

# Aromatase Inhibitors All Promote Bone Resorption

*Exemestane, letrozole, and anastrozole increased biomarkers of bone turnover about equally.*

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PHILADELPHIA — Steroidal and nonsteroidal aromatase inhibitors appear to have very similar effects on bone metabolism, which result in increased bone turnover, according to data presented at the annual meeting of the American Society for Bone and Mineral Research.

"Anastrozole, letrozole, and exemestane in this study seem to have similar effects on bone biochemical measurements, and thus bone turnover. ... The increase in bone turnover doesn't appear to be significantly different with the steroidal versus nonsteroidal aromatase inhibitors," said Dr. Eugene McCloskey, a senior clinical lecturer in metabolic bone disease at the University of Sheffield in England.

Aromatase inhibitors have been associated with increased bone turnover, particularly in the setting of adjuvant thera-

py for breast cancer. Some preclinical studies have suggested that there may be differences between the effect of the steroidal (exemestane) and nonsteroidal (letrozole and anastrozole) aromatase inhibitors on bone turnover.

With the Letrozole, Exemestane, and Anastrozole Pharmacodynamics (LEAP) trial, Dr. McCloskey and his colleagues compared the effects of these three aromatase inhibitors on safety parameters such as serum markers of bone formation and resorption, lipid profiles, and adrenal function in healthy postmenopausal women with normal bone mineral density at the spine and hip.

Letrozole (Femara) is made by Novartis Pharmaceutical Corp., exemestane (Aromasin) by Pfizer Inc., and anastrozole (Arimidex) by AstraZeneca. The study was sponsored by AstraZeneca, and Dr. McCloskey disclosed that he has received research grants from the company.

In the study, healthy postmenopausal women were randomized to receive letro-

zole (2.5 mg/day), exemestane (25 mg/day), or anastrozole (1 mg/day) once daily for 24 weeks. The women were followed for another 12 weeks after the end of therapy. Overall, 102 women were randomized and 96 are included in this analysis (32 on letrozole, 34 on exemestane, and 30 on anastrozole).

The researchers measured changes from baseline bone alkaline phosphatase (a formation marker), serum C-telopeptide crosslinks (a marker of resorption), parathyroid hormone, and propeptide of type I procollagen (a marker of formation).

For bone alkaline phosphatase (ALP) all three drugs showed a trend toward increased levels but only exemestane reached statistical significance. However, there was no statistical difference between the three groups.

There was a nonstatistical increase for all three groups in terms of propeptide of type I procollagen (P1NP) but no statistical difference between the groups.

Serum C-telopeptide crosslinks (CTX) levels were also increased in all three groups but there was no significant difference between the groups.

To look at these formation and resorption marker in-

creases in more detail, the researchers calculated the uncoupling index, which is a measure of the difference between formation and resorption. To do this, they calculated z scores for the resorption marker (CTX) and formation markers (ALP and P1NP). Z scores for formation markers were subtracted from z scores for CTX. The results indicated that resorption generally exceeds formation for all three drugs.

In terms of change in parathyroid hormone (PTH) levels, there was a greater decrease with exemestane than with anastrozole. The difference was statistically significant. It's unclear whether there are any significant differences between these drugs in terms of fracture rates, Dr. McCloskey noted.

**The investigators calculated the uncoupling index, which showed that in general, bone resorption exceeded bone formation for all three agents.**

## Effects of AIs on Bone Metabolism

Marker	Estimated % change		
	Anastrozole	Letrozole	Exemestane
Bone ALP	2.0	2.9	6.6
P1NP	13.6	11.3	23.4
CTX	16.4	27.8	23.0
PTH	-7.7	-10.7	-20.5

Note: AI = aromatase inhibitor, ALP = alkaline phosphatase, P1NP = propeptide of type I procollagen, CTX = C-telopeptide crosslinks, PTH = parathyroid hormone.

Source: Dr. McCloskey

## Zoledronic Acid Headed Off Fractures After Liver Transplants

PHILADELPHIA — Prophylactic zoledronic acid appears to reduce morbidity associated with bone mineral loss and fractures in patients who have undergone a liver transplant, Dr. Martin Bodingbauer said at the annual meeting of the American Society for Bone and Mineral Research.

Vertebral fractures after liver transplant are linked to substantial morbidity and increased mortality. Fracture rates in the first 12 months after the procedure have been reported to range from 25% to 35%.

"Bone mineral density measurements do not accurately predict the fracture risk of the transplant patients," said Dr. Bodingbauer of the surgery department at the Medical University of Vienna. The etiology of hepatic osteodystrophy is unclear.

In this preliminary study, 96 patients were randomized at the time of transplant to receive treatment with zoledronic acid (eight 4-mg IV infusions in 12 months) along with calcium (1,000 mg/day) and vitamin D (800 IU/day) supplements, or supplements alone.

Of the 96 patients, 47 were randomized to the treatment group and 49 to the control group. Results at 24 months' follow-up were available for 35 patients in the treatment group and 34 control subjects.

At 24 months, 26% of the treatment group and 46% of the control group either had a fracture or had died—the combined primary end point. The difference between the groups was statistically significant.

Analysis of bone biochemical markers indi-

cated a statistically significant lower rate of bone turnover in the treated patients than in the control group.

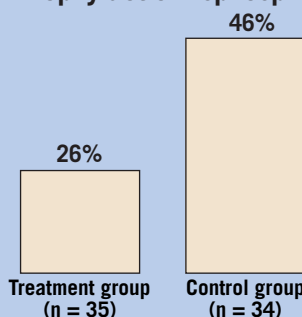
In addition, bone mineral density measurements were greater in the treatment patients than in the control subjects.

Eight deaths occurred in the treatment group and 12 among the control subjects—all due to either septicemia or posttransplantation proliferative disorder.

Infection and nausea occurred at similar rates in each group, and both side effects resolved quickly. There were seven discontinuations in each group, mostly due to liver or kidney dysfunction.

Dr. Bodingbauer disclosed that he had no conflicts of interest.

### Fractures and Mortality Reduced With Prophylactic Bisphosphonate



Note: Based on a study of liver transplant patients after 2 years of treatment.  
Source: Dr. Bodingbauer

## Antiresorptives Reduced Recurrent Hip Fracture

PHILADELPHIA — Antiresorptive therapy reduces the risk of recurrent hip fracture by more than 25%, according to one analysis presented at the annual meeting of the American Society for Bone and Mineral Research.

Patients exposed to bisphosphonate therapy following a first hip fracture had a 26% reduction in recurrent hip fracture (hazard ratio [HR] 0.74), after adjusting for age, sex, comorbidity, and medication, said Dr. Suzanne N. Morin, an internist at the McGill University Health Centre in Montreal.

Dr. Morin and her colleagues performed a retrospective cohort study, using administrative databases to identify patients aged 65 years and older who had been hospitalized for a first hip fracture between 1996 and 2003.

A total of 20,644 patients were identified and classified based on whether they had been exposed to antiresorptive therapy following hospital discharge for hip fracture. Exposure was defined as being dispensed a prescription for bisphosphonates, raloxifene, calcitonin, or hormone replacement therapy.

Of those patients, 6,779 were exposed to antiresorptive therapy (mean time to first exposure after

hospital discharge was 3 months) and 13,865 were not. Most of the patients—90% of those exposed and 73% of those not exposed—were women.

"In general, the exposed patients tended to be younger and to have less comorbidities than the nonexposed," Dr. Morin said. The antiresorptive-exposed patients were also more likely to take calcium and vitamin D supplements and to use corticosteroids. Bisphosphonates were prescribed the most frequently.

For exposed patients, follow-up began on the day that the prescription for an antiresorptive was filled. Unexposed patients were assigned starting dates that were frequency matched to those of the exposed patients. Mean follow-up was 2.2 years, during which time 9,146 patients died and 992 recurrent fractures occurred. The refracture rate was 2.2 per 100 person-years for the exposed group and 2.9 per 100 person-years for the nonexposed group.

Men were also less likely to have a recurrent hip fracture (HR 0.75). For each 1-year increase in age, the risk increased 3%. The presence of osteoporosis was associated with a twofold increase in the risk of recurrent hip fracture.