

ORIGINAL ARTICLE

Alendronate versus Calcitriol for the Prevention of Bone Loss after Cardiac Transplantation

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ABSTRACT

BACKGROUND

Osteoporosis is a well-known complication of cardiac transplantation. We conducted a randomized trial comparing alendronate with calcitriol for the prevention of bone loss during the first year after cardiac transplantation.

METHODS

A total of 149 patients were randomly assigned to receive either alendronate (10 mg per day) or calcitriol (0.5 µg per day) a mean (\pm SD) of 21 \pm 11 days after transplantation. Estimates of bone loss and the incidence of fractures among untreated patients were obtained from a reference group of 27 prospectively recruited patients who received cardiac transplants within the same period as the intervention groups.

RESULTS

At one year, the bone mineral density at the lumbar spine had decreased by a mean of 0.7 percent in the alendronate group and 1.6 percent in the calcitriol group ($P=0.25$ for the test of no difference). The bone mineral density at the femoral neck decreased by a mean of 1.7 percent in the alendronate group and 2.1 percent in the calcitriol group ($P=0.69$). In the reference group, the mean bone mineral density at the lumbar spine decreased by 3.2 percent ($P=0.03$ for the comparison with the alendronate group; $P=0.15$ for the comparison with the calcitriol group), and the mean density at the femoral neck decreased by 6.2 percent ($P=0.001$ for comparisons with both intervention groups). The incidence of vertebral fractures did not differ significantly among the groups (6.8 percent in the alendronate group, 3.6 percent in the calcitriol group, and 13.6 percent in the reference group). Hypercalciuria developed in 27 percent of the patients in the calcitriol group and 7 percent of those in the alendronate group ($P=0.01$).

CONCLUSIONS

The degree of bone loss and the rates of fracture did not differ significantly between the intervention groups. Calcitriol was associated with a higher risk of hypercalciuria. Alendronate-treated patients sustained less bone loss at the spine than those in the reference group, and both intervention groups sustained less bone loss at the hip than the reference group. The requirement for monitoring the serum and urinary calcium levels in calcitriol-treated patients makes alendronate more attractive for the prevention of bone loss early after cardiac transplantation.

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N Engl J Med 2004;350:767-76.

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OSTEOPOROSIS IS A WELL-KNOWN COMPLICATION of cardiac transplantation.¹ Rapid bone loss is reported consistently during the first year after transplantation.²⁻⁵ The prevalence of fractures ranges from 22 to 44 percent among cardiac-transplant recipients,⁶⁻⁹ and the incidence of vertebral fractures during the first three years after transplantation ranges from 18 to 35 percent.^{10,11} We conducted an interventional study with the aim of preventing bone loss after heart transplantation. We judged that the previously reported high rates of fracture necessitated a study comparing two active agents. We selected calcitriol and the bisphosphonate alendronate, which have both been shown to prevent glucocorticoid-induced osteoporosis.¹²⁻¹⁴ On the basis of published results with calcitriol¹⁵⁻¹⁷ and our previous experience with bisphosphonates,¹⁸ we hypothesized that alendronate would be more effective than calcitriol.

METHODS

STUDY DESIGN

In this one-year, double-placebo, double-blind study, patients who had undergone cardiac transplantation within the previous 30 days were randomly assigned to receive either active alendronate (Fosamax, 10 mg per day) and a placebo matching the calcitriol or active calcitriol (Rocaltrol, 0.25 µg twice daily) and a placebo matching the alendronate. Patients who declined to participate in the randomized study but who completed all study measurements constituted the reference group. All patients received calcium (945 mg per day) and vitamin D (1000 IU per day).

Men and women (of all races and ethnic groups, 18 to 70 years of age), who underwent cardiac transplantation at Columbia–Presbyterian Medical Center in New York or Newark–Beth Israel Medical Center in New Jersey were eligible. The criteria for exclusion were the presence of primary hyperparathyroidism, cancer, thyrotoxicosis, sarcoidosis, a serum creatinine concentration of more than 2.5 mg per deciliter (221 µmol per liter) by one month after transplantation, active peptic ulcer disease, nephrolithiasis, hormone-replacement therapy initiated within the previous year, or the use of bisphosphonates or calcitonin therapy. Base-line measurements of bone mineral density, radiographs of the spine, fasting serum, and 24-hour urine specimens were obtained immediately after transplantation. The measurement of bone density was repeated at 6 and

12 months, and radiography was repeated at 12 months. The primary efficacy end points were the percent changes in the bone mineral density of the lumbar spine and the femoral neck at 6 and 12 months. The primary safety end points included the serum calcium and creatinine levels and the urinary calcium and creatinine clearance at 2, 6, 9, and 12 months. The secondary outcome variables included the incidence of vertebral fractures, the serum parathyroid hormone level, and the serum N-telopeptide level.

The study was conducted in the Irving Center for Clinical Research, Metabolic Bone Diseases and Cardiac Transplantation Units of the Columbia–Presbyterian Medical Center, with the approval of the institutional review boards of the Columbia–Presbyterian Medical Center and the Newark–Beth Israel Medical Center. Written informed consent was obtained from all participants.

RECRUITMENT AND RETENTION OF PATIENTS

Of 432 patients who received a heart transplant between January 1999 and June 2001 (390 at the Columbia–Presbyterian Medical Center and 42 at the Newark–Beth Israel Medical Center), 212 were deemed ineligible (Fig. 1), most commonly because they were enrolled in another clinical trial or were younger than 18 years of age. Sixty-five patients declined to participate, of whom 27 constituted the reference group.

Six patients who underwent randomization and two patients in the reference group died of transplantation-related complications (rejection, infection, or heart failure). Eighteen patients who underwent randomization withdrew before the 6-month visit, and five withdrew before the 12-month visit. Excluding the patients who died, the rate of retention for 12 months was 85 percent in the alendronate group and 83 percent in the calcitriol group (Fig. 1). A total of 66 percent of the patients in the alendronate group completed 12 months of study treatment, as did 52 percent of those in the calcitriol group. The reasons for the discontinuation of the study treatment were gastrointestinal symptoms (in 4 patients in the alendronate group and 11 in the calcitriol group), the patient's wishes (in 4 patients, all in the calcitriol group), excessive bone loss at six months (in 3 patients, all in the alendronate group), severe transplantation-related complications (in 1 patient in the alendronate group), nephrolithiasis (in 1 patient in the alendronate group), severe hypercalcemia (in 2 patients, both in the calcitriol group),

enrollment in another trial (in 2 patients in the alendronate group and 1 in the calcitriol group), use of testosterone therapy (in 1 patient in the alendronate group) or alendronate therapy (in 1 patient in the calcitriol group), and renal insufficiency (in 1 patient in the alendronate group).

IMMUNOSUPPRESSION

All patients received glucocorticoids and calcineurin inhibitors, predominantly cyclosporine. Intravenous methylprednisolone was followed by oral prednisone, beginning at a dose of 50 mg and tapering to 30 mg by two weeks and to 5 to 10 mg by six months. Prednisone treatment was not discontinued in any of the patients. Rejection was managed with the use of high-dose oral or intravenous glucocorticoids. The trough blood cyclosporine levels were maintained between 250 and 300 ng per milliliter for the first six months and between 200 and 250 ng per milliliter for the second six months.

BONE DENSITY AND BIOCHEMICAL MEASUREMENTS

Bone density was measured with the use of dual-energy x-ray absorptiometry (QDR-4500 densitometer, Hologic) at Columbia–Presbyterian Medical Center; the short-term in vivo coefficient of variation is 0.68 percent for the spine and 1.36 percent for the femoral neck. Bone density was expressed in grams per square centimeter and in terms of T and z scores for the comparison of patients with young-normal and age-matched populations of the same race and sex. According to the criteria defined by a World Health Organization study group for white postmenopausal women, a T score of -2.5 or below indicates the presence of osteoporosis.¹⁹ Radiography was performed according to the protocol for the Study of Osteoporotic Fractures.²⁰ New fractures,²¹ defined by a 20 percent decrease (≥ 4 mm) in any vertebral height,²² were adjudicated by a skeletal radiologist.²²

All biochemical variables were measured in fasting, morning serum by means of an autoanalyzer (Technicon Instruments). Urinary calcium excretion was analyzed by means of colorimetry, and creatinine excretion by means of an autoanalyzer. Aliquots of serum were stored at -70°C for batch analyses of parathyroid hormone and N-telopeptide levels in the core laboratory with the use of a two-site immunoradiometric assay (Corning-Nichols Institute) and an enzyme-linked immunosorbent assay (Osteomark, Ostex), respectively.

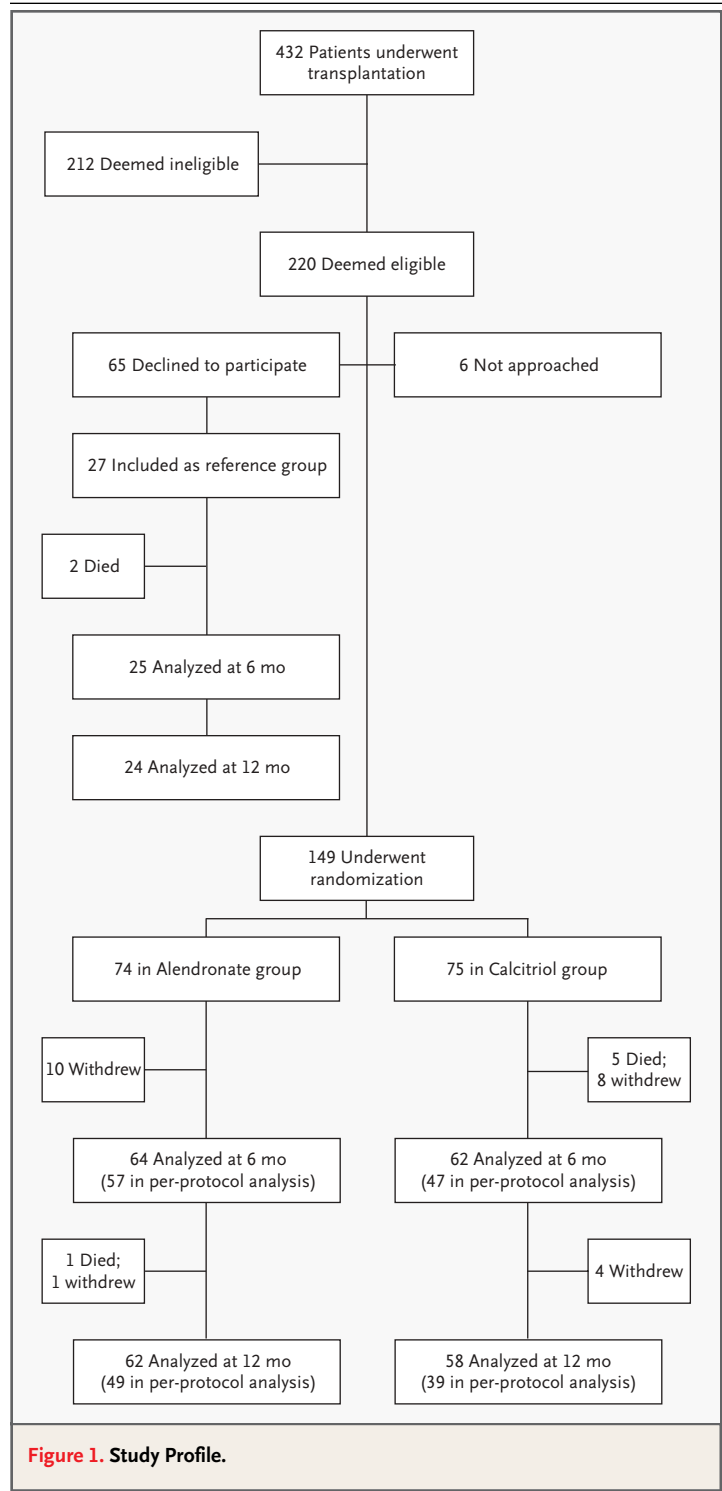


Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Alendronate Group (N=74)	Calcitriol Group (N=75)	Reference Group (N=27)
No. of days from transplantation to randomization	21±11	21±11	NA
Age — yr	54±11	53±11	56±8
Sex — no. (%)			
Male	63 (85)	59 (79)	22 (81)
Female	11 (15)	16 (21)	5 (19)
Race or ethnic group — no. (%)			
Non-Hispanic white	51 (69)	52 (69)	19 (70)
Non-Hispanic black	13 (18)	15 (20)	2 (7)
Hispanic	6 (8)	6 (8)	3 (11)
Other	4 (5)	2 (3)	3 (11)
Cardiac diagnosis — no. (%)			
Ischemic cardiomyopathy	42 (57)	36 (48)	15 (56)
Dilated cardiomyopathy	26 (35)	30 (40)	8 (30)
Other	6 (8)	9 (12)	4 (15)
Bone mineral density			
Lumbar spine			
Mean — g/cm ²	1.047±0.15	1.062±0.17	1.087±0.17
T score	-0.70±1.4	-0.59±1.6	-0.26±1.6
z score	-0.11±1.4	-0.03±1.6	0.38±1.7
Femoral neck			
Mean — g/cm ²	0.837±0.16	0.836±0.15	0.819±0.12
T score	-0.80±1.1	-0.80±0.9	-0.82±0.9
z score	0.09±1.1	0.03±0.9	0.07±0.9
Total hip			
Mean — g/cm ²	0.979±0.17	0.980±0.15	0.973±0.14
T score	-0.45±1.0	-0.41±0.9	-0.38±1.0
z score	0.04±1.0	0.04±0.9	0.09±0.9

* Plus-minus values are means ±SD. NA denotes not applicable.

ADVERSE EVENTS

At each visit, medication use, side effects of the study drugs, and adverse events (including hospitalization, rejection, infection, gastrointestinal symptoms, hypercalcemia, hypercalciuria, and fracture) were documented through history taking and a review of the chart. Occurrences of nonvertebral fractures were ascertained through the review of radiographs.

If the serum calcium level exceeded 10.4 mg per deciliter (2.6 mmol per liter) or the urinary calcium excretion exceeded 400 mg per 24 hours (10 mmol per day), calcium supplementation was reduced by one tablet (315 mg) per day. If the elevation persisted after all calcium supplementation was discontinued, the dose of calcitriol or matching placebo was reduced sequentially by 0.25 µg per day. On resolution of hypercalcemia or hypercalciuria, the patient was rechallenged with the previous dose. If the abnormality recurred, the patient was given the

lower dose. The average dose of calcitriol over the 12-month study period, including that in patients who remained in the study but discontinued treatment with the study medications, was 0.37±0.22 µg per day.

Gastrointestinal symptoms, which can be caused by mycophenolate mofetil therapy and cytomegalovirus, are common after transplantation. Since alendronate is also associated with gastrointestinal symptoms,²³ we discontinued treatment with alendronate or matching placebo in patients who had such symptoms. Gastrointestinal symptoms that resolved after the discontinuation of alendronate therapy and recurred after the resumption of treatment were considered likely to be related to alendronate. If the symptoms were not controlled by omeprazole therapy or were intolerable, the study medications were discontinued but the patient remained in the study.

A bone loss of 8 percent or more at the six-month visit prompted repeated scanning. If the loss was confirmed and the T score was below -2.0, the patient was withdrawn from the study and referred for evaluation. An independent data and safety board monitored the study end points and safety. Merck had no role in the design, conduct, or analysis of the study.

STATISTICAL ANALYSIS

The study was designed to detect differences between the groups of 2.5 percentage points (a standard deviation of 5 percent) in the percent change from base line to 12 months in the bone mineral density at the spine and femoral neck, with a power of 80 percent and a two-tailed P value of 0.05. The sample size would permit the detection of a 15 percent difference in the incidence of vertebral fractures (with a power of 80 percent) if the fracture rate was 20 percent in one group and 5 percent in the other group.

Base-line differences between the groups were assessed with the use of Student's t-test for continuous variables and Fisher's exact test for categorical variables. The percent change from base line in the bone density was tested with a mixed-model analysis of variance for repeated measures; the covariates were the fixed effect of treatment (to test the overall differences between treatments), the interaction between treatment and time (to test for differences between the groups in the percent changes at 6 and 12 months), random effects of patient and error, and the base-line bone density. Fixed effects with P val-

ues of less than 0.05 were investigated through the calculation of differences between the groups within a given period and differences within each group over time, with their 95 percent confidence intervals. The differences between groups in immunosuppression and biochemical variables were examined by means of a mixed-model analysis of variance. Adverse events and new fractures were assessed with the use of Fisher's exact test. The primary analyses compared the two randomized groups. Secondary analyses compared the randomized groups with the reference group.

All efficacy and safety analyses were conducted according to the intention-to-treat principle. Per-protocol analyses included patients who adhered to study treatment and completed the 6-month or 12-month visit. A two-sided P value of 0.05 or less was required for the rejection of the null hypothesis. The data were held and analyzed by the investigative team.

RESULTS

STUDY POPULATION

The mean age of the patients was 54 years, and patients were predominantly male and white. The randomized groups did not differ significantly in terms of age, sex, race or ethnic group, or base-line bone density (Table 1). The T score for the lumbar spine was -2.5 or lower in 6.5 percent of the women and 7.8 percent of the men. The reference group was similar to the intervention groups in all respects.

IMMUNOSUPPRESSION

The daily doses of prednisone and cyclosporine and the trough cyclosporine levels (Table 2) did not differ significantly among the groups, except that the dose of cyclosporine was lower in the alendronate group than in the other groups at randomization and was lower in the reference group than in the other groups at nine months.

CHANGE IN BONE MINERAL DENSITY

Neither the intention-to-treat analysis (Fig. 2) nor the per-protocol analysis (data not shown) revealed significant differences between the calcitriol and alendronate groups at 6 or 12 months. By 12 months, the bone density of the spine had decreased by 0.7 percent in the alendronate group (95 percent confidence interval for the change, -1.8 to 0.5 ; the positive value indicates that there was an increase in bone density in one or more patients) and by

Table 2. Immunosuppressive Therapy in the Patients.*

Immunosuppressive Drug	Base Line†	2 Mo	6 Mo	9 Mo	12 Mo
Prednisone (mg/day)					
Alendronate group	33±16	18±7	9±5	7±4	7±7
Calcitriol group	29±15	19±10	8±6	8±9	6±4
Reference group	26±6	16±7	9±6	7±7	5±4
Cyclosporine (mg/day)					
Alendronate group	355±107‡	420±118	377±132	335±115	283±99
Calcitriol group	406±129	430±125	366±127	363±129	321±157
Reference group	425±102	381±101	319±125	276±86§	262±94
Cyclosporine level (ng/dl)					
Alendronate group	253±128	287±92	263±72	256±79	225±77
Calcitriol group	242±113	318±122	267±69	255±90	214±70
Reference group	255±131	314±91	222±90	242±167	212±99

* Plus-minus values are means ±SD.

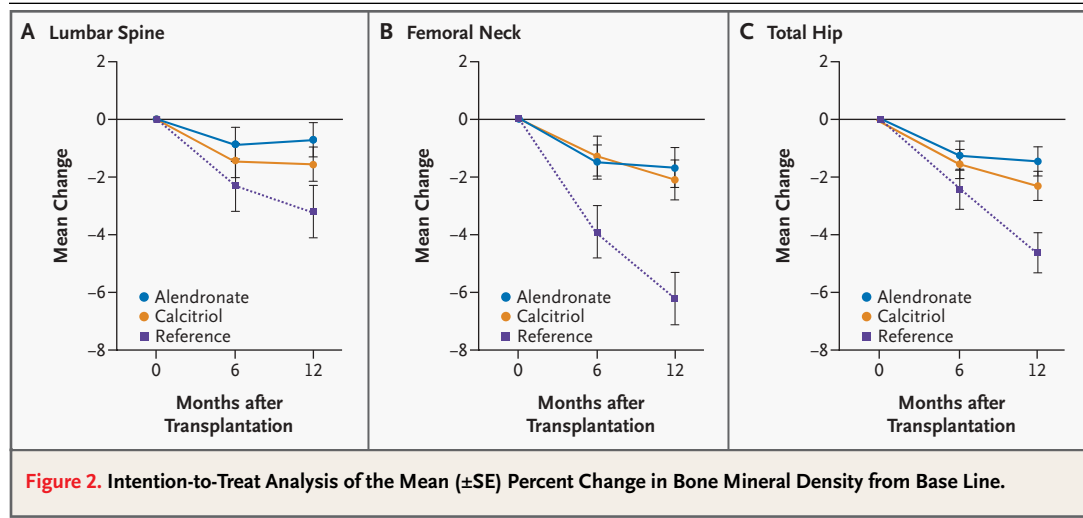
† Base-line data are for the day of randomization.

‡ P=0.03 for the comparison with the calcitriol group, and P=0.05 for the comparison with the reference group.

§ P=0.02 for the comparison with the calcitriol group.

1.6 percent in the calcitriol group (95 percent confidence interval, -2.8 to -0.5). The bone density at the femoral neck decreased by 1.7 percent in the alendronate group (95 percent confidence interval, -3.1 to -0.4) and by 2.1 percent in the calcitriol group (95 percent confidence interval, -3.5 to -0.8). The bone density of the total hip decreased by 1.5 percent in the alendronate group (95 percent confidence interval, -2.1 to -0.5) and by 2.3 percent in the calcitriol group (95 percent confidence interval, -2.9 to -0.8). At 12 months, the estimated difference between the changes in the two groups was 0.9 percentage point for the change at the spine (95 percent confidence interval, -0.7 to 2.6 ; P=0.25), 0.4 percentage point for the change at the femoral neck (95 percent confidence interval, -1.5 to 2.3 ; P=0.69), and 0.8 percentage point for the change at the total hip (95 percent confidence interval, -0.7 to 2.2 ; P=0.31).

Secondary analyses revealed that the bone loss at the spine was greater in the reference group (a decrease of 3.2 percent; 95 percent confidence interval, -5.0 to -1.4 percent) than in the alendronate group (estimated difference, 2.5 percentage points; 95 percent confidence interval, 0.4 to 4.6 ; P=0.03), but there was no significant difference between the reference group and the calcitriol group (estimated difference, 1.6 percentage points; 95 percent confidence interval, -0.5 to 3.6 ; P=0.15). Among the patients in the calcitriol group who adhered to therapy, the bone density decreased by only 0.5 percent



(95 percent confidence interval, -1.9 to 0.8), and the difference between this calcitriol subgroup and the reference group of 2.7 percentage points (95 percent confidence interval, 0.3 to 4.8) was significant ($P=0.03$).

The bone loss at the femoral neck in the reference group (a decrease of 6.2 percent; 95 percent confidence interval, -8.0 to -4.4) and the loss at the total hip in this group (a decrease of 4.6 percent; 95 percent confidence interval, -6.1 to -3.2) were significantly greater than those in both intervention groups. For the femoral neck, the estimated difference between the alendronate group and the reference group was 4.5 percentage points (95 percent confidence interval, 2.3 to 6.7 ; $P=0.001$), and the estimated difference between the calcitriol group and the reference group was 4.1 percentage points (95 percent confidence interval, 1.6 to 6.6 ; $P=0.001$). For the total hip, the estimated difference between the alendronate group and the reference group was 3.1 percentage points (95 percent confidence interval, 1.4 to 4.8 ; $P=0.001$), and the estimated difference between the calcitriol group and the reference group was 2.3 percentage points (95 percent confidence interval, 0.1 to 4.5 ; $P=0.04$).

FRACTURES

Radiographs of the spine were available for 59 patients in the alendronate group (80 percent), 56 in the calcitriol group (75 percent), and 22 in the reference group (81 percent). The rates of fracture in the three groups were not statistically different. Four patients in the alendronate group (6.8 percent of those with radiographs) sustained a total of eight

fractures, and two patients in the calcitriol group (3.6 percent of those with radiographs) sustained two fractures (difference, 3.2 percentage points; 95 percent confidence interval, -6.6 to 13.0 ; $P=0.68$). Two patients in the alendronate group (3.4 percent) and no patients in the calcitriol group had multiple fractures (difference, 3.4 percentage points; 95 percent confidence interval, -3.0 to 9.8 ; $P=0.10$). Non-vertebral fractures occurred in four patients in the alendronate group and four in the calcitriol group.

Three patients in the reference group (13.6 percent of those with radiographs) sustained a total of eight fractures; two patients in this group (9.1 percent) had multiple fractures. Although there were more fractures in the reference group, the number of fractures was small. The differences between the reference group and the alendronate group in the proportion of patients with any fracture (6.8 percentage points; 95 percent confidence interval, -25.7 to 12.0 ; $P=0.68$) and in the proportion of patients with multiple fractures (5.7 percentage points; 95 percent confidence interval, -21.7 to 10.3 ; $P=0.30$) were not significant. Similarly, the differences between the reference group and the calcitriol group in the proportion of patients with any fracture (10.0 percentage points; 95 percent confidence interval, -28.7 to 8.2 ; $P=0.14$) and in the proportion of patients with multiple fractures (9.1 percentage points; 95 percent confidence interval, -24.3 to 6.1 ; $P=0.08$) were not significant.

ADVERSE EVENTS

There were no significant differences between the intervention groups in the rates of transplantation-

related or gastrointestinal adverse events (Table 3). More patients in the calcitriol group than in the alendronate group required adjustments of the calcium and calcitriol doses; hypercalciuria and hypercalcemia also developed in more patients in the calcitriol group. One patient in the calcitriol group withdrew from the study because of severe hypercalcemia (serum calcium level, 12.2 mg per deciliter [3.04 mmol per liter]).

BIOCHEMICAL INDEXES OF MINERAL METABOLISM

The base-line serum N-telopeptide level, a marker of bone resorption, was elevated in all groups (25.5±1.6 nmol bone collagen equivalents per liter; normal range, 7.7 to 19.3); the level then decreased to the mid-normal range in both intervention groups, while remaining elevated in the reference group (Fig. 3A). By six months, the serum parathyroid hormone level (Fig. 3B) had decreased in the calcitriol group (from 44±5 to 29±5 pg per milliliter [4.4±1.1 to 3.2±1.1 pmol per liter]) and had increased in the alendronate group (from 39±4 to 51±4 pg per milliliter [4.3±0.4 to 5.6±0.4 pmol per liter]; $P<0.001$ for the comparison between groups). The pattern of change in the reference group was similar to that in the alendronate group.

DISCUSSION

We directly compared alendronate and calcitriol for the prevention of bone loss during the first year after cardiac transplantation. The primary analysis revealed no significant differences between the intervention groups in terms of bone loss or the incidence of fractures. However, patients who were treated with either drug had significantly less bone loss at the hip than patients in the reference group, and those who received alendronate had less bone loss at the spine than those in the reference group, suggesting that both alendronate and calcitriol prevent bone loss after heart transplantation. Although fewer fractures occurred in patients in the intervention groups than in those in the reference group, the differences were not significant. Hypercalcemia and hypercalciuria were more common and severe in patients in the calcitriol group.

Bone loss occurring shortly after heart transplantation is probably related to concomitant therapy with high-dose glucocorticoids and calcineurin inhibitors, particularly cyclosporine.²⁴ Glucocorticoids profoundly inhibit bone formation, with rel-

Table 3. Patients with Adverse Events.

Adverse Event	Alendronate Group (N=74)	Calcitriol Group (N=75)
	no. (%)	
Death	1 (1)	5 (7)
Event resulting in permanent discontinuation of study treatment	6 (8)	12 (16)
Hospitalization*	37 (50)	35 (47)
Infection†	24 (32)	19 (25)
Rejection‡		
≥Grade 2A	27 (36)	32 (43)
≥Grade 3A	14 (19)	13 (17)
Gastrointestinal effects§		
Any	44 (59)	43 (57)
Hemorrhage	2 (3)	1 (1)
Abdominal pain	10 (14)	9 (12)
Heartburn or acid reflux	5 (7)	12 (16)
Nausea	21 (28)	19 (25)
Alendronate or matching placebo discontinued¶	14 (19)	17 (23)
Hypercalcemia (serum calcium level >10.4 mg/dl)	1 (1)	6 (8)
Hypercalciuria (urinary calcium excretion >300 mg/24 hr)**	5 (7)	20 (27)
Serum creatinine level ≥3 mg/dl††	4 (5)	7 (9)
Creatinine clearance ≤30 ml/min	17 (23)	23 (31)
Supplemental calcium dose reduced‡‡	4 (5)	12 (16)
Calcitriol dose reduced	2 (3)	4 (5)

* Data include readmissions to the hospital after randomization.

† Data include all infections due to cytomegalovirus and all other infections that necessitated hospitalization, intravenous antibiotic therapy, or both.

‡ The severity of rejection was defined according to the criteria of the International Society for Heart and Lung Transplantation.

§ All gastrointestinal symptoms, except hemorrhage, were adjudicated by observers who were unaware of the treatment-group assignments.

¶ Data are for all patients in the intervention groups in whom alendronate or matching placebo was discontinued on one or more occasions either temporarily or permanently because of gastrointestinal symptoms.

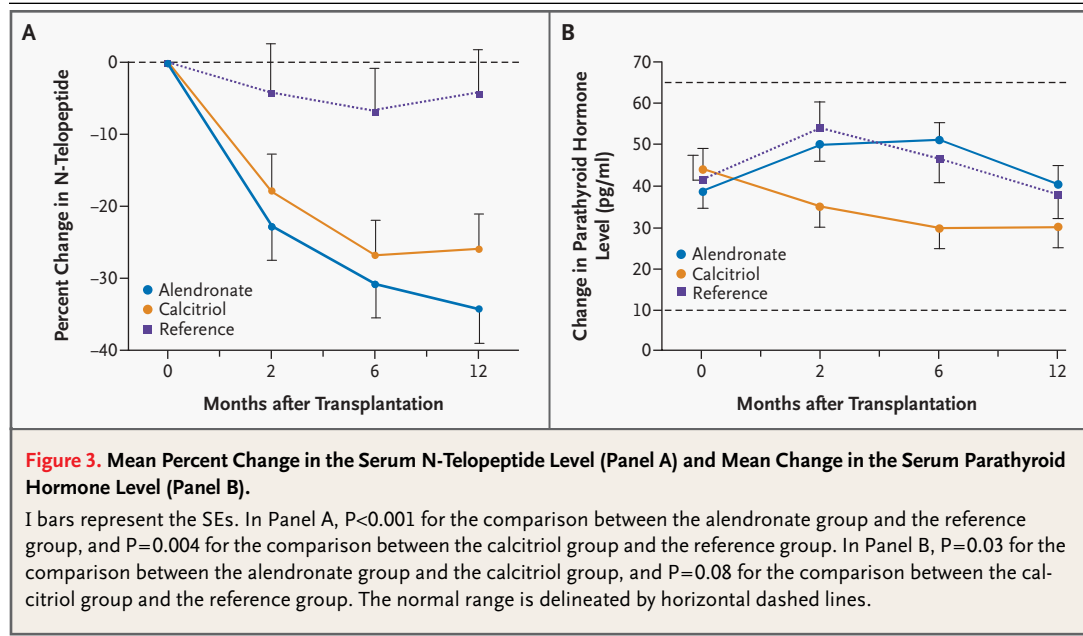
|| To convert values for serum calcium to millimoles per liter, multiply by 0.2495.

**To convert values for urinary calcium excretion to millimoles per day, multiply by 0.02495. $P=0.01$ for the comparison between the groups.

††To convert values for serum creatinine to millimoles per liter, multiply by 88.4.

‡‡ $P=0.04$ for the comparison between the groups.

atively minor effects on bone resorption.²⁵ In contrast, studies of calcineurin inhibitors in animals have demonstrated markedly increased bone resorption and formation.²⁶ Elevated levels of markers of bone resorption have consistently been demonstrated in heart-transplant recipients who receive both glucocorticoids and cyclosporine^{3,4,27,28}; such a pattern is not generally seen in patients taking glucocorticoids alone.²⁹ Both alendronate and calcitriol suppressed resorption, as evidenced by similar



decreases in serum N-telopeptide levels. However, alendronate directly inhibits osteoclast activity, whereas calcitriol appears to act by suppressing parathyroid hormone secretion.

Previous studies of heart-transplant recipients treated with pharmacologic doses of vitamin D or bisphosphonates suggested that alendronate would have greater efficacy than calcitriol. In patients receiving alfacalcidol, bone density decreased by 5 to 7 percent at the spine and femoral neck.¹⁵ Similar losses were reported in calcitriol-treated patients after heart or lung transplantation.¹⁶ Sambrook et al. reported one-year bone loss at the spine of only 2.3 percent among patients treated with calcitriol (0.5 μg per day), as compared with 2.9 percent among patients given placebo.¹⁷ However, bone loss at the femoral neck averaged 3.9 percent in the calcitriol group, as compared with 6.6 percent in the placebo group.¹⁷ In contrast, smaller studies evaluating intravenous bisphosphonates (pamidronate) after heart transplantation reported stable or improved bone density at the spine^{18,30} or smaller losses (1.4 to 1.9 percent).³¹ Pamidronate and ibandronate also prevent bone loss after kidney,^{32,33} liver,³⁴⁻³⁶ and lung³⁷ transplantation.

Although we originally hypothesized that alendronate would be superior to calcitriol, we observed clinically and statistically insignificant differences of 1.0 percentage point or less at all sites. The study's power to detect differences of this magnitude was

approximately 10 percent. Calcitriol appeared to be more effective than previously reported,^{15-17,31} perhaps because in earlier studies supplemental calcium was not provided,¹⁶ the calcitriol doses were lower,¹⁷ or higher doses of glucocorticoids were used. Moreover, the rates of bone loss and fracture in the reference group were lower than expected, perhaps because the prednisone doses were considerably lower than those used in earlier studies.^{2,3,10,11}

Both alendronate and calcitriol were tolerated well with respect to transplantation-related adverse events. The rates of adverse gastrointestinal effects, which may limit the use of oral bisphosphonates, were similar in the two groups. Hypercalcemia and hypercalciuria in patients receiving calcitriol were usually mild and easily managed. However, if intensive monitoring had not been incorporated into the study design, the severity and frequency of these adverse effects would undoubtedly have been greater. Lower doses of calcitriol or supplemental calcium might ameliorate this problem, but such improvement might come at the expense of efficacy. Combining a lower dose of calcitriol with a bisphosphonate might prevent the increase in the parathyroid hormone level and permit alendronate to be more effective. Since considerable bone loss may occur during the first weeks after transplantation, an intravenous bisphosphonate administered immediately after transplantation might have proved more effective than calcitriol.

Our study has several limitations. It is common for studies of interventions for post-transplantation osteoporosis to lack a randomized control group; we believed that ethical considerations required the design we used. Fortunately, the reference group provided a benchmark for interpreting the effects of the interventions. The rather high rate of nonadherence (only about 60 percent of the patients were receiving their assigned therapy at 12 months) appeared to be attributable mainly to transplantation-related adverse events. Since analyses including only patients who adhered to therapy were generally similar to the intention-to-treat analyses, nonadherence did not appear to affect the results materially. Finally, since the study was conducted predominantly in a single institution and included only heart-transplant recipients, the results may not apply to other centers or other types of organ transplantation.

In summary, bone loss appeared to be minimal when alendronate or calcitriol therapy was initiated during the first month after heart transplantation. Although our results did not establish any difference in efficacy, both drugs appeared to be safe

and prevented some of the bone loss that occurred in a reference group of patients who received transplants concurrently. However, the requirement for monitoring the serum and urinary calcium levels in patients receiving calcitriol may make alendronate the more attractive choice in the complicated setting of the early post-transplantation period.

Supported by grants (AR-41391 and RR-006645) from the National Institutes of Health and by a Medical School Grant from Merck.

Dr. Shane reports having received a grant from Novartis. Dr. Zucker reports having received consulting fees from Bristol-Myers Squibb, Novartis, and INO Therapeutics, lecture fees from GlaxoSmithKline and Medtronic, and grants from Fujisawa and Wyeth.

We are indebted to Merck, Rahway, N.J., for providing matched alendronate and placebo, to Hoffmann-LaRoche Pharmaceuticals, Nutley, N.J., for providing matched calcitriol and placebo, and to Mission-Pharmaceutical, San Antonio, Tex., for providing Citracal+D; to the members of the data and safety monitoring board, Murray Favus, M.D. (chair), Keith Aaronson, M.D., Steven Cummings, M.D., KyungMann Kim, Ph.D., and Lawrence Raisz, M.D.; to the physicians and nurses of the cardiac transplantation programs of Columbia-Presbyterian Medical Center and Newark-Beth Israel Medical Center for their support; to Dr. Joan McGowan, director of the Bone Biology Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, for her support; and to Dr. John Bilezikian and Dr. Shonni Silverberg for helpful discussions.

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