CV Calcification in Young Bisphosphonate Users

BY BRUCE JANCIN

ORLANDO — Bisphosphonate therapy was associated with a reduced prevalence of cardiovascular calcification in older women but a paradoxical increased prevalence in women under age 65 years, compared with bisphosphonate nonusers in the Multi-Ethnic Study of Atherosclerosis.

Since MESA is an observational study, this novel finding has to be considered hypothesis generating rather than definitive. It remains unclear whether the unexpectedly higher prevalence of cardiovascular (CV) calcification in younger bisphosphonate users in MESA is the result of their likely shorter duration of treatment, differential drug effects, age-related differences in the pathogenesis of calcification, indication bias related to osteoporosis, or even chance, Dr. Sammy Elmariah said at the annual scientific sessions of the American Heart Association.

Given the profound tolls that cardiovascular disease and osteoporosis take in women, replication of these new MESA findings should be sought in other large data sets, added Dr. Elmariah of Mount Sinai School of Medicine, New York.

MESA is an ongoing National Heart, Lung, and Blood Institute–funded longitudinal study of an ethnically diverse group of 6,814 men and women aged 45-84 years in six U.S. communities. All of the participants were free of CV symptoms at baseline.

Dr. Elmariah and his coworkers analyzed baseline data on bisphosphonate use and CV calcification in 3,636 participating women, 2,181 of whom were under age 65. MESA included 214 women on baseline bisphosphonate therapy. CV calcification was assessed via multidetector row helical CT or electron-beam CT.

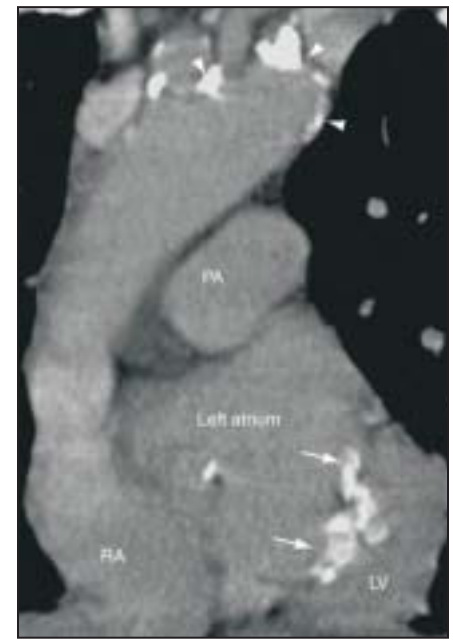
Among women aged 65 or older, bisphosphonate use was associated with a significantly lower prevalence of CV calcification at nearly all anatomic sites assessed. For example, aortic valve calcification was 33% less common in the older bisphosphonate users than in nonusers in multivariate analyses adjusted for age, body mass index, ethnicity, socioeconomic variables, CV risk factors, statins, and hormone replacement therapy. Aortic valve ring calcification was 35% less common. Calcification of the mitral annulus was 46% less common in older users, and thoracic aorta calcification was 32% less prevalent.

The only anatomic site where calcification wasn't significantly less common in older bisphosphonate users than nonusers was in the coronary arteries, where the adjusted 10% reduction in favor of the bisphosphonate users fell short of statistical significance, Dr. Elmariah continued.

The story was very different in women under 65 years of age. Younger bisphosphonate users were an adjusted fourfold more likely to have aortic valve calcification than were bisphosphonate nonusers, 1.9-fold more likely to have aortic valve ring calcification, and 2.4-fold more likely to have calcification of the mitral annulus. They also had 2.2-fold and 1.2-fold increased rates of calcification of the thoracic aorta and coronary arteries, respectively. All of these differences achieved statistical significance.

When the women were grouped in 10-year age subsets, a gradual reduction in the adjusted prevalence of CV calcification accompanied increasing age among bisphosphonate users.

The increased prevalence of CV calcification in younger bisphosphonate users came as a surprise in light of the known pharmacologic actions of the nitrogen-containing bisphosphonates, said Dr. Elmariah. He noted that the bisphosphonates have several statin-like effects stemming from their inhibition of farnesyl pyrophosphate synthase, an enzyme downstream from HMG-CoA reductase in the mevalonate pathway.



In an observational study, women under age 65 had more calcification (arrows).

Disclosures: Dr. Elmariah's work was funded by the New York Academy of Medicine, the GlaxoSmithKline Research & Education Foundation for Cardiovascular Disease and the NHLBI. ■

Disappointing Fracture Data End Phase III Arzoxifene Trial

BY BRUCE JANCIN

SAN ANTONIO — Arzoxifene, a once-promising selective estrogen-receptor modulator, experienced a fatal meltdown in a phase III trial of over 9,000 women.

The drug was being developed for prevention of both fractures and breast cancer in postmenopausal women with osteoporosis or osteopenia. But some findings in the 9,354-patient randomized, double-blind, placebo-controlled, multinational GENERATIONS trial have ended that, Dr. Trevor Powles said at the San Antonio Breast Cancer Symposium.

'We need a SERM that would reduce vertebral and nonvertebral fractures.'

DR. POWLES

The breast cancer prevention portion of GENERATIONS went well: After 48 months of follow-up, arzoxifene cut the incidence of invasive breast cancer by 56%, compared with placebo, and reduced estrogen-receptor–positive invasive breast cancer by 70%.

It also reduced the incidence of vertebral fractures by 41% after 36 months of follow-up in the subjects, who were aged 60-85 at enrollment. But it did not significantly reduce nonvertebral fractures.

"We need a SERM [selective estrogen-receptor modulator] that would reduce vertebral and nonvertebral fractures," said Dr. Powles, a medical oncologist who is professor emeritus at the Institute of Cancer Research, London. Arzoxifene also linked to increased rates of venous thromboembolism, endometrial polyps, leg cramps, hot flashes, and cholelithiasis, while offering no better protection against cardiovascular events than placebo.

"The overall benefit/risk profile of arzoxifene does not represent a meaningful advancement in the treatment of osteoporosis, so further development of this drug will not take place," he said.

The researchers are puzzling over how the earlier studies could have been so misleading. Arzoxifene is a benzothiophene SERM, like raloxifene, which is approved in postmenopausal women for the treatment and prevention of osteoporosis as well as for reducing invasive breast cancer risk in those at high risk for the cancer or who have osteoporosis. In early clinical studies, arzoxifene had greater effects on bone mineral density and bone turnover markers than raloxifene. It also resulted in increased bone density at nonvertebral sites and in the spine. ■

Disclosures: *Eli Lilly & Co. funded the trial. Dr. Powles said he has no relevant financial relationships.*

Overweight, Obese Women Are Underscreened for Osteoporosis

BY HEIDI SPLETE

WASHINGTON — Obese women are less likely to be screened for osteoporosis than are normal- or overweight women, according to findings from a study of more than 140,000 women included in an integrated health care plan database.

Previous studies have shown mixed results on the disparity in preventive health care for obese patients, compared with normal-weight patients, said Kristi Reynolds, Ph.D., of Kaiser Permanente in Pasadena, Calif., and her colleagues.

"It is largely unknown whether obesity is associated with the quality of care for osteoporosis, which is both preventable and treatable but is often undiagnosed and untreated," the researchers said. Physicians may be less inclined to screen obese women for osteoporosis because body weight is associated with higher bone density, they noted.

Data from 146,975 health care provider visits between July 1, 2007, and June 30, 2008, were reviewed.

The average age of the women was 73 years; 35% were normal weight; 35% were overweight; and 19%, 7%, and 4% fell into obesity categories I, II, and III, respectively. Normal-weight body mass index (BMI) was defined as 18.5-24.9 kg/m^2 and overweight as 25-29.9 kg/m^2; obese class I was defined as 30-34.9 kg/m^2, class II as 35-39.9 kg/m^2, and class III as 40 kg/m^2 or higher.

About 67% of the women had undergone bone mineral density testing within 4 years of the study, which was the criteria by which participants could be considered "screened." Only 52% of women with a BMI of 40 kg/m^2 or higher were screened, compared with 68% of each the normal BMI women and of the overweight women, 67% of women with a BMI of 30-34.9 kg/m^2, and 63% of women with a BMI of 35-39.9 kg/m^2.

After controlling for age, race, and income, the odds ratio of osteoporosis screening for overweight women was 0.99, while the odds ratios for women in obese classes I, II, and III groups were 0.90, 0.77, and 0.60, respectively. The findings were presented in a poster at the the annual meeting of the Obesity Society.

The results suggest that many overweight and obese women aren't screened for osteoporosis. However, more research is needed to examine the health outcomes of screened versus unscreened women, and the factors that influence providers to screen women according to BMI, the researchers said.

The researchers are employees of Kaiser Permanente. They reported having no financial conflicts of interest. ■