Effect of Alendronate on Vascular Calcification in CKD Stages 3 and 4: A Pilot Randomized Controlled Trial

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Background: Vascular calcification contributes to cardiovascular disease in patients with chronic kidney disease (CKD). Few studies have addressed interventions to decrease vascular calcification; however, experimental studies report benefits of bisphosphonates. Recent studies of hemodialysis patients also suggest benefits of bisphosphonates on vascular calcification; however, no study exists in nondialysis patients with CKD.

Study Design: We conducted a randomized controlled trial to determine the effect of bisphosphonates on vascular calcification in patients with CKD.

Setting & Participants: 51 patients with CKD stages 3-4 were recruited from a hospital outpatient setting; 50 were treated with study medication.

Interventions: Patients were randomly assigned to either alendronate, 70 mg (n = 25), or matching placebo (n = 25), administered weekly.

Outcomes: The primary outcome was change in aortic vascular calcification after 18 months. Secondary outcomes included superficial femoral artery vascular calcification, arterial compliance, bone mineral density (BMD), renal function, and serum markers of mineral metabolism.

Measurements: At baseline and 12 and 18 months, computed tomography, pulse wave velocity using SphygmoCor (AtCor Medical, PWV Inc, www.atcormedical.com), and dual-energy x-ray absorptiometry were performed to measure vascular calcification, arterial compliance, and BMD, respectively. Analysis was by intention to treat, with a random-effect linear regression model to assess differences.

Results: 46 patients completed the study (24 alendronate, 22 placebo); baseline mean age was 63.1 ± 1.8 years, estimated glomerular filtration rate was 34.5 ± 1.4 mL/min/1.73 m^2, 59% had diabetes, and 65% were men. 91% had aortic vascular calcification at the start and 78% showed progression. At 18 months, there was no difference in vascular calcification progression with alendronate compared with placebo (adjusted difference, −24.2 Hounsfield units [95% CI, −77.0 to 28.6]; $P = 0.4$). There was an increase in lumbar spine BMD (T score difference, +0.3 [95% CI, 0.03-0.6]; $P = 0.04$) and a trend toward better pulse wave velocity (−1 m/s [95% CI, −2.1 to 0.1]; $P = 0.07$) with alendronate. Femoral BMD was similar between groups. There was a nonsignificant decrease in kidney function in patients on alendronate therapy compared with placebo (−1.2 mL/min/1.73 m^2 [95% CI, −4.0 to 1.7]).

Limitations: Small sample size and baseline differences, especially with aortic vascular calcification, may have diminished any potential difference between groups.

Conclusions: Unlike previous studies of hemodialysis patients, alendronate did not decrease the progression of vascular calcification compared with placebo in patients with CKD during 18 months.
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INDEX WORDS: Alendronate; bisphosphonates; bone mineral density; cardiovascular disease; chronic kidney disease; mineral metabolism; vascular calcification.

The leading cause of mortality in patients with chronic kidney disease (CKD) is cardiovascular disease (CVD),[1-4] and up to 45% of patients with CKD may die before receiving dialysis therapy or a transplant.[5] Although traditional cardiovascular risk factors are common, much of the CVD in patients with CKD may relate to nontraditional risk factors, such as vas-

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cular calcification and arterial stiffness.[6-8] Vascular calcification is an active process similar to osteogenesis,[9] with structures resembling bone, as well as diffuse matrix calcification, found in calcified vessels.[9-11] There is an inverse relationship between bone mineral density (BMD) and CVD, including vascular calcification, in both the general population and patients with CKD,[12-17] and the term CKD-MBD (CKD–mineral and bone disorder) recently was introduced to reflect the close associations of mineral metabolism with bone abnormalities, vascular calcification, consequences of fracture, CVD, and increased mortality.[18]

Because bone remodeling and vascular calcification are closely linked, there has been interest in applying therapeutic strategies that influence this interaction. Bisphosphonates are bone antiresorptive agents widely used to treat postmenopausal or glucocorticoid-induced osteoporosis and other conditions characterized by excessive osteoclastic bone resorption. Bisphosphonates closely resemble pyrophosphate compounds, binding strongly to hydroxyapatite in bone, and provide fracture protection for patients with osteoporosis.[19] There is a paucity of data about bisphosphonates in patients with CKD because studies of osteoporosis generally have excluded patients with significant CKD; however, bisphosphonates likely have a role in patients with less severe kidney impairment.[20,21] Experimental studies and recent clinical studies also have reported effects of bisphosphonates on decreasing the progression of extraosseous calcification,[22-28] and although the mechanism for vascular calcification inhibition is not completely clear, bisphosphonates potentially may be beneficial in patients with CKD by improving BMD and concurrently decreasing vascular calcification.

All clinical studies reporting benefits of bisphosphonates on vascular calcification have been in Japanese hemodialysis (HD) patients involving the use of etidronate,[25-28] and only 2 are randomized, but not placebo-controlled, studies.[26,27] No clinical study to date has addressed this issue in the nondialysis CKD population. The main aim of this study is to evaluate the effects of bisphosphonates on vascular calcification and arterial compliance in patients with CKD stages 3-4 in a randomized controlled trial.

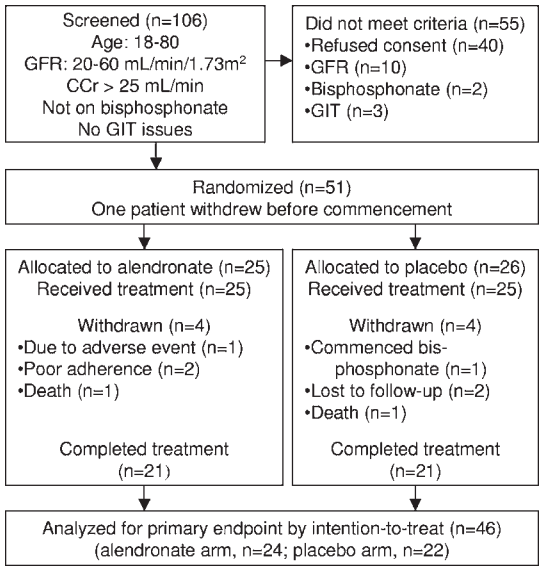

Figure 1. Patient disposition. Abbreviations: CCr, creatinine clearance; GFR, glomerular filtration rate; GIT, gastrointestinal tract.

METHODS

Study Participants

Fifty-one patients were recruited between January and June 2007 from outpatient clinics and private consulting rooms by nephrologists at Monash Medical Centre, Clayton, Australia (Fig 1). Inclusion criteria were age 18-80 years, patients willing to give informed consent, and those with decreased glomerular filtration rate (GFR) of 20-60 mL/min/1.73 m^2, estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[29] In addition, because alendronate is not recommended by the manufacturer for patients with creatinine clearance $<$35 mL/min, we elected to enroll only patients with creatinine clearance $>$25 mL/min. Exclusion criteria were patients already using bisphosphonates; on renal replacement therapy or scheduled to receive a kidney transplant within 12 months after recruitment; with active gastroesophageal reflux disease, peptic ulcer disease, or other serious gastrointestinal disorders; with a recent fracture (within the previous 3 months); and who were pregnant or planning to become pregnant (within 18 months after recruitment). The protocol was approved by the local ethics committee, and all patients gave written consent.

Study Protocol

Patients were randomly assigned in a 1:1 ratio to receive either alendronate (Fosamax; Merck & Co Inc, www.merck.com), 70 mg/wk, orally or placebo once weekly for 18 months, and medications were administered with water first in the morning before patients ate or drank. This administration schedule was established to decrease adverse effects, mainly related to gastrointestinal side effects. The randomization process was computer generated in block groups of 2

to maintain the 1:1 treatment ratio, and allocation concealment involved sealed envelopes held by the pharmacy department, which dispensed the medications to the appropriate treatment arm. Study participants, treating physicians, investigators, and outcome assessors were blinded to treatment allocation. Adherence to treatment was assessed using pill counts at 6-month intervals. During the study, phosphate binders and vitamin D supplements were adjusted by the treating physicians according to usual care for best management of abnormalities of mineral metabolism in patients with CKD. Safety was evaluated by tabulation of adverse events and laboratory assessments.

Outcome Measures

The primary outcome measure in this study was change from baseline in degree of abdominal aortic calcification, determined using spiral computed tomography (CT), at 18 months. Other prespecified secondary outcomes included changes in superficial femoral artery vascular calcification, pulse wave velocity (PWV), BMD, serum markers of bone and mineral metabolism, and kidney function at 18 months.

Computed Tomography

The primary end point of the study was the difference in aortic calcification between groups. Noncontrast CT of the abdominal aorta and bilateral superficial femoral arteries of patients, from which vascular calcification scores were determined, was performed at baseline, 12 months, and 18 months. The noncontrast CT was performed using the Lightspeed 16 multislice spiral computed tomographic scanner (120 kVp, 75 mA for abdominal aorta, 25-75 mA for superficial femoral arteries, and 1.375 pitch; General Electric Medical Services, www.gehealthcare.com). Images were acquired in a spiral mode with the patient supine. Scanning range was from the top of the L1 vertebral level to the bottom of the L4 vertebral level for the abdominal aorta and from the level of the lesser trochanter to that of the knees (20 cm of the distal thighs just above the upper pole of the patella) for the bilateral superficial femoral arteries. Images were reconstructed back to 10 mm for viewing on the workstation. Hounsfield units (HU) of any vascular calcification in the aorta and superficial femoral artery were noted by a single radiologist (K.K.L.) who was blinded to patient demographics, arterial compliance, BMD, and treatment arm. Number of calcifications and highest Hounsfield units of calcifications in the anterior, posterior, right lateral, and left lateral walls of the infrarenal abdominal aorta and distal superficial femoral arteries were recorded.

Pulse Wave Velocity

Arterial stiffness was assessed at baseline, 12 months, and 18 months using a SphygmoCor device (AtCor Medical, PWV Inc, www.atcormedical.com) to measure PWV and augmentation index, the latter a composite parameter reflecting both large and distal arterial properties. Pulse waveforms at the radial (for augmentation index), carotid, and femoral arterial sites were obtained as previously described,[30] and carotid-femoral PWV was recorded. Brachial blood pressure was measured before each PWV determination. All measurements were made by a single operator (N.D.T.) blinded to treatment arm. Determination of PWV on 2 patients was not possible because of technical difficulty; therefore, 44 of 46 patients at completion of the study had arterial compliance documented for analysis.

Bone Mineral Density

BMD was assessed using dual-energy x-ray absorptiometry (DXA) scans at baseline and 18 months. Absolute BMD values, *z* scores, and T scores (number of standard deviations less than the BMD of a younger reference group) for the lumbar spine and right femoral neck were reported, and mean scores for all patients were calculated. The DXA scan used was a GE-Lunar Prodigy (General Electric Medical Services), with the same densitometer used for all patients for accurate comparisons. One investigator (B.J.S.) reported BMD readings blinded to patient demographics, clinical history, and study treatment arm. As a result of obesity, 1 patient was not able to have vertebral and femoral BMD measured, and instead, DXA of his right radius was used for determination of BMD.

Laboratory Values

At baseline, 12 months, and 18 months, all patients performed 24-hour urine collections for measurement of creatinine clearance (corrected for body surface area) and protein excretion. Serum creatinine was analyzed using an automated Jaffé rate reaction, and estimated GFR (eGFR) was calculated using the MDRD Study equation. Other serum markers measured were those addressing mineral metabolism, including calcium (corrected), phosphate, calcium-phosphorus product, intact parathyroid hormone (PTH), alkaline phosphatase (ALP), hemoglobin, albumin, ferritin, erythrocyte sedimentation rate, C-reactive protein, and lipid profile. Blood samples were drawn in the fasting state, and serum was analyzed using a Synchron LX 20 Pro autoanalyzer (Beckman Coulter Inc, www.beckman.com). Total serum calcium level was adjusted for albumin level using the following conversion factor: corrected calcium = calcium + 0.02 mmol/L × (40 − albumin).[31] Intact PTH was measured using immunometric assay (Immunolite 1000; Diagnostic Products Corp, Siemens, www.siemens.com).

Clinical Characteristics

Medical charts were reviewed for clinical history and medications and supplemented with information obtained directly from patients. Weight and height were measured to calculate body mass index. Patients were considered to have diabetes mellitus if they had a previous fasting blood glucose level ≥7 mmol/L or were using oral hypoglycemic agents or insulin therapy. Patients were considered to have CVD if they had coronary artery disease, peripheral vascular disease, and/or cerebrovascular disease. Coronary artery disease was defined as previous abnormal cardiac investigation result or history of myocardial infarction or angina. Peripheral vascular disease was considered present if there was a history of intermittent claudication, leg ulceration, or previous abnormal peripheral angiography or Doppler ultrasound result. Hypertension was defined as a documented history of high blood pressure and using or having used blood pressure–lowering agents. Medications were re-

corded, including calcium-based phosphate binders, antihypertensive agents, vitamin D therapy, and cholesterol-lowering agents.

Statistical Analysis

Baseline results are expressed as mean ± standard deviation, median and range, or frequency and proportion. Analysis was by intention to treat. A random-effect linear regression (panel) model was performed to assess for differences between alendronate and placebo, with adjustment for baseline differences in the dependent variable (model 1). Two additional models of analysis were performed: model 2 also adjusted for age, CVD, and diabetes (because these are important predictors of vascular calcification and therefore important potential confounders), and model 3 additionally adjusted for C-reactive protein level (because there was a statistically significant difference at baseline in this variable), as well as age, CVD, and diabetes. For outcome analyses, $P < 0.05$ is considered to be statistically significant. Intercooled Stata 10.1 (StataCorp, www.stata.com) was used for all statistical analyses.

Power

This clinical trial was a pilot study, with no previous results for changes in vascular calcification with bisphosphonates in nondialysis patients with CKD to determine expected outcomes. However, we hypothesized that a difference of at least 150 HU in aortic calcification between those using alendronate and those using placebo might be achievable and significant. Therefore, assuming no change in vascular calcification in those in the alendronate arm (mean, 400 ± 150 HU) and progression in patients using placebo (to a mean of 550 ± 150 HU) after 18 months, 44 patients (22 in each group) would be required for 90% power to detect a mean difference of 150 HU.

RESULTS

Characteristics of Study Groups

Fifty-one patients were recruited and randomly assigned in this study (Fig 1). One patient who withdrew after randomization and initial investigations, but before the start of study medication, was replaced to maintain treatment allocation in a 1:1 randomization so that 25 patients were allocated to alendronate and 25 were allocated to placebo. During the study period, 2 patients (1 in each group) died of conditions unrelated to the study and 2 were lost to follow-up (both in the placebo group) before the 12-month follow-up visit and therefore did not undergo further measurements after baseline investigations. After 18 months, 46 participants (30 men, 16 women) completed follow-up investigations, 24 in the alendronate arm and 22 in the placebo arm. However, only 42 of these participants completed the study on treatment (21 in each arm) because 3 patients discontinued using the study medication in the alendronate arm (1 from side effects, 2 from treatment nonadherence) and 1 patient started alendronate therapy in the placebo arm. At study completion, adherence to alendronate therapy was 88%, and to placebo, 92%.

Baseline demographics, clinical characteristics, and laboratory markers of the 50 patients who started the study are listed in Table 1, with differences between treatment groups shown. Overall, patients were predominantly men (70.8%) with a median age of 64.5 years (range, 26-80 years). Patients randomly assigned to alendronate therapy were older than those using placebo (66 vs 59 years, respectively), although this difference was not statistically significant. Fifty-four percent had diabetes, and diabetes mellitus was the main cause of CKD (47.9%), with hypertensive nephrosclerosis the next most common cause (27.1%). Very few patients were using phosphate binders (all calcium carbonate) in either group, and there were no significant differences in prescriptions of binders during the study period between treatment arms. Mean serum creatinine and eGFR values were 2.1 mg/dL and 35.1 mL/min/1.73 m^2, respectively. Proteinuria (protein excretion >0.10 g/d) was found in 82% of patients. At baseline, most patients had serum markers of mineral metabolism and lipid levels within the reference range; the latter likely was related to most patients being administered cholesterol-lowering agents (68.8%).

Table 2 lists the primary and secondary outcome measures at baseline, including vascular calcification, PWV, and BMD. Aortic calcification was present in 91% of patients at baseline and was higher in the alendronate group compared with the placebo group (mean, 519.8 vs 322.3 HU; $P = 0.006$). Baseline T scores according to the World Health Organization showed osteopenia in 15% and 39% and osteoporosis in 4% and 13% at the lumbar spine and femoral neck, respectively. BMD and T scores were similar between patients in the alendronate and placebo groups.

Vascular Calcification

Table 3 lists differences between the alendronate and placebo groups for vascular calcifica-

Table 1. Baseline Characteristics of Patients

	Alendronate (n = 25)	Placebo (n = 25)	*P*
Age (y)	66.0 ± 10.7	59.1 ± 12.1	0.05
Men (%)	68	64	0.8
Diabetes (%)	56	60	0.8
BMI (kg/m^2)	30.3 ± 6.1	32.3 ± 7.8	0.3
CVD[a] (%)	28	52	0.08
HTN (%)	92	100	0.1
Cause of CKD (%)			
Diabetes	48	52	0.8
HTN	24	28	
GN	12	8	
Other	16	12	
Statins[b] (%)	66.7	70.8	0.8
ACEi (%)	60	69.5	0.5
ARB (%)	40	39.1	0.9
Calcitriol (%)	20	20.8	0.9
Cholecalciferol (%)	20	24	0.7
Phosphate binders (%)	4	4	0.9
eGFR (mL/min/1.73 m^2)[c]	33.8 ± 11.0	35.6 ± 9.3	0.5
CCr (mL/min)[d]	46.7 ± 18.4	54.1 ± 20.8	0.2
Proteinuria (g/d)	1.0 ± 1.2	1.4 ± 1.9	0.3
Calcium (mg/dL)	9.32 ± 0.48	9.36 ± 0.48	0.8
Phosphate (mg/dL)	3.93 ± 0.62	3.77 ± 0.56	0.4
PTH (pmol/L)	15.3 ± 10.0	14.6 ± 10.5	0.8
ALP (U/L)	98.0 ± 48.6	93.6 ± 41.0	0.7
Total cholesterol (mg/dL)	176.9 ± 50	173.1 ± 46.2	0.7
Triglycerides (mmol/L)	190.9 ± 154.5	172.7 ± 81.8	0.6
Albumin (g/L)	38.2 ± 2.8	37.3 ± 3.4	0.3
CRP (mg/L)[e]	2.7 (0.2-13)	5.1 (0.2-57.5)	0.03
SBP (mm Hg)	128.7 ± 17.4	131.6 ± 17.1	0.6
DBP (mm Hg)	74.2 ± 10.2	71.8 ± 11.9	0.4

Note: N = 50. Results expressed as mean ± standard deviation or median (range). $P < 0.05$ is considered statistically significant. Conversion factors for units: eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; CCr in mL/min to mL/s, ×0.01667; calcium in mg/dL to mmol/L, ×0.2495; total cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mmol/L to mg/dL, ×88.6; albumin in g/L to g/dL, ×0.1.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; ARB, angiotensin II receptor blocker; BMI, body mass index; CCr, creatinine clearance; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; GN, glomerulonephritis; PTH, parathyroid hormone; SBP, systolic blood pressure.

[a]The presence of coronary artery disease, cerebrovascular disease, and/or peripheral vascular disease.

[b]In other words, cholesterol-lowering 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

[c]Calculated using the Modification of Diet in Renal Disease Study equation.

[d]Calculated using 24-hour urine collection.

[e]Missing data, n = 45 for this variable.

Table 2. Baseline Characteristics of Patients for Vascular Calcification, PWV, and BMD

	Alendronate (n = 25)	Placebo (n = 25)	*P*
Vascular calcification (HU)			
Aorta	527.8 (69-1,019.5)	343.0 (0-641.9)	0.006
Left SFA	143.5 (0-1,144.9)	100.5 (0-614.8)	0.5
Right SFA	144 (0-945.5)	0 (0-576.5)	0.4
Pulse wave analysis[a]			
PWV (m/s)	10.5 ± 4.7	9.5 ± 4.1	0.4
Augmentation index (%)	24.1 ± 9.2	22.6 ± 9.9	0.6
BMD lumbar spine			
T score[b]	0.40 ± 1.48	0.37 ± 2.11	0.9
z score	0.84 ± 1.38	0.54 ± 1.89	0.4
BMD femoral neck			
T score[b]	−1.28 ± 0.98	−1.26 ± 1.38	0.9
z score	−0.31 ± 0.88	−0.55 ± 1.18	0.4

Note: Results shown as mean ± standard deviation or median (range). $P < 0.05$ is considered statistically significant.

Abbreviations: BMD, bone mineral density; HU, Hounsfield units; PWV, pulse wave velocity; SD, standard deviation; SFA, superficial femoral artery.

[a]Only 48 patients had PWV measured.

[b]Compared with the young-normal reference range. World Health Organization definitions: normal, T score of −1.0 or greater; osteopenia, T score of −1.0 to −2.5 SD; and osteoporosis, T score of −2.5 SD or less.

tion during the 18-month period. Most patients showed progression of aortic vascular calcification (78%) at 18 months and mean aortic vascular calcification progressed significantly in both groups (Fig 2A; difference from baseline for the entire cohort, +119.6 HU [95% confidence interval [CI], 77.0-162.1]; $P < 0.001$). Patients with diabetes had significantly greater progression of vascular calcification than nondiabetic individuals (+50.5 HU [95% CI, 2.4-98.7]; $P = 0.04$). There was no significant difference in the primary end point of aortic vascular calcification progression with alendronate compared with placebo (−24.2 HU [95% CI, −77.0 to 28.6]; $P = 0.4$). There also was no difference in right or left superficial femoral artery vascular calcification change (15.5 HU [95% CI, −21.3 to 52.3]; $P = 0.4$; and 11.7 HU [95% CI, −34.3 to 57.7]; $P = 0.6$, respectively) between groups.

PWV and BMD

Table 4 lists the differences between alendronate and placebo for PWV, BMD, and biochemical parameters during the 18-month period. Mean PWV increased significantly in both groups throughout the study (+0.63 m/s [95% CI, 0.50-0.75]; $P < 0.001$), and this change was significantly greater in patients with diabetes compared

Table 3. Results of Vascular Calcification Outcomes (primary and secondary) Showing Differences Between Alendronate and Placebo

Vascular Calcification Outcome	Model 1	Model 2	Model 3
Aorta (HU)[a]	−24.2 (−77.0 to 28.6)	−33.2 (83.7 to 17.7)	−32.4 (−83.4 to 18.6)
Left SFA (HU)	15.5 (−21.3 to 52.3)	26.9 (−11.9 to 65.8)	26.4 (−15.7 to 68.6)
Right SFA (HU)	11.7 (−34.3 to 57.7)	21.2 (−27.5 to 70.0)	11.7 (−43.1 to 66.1)

Note: Data based on 46 participants. Values expressed as difference between alendronate and placebo arms (95% confidence interval). Model 1 adjusted for baseline differences in the outcome variable only; model 2 adjusted for baseline differences and also age, diabetes, and cardiovascular disease; and model 3 adjusted for baseline differences and also age, diabetes, cardiovascular disease, and C-reactive protein level. All *P* values >0.10.

Abbreviations: HU, Hounsfield unit; SFA, superficial femoral artery.

[a]Primary outcome.

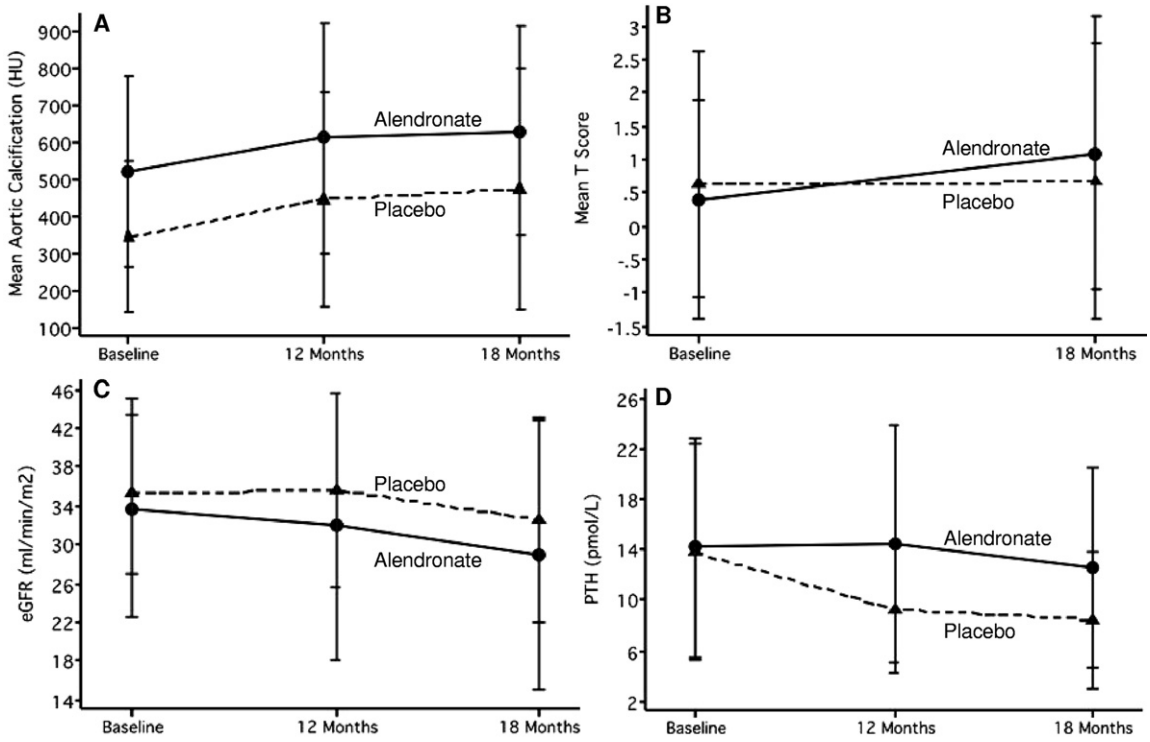

Figure 2. Changes in (A) aortic calcification, (B) lumbar spine T score, (C) estimated glomerular filtration rate (eGFR), and (D) parathyroid hormone (PTH) level after 18 months. Error bars represent standard deviation.

with nondiabetic individuals (+1.3 m/s; P = 0.02). There was a trend toward better PWV with alendronate compared with placebo (−0.8 m/s [95% CI, −1.9 to 0.3]; P = 0.1; Table 3). There was an increase in lumbar spine BMD, with an increase in vertebral T score (adjusted difference, +0.3 [95% CI, 0.03-0.6]; P = 0.03; Fig 2B). Femoral BMD was similar between groups (T score difference, 0.03 [95% CI, −0.05 to 0.1]; P = 0.5).

Biochemical Parameters and Other Outcomes

Kidney function was decreased in both groups at 18 months, with a mean eGFR difference of −1 mL/min/1.73 m^2 (95% CI, −0.88 to −1.12; P < 0.001) compared with baseline (Fig 2C). Patients in the alendronate group had lower eGFRs at 18 months compared with placebo (−1.2 mL/min/1.73 m^2 [95% CI, −4.0 to 1.7]; P = 0.3), although this was not a clinically or statistically significant difference. On adjustment for age, CVD, and diabetes (model 2), there was a trend toward a statistical difference (−2.3 mL/min/1.73 m^2 [95% CI, −4.8 to 0.1]; P = 0.06). There was a significant increase in PTH levels with alendronate versus placebo (+3.2 pmol/L [95% CI, 0.8-5.5]; P = 0.009) at 18 months (Fig 2D). There were also lower serum calcium and ALP levels in those treated with alendronate compared with placebo, although these differences were not statistically significant (−0.03 mg/dL [P = 0.07] and −8.6 U/L [P = 0.09], respectively).

Two patients developed clinically evident fractures during the study period (one had a hip fracture and the other had a crush fracture of lumbar vertebrae) and both had been randomly assigned to the placebo arm (Table 5). Twelve patients were hospitalized during the 18-month period for conditions unrelated to the trial (6 in each treatment arm), and 2 patients developed end-stage renal disease and required ongoing dialysis support (only 1 was randomly assigned to alendronate and had developed worsened renal function related to a prolonged intensive care admission secondary to sepsis). Only 1 patient ceased the study medication as a result of adverse effects of treatment. This patient was randomly assigned to alendronate and developed

Table 4. Results of Secondary Outcomes Showing Differences Between Alendronate and Placebo

Outcome	Model 1[a]	Model 2	Model 3
PWV (m/s)[a]	−1.0 (−2.1 to 0.1)[b]	−1.0 (−2.1 to 0.09)[b]	−0.7 (−1.9 to 0.5)
Lumbar spine			
T score	0.3 (0.03 to 0.6)[c]	0.3 (−0.04 to 0.6)[b]	0.4 (−0.04 to 0.7)[b]
BMD (g/cm^2)	0.02 (−0.003 to 0.04)[b]	0.008 (−0.01 to 0.03)	0.02 (−0.009 to 0.04)
Femoral neck			
T score	0.03 (−0.05 to 0.1)	0.02 (−0.07 to 0.1)	−0.002 (−0.1 to 0.1)
BMD (g/cm^2)	0.01 (−0.01 to 0.04)	0.006 (−0.02 to 0.03)	0.005 (−0.03 to 0.04)
eGFR (mL/min/1.73 m^2)	−1.2 (−4.0 to 1.7)	−2.3 (−4.8 to 0.1)[b]	−1.9 (−4.4 to 0.7)
Calcium (mg/dL)	−0.03 (−0.06 to 0.1)[b]	−0.03 (−0.07 to 0.006)	−0.03 (−0.07 to 0.005)[b]
Phosphate (mg/dL)	0.02 (−0.06 to 0.1)	0.03 (−0.06 to 0.1)	0.01 (−0.08 to 0.1)
PTH (pmol/L)	3.2 (0.8 to 5.5)[d]	3.0 (0.3 to 5.6)[c]	3.1 (0.2 to 6.0)[c]
ALP (U/L)	−8.6 (−18.6 to 1.4)[b]	−7.8 (−18.6 to 3.0)	−9.5 (−21.4 to 2.4)

Note: Data based on 46 participants. Values expressed as difference between alendronate and placebo arms (95% confidence interval). Model 1 adjusted for baseline differences in the outcome variable only; model 2 adjusted for baseline differences and also age, diabetes, and cardiovascular disease; and model 3 adjusted for baseline differences and also age, diabetes, cardiovascular disease, and C-reactive protein level. Conversion factors for units: eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; calcium in mg/dL to mmol/L, ×0.2495.

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; PWV, pulse wave velocity.

[a]Only 45 patients had PWV performed.

[b]$P < 0.10$; [c]$P < 0.05$; [d]$P < 0.01$; [e]$P < 0.001$.

gastrointestinal side effects after 6 weeks of use, which resolved on withdrawal of the drug. No significant difference was observed between the 2 groups in relation to prescribed doses of phosphate binders, calcitriol, or 25-hydroxyvitamin D.

DISCUSSION

The present study is the first randomized trial to assess the efficacy of bisphosphonates on decreasing the progression of vascular calcification in the stage 3-4 CKD population. Despite experimental evidence and some clinical studies suggesting that bisphosphonates, potent inhibitors of bone resorption, may decrease the progression of extraosseous calcification and potentially inhibit atherosclerosis, we found no significant difference in the progression of aortic or superficial femoral artery vascular calcification between groups during the 18-month study period. There was progression of vascular calcification during the study period in most patients with CKD, especially those with diabetes, with aortic calcification reported to be greater in 78% of participants at the 18-month follow-up.

Table 5. Adverse Events Within Groups

	Alendronate (n = 25)	Placebo (n = 25)
Medication side effects[a]	1 (4)	0 (0)
Hospitalization	6 (24)	6 (24)
Fractures[b]	0 (0)	2 (8)
ESRD requiring dialysis	1 (4)	1 (4)
Death	1 (4)	1 (4)

Note: Values expressed as number (percentage).

Abbreviation: ESRD, end-stage renal disease.

[a]Gastrointestinal symptoms resolved on cessation of medication.

[b]One vertebral and 1 hip fracture.

Previous clinical studies have reported varying responses to bisphosphonate use for vascular calcification. Two prospective well-conducted studies of the general population reported no difference in vascular calcification with bisphosphonates compared with control. One study assessed coronary artery calcification in alendronate-treated osteoporotic patients compared with matched controls and showed significant progression over 24 months with no between-group

differences.[32] Another study analyzed aortic vascular calcification assessed using lateral abdominal x-rays in elderly women participating in two 3-year randomized placebo-controlled studies involving ibandronate and reported no difference in the rate of change.[33] Similar to these post hoc analyses of clinical studies of bisphosphonates in the general population, our study failed to show differences in vascular calcification with alendronate in patients with CKD stages 3-4. This may occur because the bisphosphonate dose was inadequate compared with that used in experimental studies showing a decrease in vascular calcification or perhaps as a result of insufficient treatment duration or insufficient study patient sample size in this trial.

In contrast to our study, in the end-stage kidney disease population, several Japanese studies assessing the use of bisphosphonates in HD patients have reported beneficial effects on vascular calcification.[25-28] One study of 35 HD patients followed up for 12 months reported a decrease in coronary artery calcification progression after administration of etidronate, but no change in BMD.[25] In a randomized study of 18 HD patients, inhibition of vascular calcification progression was reported with etidronate,[26] and more recently, a study of 14 HD patients randomly assigned to etidronate or control showed no difference in coronary artery calcification, but a decrease in aortic vascular calcification in the etidronate-treated group at 12 months compared with progression in the control group.[27] Interestingly, in all these clinical studies with small numbers, etidronate was administered and reported to be beneficial. Etidronate is a simpler and less potent non–nitrogen-containing bisphosphonate compared with alendronate. However, it should be noted that with prolonged use at high doses, as used in these dialysis studies, etidronate therapy likely would result in crystal coating, inhibition of crystal formation and aggregation, and the development of osteomalacia in most patients.

Experimental studies of alendronate, ibandronate, and pamidronate have provided evidence implicating bone resorption in the pathogenesis of uremia-related vascular calcification with inhibition of soft-tissue calcification without impacting on serum calcium and phosphate levels.[34-38] The exact mechanism by which bisphosphonates inhibit vascular calcification in these experimental studies is not clear. One explanation may be inhibition of bone resorption with decreased efflux of calcium and phosphate, limiting their availability for deposition in the vasculature,[39] or the ability to influence activity of the vascular smooth muscle cell sodium phosphate cotransporter. Alternatively, bisphosphonates may have direct effects on the vessel wall and, like pyrophosphate, on crystal formation. However, despite theoretical mechanisms for bisphosphonates decreasing vascular calcification in patients with CKD, our trial did not show a clinically beneficial effect of alendronate on vascular calcification.

In our study, we also found no significant difference in vascular stiffness (PWV and augmentation index) between patients with CKD stages 3-4 administered alendronate versus placebo, although there was a trend toward better PWV with alendronate. Bisphosphonates have been reported to affect the vasculature and decrease atherosclerosis, with reports of accumulation in atherosclerotic aortas and healthy aortas without atheroma.[40,41] Although they may bind with high affinity to calcium in atherosclerotic deposits, bisphosphonates also may be taken up into arteries by macrophage phagocytosis and affect the ability of macrophages to internalize atherogenic low-density lipoprotein cholesterol.[42,43] Experimental studies have shown inhibition of atherosclerosis by bisphosphonates without affecting cholesterol or lipid profiles.[44-48] Koshiyama et al[49] studied carotid arterial intima-media thickness in 57 patients with type 2 diabetes associated with osteopenia and reported a significant decrease in intima-media thickness with etidronate compared with control at 12 months. Although a trend toward improved PWV was seen with alendronate in our study, PWV is influenced by ionized calcium, and therefore the observed decrease in calcium levels with alendronate theoretically could be sufficient to explain changes in arterial stiffness.

Used appropriately, bisphosphonates clearly provide fracture protection for patients with osteoporosis in the general community, and many patients with CKD are treated with bisphosphonates in the hope of similar efficacy.[50,51] In our study, there was improvement in DXA-measured lumbar vertebrae BMD at 18 months in partici-

pants administered alendronate compared with placebo, although there was no difference in femoral neck BMD between groups. However, a limitation with the use of anteroposterior DXA to assess the lumbar spine in patients with CKD is potential confounding from the presence of extensive aortic vascular calcification. Aortic vascular calcification may contribute to artifactually increased lumbar spine BMD; therefore, different degrees of vascular calcification and varying rates of change between groups potentially may impact on vertebral BMD differences.

The presence of kidney disease has been a general exclusion criterion in studies of bisphosphonate efficacy. However, based on eGFR, considerable numbers of patients with CKD participated in these studies.[52,53] However, for patients with CKD stages 3-4, treatment of low BMD using standard therapies for osteoporosis is not without potential for harm, and bisphosphonates should be used with caution in carefully selected patients and after consideration of bone biopsy because of the possibility of worsening low bone turnover and osteomalacia.

Our study showed decreased kidney function at 18 months in patients using alendronate compared with those using placebo, with an eGFR difference of -1.2 mL/min/1.73 m^2, although this difference was not clinically or statistically significant. Nephrotoxicity is a potential adverse effect of bisphosphonates. However, previous studies of patients with CKD have not shown greater deterioration in kidney function in participants using bisphosphonates compared with control groups.[52,53] In the FIT (Fracture Intervention Trial), there was a small increase in serum creatinine levels over 3 years, with no difference between placebo- and alendronate-treated groups,[53] and in a pooled analysis by Miller et al,[52] evaluation of changes from baseline in serum creatinine levels showed no difference in renal function between the placebo and risedronate groups in the kidney impairment subgroups.

Bisphosphonates can be used clinically to treat hypercalcemia of malignancy, and we noted in our study a nonsignificant decrease in serum calcium levels in participants treated with alendronate. Serum ALP levels also were lower in the alendronate group, and there was a statistically significant difference in PTH levels, with patients using alendronate having greater levels at follow-up than those using placebo, perhaps secondary to decreased calcium levels. The main effect of bisphosphonates is inhibition of bone metabolism with subsequent decreases in ALP levels, which may inhibit bone turnover, and biochemical changes of lower ALP and increased PTH levels have been reported previously with bisphosphonate use in dialysis patients.[25,26]

One limitation of our study is the baseline differences between groups at study start. Despite randomization, participants in the alendronate group were older and had more aortic vascular calcification (although less CVD) at baseline than those using placebo. However, the method of statistical analysis using analysis of covariance in this study adjusts for baseline differences. The small sample size may account for the baseline differences and potentially for the study showing no difference in the primary end point between groups. Another reason for failure to show a difference in vascular calcification is that greater baseline vascular calcification scores have been reported to progress more rapidly over time; therefore, despite adjustment for initial differences, that patients randomly assigned to alendronate had greater vascular calcification at baseline than the placebo group may have diminished any potential difference with treatment. Another baseline difference was C-reactive protein level, which was significantly higher in the placebo group compared with those using alendronate. However, adjustment for this difference in statistical analysis did not influence results.

Another limitation to our study was that apart from PTH and ALP levels, no other markers of bone turnover were measured and bone biopsies were not performed. Therefore, different degrees of renal osteodystrophy in patients with CKD at baseline or after treatment could not be established, but would definitely be important. Vitamin D status at the study start also was not measured, although 25-hydroxyvitamin D levels in all patients completing the study (mean, 67.8 ± 30.9 nmol/L) showed no significant differences between groups. Another limitation is the inability of CT to distinguish between intimal (atherosclerotic) and medial vascular calcification. Although both carry a negative prognosis for CVD, it was not possible to separate these 2 entities in this study. Finally, the impact of bisphosphonate

therapy on cardiovascular outcomes as opposed to surrogate markers of CVD, such as vascular calcification and intima-media thickness, is unknown.

In conclusion, vascular calcification and arterial stiffness are highly prevalent in patients with CKD, and with the complex interaction between vascular calcification and abnormalities of bone and mineral metabolism, the possibility of using pharmacologic agents that may effectively treat these processes is attractive. We report the first randomized controlled trial in patients with CKD stages 3-4 to show no difference in vascular calcification after 18 months with administration of alendronate compared with placebo. Further interventional studies are required to determine effective treatment of patients with vascular calcification and establish the benefits of bisphosphonates in this population.

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