Calcium Builds Bones But May Weaken Heart

By Chris Kaiser, Cardiology Editor, MedPage Today
April 19, 2011

A re-examination of the Women's Health Initiative study revealed a modest increase in risk of MI and stroke for those taking calcium supplements, with or without vitamin D.

The Women's Health Initiative Calcium/Vitamin D Supplementation (WHI CaD) Study originally found no risk associated with the supplements after studying more than 36,000 patients over seven years.

However, 54% and 47% of those participants were taking personal calcium and vitamin D supplements, respectively, effectively rendering the trial a comparison of higher dose and lower dose calcium and vitamin D for most of the participants, according to Mark J. Bolland, senior research fellow at the University of Auckland, New Zealand, and colleagues.

The findings suggest the use of these supplements in managing osteoporosis should be re-assessed, researchers reported online today in the *BMJ*.

In the new study, researchers analyzed data from 16,718 women who were not taking personal calcium supplements at the start of the trial and found that those allocated to combined calcium and vitamin D supplements were at an increased risk of cardiovascular events, especially MI.

By contrast, in women who were taking calcium supplements before entering the trial, combined calcium and vitamin D supplements did not alter their cardiovascular risk.

In women not taking calcium at baseline, the hazard ratios with calcium and vitamin D were 1.16 (*P*=0.04) for the composite endpoint of clinical MI or coronary revascularization; 1.16 (*P*=0.05) for clinical MI or stroke; 1.22 (*P*=0.05) for MI; and 1.13 to 1.20 for the other cardiovascular endpoints. By contrast, in women taking personal calcium supplements, the hazard ratios for these endpoints with calcium and vitamin D were 0.83 to 1.08.

Researchers also found no relation between the dose of the supplements and the cardiovascular risk.

The authors suspect that the abrupt change in blood calcium levels after taking a supplement causes the adverse effect, rather than it being related to the total amount of calcium consumed.

"The process of vascular calcification is a complex, regulated process similar to osteogenesis," they wrote. "It is possible that the increase in serum calcium concentrations from calcium supplements influences vascular calcification by altering regulators of calcification such as fetuin A, pyrophosphate, and bone morphogenic

protein-7, or by directly binding to the calcium-sensing receptor that is expressed on vascular smooth muscle cell."

Bolland and colleagues said that this analysis by itself does not provide definitive evidence regarding calcium supplements and cardiovascular risk. However, the researchers also pooled previously unpublished data from two other placebo-controlled trials of calcium and vitamin D, with consistent increases in the risk of MI and stroke.

To further bolster the evidence, Bolland et al. suggested that a similar risk is evident from 13 other trials, involving 29,000 people altogether, including studies involving calcium monotherapy.

"The size of this increase [in risk] is modest, about 25% to 30% for myocardial infarction and 15% to 20% for stroke, but, because of the widespread use of calcium supplements either alone or with vitamin D, even small increases in cardiovascular disease incidence may translate to a substantial population burden of disease, particularly in older age groups," researchers wrote.

They noted the risk to benefit profile is unfavorable. "In our analysis, treating 1,000 patients with calcium or calcium and vitamin D for five years would cause an additional six myocardial infarctions or strokes (number needed to harm of 178) and prevent only three fractures (number needed to treat of 302)."

In an accompanying editorial, Bo Abrahamsen, MD, from Gentofte Hospital, Copenhagen, Denmark, and Opinder Sahota, MD, from Queen's Medical Center, Nottingham, England, argue that there is insufficient evidence available to support or refute the association.

"Unfortunately, although it is straightforward to remove those who were taking their own supplements from the cohort when they make up uneven parts of the randomised arms, interpreting the results is difficult because of the loss of equal randomization," Abrahamsen and Sahota wrote. "Clearly further studies are needed and the debate remains ongoing."

Andrea LaCroix, PhD, co-principal investigator on the original WHI CaD study, and not involved in this analysis, told *MedPage Today* that she and her colleagues had found no significantly increased risk of acute MI or coronary heart disease death -- the primary endpoints. "[Bolland and colleagues] looked very hard to find this association" in their post hoc analysis, which looked at "a number of different definitions of coronary heart disease and stroke."

LaCroix said she suspects that the authors explored a large number of subgroup analyses "before settling on these particular findings for publication."

She concluded, "The findings presented here for certain endpoints -- not prespecified as primary trial endpoints -- appear to result from a higher rate of certain clinical coronary heart disease indicators in women who were not taking personal calcium supplements compared to all the other groups. There were no such associations observed in the strata of women taking very little calcium (< 500 mg/day), or at any higher dose of personal supplements, which makes these findings look less plausible."

Nevertheless, these findings warrant further attention, say others.

"The paper presents a persuasive case that the calcium supplements could be a problem," Harlan Krumholz, MD, from Yale University School of Medicine, told *MedPage Today*.

"The relative risk is on the order of what was found for Vioxx [the controversial arthritis drug] -- the absolute rates are low so that the vast majority do not have events. Because it is not a straightforward analysis, it should be considered more exploratory, and should prompt other studies to investigate whether these results can be replicated," Krumholz said.

"The question for any person is how important is it for them to take the supplements: The assumption should not be that they can't hurt and might help. We should all want strong evidence of benefit and assurance of safety before making choices to take supplements. And in this case, part of this paper uses a limited dataset of a U.S. government funded study. The NIH should replicate these findings with the full dataset so that it is clear that it reflects accurately what the study shows," he concluded.