

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.

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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-analysis³ 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 risk⁵ (possibly through β_2 -adrenergic blockade of receptors present on osteoclasts⁶), although a review article⁷ 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- κ B 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 study¹⁶ 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

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.

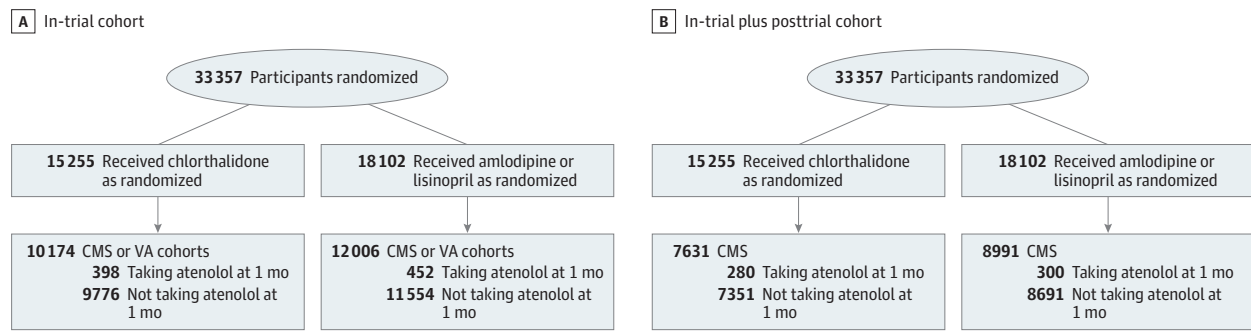
the cohort beginning 1 year after the onset of the study. Although randomization is not strictly maintained with this approach, this was done for 2 reasons: to allow for the effect of antihypertensive medications on bone to take place and to avoid including early fractures associated with falls related to use of new antihypertensive medications. Several studies have reported increased risk of falls (a proximate event in 90%-95% of hip fractures¹⁸) 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.

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 hos-

pitalization. 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.

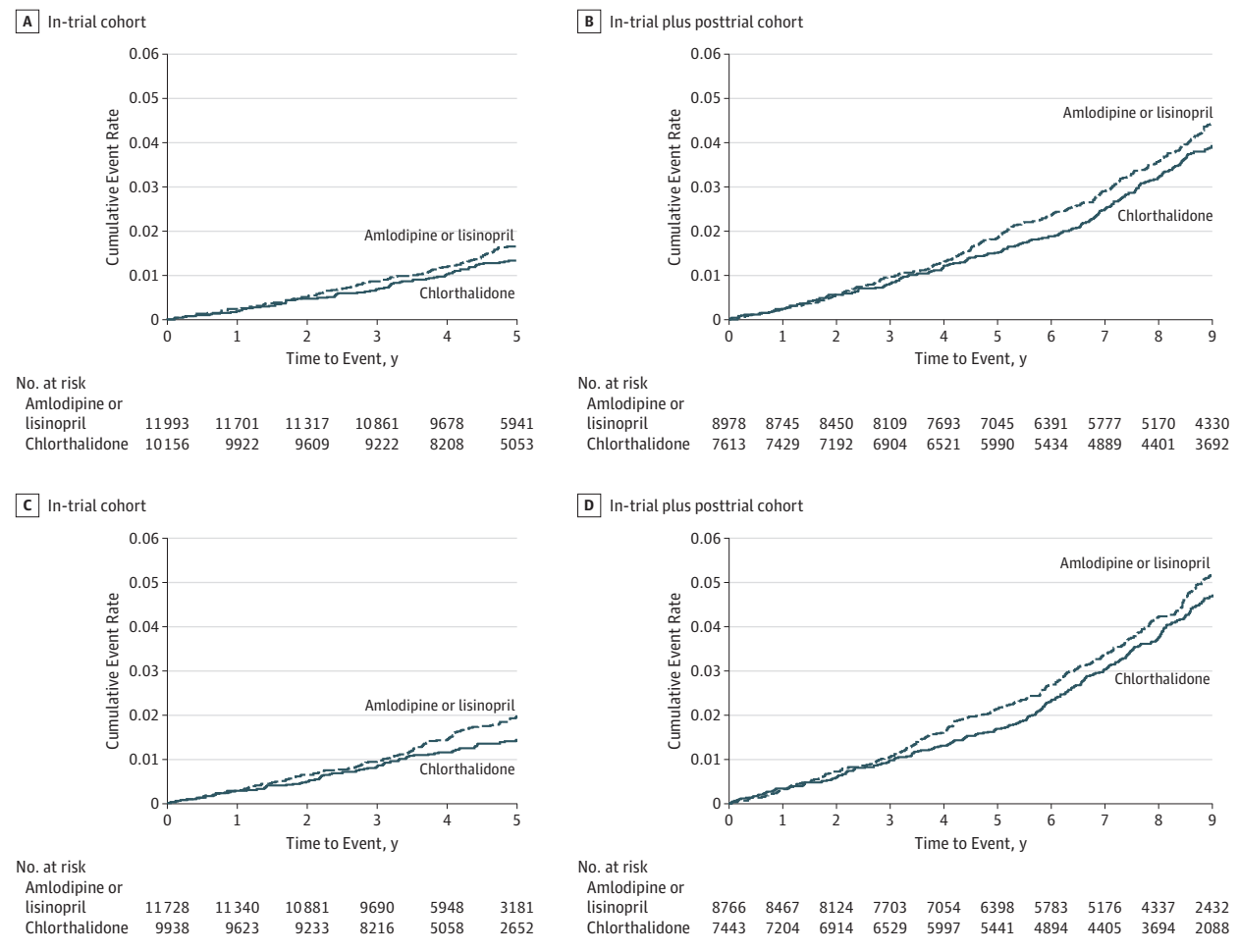
Atenolol use was not ascertained at baseline. Because participants who were already taking atenolol at baseline were allowed to continue to take atenolol and atenolol was a step 2 drug, participants taking atenolol at the first follow-up visit (1 month) were assumed to be taking atenolol at baseline.

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 m²).

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 \times 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 post-trial (B) cohorts and curves from year 1 onward after randomization for the in-trial (C) and in-trial plus post-trial (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 post-trial 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 post-trial 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 post-trial 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

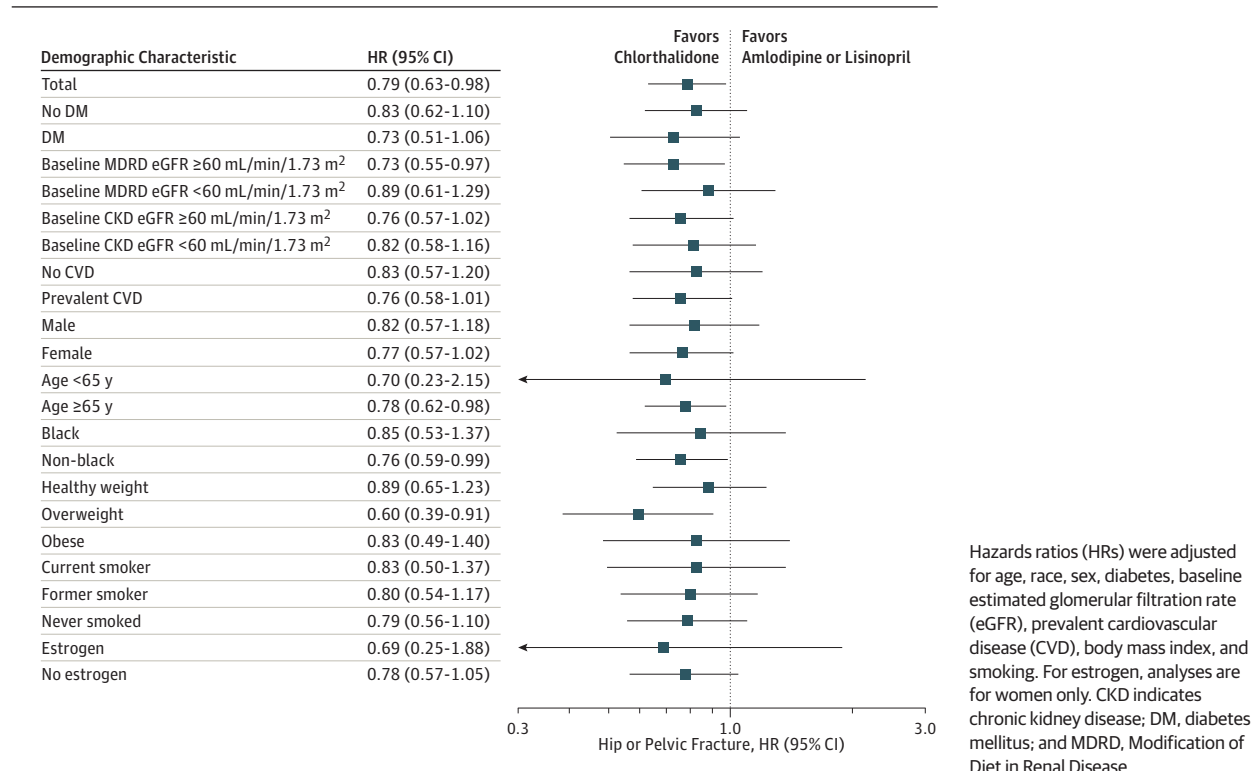
(95% CI, 0.67-3.07). Adjustment for demographic and clinical variables marginally changed this estimate (HR, 1.29; 95% CI, 0.56-2.95).

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 m² 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 m², 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



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-analysis³ 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 non-chlorthalidone users might have begun to take a thiazide diuretic. A population study²⁵ 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 study¹⁸ 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 mechanisms¹⁰ but is consistent with several clinical studies.^{12-15,27} A 4-year observational study²⁷ 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 study¹² 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 par-

ticipants 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.

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REFERENCES

- Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. *Calcif Tissue Int*. 2009;84(2):103-111.
- Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA; Study of Osteoporotic Fractures Research Group. High blood pressure and bone-mineral loss in elderly white women: a prospective study. *Lancet*. 1999;354(9183):971-975.
- Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. *Cochrane Database Syst Rev*. 2011;(10):CD005185.
- Lau KH, Song XD, Ochi M, Wergedal JE. Mitogenic action of hydrochlorothiazide on human osteoblasts in vitro: requirement for platelet-derived growth factor. *Calcif Tissue Int*. 1996;59(6):505-510.
- Pasco JA, Henry MJ, Sanders KM, Kotowicz MA, Seeman E, Nicholson GC; Geelong Osteoporosis Study. β -Adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone Miner Res*. 2004;19(1):19-24.
- Bonnet N, Benhamou CL, Malaval L, et al. Low dose beta-blocker prevents ovariectomy-induced bone loss in rats without affecting heart functions. *J Cell Physiol*. 2008;217(3):819-827.
- Reid IR, Gamble GD, Grey AB, et al. β -Blocker use, BMD, and fractures in the study of osteoporotic fractures. *J Bone Miner Res*. 2005;20(4):613-618.
- Nakagami H, Osako MK, Morishita R. Potential effect of angiotensin II receptor blockade in adipose tissue and bone. *Curr Pharm Des*. 2013;19(17):3049-3053.
- Shimizu H, Nakagami H, Osako MK, et al. Angiotensin II accelerates osteoporosis by activating osteoclasts. *FASEB J*. 2008;22(7):2465-2475.
- Ghosh M, Majumdar SR. Antihypertensive medications, bone mineral density, and fractures: a review of old cardiac drugs that provides new insights into osteoporosis. *Endocrine*. 2014;46(3):397-405.
- Rejnmark L, Vestergaard P, Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: a nationwide case-control study. *J Hypertens*. 2006;24(3):581-589.
- Kwok T, Leung J, Zhang YF, et al; Osteoporotic Fractures in Men (MrOS) Research Group. Does the use of ACE inhibitors or angiotensin receptor blockers affect bone loss in older men? *Osteoporos Int*. 2012;23(8):2159-2167.
- Masanari N, Fujiwara S, Nakata Y, Furukawa K, Kasagi F. Effect of angiotensin converting enzyme inhibitor and benzodiazepine intake on bone loss in older Japanese. *Hiroshima J Med Sci*. 2008;57(1):17-25.
- Solomon DH, Mogun H, Garneau K, Fischer MA. Risk of fractures in older adults using antihypertensive medications. *J Bone Miner Res*. 2011;26(7):1561-1567.
- Solomon DH, Ruppert K, Zhao Z, et al. Bone mineral density changes among women initiating blood pressure lowering drugs: a SWAN cohort study. *Osteoporos Int*. 2016;27(3):1181-1189.
- Halici Z, Borekci B, Ozdemir Y, Cadirci E, Suleyman H. Protective effects of amlodipine and lisdipine on ovariectomy-induced bone loss in rats. *Eur J Pharmacol*. 2008;579(1-3):241-245.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288(23):2981-2997.
- Schoofs MWCJ, van der Klift M, Hofman A, et al. Thiazide diuretics and the risk for hip fracture. *Ann Intern Med*. 2003;139(6):476-482.
- Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. *Arch Intern Med*. 2012;172(22):1739-1744.
- Gribbin J, Hubbard R, Gladman JRF, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: population-based case-control study. *Age Ageing*. 2010;39(5):592-597.
- Davis BR, Cutler JA, Gordon DJ, et al; ALLHAT Research Group. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens*. 1996;9(4, pt 1):342-360.
- Cushman WC, Davis BR, Pressel SL, et al; ALLHAT Collaborative Research Group. Mortality and morbidity during and after the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *J Clin Hypertens (Greenwich)*. 2012;14(1):20-31.
- Virning B, Durham SB, Folsom AR, Cerhan J. Linking the Iowa Women's Health Study cohort to Medicare data: linkage results and application to hip fracture. *Am J Epidemiol*. 2010;172(3):327-333.
- Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med*. 2012;156(11):785-795.
- Petitti DB, Xie F, Barzilay JI. Prescribing patterns for thiazide diuretics in a large health maintenance organization: relationship to participation as an ALLHAT clinical center. *Contemp Clin Trials*. 2006;27(5):397-403.
- Transbøl I, Christensen MS, Jensen GF, Christiansen C, McNair P. Thiazide for the postponement of postmenopausal bone loss. *Metabolism*. 1982;31(4):383-386.
- Zhang YF, Qin L, Leung PC, Kwok TC. The effect of angiotensin-converting enzyme inhibitor use on bone loss in elderly Chinese. *J Bone Miner Metab*. 2012;30(6):666-673.
- Gerber Y, Melton LJ III, McNallan SM, Jiang R, Weston SA, Roger VL. Cardiovascular and noncardiovascular disease associations with hip fractures. *Am J Med*. 2013;126(2):169.e19-169.e26.
- Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM. Hip fracture in patients with non-dialysis-requiring chronic kidney disease [published online May 4, 2016]. *J Bone Miner Res*. doi:10.1002/jbmr.2862
- Wysowski DK, Greene P. Trends in osteoporosis treatment with oral and intravenous bisphosphonates in the United States, 2002-2012. *Bone*. 2013;57(2):423-428.