

Does Widespread Calcium Supplementation Pose Cardiovascular Risk?

Yes: The Potential Risk Is a Concern

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Use of calcium supplements produces small, beneficial changes in blood pressure and circulating lipid levels.^{1,2} To determine whether these changes lead to fewer acute myocardial infarctions (MIs) and strokes, we prespecified cardiovascular outcomes as secondary end points in a randomized controlled trial (RCT) of calcium supplementation in 1,471 women late in the postmenopausal period.³ We were greatly surprised to find a significantly increased risk of acute MI, and an upward trend for stroke. Although we were initially skeptical, evidence of increased mortality (mainly cardiovascular)⁴ and accelerated coronary artery calcification⁵ associated with calcium supplement use caused us to take these findings seriously.

Usually, an unexpected finding in a controlled trial leads to a definitive trial to provide confirmation. However, we believe that this is unethical when the hypothesis is that the intervention is harmful. Therefore, we tested the hypothesis by pooling existing data in a meta-analysis.⁶ We requested patient-level cardiovascular adverse effects data from the authors of all of the major calcium RCTs (or trial-level data if patient-level data were not available). Meta-analyses of these data showed remarkable consistency across the major studies, with acute MI incidence increasing by 20 to 30 percent in persons randomized to calcium supplementation, and a relative risk of 1.27 (95% confidence interval [CI], 1.01 to 1.59) in the entire study population of almost 12,000. A second trial-level meta-analysis reported similar findings, although those results were not statistically significant because the



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► See related editorial at <http://www.aafp.org/afp/2013/0201/od2.html>.

authors relied solely on published data, for which the study population was only one-third that of our meta-analysis.⁷

Our analysis did not assess the effect of calcium coadministered with vitamin D. The Women's Health Initiative used this combined intervention, and cardiovascular findings appeared to be reassuring.⁸ However, this study permitted patients to self-administer calcium, which we hypothesized might have obscured an adverse effect. Therefore, we proposed an analysis to address this question (approved by the National Institutes of Health before the data were released to us). This demonstrated that calcium plus vitamin D increased the risk of acute MI and stroke in those not already taking calcium supplements,⁹ suggesting that this effect had been obscured in the whole cohort by the widespread use of nontrial calcium supplements. We subsequently broadened our meta-analysis to include all trials of calcium with or without vitamin D, with a total study population of almost 29,000 men and women. With calcium use, the relative risk was 1.24 (95% CI, 1.07 to 1.45) for acute MI and was 1.15 (95% CI, 1.00 to 1.32) for stroke.⁹

It is not surprising that these unexpected findings have not been universally accepted, because calcium is widely used and thought to be safe. Critics point out that other events (e.g., gastrointestinal) might have been misclassified as cardiovascular. However, the increased risk is consistent across the trials, whether the events were fully adjudicated or

from hospital discharge summaries, death certificates, or self-report. Others have suggested that because the trials were not primarily designed to assess cardiovascular outcomes, the results are invalid. That line of reasoning would make it impossible to accept unexpected adverse effects from any intervention. Some have suggested that more research is required before changing clinical practice, but it is not clear what this research might be or when it might happen. No major trials of calcium supplementation are underway that could significantly influence the results from the recent meta-analyses, and a definitive RCT with acute MI as the primary end point is not likely to be undertaken for ethical reasons.

Thus, physicians are confronted with a consistent body of data indicating an increased vascular risk associated with the use of calcium supplements, and need to balance this against the evidence for a marginal reduction in fracture rates.¹⁰ In both of our meta-analyses, calcium supplementation was more likely to cause vascular events than to prevent fractures.^{6,9} Therefore, the bolus administration of this micronutrient should be abandoned in most circumstances, and patients should be encouraged to obtain their calcium intake from an appropriately balanced diet. For those at high risk of fracture, effective interventions with a fully documented safety profile superior to that of calcium are available. We should return to seeing calcium as an important component of a balanced diet and not as a low-cost panacea to postmenopausal bone loss.

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