

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Clarithromycin Safety in Heart Disease

A large-scale clinical trial found an unexpected increase in heart problems and deaths among patients with coronary heart disease who had received a 2-week course of clarithromycin (*Biaxin*). The increase in risk was not apparent until patients had been followed for ≥ 1 year. Although there is no clear explanation for the increase, the FDA is urging caution and suggests considering an alternate agent when prescribing antibiotics for patients with heart disease. Warnings about the increased risk have been added to the labeling for clarithromycin, and the FDA continues to monitor safety reports for the drug.

Clarithromycin (Biaxin): Drug Safety Communication—Potential increased risk of heart problems or death in patients with heart disease. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm597862.htm.

Contraceptives and Breast Cancer Risk

Use of modern formulations of hormonal contraceptives was associated with a 20% increase in risk of breast cancer in a nationwide cohort of Danish women.¹ The absolute excess in risk is small and counterbalanced by the effect of hormonal contraceptives in reducing risk of other types of cancer.²

Methods: This analysis, part of the ongoing Danish Sex Hormone Register study, included all women who were aged 15–49 years on January 1, 1995, as well as those who turned age 15 years before the end of 2012. Women with a cancer diagnosis were excluded. Information on the use of

hormonal contraception, breast cancer onset, and confounding factors was obtained from linked registries.

Results: The cohort consisted of about 1.8 million women, with a mean follow-up of nearly 11 years. During follow-up, there were 9101 incident cases of invasive breast cancer. Women who were current or recent users of hormonal contraceptives (within the past 6 months) had a 20% increase in breast cancer risk (relative risk,* 1.20). Risk was increased to a similar degree in women who used combined or progestin-only contraceptives and, within each of these categories, in users of oral and non-oral formulations. There were no robust associations of increased risk with any individual formulation, relative to the overall effect of all contraceptives. Risk was associated with duration of use and was statistically significant for 5–10 years of use (relative risk, 1.33) and for >10 years of use (relative risk, 1.52). The absolute difference in cancer incidence between women who had never used hormonal contraceptives and current or recent users was small at 13 cases per 100,000 person-years. Approximately 1 extra breast cancer case was diagnosed for every 7700 women using hormonal contraception for 1 year.

Discussion: The 20% excess breast cancer risk demonstrated in this study is similar to rates reported in studies from the 1980s, with older, high-dose formulations. The present observations should be viewed in the context of the low incidence of breast cancer in young women. Most of the cases that occurred in this cohort were in

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women who used hormonal contraception in their 40s, and the excess risk in women younger than 35 years was only 2 per 100,000.

¹Morch L, et al: Contemporary hormonal contraception and the risk of breast cancer. *NEJM* 2017;377 (December 7):2228–2239. From the University of Copenhagen, Denmark; and the University of Aberdeen, U.K.

Funded by the Novo Nordisk Foundation. Two of 6 study authors disclosed financial relationships with commercial sources including Novo Nordisk; the remaining authors declared no competing interests.

²Hunter D: Oral contraceptives and the small increased risk of breast cancer (editorial). *NEJM* 2017;377 (December 7):2276–2277. From the University of Oxford, U.K. **The author declared no competing interests.**

*See Reference Guide.

Teriparatide vs Risedronate for Osteoporosis

In a randomized trial, postmenopausal women with severe osteoporosis who received the bone-forming agent teriparatide experienced fewer osteoporotic fractures over 2 years than those who received the antiresorptive agent risedronate.

Background: Approved treatments for postmenopausal osteoporosis include antiresorptive and bone-forming drugs. Although several studies have compared the effects of the 2 drug classes on surrogate markers of bone quality and strength, there have been no previous, adequately powered head-to-head studies that compared the effects of antiresorptives and bone-forming drugs using fractures as the primary outcome.

Methods: Study participants were postmenopausal women, aged >45 years, with a bone mineral density T score of -1.50 standard deviations or less at the femoral neck, total hip, or lumbar spine, and radiographic evidence of at least 1 severe or 2 moderate vertebral fragility fractures. For study entry, patients were required to have baseline serum calcium, parathyroid hormone, and free thyroxine concentrations in the normal range, as well as 25-hydroxy-vitamin D concentrations >23 nmol/L. Previous treatment with most osteoporosis medications was permitted if these agents were discontinued at study entry. Study subjects were randomly assigned to receive either 20 µg/day injectable subcutaneous teriparatide plus an oral weekly placebo, or 35 mg/week oral risedronate with an injectable daily placebo. Study participants also received calcium and vitamin D supplements. The primary efficacy outcome was the percentage of patients with ≥1 new vertebral fracture assessed with spinal radiographs at 12 and 24 months. Clinical vertebral fractures were

defined as an episode of suggestive signs or symptoms, such as acute onset of back pain, confirmed by radiography.

Results: Of 1360 women enrolled who received randomized treatment, 75% completed the trial. Patients had a mean age of 72 years and a mean of nearly 3 fractures before study entry; 36% had a clinical vertebral fracture in the year before enrollment, and 72% had received a previous osteoporosis medication.

The 24-month incidence of new vertebral fractures in the teriparatide group was less than half that in the risedronate group (5% vs 12%; $p < 0.0001$; effect size,* 0.44). Teriparatide was also associated with reduced incidence of pooled new and worsened vertebral fractures (effect size, 0.46) and of clinical vertebral and non-vertebral fragility fractures (effect size, 0.48). The number needed to treat* (NNT) with teriparatide to prevent 1 fracture was 15, and the NNT to prevent 1 clinical fracture was 20. Teriparatide was associated with numerically fewer non-vertebral fragility fractures than risedronate, but the difference was not statistically significant.

Patients in both groups reported comparable improvement from baseline in back pain and health-related quality of life. Overall adverse-event rates were similar in the 2 treatment groups. Rates of dizziness and limb pain, known adverse effects of teriparatide, were higher in the teriparatide group. There were no instances of osteonecrosis of the jaw or atypical femur fractures.

Discussion: These results support those of previous research using surrogate markers for bone health and suggest that teriparatide should be considered over risedronate for optimal management of patients with severe osteoporosis.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Kendler D, et al: Effects of teriparatide and risedronate on new fractures in postmenopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* 2018;391 (January 20):230–240. From the University of British Columbia, Canada; and other institutions. **Funded by Lilly. Eleven of 16 study authors disclosed financial relationships with commercial sources, including Lilly, manufacturer of Forteo; the remaining authors declared no competing interests.**

Common Drug Trade Names: risedronate—*Actonel*; teriparatide—*Forteo*

*See Reference Guide.

Fatty Acids: Cardiovascular Effects

The American Heart Association recommendations suggest that use of omega-3 fatty acids for prevention of coronary heart disease (CHD) is probably justified for patients with prior CHD and those with heart failure and reduced ejection fractions. However, the results of a meta-analysis of clinical trials involving nearly 80,000 patients indicate that supplementation with omega-3 fatty acids has no effect on cardiovascular outcomes.

Methods: A comprehensive literature search identified randomized controlled trials of marine-derived omega-3 fatty acid supplements, with either a placebo or an open-label control. Included trials had a sample size of ≥ 500 and provided ≥ 1 year of treatment. Studies were excluded if the intervention was dietary advice to eat fish. The main study outcomes included nonfatal MI, cardiovascular death, revascularization, major vascular events, and all-cause mortality. Multiple prespecified subgroup analyses were carried out to identify any groups that might benefit from supplementation.

Results: The analysis included 8 placebo-controlled trials and 2 open-label trials. Sample sizes ranged from 563 to $>18,000$ (total, 77,917), and the mean treatment duration ranged from 1 to 6.2 years. Mean eicosapentaenoic acid dosages ranged from 226 to 1800 mg/day, and mean docosahexaenoic acid dosages ranged from 0 to 1700 mg/day. Study subjects had a mean age of 64 years, and about 61% were men. About two-thirds of subjects had a history of CHD.

About 12,000 major vascular events occurred during the studies. Omega-3 supplementation was not associated with the rate of these events (relative risk,* 0.96), all-cause mortality (relative risk 0.96), or any other study outcome. Omega-3 fatty acids had no significant association with major vascular events in subgroup analyses stratified by gender, history of CHD, history of diabetes, use of statin therapy, or baseline levels of total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides.

Discussion: Previous large clinical trials have generally failed to show a protective association of omega-3 fatty acids with cardiovascular outcomes, but it was not clear whether the effect was consistent across outcomes, in different patient groups, or for primary and secondary

prevention. Reasons for the discrepant results of prior trials may include different patient selection criteria, effects of other preventive interventions, and failure to account for the effect of increasing use of statins to control lipids. While the present results do not support a protective effect of fatty acids, 2 large trials of much higher, triglyceride-reducing doses of omega-3 fatty acids are underway and could provide additional evidence.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Aung T, et al: Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals. *JAMA Cardiology* 2018; doi 10.1001/jamacardio.2017.5205. From the University of Oxford, U.K.; and other institutions. **Funded by the British Heart Foundation; and the Medical Research Council. Six of 16 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

*See Reference Guide.

Fraudulent Flu Products

This year's severe flu season has impacted millions of patients across the country, resulting in a large number of flu-related hospitalizations. The FDA has issued a reminder/warning that there are no legally marketed over-the-counter (OTC) drugs to prevent or cure the flu and that any OTC products that claim to do so are fraudulent. According to the agency, the following are claims that may indicate an OTC product is fraudulent and should be avoided:

- Reduces severity and length of the flu
- Boosts immunity naturally without a flu shot
- Safe and effective alternative to the flu vaccine
- Prevents catching the flu
- Effective treatment for the flu
- Faster recovery from the flu
- Supports your body's natural immune defenses to fight off the flu.

FDA News Release: FDA warns of fraudulent and unapproved flu products. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm599223.htm.

Safety of Serotonergic Coprescription

Incidence of serotonin syndrome was low in patients who received concomitantly prescribed triptan antimigraine drugs and serotonergic antidepressants, according to an analysis of 14 years of electronic medical records from a large registry.

Background: In 2006, the FDA issued a warning regarding the risk of serotonin syndrome with concomitant use of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs). However, the warning was based on a small number of cases, and population-based studies were not conducted to confirm the association. In addition, based on their receptor affinity, the biological plausibility of triptans as a cause of serotonin syndrome is questionable.

Methods: The present analysis was based on the Partners Research Patient Data Registry, which includes information on >6.5 million patients receiving care in the Boston area. Patients were identified who received prescriptions for a triptan and an SSRI or SNRI in 2001–2014. Within this population, investigators searched for all cases of potential serotonin syndrome and examined the records of these patients.

Results: The number of patients who received prescriptions for triptans increased steadily during the study period. In spite of the warning, the proportion of patients who concomitantly received an SSRI or SNRI remained stable between 21% and 29%.

More than 19,000 patients received prescriptions for both a triptan and an SSRI or SNRI during the study period, of whom 229 (0.01%) experienced

extrapyramidal symptoms. Serotonin syndrome was clinically suspected in 17 of these patients. Of these, 7 cases met criteria for serotonin syndrome based on ≥ 1 set of standardized criteria. Detailed records review indicated that triptans had been used in close temporal association with serotonin syndrome-like symptoms in only 2 cases, but in both cases symptoms had onset before triptans were started. Using a strict, conservative case definition, the incidence of serotonin syndrome in this population was 0.6 per 10,000 person-years. Assuming, less conservatively, that serotonin syndrome occurred in all 17 suspected cases, the estimated incidence was 2.3 per 10,000 person-years. No cases of serotonin syndrome, either suspected or confirmed, were life-threatening.

Discussion: These observations suggest there is reason to be skeptical that triptans increase the risk of serotonin syndrome beyond that associated with SSRIs and SNRIs alone. They also provide evidence that patients with affective disorders and migraine do not necessarily need to forgo treatment of 1 disorder to manage the other.

Orlova Y, et al: Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. *JAMA Neurology* 2018; doi 10.1001/jamaneurol.2017.5144. From Brigham and Women's Hospital, Boston, MA; and other institutions. Funded by Harvard Catalyst; and other sources. The authors declared no competing interests.

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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