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

John A Ford, Graeme S MacLennan, Alison Avenell, Mark Bolland, Andrew Grey, and Miles Witham for the RECORD Trial Group

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 D_3 (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) 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* 2014;100:746–55.

INTRODUCTION

Low 25-hydroxyvitamin D [25(OH)D][5] 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

[1] From the Health Services Research Unit, University of Aberdeen, Aberdeen, United Kingdom (JAF, GSM, and AA); the Department of Medicine, University of Auckland, Auckland, New Zealand (MB and AG); and the Section of Aging and Health, University of Dundee, Dundee, United Kingdom (MW).

[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.

[4] Address reprint requests and correspondence to JA Ford, Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Chancellors Drive, Norwich NR4 7TJ, United Kingdom. E-mail: john.ford@uea.ac.uk.

[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.

Received December 29, 2013. Accepted for publication June 29, 2014.

First published online July 23, 2014; doi: 10.3945/ajcn.113.082602.

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).

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 D_3 (800 IU/d) plus calcium (1000 mg calcium carbonate/d), vitamin D_3 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 $\geq$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 $\geq$80 y), sex, time since initial fracture ($\leq$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 D_3, 1000 mg Ca, combined vitamin D_3 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; $P = 0.84$), 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:

TABLE 1
RECORD trial baseline characteristics[1]

Variable	Vitamin D (n = 2649)	Placebo (n = 2643)
Age[2] (y)	77.5 ± 5.6	77.4 ± 5.6
Calcium [n (%)]	1306 (49.3)	1311 (49.6)
F [n (%)]	2240 (84.6)	2241 (84.8)
White [n (%)]	2629 (99.2)	2623 (99.2)
Type of enrolling fracture [n (%)]		
Proximal femur	459 (17.3)	445 (16.8)
Distal forearm	924 (34.9)	922 (34.9)
Clinical vertebral	4 (0.2)	4 (0.2)
Other	1262 (47.6)	1272 (48.1)
Time since enrolling fracture ≥3 mo [n (%)]	469 (17.7)	475 (18.0)
Diabetes [n (%)]	208 (7.9)	212 (8.0)
Oral hypoglycemics [n (%)]	119 (4.5)	108 (4.1)
Insulin [n (%)]	40 (1.5)	50 (1.9)
Current smoker [n (%)]	298 (11.3)	320 (12.1)
Ambulant in community[3] [n (%)]	2492 (94.1)	2487 (94.1)
Oral steroids ≥7.5 mg prednisolone/d [n (%)]	49 (1.9)	44 (1.7)

[1] RECORD, Randomised Evaluation of Calcium Or vitamin D.
[2] Values are means ± SDs.
[3] Able to walk outdoors unaccompanied.

TABLE 2
Estimated effects of vitamin D on outcomes for on trial plus off trial

Outcome	Vitamin D (n = 2649)	Placebo (n = 2643)	HR (95% CI)[1]	P
No. of fatal and nonfatal events				
Cardiac failure	102	136	0.75 (0.58, 0.97)	0.027
MI[2]	114	117	0.97 (0.75, 1.26)	0.84
Stroke	160	149	1.06 (0.85, 1.32)	0.61
Composite outcome	339	363	0.92 (0.80, 1.08)	0.32
No. of fatal events only				
Cardiac failure	89	127	0.70 (0.53, 0.91)	0.009
MI	87	88	0.99 (0.73, 1.33)	0.92
Stroke	102	101	0.99 (0.75, 1.30)	0.94
Composite outcome	256	291	0.87 (0.73, 1.03)	0.11

[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 not 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. Eight studies reported suitable cardiovascular outcomes in published reports (16–23). Authors of 11 studies provided supplementary data on cardiovascular events (24–33). Unpublished data from Avenell et al (34) were available locally from the Health Services Research Unit, University of Aberdeen. For consistency with other trials, on-study data from the analysis of the RECORD study was included in the primary meta-analysis. In total, 21 studies met the inclusion criteria for the meta-analysis. Three studies did not report any event in either arm and, therefore, did not contribute to the meta-analysis (23, 24, 32).

Characteristics of included studies are shown in **Table 3**. Thirteen studies included only women, one study included only men, and the remaining studies included both women and men. Eight studies included only participants at higher risk of fracture (ie, had a previous fracture, osteoporosis, or osteopenia). Cholecalciferol was used in 10 studies. Doses of cholecalciferol were given daily, monthly, or yearly; expressed as the dose per day, doses ranged from 800 to 4000 IU/d. Calcitriol was used in 4 studies, and doses ranged from 0.25 to 0.50 μg/d, and 2 studies included a dose-escalation protocol. Ergocalciferol was used in 2 studies. In 5 studies, a vitamin D analog was used [doxercalciferol, alfacalcidol, 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3, or 1α,25-dihydroxy-2β-(3-hydroxypropyloxy)vitamin D_3]. In 13 studies, the follow-up period was 12 mo. The follow-up of remaining studies ranged from a median of 17.6 mo to 6.2 y.

Studies were generally of low or unclear risk of bias (*see* Supplementary Table 2 under "Supplemental data" in the online issue). Xia et al (27) and Avenell et al (34) were open-label studies.

In total, 13,033 participants were included. Mean ages ranged from 61 to 77 y (*see* Supplementary Table 3 under "Supplemental data" in the online issue). Baseline 25(OH)D was recorded in 11 studies and ranged from 24 to 80 nmol/L.

Vitamin D did not significantly reduce risk of cardiac failure compared with no vitamin D (68 compared with 80 events; HR: 0.82; CrI: 0.58, 1.1) (**Table 4**). There was no significant difference in MI or stroke events between vitamin D and no vitamin D [320 compared with 334 events (HR: 0.96; CrI: 0.83, 1.10; 251) compared with 226 events (HR: 1.07; CrI: 0.91, 1.29), respectively]. There was low statistical heterogeneity throughout. Forest plots produced by the traditional random-effects meta-analysis are 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 (CrI: 0.82, 1.10); stroke HR: 1.08 (CrI: 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; CrI: 0.59, 0.99). No significant differences were shown for MI (HR: 0.99; CrI: 0.87, 1.11) or stroke (HR: 1.07; CrI: 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 3
Study characteristics[1]

First author, year of publication (ref); location	Participants	Interventions given to all participants	Intervention	Comparator	Primary outcome	Follow-up
Aloia, 1988 (18); United States	Postmenopausal women with osteoporosis aged 50–80 y	Intake of 400 IU vitamin D (unspecified)/d and calcium 1000 mg Ca/d	0.50 μg calcitriol/d with dose escalation if necessary	Placebo	Bone biopsy, mineral and urinary measurements, and radiographs	2 y
Attia, 2008 (23); United States	Men with metastatic prostate cancer without starting chemotherapy	Docetaxel plus dexamethasone on cycle days 1, 8, and 15	10 μg doxercalciferol/d	Placebo	PSA, median progression-free survival	Median: 17.6 mo
Avenell, 2004 (34); United Kingdom	Men and women aged ≥70 y with a previous low trauma osteoporotic fracture	None	1 g oral Ca/d, 800 IU oral cholecalciferol/d, or both	Placebo	Eligible participants recruited	1 y
DeLuca, 2011 (24); United States	Postmenopausal women with osteopenia aged 55–80 y	600 IU cholecalciferol/d	2MD 220 or 440 μg/d	Placebo	Percentage of change in lumbar BMD	1 y
Gallagher, 2001 (16); United States	Women aged 65–77 y with no evidence of osteopenia	None	0.25 μg calcitriol twice a day HRT alone, or HRT plus calcitriol	Placebo	Femoral and spine BMD	3 y
Gallagher, 2012 (17); United States	White postmenopausal women aged 57–90 y with vitamin D insufficiency	Daily calcium to maintain intake of 1200–1400 mg	400, 800, 1600, 2400, 3200, 4000, or 4800 IU cholecalciferol once daily	Placebo	25(OH)D and PTH	1 y
Gorai, 2010 (25); Japan	Postmenopausal women living in Japan	None	1.0 μg alfacalcidol/d or 60 mg raloxifene plus vitamin D/d	60 mg raloxifene/d	Adherence to treatment	1 y
Lehouck, 2012 (29); Belgium	Current or former smokers >50 y old with COPD	None	100,000 IU cholecalciferol/mo	Placebo	Time to first exacerbation	1 y
Majima, 2008 (22); Japan	Postmenopausal women living in Japan	None	1.0 μg alfacalcidol/d or 60 mg raloxifene plus alfacalcidol/d	Raloxifene 60 mg daily	BMD	1 y
Matsumoto, 2005 (26); Japan	Postmenopausal women with osteoporosis >60 y old	400 IU cholecalciferol/d if <50 nmol 25(OH)D/L or 200 IU cholecalciferol/d if ≥50 nmol 25(OH)D/L	0.5, 0.75, or 1.0 μg ED-71/d	Placebo	Change in lumbar BMD	1 y
Ott, 1989 (19); United States	Postmenopausal women with ≥2 compression fractures	Calcium to maintain intake of 24.9 mmol/d	0.25 μg calcitriol twice daily with dose escalation if needed	Placebo	Change in BMD	2 y
Prince, 2008 (32); Australia	Women with vitamin D deficiency aged 70–90 y	Calcium 1000 mg/d	1000 IU ergocalciferol/d	Placebo	Incidence of falls	1 y
RECORD, 2005 (13); United Kingdom	Men and women aged >70 y with previous low trauma fracture	None	800 IU cholecalciferol/d, 1 g Ca/d, or both	Placebo	Low-energy fractures	Median: 6.18 y
Sanders, 2010 (20); Australia	Women aged >70 y with high risk of fracture	None	500,000 IU cholecalciferol once yearly	Placebo	Numbers of falls and fractures	3–5 y
Toss, 2011 (30); Sweden	Community-dwelling men and women aged 55–85 y	None	1600 IU cholecalciferol plus 1000 mg Ca/d	1000 mg Ca/d	Serum 25(OH)D	1 y
Trivedi, 2003 (21); United Kingdom	Men and women aged 65–85 y from British doctors' and general practice registers	None	100,000 IU cholecalciferol every 4 mo	Placebo	Fracture incidence and total mortality	5 y

(Continued)

TABLE 3 (*Continued*)

First author, year of publication (ref); location	Participants	Interventions given to all participants	Intervention	Comparator	Primary outcome	Follow-up
Witham, 2013 (33); United Kingdom	Men and women aged >70 y with BP >140 mm Hg systolic and 25(OH)D <75 nmol/L	None	100,000 IU cholecalciferol every 3 mo	Placebo	Change in BP	1 y
Witte (unpublished); United Kingdom	Men and women with stable cardiac failure	None	4000 IU cholecalciferol/d	Placebo	Left-ventricular function	1 y
Macdonald, 2012 (31); United Kingdom	Postmenopausal women living in Scotland	None	400 or 1000 IU cholecalciferol/d	Placebo	Serum lipid profile, estimate of insulin resistance, inflammatory biomarkers, and BP	1 y
Xia, 2009 (27); China	Postmenopausal women aged >65 y living in China	None	0.25 μg calcitrol plus calcium carbonate plus vitamin D (calcium 600 mg Ca and 125 IU cholecalciferol)/d	Calcium carbonate plus vitamin D alone (calcium 600 mg and 125 IU cholecalciferol)/d	Percentage of change in lumbar and hip BMD	1 y
Zhu, 2008 (28); Australia	Women aged >70 y selected from electoral register	None	1200 mg Ca with 1000 IU ergocalciferol/d	1200 mg Ca with placebo vitamin D/d	Hip BMD	5 y

[1] BMD, bone mineral density; BP, blood pressure; COPD, chronic obstructive pulmonary disease; ED-71, 1α,25-dihydroxy-2β-(3-hydroxypropyloxy)vitamin D_3; HRT, hormone replacement therapy; PSA, prostate specific antigen; PTH, parathyroid hormone; RECORD, Randomised Evaluation of Calcium Or vitamin D; ref, reference; 2MD, 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3; 25(OH)D, 25-hydroxyvitamin D.

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), Hagstrōm 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 RAAS activation (43). However, in randomized trials, Witham et al (40) and Boxer et al (44) showed no significant effect on RAAS in patients with heart failure, perhaps in part because of the high prevalence of RAAS system-blocker use in heart-failure patients. The mechanism is not clear, but postulated mechanisms include the upregulation of vascular endothelial growth factor and mediation through calcium myocyte handling with improved cardiac muscle strength (1). It was not possible to explore J- or U-shaped associations between outcomes and 25(OH)D concentrations because of limited 25(OH)D data in the RECORD trial.

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

TABLE 4
Meta-analysis results including on-trial only results from the RECORD trial[1]

Outcome	Risk ratio (95% CI)[2]	HR (95% CrI)[3]
Cardiac failure	0.83 (0.60, 1.13)	0.82 (0.58, 1.15)
MI	0.96 (0.83, 1.10)	0.96 (0.83, 1.10)
Stroke	1.09 (0.92, 1.30)	1.07 (0.91, 1.29)

[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.

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.

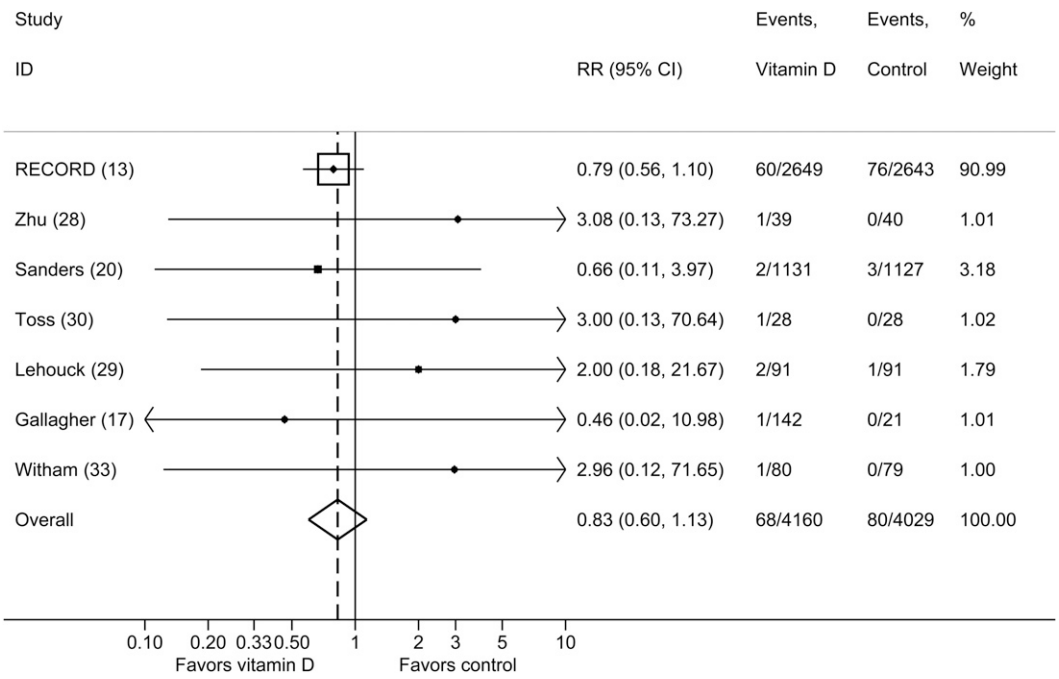

FIGURE 1. Cardiac failure forest plots for illustrative purposes including on-trial only results from the RECORD. Squares or diamonds indicate the point estimate of the study or overall effect; the size of the square or diamond reflects the CI. The dashed vertical line indicates the pooled estimate. ID, identifier; RECORD, Randomised Evaluation of Calcium Or vitamin D trial; RR, risk ratio.

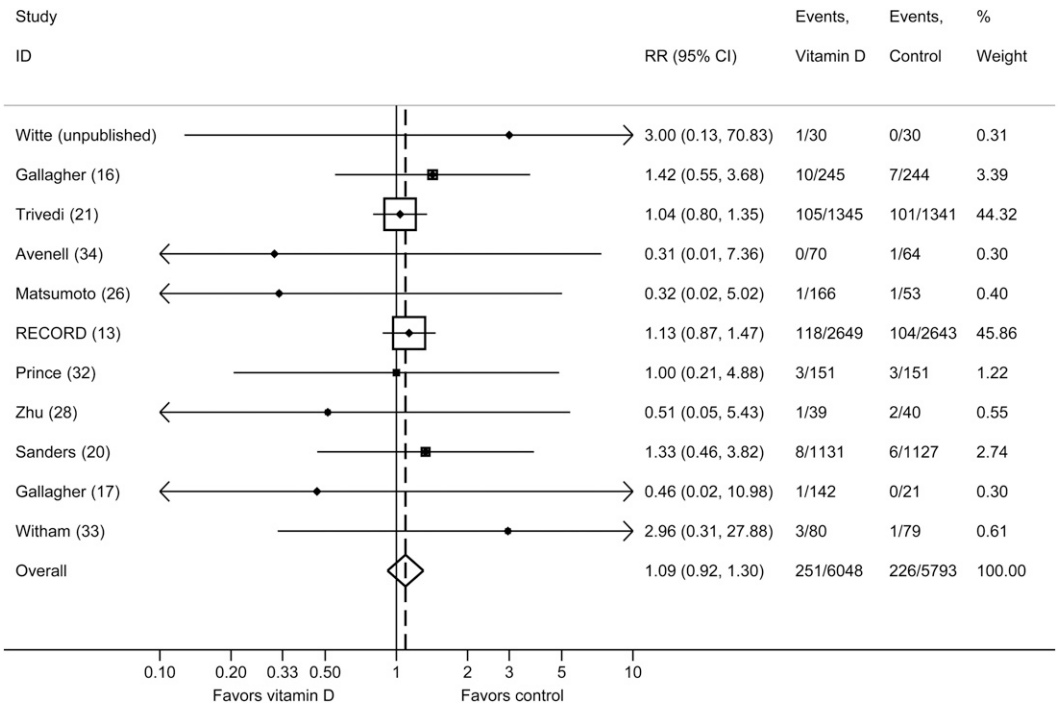

FIGURE 2. Stroke forest plots for illustrative purposes including on-trial only results from the RECORD. Squares or diamonds indicate the point estimate of the study or overall effect; the size of the square or diamond reflects the CI. The dashed vertical line indicates the pooled estimate. ID, identifier;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

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

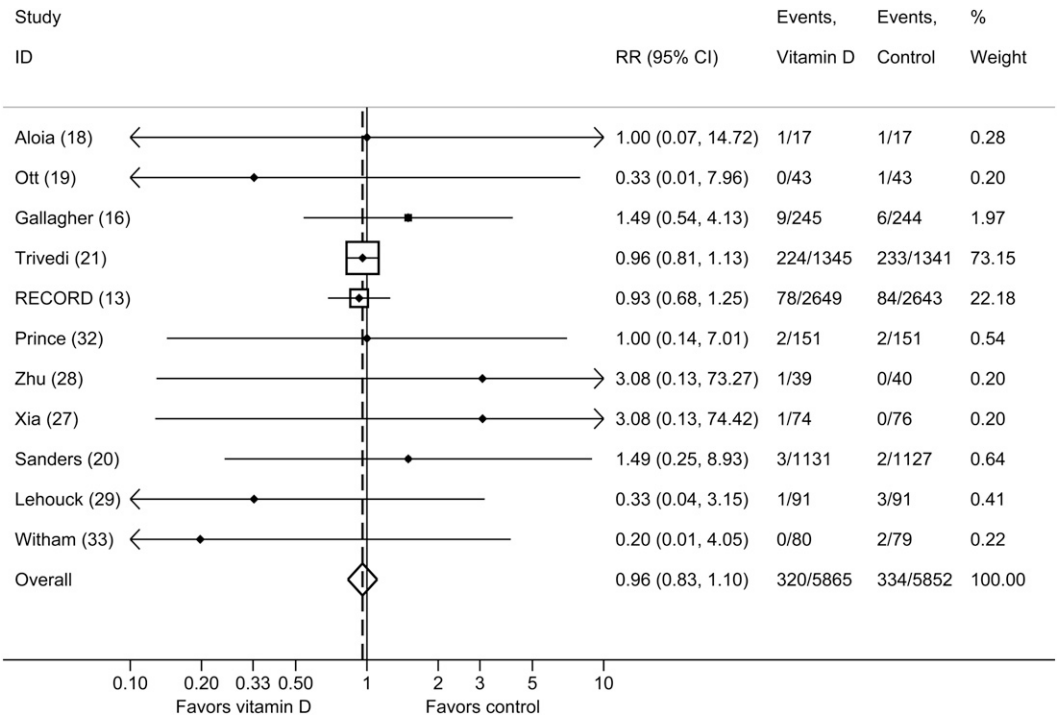

FIGURE 3. Myocardial infarction forest plots for illustrative purposes including on-trial only results from the RECORD. Squares or diamonds indicate the point estimate of the study or overall effect; the size of the square or diamond reflects the CI. The dashed vertical line indicates the pooled estimate. 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 aged 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 trial data alone.

We thank the patients who took part in the RECORD study without whose help this study would not have been possible. We also thank the following study authors for supplying additional data and clarifications: Cyrus Cooper, Itsuo Goari, Hazel Inskip, Wim Janssens, Glenn Liu, Per Magnusson, JoAnn Manson, Toshio Matsumoto, Susan Ott, Kerrie Sanders, Klaus Witte, Weino Xia, and Kun Zhu. We thank Daryll Archibald for checking data extraction in trials that involved AA. The RECORD Trial Group included the RECORD Trial Management Group [the Health Services Research Unit, University of Aberdeen, Aberdeen, United Kingdom (AM Grant, A Avenell, MK Campbell, AM McDonald, GS MacLennan, an dGC McPherson); the University of Southampton, Southampton, United Kingdom (FH Anderson); the Medical Research Council Epidemiology Resource Centre, University of Southampton, Southampton, United Kingdom (C Cooper); the Newcastle University, Newcastle, United Kingdom (RM Francis); the Glasgow Caledonian University, Glasgow, United Kingdom (C Donaldson); The Hull York Medical School, Hull, United Kingdom (WJ Gillespie); the Royal Infirmary of Edinburgh, Edinburgh, United Kingdom (CM Robinson); the Department of Health Sciences, York, United Kingdom (DJ Torgerson); and the Queens Medical Centre, Nottingham, United Kingdom (WA Wallace). Additional members of the RECORD Trial Group are listed in the RECORD trial.

The authors' responsibilities were as follows—AA, GSM, and MW: conceived the idea; JAF, AA, and GSM: undertook the hands-on research including the data collection and statistical analysis; JAF: wrote the first draft of the manuscript; AA: had primary responsibility for the final content of the manuscript; and all authors: made major, significant contributions to redrafting of the manuscript and contributed to the research design. AA and GSM took part in two of the trials in the systematic review. MW took part in one of the trials in the systematic review. JAF, MB, and AG had no other conflicts of interest. Details of conflicts of interest for other members of the RECORD Trial Group are provided in reference 13. Shire Pharmaceuticals and Nycomed were given the opportunity to comment on the penultimate version of the RECORD main trial report in *The Lancet*.

REFERENCES

1. Beveridge LA, Witham MD. Vitamin D and the cardiovascular system. Osteoporos Int 2013;24:2167–80.
2. Sokol SI, Tsang P, Aggarwal V, Melamed ML, Srinivas VS. Vitamin D status and risk of cardiovascular events: Lessons learned via systematic review and meta-analysis. Cardiol Rev 2011;19:192–201.
3. Reid D, Toole BJ, Knox S, Talwar D, Harten J, O'Reilly DS, Blackwell S, Kinsella J, McMillan DC, Wallace AM. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr 2011;93:1006–11.
4. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev 2014;1:CD007470.
5. Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, et al. Vitamin D and calcium: a systematic review of health outcomes. Evid Rep Technol Assess (Full Rep) 2009;183:1–420.
6. Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:1931–42.
7. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM. Systematic review: vitamin D and cardiometabolic outcomes. Ann Intern Med 2010;152:307–14.
8. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med 2010;152:315–23.
9. Witham MD. Vitamin D in chronic heart failure. Curr Heart Fail Rep 2011;8:123–30.
10. Meems LM, van der Harst P, van Gilst WH, de Boer RA. Vitamin D biology in heart failure. Curr Drug Targets 2011;12:29–41.
11. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events. BMJ 2010;341:c3691.
12. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events. BMJ 2011;342:f2040.
13. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, Anderson FH, Cooper C, Francis RM, Donaldson C, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people. Lancet 2005;365:1621–8.
14. Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane handbook. 5.1.0 ed. Chichester, United Kingdom: John Wiley & Sons Ltd, 2011.
15. Stata. Stata statistical software: release 12. College Station, TX: StataCorp, 2011.
16. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab 2001;86:3618–28.
17. Gallagher JC, Sai A, Templin T, Smith L. Dose response to vitamin D supplementation in postmenopausal women a randomized trial. Ann Intern Med 2012;156:425–37.
18. Aloia JF, Vaswani A, Yeh JK, Ellis K, Yasumura S, Cohn SH. Calcitriol in the treatment of postmenopausal osteoporosis. Am J Med 1988;84:401–8.
19. Ott SM, Chesnut CH III. Calcitriol treatment is not effective in postmenopausal osteoporosis. Ann Intern Med 1989;110:267–74.
20. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson CG. Annual high-dose oral vitamin D and falls and fractures in older women. JAMA 2010;303:1815–22.
21. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community. BMJ 2003;326:469.
22. Majima T, Komatsu Y, Shimatsu A, Satoh N, Fukao A, Ninomiya K, Matsumura T, Nakao K. Efficacy of combined treatment with raloxifene and alfacalcidol on bone density and biochemical markers of bone turnover in postmenopausal osteoporosis. Endocr J 2008;55:127–34.
23. Attia S, Eickhoff J, Wilding G, McNeel D, Blank J, Ahuja H, Jumonville A, Eastman M, Shevrin D, Glode M, et al. Randomized, double-blinded phase II evaluation of docetaxel with or without doxercalciferol in patients with metastatic, androgen-independent prostate cancer. Clin Cancer Res 2008;14:2437–43.
24. DeLuca HF, Bedale W, Binkley N, Gallagher JC, Bolognese M, Peacock M, Aloia J, Clagett-Dame M, Plum L. The vitamin D analogue 2MD increases bone turnover but not BMD in postmenopausal women with osteopenia. J Bone Miner Res 2011;26:538–45.
25. Gorai I, Tanaka Y, Hattori S, Iwaoki Y. Assessment of adherence to treatment of postmenopausal osteoporosis with raloxifene and/or alfacalcidol in postmenopausal japanese women. J Bone Miner Metab 2010;28:176–84.

26. Matsumoto T, Miki T, Hagino H, Sugimoto T, Okamoto S, Hirota T, Tanigawara Y, Hayashi Y, Fukunaga M, Shiraki M, et al. A new active vitamin D, ED-71, increases bone mass in osteoporotic patients under vitamin D supplementation. J Clin Endocrinol Metab 2005;90:5031–6.
27. Xia WB, Zhang ZL, Wang HF, Meng XW, Zhang Y, Zhu GY, Xing XP, Liu JL, Wang LH, Jiang Y, et al. The efficacy and safety of calcitriol and/or caltrate D in elderly chinese women with low bone mass. Acta Pharmacol Sin 2009;30:372–8.
28. Zhu K, Devine A, Dick IM, Wilson SG, Prince RL. Effects of calcium and vitamin D supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory australian women. J Clin Endocrinol Metab 2008;93:743–9.
29. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, van Eldere J, Decallonne B, Bouillon R, Decramer M, Janssens W. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease. Ann Intern Med 2012;156:105–14.
30. Toss G, Magnusson P. Is a daily supplementation with 40 microgram vitamin D(3) sufficient? Eur J Nutr 2012;51:939–45.
31. Macdonald HM, Wood AD, Aucott LS, Black AJ, Fraser WD, Mavroeidi A, Reid DM, Secombes KR, Simpson WG, Thies F. Hip bone loss is attenuated with 1000 IU but not 400 IU daily vitamin D3. J Bone Miner Res 2013;28:2202–13.
32. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. Arch Intern Med 2008;168:103–8.
33. Witham MD, Price RJ, Struthers AD, Donnan PT, Messow CM, Ford I, McMurdo ME. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension. JAMA Intern Med 2013;173:1672–9.
34. Avenell A, Grant AM, McGee M, McPherson GC, Campbell MK, Group RTM. The effects of an open design on trial participant recruitment, compliance and retention–a randomized controlled trial comparison with a blinded, placebo-controlled design. Clin Trials 2004;1:490–8.
35. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. Lancet 1997;350:829–33.
36. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure. J Hypertens 2009;27:1948–54.
37. Nieminen MS, Harjola VP, Hochadel M, Drexler H, Komajda M, Brutsaert D, Dickstein K, Ponikowski P, Tavazzi L, Follath F, et al. Gender related differences in patients presenting with acute heart failure. Eur J Heart Fail 2008;10:140–8.
38. Shedeed SA. Vitamin D supplementation in infants with chronic congestive heart failure. Pediatr Cardiol 2012;33:713–9.
39. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure. Am J Clin Nutr 2006;83:754–9.
40. Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure. Circ Heart Fail 2010; 3:195–201.
41. Hagström E, Hellman P, Larsson TE, Ingelsson E, Berglund L, Sundstrom J, Melhus H, Held C, Lind L, Michaelsson K, et al. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. Circulation 2009;119:2765–71.
42. Schroten NF, Ruifrok WP, Kleijn L, Dokter MM, Sillje HH, Lambers Heerspink HJ, Bakker SJ, Kema IP, van Gilst WH, van Veldhuisen DJ, et al. Short-term vitamin D3 supplementation lowers plasma renin activity in patients with stable chronic heart failure: an open-label, blinded end point, randomized prospective trial (VitD-CHF trial). Am Heart J 2013;166:357–64.
43. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, Marz W. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system. Clin Chim Acta 2010;411:1354–60.
44. Boxer RS, Kenny AM, Schmotzer MS, Vest M, Fiutem MS, Pina IL. A randomized controlled trial of high-Dose Vitamin D3 in patients with heart failure. JACC Heart Fail 2013;1:84–90.
45. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SAA, Black HR, Blanchette P, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669–83.
46. Donneyong MM, Taylor KC, Baumgartner RN, Myers J, Song WL, Martin LW. Calcium plus vitamin D supplementation and the risk of heart failure: the calcium and vitamin D trial of the women's health initiative study. Am J Epidemiol 2013;177:S128.
47. Bolland MJ, Grey A, Gamble GD, Reid IR. The eff ect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol 2014;2:307–20.
48. den Uyl D, Nurmohamed MT, van Tuyl LDH, Raterman HG, Lems WF. (Sub)clinical cardiovascular disease is associated with increased bone loss and fracture risk. Arthritis Res Ther 2011;13:R5.
49. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, et al. The VITamin D and OmegA-3 TriaL (VITAL). Contemp Clin Trials 2012;33:159–71.
50. Pilz S, Rutters F, Dekker JM. Disease prevention: vitamin D trials. Science 2012;338:883.