Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology

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Calcium is the dominant mineral present in bone and a shortfall nutrient in the American diet (1). Supplements have been recommended for persons who do not consume adequate calcium from their diet as a standard strategy for the prevention of osteoporosis and related fractures. Whether calcium with or without vitamin D supplementation is beneficial or detrimental to vascular health is not known.

**Description:**
Calcium is a component of the dominant mineral (hydroxyapatite) present in bone and a shortfall nutrient in the American diet (1). Supplements have been recommended for persons who do not consume adequate calcium from their diet as a standard strategy for the prevention of osteoporosis and related fractures. The U.S. Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center at Tufts University published an evidence report in 2009 (2) reviewing the existing data on the effect of both vitamin D and calcium on health outcomes, including cardiovascular disease. Since then, conflicting reports have suggested that calcium intake, particularly from supplements, may have either beneficial or harmful effects on cardiovascular outcomes. The National Osteoporosis Foundation (NOF) contracted an independent evidence review team at Tufts University to update the 2009 AHRQ evidence report on cardiovascular disease outcomes and end points (2). The expert panel, informed by the updated report (3), was assembled by the NOF and American Society for Preventive Cardiology (ASPC) and was ultimately responsible for writing this clinical guideline.

**Recommendation:**
The National Osteoporosis Foundation and American Society for Preventive Cardiology adopt the position that there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time. In light of the evidence available to date, calcium intake from food and supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000 to 2500 mg/d) should be considered safe from a cardiovascular standpoint.

**GUIDELINE DEVELOPMENT PROCESS**
To develop this guideline, the NOF and ASPC adhered to the methods previously published by the NOF (4). The authors served as the expert panel tasked with evaluating and grading the strength of evidence based on an externally developed evidence report (3). The evidence report was developed by the evidence review team at Tufts University and reflects the peer-reviewed scientific literature as of 1 July 2016. All members of the panel and evidence review team have disclosed their relationships in the prior 2 years (available at www.nof.org/news/nof-and-aspc-position-statement-on-calciuand-cardiovascular-disease), and disclosures were verbally affirmed during the project. The guideline is based largely on the findings of the evidence report. The evidence review team presented their findings to the expert panel via Webcast. Expert panel members were able to ask questions specific to the evidence report but were not permitted to influence the final study design or outcomes. An animal and mechanistic study (5), and comments submitted by scientists and other scientific bodies during a 14-day public comment period ending on 21 June 2016, were considered during
the development of the final guideline. The expert panel and authors of the evidence report were blinded to the funding source for the evidence report (no corporate funds were accepted for development of the guideline) until both manuscripts were approved by both societies' boards and submitted for publication.

**Recommendation**

Recommendation: The NOF and ASPC adopt the position that there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) with the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time. In light of the evidence available to date, calcium intake from food and supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000 to 2500 mg/d [6]) should be considered safe from a cardiovascular standpoint.

Obtaining calcium from food sources is preferred. Supplemental calcium can be safely used to correct any shortfalls in intake. Discontinuation of supplemental calcium for safety reasons is not necessary and may be harmful to bone health when intake from food is suboptimal. This guideline is based on the peer-reviewed scientific literature as of 1 July 2016 and supports the findings of the accompanying evidence report (2). In addition to the evidence report, the panel considered a recent animal and mechanistic study, which found no detectable effect of high-calcium diets (for example, dairy or calcium carbonate) on coronary artery calcium phosphate deposition in swine with diet-induced metabolic syndrome (5). Currently, no established biological mechanism supports an association between calcium and cardiovascular disease. This official guideline was adopted by the boards of directors of both societies on 22 July 2016.

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**References**


Romosozumab Treatment in Postmenopausal Women with Osteoporosis


ABSTRACT

BACKGROUND
Romosozumab, a monoclonal antibody that binds sclerostin, increases bone formation and decreases bone resorption.

METHODS
We enrolled 7180 postmenopausal women who had a T score of -2.5 to -3.5 at the total hip or femoral neck. Patients were randomly assigned to receive subcutaneous injections of romosozumab (at a dose of 210 mg) or placebo monthly for 12 months; thereafter, patients in each group received denosumab for 12 months, at a dose of 60 mg, administered subcutaneously every 6 months. The coprimary end points were the cumulative incidences of new vertebral fractures at 12 months and 24 months. Secondary end points included clinical (a composite of nonvertebral and symptomatic vertebral) and nonvertebral fractures.

RESULTS
At 12 months, new vertebral fractures had occurred in 16 of 3321 patients (0.5%) in the romosozumab group, as compared with 59 of 3322 (1.8%) in the placebo group (representing a 73% lower risk with romosozumab; P<0.001). Clinical fractures had occurred in 58 of 3589 patients (1.6%) in the romosozumab group, as compared with 90 of 3591 (2.5%) in the placebo group (a 36% lower risk with romosozumab; P=0.008). Nonvertebral fractures had occurred in 56 of 3589 patients (1.6%) in the romosozumab group and in 75 of 3591 (2.1%) in the placebo group (P=0.10). At 24 months, the rates of vertebral fractures were significantly lower in the romosozumab group than in the placebo group after each group made the transition to denosumab (0.6% [21 of 3325 patients] in the romosozumab group vs. 2.5% [84 of 3327] in the placebo group, a 75% lower risk with romosozumab; P<0.001). Adverse events, including instances of hyperostosis, cardiovascular events, osteoarthritis, and cancer, appeared to be balanced between the groups. One atypical femoral fracture and two cases of osteonecrosis of the jaw were observed in the romosozumab group.

CONCLUSIONS
In postmenopausal women with osteoporosis, romosozumab was associated with a lower risk of vertebral fracture than placebo at 12 months and, after the transition to denosumab, at 24 months. The lower risk of clinical fracture that was seen with romosozumab was evident at 1 year. (Funded by Amgen and UCB Pharma; FRAMES ClinicalTrials.gov number, NCT01575834.)
Women were randomly assigned, in a 1:1 ratio, to receive subcutaneous injections of 210 mg of romosozumab or placebo once monthly for 12 months during the double-blind phase of the trial. Patients then received open-label denosumab, administered subcutaneously at a dose of 60 mg every 6 months for an additional 12 months; the initial group assignment was still blinded. Patients were stratified according to age (<75 years vs. ≥75 years) and prevalent vertebral fracture (yes vs. no). In a substudy of the overall population that involved 128 patients, bone mineral density was assessed at baseline and every 6 months. In a substudy of the overall population that involved 128 patients, the levels of bone turnover markers were assessed at baseline, at day 14, and at months 1, 3, 6–12, 18, 24. After the 24-month trial period, patients continue to receive open-label denosumab in a 1-year extension study (data not shown).

PROCEDURES

Lateral radiographs of the spine were obtained at scheduled visits (Fig. 1) or if back pain occurred that was suggestive of vertebral fracture. Radiographs were assessed with the use of the Genant grading scale (grades range from 0 to 3, with higher grades indicating greater severity) (see the Supplementary Appendix, available at NEJM.org at a central imaging vendor (BioClinica). Patients were considered to have new vertebral fractures if there was an increase of at least one grade in previously normal vertebrae; determination that preexisting fractures had worsened also required an increase of at least one grade. The staff at the central imaging vendor, who were unaware of the treatment assignments, confirmed nonvertebral fractures by diagnostic imaging or by review of the radiologist's report. Fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures, and fractures that were associated with severe trauma were excluded.

In a substudy involving 128 patients, the bone mineral density at the lumbar spine and proximal femur was evaluated by means of dual-energy x-ray absorptiometry (Lunar or Hologic) at baseline and every 6 months (Fig. 1). Serum concentrations of the bone-turnover markers procollagen type 1 N-terminal propeptide (PINP) and β-isomer of C-terminal telopeptide of type 1 collagen (β-CTX) were measured in a substudy involving 129 patients (Fig. 1).

Adverse events were reported by trial-site physicians. Serious adverse events that were potentially cardiovascular-related, including deaths, and potential cases of osteonecrosis of the jaw and atypical femoral fracture were identified with the use of prespecified search strategies and adjudicated by independent committees. Adverse events of interest included those that were relevant to the injection of a monoclonal antibody or to calcium homeostasis and events that were considered to be potentially related to hyperostosis (as seen with excessive bone growth in genetic syndromes of sclerostin deficiency). Anti-romosozumab antibodies were assessed at baseline and at months 1, 3, 6, 12, 15, and 24.
groups. The demographic and clinical characteristics of the patients at baseline were balanced in the two groups (Table 1). The mean age of the patients was 70.9 years. The mean bone mineral density T scores were $-2.72$ at the lumbar spine, $-2.47$ at the total hip, and $-2.75$ at the femoral neck. A total of 1337 patients (19.3%) had a prevalent vertebral fracture (the majority of which were mild in severity), and 1560 (21.7%) had a previous nonvertebral fracture. The geographic regions with the highest enrollment were Latin America (3084 patients) and Central or Eastern Europe (2093 patients).

24-MONTH FRACTURE EFFICACY
Romosozumab was associated with a risk of new vertebral fracture that was 79% lower than the risk with placebo at 12 months (incidence, 0.5% [96 of 3325 patients] in the romosozumab group vs. 1.8% [59 of 3222] in the placebo group; risk ratio, 0.27; 95% confidence interval [CI], 0.16 to 0.47; $P<0.001$) (Fig. 2A, and Table S2 in the Supplementary Appendix). By 6 months, new vertebral fractures had occurred in 14 patients in the romosozumab group and 27 in the placebo group. Between 6 months and 12 months, fractures occurred in 2 additional patients in the romosozumab group, as compared with 3 additional patients in the placebo group. Romosozumab was also associated with a risk of clinical fracture that was 36% lower than the risk with placebo at 12 months; fractures occurred in 58 of 3589 patients (1.6%) in the romosozumab group vs. 90 of 3591 (2.5%) in the placebo group (risk ratio, 0.54; 95% CI, 0.46 to 0.69; $P<0.001$) (Fig. 2B, and Table S2 in the Supplementary Appendix).

Nonvertebral fractures constituted the majority (>85%) of clinical fractures. Nonvertebral fractures occurred in 56 patients (1.6%) in the romosozumab group and in 75 (2.1%) in the placebo group (hazard ratio, 0.75; 95% CI, 0.53 to 1.05; $P=0.10$) (Fig. 2C, and Table S2 in the Supplementary Appendix). Owing to the lack of statistical significance for the nonvertebral end point and the prespecified testing sequence, all other 12-month fracture end-point analyses were considered to be exploratory (Table S2 in the Supplementary Appendix).

The treatment effect in prespecified subgroups was consistent with regard to new vertebral, clinical, and nonvertebral fractures (data not shown), except with regard to clinical and nonvertebral fractures across geographic regions, for which significant treatment-by-region interactions were observed ($P=0.03$ and $P=0.04$, respectively). These findings were evaluated in a post hoc analysis that showed that the incidence of nonvertebral fracture in the region of Latin America was 1.5% (24 of 1595 patients) in the romosozumab group versus 1.2% (19 of 1534) in the placebo group (hazard ratio, 1.25; 95% CI, 0.68 to 2.27). By contrast, among the patients outside the region of Latin America, the incidence was 1.6% (32 of 2039) in the romosozumab group versus 2.7% (56 of 2057) in the placebo group, representing a risk that was 42% lower in the romosozumab group (hazard ratio, 0.58; 95% CI, 0.37 to 0.89; $P=0.04$ for the treatment-by-region interaction). The corresponding baseline 10-year risk of major osteoporotic fracture, as assessed by the Fracture Risk Assessment Tool (FRAX; developed by the World Health Organization [www.shef.ac.uk/frax/]), was 8.7% in Latin America and 17.0% elsewhere.

24-MONTH FRACTURE EFFICACY
All the patients made the transition to denosumab in the second year. The cumulative 24-month incidence of new vertebral fracture was lower in the group that had originally received romosozumab (22 of 3325 patients [0.6%]) than in the group that had originally received placebo (84 of 3327 [2.5%]), with a 75% lower risk in the romosozumab group (risk ratio, 0.25; 95% CI, 0.16 to 0.40; $P<0.001$) (Fig. 2A). In the second year, 5 patients in the group that had originally received romosozumab and 25 in the group that had originally received placebo had a new vertebral fracture.

There was no significant difference in the risk of nonvertebral fracture at 24 months (56 of 3589 patients [2.7%] in the romosozumab group and 129 of 3591 [3.6%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.57 to 0.97; nominal $P=0.03$; adjusted $P=0.06$). Owing to the prespecified testing sequence, treatment comparisons for other fracture end points at 24 months were considered to be exploratory. There was no significant difference in the risk of clinical fracture between the group that had originally received romosozumab and the group that had originally received placebo (99 patients and 147 patients, respectively, hazard ratio, 0.67; 95% CI, 0.52 to 0.87; nominal $P=0.002$; adjusted $P=0.10$) (Fig. 2B). Details are provided in Table S2 in the Supplementary Appendix.
ROMOSOZUMAB IN POSTMENOPAUSAL WOMEN WITH OSTEOSAROSIS

A. Incidence of New Vertebral Fracture

![Graph showing incidence of new vertebral fractures](image)

- Placebo
- Romosozumab
- Placebo + Denosumab
- Romosozumab + Denosumab

Risk ratio, 0.27
P < 0.001

B. First Clinical Fracture in Time-to-Event Analysis

![Graph showing cumulative incidence of first clinical fractures](image)

No. at risk
Placebo
Romosozumab
3591
3316

12 Mo
24 Mo
Risk ratio, 0.27
P < 0.001

C. First Nonvertebral Fracture in Time-to-Event Analysis

![Graph showing cumulative incidence of first nonvertebral fractures](image)

No. at risk
Placebo
Romosozumab
3591
3316

Figure 2. Incidence of New Vertebral, Clinical, and Nonvertebral Fractures.

The coprimary end points were the cumulative incidences of new vertebral fracture at 12 months and at 24 months (Panel A). The risk ratio was assessed among patients in the romosozumab group as compared with those in the placebo group at 12 months (end of the double-blind period) and at 24 months (by which time patients in both groups had received open-label denosumab for 12 months). Data from patients who underwent randomization and had a baseline radiograph and at least one radiograph obtained after the baseline visit are included here. Kaplan-Meier curves of the first clinical fracture (Panel B) and the first nonvertebral fracture (Panel C) from the time-to-event analysis are shown, including the double-blind period through 12 months and the period with open-label denosumab from 12 to 24 months. The insets show the same data on an enlarged y axis. Data from patients who withdrew from the trial or who reached the end of the reporting period without having a fracture were censored at the last observation time. *P* values are for results at 12 months and 24 months and are based on a Cox proportional-hazards model with adjustment for age and prevalent vertebral fracture, adjusted for multiple comparisons.

BONE DENSITY AND MARKERS OF BONE TURNOVER

Romosozumab increased bone mineral density by 6 months, and at 12 months the percentage change from baseline was greater with romosozumab than with placebo at the lumbar spine, by 13.3 percentage points (95% CI, 11.9 to 14.7), at the total hip, by 6.9 percentage points (95% CI, 5.6 to 8.1), and at the femoral neck, by 5.9 percentage points (95% CI, 4.3 to 7.4) (*P* < 0.001 for all comparisons) (Fig. 3A, 3B, and 3C). Bone mineral density continued to increase in the romosozumab group after the transition to denosumab.
Figure 3 (facing page). Percentage Change from Baseline in Bone Mineral Density and Levels of Bone-Turnover Markers.

Shown are the least-squares mean percentage changes in bone mineral density at the lumbar spine (Panel A), total hip (Panel B), and femoral neck (Panel C) for the 128 patients who were enrolled in the substudy on bone mineral density who had a baseline measurement and at least one measurement obtained after the baseline with (two patients done in each group) were missing the baseline assessment for the lumbar spine. Least-squares mean differences between the groups for each time point are shown in Table S5 in the Supplementary Appendix; estimated between-group mean differences may differ from those derived from the presented least-squares mean estimates owing to rounding. *P < 0.001 for the between-group comparisons of the mean percentage change from baseline at all time points for all skeletal sites. The median percentage-change values for the levels of serum procollagen type 1 N-terminal propeptide (PINP; Panel D) and the β-isomer of C-telopeptide of type I collagen (β-CTX; Panel E) are shown for patients who were enrolled in the substudy in 12 sets of bone-turnover markers. Bees indicate pointwise 95% confidence intervals for the values of bone mineral density and integrative ranges for the levels of bone-turnover markers for patients who had a baseline measurement and at least one measurement obtained after the baseline visit; the numbers of patients in each group with missing data at baseline are provided in Table S5 in the Supplementary Appendix. Between-group comparisons of the percentage change in bone mineral density were analyzed with the use of analysis-of-covariate models with adjustment for baseline bone mineral density, machine type, and interaction of baseline bone mineral density with machine type. Missing values were imputed by the last-observation-carried-forward method, and a sensitivity analysis with the use of a repeated measures model showed similar results. For the comparisons of the mean percentage change from baseline in PINP values: 0.01, for the comparisons at 14 days and at months 3, 6, and 12 months; month 9, P = 0.05; months 12, 18, and 24, P = 0.81. For the comparisons of the mean percentage change from baseline in β-CTX levels: 0.001 for the comparisons at 14 days and at months 3, 6, plus 12 months; and months 12, 18, and 24. For PINP and β-CTX levels, the comparisons were calculated with the use of the Wilcoxon rank-sum test.

ADVERSE EVENTS AND SAFETY

The incidence of adverse events and serious adverse events was balanced in the two groups, as was the incidence of events that were categorized as osteoarthritis, hyperostosis, cancer, hypersensitivity, and adjudicated serious cardiovascular events (Table 2). Serious adverse events that were potentially indicative of hypersensitivity occurred in 7 patients in the romosozumab group in the first year. Injection-site reactions, which were mostly mild in severity, were reported over the 12-month period in 157 patients (5.2%) in the romosozumab group and in 104 (2.9%) in the placebo group.

Two events that occurred in patients in the romosozumab group were adjudicated as being consistent with the definition of osteonecrosis of the jaw. One event occurred after 12 months of romosozumab treatment in the context of ill-fitting dentures, and the other event occurred after 12 months of romosozumab treatment and one dose of denosumab after a tooth extraction and subsequent osteonecrosis of the jaw. One event that was adjudicated as being consistent with the definition of atypical femoral fracture occurred 3.5 months after the first dose of romosozumab; the patient had reported a history of prodromal pain at the site of fracture beginning before enrollment.

During the first 15 months of the trial, binding anti-romosozumab antibodies developed in 646 patients in the romosozumab group (18.0%), and neutralizing antibodies developed in 25 patients in the romosozumab group (0.7%), with no detectable effect on efficacy or safety (Tables S4 and S5 in the Supplementary Appendix). The median albumin-corrected serum calcium levels were lower at 1 month in the romosozumab group than in the placebo group (median change from baseline, −2.2% vs. 0.0%).

DISCUSSION

In this phase 3 trial involving patients with osteoporosis, romosozumab was associated with a lower risk of new vertebral fractures than placebo at 12 months. The effect of romosozumab on the risk of vertebral fracture was rapid, with only 2 additional vertebral fractures (of a total of 16 such fractures in the romosozumab group) occurring in the second 6 months of therapy. The risk of clinical fracture (a composite of nonvertebral fracture and symptomatic vertebral fracture) was also significantly lower in the romosozumab group within 12 months after the start of treatment than in the placebo group. Because vertebral and clinical fractures are associated with
expected, which was driven by a geographic region with high enrollment (Latin America) in which the incidence in the placebo group at 12 months was one third the expected rate, with no detectable treatment effect. The regional-subgroup data warrant cautious interpretation owing to a lack of adjustment for multiple comparisons and the possibility of type I error. However, the low rate of nonvertebral fracture in the placebo group in the Latin American geographic region is consistent with the low mean baseline FRAX score that was observed in the patients enrolled in that region and with recent epidemiologic reports.25,26 In a post hoc analysis that included patients outside Latin America, a higher rate of nonvertebral fracture was observed in the placebo group (2.7% vs. 1.2% in the placebo group in Latin America), and 12 months of romosozumab treatment resulted in a risk of fracture that was 42% lower than the risk with placebo. These findings merit further evaluation.

The results regarding bone-turnover markers confirm those reported previously20 and support the dual effect of romosozumab in increasing bone formation and decreasing bone resorption by means of sclerostin inhibition. Sclerostin blocks canonical Wnt signaling, which results in decreased osteoblast-mediated bone formation21,22 and increased bone resorption,23 both of which are counteracted by romosozumab.12,24 The transient increases in the P1NP level after repeated dosing may provide insight into the observed gains in bone mineral density over the treatment period. This effect of romosozumab on bone formation and resorption translated into large increases in bone mineral density at the spine and hip, and clinically significant increases were seen as early as 6 months, as reported previously.20 Additional gains were observed after the transition to denosumab.

Adverse events were balanced in the two groups. Serious adverse events of hypersensitivity reactions were observed in the romosozumab group, although these events were uncommon. Cases of osteonecrosis of the jaw and an atypical femoral fracture were observed, albeit rarely, in patients with confounding factors that may have contributed to the event or that raise questions about causality.

In conclusion, romosozumab is a monoclonal antibody that increases bone formation and decreases bone resorption. One year of romosozumab treatment in postmenopausal women with osteoporosis resulted in a lower risk of vertebral and clinical fractures than the risk with placebo. Substantial gains in bone mineral density at the spine and hip with romosozumab provided a foundation for an ongoing reduction in the risk of fracture during sequential treatment with denosumab.

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APPENDIX

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