'Abrupt Change' After Ingestion?

MI Risk *from page 1*

colleagues argued, may have masked any harmful effect from the supplements used in the trial.

Dr. Bolland and colleagues found that the hazard ratios for four cardiovascular events – myocardial infarction, coronary revascularization, death from coronary heart disease, and stroke – among nonsupplementing women assigned to calcium and vitamin D, ranged from 1.13 to 1.22, and all reached statistical significance. For the women who had been taking personal supplements at enrollment, by contrast, cardiovascular risk was unchanged with allocation to the study calcium and vitamin D.

The hazard ratios for four cardiovascular events among nonsupplementing women assigned to calcium and vitamin D were 1.13-1.22, and all reached statistical significance.

Finally, the researchers pooled the data with previously unpublished data from two other placebo-controlled trials of calcium and vitamin D and found increases in the risk of MI similar to that observed in studies of calcium-only supplements.

Adding results for calcium and vitamin D trials to those from trials of calcium alone, Dr. Bolland and colleagues found "consistent evidence from 13 randomized, placebo controlled trials involving about 29,000 participants with about 1,400 incident myocardial infarctions and strokes that calcium supplements with or without vitamin D increase the risk of cardiovascular events," Dr. Bolland and colleagues wrote, putting the pooled increased risk at 25%-30% for myocardial infarction and 15%-20% for stroke.

The researchers acknowledged that there was much to be learned about how calcium and vitamin D supplementation might affect cardiac risk, and that more research was necessary, but hypothesized that an "abrupt change in plasma calcium concentration after supplement ingestion" may cause an adverse cardiac effect. The findings, they concluded, "justify a reassessment of the use of calcium supplements in older people."

In an editorial accompanying the current article, Dr. Bo Abrahamsen of Gentofte Hospital in Copenhagen, and Dr. Opinder Sahota of Nottingham (England) University Hospitals voiced concerns about the post hoc analysis used by Dr. Bolland and colleagues in reevaluating data from the 2007 trial, and emphasized that "insufficient evidence is available to support or refute the association" (BMJ 2011 April 20 [doi:10.1136/bmj.d2040]).

While as a whole, "randomisation can be assumed to have been equal across the two arms in terms of confounders, measured and unmeasured, this may not have been true for the additional strata created in the post hoc analysis," they wrote. "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 randomisation."

The current study was funded by the Health Research Council of New Zealand and the University of Auckland School of Medicine Foundation. Three authors, including Dr. Bolland, declared that they had no competing interests. Dr. Alison Avenell has had calcium used in studies supplied by Shire and Nycomed, and Dr. Ian R. Ried is a consultant to Fonterra, and has used calcium supplements provided by Mission Pharmacal in clinical trials.

Dr. Abrahamsen has received consultant fees from Novartis, is an adviser for Amgen and Nycomed, and has received lecture fees from Eli Lilly and Procter and Gamble. Dr. Sahota has received consultant fees from Shire, is an adviser for Amgen and Medtronic, and has received lecture fees from Eli Lilly and Amgen. ■

VIEW ON THE NEWS

Meet Calcium Needs With Food

"It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so."
–Mark Twain

We base many of our everyday decisions on assumptions that are untested. In medicine, these assumptions are often passed down from our early training and form the foundation on which we build our practice of medicine. Some are so basic that few of us would bother to question them. The mantra for preventive bone health has traditionally been calcium, vitamin D, and exercise. Clearly all have proven importance, but the specifics have never been fully explored. Controversies regarding the type of exercise most beneficial to bone health versus benefit to balance and muscle function are commonplace. Heated discussions on the optimal range for 25-hydroxyvitamin D, assay characteristics, dosing, and type of vitamin D supplementation are a regular feature in many journals as well as newspaper articles. These controversies and ever-changing recommendations often prompt confusion among physicians and patients over what is optimal in the prevention and treatment of osteoporosis.

On the other hand, calcium recommendations have generally provided a reassuring and solid bedrock, like the apparently steadfast White Cliffs of Dover, for our discussions with patients. But like the White Cliffs of Dover, occasionally big pieces break off. The cracks started appearing over the past few years and a chasm has now formed. Calcium supplementation is a big industry. The proliferation of calcium products feeds off of an aging population and an inherent desire to improve ourselves and take an active role in maintaining our health. Many people strongly (and wrongly) believe that if they only take enough calcium, they won't develop osteoporosis or may not need prescription medications if they are at significant fracture risk. The possible link between calcium supplements and cardiovascular events has forced us to reexamine our need for supplements as opposed to calcium rich foods. Many people who take sufficient calcium take calcium supplements as well in the mistaken notion that the 1,200 mg of calcium recommendation applies to the supplement dosing and does not include dietary calcium.

Testing of the 24-hour urine calcium in osteoporosis patients often demonstrates this calcium excess and can serve as a valuable educational tool for the patient as well as the physician as to how much calcium is needed for a given individual.

These recent studies provide a valuable opportunity for discussing with patients how adequate calcium needs can be met with food and how calcium supplements are not necessary for many patients on a reasonably healthy diet. With whole stores devoted to supplements of various kinds, it is refreshing to have the opportunity to educate ourselves and our patients about healthy eating habits as a sufficient and more desirable source for nearly all of our nutritional needs.

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Denosumab's Bone Benefits Persist at 5 Years of Therapy

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

SAN DIEGO – Bone density and fracture risk continued to improve from baseline in postmenopausal women taking denosumab for osteoporosis, based on data from a 2-year extension of the FREEDOM study in more than 4,000 women.

The original FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) enrolled 7,808 postmenopausal women aged 60-80 years with osteoporosis to receive either a subcutaneous injection of denosumab (60 mg) or placebo along with daily calcium and vitamin D supplements every 6 months. All subjects had bone mineral density (BMD) T scores of less than –2.5 but not less than –4.0 at the lumbar spine or total hip. At 36 months, denosumab was associated with reductions of 68% in vertebral fracture and 40% in hip fracture (N. Engl. J. Med. 2009;361:756-65).

These results were the basis of the Food and Drug Administration's approval of denosumab in June 2010.

In the extension study, 2,343 patients from the original treatment group and 2,207 patients in the control group received the denosumab treatment for 2 years (as well as calcium and vitamin D), yielding follow-up data for up to 5 years of drug exposure, said Dr. Cesar Libanati at the meeting.

Women in the long-term group who received denosumab for 5 years showed significant BMD improvements from baseline, of 13.7% in the lumbar spine and 7.0% in the total hip. Women in crossover group showed significant BMD improvements from the start of the extension study, of 7.9% in the lumbar spine and 4.1% in the total hip.

Patients in the crossover group showed significant increase in BMD from the extension study baseline similar to those seen in the long-term patients during their first 2 years of denosumab use, noted Dr. Libanati, clinical research medical director at Amgen Pharmaceuticals, maker of denosumab (Prolia), in Newbury Park, Calif.

During years 4 and 5, the annualized yearly incidence of new vertebral fractures in the long-term patients was steady at 1.4%, compared with 1.1% at the end of the 3-year FREEDOM study. The yearly incidence in the crossover treatment group was 0.9% for their first 2 years of denosumab exposure, compared with 2.5% in the first 2 years of the FREEDOM study.

The yearly incidence of nonvertebral fractures in the long-term patients was 1.4% after 4 years and 1.1% after 5 years.

Denosumab remained well tolerated during the extension study. The adverse event profile was "similar in years 4 and 5 to that observed in the 3 years of the placebo-controlled FREEDOM study," Dr. Libanati said. Long-term patients also maintained the reductions in bone turnover seen during the original FREEDOM study, he added. ■