Prevention of Nonvertebral Fractures With Oral Vitamin D and Dose Dependency

A Meta-analysis of Randomized Controlled Trials

Heike A. Bischoff-Ferrari, DrPH; Walter C. Willett, DrPH; John B. Wong, MD; Andreas E. Stuck, MD; Hannes B. Staehelin, MD; E. John Orav, PhD; Anna Thoma, MD; Douglas P. Kiel, MD; Jana Henschkowsk, MD

Background: Antifracture efficacy with supplemental vitamin D has been questioned by recent trials.

Methods: We performed a meta-analysis on the efficacy of oral supplemental vitamin D in preventing nonvertebral and hip fractures among older individuals (≥65 years). We included 12 double-blind randomized controlled trials (RCTs) for nonvertebral fractures (n=42,279) and 8 RCTs for hip fractures (n=40,886) comparing oral vitamin D, with or without calcium, with calcium or placebo. To incorporate adherence to treatment, we multiplied the dose by the percentage of adherence to estimate the mean received dose (dose × adherence) for each trial.

Results: The pooled relative risk (RR) was 0.86 (95% confidence interval [CI], 0.77-0.96) for prevention of nonvertebral fractures and 0.91 (95% CI, 0.78-1.05) for the prevention of hip fractures, but with significant heterogeneity for both end points. Including all trials, antifracture efficacy increased significantly with a higher dose and higher achieved blood 25-hydroxyvitamin D levels for both end points. Consistently, pooling trials with a higher received dose of more than 400 IU/d resolved heterogeneity. For the higher dose, the pooled RR was 0.80 (95% CI, 0.72-0.89; n=33,265 subjects from 9 trials) for nonvertebral fractures and 0.82 (95% CI, 0.69-0.97; n=31,872 subjects from 5 trials) for hip fractures. The higher dose reduced nonvertebral fractures in community-dwelling individuals (−29%) and institutionalized older individuals (−15%), and its effect was independent of additional calcium supplementation.

Conclusion: Nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older.

Arch Intern Med. 2009;169(6):551-561
fracture efficacy by received dose, achieved 25-hydroxyvitamin D levels, and in predefined subgroups.

METHODS

SEARCH STRATEGY AND DATA EXTRACTION

We conducted a systematic review of all English and non-English articles using MEDLINE (Ovid, PubMed) and the Cochrane Controlled Trials Register from January 1960 through August 2008 and EMBASE from January 1991 through August 2008. Additional studies were identified from reference lists, contacts with experts in the field, and abstracts presented at the American Society for Bone and Mineral Research from 1995 through 2007.

The medical subject headings (MeSH terms) included trials (randomized-controlled-trial or controlled-clinical-trial or random-allocation or double-blind-method or single-blind-method or uncontrolled-trials), vitamin D (cholecalciferol or 25-hydroxycholecalciferol or calcifediol or dihydroxycholecalciferol or calcitriol or vitamin D3 [analogues and derivates] or ergocalciferol or vitamin D/3 [blood]), fractures (femoral fractures, femoral neck fractures, hip fractures, humerus fractures, forearm fractures, radius fractures, ankle fractures, nonvertebral fractures), accidental falls or falls, humans, elderly, bone fractures (femoral fractures, femoral neck fractures), vitamin D supplementation (cholecalciferol or random-allocation or double-blind-controlled-trial or controlled-clinical-trial or double-blind-regimen or placebo), vitamin D dose received.

We excluded uncontrolled trials, observational studies, and animal studies. Because our target population consisted of older persons, the mean age of study subjects had to equal or exceed 65 years. To be included in the primary analysis, we required a double-blind study design, a report of blinded study design, and a statement explaining adherence: and a statement explaining adherence to treatment allocation. Trials that met all features but had an open study design were included in sensitivity analyses. Twelve studies (listed in Table 1) for supplemental vitamin D were identified through our MeSH term search. Four additional studies with an open study design were identified for the sensitivity analysis3,26-28 (Table 2 and Figure 1).

QUALITY ASSESSMENT AND STUDIES IDENTIFIED

To be included as trials with minimal bias, studies had to be randomized and masked to treatment allocation. Trials that met all features but had an open study design were included in sensitivity analyses. Twelve studies (listed in Table 1) for supplemental vitamin D were identified through our MeSH term search. Four additional studies with an open study design were identified for the sensitivity analysis3,26-28 (Table 2 and Figure 1).

STATISTICAL ANALYSIS

Outcomes were analyzed on an intention-to-treat basis with random effects models.27 We calculated the risk difference to determine the number needed to treat (NNT) to prevent 1 fracture. Heterogeneity among studies was explored by predefined covariates using the Q-statistic as a test (considered significant for P < .10). The presence of heterogeneity suggests that the studies should not be pooled because of significant differences in results.29 In such cases, we explored heterogeneity by received dose (dose × adherence: ≤400 IU/d vs >400 IU/d of vitamin D)12 and achieved 25-hydroxyvitamin D level using visual inspection, and random-effects metaregression analysis. Predefined subgroup analyses included age, type of dwelling, and additional calcium supplementation. To evaluate publication bias, we used Begg and Egger tests with all 12 trials from the primary analysis or all 16 trials from the sensitivity analysis. Although the Begg funnel plot suggested a possible absence of negative studies involving small sample sizes, the trim and fill analysis did not confirm this suggestion.30 Statistical analysis was performed with Stata software (version 8.0; StataCorp LP, College Station, Texas).

Table 1 shows characteristics of the 12 double-blind RCTs that were included in the primary analysis for the prevention of nonvertebral fractures, 8 of which were also included in the primary analysis for hip fracture. The 12 trials included 42 279 individuals with a mean age of 78 years, and 89% were women. The received dose of vitamin D (dose × adherence) was 400 IU/d or less in 3 trials2,19,22 whereas the other 9 RCTs had mean intakes of 482 to 770 IU/d. A total of 500 to 1200 mg/d of calcium supplementation was used in combination with vitamin D supplementation in 7 RCTs. Treatment duration varied from 12 to 84 months.

NONVERTEBRAL FRACTURES

In the 12 high-quality RCTs (listed in Table 1) (n = 42 279 participants), the pooled RR for any dose of vitamin D preventing nonvertebral fractures was 0.86 (95% CI, 0.77-0.96). However, heterogeneity in results was seen among studies (Q test: P = .04). After stratifying trials by received dose, heterogeneity was resolved. For the 3 high-quality trials3,19,22 (9014 individuals) with a received low dose of 400 IU/d or less of vitamin D (340-380
IU/d) of vitamin D or less did not reduce nonvertebral fracture risk (Table 3). For 9 trials with a higher received dose of more than 400 IU/d of vitamin D (482-770 IU; 33,265 individuals; Table 4), the pooled RR was 0.80 (95% CI, 0.72-0.89; Q-test: $P = .31$) suggesting that 482 to 770 IU/d of vitamin D reduced nonvertebral fracture risk by 20% (Figure 2A). The pooled risk difference for the higher received dose
Table 2. Supplemental Vitamin D: Open Study Design Randomized Controlled Trials Excluded From the Primary Analyses

<table>
<thead>
<tr>
<th>Source</th>
<th>Participants, No.</th>
<th>Treatment/d, % Adherence</th>
<th>Dwelling</th>
<th>Age, Mean, y</th>
<th>Duration, mo</th>
<th>25-Hydroxyvitamin D Levels, mean nmol/L, a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porthouse et al</td>
<td>3314 women</td>
<td>800 IU cholecalciferol + 1000 mg calcium (calcium carbonate) vs control group (advise on fall prevention and adequate calcium and vitamin D intake) &lt;60</td>
<td>Community-dwelling</td>
<td>≥70</td>
<td>Median follow up: 25</td>
<td>ND</td>
</tr>
<tr>
<td>Harwood et al</td>
<td>76 women</td>
<td>800 IU cholecalciferol + 1000 mg calcium vs control group (no placebo)</td>
<td>Rehabilitation ward, previous community-dwelling</td>
<td>82 (67-92)</td>
<td>12</td>
<td>29 (6-75), to 50 at 12-mo follow-up, n=58</td>
</tr>
<tr>
<td>Law et al</td>
<td>3717 (76% women)</td>
<td>1100 IU ergocalciferol (as 100 000 IU ergocalciferol every 3 mo) vs no treatment (no placebo); no data on adherence</td>
<td>Living in residential accommodation</td>
<td>85</td>
<td>Median= 10 (IQR, 7-14)</td>
<td>47 (35-102), to 74 (52-110) at 3-mo follow-up, n=18 (1% of the treated population)</td>
</tr>
<tr>
<td>Larsen et al</td>
<td>7073 (4256 women, 2817 men)</td>
<td>400 IU cholecalciferol + 1000 mg calcium (calcium carbonate) vs control group (no placebo)</td>
<td>Community-dwelling</td>
<td>75</td>
<td>42</td>
<td>37 (19), at 24-mo follow-up: 47 (20), n=85</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; ND, not determined in the trial population during the course of the trial.

Conventional unit conversion factor: To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496.

Values are given as either mean or mean (range).

Figure 1. Flowchart of studies.

was 1.1% (95% CI, 0.6%-1.5%, P < .001), so the NNT was 93 [95% CI, 66-160] for 12 to 84 months.

In metaregression analyses, a greater reduction in nonvertebral fractures was seen both with a higher received dose (P = .003; Figure 3A) and with higher achieved 25-hydroxyvitamin D levels (P = .04; Figure 3B).

In subgroup analyses (Table 4), the pooled RR for nonvertebral fractures was 10% in trials that used ergocalciferol compared with 23% for trials that used cholecalciferol (for metaregression, P = .07). The effect of vitamin D was significant among all subgroups according to age and dwelling, with a somewhat greater effect among younger persons and those living in the community, but the differences were not significant (see Table 4 for Q-test P values). The combined effect of calcium plus vitamin D compared with placebo was tested in 4 trials (all using cholecalciferol) with a pooled RR reduction of 21%. The effect of vitamin D alone (either vitamin D vs placebo or vitamin D plus calcium compared with calcium alone) was tested in 5 trials, also with a pooled RR reduction of 21%. Thus, the addition of calcium to adequate intakes of vitamin D does not seem to enhance the effect of vitamin D in reducing nonvertebral fractures. Based on limited data for men (n = 2037), there was no significant heterogeneity by sex (Q test: P = .93).

SENSITIVITY ANALYSES FOR NONVERTEBRAL FRACTURES

For any received dose, after adding the 4 open study design trials to the 12 double-blinded trials, the pooled RR for vitamin D preventing any nonvertebral fracture, including 56 459 individuals, was 0.88 (95% CI, 0.80-0.97), and significant heterogeneity among studies remained (Q test:...
We therefore again stratified studies by dose received. For the lower received dose, after adding 1 open study design trial to the 3 double-blind trials (16 087 individuals), the pooled RR was 0.96 (95% CI, 0.84-1.01; Table 3). For the higher received dose, after adding 3 open study design trials to the 9 double-blind trials (40 372 individuals), the pooled RR was 0.83 (95% CI, 0.74-0.95; Table 4). However, variation in results was seen between open study design (summarized in Table 5) and double-blind trials (Q test: 0.07), suggesting that trial quality introduces heterogeneity.

HIP FRACTURES

In the 8 high-quality trials (40 886 individuals), the pooled RR for any dose of vitamin D preventing hip fractures was 0.91 (95% CI, 0.78-1.05). However, heterogeneity in results was seen among studies (Q test: 0.08). After stratifying trials by received dose, heterogeneity was resolved. For the 3 high-quality trials (9014 individuals) on a received low dose of less than 400 IU/d of vitamin D (340-380 IU; all using cholecalciferol), the pooled RR was 1.09 (95% CI, 0.90-1.32; Q test: 0.81 (Table 6).

For the 5 trials with a higher received dose of more than 400 IU/d (482-770 IU; 31 872 individuals) (Table 7), the pooled RR was 0.82 (95% CI, 0.69-0.97; Q test: 0.18).
Thus, the higher dose of vitamin D reduced hip fracture risk by 18% (Figure 2B). The pooled risk difference for the higher received dose was 0.60% (0.23%-0.96%; P = .02), so the NNT was 168 (95% CI, 104-440) for 12 to 84 months.

In metaregression analyses, a greater reduction in hip fractures was seen both with higher received dose (P = .07; Figure 4A) and higher achieved 25-hydroxyvitamin D levels in the treatment group (P = .01; Figure 4B). Owing to the smaller number of trials with a fracture end point, subgroup analyses were limited because there was only 1 trial using ergocalciferol at a higher dose, 3 1 trial among individuals 65 to 74 years of age, 3 1 trial among men, 17 and 2 trials using vitamin D alone. 4 17 (Table 7).

Sensitivity Analyses for Hip Fracture Prevention

For any received dose, after adding 2 open study design trials to the 8 double-blinded trials (47 917 individuals), the pooled RR was 0.92 (95% CI, 0.80-1.06), but variation among studies remained significant (Q test: P = .10).

For the higher received dose, after adding 2 open study design trials to the 5 double-blinded trials (38 903 individuals), the pooled RR was 0.84 (95% CI, 0.71-0.99; Q test: P = .17; Table 7; higher-dose open study design trials are summarized in Table 8). For hip fractures, there were no lower-dose trials with an open study design.

1α-Hydroxylated Vitamin D and Nonvertebral Fracture Prevention

Table 9 shows characteristics of 7 RCTs that were included in the analysis for 1α-hydroxylated vitamin D. 32-38 None of the trials reported separate data for hip fractures. The 7 trials included 1484 individuals, all 65 to 74 years of age and 99.7% of whom were women.

The pooled RR for any type of 1α-hydroxylated vitamin D preventing nonvertebral fractures compared with placebo or calcium was 0.58 (95% CI, 0.37-0.92), similar to the RR for a higher dose of supplemental vitamin D in the same age group (Table 4 and Table 10; the ratio of the 2 effect sizes: pooled RR of supplemental vitamin D to pooled RR of 1α-hydroxylated vitamin D = 0.67/0.58 = 1.16; 95% CI, 0.44-3.03).

COMMENT

In this meta-analyses of 12 double-blinded trials among individuals aged 65 years or older, the antifracture efficacy of supplemental vitamin D increased significantly with higher received dose or higher achieved 25-hydroxyvitamin D levels for any nonvertebral fractures and for hip fractures. No fracture reduction was observed for a received dose of 400 IU/d or less, whereas a higher received dose of 482 to 770 IU/d of supplemental vitamin D reduced nonvertebral fractures by 20% and hip fractures by 18%. Subgroup analyses for the prevention of nonvertebral fractures with the higher received dose suggested possibly better fracture reduction with cholecalciferol compared with ergocalciferol, whereas additional calcium did...
not further improve antifracture efficacy. Nonvertebral fracture reduction with the higher received dose was significant among all subgroups by age and dwelling, including younger individuals aged 65 to 74 years and those living in the community (see Table 4 for P values).

In August 2007, a review and meta-analysis3 by the US Department of Health and Human Services (DHHS) addressed the effect of vitamin D supplementation on all fractures in postmenopausal women and men aged 50 years or older. The pooled results for all fractures included 10 double-blinded and 3 open study design trials (n = 58,712) and did not support a significant reduction of fractures with vitamin D (pooled odds ratio, 0.90; 95% CI, 0.81-1.02). The report3 suggested that the benefit of vitamin D may depend on additional calcium and may be primarily seen in institutionalized individuals, which is consistent with the meta-analysis of Boonen et al.6 However, in both reports,3,6 heterogeneity by dose may have been missed owing to the inclusion of open study design trials plus a dose evaluation that did not incorporate adherence. Biologically, the exclusion of heterogeneity by dose seems implausible even if a formal test of heterogeneity is not statistically significant.

In our meta-analysis, the dose of vitamin D and achieved 25-hydroxyvitamin D levels were identified as important sources of variation in the antifracture efficacy of supplemental vitamin D. Our findings confirm the findings of an earlier 2005 primary prevention meta-analysis12 after including 5 additional trials.

### Figure 3. Nonvertebral fracture prevention by received dose and achieved 25-hydroxyvitamin D levels in treatment group. Triangles indicate trials with cholecalciferol; circles, trials with ergocalciferol. The solid curves indicate the relative risk (RR) of 1.0, the dashed curves indicate a trend line through the point estimates of all trials (RRs of individual trials). All 12 high-quality trials were included for the received dose metaregression (n = 42,279 individuals). For achieved 25-hydroxyvitamin D levels 2 trials13,15 did not provide serum 25-hydroxyvitamin D levels measured in the study population during the trial period. For these trials, the achieved 25-hydroxyvitamin D levels were estimated from the serum 25-hydroxyvitamin D levels measured during the trial period. The solid curves indicate the relative risk (RR) of 1.0; the dashed curves indicate a trend line through the point estimates of all trials (RRs of individual trials). All 12 high-quality trials were included for the received dose metaregression (n = 42,279 individuals). For achieved 25-hydroxyvitamin D levels 2 trials13,15 did not provide serum 25-hydroxyvitamin D levels measured in the study population during the trial period. For these trials, the achieved 25-hydroxyvitamin D levels were estimated from the serum 25-hydroxyvitamin D levels measured during the trial period. The solid curves indicate the relative risk (RR) of 1.0; the dashed curves indicate a trend line through the point estimates of all trials (RRs of individual trials). All 12 high-quality trials were included for the received dose metaregression (n = 42,279 individuals). For achieved 25-hydroxyvitamin D levels 2 trials13,15 did not provide serum 25-hydroxyvitamin D levels measured in the study population during the trial period. For these trials, the achieved 25-hydroxyvitamin D levels were estimated from the serum 25-hydroxyvitamin D levels measured during the trial period.

### Table 5. Trials With Higher Received Dose for Nonvertebral Fracture Prevention With Open Study Design and Excluded From the Primary Analysis

<table>
<thead>
<tr>
<th>Source and Type of Vitamin D Supplement</th>
<th>Received Dose × Treatment</th>
<th>Year</th>
<th>No./Total Treated</th>
<th>No./Total Control</th>
<th>Effect RR (95% CI)</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porthouse et al1 (cholecalciferol)</td>
<td>480 (cholecalciferol)</td>
<td>2005</td>
<td>58/1321</td>
<td>91/1993</td>
<td>0.962 (0.697-1.327)</td>
<td>3314</td>
</tr>
<tr>
<td>Law et al2 (ergocalciferol)</td>
<td>1100 (ergocalciferol)</td>
<td>2006</td>
<td>64/1782</td>
<td>51/1955</td>
<td>1.385 (2.017-2.185)</td>
<td>3717</td>
</tr>
<tr>
<td>Harwood et al2 (cholecalciferol)</td>
<td>800 (cholecalciferol)</td>
<td>2004</td>
<td>3/39</td>
<td>5/37</td>
<td>0.569 (0.148-2.185)</td>
<td>76</td>
</tr>
<tr>
<td>Pool results for 3 HD OSD trials (these trials were included in the sensitivity analysis in Table 1)</td>
<td>125/3272</td>
<td>147/3985</td>
<td>1.10 (0.78-1.55)</td>
<td>7107</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HD, higher dose; OSD, open study design; RR, relative risk.

*There was a greater than 10% reduction in nonvertebral fractures, and the P value for the Q test was .20.
Despite the well-documented inter-vitamin D and fracture reduction. presence of a dose-response rela-
tionship between supplemental vitamin D and fracture reduction. Despite the well-documented inter-

Table 6. Primary Pooled Analysis for a Lower Received Dose of Supplemental Vitamin D (340-380 IU/d) and the Prevention of Hip Fractures

<table>
<thead>
<tr>
<th>Source and Type of Vitamin D Supplement</th>
<th>Received Dose= Treatment Dose × Adherence, IU/d</th>
<th>Year</th>
<th>No./Total Treated</th>
<th>No./Total Control</th>
<th>Effect RR (95% CI)</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant et al16 (cholecalciferol)</td>
<td>376</td>
<td>2005</td>
<td>93/2649</td>
<td>90/2643</td>
<td>1.031 (0.776-1.371)</td>
<td>5292</td>
</tr>
<tr>
<td>Meyer et al15 (ergocalciferol)</td>
<td>380</td>
<td>2002</td>
<td>50/569</td>
<td>47/575</td>
<td>1.075 (0.734-1.574)</td>
<td>1144</td>
</tr>
<tr>
<td>Lips21 (ergocalciferol)</td>
<td>340</td>
<td>1996</td>
<td>58/1291</td>
<td>48/1287</td>
<td>1.205 (0.829-1.751)</td>
<td>2578</td>
</tr>
<tr>
<td>Pooled results for 3 LD DB trials</td>
<td></td>
<td></td>
<td>Pooled</td>
<td>201/4509</td>
<td>1.99 (0.90-3.32)</td>
<td>9014</td>
</tr>
</tbody>
</table>

Primary subgroup analyses for HD DB trials with > 1 trial per subgroup

| Cholecalciferol13,18,23 | 640 | 2007 | 112/1725 | 104/1715 | 1.071 (0.827-1.386) | 3440     |
| Age > 75 y17,18,23 | 482 | 2006 | 146/1148 | 186/1142 | 0.782 (0.631-0.970) |        |
| Excluding ergocalciferol trial from those aged > 75 y | 482 | 2006 | 146/1148 | 186/1142 | 0.782 (0.631-0.970) |        |
| Excluding ergocalciferol trial from institutionalized persons14,18,23 | 640 | 2003 | 21/1345 | 24/1341 | 0.85 (0.47-1.53) | 2686     |
| Excluding ergocalciferol trial from institutionalized persons | 760 | 2002 | 27/393 | 21/190 | 0.622 (0.362-1.068) | 553      |
| Pooled result for all 5 HD DB trials | 664 | 1994 | 137/1176 | 178/1127 | 0.738 (0.6-0.907) | 2303     |

Primary subgroup analyses for HD DB trials with > 1 trial per subgroup

| Vitamin D with calcium2 | 434/16 087 | 513/15 785 | 0.82 (0.69-0.97) | 31 872 | .18 |

Abbreviations: DB, double-blind; FX, fracture; HD, higher-dose; OSD, open study design; RR, relative risk. 

Q Test: P < .05 indicates heterogeneity.

Limited data for vitamin D without calcium: 1 ergocalciferol trial; 1 trial not powered for hip fracture reduction.

high-quality, double-blinded trials (2005: total n = 9820; 2008: total n = 42 279). New to these analyses is the primary use of received dose (dose × adherence) as opposed to treatment dose. The received dose allows assessment of antifracture ef-
ficacy by a dose that accounts for the low adherence in several recent large trials.1,3 The consistency of our results for both received dose and achieved 25-hydroxyvitamin D levels in the treatment group across all 12 masked trials lends support to the presence of a dose-response rela-
tionship between supplemental vitamin D and fracture reduction. Despite the well-documented inter-
laboratory and interassay variation for 25-hydroxyvitamin D,39,40 the consistency in the dose-response analyses for both received dose and achieved 25-hydroxyvitamin D level also lends support to our use of 25-
hydroxyvitamin D levels from different trials.

Confirming our findings with some limitations, Tang et al7 suggested in their meta-analysis that, to-
gether with calcium supplementation, a daily intake of at least 800 IU of vitamin D increases total frac-
ture reduction by 3% compared with daily doses of vitamin D of less than 800 IU. However, with their focus on calcium, Tang et al7 excluded 4 high-quality trials of vitamin D alone compared with placebo.3,17,19,22

The pooled RR reduction was 21% with or without additional calcium for the higher dose of vitamin D. Previ-
ous meta-analyses may have missed this finding owing to their analyses in-
cluding all doses of vitamin D. Physi-
ologically, the calcium-sparing effect of vitamin D may explain why we did not see an additional benefit of cal-
cium supplementation at a higher dose of vitamin D.39,40 Similarly, our findings suggest that, at a suffi-
ciently high dose, vitamin D benefits are not limited to institutionalized and frail individuals, as suggested by the DHHS report.3
To our knowledge, the type of supplemental vitamin D was not addressed previously. With a higher received dose, the pooled effect of cholecalciferol was significant with 23% fracture reduction, whereas the pooled effect with ergocalciferol was not significant with 10% fracture reduction. One explanation may be that ergocalciferol is less potent than cholecalciferol in maintaining 25-hydroxyvitamin D levels, as suggested by 2 direct comparison trials, although this was challenged by a recent trial showing similar potency of daily ergocalciferol and daily cholecalciferol. Another explanation may be that ergocalciferol trials dosed intermittently, which may have decreased efficiency. However, the higher-dose cholecalciferol supplement given either daily or intermittently did reduce fractures. Thus, future research efforts may wish to simply focus on higher doses of cholecalciferol.

We performed sensitivity analyses, including 4 open study design trials. This increased the number of trials to 16 and the number of individuals to 56,459 for nonvertebral fractures. The pooled RR risk from these 16 trials was 0.88 (95% CI, 0.80-0.97), suggesting that with all evidence considered, supplemental vitamin D should reduce nonvertebral fracture risk by 12% among individuals 65 years or older. However, the study variation was larger than expected for the pooled result from all 16 trials. Even within the higher received dose, adding 3 open study design trials to the 9 double-blinded trials, variation was larger than expected (pooled RR, 0.83; 95% CI, 0.74-0.95) supporting our pre-defined strategy of focusing on fracture efficacy from double-blinded trials.

Based on the pooled results, 1α-hydroxylated vitamin D reduced nonvertebral fractures by 42% and among individuals of comparable age a higher dose of supplemental cholecalciferol reduced these fractures by 33%. Thus, although the number of studies...
Table 9. 1α-Hydroxylated Vitamin D

<table>
<thead>
<tr>
<th>Source</th>
<th>Participants, No.</th>
<th>Treatment/d</th>
<th>Dwelling</th>
<th>Age, Mean (SD), y</th>
<th>Duration, mo</th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto et al32</td>
<td>219 (215 women, 4 men)</td>
<td>0.5 or 0.75 or 1 µg of ED-71; all subjects received cholecalciferol; if 25-hydroxyvitamin D level &lt;50, 400 IU; if &gt;75, 200 IU vs placebo</td>
<td>CD (with OP)</td>
<td>67 (7)</td>
<td>12</td>
<td>All ED-71 groups: 42.8 (14.3) to 68 (from graph32) at 3-mo follow-up</td>
<td>43.1 (14.2) to 68 at 3-mo follow-up</td>
</tr>
<tr>
<td>Gallagher et al33</td>
<td>246 women</td>
<td>0.5 µg of calcitriol vs placebo</td>
<td>CD</td>
<td>71 (4)</td>
<td>36</td>
<td>78 (21.6) to 60.7 at 36-mo follow-up (Δ change: -17.3 [19.7])</td>
<td>80.5 (27.4) to 63.2 at 36-mo follow-up (Δ change: -17.3 [20.5])</td>
</tr>
<tr>
<td>Ishida and Kawai34</td>
<td>132 women (only control and 1α-calcidiol group)</td>
<td>1 µg of 1α-calcidiol vs no treatment; OSD</td>
<td>CD (with OP)</td>
<td>70 (10)</td>
<td>24</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Shikari et al35</td>
<td>113 women</td>
<td>0.75 µg of 1α-calcidiol + 300 mg of calcium (calcium lactate) vs placebo + 300 mg of calcium carbonate/lactogluconate</td>
<td>CD (with OP)</td>
<td>71 (6)</td>
<td>24</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Menczel et al36</td>
<td>66 women</td>
<td>0.5 µg of 1α-calcidiol + 1000 mg of calcium (calcium carbonate/lactogluconate) vs placebo + 1000 mg of calcium carbonate/lactogluconate</td>
<td>CD (with OP)</td>
<td>67 (8)</td>
<td>36</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Tilyard et al37</td>
<td>622 women</td>
<td>0.5 µg of calcitriol vs 1000 mg of calcium (calcium gluconate) OSD</td>
<td>CD (with OP)</td>
<td>64 (7)</td>
<td>36</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Ott and Chestnut38</td>
<td>86 women</td>
<td>0.5 µg of calcitriol, followed by dose adjustment (to 2 µg/d, mean intake was 0.43 µg) + mean calcium intake 1 g (diet + supplement) vs placebo + mean calcium intake 1 g</td>
<td>CD (with OP)</td>
<td>Control: 67.1 (1.2), treatment group: 67.9 (1.0)</td>
<td>24</td>
<td>Only at baseline, 66.8 (4.8)</td>
<td>Only at baseline, 65.8 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: CD, community-dwelling; ED-71, 1α,25-dihydroxy-2R,3R(3-hydroxypropoxy); ND, not determined in the trial population during the course of the trial; OP, osteoporosis; OSD, open study design.

Conventional unit conversion factor: To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496.

Values in parentheses or brackets indicate SD of the preceding mean.

Table 10. Primary Pooled Analysis for 1α-Hydroxylated Vitamin D and the Prevention of Nonvertebral Fractures (Ages 65-74 Years)

<table>
<thead>
<tr>
<th>Source</th>
<th>Vitamin D Supplement</th>
<th>Year</th>
<th>No./Total Treated</th>
<th>No./Total Control</th>
<th>Effect RR (95% CI)</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto et al32</td>
<td>(ED-71 + 200-400 D₃)</td>
<td>2005</td>
<td>4/166</td>
<td>1/53</td>
<td>1.277 (0.146-11.137)</td>
<td>219</td>
</tr>
<tr>
<td>Ishida and Kawai34</td>
<td>(1α-hydroxvitamin D₃)</td>
<td>2004</td>
<td>1/86</td>
<td>3/66</td>
<td>0.333 (0.04-2.801)</td>
<td>132</td>
</tr>
<tr>
<td>Gallagher et al33</td>
<td>(1,25-dihydroxyvitamin D₃)</td>
<td>2001</td>
<td>6/123</td>
<td>13/123</td>
<td>0.462 (0.186-1.145)</td>
<td>246</td>
</tr>
<tr>
<td>Shiraki et al35</td>
<td>(1α-hydroxvitamin D₃)</td>
<td>1996</td>
<td>0/37</td>
<td>3/42</td>
<td>0.162 (0.009-3.03)</td>
<td>79</td>
</tr>
<tr>
<td>Menczel et al36</td>
<td>(1α-hydroxvitamin D₃)</td>
<td>1994</td>
<td>2/24</td>
<td>5/42</td>
<td>0.7 (0.148-3.311)</td>
<td>66</td>
</tr>
<tr>
<td>Tilyard et al37</td>
<td>(1,25-dihydroxyvitamin D₃)</td>
<td>1992</td>
<td>11/314</td>
<td>22/308</td>
<td>0.49 (0.246-0.978)</td>
<td>622</td>
</tr>
<tr>
<td>Ott and Chestnut38</td>
<td>(1,25-dihydroxyvitamin D₃)</td>
<td>1989</td>
<td>5/41</td>
<td>2/42</td>
<td>2.56 (0.559-11.733)</td>
<td>83</td>
</tr>
<tr>
<td>Pooled result for all 7 trials with 1α-hydroxylated vitamin D³</td>
<td></td>
<td></td>
<td>29/771</td>
<td>49/676</td>
<td>0.58 (0.37-0.92)</td>
<td>1447</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ED-71, 1α,25-dihydroxy-2R,3R(3-hydroxypropoxy); RR, relative risk.

³The reduction in nonvertebral fractures was 42%, and the P value Q test score was .46.

ies for 1α-hydroxylated vitamin D was small and differences in efficacy could not be excluded, our analyses do not support prevention of nonvertebral fractures with 1α-hydroxylated vitamin D owing to its higher cost and higher risk profile compared with an adequate dose of supplemental vitamin D. Importantly, the efficacy of 1α-hydroxylated vitamin D adds to the evidence that improved vitamin D status will reduce fracture risk.

In conclusion, a higher received dose of supplemental vitamin D (482-770 IU/d) should reduce nonvertebral fractures by at least 20% and hip fractures by at least 18%. The greater fracture reduction with a higher received dose or higher achieved 25-hydroxyvitamin D levels for both any nonvertebral fractures and hip fractures suggests that higher doses of vitamin D should be explored in future research to optimize antifracture efficacy. Also, it is possible that greater benefits may be achieved with earlier initiation of vitamin D supplementation and longer duration of use. Our results do not support use of low-
dose vitamin D with or without calcium in the prevention of fractures among older individuals.

Accepted for Publication: October 1, 2008.

Correspondence: Heike A. Bischoff-Ferrari, DrPH, Centre on Aging and Mobility, University of Zurich, University Hospital, Gloriastrasse 25, Zurich 8091, Switzerland (heike.bischoff@usz.ch).

Author Contributions: Study concept and design: Bischoff-Ferrari, Stuck, and Staehelin. Acquisition of data: Bischoff-Ferrari and Henschkowski. Analysis and interpretation of data: Bischoff-Ferrari, Wong, Orav, Thoma, Kiel, and Henschkowski. Drafting of the manuscript: Bischoff-Ferrari, Thoma, and Henschkowski. Critical revision of the manuscript for important intellectual content: Willett, Wong, Stuck, Staehelin, Orav, and Kiel. Statistical analysis: Bischoff-Ferrari, Willett, Wong, Orav, and Henschkowski. Obtained funding: Bischoff-Ferrari and Stuck. Administrative, technical, and material support: Thoma. Study supervision: Willett, Staehelin, and Kiel.

Financial Disclosure: None reported.

Funding/Support: This study was supported by a Swiss National Foundation Professorship grant and a fellowship grant by the Robert Bosch Foundation.

REFERENCES


27. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab. 2007;92(5):1842-1846.

(Reprinted) Arch Intern Med/Vol 169 (No. 6), Mar 23, 2009 www.archinternmed.com

561

Downloaded from www.archinternmed.com at Life Chiropractic College, on April 7, 2009©2009 American Medical Association. All rights reserved.