

Does Widespread Calcium Supplementation Pose Cardiovascular Risk?

No: Concerns Are Unwarranted

RAJIB K. BHATTACHARYA, MD, *University of Kansas Medical Center, Kansas City, Kansas*

Calcium supplements are widely used in the United States and other developed nations, most commonly to reduce the risk of fracture in women with low bone mineral density.¹⁻³ However, concern has been expressed that calcium supplementation may increase the risk of atherosclerotic vascular disease.^{4,5} The data are conflicting, and most of the earlier trials had osteoporotic fractures, not cardiovascular events, as their primary end points.

The controversy started with a secondary analysis of a randomized placebo-controlled trial of calcium supplements given to women in the postmenopausal period for five years.⁵ Women treated with calcium supplements had a statistically significant increase in myocardial infarction (MI), compared with those treated with placebo. The composite end point of MI, stroke or cerebrovascular accident, or sudden death was higher in the calcium group, but statistical significance was not demonstrated when the researchers attempted to confirm the events with a national registry. In addition, adequate documentation of concomitant use of cardiovascular medications was lacking.

Next, a meta-analysis of 11 studies showed that calcium supplementation (more than 500 mg per day for longer than one year) was associated with a 30 percent increase in the incidence of MI, and a smaller nonsignificant increase in the risk of cardiovascular accident and death.⁵ None of the trials had cardiovascular events as the primary end point, and data on cardiovascular events were not gathered in a standardized manner. Seven trials had incomplete or no data on cardiovascular outcomes; this comprised about 15 percent of the total participants.



This is one in a series of pro/con editorials discussing controversial issues in family medicine.

► See related editorial at <http://www.aafp.org/afp/2013/0201/od1.html>.

None of the trials were designed to normalize the baseline characteristics of the participants in terms of cardiac risk factors.

In contrast, the Women's Health Initiative did not show any concerning cardiovascular risk from calcium supplementation. The study was a randomized controlled trial of calcium (500 mg) plus vitamin D (200 IU twice daily) versus placebo in 36,282 postmenopausal women 50 to 79 years of age; cardiovascular disease was a prespecified secondary efficacy outcome. This study revealed that calcium/vitamin D supplementation did not affect the risk of coronary events or stroke in generally healthy postmenopausal women throughout the seven-year trial.⁶ A limitation was that women in the placebo group were allowed to continue their personal use of calcium supplements, which could have influenced the effect of randomization to calcium and vitamin D in regard to cardiovascular risk.

A prospective cohort study, including 34,486 postmenopausal women 55 to 69 years of age who had no history of ischemic heart disease, investigated whether greater intakes of calcium, vitamin D, or milk products would protect against ischemic heart disease mortality. The study found an inverse association (no evidence of causality) between the risk of dying of ischemic heart disease and higher levels of calcium intake after eight years of follow-up. There was an estimated statistically significant 33 percent risk reduction for persons in the

highest quartile of total calcium intake (i.e., from diet, supplements, or both).⁷ One limitation of the study was that the duration of supplemental vitamin and mineral use was unknown.

Finally, a recent randomized controlled trial comparing calcium carbonate supplementation (1,200 mg per day) with placebo evaluated the risk of vascular events and mortality as a primary end point. The five-year study included 1,460 women (mean age = 75 years) and 4.5 years of posttrial follow-up. In this intention-to-treat analysis, the intervention group did not have a higher risk of death or first-time hospitalization from atherosclerotic vascular disease compared with the placebo group.⁸

In summary, when patients are randomized and cardiovascular events are carefully adjudicated, there is no compelling evidence that calcium supplementation increases the rate of major cardiovascular events. Earlier trials may have had unforeseen ascertainment bias, causing the perception of an increase in cardiovascular events.

Address correspondence to Rajib K. Bhattacharya, MD, at rbhattacharya@kumc.edu. Reprints are not available from the author.

Author disclosure: No relevant financial affiliations to disclose.

REFERENCES

1. Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med*. 1990; 323(13):878-883.
2. Elders PJ, Lips P, Netelenbos JC, et al. Long-term effect of calcium supplementation on bone loss in perimenopausal women. *J Bone Miner Res*. 1994;9(7):963-970.
3. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial [published correction appears in *Am J Clin Nutr*. 2008;87(3):794]. *Am J Clin Nutr*. 2007;85(6):1586-1591.
4. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008; 336(7638):262-266.
5. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341: c3691.
6. Hsia J, Heiss G, Ren H, et al.; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events [published correction appears in *Circulation*. 2007;115(19):e466]. *Circulation*. 2007; 115(7):846-854.
7. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. *Am J Epidemiol*. 1999;149(2): 151-161.
8. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. *J Am Miner Res*. 2011;26(1): 35-41. ■