News in Brief

ALENDRONATE MAY INCREASE RISK OF ATRIAL FIBRILLATION IN WOMEN

Women who take alendronate (a bisphosphonate) for osteoporosis may have an almost double risk of atrial fibrillation (AF), even after the drug is stopped.

Researchers from the University of Washington found, in a population-based case-control study, that women who had used alendronate at any time were 1.86 times more likely to develop AF than those who had never used a bisphosphonate.

The risk was greater for past use than current use (OR 3.27 versus 1.42, P=0.08). This suggests that the effect was not an acute adverse event.

The findings have clinically important implications because AF increases the risk of stroke. However, the benefit of bisphosphonate could likely outweigh the risk of AF in women with osteoporosis. This was because the association of bisphosphonate use and AF risk has not been consistently reported. In addition, the biological plausibility of the finding is uncertain. Still, the authors suggest that doctors should be more cautious prescribing alendronate for women with a slightly increased elevated fracture risk and who are also at risk for AF because of diabetes mellitus, coronary artery disease, or cardiac failure.

The risk of AF had previously been unexpectedly shown in the HORIZON trial of once-yearly zoledronic acid for post-menopausal osteoporosis. An elevated risk (but not statistically significant) was found for alendronate in the Fracture Intervention Trial.

The researchers thus looked into the risk in an ongoing case-control study conducted at Group Health (a healthcare delivery system Washington state). There were 719 women with confirmed AF, and 966 controls with no AF (matched for age and treated hypertension).

In the Group Health formulary, alendronate was the preferred drug, although other bisphosphonates were available. 6.5% of AF cases and 4.1% of controls had used alendronate (P=0.03). For past use, the percentages were 2.8% and 1%, respectively (P=0.01).

Women who had used alendronate at any time had a 1.86 times increased risk of AF, compared to never-users. This was after adjustment for osteoporosis, cardio-vascular disease, and other variables (95% CI 1.09 to 3.15). The odds were 1.83, after adjustment for race, physician visits, body mass index, diabetes, valvular heart disease, HDL cholesterol, and oestrogen use (95% CI 1.04 to 3.24).

The risk was not increased with cumulative dose or time since first use, but these patients were more likely to have sustained AF than transitory/intermittent AF (OR 5.75 versus 1.93 and 1.25, P=0.005).

The authors suggest that the mechanism by which alendronate may increase AF risk is through electrolyte imbalance (hypocalcaemia), or inflammation (but this view is controversial).

The study has some weaknesses. It was an observational without random assignment to

Page 25 ▶

◀ Page 24 – News in Brief

alendronate, and there could have been unmeasured confounding factors. Osteoporosis and AF have common risk factors, such as female sex and hyperthyroidism. The number of AF cases was relatively small. There were too few women who used other bisphosphonates to assess what the effects of the other agents are. Elevated risk has been observed with zoledronic acid and alendronate (of the bisphosphonates, these have the strongest binding affinity for bone), while a meta-analysis showed no increased risk for risedronate (which has low bone-binding affinity).

An editorial in the same issue notes that the US FDA is monitoring post-marketing reports of AF among patients on bisphosphonates.

(Source: Heckbert SR, et al. Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med 2008; 168: 826-831.)

USE OF GLITAZONES MAY INCREASE FRACTURE RISK

A case-control study has found that the use of the glitazone class of drugs for diabetes is significantly associated with low-trauma fractures.

Researchers from University Hospital Basel found that diabetics treated for at least a year with glitazones had an adjusted odds ratio of 2.43 (95% CI 1.49 to 3.95) for a low-trauma fracture, compared with those who took other diabetes drugs or who took no drugs.

The researchers looked at a database of five million British patients of generalists. They identified 1,020 diabetic patients with a first-time diagnosis of low-trauma fracture (vertebrae, hip, wrist, forearm, proximal humerus, or ribs). There were 3,728 patients with diabetes but without fractures, matched to the fracture cases for age, gender, and clinic. Patients who were excluded from the study included those with type 1 diabetes, those who had been diagnosed with diabetes for less than three years, those with alcoholism, and those with a cancer history. Adjustments were made for age, gender, smoking, body mass index, epilepsy, chronic renal failure, and other conditions.

The researchers looked at those receiving troglitazone, pioglitazone and rosiglitazone (only the last is available now), and at other classes of anti-diabetic agents (sulfonylureas, metformin, and insulin).

For patients who had at least eight current glitazone prescriptions (estimated to be equivalent to one year of therapy) as of when the fracture occurred, there was significant association with fractures. The increased fracture risks varied with the type of glitazone drug and with dose, but there was considerable overlap in the confidence intervals.

For eight to 14 current glitazone prescriptions, there was an adjusted odds ratio of 1.85 (95% CI 0.86 to 3.98) for low-trauma fracture compared with patients not taking glitazones. For 15 or more prescriptions, the adjusted odds ratio for fractures was 2.86 (95% CI 1.57 to 5.22). When the two groups were combined (to gain statistical power), the overall odds ratio for fractures was 2.43 for all patients with at least eight glitazone prescriptions.

Fractures of the hip, femur, wrist, and forearm were significantly more common in patients receiving at least eight prescriptions of glitazones. The risk of humerus fracture was not significantly increased. There were too few vertebral or rib fractures for meaningful analysis. The researchers concluded that current use of rosiglitazone and pioglitazone in women and men with type 2 diabetes mellitus may be associated with an approximately two to three fold increased risk of hip and non-vertebral osteoporotic fractures. The researchers noted that the increased fracture risk could be a class effect.

The main weakness in the study was that the researchers did not have bone mineral density data. There was also no data on socioeconomic status, diet and exercise (which affect fracture risk). The authors also noted that the database may have missed or mis-classified fractures.

In an accompanying commentary, the study results were described as strong, consistent, and plausible. The commentary also noted that there was evidence of cardio-vascular disease and liver damage with glitazone drugs, which were also expensive. The commentary authors stated that in the absence of long-term trials demonstrating the benefit of glitazones in reducing clinical outcomes, the older oral hypoglycemic agents (2nd generation sulfonylureas and metformin) should be preferentially used for patients with type 2 diabetes.

(Source: Meier C, et al. Use of thiazolidinediones and fracture risk. Arch Intern Med 2008; 168: 820-25.)

LOW-NORMAL THYROID FUNCTION IN WOMEN AND CARDIAC DEATH

Women with thyroid function at the low end of normal (as indicated by slightly elevated thyrotropin) appear to be at significantly increased risk for death from coronary artery

Page 26 ▶

◀ Page 25 – News in Brief

disease (CAD), according to researchers from the Norwegian University of Science and Technology. No significant relationship between thyrotropin levels and CAD mortality was seen in men. However, researchers said that it would be premature to recommend thyroid hormone supplements for women with slightly elevated thyrotropin.

Women with thyrotropin levels of 2.5 to 3.5 mIU/L had a hazard ratio of 1.69 (95% CI 1.14 to 2.52) for death from CAD, compared to those with thyrotropin levels of 0.5 to 1.4 mIU/L (normal range 0.5 to 3.5 mIU/L; with increasing thyrotropin levels reflecting decreased thyroid function, and vice versa). Women with intermediate thyrotropin levels (1.5 to 2.4 mIU/L) had a hazard ratio of 1.41 (95% CI 1.02 to 1.96).

The date was collected from the Nord-Trondelag Health Study or HUNT (Norwegian acronym). Over 92,000 Norwegian adults were enrolled in the study from 1995 to 1997, and followed up to 2004.

There were 25,313 participants who had no clinical evidence of thyroid disease, no major cardio-vascular disease, no baseline diabetes, and for whom baseline thyrotropin values were known. Nearly two-thirds of these were women. 228 women and 182 men died of CAD (median follow-up 8.3 years).

After adjusting for age and smoking, for every increase of 1 mIU/L in thyrotropin levels in women, there was an observed hazard ratio of CAD death of 1.37 (95% CI 1.12 to 1.68). The risk remained significant even after adjusting for serum lipid, body mass index, blood pressure, and use of anti-hypertensives (HR 1.30, 95% CI 1.06 to 1.60).

The researchers said that the confidence intervals were relatively wide, and the findings were only preliminary, and should be confirmed or replicated by other studies. They could explain the different findings in women and men, and felt that the finding could be due only to chance. Thus the researchers said that it was premature to consider whether or not the normal range of thyrotropin should be re-evaluated, and whether thyroid hormone supplements should be recommended for women with slightly elevated thyrotropin. ■

(Source: Asvold B, et al. Thyrotropin levels and risk of fatal coronary heart disease: The HUNT study. Arch Int Med 2008; 168: 855-60.)