Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women

A Randomized Controlled Trial

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Context Improving vitamin D status may be an important modifiable risk factor to reduce falls and fractures; however, adherence to daily supplementation is typically poor.

Objective To determine whether a single annual dose of 500 000 IU of cholecalciferol administered orally to older women in autumn or winter would improve adherence and reduce the risk of falls and fracture.

Design, Setting, and Participants A double-blind, placebo-controlled trial of 2256 community-dwelling women, aged 70 years or older, considered to be at high risk of fracture were recruited from June 2003 to June 2005 and were randomly assigned to receive cholecalciferol or placebo each autumn to winter for 3 to 5 years. The study concluded in 2008.

Intervention 500 000 IU of cholecalciferol or placebo.

Main Outcome Measures Falls and fractures were ascertained using monthly calendars; details were confirmed by telephone interview. Fractures were radiologically confirmed. In a substudy, 137 randomly selected participants underwent serial blood sampling for 25-hydroxycholecalciferol and parathyroid hormone levels.

Results Women in the cholecalciferol (vitamin D) group had 171 fractures vs 135 in the placebo group; 837 women in the vitamin D group fell 2892 times (rate, 83.4 per 100 person-years) while 769 women in the placebo group fell 2512 times (rate, 72.7 per 100 person-years; incidence rate ratio [RR], 1.15; 95% confidence interval [CI], 1.02-1.30; $P=.03$). The incidence RR for fracture in the vitamin D group was 1.26 (95% CI, 1.00-1.59; $P=.047$) vs the placebo group (rates per 100 person-years, 4.9 vitamin D vs 3.9 placebo). A temporal pattern was observed in a post hoc analysis of falls. The incidence RR of falling in the vitamin D group vs the placebo group was 1.31 in the first 3 months after dosing and 1.13 during the following 9 months (test for homogeneity; $P=.02$). In the substudy, the median baseline serum 25-hydroxycholecalciferol was 49 nmol/L. Less than 3% of the substudy participants had 25-hydroxycholecalciferol levels lower than 25 nmol/L. In the vitamin D group, 25-hydroxycholecalciferol levels increased at 1 month after dosing to approximately 120 nmol/L, were approximately 90 nmol/L at 3 months, and remained higher than the placebo group 12 months after dosing.

Conclusion Among older community-dwelling women, annual oral administration of high-dose cholecalciferol resulted in an increased risk of falls and fractures.

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THE RESULTS OF RANDOMIZED controlled trials investigating the effects of cholecalciferol (vitamin D) supplementation on falls and fractures have been inconsistent.[1-13] Some meta-analyses conclude that 700 to 800 IU of vitamin D daily reduces fracture risk by 13% to 26%,[14-18] whereas others conclude that vitamin D is ineffective. A Cochrane analysis[19] and the Vitamin D Individual Patient Analysis of Randomized Trials (DIPART) group,[20] published after this study commenced, showed a nonstatistically significant increase in hip fracture risk associated with vitamin D supplementation.[19-21] Studies have observed those living in long-term care facilities as having greater fracture risk reduction than community-dwelling elders. Similarly, fewer fractures were observed in participants whose study treatment was coadministered with calcium.[4,5,16,22] Furthermore, many studies have found treatment adherence to be low[1,2,6] and fracture risk reduction was greater among adherent than nonadherent pa-

For editorial comment see p 1861.

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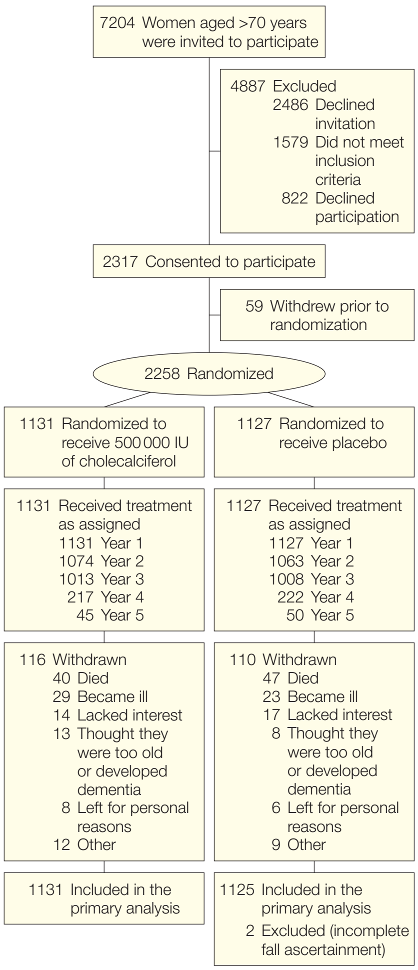
Figure 1. Patient Flow Diagram



tients.[1,16,22] The evidence of vitamin D efficacy in preventing falls suggests that daily doses of at least 700 IU reduce falls by 19% to 26%.[23]

We hypothesized that high-dose cholecalciferol (500 000 IU) given orally once a year to community-dwelling older women would reduce falls and fractures. The rationale for this dose was based on data that an oral dose of 500 000 IU (administered as 50 000 IU daily for 10 days) produced a mean (SD) increase in 25-hydroxycholecalciferol of 32 (15) nmol/L at 17 (7) weeks after dose[24] and was supported by fracture-reduction benefits using 300 000 of IU cholecalciferol (administered as 100 000 IU every 4 months)[3] and 150 000 to 300 000 IU of ergocalciferol administered intramuscularly as a single annual dose.[7] The study was designed so that the vitamin D treatment would prevent decreases in 25-hydroxycholecalciferol over winter,[25] address low adherence, and be a practical intervention easily translated to clinical practice.

METHODS

Study Design

The Vital D study was a single-center, double-blind, randomized, placebo-controlled trial involving women 70 years or older residing in southern Victoria, Australia (latitude 38°S). The participants were recruited between 2003 and 2005 and were randomly assigned to receive either a single oral dose of cholecalciferol 500 000 IU or matched placebo each year for 3 to 5 years (in autumn or winter). Participants were followed up for 12 months after their last dose of study medication in 2007.

The study was approved by the institutional review boards of Barwon Health and the University of Melbourne and carried out in compliance with the Helsinki Declaration. All participants provided written informed consent.

The study recruited 2317 community-dwelling women as previously described.[26] Invitation letters were sent to all age-eligible women listed on the electoral roll of the region surrounding the study center. Voting is compulsory in Australia.

Women were included in the study if they were at higher risk of hip fracture,[27] defined by criteria such as maternal hip fracture, past fracture, or self-reported faller.[26] Women were excluded if they could not provide informed consent or information about falls or fractures; permanently resided at a high-level care facility; had an albumin-corrected calcium level higher than 2.65 mmol/L; or had a creatinine level higher than 150 µmol/L, or currently took vitamin D doses of 400 IU or more, calcitriol, or antifracture therapy. (To convert calcium from mmol/L to mg/dL, divide by 0.25; creatinine from µmol/L to mg/dL, divide by 88.4; and serum vitamin D from nmol/L to ng/mL, divide by 2.496.)

Eligible participants were randomized to receive either 500 000 IU of cholecalciferol or identical placebo. Allocation was performed by an independent statistician using computer-generated randomization of numbers performed in blocks of 500. Treatment allocation status was e-mailed directly to the hospital clinical trials pharmacist responsible for dispensing study medication. The participants and study staff were blinded to intervention group.

Study medication was supplied by PSM Healthcare, Auckland, New Zealand. Ten tablets were mailed to participants annually (March-August, determined by recruitment date) with instructions to take all tablets on a single day. Study staff confirmed by telephone the ingestion of study medication within 2 weeks. Subsequent dosing occurred within 2 weeks of the anniversary of the first dose.

Outcome Measures

Participants' age, calcium intake, and fracture-risk profile were collected at baseline by questionnaire. *Falls* were defined as "an event reported either by the faller or a witness, resulting in a person inadvertently coming to rest on the ground or another lower level, with or without loss of consciousness or injury."[28] This definition was explained to participants and reinforced twice yearly via newsletter.

All contact with participants was by mail and telephone. Falls and fractures were recorded using postcard calendars completed daily by writing *F* if they had a fall, fracture, or both and *N* if they did not and were returned monthly by prepaid post.[26,29] Participants unable to send postcards were telephoned monthly.

When a fall or fracture was indicated, a standardized questionnaire recording details was administered by telephone. Only fractures radiologically confirmed were included in the analyses. Seventy-three self-reports were unconfirmed because of 1 of the following reasons: (1) not x-rayed (eg, suspected rib fracture), 13 vitamin D vs 15 placebo; (2) radiologist's report stated no fracture, 19 vitamin D vs 23 placebo; and (3) vertebral deformity with less than 20% height reduction, 2 vitamin D vs 1 placebo. Falls were classified as "resulting from active behavior"' when the participant, at the time of the fall, was walking, gardening, shopping, doing housework, engaging in sports, rushing, or climbing a ladder or chair. Other circumstances surrounding falls were classified as nonactive behavior. Calcium intake was quantified annually by questionnaire.[30]

The 150 substudy participants were randomly selected and results were assayed in a manner blinded to treatment group. Serum 25-hydroxycholecalciferol (DiaSorin, Stillwater, Minnesota) and intact parathyroid hormone ([PTH]; Advia Centaur Siemens, Deerfield, Illinois) was measured at baseline and 12 months after dose. In 2006 and 2007, measurements were also performed 1 and 3 months after dose.

Table 1. Baseline Characteristics of Participants[a]

	Vitamin D (n = 1131)	Placebo (n = 1125)
Age, median (IQR), y	76.0 (73.1-80.2)[b]	76.1 (73.0-79.7)[b]
Baseline risk profile reported by participant		
Self- or physician-reported high risk of falling	449 (39.7)	429 (38.1)
Broken bone since age 50 y[b]	384 (36.5)	343 (32.7)
Mother had broken hip[c]	98 (10.0)	99 (10.1)
Ever used walking aid	294 (26.0)	275 (24.4)
Baseline calcium intake, mg[d]		
<800	382 (34)	352 (32)
800-1100	318 (28)	283 (25)
1101-1300	135 (12)	168 (15)
>1300	273 (24)	296 (26)
Biochemical measures, median (IQR)[e]		
25-hydroxycholecalciferol, nmol/L	53 (40-65)	45 (40-57)
PTH, pmol/L	4.3 (2.9-7.0)	5.0 (3.7-6.6)

Abbreviations: IQR, interquartile range, PTH, parathyroid hormone.
SI conversion factors: To convert 25-hydroxycholecalciferol from nmol/L to ng/mL, divide by 2.496; PTH from pmol/L to pg/mL, divide by 0.1053.
[a] Results are expressed as No. (%) of participants in the groups unless otherwise specified.
[b] Total number of participants who completed the question were 1053 in the vitamin D group and 1050 in the placebo group.
[c] Total number of participants who completed the question were 985 in the vitamin D group and 985 in the placebo group.
[d] Baseline calcium questionnaire not completed by 49 participants: 23 in the vitamin D group and 26 in the placebo group.
[e] Biochemical measures were performed on a subset of 131 participants: 74 in the vitamin D group and 57 in the placebo group.

Sample Size

Based on 80% power and 5% level of significance, we calculated that 6855 person-years were needed to detect a 22% relative difference in fracture rates.[7] Our previous work demonstrates a 3.3% fracture rate among women older than 70 years[31] and suggests that hip and forearm fractures could be reduced by 16% and 31%, respectively, if summertime fracture rates were maintained throughout the year.[32] By using inclusion criteria based on risk factors for hip fracture, we estimated that our study participants would have a fracture rate 3-fold higher than community-dwelling women of the same age.

Statistical Methods

All analyses were intention-to-treat. Fall and fracture data were inclusive from date of first study medication to either completion or the last complete month of data (withdrawn or lost to follow-up). Initial comparisons of outcome measures between treatment groups were performed using χ^2 tests or Wilcoxon rank-sum tests, as appropriate. The primary outcome measures, numbers of falls and fractures, were analyzed using Poisson regression models with robust standard errors to allow for nonindependence of multiple events for the same participant. The models included only treatment group but were also fitted adjusting for baseline calcium intake (<800 mg, 800-1100 mg, 1100-1300 mg, or >1300 mg) and age. The data were also analyzed using negative binomial regression models that explicitly allow for overdispersion. For comparison with similar studies, time to first fracture and fall was analyzed using Cox proportional hazards models. Kaplan-Meier plots of cumulative incidence are presented.

Post hoc analyses were undertaken to investigate the relationship between the treatment effect and time since ingesting the annual dose. Each year of follow-up was split into 2 follow-up segments: at 3 months and 9 months after dosing. A generalized estimating equation approach was used to allow for correlation between a participant's falls and fractures at the different time periods. Estimated incidence rate ratios (RRs) for 0 through 3 months and 4 through 12 months after dosing are presented with the *P* value testing for homogeneity of the 2 incidence RRs.

No adjustment was made for multiple testing. All *P* values are 2-sided to detect differences, $P < .05$. Analyses were performed in Stata 10.1 (StataCorp, College Station, Texas).

Although adverse events were monitored, there was not a data and safety monitoring board or stopping rules because at the time the study commenced, these were not usual practice for vitamin D randomized controlled trials. US Food and Drug Administration and European Medicines Agency guidelines did not indicate a need, and based on published data, we had no expectation of harm.

RESULTS

Enrollment and outcomes are shown in FIGURE 1. There was no difference between the treatment groups in the proportion who withdrew nor in the reasons for withdrawal. All other participants were followed up until the predetermined study end in 2008. The proportion who commenced antifracture therapy during the intervention period did not differ (90 of 1131 in the vitamin D vs 87 of 1125 in the placebo group; $P = .84$).

The groups did not differ significantly by age, risk profile, calcium intake, or biochemistry (TABLE 1). The proportion who received medication in each month (March-August) was evenly distributed between the groups ($P = .66$).

On 163 occasions, participants did not receive a dose of study medication but continued to participate in the study and were included in the analysis. On 105 of these occasions, doses were held because 44 in the vitamin D and 61 in the placebo group reported taking more than 400 IU of vitamin D supplementation. On 58 occasions, 33 in the vitamin D and 25 in the placebo group declined a dose of study medication. Ingestion of study medication was confirmed annually for all other participants. At the end of the study, approximately 6% in the placebo group (as of 2008, 65 of 1125) and 3% (38 of 1131) in the vitamin D group were taking more than 400 IU/d of vitamin D supplements.

Table 2. Summary of Falls and Fractures[a]

Follow-up	Vitamin D (n = 1131)	Placebo (n = 1125)	*P* Value[b]
Intervention, median (IQR), y	2.96 (2.92-3.00)	2.96 (2.92-3.00)	.60
Total intervention time, y	3467.8	3457.4	
Total No. of falls and fractures[c]	2926	2538	
Falls, No. (%)			
0	294 (26.0)	356 (31.6)	.01
1	279 (24.7)	246 (21.9)	
≥2	558 (49.3)	523 (46.5)	
≥4	258 (22.8)	235 (20.9)	
≥8	72 (6.4)	55 (4.9)	
≥1 fall	837 (74.0)	769 (68.4)	.003
Falls and outcomes, No.			
Total falls[d]	2892	2512	
With fracture[d]	137	109	
Without fracture[d]	2755	2403	
With soft tissue injury[d,e]	1710	1488	.02[e]
Fractures, No.			
Total fractures[d]	171	135	
Without fall[d]	34	26	
≥1 Nonvertebral fracture[f]	124	101	

[a] Results are expressed as number (%) of participants in the groups unless otherwise specified.
[b] χ^2 Tests for binary outcomes, Wilcoxon rank-sum tests for continuous outcomes.
[c] Falls resulting in a fracture are counted as one event.
[d] Counting each event; one person can contribute more than once.
[e] Refers to bruise, abrasion, or muscle injury without fracture; *P* value refers to incidence rate ratio (1.15, 95% confidence interval, 1.02-1.29).
[f] The number of participants with at least 1 nonvertebral fracture. The number of participants with at least 1 fracture at the following sites were (vitamin D, placebo groups, respectively) hip (19, 15), colles (26, 23), other forearm (14, 7), vertebral (35, 28), humerus (15, 14), ribs (6, 7), clavicle/scapula (4, 1), pelvis (8, 4), upper leg/patella (8, 6), lower leg (6, 5), ankle (8, 12), foot/toes (17, 12), hand/fingers (6, 3), and skull/facial bones (8, 4).

Table 3. Incidence Rate Ratio for Falls and Fractures and Analysis Adjusted by Calcium Intake

	Incidence Rate Ratio for Vitamin D Group, Estimate (95% Confidence Interval)	*P* Value
No adjustment, No.		
Falls	1.15 (1.02-1.30)	.03
Fractures	1.26 (1.00-1.59)	.047
Nonvertebral fractures	1.28 (1.00-1.65)	.06
Adjusted for calcium intake, No.		
Falls adjusted	1.16 (1.03-1.31)	.02
Fractures adjusted	1.25 (0.99-1.58)	.06
Nonvertebral fractures	1.27 (0.98-1.65)	.08

Fall Outcomes

The 2256 participants had a total of 5404 falls over 6925 person-years. Seventy-four percent of 1131 women in the vitamin D group and 68% of 1125 women in the placebo group had at least 1 fall (TABLE 2). The vitamin D group had 2892 falls at a rate of 83.4 per 100 person-years vs 2512 in the placebo group at a rate of 72.7 per 100 person-years (incidence RR, 1.15; (95% CI, 1.02-1.30; $P = .03$; TABLE 3). The results did not change after adjusting for age nor when analyzed using negative binomial regression to allow for overdispersion. The cumulative incidence of first fall was increased in the vitamin D group (hazard ratio [HR], 1.16; 95% CI, 1.05-1.28; $P = .003$; FIGURE 2).

Increased falls in the vitamin D group were observed for each classification of falls: falls with fracture, falls without fracture, and falls with soft tissue injury (Table 2). The proportion of falls that resulted in a physician visit did not differ: 27.2% (778 of 2892) in the vitamin D group vs 26.1% (657 of 2512) in the placebo group.

Fracture Outcomes

One hundred fifty-five women receiving vitamin D sustained 171 fractures and 125 receiving placebo sustained 135 fractures (Table 2). The fracture rate in the vitamin D group was 4.9 per 100 person-years vs 3.9 in the placebo group. The incidence RR for fracture was 1.26 (95% CI, 1.00-1.59; $P = .047$) compared with the placebo group. Similarly, the nonvertebral fracture RR was 1.28 in the vitamin D group (incidence RR, 1.28; 95% CI, 1.00-1.65; $P = .06$). The HR cumulative incidence of first fracture was 1.26 in the vitamin D group compared with the placebo group (95% CI, 0.99-1.59; $P = .06$; Figure 2).

The frequency of falls among women who sustained a fracture did not differ between groups with a median of 2 falls (interquartile range [IQR], 1-4) throughout the study course.

Temporal Effect of Annual Dose

The incidence RR of falls in the vitamin D group was 1.31 in the first 3 months (95% CI, 1.12-1.54) following dosing, but only 1.13 (95% CI, 0.99-1.29) during the remaining 9 months of the year (*P* value for homogeneity=.02; TABLE 4). The temporal pattern of excess falls was observed each year except the first year.

Although not statistically significant, the temporal pattern observed in falls was also observed in fractures (Table 3). The vitamin D fracture incidence RR compared with the placebo group was 1.53 (95% CI, 0.95-2.46) in the first 3 months after dosing and 1.18 (95% CI, 0.91-1.54) during the following 9 months.

Calcium Intake and Questionnaire Data

The proportion of participants with calcium intake of less than 800 mg/d decreased from 33% at baseline to 27% over the subsequent annual assessments, whereas the proportion consuming 1100 mg or more increased from 40% to 46%. There was no difference between the groups in the categories of calcium intake (Table 1). The median daily calcium intake was 976 mg (IQR, 691-1311 mg).

The increased risk of both falls and fractures in the vitamin D group did not change after adjusting for baseline calcium intake. The overall calcium-adjusted incidence RR of falling was 1.16 (95% CI, 1.03-1-31); for fracture, 1.25 (95% CI, 0.99-1-58; Table 3) in the vitamin D group. The groups had a similar proportion of falls occurring during active behavior (79% vs 81%, respectively).

Biochemistry Substudy

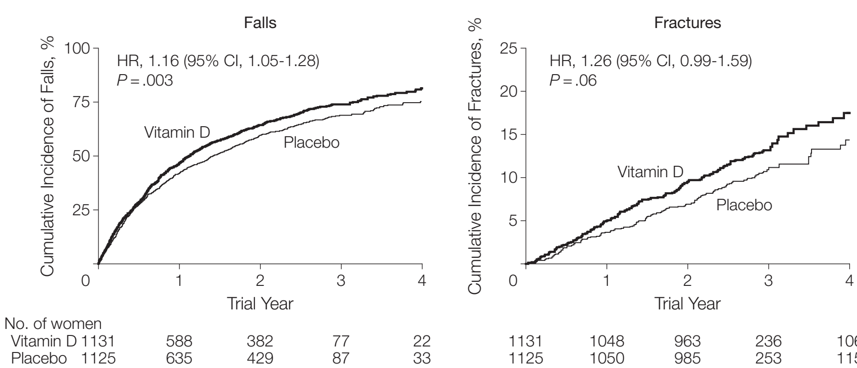
Ninety-one percent (137 of 150) of those invited to participate in the biochemistry substudy consented. Baseline samples were collected from 133 participants, 75 from the vitamin D group and 58 from the placebo group. One sample from each group was excluded because 25-hydroxycholecalciferol levels of 123 nmol/L and 115 nmol/L suggested that the women were taking more than 400 IU vitamin D supplementation per day.

At baseline, the median 25-hydroxycholecalciferol level was 49 nmol/L (IQR, 40-63; normal lower limit, >50 nmol/L). Less than 3% of the substudy participants had 25-hydroxycholecalciferol levels lower than 25 nmol/L. The 25-hydroxycholecalciferol and PTH levels did not differ between the groups (Table 1). Approximately half of the substudy participants had 25-hydroxycholecalciferol levels of 50 nmol/L or lower (vitamin D, 45.9% vs 61.4%, placebo) but less than 5% had levels of 25 nmol/L or lower (vitamin D, 4.0% vs 3.5%, placebo).

In each year of the study, samples were obtained 12 months after dose (ie, just prior to the second through fifth annual dose administrations and at study completion). There was a marked increase in 25-hydroxycholecalciferol levels in the vitamin D group with some evidence of this increase trailing off toward the end of the trial. The median 25-hydroxycholecalciferol levels 12 months after dose in the vitamin D group ranged from 55 nmol/L to 74 nmol/L over the 5 intervals with individual values ranging from 25 nmol/L to 120 nmol/L (FIGURE 3). The medians and IQRs of the PTH levels remained stable 12 months after dosing.

In 2006 and 2007, samples were collected at 1 and 3 months after dose in 102 (74%) of the substudy participants. The median 25-hydroxycholecalciferol level in the vitamin D group 1 month after dose was slightly more than 120 nmol/L with 82% at 100 nmol/L or higher and 24% at

Figure 2. Kaplan-Meier Plots of Cumulative Incidence of Time to First Fracture and First Fall



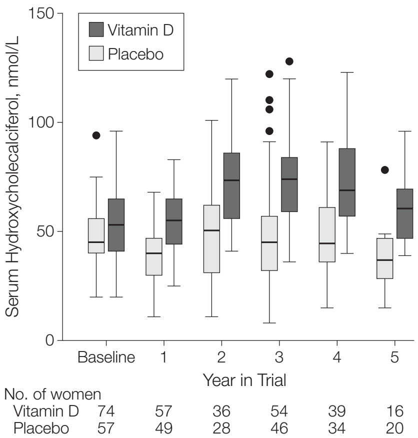
This analysis censors data after first fall or fracture. Time to first fracture and fall was analyzed using Cox proportional hazards models. CI indicates confidence intervals; HR, hazard ratio.

Table 4. Temporal Pattern of Risk in Falls and Fracture 0 to 3 Months and 4 to 12 Months After Treatment

	Incidence Rate Ratio for Vitamin D Group, Estimate (95% Confidence Interval)[a]	*P* Value
Time after treatment, mo		
Falls		
Within 3	1.31 (1.12-1.54)	.001
After 3	1.13 (0.99-1.29)	.08
Fracture		
Within 3	1.53 (0.95-2.46)	.08
After 3	1.18 (0.91-1.54)	.21

[a] The incidence rate ratio refers to the risk ratio of the vitamin D group compared with the placebo group. The rate ratio within 3 months after treatment is significantly different from the rate ratio of the remaining 9 months after treatment for falls (*P* = .02) but not for fracture (*P* = .36).

Figure 3. Serum 25-Hydroxycholecalciferol Levels at Baseline and 12 Months After Dose for Each Year of the Intervention



Serum 25-hydroxycholecalciferol levels in the vitamin D group differ from those of the placebo group at all 12-month assessments after dose ($P<.05$). The medians are shown as the horizontal bar within the rectangle and the interquartile range as the ends of the rectangle. The 5th and 95th percentiles are shown as lines (whiskers), and the closed circles represent outliers. The proportion of biochemistry substudy participants categorized into 25-hydroxycholecalciferol status is (vitamin D group, n=74 vs placebo group, n=57, respectively) 25 nmol/L or less: 4% vs 3.5%; 26 to 50 nmol/L: 41.9% vs 57.9%; 51 to 74 nmol/L: 44.5% vs 33.3%; 75 nmol/L or higher: 9.5% vs 5.3%. To convert 25-hydroxycholecalciferol from nmol/L to ng/mL, divide by 2.496.

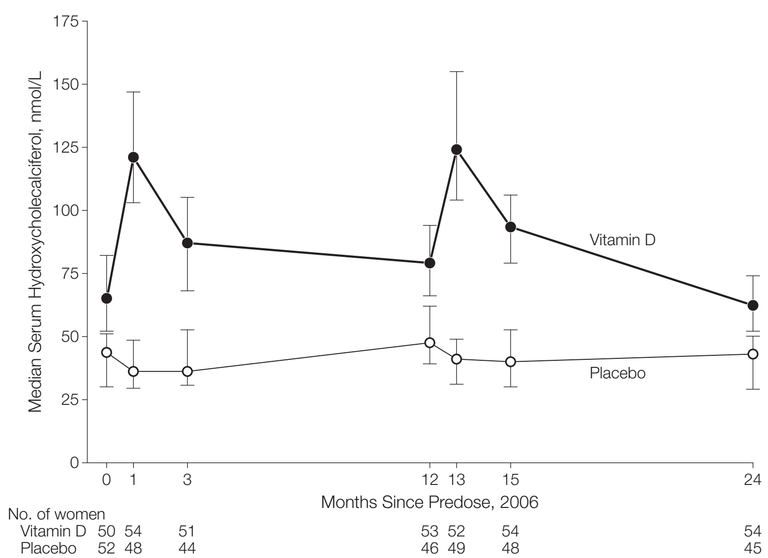
150 nmol/L or higher (FIGURE 4). By 3 months, the after-dose median 25-hydroxycholecalciferol levels decreased to approximately 90 nmol/L in the vitamin D group.

Adverse Events

A similar number of participants in each group reported at least 1 adverse event: 19.7% in the vitamin D and 17.8% in the placebo group. The most common adverse events were injury including fracture—15.2% (172 of 1131) of women taking vitamin D vs 12.1% (136 of 1125) taking placebo ($P=.03$)—and cardiovascular events—1.5% (171 of 1131) vs 1.2% (13 of 1125), respectively. Seven women (0.6%) in the vitamin D group vs 10 (0.9%) in the placebo group were diagnosed with cancer.

Serious adverse events (International Conference on Harmonization/WHO Good Clinical Practice definition including hospitalization or death) did not differ significantly: 244 among women taking vitamin D vs 207 women taking placebo ($P=.06$). Eighty-seven participants died during the study, 40 taking vitamin D vs 47 taking placebo. None of the serious adverse events were considered related to study medication.

Figure 4. Serum 25-Hydroxycholecalciferol Levels Before Dose, and at 1, 3, and 12 Months After Dose



The points refer to the median level of 25-hydroxycholecalciferol at the time of blood sampling and the error bars represent the interquartile range. These 7 blood sampling time points took place in 2006, 2007, and 2008, and refer to the biochemistry substudy participants.

COMMENT

Contrary to our hypothesis, participants receiving annual high-dose oral cholecalciferol experienced 15% more falls and 26% more fractures than the placebo group. Women not only experienced excess fractures after more frequent falls but also experienced more fractures that were not associated with a fall. A post hoc analysis found that the increased likelihood of falls in the vitamin D group was exacerbated in the 3-month period immediately following the annual dose and a similar temporal trend was observed for fractures. An increased risk (albeit, not significant because of smaller numbers) of falls and fracture in the vitamin D group was apparent for each year of the intervention. The results were similar after adjustment for baseline calcium intake; age was not included in the models because its inclusion did not affect the model estimates.

Data from the substudy indicate that the participants had intermediate 25-hydroxycholecalciferol levels at baseline, typical of community-dwelling older women of the region[25] and typical of older women in Northern Europe and North America.[33] The intervention effectively increased background 25-hydroxycholecalciferol levels. Predictably, the levels increased substantially 1 month after dosing and thereafter declined toward baseline but remaining on average 41% higher than levels in the placebo group at 12 months. The pattern is consistent with serial measurements done in older New Zealanders supplemented with 500 000 IU cholecalciferol.[34]

Only 1 other study has reported an increase in fracture associated with vitamin D treatment.[8] Participants (4354 men, 5086 women) 75 years or older received an annual injection of 300 000 IU vitamin D_2 as ergocalciferol or placebo. In men, treatment had no effect on fractures. However women treated with vitamin D had increased risk of nonvertebral (HR, 1.21), hip/femur (HR, 1.80), and hip/femur/wrist/forearm fractures

(HR, 1.59). No effect on falls was observed; however, falls were a secondary outcome and ascertainment was based on 6-month recall. Baseline and changes in 25-hydroxycholecalciferol and PTH levels were very similar to our results. Another common feature was that calcium supplements were not given. Whether calcium supplementation is beneficial in vitamin D intervention studies is uncertain. Studies that have shown reductions in fracture with vitamin D therapy have variously used[4,9,10] or not used[3,7] a calcium supplement. The RECORD (Randomised Evaluation of Calcium or Vitamin D)[2] study showed no benefit of adding calcium to vitamin D, using a factorial randomized study design.

The study of Chapuy et al[4] treated female nursing home residents (mean 25-hydroxycholecalciferol level, 36 nmol/L) with 800 IU of oral cholecalciferol plus 1.2 g of calcium or placebo taken daily. Hip and nonvertebral fractures were significantly reduced by about 25%. Likewise, in community-dwelling men and women randomized to receive 100 000 IU of oral cholecalciferol in 4 monthly doses, Trivedi et al[3] showed reductions in any fracture and fracture at the hip, wrist, forearm, or spine. Other studies report either reductions[7,9,10] or no effect[1,2,6,11,35] in fracture rates in the active groups. The Women's Health Initiative study[1] showed no effect of daily calcium plus 400 IU of cholecalciferol on fractures. The RECORD study[2] showed no effect in secondary prevention of fractures or falls in elderly participants treated daily with 800 IU of cholecalciferol alone, cholecalciferol plus calcium, or calcium alone, although only 54% were still taking study medication at 24 months. Other studies using intermittent oral vitamin D in older people living in residential care did not show any reduction in fractures.[11,13]

Meta-analyses suggest that there is a threshold level for vitamin D supplementation of more than 400 IU daily for fracture risk reduction and that reductions in hip and nonvertebral fractures are independent of calcium supplementation.[14-18] Doses of 700 to 800 IU daily reduced the risk of nonvertebral and hip fractures with stronger evidence of benefit in reducing hip fracture risk when the analysis was restricted to institutionalized adults.[18] By contrast, a Cochrane review[20] concluded that vitamin D therapy alone appeared unlikely to be effective in preventing fracture.

Evidence of risk reduction of falls with vitamin D supplementation with and without calcium is also inconsistent. Overall there appears to be an 11% to 19% reduction in fall risk with supplementation and a possible dose threshold of 700 to 1000 IU daily.[18,23] No fall risk reduction was observed for doses of less than 700 IU or achieved serum 25-hydroxycholecalciferol levels of less than 60 nmol/L, consistent with an earlier review of trials using varying doses of vitamin D that concluded that there was insufficient evidence that cholecalciferol treatment reduced falls.[36] Currently 600 IU (15 μg) per day is recommended for adults 70 years or older in the United States and Canada [37,38] with an upper limit of 2000 IU per day (~700 000 IU per year). Cholecalciferol 1000 IU is listed on the Australian Register of therapeutic goods. Although our results cannot necessarily be applied to high-dose vitamin D administered in divided doses over the year, they suggest that further study to assess safety is needed.

The major strength of our study is that it was a large randomized, double-blind, placebo-controlled trial. Falls and fracture ascertainment were robust,[29,39] although nonclinical vertebral fractures would have been missed. The pragmatic design of the study provided high potential for translation into public health policy and clinical practice. The main weaknesses of the study are also related to its pragmatic design—the participants were not evaluated at the study center so that baseline clinical information may have been missed. Biochemical assessment of all participants was not possible. We do not expect that any participants reached toxic levels of 25-hydroxycholecalciferol of 375 to 500 nmol/L[40] because the highest level at 1 month in the biochemistry substudy was 208 nmol/L. Pharmacokinetic studies in humans given a single, large oral dose of cholecalciferol indicate that 25-hydroxycholecalciferol levels peak at 7 to 21 days and thereafter decrease slowly (half-life, 60-90 days), so it is likely the peak levels were only marginally higher than the 1-month levels.[24,41] Furthermore, the incremental increase in 25-hydroxycholecalciferol is likely to be lower in those already replete prior to supplementation.[34]

This is the first study to demonstrate increased risk of falls associated with any vitamin D intervention and the second study to demonstrate an increased fracture risk associated with annual high-dose vitamin D therapy in elderly women. Our study used the largest total annual dose of vitamin D (500 000 IU) reported in any large randomized controlled trial, raising the possibility that the adverse outcome is dose-related. The opposing outcomes of 2 studies[3,8] that used the same total annual dose (300 000 IU intramuscularly) suggest that the dosing regimen (ie, 4 monthly vs annually) rather than the total dose might determine the outcome. This line of reasoning is supported by the temporal risk pattern that we observed and the fact that harm has not been reported in the numerous studies that have used more frequent dosing. Thus, it is reasonable to speculate that high serum levels of vitamin D or metabolites resulting from the large annual dose, subsequent decrease in the levels, or both might be causal. Furthermore, because the levels of 25-hydroxycholecalciferol demonstrated in this study could occur with other recommended dosing regimens,[42,43] the outcome of this study suggests that safety of high-dose vitamin D supplementation warrants further study.

Author Contributions: Dr Sanders had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sanders, Kotowicz, Young, Nicholson.

Acquisition of data: Sanders, Stuart.
Analysis and interpretation of data: Sanders, Stuart, Williamson, Simpson, Kotowicz, Nicholson.
Drafting of the manuscript: Sanders, Stuart.
Critical revision of the manuscript for important intellectual content: Sanders, Williamson, Simpson, Kotowicz, Nicholson.
Statistical analysis: Sanders, Stuart, Williamson, Simpson.
Obtained funding: Sanders, Kotowicz, Young, Nicholson.
Administrative, technical, or material support: Stuart, Nicholson.
Study supervision: Sanders, Nicholson.
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Role of the Sponsor: The funding organizations were independent of the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
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Financial Disclosures: Dr O'Brien reported receiving compensation as the national medical director for the American Institute of Gastric Banding since 2007, and receiving compensation as author of the book *The Lap-Band Solution: A Partnership for Weight Loss*. Dr Dixon reported that he has a consultancy with Allergan and is a member of the Allergan diabetes advisory board; has consultancies with Bariatric Advantage, Scientific Intake, and SP Health Co; serves on the Optifast medical advisory board, the diabetes advisory board for Allergan Inc, and the medical advisory board for Bariatric Advantage; and has served on speakers' bureaus for Abbott Australasia, Allergan Inc, Bariatric Advantage, Eli Lilly Australia, Merck Sharp & Dohme Australia, Nestle Australia, and Roche Products Australia. No other disclosures were reported.

1. Oude Luttkhuis H, Baur L, Jansen H, et al. Interventions for treating obesity in children. *Cochrane Database Syst Rev*. 2009;(1):CD001872.

Failure to Report Financial Disclosure Information in a Study of Gastric Banding in Adolescent Obesity

To the Editor: I would like to apologize to the editors and readers of *JAMA* for a misunderstanding of the *JAMA* policy for reporting financial disclosures. In the study of gastric banding in adolescent obesity published in the February 10, 2010, issue of *JAMA*,[1] I reported no conflicts of interest. However, on advice from the editors of the journal, I report 2 additional associations that may be relevant to readers, and I apologize for the failure to disclose these. I also provide a correction of an earlier declaration.

First, I receive compensation as the national medical director of the American Institute of Gastric Banding, a multicenter clinical facility based in Dallas, Texas, that treats obesity predominantly by gastric banding. Second, I have written a patient information book entitled *The Lap-Band Solution: A Partnership for Weight Loss*, which was published by Melbourne University Publishing in 2007. Most copies are given to patients without charge but I derive a financial benefit from the copies that are sold.

In another study published in the January 23, 2008, issue of *JAMA*,[2] I inaccurately reported receiving research grants from the National Health and Medical Research Council (Australia), Allergan Health, and Novartis. The grants were in fact awarded to the Centre for Obesity Research and Education (CORE) of Monash University; I am the director of CORE but am not paid any remuneration by CORE or by Monash University. I also inaccurately reported receiving compensation for serving on the speakers' panel and the medical advisory board of Allergan Health. However, I had provided these services in the past to Inamed Corporation prior to its purchase by Allergan 5 years ago but have never provided these services to Allergan.

The complete disclosure information is provided below and in an accompanying correction. I regret any lack of transparency that my failure to provide this information may have created.

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1. O'Brien PE, Sawyer SM, Laurie C, et al. Laparoscopic adjustable gastric banding in severely obese adolescents: a randomized trial. *JAMA*. 2010;303(6): 519-526.
2. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA*. 2008; 299(3):316-323.

CORRECTIONS

Incomplete Financial Disclosures: In the Original Contribution entitled "Laparoscopic Adjustable Gastric Banding in Severely Obese Adolescents: A Randomized Trial," published in the February 10, 2010, issue of *JAMA* (2010;303[6]:519-526), the financial disclosures were incomplete. In addition to what was published, the following should also have appeared: "Dr O'Brien reported receiving compensation as the national medical director for the American Institute of Gastric Banding since 2007, and receiving compensation as author of the book *The Lap-Band Solution: A Partnership for Weight Loss*." A letter of apology accompanies this correction.

Financial Disclosure Clarification: In an Editorial entitled "Surgical Treatment of Obesity in Adolescence," published in the February 10, 2010, issue of *JAMA* (2010; 303[6]:559-560), the financial disclosure section should have read: Dr Livingston reported that in 2008 he received an honorarium from Allergan for attending an advisory board meeting. He reported that he has had no direct or indirect financial relationship with Allergan before that single meeting and has had none since.

Errors in Reference Citations: In the Care of the Aging Patient article entitled "The Older Adult Driver With Cognitive Impairment: 'It's a Very Frustrating Life,' " published in the April 28, 2010, issue of *JAMA* (2010;303[17]:1632-1641), there were errors in the reference citations and in the order of citations. The article was corrected online on May 17, 2010.

Incorrect Data: In the Original Contribution entitled "Annual High-Dose Oral Vitamin D and Falls and Fractures in Elderly Women: A Randomized Controlled Trial," published in the August 18, 2004, issue of *JAMA* (2010;303[18]:1815-1822), an error occurred on page 1818. In the second sentence of the "Falls Outcomes" subsection of the "Results" section on page 1818 that read "Seventy-four percent of 837 women in the vitamin D group and 68% of 769 women in the placebo group had at least 1 fall (Table 2)" should have read "Seventy-four percent of 1131 women in the vitamin D group and 68% of 1125 women in the placebo group had at least 1 fall (Table 2)."