (fracture) or censoring (death or end of follow-up), thus maintaining the randomized allocation of participants. Second, as a sensitivity analysis, we examined the cohort beginning 1 year after the onset of the study. Although randomization is not strictly maintained with this approach, this was done for 2 reasons: to allow for the effect of antihypertensive medications on bone to take place and to avoid including early fractures associated with falls related to use of new antihypertensive medications. Several studies have reported increased risk of falls (a proximate event in 90%-95% of hip fractures[18]) in new users of antihypertensive medications.[19,20] This study examines whether the use of thiazide diuretics for the treatment of hypertension is associated with reduced fracture risk compared with nonuse. We hypothesized fewer in-trial fracture hospitalizations in those randomized to chlorthalidone vs comparators and that this benefit would persist into the posttrial surveillance period when participants were no longer randomized to study medications.

Key Points

Question Do thiazide diuretics protect against fracture risk?

Findings Use of the thiazide-like diuretic chlorthalidone was associated with a 21% significantly lower risk of hip and pelvic fractures compared with either lisinopril or amlodipine and a significantly lower risk compared with lisinopril alone during approximately 4.9 years of follow-up. During 5 additional years of posttrial follow-up, when medication use was not constrained by study protocol, fracture risk continued to be lower in users of chlorthalidone compared with lisinopril or amlodipine together or alone.

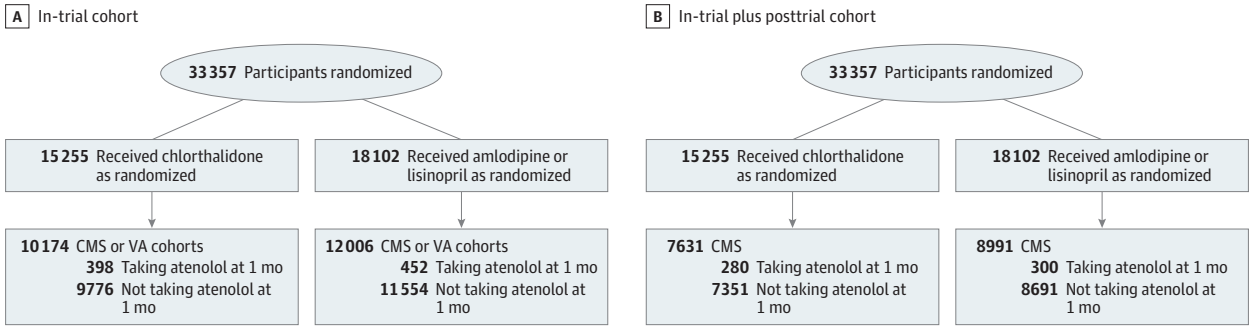
Meaning The present results of short-term and long-term fracture protection with thiazide antihypertensive therapy compared with other antihypertensive medications strongly recommend use of a thiazide for hypertension treatment in addition to its long track record of cardiovascular protection.

Methods

ALLHAT was a randomized, double-blind, active-controlled, clinical hypertension trial that compared first-step treatment with the thiazide-type diuretic chlorthalidone (n = 15 255), the CCB amlodipine (n = 9048), the α-receptor blocker doxazosin (n = 9061), or the ACEi lisinopril (n = 9054).[21] The doxazosin arm was stopped early because of a higher risk of CVD compared with chlorthalidone and is not considered here. All participants gave written informed consent, and all centers obtained institutional review board approval for the trial. The institutional review board of The University of Texas Health Science Center at Houston approved the posttrial follow-up study. The authors outside the Coordinating Center did not have access to participant-level identifying data.

Eligible participants for ALLHAT were men and women 55 years or older who had systolic blood pressure of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg or took medication for hypertension and had at least 1 additional risk factor for CHD. These risk factors included previous myocardial infarction or stroke, left ventricular hypertrophy by electrocardiography or echocardiography, history of

Figure 1. CONSORT Diagrams



Atenolol status at 1 month for the in-trial (A) and in-trial plus posttrial (B) cohorts. CMS indicates Centers for Medicare & Medicaid Services; VA, Veterans Affairs.

type 2 diabetes, current cigarette smoking, and low high-density lipoprotein cholesterol level. Exclusion criteria included myocardial infarction, stroke, or angina pectoris within 6 months of study entry; symptomatic heart failure or ejection fraction less than 35%; creatinine level greater than 2 mg/dL (to convert to micromoles per liter, multiply by 88.4); and systolic blood pressure higher than 180 mm Hg or diastolic blood pressure higher than 110 mm Hg on 2 separate readings during screening.[21]

Medications

The step 1 study medications (chlorthalidone, 12.5-25 mg; amlodipine, 2.5-10 mg; and lisinopril, 10-40 mg) were formulated to look alike so that the identity of each agent was double-masked. The doses were titrated to achieve a blood pressure lower than 140/90 mm Hg. If goal blood pressure was not achieved using the maximum tolerated dose, open-label step 2 (reserpine, clonidine, or atenolol) or step 3 (hydralazine) medications could be added.

Recruitment and Follow-up

Recruitment was from February 1, 1994, through January 31, 1998; in-trial follow-up ended March 31, 2002. The mean (SD) follow-up was 4.9 (1.5) years. Posttrial follow-up was conducted through the end of 2006, using passive surveillance via national databases.[22]

Hip and Pelvic Fracture Cohorts

Fracture data were ascertained through the Centers for Medicare & Medicaid Services and Veterans Affairs (VA) hospitalization data from February 1, 1994, through December 31, 2006, for beneficiaries with valid Medicare or Social Security identifiers. Participants younger than 65 years at randomization enrolled by non-VA clinics and participants from Canada were not included because they would not have had continuous coverage in either data source. The VA data files were not available for the posttrial follow-up (2002-2006); therefore, the posttrial cohort was limited to US citizens with Medicare Part A insurance at randomization (**Figure 1**). Hospitalized hip and pelvic fractures (*International Classification of Diseases, Ninth Revision*, codes 820.x and 808.x, respectively) were chosen as end points because they are almost always associated with hospitalization. Such ascertainment results in less underestimation of hip fracture incidence than methods based on self-report.[23] For each participant, the time to first fracture was calculated for the maximal period of follow-up from baseline. For sensitivity analyses, the incidence of fractures was calculated beginning 1 year after study enrollment.

Statistical Analysis

Data are summarized as means (SDs) for continuous variables and numbers (percentages) of study participants for categorical variables. Baseline characteristics were compared across the treatment groups using 2-tailed, unpaired *t* tests for continuous variables and χ^2 contingency table analyses for categorical variables.

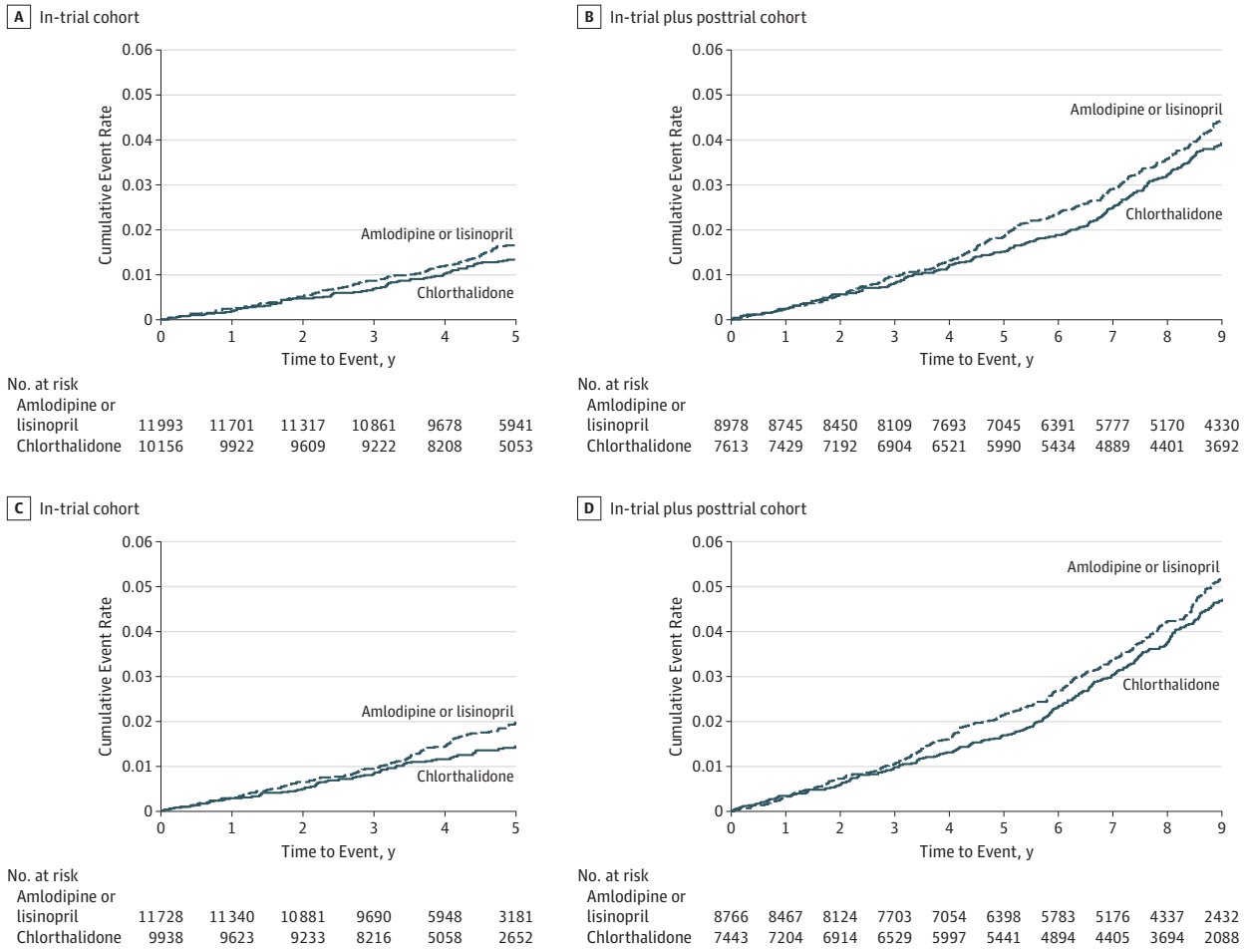
Atenolol use was not ascertained at baseline. Because participants who were already taking atenolol at baseline were allowed to continue to take atenolol and atenolol was a step 2 drug, participants taking atenolol at the first follow-up visit (1 month) were assumed to be taking atenolol at baseline.

The estimated glomerular filtration rate (eGFR) was measured using the Modification of Diet in Renal Disease Study and the Chronic Kidney Disease Epidemiology Collaboration equations.[24] Both estimations were used because outcomes vary, and we wished to capture any possible diminished renal function (eGFR <60 mL/min/1.73 m^2).

Outcomes analysis used an intention-to-treat approach. Fracture rates and graphs used the Kaplan-Meier method. The Cox proportional hazards regression model was used to determine hazard ratios (HRs) and 95% CIs. Individuals were censored for outcomes if they died, had no outcome in the database by the end of the study, or were lost to follow-up. Proportional hazards were tested by including a time × treatment variable in the Cox proportional hazards regression models and found to hold. Adjusted Cox proportional hazards regression models included age, race, sex, diabetes, eGFR, prevalent CVD, body mass index, and smoking. For the primary analyses, we combined those separately assigned to amlodipine and lisinopril into 1 group for greater statistical power. Separate comparisons of amlodipine and lisinopril to chlorthalidone were conducted as secondary analyses.

Heterogeneity of treatment effects on outcomes was examined using treatment-variable interaction terms in Cox pro-

Figure 2. Kaplan-Meier Curves for Hip and Pelvic Fractures



Initial curves for the in-trial (A) and in-trial plus posttrial (B) cohorts and curves from year 1 onward after randomization for the in-trial (C) and in-trial plus posttrial (D) cohorts. For the initial curves (A and B), in the in-trial cohort, the unadjusted hazard ratio (HR) was 0.79 (95% CI, 0.63-0.97) and the adjusted HR was 0.79 (95% CI, 0.63-0.98) for chlorthalidone vs amlodipine or lisinopril; in the in-trial plus posttrial cohorts, the unadjusted HR was 0.87 (95% CI, 0.74-1.02) and the adjusted HR was 0.87 (95% CI, 0.74-1.03) for chlorthalidone vs amlodipine or lisinopril. For the curves from year 1 onward after randomization (C and D), in the in-trial cohort, the unadjusted hazard ratio (HR) was 0.78 (95% CI, 0.62-0.98) and the adjusted HR was 0.77 (95% CI, 0.60-0.98) for chlorthalidone vs amlodipine or lisinopril; in the in-trial plus posttrial cohorts, the unadjusted HR was 0.88 (95% CI, 0.75-1.03) and the adjusted HR was 0.87 (95% CI, 0.73-1.03) for chlorthalidone vs amlodipine or lisinopril.

portional hazards regression models, with $P < .05$ indicating statistical significance. Heterogeneity was assessed for age, race, sex, diabetes, eGFR, incident and prevalent CVD, body mass index, smoking, and (for females) hormone replacement therapy. Given the many subgroup and interaction analyses performed, statistical significance at the $P < .05$ level should be interpreted with caution. All statistical analyses were performed using STATA software, version 13 or 14 (StataCorp).

Results

A total of 22 180 participants (mean [SD] age, 70.4 [6.7] years; 43.0% female; and 49.9% white non-Hispanic, 31.2% African American, and 19.1% other ethnic groups) were followed up for as long as 8 years (mean [SD], 4.9 [1.5] years) during masked therapy. After trial completion, 16 622 participants for whom claims data were available were followed up for as long as 5 additional years (mean [SD] total follow-up, 7.8 [3.1] years). The in-trial cohort consisted of participants randomized to chlorthalidone, amlodipine, or lisinopril, with or without atenolol at month 1 of follow-up from baseline (Figure 1A). Of 33 357 participants, 22 180 (66.5%) were in the Medicare or the VA system databases. Details of the cohort (n = 16 622) with in-trial and posttrial follow-up are shown in Figure 1B. Baseline characteristics of the 2 cohorts are given in eTable 1 and eTable 2 in the Supplement. The groups were equally balanced in all aspects except that in-trial participants randomized to receive chlorthalidone had more baseline CHD than the amlodipine and lisinopril groups (29.3% vs 27.8%, $P < .05$). **Figure 2** shows the cumulative fracture rates for both cohorts.

Table. Mean (SD) Hip or Pelvic Fracture Rates per 100 Person-years From Baseline Onward During the In-Trial Period[a]

Rate	Chlorthalidone (n = 10 174)	Amlodipine or Lisinopril (n = 12 006)	Total (N = 22 180)
No. of hip or pelvic fractures	135	203	338
Unadjusted rate			
Year 1	0.19 (0.04)	0.23 (0.04)	0.21 (0.03)
Year 2	0.47 (0.07)	0.51 (0.07)	0.50 (0.05)
Year 3	0.68 (0.08)	0.87 (0.09)	0.78 (0.06)
Year 4	1.02 (0.10)	1.18 (0.10)	1.11 (0.07)
Year 5	1.33 (0.12)	1.65 (0.13)	1.50 (0.09)
Age-adjusted rate			
Year 1	0.12 (0.03)	0.17 (0.03)	0.15 (0.02)
Year 2	0.30 (0.04)	0.39 (0.05)	0.35 (0.03)
Year 3	0.44 (0.05)	0.67 (0.07)	0.56 (0.04)
Year 4	0.68 (0.07)	0.92 (0.08)	0.81 (0.05)
Year 5	0.90 (0.08)	1.30 (0.10)	1.11 (0.07)
Age- and sex-adjusted rate			
Year 1	0.12 (0.03)	0.17 (0.03)	0.14 (0.02)
Year 2	0.30 (0.04)	0.38 (0.05)	0.34 (0.03)
Year 3	0.43 (0.05)	0.64 (0.06)	0.54 (0.04)
Year 4	0.66 (0.07)	0.88 (0.08)	0.78 (0.05)
Year 5	0.88 (0.08)	1.24 (0.09)	1.07 (0.06)
Age-, sex-, and race-adjusted rate			
Year 1	0.11 (0.03)	0.16 (0.03)	0.13 (0.02)
Year 2	0.28 (0.04)	0.35 (0.05)	0.32 (0.03)
Year 3	0.40 (0.05)	0.60 (0.06)	0.51 (0.04)
Year 4	0.62 (0.06)	0.83 (0.07)	0.73 (0.05)
Year 5	0.82 (0.08)	1.17 (0.09)	1.01 (0.06)

[a] The hazard ratios (95% CIs) for taking chlorthalidone vs not taking chlorthalidone are as follows: unadjusted rate, 0.78 (0.63-0.97); age-adjusted rate, 0.79 (0.63-0.98); age- and sex-adjusted rate, 0.78 (0.63-0.97); and age-, sex-, and race-adjusted rate, 0.78 (0.63-0.97).

In-Trial Cohort

Thirty-four participants had pelvic fractures and 307 participants had hip fractures during the in-trial period (mean [SD] follow-up, 4.9 [1.5] years). Three of these individuals had both hip and pelvic fractures. Cumulative fracture rates and HRs are given in the **Table** and Figure 2A. In unadjusted analyses, participants randomized to receive chlorthalidone had significantly decreased risk (HR, 0.78; 95% CI, 0.63-0.97; $P = .03$) of fractures compared with those randomized to receive lisinopril or amlodipine. The increased risk appeared by the second year after randomization for those taking amlodipine or lisinopril. Similar results were noted after adjustment for demographic and clinical variables (HR, 0.79; 95% CI, 0.63-0.98; $P = .04$). Similar trends were found when chlorthalidone use was compared with lisinopril or amlodipine use separately (eFigure 1 in the Supplement). Chlorthalidone use was associated with a significantly lower risk of fracture compared with lisinopril use (HR, 0.75; 95% CI, 0.58-0.98; $P = .04$), whereas the risk with amlodipine use was not statistically significant (HR, 0.82; 95% CI, 0.63-1.08; $P = .15$).

The potential effect of atenolol use on fracture risk in participants taking chlorthalidone during the in-trial period is presented in eTable 3 and eFigure 2 in the Supplement. No significant difference was found between those taking or not taking atenolol. The unadjusted HR for atenolol users was 1.43 (95% CI, 0.67-3.07). Adjustment for demographic and clinical variables marginally changed this estimate (HR, 1.29; 95% CI, 0.56-2.95).

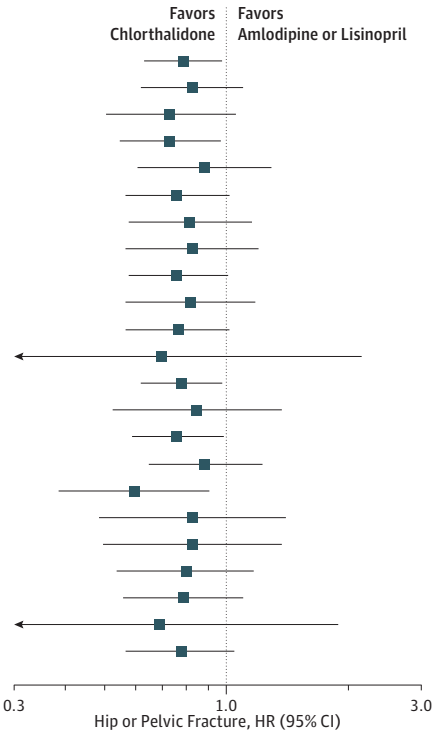
Fully adjusted hip and pelvic fracture HRs, stratified by selected variables, are shown for the in-trial cohort in **Figure 3** and eFigure 3 in the Supplement. In all instances, use of chlorthalidone was associated with a lower risk of fracture than amlodipine or lisinopril. In several instances, the use of chlorthalidone was associated with a significantly lower risk (eGFR ≥60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease formula, age ≥65 years, race other than black, and overweight). Interaction terms were not statistically significant (with P values ranging from .16 to .99). Similar findings were present when lisinopril or amlodipine use vs chlorthalidone use was examined separately (eFigure 3 in the Supplement), with a higher fracture risk in more subgroups treated with lisinopril (Modification of Diet in Renal Disease eGFR >60 mL/min/1.73 m^2, prevalent CVD, male sex, age >65 years, race other than black) compared with amlodipine (overweight).

Cohort With In-Trial and Posttrial Follow-up

Seventy pelvic and 576 hip fractures occurred in the cohort with in-trial and posttrial follow-up. Cumulative fracture rates are shown in Figure 2B. The fracture rates were somewhat higher

Figure 3. Adjusted In-Trial Hazard Ratios for Hip or Pelvic Fracture in Those Randomized to Receive Chlorthalidone Compared With Amlodipine or Lisinopril

Demographic Characteristic	HR (95% CI)
Total	0.79 (0.63-0.98)
No DM	0.83 (0.62-1.10)
DM	0.73 (0.51-1.06)
Baseline MDRD eGFR ≥60 mL/min/1.73 m^2	0.73 (0.55-0.97)
Baseline MDRD eGFR <60 mL/min/1.73 m^2	0.89 (0.61-1.29)
Baseline CKD eGFR ≥60 mL/min/1.73 m^2	0.76 (0.57-1.02)
Baseline CKD eGFR <60 mL/min/1.73 m^2	0.82 (0.58-1.16)
No CVD	0.83 (0.57-1.20)
Prevalent CVD	0.76 (0.58-1.01)
Male	0.82 (0.57-1.18)
Female	0.77 (0.57-1.02)
Age <65 y	0.70 (0.23-2.15)
Age ≥65 y	0.78 (0.62-0.98)
Black	0.85 (0.53-1.37)
Non-black	0.76 (0.59-0.99)
Healthy weight	0.89 (0.65-1.23)
Overweight	0.60 (0.39-0.91)
Obese	0.83 (0.49-1.40)
Current smoker	0.83 (0.50-1.37)
Former smoker	0.80 (0.54-1.17)
Never smoked	0.79 (0.56-1.10)
Estrogen	0.69 (0.25-1.88)
No estrogen	0.78 (0.57-1.05)



Hazards ratios (HRs) were adjusted for age, race, sex, diabetes, baseline estimated glomerular filtration rate (eGFR), prevalent cardiovascular disease (CVD), body mass index, and smoking. For estrogen, analyses are for women only. CKD indicates chronic kidney disease; DM, diabetes mellitus; and MDRD, Modification of Diet in Renal Disease.

than in the in-trial cohort, likely because of the older age of the cohort with extended follow-up. No significant difference was found in the risk of fractures between those randomized to receive chlorthalidone vs those randomized to receive amlodipine or lisinopril (unadjusted HR, 0.87; 95% CI, 0.74-1.02; P = .09; adjusted HR, 0.87; 95% CI, 0.74-1.03; P = .10), although users of chlorthalidone had persistently nonsignificantly lower risk after year 3 of follow-up. When fracture risk was examined by amlodipine or lisinopril use vs chlorthalidone use separately (eFigure 1 in the Supplement), no significant differences were found between use of lisinopril or amlodipine vs chlorthalidone use (chlorthalidone vs amlodipine: unadjusted HR, 0.85; 95% CI, 0.70-1.02; P = .08; adjusted HR, 0.87; 95% CI, 0.71-1.09; P = .16; chlorthalidone vs lisinopril: unadjusted HR, 0.90; 95% CI, 0.75-1.08; P = .28; adjusted HR, 0.87; 95% CI, 0.71-1.09; P = .17), although chlorthalidone use was associated with a lower risk of fracture.

Sensitivity Analyses

Analyses were repeated beginning 1 year after randomization to gauge the effects of the medications on fracture risk after trial participants had been exposed to the bone effects of the medications for 1 year. In the in-trial cohort, 21 721 (65%) of the 33 357 participants in the Medicare or VA system databases survived 1 year after randomization. There were 16 263 with in-trial and posttrial follow-up.

During the in-trial period (mean [SD] follow-up, 3.8 [1.6] years), 32 participants had a pelvic fracture and 266 had a hip fracture. In the cohort with in-trial and posttrial follow-up, 69 pelvic and 545 hip fractures occurred during the in-trial and posttrial periods. The in-trial and the in-trial plus posttrial results 1 year after randomization (Figure 2C and D) were similar to the in-trial and in-trial plus posttrial results from the time of randomization (Figure 2A and B).

Discussion

This post hoc analysis of an older cohort randomly assigned to 3 classes of first-step antihypertensive medication has 2 main findings. First, the risk of hip and pelvic fractures during in-trial follow-up was lowest in participants assigned to first-step therapy with chlorthalidone compared with amlodipine or lisinopril. This finding was consistent in all subgroup comparisons. Similar results were obtained in sensitivity analyses, where the first year of follow-up after randomization was excluded. To our knowledge, this analysis provides the first randomized comparison of different antihypertensive medications on risk of hip or pelvic fractures. Consistent with our findings, a meta-analysis[3] of 21 case-control and cohort studies concluded that treatment with thiazide diuretics was associated with a 24% lower risk of hip fracture compared with other antihypertensive agents (HR, 0.76; 95% CI, 0.64-0.89).

Second, analyses that included in-trial and posttrial follow-up yielded a fracture risk that was no longer significantly different between the treatment groups, albeit it was still numerically lowest in the chlorthalidone group. Our analyses based on posttrial and in-trial experience were not based on a

randomized comparison and thus are subject to bias. Moreover, during the posttrial period, the choice of blood pressure medication was no longer constrained by the study protocol; therefore, those originally randomized to receive chlorthalidone might have stopped using this medication and nonchlorthalidone users might have begun to take a thiazide diuretic. A population study[25] found that thiazide diuretic use increased in the United States after publication of the ALLHAT results. Despite these caveats, participants randomized to receive chlorthalidone during the in-trial period continued to have a lower point estimate of fracture risk 5 years after study completion, suggesting (but not proving) a legacy effect. Such a finding is at odds with 2 other studies.[18,26] In a study of healthy women early in menopause,[26] use of a thiazide diuretic for 2 years prevented loss of bone mineral density (BMD) in the forearm compared with placebo. One year after the thiazide use was stopped, there was no difference in BMD compared with the placebo group, suggesting rapid loss of the beneficial effect of the diuretic. The Rotterdam study[18] reported that the presumed hip fracture protective effect of thiazides disappeared 4 months after discontinuation of diuretic therapy.

When we examined the in-trial fracture risk in users of lisinopril and amlodipine separately, we found a significantly higher risk in those randomized to receive lisinopril but not amlodipine compared with chlorthalidone. This finding contradicts the positive effects that ACEis are believed to exert on bone physiologic mechanisms[10] but is consistent with several clinical studies.[12-15,27] A 4-year observational study[27] from Hong Kong found that continuous use of ACEis compared with nonuse was associated with greater BMD loss in the total hip and femoral neck in women. In a prospective cohort study[12] of 5995 older men from the Osteoporotic Fractures in Men Study, with 4.6 years of follow-up, continuous use of ACEis compared with nonuse was associated with a small but significantly higher loss of BMD in the trochanter and total hip. Increased BMD loss with ACEi use vs nonuse was noted in a Japanese cohort.[13] In a study of Medicare data,[14] the number of hip fractures was approximately 14% higher in users of ACEis compared with thiazide diuretics, although the HR was not statistically significant. In the Study of Women's Health Across the Nation,[15] thiazide use was associated with less annualized BMD loss compared with nonusers and compared with ACEis and β-blockers. Given these results and the widespread use of ACEis for the treatment of hypertension in older adults, our finding has potentially important public health implications. However, a higher risk of fracture or lower BMD in ACEi users has not been a universal finding, and some studies[10,11] report a protective effect of renin angiotensin blockade.

In our study, the β-blocker atenolol did not seem to act synergistically with chlorthalidone to yield a lower fracture risk. In fact, use of atenolol together with chlorthalidone was associated with a nonsignificantly increased risk of fracture compared with use of chlorthalidone alone. Given that atenolol was used as an add-on medication in ALLHAT, this finding should be viewed with a great deal of caution.

This study has important strengths. We were able to examine treatment effects for an extended period. Our cohort was large and well characterized, allowing adjustment for variables that affect bone health. Our sample was based on participants who had been randomized to their treatment group, minimizing differences between the treatment groups.

Limitations

Study weaknesses should also be acknowledged. First, analyses, although performed in a randomized setting, were conducted post hoc, and results are subject to unmeasured bias.

Second, participation in ALLHAT excluded several groups of participants at high risk for fracture, such as those with active coronary artery disease and heart failure[10,28] and chronic kidney disease.[29] Our results cannot be extrapolated to these groups. In addition, as in many large trials, only variables that were important to the primary goal of the study were collected; thus, we lacked covariates such as menstrual history (women), testosterone levels (men), history of falls (a proximate event in most hip and pelvic fractures), and bisphosphonate use. We note that alendronate, the first approved bisphosphonate, was approved by the US Food and Drug Administration in late 1995, approximately 18 months after the onset of ALLHAT. It would have become available in the market 6 months later at the earliest. Therefore, bisphosphonate use would not have influenced the early in-trial results of ALLHAT. Moreover, the use of bisphosphonates became common only in the early 2000s, after the release of several large fracture trials.[30] Thus, it is unlikely that the in-trial fracture rate was strongly influenced by the use of these agents. In addition, it is unlikely that bisphosphonate use would differ by randomized treatment arm.

Third, we relied on databases (rather than medical records) to ascertain fracture occurrence. Although this approach is highly accurate for diagnosing fractures,[23] participants eligible for Medicare who were enrolled in managed care would not have hospitalizations recorded with Medicare, thereby lowering the number of participants with fractures. In ALLHAT, approximately 20% of Medicare eligible patients were in managed care at some point during follow-up and thus were not eligible to have hospitalization records in the database; 8% (40% of participants with managed care indicators) did not have such indicators in the CMS database until the last 2 years of posttrial follow-up (2005 and 2006).

Fourth, although randomization was generally well maintained during the trial period, there was crossover of medication use.[17] Among all participants, 80.5% of the chlorthalidone, 80.4% of the amlodipine, and 72.6% of the lisinopril groups were taking their assigned medications (or one in an equivalent class) at their 5-year follow-up visit. Among all participants, 9.0% of the chlorthalidone group were taking a CCB or an ACEi without a diuretic at 5 years; 23.5% of the amlodipine group and 24.2% of the lisinopril group were taking a diuretic with or without their assigned study medications at 5 years. Such crossover would tend to decrease differences in fracture outcomes between medication classes.

Conclusions

This secondary analysis of a randomized clinical trial confirms previous observational reports that use of thiazide-

type diuretics is associated with significantly lower risk of hip and pelvic fractures compared with treatment with an ACEi or a CCB. This effect is consistently observed in a variety of subgroups and appears to last for several years.

ARTICLE INFORMATION

Accepted for Publication: September 15, 2016.

Published Online: November 21, 2016. doi:10.1001/jamainternmed.2016.6821

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Conflict of Interest Disclosures: Dr Cushman reports receiving honoraria from Takeda. Dr Oparil reports receiving honoraria from Daiichi Sankyo and Novartis. No other disclosures were reported.

Funding/Support: This research was supported by contracts NO1-HC-35130 and HHSN268201100036C from the National Heart, Lung, and Blood Institute. The ALLHAT investigators acknowledge contributions of study medications supplied by Pfizer Inc (amlodipine and doxazosin), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin) and financial support provided by Pfizer Inc. No specific funding was allocated for the work presented in this article.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

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Special Recognition: Special recognition is due to 3 ALLHAT leaders who died after making very significant contributions to initiating the trial and overseeing most of its course: Richard Carleton, MD, Chairman of the Data and Safety Monitoring Board (1994-2000); H. Mitchell Perry Jr, MD, member of the Steering Committee and Deputy Physician Coordinator for Region 1 (1994-2001); and Peter Frommer, MD, NHLBI Deputy Director Emeritus, advisor to the Project Officers, and liaison to participating pharmaceutical companies (1993-2002).

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Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official positions of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services.

Additional Contributions: Kara Elam, MS, The University of Texas School of Public Health, provided early editorial assistance in the preparation of the manuscript and was compensated for her work as an employee of the Coordinating Center.

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Supplementary Online Content

Puttnam R, Davis BR, Pressel SL, et al; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Collaborative Research Group. Association of 3 different antihypertensive medications with hip and pelvic fracture risk in older adults: secondary analysis of a randomized clinical trial. *JAMA Intern Med.* Published online November 21, 2016. doi:10.1001/jamainternmed.2016.6821

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline Characteristics for the In-Trial Cohort

	Chlorthalidone	Amlodipine/Lisinopril	Total
N	10174	12006	22180
Age – mean (sd) years	70.4 (6.7)	70.4 (6.8)	70.4 (6.7)
55-64 – n (%)	1531 (15.1)	1798 (15.0)	3329 (15.0)
65+ - n (%)	8643 (85.0)	10208 (85.0)	18851 (85.0)
Female – n (%)	4413 (43.4)	5118 (42.6)	9531 (43.0)
Ethnicity			
White non-Hispanic – n (%)	5072 (49.9)	5996 (49.9)	11068 (49.9)
Black non-Hispanic – n (%)	3169 (31.2)	3742 (31.2)	6911 (31.2)
White Hispanic – n (%)	1204 (11.8)	1432 (11.9)	2636 (11.9)
Black Hispanic – n (%)	311 (3.1)	371 (3.1)	682 (3.1)
Other n (%)	418 (4.1)	465 (3.9)	883 (4.0)
Education, mean (sd) years	10.7 (4.1)	10.7 (4.1)	10.7 (4.1)
Receiving antihypertensive treatment – n (%)	9264 (91.1)	10969 (91.4)	20233 (91.2)
Blood pressure – mean (sd) mm Hg			
SBP	146.6 (15.8)	146.6 (15.6)	146.6 (15.7)
DBP	82.8 (10.1)	82.7 (10.1)	82.8 (10.1)
Treated at baseline			
SBP	145.6 (15.8)	145.6 (15.6)	145.6 (15.7)
DBP	82.3 (10.1)	82.3 (10.0)	82.3 (10.0)
Untreated at baseline			
SBP	156.6 (11.6)	157.1 (11.7)	156.9 (11.7)
DBP	87.8 (9.0)	87.6 (9.5)	87.7 (9.3)
Eligibility risk factors—n (%):			
Current smoking	1915 (18.8)	2229 (18.6)	4144 (18.7)
Atherosclerotic CVD	5756 (56.6)	6673 (55.6)	12429 (56.0)
History of MI or stroke	2744 (27.0)	3125 (26.0)	5869 (26.5)
History of coronary revascularization	1510 (14.8)	1746 (14.5)	3256 (14.7)
Other ASCVD	2611 (25.7)	3083 (25.7)	5694 (25.7)
Major ST depression or T-wave inversion	1064 (10.6)	1247 (10.5)	2311 (10.5)
Diabetes †	4011 (42.5)	4785 (42.9)	8796 (42.7)
HDL-C < 35 mg/dL	1232 (12.1)	1462 (12.2)	2694 (12.2)
LVH by electrocardiogram	1702 (16.7)	2027 (16.9)	3729 (16.8)
LVH by echocardiogram	500 (5.0)	587 (5.0)	1087 (5.0)
History of CHD at baseline	2959 (29.3)	3305 (27.8)*	6264 (28.5)
Body mass index – mean (sd)	29.1 (5.8)	29.1 (5.8)	29.1 (5.8)
Medication use at baseline – n (%)			
Aspirin	3904 (38.4)	4704 (39.2)	8608 (38.8)
Estrogen supplementation– FEMALES ONLY	614 (13.9)	684 (13.4)	1298 (13.6)
Atenolol use at 1 month	398 (3.9)	452 (3.8)	850 (3.8)
Cholesterol– mean (sd, N)			
Total	214.6 (43.2, 9700)	214.3 (42.7, 11392)	214.4 (42.9, 21092)
HDL	46.7 (14.7, 9699)	46.8 (14.7, 11386)	46.7 (14.7, 21085)

LDL	135.2 (36.7, 9157)	135.0 (36.4, 10791)	135.1 (36.5, 19948)
Serum creatinine – mean (sd, N)	1.1 (0.3, 9751)	1.0 (0.3. 11446)	1.1 (0.3, 21197)
eGFR-–– mean (sd, N)			
Baseline --MDRD	74.9 (19.5, 9751)	75.3 (19.4, 11446)	75.1 (19.4, 21197)
Baseline – CKD-Epi	70.7 (17.6, 9751)	71.0 (17.5, 11446)	70.8 (17.6, 21197)
Lipid trial participants – n (%)	2423 (23.8)	2783 (23.2)	5206 (23.5)

Abbreviations: ASCVD, arteriosclerotic cardiovascular disease**;** CCVD, combined cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction

*$p < 0.05$

†History of diabetes OR fasting glucose 126+ OR non-fasting glucose 200+

eTable 2. Baseline Characteristics for the In-Trial Plus Posttrial Cohort

	Chlorthalidone	Amlodipine/Lisinopril	Total
N	7631	8991	16622
Age – mean (sd) years	71.3 (6.6)	71.4 (6.6)	71.4 (6.6)
55-64 – n (%)	656 (8.6)	782 (8.7)	1438 (8.7)
65+ - n (%)	6975 (91.4)	8209 (91.3)	15184 (91.4)
Female – n (%)	4362 (57.2)	5053 (56.2)	9415 (56.6)
Ethnicity			
White non-Hispanic – n (%)	3483 (45.6)	4069 (45.3)	7552 (45.4)
Black non-Hispanic – n (%)	2401 (31.5)	2837 (31.6)	5238 (31.5)
White Hispanic – n (%)	1108 (14.5)	1340 (14.9)	2448 (14.7)
Black Hispanic – n (%)	285 (3.7)	331 (3.7)	616 (3.7)
Other n (%)	354 (4.6)	414 (4.6)	768 (4.6)
Education, mean (sd) years	10.4 (4.2)	10.4 (4.3)	10.4 (4.2)
Receiving antihypertensive treatment – n (%)	6903 (90.5)	8194 (91.1)	15097 (90.8)
Blood pressure – mean (sd) mm Hg			
SBP	147.4 (15.6)	147.4 (15.5)	147.4 (15.5)
DBP	83.2 (10.1)	83.0 (10.1)	83.1 (10.1)
Treated at baseline			
SBP	146.4 (15.6)	146.4 (15.5)	146.4 (15.5)
DBP	82.7 (10.0)	82.5 (10.0)	82.6 (10.0)
Untreated at baseline			
SBP	157.0 (12.0)	157.6 (11.7)	157.3 (11.9)
DBP	88.1 (8.9)	88.0 (9.3)	88.1 (9.1)
Eligibility risk factors– n (%)			
Current smoking	1282 (16.8)	1493 (16.6)	2775 (16.7)
Atherosclerotic CVD	4339 (56.9)	5010 (55.7)	9349 (56.2)
History of MI or stroke	1923 (25.2)	2196 (24.4)	4119 (24.8)
History of coronary revascularization	1082 (14.2)	1230 (13.7)	2312 (13.9)
Other ASCVD	2086 (27.3)	2456 (27.3)	4542 (27.3)
Major ST depression or T-wave inversion	807 (10.7)	934 (10.5)	1741 (10.6)
Diabetes†	3031 (43.1)	3604 (43.5)	6635 (43.3)
HDL-C < 35 mg/dL	776 (10.2)	954 (10.6)	1730 (10.4)
LVH by electrocardiogram	1254 (16.4)	1458 (16.2)	2712 (16.3)
LVH by echocardiogram	414 (5.5)	499 (5.6)	913 (5.5)
History of CHD at baseline	2099 (27.7)	2383 (26.7)	4482 (27.1)
Body mass index – mean (sd)	29.1 (6.0)	29.2 (6.1)	29.2 (6.1)
Medication use at baseline – n (%)			
Aspirin	2683 (35.2)	3208 (35.7)	5891 (35.4)
Estrogen supplementation– FEMALES ONLY	597 (13.7)	661 (13.1)	1258 (13.4)
Atenolol use at 1 month	280 (3.7)	300 (3.3)	580 (3.5)
Cholesterol– mean (sd, N)			
Total	217.5 (44.1, 7239)	216.6 (43.6, 8480)	217.0 (43.9, 15719)
HDL	48.2 (15.0, 7238)	48.2 (14.9, 8476)	48.2 (14.9, 15714)

LDL	136.6 (37.5, 6865)	135.9 (36.9, 8051)	136.2 (37.2, 14916)
Serum creatinine – mean (sd, N)	1.0 (0.3, 7275)	1.0 (0.3, 8519)	1.0 (0.3. 15794)
eGFR– mean (sd, N)			
Baseline– MDRD	73.9 (19.8, 7275)	74.1 (19.5, 8519)	74.0 (19.6, 15794)
Baseline – CKD-Epi	69.7 (17.8, 7275)	69.8 (17.7, 8519)	69.8 (17.7, 15794)
Lipid trial participants – n (%)	1847 (24.2)	2092 (23.3)	3939 (23.7)

Abbreviations: ASCVD, arteriosclerotic cardiovascular disease**;** CCVD, combined cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; HDL high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction

† History of diabetes OR fasting glucose 126+ OR non-fasting glucose 200+

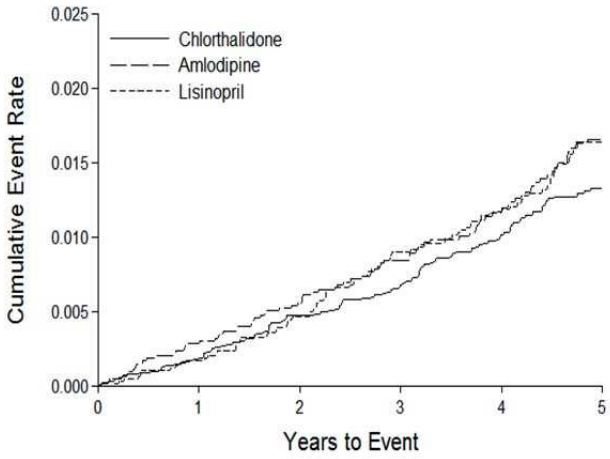
eTable 3. Hip or Pelvis Fracture Rates per 100 and Hazard Ratios From Baseline Onward During the In-Trial Period for Chlorthalidone Only With or Without Atenolol Use at 1 Month

	Total	Not on Atenolol at 1 month	On Atenolol at 1 month
N (denominator)	10174	9776	398
Hip or pelvic fractures			
Events	135	128	7
1-y rate	0.19 (0.04)	0.20 (0.05)	0.00 (-)
2-y rate	0.47 (0.07)	0.45 (0.07)	1.04 (0.52)
3-y rate	0.68 (0.08)	0.66 (0.08)	1.04 (0.52)
4-y rate	1.02 (0.10)	0.98 (0.10)	1.91 (0.72)
5-y rate	1.33 (0.12)	1.30 (0.12)	1.91 (0.72)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.43 (0.67-3.07)		
Age-Adjusted			
1-y rate	0.12 (0.03)	0.12 (0.03)	0.00 (-)
2-y rate	0.30 (0.04)	0.28 (0.04)	0.90 (0.45)
3-y rate	0.44 (0.05)	0.42 (0.05)	0.90 (0.45)
4-y rate	0.67 (0.07)	0.64 (0.07)	1.66 (0.63)
5-y rate	0.89 (0.08)	0.86 (0.08)	1.66 (0.63)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.67 (0.78-3.58)		
Age and sex-adjusted			
1-y rate	0.12 (0.03)	0.12 (0.03)	0.00 (-)
2-y rate	0.30 (0.04)	0.28 (0.04)	0.89 (0.44)
3-y rate	0.43 (0.05)	0.41 (0.05)	0.89 (0.44)
4-y rate	0.66 (0.07)	0.63 (0.07)	1.65 (0.62)
5-y rate	0.88 (0.08)	0.85 (0.08)	1.65 (0.62)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.66 (0.77-3.55)		

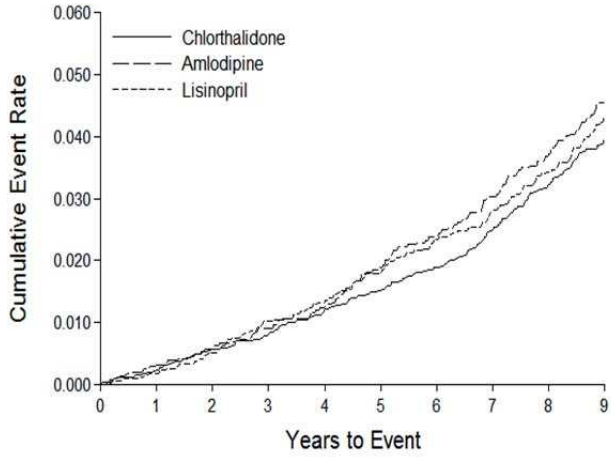
Age, sex, and race-adjusted			
1-y rate	0.11 (0.03)	0.11 (0.03)	0.00 (-)
2-y rate	0.28 (0.04)	0.26 (0.04)	0.88 (0.44)
3-y rate	0.40 (0.05)	0.39 (0.05)	0.88 (0.44)
4-y rate	0.62 (0.06)	0.59 (0.06)	1.61 (0.61)
5-y rate	0.82 (0.08)	0.80 (0.08)	1.61 (0.61)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.50 (0.70-3.22)		

eFigure 1. Kaplan-Meier Curves for Hip and Pelvic Fractures by the Three Primary Antihypertensive Medications Used in ALLHAT. Curves A and B are from the time of randomization during the in-trial and during the in-trial and posttrial periods. Curves C and D are from one year after randomization for the in-trial and the in-trial and posttrial periods.

A. In-trial cohort



B. In-trial plus post-trial cohort

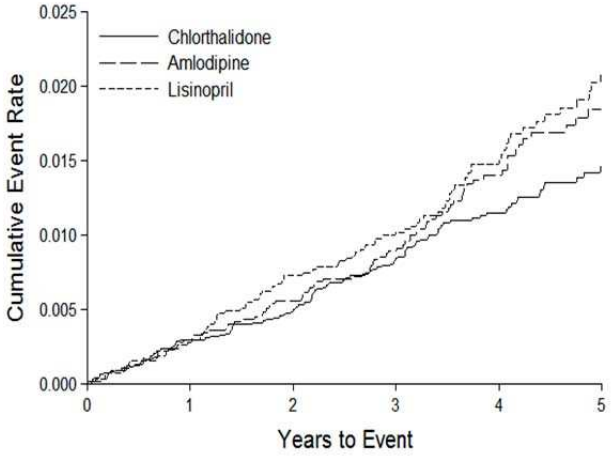


	Hazard Ratio (95% CI), *P*	Hazard Ratio (95% CI), *P*
Unadjusted	A/C = 1.27 (0.98 – 1.64), *P* = 0.071 L/C = 1.28 (0.99 – 1.66), *P* = 0.058	A/C = 1.18 (0.98 – 1.42), *P* = 0.078 L/C = 1.11 (0.92 – 1.34), *P* = 0.279
Adjusted*	A/C = 1.22 (0.93 – 1.59), *P* = 0.148 L/C = 1.33 (1.02 – 1.73), *P* = 0.036	A/C = 1.15 (0.95 – 1.40), *P* = 0.161 L/C = 1.15 (0.94 – 1.40), *P* = 0.171

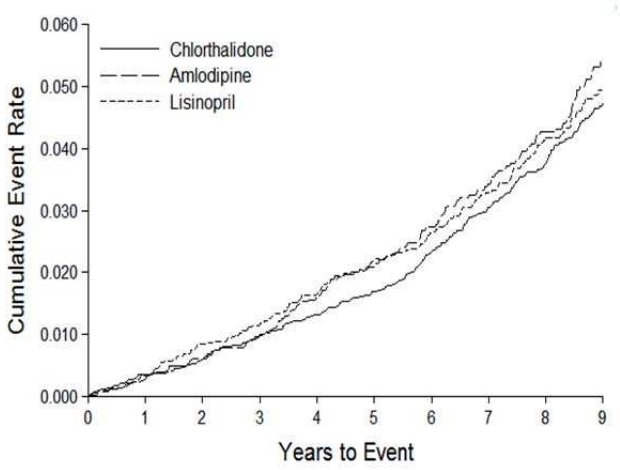
Abbreviations: A, amlodipine; C, chlorthalidone; L, lisinopril

*Adjusted for age, race, gender, diabetes, prevalent cardiovascular disease (CVD), baseline glomerular filtration rate (eGFR), body mass index (BMI) and smoking.

C. In-trial cohort



D. In-trial plus post-trial cohort

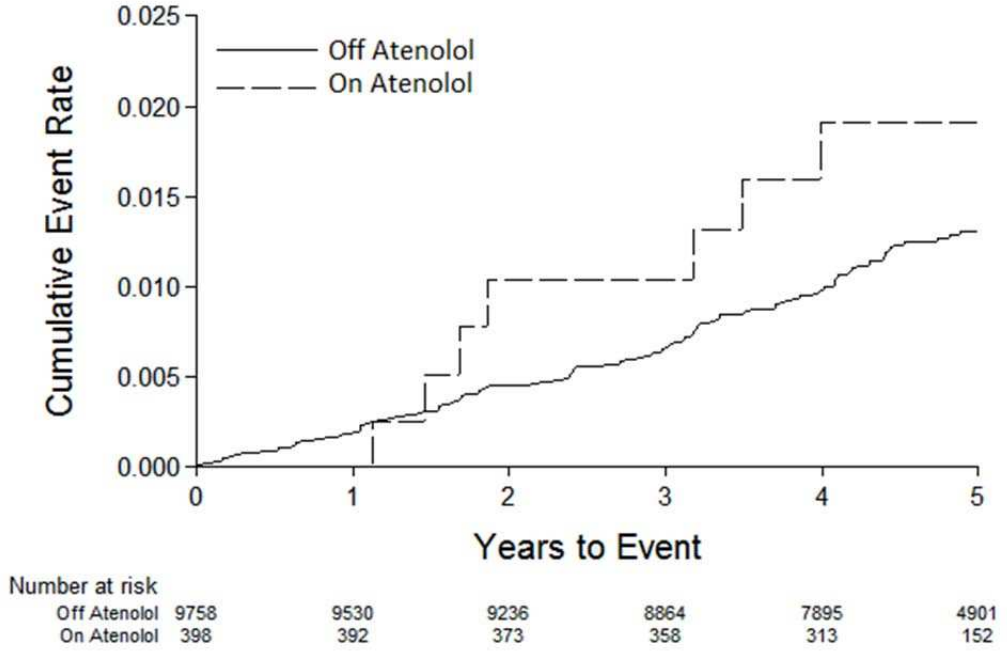


	Hazard ratio (95% CI), *P*	Hazard ratio (95% CI), *P*
Unadjusted	A/C = 1.23 (0.93 - 1.63), *P* = 0.14 L/C = 1.34 (1.02 - 1.76), *P* = 0.04	A/C = 1.16 (0.96 - 1.41), *P* = 0.12 L/C = 1.12 (0.92 - 1.36), *P* = 0.25
Adjusted*	A/C = 1.21 (0.91 - 1.62), *P* = 0.19 L/C = 1.39 (1.05 - 1.84), *P* = 0.02	A/C = 1.15 (0.94 - 1.40), *P* = 0.18 L/C = 1.16 (0.95 - 1.43), *P* = 0.15

Abbreviations: A, Amlodipine; C, chlorthalidone; L, Lisinopril

*Adjusted for age, race, gender, diabetes, baseline or at year 1 estimated glomerular filtration ratio (eGFR), incident at year 1 and prevalent cardiovascular disease, body mass index, and smoking.

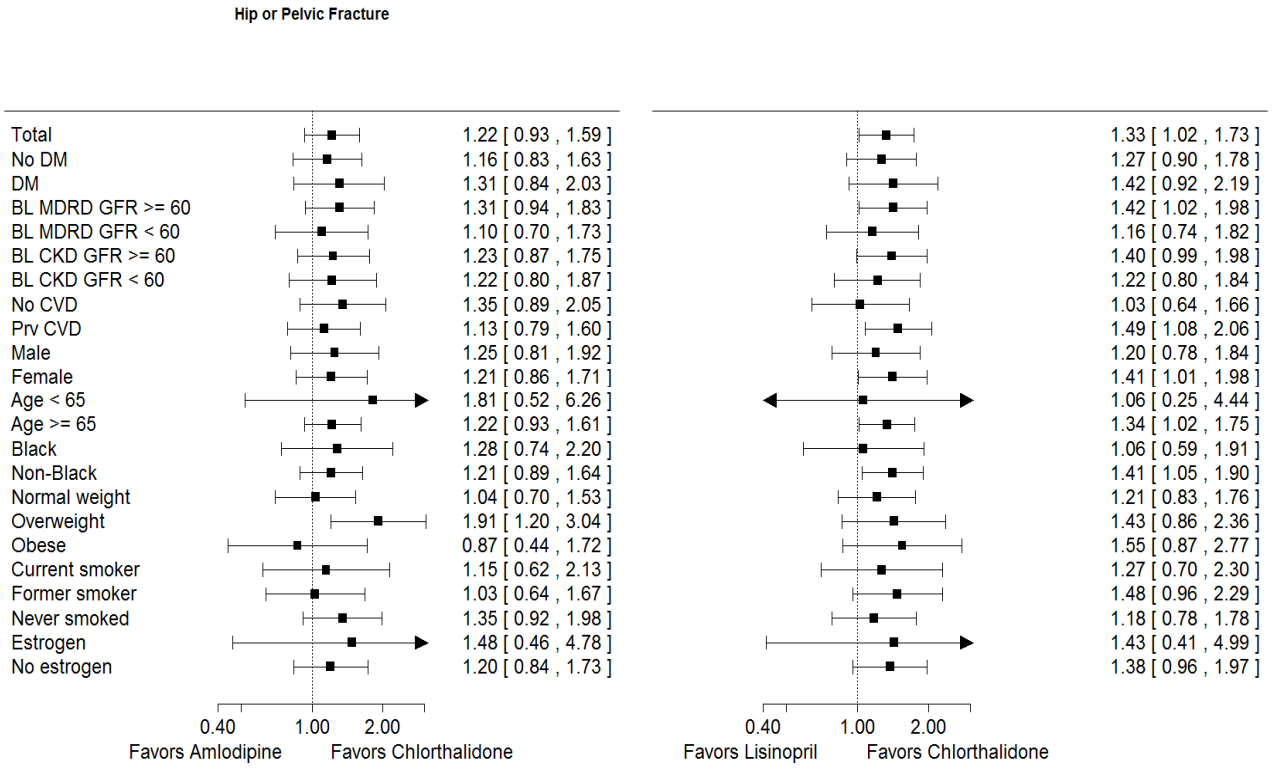
eFigure 2. Kaplan-Meier Curves for Hip and Pelvic Fractures for the In-Trial Cohort in the Chlorthalidone Group by Atenolol Use at 1 Month



	Hazard ratio (95% CI), *P*
Unadjusted	1.43 (0.67 – 3.07), *P* = 0.352
Adjusted*	1.29 (0.56 – 2.95), *P* = 0.548

*Adjusted for age, race, gender, diabetes, baseline estimated glomerular filtration ratio (eGFR), prevalent cardiovascular disease, body mass index, and smoking.

eFigure 3. Adjusted In-Trial Hazard Ratios for Hip or Pelvic Fracture in Those Randomized to Chlorthalidone Compared With Amlodipine or Chlothalidone Compared With Lisinopril, by Various Demographic and Health Characteristics[*†]



Abbreviations: BL, baseline; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; Prv, prevalent; Yr, year.

[*]Adjusted for age, race, gender, diabetes, baseline estimated glomerular filtration rate (eGFR), prevalent cardiovascular disease, body mass index (BMI) and smoking.

[†]For estrogen, women only.