Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women
A Randomized Controlled Trial

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T HE 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%,1,16 whereas others conclude that vitamin D is ineffective. A Cochrane analysis19 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 low1,2,6 and fracture risk reduction was greater among adherent than nonadherent participants.

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.

Trial Registration anzctr.org.au Identifier: ACTRN1260500658617; isrctn.org Identifier: ISRCTN83409867

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For editorial comment see p 1861.
ciferol administered intramuscularly as a single annual dose.' The study was designed so that the vitamin D treatment would prevent decreases in 25-hydroxycholecalciferol over winter, 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. 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, defined by criteria such as maternal hip fracture, past fracture, or self-reported faller. 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.” 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. 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 study 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 dosing. In 2006 and 2007, measured falls and fractures, were analyzed using Poisson regression models that explicitly allow for overdispersion. 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).

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 par-

### Table 1. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Age, median (IQR), y</th>
<th>Vitamin D (n = 1131)</th>
<th>Placebo (n = 1125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>76.0 (73.1-80.2)</td>
<td>76.1 (73.0-79.7)</td>
<td></td>
</tr>
<tr>
<td>Baseline risk profile reported by participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self- or physician-reported high risk of falling</td>
<td>449 (39.7)</td>
<td>428 (38.1)</td>
</tr>
<tr>
<td>Broken bone since age 50 y²</td>
<td>384 (36.5)</td>
<td>343 (32.7)</td>
</tr>
<tr>
<td>Mother had broken hip⁵</td>
<td>98 (10.0)</td>
<td>99 (10.1)</td>
</tr>
<tr>
<td>Ever used walking aid⁶</td>
<td>294 (26.0)</td>
<td>275 (24.4)</td>
</tr>
<tr>
<td>Baseline calcium intake, mg²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;800</td>
<td>382 (34)</td>
<td>352 (32)</td>
</tr>
<tr>
<td>800-1100</td>
<td>318 (28)</td>
<td>283 (25)</td>
</tr>
<tr>
<td>1101-1300</td>
<td>135 (12)</td>
<td>168 (15)</td>
</tr>
<tr>
<td>&gt;1300</td>
<td>273 (24)</td>
<td>296 (26)</td>
</tr>
<tr>
<td>Biochemical measures, median (IQR)⁸</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-hydroxycholecalciferol, nmol/L</td>
<td>53 (40-65)</td>
<td>45 (40-57)</td>
</tr>
<tr>
<td>PTH, pmol/L</td>
<td>4.3 (2.9-7.0)</td>
<td>5.0 (3.7-6.6)</td>
</tr>
</tbody>
</table>

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.

²Results are expressed as No. (%) of participants in the groups unless otherwise specified.

³Total number of participants who completed the question were 1053 in the vitamin D group and 1050 in the placebo group.

⁴Total number of participants who completed the question were 985 in the vitamin D group and 985 in the placebo group.

⁵Baseline calcium questionnaire not completed by 49 participants: 23 in the vitamin D group and 26 in the placebo group.

⁶Biochemical measures were performed on a subset of 131 participants: 74 in the vitamin D group and 57 in the placebo group.

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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 23 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.

### Fall Outcomes

The 2256 participants had a total of 3404 falls over 6923 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).

![Table 2. Summary of Falls and Fractures](https://jama.jamanetwork.com/)

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

\( a \)Results are expressed as number (%) of participants in the groups unless otherwise specified.

\( b \) \( x \) 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, 1.02-1.28).

\( f \) The number of participants with at least 1 vertebral fracture. The number of participants with at least 1 fracture at the following sites were (vitamin D, placebo groups, respectively) hip (19, 15), coteis (26, 23), other forearm (14, 7), vertebra (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](https://jama.jamanetwork.com/)

<table>
<thead>
<tr>
<th>Incidence Rate Ratio for Vitamin D Group, Estimate (95% Confidence Interval)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjustment, No.</td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>1.15 (1.02-1.30)</td>
</tr>
<tr>
<td>Fractures</td>
<td>1.26 (1.00-1.59)</td>
</tr>
<tr>
<td>Nonvertebral fractures</td>
<td>1.28 (1.00-1.65)</td>
</tr>
<tr>
<td>Adjusted for calcium intake, No.</td>
<td></td>
</tr>
<tr>
<td>Falls adjusted</td>
<td>1.16 (1.03-1.31)</td>
</tr>
<tr>
<td>Fractures adjusted</td>
<td>1.26 (0.99-1.58)</td>
</tr>
<tr>
<td>Nonvertebral fractures</td>
<td>1.27 (0.98-1.65)</td>
</tr>
</tbody>
</table>
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

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**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>
<thead>
<tr>
<th>Table 4. Temporal Pattern of Risk in Falls and Fractures 0 to 3 Months and 4 to 12 Months After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence Rate Ratio for Vitamin D Group, Estimate (95% Confidence Interval)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Time after treatment, mo</strong></td>
</tr>
<tr>
<td><strong>Within 3</strong></td>
</tr>
<tr>
<td><strong>After 3</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup>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=.001) but not for fracture (P=.36).

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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 28.6%; 75 nmol/L or higher: 9.5% vs 5.3%. To convert 25-hydroxycholecalciferol from nmol/L to ng/ml, divide by 2.496.

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.

**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 and typical of older women in Northern Europe and North America. 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.

Only 1 other study has reported an increase in fracture associated with vitamin D treatment. 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.
Evaluation of Calcium or Vitamin D
et al3 showed reductions in any frac-
ture and fracture at the hip, wrist, fore-
arm, or spine. Other studies report
in fracture rates in the active groups.
The Women’s Health Initiative study1
showed no effect of daily calcium plus
400 IU of cholecalciferol on fractures. The RECORD study2 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 cal-
cium alone, although only 54% were
still taking study medication at 24
months. Other studies using intermit-
tent oral vitamin D in older people liv-
ing in residential care did not show any
reduction in fractures.11,13

Meta-analyses suggest that there is a
threshold level for vitamin D supple-
mentation of more than 400 IU daily for fracture risk reduction and that re-
ductions in hip and nonvertebral frac-
tures are independent of calcium
supplementation.14-16 Doses of 700 to
800 IU daily reduced the risk of non-
vertebral and hip fractures with stron-
ger evidence of benefit in reducing hip
fracture risk when the analysis was re-
stricted to institutionalized adults.18 By
contrast, a Cochrane review19 con-
cluded that vitamin D therapy alone ap-
peared unlikely to be effective in pre-
venting fracture.

Evidence of risk reduction of falls
with vitamin D supplementation with-
out and with calcium is also inconsist-
ent. Overall there appears to be an 11% to
19% reduction in fall risk with supple-
mentation 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
peak levels were only marginally higher
than the 1-month levels.24,41 Further-
more, 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 demon-
strate increased risk of falls associated
with any vitamin D intervention and the
second study to demonstrate an in-
creased fracture risk associated with an-
nual high-dose vitamin D therapy in el-
derly women. Our study used the
largest total annual dose of vitamin D
(500 000 IU) reported in any large ran-
donized controlled trial, raising the
possibility that the adverse outcome is
dose-related. The opposing outcomes
of 2 studies3,8 that used the same total
annual dose (300 000 IU intramuscu-
larly) suggest that the dosing regimen
(ie, 4 monthly vs annually) rather than
the total dose might determine the out-
come. This line of reasoning is sup-
ported 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 specu-
late that high serum levels of vitamin D
or metabolites resulting from the
large annual dose, subsequent de-
crease in the levels, or both might be
causal. Furthermore, because the lev-
els of 25-hydroxycholecalciferol dem-
onstrated in this study could occur with
other recommended dosing regi-
mens,12,43 the outcome of this study sug-
gests 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.

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