Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis 1–4

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ABSTRACT

Background: Low 25-hydroxyvitamin D status has been associated with increased cardiovascular events in epidemiologic studies.

Objective: We assessed whether vitamin D supplementation reduces cardiac failure, myocardial infarction (MI), and stroke through an analysis of the Randomised Evaluation of Calcium Or vitamin D (RECORD) randomized controlled trial (RCT), a systematic review, and a meta-analysis.

Design: Two analyses were undertaken. The first analysis was a trial analysis. The RECORD was a factorial RCT that compared vitamin D3 (800 IU/d), calcium (1000 mg/d), vitamin D plus calcium, and a placebo. Cardiovascular events were collected throughout the trial and 3-y posttrial follow-up. Data were analyzed by using Cox regression. The second analysis was a systematic review. MEDLINE, EMBASE, CENTRAL, conference abstracts, and ongoing trials were searched for RCTs that evaluated vitamin D from 1980 to 2013. RCTs with ≥1 y of follow-up and participants mean or median age ≥60 y were included. Meta-analyses were based on a Bayesian fixed-effects model by using a complementary log-log link function to account for varying lengths of follow-up.

Results: In the trial analysis, we showed that, for the 5292 participants in the RECORD trial, HRs (95% CIs) for vitamin D compared with no vitamin D for cardiac failure, MI, and stroke were 0.75 (0.58, 0.97), 0.97 (0.75,1.26), and 1.06 (0.8, 1.32), respectively. Twenty-one studies met the inclusion criteria for the systematic review (n = 13,033). Estimated HRs [credible intervals (CrIs)] for vitamin D compared with the placebo or control for on-study events for cardiac failure, MI, and stroke were 0.82 (0.58, 1.15), 0.96 (0.83, 1.10), and 1.07 (0.91, 1.29), respectively.

Conclusion: Vitamin D supplementation might protect against cardiac failure in older people but does not appear to protect against MI or stroke. Am J Clin Nutr doi: 10.3945/ajcn.113.082602.

INTRODUCTION

Low 25-hydroxyvitamin D [25(OH)D]3 status has been associated with cardiovascular disease in epidemiologic studies (1). Lower 25(OH)D concentrations are seen in patients with higher blood pressure, metabolic syndrome, heart failure, and stroke than in patients without these disorders (1). Suggested pathophysiologic mechanisms by which vitamin D deficiency could lead to cardiovascular disease, including heart failure, are as follows: overactivity of the renin-angiotensin-aldosterone system (RAAS); endothelial dysfunction; direct effects on calcium flux leading to decreased myocyte contractility; hyperparathyroidism, which is associated with left ventricular hypertrophy; the promotion of chronic inflammation; and increased risk of metabolic syndrome and type 2 diabetes (1). However, the causality of these relations has been debated, and the quality of available studies has been criticized (2). Known risk factors for cardiovascular disease, including smoking, obesity, inactivity (and, thus, reduced sun exposure), and advanced age, are associated with lower 25(OH)D, which make the dissection of the causal role of low 25(OH)D status in cardiovascular disease difficult. Finally, recent evidence has suggested that 25(OH)D may be a negative acute-phase reactant; and thus, chronic disease may lead to low 25(OH)D even in the presymptomatic phases of cardiovascular disease (3).

There have been several previous systematic reviews that have evaluated vitamin D supplementation and cardiovascular outcomes, but these reviews have not focused on cardiac failure (4–8), which is an area of growing interest (9, 10). The most-recent reviews showed no effect on cardiovascular mortality (risk ratio: 0.98; 95% CI: 0.90, 1.07) (4) or the incidence of myocardial infarction (MI) (risk ratio: 1.02; 95% CI: 0.93, 1.13) or stroke (risk ratio: 1.05; 95% CI: 0.88, 1.25) (6). Wang et al (8) showed a statistically nonsignificant reduction in cardiovascular disease with moderate to high doses of vitamin D (risk ratio: 0.90; 95% CI: 0.77, 1.05).

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2 The trial was conducted, analyzed, and reported independently of all funders.

3 The Medical Research Council funded the central organization of RECORD, and Shire Pharmaceuticals funded the drugs, which were co-funded and manufactured by Nycomed. The Health Services Research Unit, University of Aberdeen, is funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates.

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5 Abbreviations used: CrI, credible interval (Bayesian statistics); ICD, International Classification of Diseases; MI, myocardial infarction; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; RECORD, Randomised Evaluation of Calcium Or vitamin D; 25(OH)D, 25-hydroxyvitamin D.

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Previous systematic reviews used narrow search strategies by including cardiovascular terms included vitamin D plus calcium compared with placebo or control randomized controlled trials (RCTs), wrongly assuming that there is no effect of calcium on cardiovascular disease (11, 12), and did not seek unpublished data. We undertook an extensive search for new published and unpublished trial data by using a broad search strategy and included unpublished data from the Randomised Evaluation of Calcium Or vitamin D (RECORD) trial for the secondary prevention of fractures (13).

METHODS

RECORD trial

Study design and participants

Full details of the RECORD study (ISRCTN 51647438) have been published (13). This was a factorial trial that randomly assigned 5292 participants with a previous fracture to receive oral vitamin D₃ (800 IU/d) plus calcium (1000 mg calcium carbonate/d), vitamin D₃ alone, calcium alone, or a placebo. Participants were recruited between 1 February 1999 and 31 March 2002. The primary outcome was a low-trauma fracture. Major inclusion criteria were age ≥70 y and a fracture in the past 10 y. Exclusion criteria included cognitive impairment, daily supplement intake of vitamin D or calcium (maximum: 200 IU and 500 mg, respectively), and bone-altering medications. Ethical approval was obtained from the Multicentre Research Ethics Committee for Scotland and the local research ethics committee of each hospital, and participants gave written informed consent.

Random assignment and masking

Participants were randomly assigned by a central computerized system that minimized by age (<80 or ≥80 y), sex, time since initial fracture (≤3 or >3 mo), and type of fracture (proximal femur, distal forearm, clinical vertebral, or other). Participants were allocated to daily doses of 800 IU vitamin D₃, 1000 mg Ca, combined vitamin D₃ plus calcium, or a placebo. Allocation remained concealed until the final analysis. Tablets were posted to participants every 4 mo. Participants and researchers were blinded to the intervention.

Procedures

Deaths attributed to cardiovascular or cerebrovascular disease were prespecified as outcomes in the main trial protocol. In addition, cardiovascular outcome data were collected from questionnaires, hospital and family doctor reports, nominated friends or family, and death certificates. After the trial closeout, data were only collected from the main cause of death from death registrations, which were provided by the General Register Office for Scotland for all UK participants; these data were collected independently of the trial as part of routine national statistics. On-study data collected during the RECORD trial were adjudicated by researchers independent from the trial with advice from cardiologists. All participants alive at trial closure were included in a 3-y, off-study, postintervention follow-up period.

The following 4 prespecified outcomes that compared vitamin D (with or without calcium) with no vitamin D (with or without calcium) supplementation as per a factorial trial design from both on-study (24–62 mo of follow-up) and off-study (3 y after trial closure) periods were assessed: the time to first cardiac failure, time to first MI, time to first stroke, and time to first composite outcome of cardiac failure, MI, or stroke. The inclusion of the off-study period was justified because it allowed the potential lag effect of vitamin D to be examined whereby remodeling could occur several years before clinically overt heart failure.

The following definitions were used:

1) Cardiac failure: heart failure, pulmonary edema, synonymous terms, or any of International Classification of Diseases (ICD)-9 codes 125.5, 111.0, 142.0, 142.7, 142.8, 142.9, 150.0, 150.1, and 150.9.

2) MI: MI, heart attack, or ICD-9 code 410.

3) Stroke: stroke, cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, cerebrovascular accident, or any of ICD-9 codes 430, 431, 433, and 434.

4) Composite: cardiac failure, MI, or stroke as previously defined.

Statistical analysis

RECORD trial outcomes were analyzed in a time-to-event framework by using Cox proportional hazards regression models. The potential for any effect modification that was due to an interaction with calcium was explored in a subgroup analysis and summarized graphically by using a forest plot that presented the treatment effect in the calcium and no-calcium subgroups and the interaction effect (which tested the difference between these subgroups). A sensitivity analysis was used to explore effects of compliance with treatment allocation. A post hoc analysis of fatal events was undertaken by replicating the primary analysis. All estimates of treatment effects are presented as HRs and 95% CIs. See supplementary material under “Supplemental data” in the online issue for additional details of the regression model and compliance sensitivity analysis.

Systematic review and meta-analyses

Data sources and searches

A systematic search for randomized trials of vitamin D supplementation was undertaken. Published studies were identified from MEDLINE [January 2005 to February 2013, accessed via OVID (http://gateway.ovid.com/)], EMBASE [January 2006 to February 2013, accessed via OVID (http://gateway.ovid.com/)], and CENTRAL (January 1980 to February 2013; http://onlinelibrary.wiley.com/cochranelibrary). MEDLINE search terms (see supplementary material under “Supplemental data” in the online issue) were adapted as appropriate for other databases. References of included studies and published systematic reviews were screened. Gray literature was identified from the hand searching of conference abstracts of the American Society for Bone and Mineral Research 2007–2012 (http://www.asbmr.org). The International Clinical Trials Registry Platform (http://www.who.int/ictrp) was searched for unpublished and ongoing trials.
Study selection

Only RCTs that included participants with a mean or median age ≥ 60 y (with an older age reflecting higher risk of vitamin D deficiency) and ≥ 1 y of follow-up were included. Any vitamin D or vitamin D analog intervention was eligible because we were looking for a class effect. Coadministration with other medications, such as calcium, was allowed provided that the comparator group received the same medication. There were no language restrictions. Studies that assessed vitamin D supplementation in participants selected solely on the basis of renal impairment (estimated glomerular filtration rate: 60 mL · min⁻¹ · 1.73 m⁻²), steroid-induced osteoporosis, or psoriasis were excluded.

To locate unpublished data, authors were contacted for studies that met the inclusion criteria but did not report cardiovascular outcomes or were completed but unpublished. Authors were also contacted to resolve any uncertainties in published data.

Data extraction and quality assessment

Data were extracted by one author, double-checked by a second reviewer, and discrepancies resolved through discussion. Data were extracted per patient rather than per event. Risk of bias within studies was assessed by using the Cochrane risk of bias tool (14).

Data synthesis and analysis

RCTs included in the study reported outcomes at varying lengths of follow-up. A standard meta-analysis ignores the variation in follow-up that may be suboptimal when longer follow-up results in more events as was the case here. Therefore, a Bayesian fixed-effects model by using a complementary log-log link function to account for the varying length of follow-up was used. See supplementary information under “Supplemental data” in the online issue for additional details. Results are presented as HRs and 95% credible intervals [CrIs (Bayesian statistics)], on the basis of fixed-effects models. Random-effects models were also run and compared with fixed models by using the residual deviance. Traditional random-effects meta-analysis models were run with Stata 12 software (StataCorp LP) by using only the proportions of participants who experienced events; these results are presented as risk ratios and 95% CIs for comparison. Forest plots are presented for illustrative purposes. All analyses, for both the trial analysis and meta-analysis, were undertaken with Stata 12 software (15).

RESULTS

RECORD trial

Full details of the recruitment and participant flow for the RECORD trial were published elsewhere (13). There were 2649 participants who were randomly assigned to receive vitamin D and 2643 participants to not receive vitamin D. Groups were similar at baseline (Table 1). The mean (±SD) age was 77.5 ± 5.6 y. Most participants were white and women. Only a small number of participants had diabetes or were smokers. In the vitamin D group, 438 participants died during the on-study period compared with 460 participants in the no–vitamin D group. The median time from random assignment to the final posttrial follow-up was 6.2 y in the vitamin D group (IQR: 5.1–7.0) and 6.2 y in the no–vitamin D group (IQR: 4.9–7.0).

Descriptive information on outcomes for the entire follow-up period and estimated treatment effects are presented in Table 2 (also see Supplementary Table 1 under “Supplemental data” in the online issue). Risk of first cardiac failure was lower in the vitamin D group than in the no–vitamin D group (adjusted HR: 0.75; 95% CI: 0.58, 0.97; P = 0.027) (Table 2; see Supplementary Figure 1 under “Supplemental data” in the online issue). There was no evidence of a difference in risk of MI (HR: 0.97; 95% CI: 0.75, 1.26; P = 0.4), stroke (HR: 1.06; 95% CI: 0.85, 1.32; P = 0.61), or the composite outcome (HR: 0.92; 95% CI: 0.80, 1.08; P = 0.32).

Risk of fatal cardiac failure was lower in the vitamin D group than in the no–vitamin D group (adjusted HR: 0.70; 95% CI: 0.61–0.81).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vitamin D (n = 2649)</th>
<th>Placebo (n = 2643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>77.5 ± 5.6</td>
<td>77.4 ± 5.6</td>
</tr>
<tr>
<td>Calcium [n (%)]</td>
<td>1306 (49.3)</td>
<td>1311 (49.6)</td>
</tr>
<tr>
<td>F [n (%)]</td>
<td>2240 (84.6)</td>
<td>2241 (84.8)</td>
</tr>
<tr>
<td>White [n (%)]</td>
<td>2629 (99.2)</td>
<td>2623 (99.2)</td>
</tr>
<tr>
<td>Type of enrolling fracture [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal femur</td>
<td>459 (17.3)</td>
<td>445 (16.8)</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>924 (34.9)</td>
<td>922 (34.9)</td>
</tr>
<tr>
<td>Clinical vertebral</td>
<td>4 (0.2)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1262 (47.6)</td>
<td>1272 (48.1)</td>
</tr>
<tr>
<td>Time since enrolling fracture ≥ 3 mo [n (%)]</td>
<td>469 (17.7)</td>
<td>475 (18.0)</td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>208 (7.9)</td>
<td>212 (8.0)</td>
</tr>
<tr>
<td>Oral hypoglycemics [n (%)]</td>
<td>119 (4.5)</td>
<td>108 (4.1)</td>
</tr>
<tr>
<td>Insulin [n (%)]</td>
<td>40 (1.5)</td>
<td>50 (1.9)</td>
</tr>
<tr>
<td>Current smoker [n (%)]</td>
<td>298 (11.3)</td>
<td>320 (12.1)</td>
</tr>
<tr>
<td>Ambulant in community ≥ 1 y [n (%)]</td>
<td>2492 (94.1)</td>
<td>2487 (94.1)</td>
</tr>
<tr>
<td>Oral steroids ≥ 7.5 mg prednisolone/d [n (%)]</td>
<td>49 (1.9)</td>
<td>44 (1.7)</td>
</tr>
</tbody>
</table>

1RECORD, Randomised Evaluation of Calcium Or vitamin D.
2Values are means ± SDs.
3Able to walk outdoors unaccompanied.
TABLE 2
Estimated effects of vitamin D on outcomes for on trial plus off trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vitamin D (n = 2649)</th>
<th>Placebo (n = 2643)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of fatal and nonfatal events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>102</td>
<td>136</td>
<td>0.75 (0.58, 0.97)</td>
<td>0.027</td>
</tr>
<tr>
<td>MI</td>
<td>114</td>
<td>117</td>
<td>0.97 (0.75, 1.26)</td>
<td>0.84</td>
</tr>
<tr>
<td>Stroke</td>
<td>160</td>
<td>149</td>
<td>1.06 (0.85, 1.32)</td>
<td>0.61</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>339</td>
<td>363</td>
<td>0.92 (0.80, 1.08)</td>
<td>0.32</td>
</tr>
<tr>
<td>No. of fatal events only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>89</td>
<td>127</td>
<td>0.70 (0.53, 0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>MI</td>
<td>87</td>
<td>88</td>
<td>0.99 (0.73, 1.33)</td>
<td>0.92</td>
</tr>
<tr>
<td>Stroke</td>
<td>102</td>
<td>101</td>
<td>0.99 (0.75, 1.30)</td>
<td>0.94</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>256</td>
<td>291</td>
<td>0.87 (0.73, 1.03)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

1 Cox regression adjusted for age (<80 or ≥80 y), sex, time since fracture (previous ≥3 mo), type of fracture (proximal femur, distal forearm, clinical vertebral, or other), diabetic status, and smoking status.

2 MI, myocardial infarction.

0.53, 0.91; P = 0.009), but risk of fatal events was lower for other outcomes (Table 2).

According to the prespecified definition of adherence, 2268 (42.9%) participants were adherent. Adherence was similar between the vitamin D group (43.8%) and no–vitamin D group (42.0%). For the composite outcome, the HR adjusted for adherence was 0.99 (95% CI: 0.59, 2.31). This result was similar to the analysis that was not adjusted for adherence (HR: 0.92; 95% CI: 0.80, 1.08). The interaction between vitamin D and calcium was small, but there was considerable uncertainty (see Supplementary Figure 2 under “Supplemental data” in the online issue).

Systematic review and meta-analysis

The literature search identified 8907 records (see Supplementary Figure 3 under “Supplemental data” in the online issue). Full texts of 197 articles were assessed, and 132 articles were excluded. The commonest reason for study exclusion was the comparison of calcium plus vitamin D compared with s placebo. Fifty-six studies met the inclusion criteria. According to the prespecified definition of adherence, 2268 (42.9%) participants were adherent. Adherence was similar between the vitamin D group (43.8%) and no–vitamin D group (42.0%). For the composite outcome, the HR adjusted for adherence was 0.99 (95% CI: 0.59, 2.31). This result was similar to the analysis that was not adjusted for adherence (HR: 0.92; 95% CI: 0.80, 1.08). The interaction between vitamin D and calcium was small, but there was considerable uncertainty (see Supplementary Figure 2 under “Supplemental data” in the online issue).

No significant difference was shown in MI or stroke events between vitamin D and no vitamin D [320 compared with 334 events (HR: 0.96; 95% CI: 0.83, 1.10; 251) compared with 226 events (HR: 1.07; 95% CI: 0.91, 1.29), respectively]. There was low statistical heterogeneity throughout. Forest plots produced by the traditional random-effects meta-analysis were shown in Figures 1–3 for illustrative purposes.

In a post hoc sensitivity analysis, only trials that evaluated cholecalciferol or ergocalciferol were examined in the meta-analysis. Results were virtually identical [MI HR: 0.95 (95% CI: 0.82, 1.10); stroke HR: 1.08 (95% CI: 0.91, 1.29)]. There were no trials of vitamin D analogs that provided data on cardiac failure. Funnel plot inspections did not suggest publication bias.

In the sensitivity analysis, which included off-study events from the RECORD trial, risk of cardiac failure event was significantly lower in vitamin D compared with no–vitamin D groups (overall HR: 0.79; 95% CI: 0.59, 0.99). No significant differences were shown for MI (HR: 0.99; 95% CI: 0.87, 1.11) or stroke (HR: 1.07; 95% CI: 0.91, 1.24).

DISCUSSION

The analysis of the whole follow-up period of the RECORD trial showed a significant, clinically important reduced risk of cardiac failure events with vitamin D, but vitamin D had no significant effect on MI, stroke, or the composite outcome. The meta-analysis showed that vitamin D did not reduce risk of cardiac failure during on-study periods in trials, but the inclusion of the RECORD off-study events generated a significant effect. No significant difference was shown in...
<table>
<thead>
<tr>
<th>First author, year of publication (ref); location</th>
<th>Participants</th>
<th>Interventions given to all participants</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloia, 1988 (18); United States</td>
<td>Postmenopausal women with osteoporosis aged 50–80 y</td>
<td>Intake of 400 IU vitamin D (unspecified)/d and calcium 1000 mg Ca/d</td>
<td>0.50 μg calcitriol/d with dose escalation if necessary</td>
<td>Placebo</td>
<td>Bone biopsy, mineral and urinary measurements, and radiographs</td>
<td>2 y</td>
</tr>
<tr>
<td>Attia, 2008 (23); United States</td>
<td>Men with metastatic prostate cancer without starting chemotherapy</td>
<td>Docetaxel plus dexamethasone on cycle days 1, 8, and 15</td>
<td>10 μg doxercalciferol/d</td>
<td>Placebo</td>
<td>PSA, median progression-free survival</td>
<td>Median: 17.6 mo</td>
</tr>
<tr>
<td>Avenell, 2004 (34); United Kingdom</td>
<td>Men and women aged ≥70 y with a previous low trauma osteoporotic fracture</td>
<td>None</td>
<td>1 g oral Ca/d, 800 IU oral cholecalciferol, or both</td>
<td>Placebo</td>
<td>Eligible participants recruited</td>
<td>1 y</td>
</tr>
<tr>
<td>Deluca, 2011 (24); United States</td>
<td>Postmenopausal women with osteopenia aged 55–80 y</td>
<td>600 IU cholecalciferol/d</td>
<td>2MD 220 or 440 μg/d</td>
<td>Placebo</td>
<td>Percentage of change in lumbar BMD</td>
<td>1 y</td>
</tr>
<tr>
<td>Gallagher, 2001 (16); United States</td>
<td>Women aged 65–77 y with no evidence of osteopenia</td>
<td>None</td>
<td>0.25 μg calcitriol twice a day HRT alone, or HRT plus calcitriol</td>
<td>Placebo</td>
<td>Femoral and spine BMD</td>
<td>3 y</td>
</tr>
<tr>
<td>Gallagher, 2012 (17); United States</td>
<td>White postmenopausal women aged 57–90 y with vitamin D insufficiency living in Japan</td>
<td>Daily calcium to maintain intake of 1200–1400 mg</td>
<td>400, 800, 1600, 2400, 3200, 4000, or 4800 IU cholecalciferol once daily</td>
<td>Placebo</td>
<td>25(OH)D and PTH</td>
<td>1 y</td>
</tr>
<tr>
<td>Gorai, 2010 (25); Japan</td>
<td>Postmenopausal women living in Japan</td>
<td>None</td>
<td>1.0 μg alfacalcidol/d or 60 mg raloxifene plus vitamin D/d</td>
<td>Placebo</td>
<td>Adherence to treatment</td>
<td>1 y</td>
</tr>
<tr>
<td>Lehouck, 2012 (29); Belgium</td>
<td>Current or former smokers ≥50 y old with COPD</td>
<td>None</td>
<td>100,000 IU cholecalciferol/mo</td>
<td>Placebo</td>
<td>Time to first exacerbation</td>
<td>1 y</td>
</tr>
<tr>
<td>Majima, 2008 (22); Japan</td>
<td>Postmenopausal women living in Japan</td>
<td>None</td>
<td>1.0 μg alfacalcidol/d or 60 mg raloxifene plus alfacalcidol/d</td>
<td>Placebo</td>
<td>BMD</td>
<td>1 y</td>
</tr>
<tr>
<td>Matsumoto, 2005 (26); Japan</td>
<td>Postmenopausal women with osteoporosis ≥60 y old</td>
<td>400 IU cholecalciferol/d if &lt;50 nmol 25(OH)D/L or 200 IU cholecalciferol/d if ≥50 nmol 25(OH)D/L</td>
<td>0.5, 0.75, or 1.0 μg ED-71/d</td>
<td>Placebo</td>
<td>Change in lumbar BMD</td>
<td>1 y</td>
</tr>
<tr>
<td>Ott, 1989 (19); United States</td>
<td>Postmenopausal women with ≥2 compression fractures</td>
<td>Calcium to maintain intake of 24.9 mmol/d</td>
<td>0.25 μg calcitriol twice daily with dose escalation if needed</td>
<td>Placebo</td>
<td>Change in BMD</td>
<td>2 y</td>
</tr>
<tr>
<td>Prince, 2008 (32); Australia</td>
<td>Women with vitamin D deficiency aged 70–90 y</td>
<td>Calcium 1000 mg/d</td>
<td>1000 IU ergocalciferol/d</td>
<td>Placebo</td>
<td>Incidence of falls</td>
<td>1 y</td>
</tr>
<tr>
<td>RECCORD, 2005 (13); United Kingdom</td>
<td>Men and women aged &gt;70 y with previous low trauma fracture</td>
<td>None</td>
<td>800 IU cholecalciferol/d, 1 g Ca/d, or both</td>
<td>Placebo</td>
<td>Low-energy fractures</td>
<td>Median: 6.18 y</td>
</tr>
<tr>
<td>Sanders, 2010 (20); Australia</td>
<td>Women aged ≥70 y with high risk of fracture</td>
<td>None</td>
<td>500,000 IU cholecalciferol once yearly</td>
<td>Placebo</td>
<td>Numbers of falls and fractures</td>
<td>3–5 y</td>
</tr>
<tr>
<td>Toss, 2011 (30); Sweden</td>
<td>Community-dwelling men and women aged 55–85 y</td>
<td>None</td>
<td>1600 IU cholecalciferol plus 1000 mg Ca/d</td>
<td>Placebo</td>
<td>Serum 25(OH)D</td>
<td>1 y</td>
</tr>
<tr>
<td>Trivedi, 2003 (21); United Kingdom</td>
<td>Men and women aged 65–85 y from British doctors' and general practice registers</td>
<td>None</td>
<td>100,000 IU cholecalciferol every 4 mo</td>
<td>Placebo</td>
<td>Fracture incidence and total mortality</td>
<td>5 y</td>
</tr>
</tbody>
</table>
the meta-analysis for MI or stroke. There was no indication of adverse effects of vitamin D on cardiovascular disease.

What do these results mean?

Results suggested that there is insufficient evidence to support vitamin D supplementation for the reduction of cardiovascular events but raised the possibility that vitamin D supplementation might have an effect on heart failure. This effect might occur by preventing the development of heart failure or mitigating its progression. Key drivers for heart failure in older patients are ischemic heart disease and hypertension (35), but the lack of effect of vitamin D on MI did not support this mechanism. This result may suggest that vitamin D affects the chronic pathogenesis of heart failure. A systematic review of trials of vitamin D supplementation showed that there may be a beneficial effect on blood pressure (36); this effect may have been of particular significance in this study because hypertension is a common cause of heart failure in older women (37).

If vitamin D does not prevent the onset of heart failure, it could mitigate the severity of the syndrome once established. Existing trial data have been contradictory. Vitamin D supplements improved echocardiographic markers of heart failure and proinflammatory cytokines in an RCT in Egyptian infants with a 25(OH)D concentration of 35 nmol/L (38). In an RCT of adults with cardiac failure [baseline 25(OH)D concentration: 36 nmol/L (39)], 2000 IU cholecalciferol/d improved proinflammatory cytokines, but had no significant effect on echocardiographic variables or N-terminal propeptide of brain natriuretic peptide. In a small, short-term trial, Witham et al (40) showed that vitamin D supplementation (100,000 IU ergocalciferol every 10 wk) improved brain natriuretic peptide compared with a placebo, but had no effect on symptoms, exercise capacity, or quality of life in older patients with heart failure despite low baseline 25(OH)D concentrations (mean: 21 nmol/L).

Vitamin D supplementation reduces parathyroid hormone (PTH), which is known to be vasculotoxic and associated with left ventricular hypertrophy (1). In a cohort study (n = 864), Hagström et al (41) showed that high PTH concentrations were associated with increased cardiac failure hospitalizations (HR for 1-SD increase of PTH: 1.41; 95% CI: 1.12, 1.77).

Vitamin D could reduce cardiac failure through the RAAS system (42). In a very large cohort of individuals without heart failure, low vitamin D status was associated with increased cardiac failure hospitalizations (HR for 1-SD increase of PTH: 1.41; 95% CI: 1.12, 1.77).

Context of these results

Previous systematic reviews (4, 6, 8) of RCTs of vitamin D on cardiovascular endpoints failed to report significant benefits but may have been subject to a potential bias through limited searching
and the failure to obtain unpublished data. Some reviews included trials that compared calcium and vitamin D compared with a placebo or control as well as trials of vitamin D alone, which is problematic because calcium has been shown to increase risk of cardiovascular events (11, 12). In the Women’s Health Initiative trial (45), coadministered calcium and vitamin D had no effect on chronic heart failure in the entire cohort but might have reduced risk of chronic heart failure in women at low risk of cardiovascular disease but not in those at high risk of cardiovascular disease (46).

A Cochrane review of RCTs that evaluated vitamin D and overall mortality, undertook a subgroup analysis of cardiovascular mortality and showed no difference, although overall mortality was slightly reduced (risk ratio: 0.97; 95% CI: 0.94, 0.99) (4). Because of the findings of this review, we decided to test the robustness of RECORD trial results to a post hoc sensitivity analysis to explore the potential influence of death from all other causes within a competing-risks framework. These results (not presented) were practically identical to the results shown in Table 2 and were robust to death from other causes. Similarly, Elamin et al (6), in a meta-analysis that included RCTs, showed no difference for MI or stroke. Wang et al (8) undertook a meta-analysis of 2 trials and showed a nonsignificant reduction in cardiovascular outcomes. In a trial sequential meta-analysis, Bolland et al (47) showed that vitamin D did not reduce skeletal or nonskeletal outcomes >15%.

**Strengths and weaknesses**

The RECORD was a trial of secondary prevention of fractures. Osteoporosis has been associated with increased risk of cardiovascular disease (48), and thus, participants in the RECORD trial may have been at higher risk of cardiovascular events than was the general population, although participants were mainly women, and only 8% of subjects were diabetic. Although cardiovascular outcomes were prespecified, the RECORD trial was not designed as a cardiovascular trial, and events were not verified against participants’ medical records. The compliance with tablets was poor, which reduced the examination of efficacy, but this outcome reflected the likely compliance in clinical practice. Data after the trial close out were only collected from death certificates, and thus, nonfatal events were missed. However, the longer follow-up allowed the potential lag effect of vitamin D to be examined. We used a robust search strategy for the systematic review. Studies were shown that reported cardiovascular events in the full text but not abstract or title in databases. Unpublished data from 12 trials were included. However, the method of collecting cardiovascular data varied between studies. A meta-analysis was driven by 2 studies (13, 21). Therefore, results were sensitive to the population and vitamin D dose of studies.

**Future research**

Additional mechanistic studies are needed to explore mechanisms by which vitamin D could influence the development or progression of heart failure in high-risk groups.

**TABLE 4**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk ratio (95% CI)</th>
<th>HR (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>0.83 (0.60, 1.13)</td>
<td>0.82 (0.58, 1.15)</td>
</tr>
<tr>
<td>MI</td>
<td>0.96 (0.83, 1.10)</td>
<td>0.96 (0.83, 1.10)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.09 (0.92, 1.30)</td>
<td>1.07 (0.91, 1.29)</td>
</tr>
</tbody>
</table>

1 CrI, credible interval (Bayesian statistics); MI, myocardial infarction; RECORD, Randomised Evaluation of Calcium Or vitamin D.

2 Calculated by using a Bayesian fixed-effects model to combine both HRs and risk ratios.

3 Calculated by using traditional random-effects meta-analysis methods.

![FIGURE 1. Cardiac failure forest plots for illustrative purposes including on-trial only results from the Record. Squares or diamonds indicate the point estimate of the study or overall effect. This size of the square or diamond reflects the CI. The dashed vertical line indicates the pooled estimate. ID, identifier; RECORD, Randomised Evaluation of Calcium Or vitamin D trial; RR, risk ratio.](image-url)
Sufficiently powered, high-quality RCTs are needed to investigate the relation between cardiovascular disease and vitamin D. The Vitamin D and Omega-3 Trial randomly assigned 20,000 healthy participants to receive 2000 IU cholecalciferol/d or a placebo for 5 y with primary outcomes including MI, stroke, and death from cardiovascular disease (49). However, participants are allowed to take nonprotocol supplements of ≤800 IU vitamin D/d and 1 g Ca/d. The Vitamin D Assessment Trial

FIGURE 2. Stroke forest plots for illustrative purposes including on-trial only results from the Record. Squares or diamonds indicate the point estimate of the study or overall effect. This size of the square or diamond reflects the CI. The dashed vertical line indicates the pooled estimate. ID, identifier; Record, Randomised Evaluation of Calcium Or vitamin D trial; RR, risk ratio.

FIGURE 3. Myocardial infarction forest plots for illustrative purposes including on-trial only results from the Record. Squares or diamonds indicate the point estimate of the study or overall effect. This size of the square or diamond reflects the CI. The dashed vertical line indicates the pooled estimate. ID, identifier; Record, Randomised Evaluation of Calcium Or vitamin D trial; RR, risk ratio.
(http://www.anzctr.org.au/; ACTRN12611000402943) is assessing effects of 100,000 IU cholecalciferol/mo on cardiovascular disease in 5100 men and women ages 50–84 y. The Finnish Vitamin D Trial (http://clinicaltrials.gov/show/NCT01463813) is examining effects of 1600 IU cholecalciferol/d, 3200 IU cholecalciferol/d, or a placebo on cardiovascular disease in 18,000 men and women ≥60 y old. An ongoing trial (http://clinicaltrials.gov/ct2/show/NCT01326650) will randomly assign 1000 participants with cardiac failure to received vitamin D or a control and measure the symptom improvement and mortality at 3 y. However, to our knowledge, no studies are currently aiming to prevent heart failure in patients at high risk (eg, MI with a reduced ejection fraction). These trials are using high doses of vitamin D, although none of them have set vitamin D deficiency as an entry criterion (50).

In conclusion, long-term RECORD trial results show that vitamin D compared with no vitamin D resulted in a significant reduction in cardiac-failure events. In the meta-analysis, there is evidence to suggest that vitamin D supplementation may reduce cardiac failure events in older people when these RECORD data are included but not for on-study data alone.

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