A Meta-Analysis Raises Concerns About the Cardiovascular Risks of Calcium Supplementation

Bolland M, Avenell A, Baron J, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010; 341: c3691.

Study Overview

Objective. To examine the association of calcium supplementation with cardiovascular events.

Design. Meta-analysis of randomized, placebo-controlled trials of calcium supplementation. Trial inclusion criteria were the use of calcium supplements of ≥ 500 mg/day for more than 1 year and ≥ 100 participants with a mean age of 40 years or older. Exclusions included trials of combined calcium and vitamin D, trials in which calcium was given as a dietary modification or complex nutritional supplement, and trials in which most participants had a major chronic disease other than osteoporosis.

Setting and participants. 15 trials met inclusion criteria but only 11 trials had data on cardiovascular outcomes. The 11 trials were published between 1993 and 2008, with 5 trials providing patient-level data on cardiovascular outcomes from 8151 patients. All 11 trials provided summary trial-level data for 11,921 patients.

Main outcome measures. Time to first myocardial infarction, time to first stroke, and time to first event (composite endpoint of myocardial infarction, stroke, or sudden death) were the primary endpoints. The secondary endpoint was all-cause mortality.

Main results. Authors identified 11,363 trials for examination, with 190 trials fully screened. Of those studies excluded, 111 did not meet the study size inclusion criteria of ≥ 100 patients, 30 had a study duration < 1 year, and 21 did not meet the additional study design inclusion and exclusion criteria. For the patient-level data analysis, the mean age was 73 years old, and 78% of subjects were female. Median follow-up was 3.6 years. 143 patients in the calcium supplements groups had a myocardial infarction compared with 111 in the placebo groups (hazard ratio [HR], 1.31 [95% confidence interval {CI}, 1.02–1.67]; P = 0.035). Stroke was nonsignificantly higher in the calcium groups (HR, 1.20 [95% CI, 0.96-1.50]; P = 0.11) as was the composite endpoint (HR, 1.18 [95% CI, 1.00–1.39]; P = 0.057) and death (HR, 1.09 [95% CI, 0.96–1.23], P = 0.18). For the trial-level data analysis, the mean age was 72 years, and 83% were female. Median duration of follow-up was 4.0 years. Results were similar to the patient-level data, with myocardial infarctions occurring in 166 subjects in the calcium groups and 130 in the placebo groups (relative risk 1.27 [95% CI, 1.01–1.59], P = 0.038). No statistical heterogeneity between trials was evident, and funnel plots showed no evidence for publication bias.

Conclusion. Use of calcium supplementation was associated with a higher risk of myocardial infarction.

Commentary

Use of calcium supplementation to improve bone health and prevent fractures has been a mainstay of clinical practice, especially among postmenopausal women. The data to

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support its use are relatively modest, but the benefits have been commonly viewed to outweigh the risks. Few studies have examined in detail the downside of supplementation, especially with respect to cardiovascular outcomes [1]. In this study, Bolland and colleagues combined the results of 11 prior randomized controlled trials in a meta-analysis to determine whether calcium supplementation was associated with cardiovascular events.

The meta-analysis was appropriately conducted and utilized data from over 11,000 patients, including patient-level data collected from individual trial authors on over 8000 patients. Authors found consistent relationships, using both the patient-level and trial-level data, between calcium supplementation and myocardial infarction. Stroke and a composite endpoint of myocardial infarction, stroke, and sudden death were also higher in the calcium supplement group, but the associations were not significant. In a prespecified subgroup analysis of subjects with high dietary calcium intake, defined as intake above the median of 805 mg/day, supplementation with calcium was associated with an increased risk of myocardial infarction (HR, 1.85 [95% CI, 1.28–2.67]). No association was evident for those with dietary calcium intake below the median.

The results of this study are notable, especially because of prior evidence supporting the potential cardiovascular benefits of calcium supplementation. A meta-analysis of 42 trials of calcium supplementation found a small but significant decrease in blood pressure with calcium compared with placebo [2]. Prior observational studies have shown consistent relationships between higher calcium intake and lower cardiovascular mortality or stroke [3,4]. Bolland et al could not evaluate possible pathways whereby calcium may be associated with cardiovascular events. They discuss the possibility that an increase in serum calcium levels, which is modest with calcium supplementation, could lead to vascular calcification.

The limitations of this meta-analysis are important and should be considered when deciding the clinical implications of this study. First, this meta-analysis looked only at trials that used calcium supplementation alone and excluded those trials of combined calcium and vitamin D supplementation. Clinicians usually recommend combinations of calcium and vitamin D as supplements to improve bone health. Many patients who take calcium also take a multivitamin, which invariably includes the recommended daily allowance of vitamin D, and authors did not account for multivitamin use in the analysis. Ultimately, the failure to include studies combining calcium and vitamin D limits the applicability of this study to standard clinical practice. Second, 1 study dominated this meta-analysis, contributing nearly half of the subjects for the trial-level analysis and 65% of the subjects for the patient-level analysis. This disproportionate weight allows that trial to dominate the results rather than more uniform contribution from multiple studies. Third, the ascertainment of the outcome—myocardial infarction, stroke, and sudden death—was different for each of the studies included in the meta-analysis, with only 2 of the trials using independent adjudication of the cardiovascular end points. The other trials used self report from subjects, hospital discharge data, physician reports, or death certificates, which were in some cases adjudicated by physicians involved with the study, or not at all, rather than independently. Fourth, patient-level data were only available for a small number of the RCTs identified, and no data were available from 4 studies. As the authors point out, these 4 studies were small and unlikely to change the outcome.

The Institute of Medicine recently released new recommendations on the use of the calcium and vitamin D, with a general theme that more of these supplements is not necessarily better [5]. While they did not seem to use this study by Bolland et al to guide their recommendations, the expert panel concluded that evidence to support the use of vitamin D and calcium supplements at high levels was unjustified and that most North Americans are getting adequate calcium and vitamin D even without supplements. The panel revised the recommended dietary allowance of calcium to 1000 mg for most people, with slightly higher levels for postmenopausal women and adolescents, and to 600 IU for vitamin D, with higher levels for individuals > 70 years old. They also warned of excess intake, especially of calcium, primarily because of associations with nephrolithiasis.

Applications for Clinical Practice

Calcium supplementation without vitamin D may be associated with higher rates of myocardial infarction. Additional studies must confirm this association before clinicians can make definitive conclusions about the risk of calcium supplementation. However, unless there are compelling reasons, clinicians should continue to use combination calcium and vitamin D supplementation over calcium monotherapy for bone health in their patients.

—Review by Jason P. Block, MD, MPH

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