

Denosumab reduces fracture risk better than placebo

Clinical question Is denosumab safe and effective for the prevention of fractures in women with osteoporosis?

Bottom line Like bisphosphonates, denosumab modestly decreases the risk of clinical fracture in postmenopausal women with significant osteoporosis (T score = -2.5 to -4). Denosumab was not compared with bisphosphonates because it is unlikely that this new drug is more effective. We should therefore only prescribe it for women who cannot tolerate bisphosphonates, as the cost of denosumab is approximately \$1,000 per year, which is much higher than generic bisphosphonates. (Level of evidence = 1b)

Synopsis These authors included women between the ages of 60 years and 90 years with a bone mineral density T score between ≥ 2.5 and ≥ 4.0 at

the lumbar spine or hip. Women were excluded as being inappropriately high risk for a placebo-controlled study if they had one severe vertebral fracture (or at least two of any severity). The 7,808 included women were randomized to receive denosumab (an injected human monoclonal antibody that inhibits osteoclast-mediated bone resorption) or placebo. The drug is given at a dosage of 60 mg subcutaneously every 6 months. Women underwent radiography once a year to look for vertebral fractures, and were followed up for a total of 3 years. The mean age of women was 72 years, most were from Europe, and 24% had a prevalent radiologic vertebral fracture on enroll-

ment. Analysis was by intention to treat, but procedures for concealment of allocation to groups were not described. After 3 years, the patients receiving denosumab had a reduced risk of new clinical vertebral fracture (0.8% vs 2.6%; $P < .001$; number needed to treat [NNT] = 56 for 3 years) and a slightly reduced risk of hip fracture (0.7% vs 1.2%; $P = .04$; NNT = 200 for 3 years). Eczema and cellulitis were more common in patients receiving the active drug, but, oddly, falling and concussion were less common in those women.

Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361(8):756-765.

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Mediterranean diet delays need for diabetes treatment

Clinical question In overweight patients with newly diagnosed type 2 diabetes, does a Mediterranean-style diet delay the need for antihyperglycemic treatment?

Bottom line For patients with newly diagnosed diabetes, perhaps we need to pay attention to diet interventions before reaching for the prescription pad. A Mediterranean diet, consisting of grains, poultry, and fish, with a sizeable (>30%) proportion of fat, kept the hemoglobin A1C (Hb A1C) level below 7% in more than 50% of patients for 4 years after being diagnosed with type 2 diabetes, allowing them to avoid antihyperglycemic therapy. In comparison, a low-fat, higher-carbohydrate diet prevented drug therapy in only 30% of patients. Both diets restricted caloric intake, which is probably at least as important as the diet itself. Both groups received monthly counseling with a dietitian or nutritionist for 1 year and then every other month from then on, which is a much larger intervention than simply giving patients a diet hand-out and wishing them the best of luck. (Level of evidence = 1b)

Synopsis The value of treatment for hyperglycemia in patients with type 2 diabetes continues to drop as more studies demonstrate a lack of benefit. Still, so-called quality and performance measures, as well as patient expectations, will prompt most clinicians to begin treatment, and avoidance of drug therapy can be considered a patient-oriented outcome. The 215 participants were overweight, had newly diagnosed type 2 diabetes, were not treated with medicines, and had an Hb A1C of less than 11%. The patients were randomly assigned, using concealed allocation, to either a low-fat American Heart Association diet or a Mediterranean diet. This Mediterranean diet consisted of vegetables and whole grains, with poultry and fish instead of red meat, and no less than 30% fat, mostly from olive oil. Both groups

had diets restricted to 1,500 calories per day for women and 1,800 calories per day for men. To implement these diets, patients in both groups met with dietitians monthly in the first year and bi-monthly thereafter. Patients measured portion size and kept food diaries. After 4 years, 44% of patients in the Mediterranean diet group had at least two consecutive quarterly measured Hb A1C percentages of at least 7, which is the American Diabetes Association criterion for beginning drug therapy, compared with 70% of patients assigned to the low-fat diet (hazard ratio = 0.63; 95% CI, 0.51-0.86). Patients in this Mediterranean diet group also lost more weight. The study was performed in Italy, and the same adherence rates—and benefits—may not be seen in countries that are not in the heart of the Mediterranean.

Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes. *Ann Intern Med.* 2009;151(5):306-314.

Aspirin use after diagnosis of colon cancer reduces mortality

Clinical question Does aspirin use after the diagnosis and treatment of nonmetastatic colon cancer reduce mortality?

Bottom line Regular aspirin use after the diagnosis and treatment of nonmetastatic colon cancer reduces cancer-specific and all-cause mortality. The benefit is strongest in patients with primary tumors that overexpress cyclooxygenase 2 (COX-2). This study found no benefit in reduced mortality among patients regularly using aspirin before the diagnosis of colorectal cancer. (Level of evidence = 2b)

Synopsis Although regular aspirin use reduces the risk of developing colon cancer, it remains uncertain if aspirin use also reduces mortality in patients with established colon cancer. These investigators analyzed data from two large nationwide prospective cohort studies—the Nurses' Health Study and

the Health Professionals Follow-up Study—to study the effect of aspirin use on patients with nonmetastatic colorectal cancer (stages I, II, and III). Study participants received a questionnaire at baseline and every 2 years thereafter inquiring about regular aspirin use. Individuals masked to drug exposure data reviewed all medical records for cancer diagnosis and cause of death. Follow-up occurred for more than 92% of patients for a median time of 11.8 years. Regular use of aspirin after diagnosis significantly reduced the risk of colorectal cancer-specific mortality (hazard ratio [HR] = 0.71; 95% CI, 0.53-0.95) and all-cause mortality (HR = 0.79; 0.65-0.97). The benefit of aspirin remained significant for stage I, stage II, and stage III disease. However, aspirin use before cancer diagnosis was not significantly associated with reduced cancer-specific mortality or all-cause mortality. The benefit of aspirin use after cancer diagnosis was strongest in patients whose primary tumors overexpressed COX-2.

Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA.* 2009;302(6):649-659.

Corticosteroids hasten resolution of sore throat symptoms in adults

Clinical question Do systemic corticosteroids reduce symptoms in adults and children with sore throat?

Bottom line When added to treatment with antibiotics and analgesia, a single dose of a corticosteroid triples the likelihood that adults would be completely pain free within 24 hours, with one additional patient being pain free for every four patients treated. None of the studies show a benefit of corticosteroid treatment in children. (Level of evidence = 1a)

Synopsis More than 100 years ago, Jane Austen described a sentiment similarly held by many people today: "No one's sore throats, you know, are as bad as mine." These authors combined the results of eight randomized trials

enrolling a total of 369 children and 374 adults with sore throat (44% were positive for group A beta-hemolytic streptococcus). Several studies enrolled patients with severe symptoms. They identified the studies by searching six databases. Two authors independently performed the searches and then extracted the data. The quality of the research was high. When added to antibiotics and analgesia in four trials, an oral corticosteroid increased the likelihood of adults being pain free within 24 hours, with one additional patient being pain free for every four patients treated with a corticosteroid (number needed to treat [NNT] = 3.7; 95% CI, 2.8-5.9). Similarly, in three studies the treatment increased the likelihood of complete resolution within 48 hours in adults (NNT = 3.3; 2.4-5.6). The studies used single oral or IM doses of 60 mg prednisone or 10 mg dexamethasone equivalents. Treatment was not shown to be beneficial in children.

Hayward G, Thompson M, Heneghan C, et al. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. *BMJ*. 2009;339:b2976. doi:10.1136/bmj.b2976.

Antivirals have a small benefit in children

Clinical question Do antivirals hasten symptom resolution or prevent influenza in children?

Bottom line The antivirals oseltamivir (Tamiflu) and zanamivir (Relenza) decrease symptoms by 0.5 days to 1.5 days in children with confirmed influenza; the average benefit is less in children with clinically diagnosed influenza. Postexposure prophylaxis will prevent one additional child from contracting influenza for every 12 children treated. Neither of these medications has been evaluated for the treatment of the current H1N1 influenza. (Level of evidence = 1b)

Synopsis The British researchers conducting this study combined the results of seven randomized studies of 1,766 children (1,243 with confirmed influenza) evaluating the effectiveness of

either oseltamivir or zanamivir in shortening the duration of symptoms or preventing influenza in children with known exposure. To identify these studies they searched several databases, including the Cochrane Central Register, as well as reference lists of retrieved papers. They also received unpublished data from the manufacturers. Two authors independently selected the articles for inclusion and extracted the data. The quality of the research was only moderate. In four studies of treatment of children with confirmed influenza, symptom resolution occurred 0.5 to 1.5 days earlier with treatment. Only one study reported on treatment of children with clinical influenza, finding an average reduction of symptoms of 0.5 days (from 5.0 days to 4.5 days). Postexposure prophylaxis resulted in an 8% decrease in the incidence of symptomatic influenza (95% CI, 5%-12%). None of the studies have evaluated the effect of these antivirals on the current H1N1 influenza strain.

Shun-Shin M, Thompson M, Heneghan C, et al. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2009;339:b3172. doi:10.1136/bmj.b3172.

Highly sensitive troponin I is a more accurate test for AMI

Clinical question Are the new, highly sensitive cardiac troponin tests more accurate for early diagnosis of acute MI (AMI) than older assays?

Bottom line New, highly sensitive cardiac troponin tests are more sensitive and have a better negative predictive value than older assays for patients presenting within the first few hours of the onset of chest pain. (Level of evidence = 2b)

Synopsis Cardiac troponins I and T are unique to heart muscle and rise quickly in the presence of myocardial damage. In combination with clinical evaluation and ECG findings, they are a key part of the diagnosis of patients with chest pain. However, the sensitivity of troponins is relatively poor in the first 6

hours after the onset of chest pain. A new family of highly sensitive cardiac troponin I tests is able to detect lower levels, and should therefore improve the ability to confidently diagnosis AMI closer to the time of onset. This was a multicenter trial in several European countries: 786 consecutive patients presenting to the emergency department (ED) within 12 hours of the onset of chest pain suggestive of AMI were recruited, and 718 were included in the final study population. The patients underwent a number of cardiac enzyme tests—including highly sensitive troponin I, cardiac troponin T, CK-MB, and myoglobin—on admission and 1, 2, 3, and 6 hours later. The final diagnosis was determined using standard criteria following an independent review of all clinical data by two cardiologists. The mean age of patients was 64 years, 66% were male, and 35% had a history of coronary artery disease. At presentation to the ED, the area under the receiver operating characteristic curve, a measure of the ability of a test to discriminate diseased from nondiseased, was better for all four novel assays than for the standard troponin T test. This was especially true for patients presenting within 3 hours of symptom onset. The negative predictive value of these tests on admission to the ED was very good, in the 97% to 99% range depending on the cut-off chosen. Positive predictive values were 50% to 73% using the 99th percentile as the cutoff, with sensitivities of 84% to 95%. A second study in the same issue (*N Engl J Med*. 2009;361[9]:868-877) compared the sensitive troponin I to the standard troponin T and myoglobin tests and found that it was more sensitive with similar specificity.

Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med*. 2009;361(9):858-867.

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