

Lipid drugs have varying effects on overall mortality

Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality. A systematic review. *Arch Intern Med* 2005; 165:725–730.

■ Clinical Question

What methods of lipid lowering decrease overall mortality for patients with hyperlipidemia?

■ Bottom Line

Only statin lipid-lowering drugs have been shown to decrease overall mortality for patients with high cholesterol but without evidence of heart disease. However, most patients treated with one of these drugs do not benefit: 228 have to be treated for 3.3 years to prevent 1 additional death during this period.

For patients with known heart disease, statins and fish oil both have been shown to decrease mortality. Niacin, resins, and diet have not been shown to decrease mortality. Fibrates (gemfibrozil and others) actually increase overall mortality and at the same time decrease cardiac mortality. (Level of evidence [LOE]=1a)

Study Design

Meta-analysis
(randomized controlled trials)

Setting

Various (meta-analysis)

Synopsis

Do all lipid-lowering drugs make people live longer, on average? These researchers searched 4 databases to find randomized trials addressing this question. Two authors then independently determined whether each study was suitable for inclusion, only including studies that were randomized and were conducted over at least 3 months. They included studies that enrolled patients without evidence of heart disease—primary prevention as well as secondary prevention studies that enrolled patients with known heart disease. They included studies written in any language, and ended up with 97 studies enrolling more than 275,000 patients.

Only statins and n-3 fatty acids (fish oils or linolenic acid) decreased overall mortality, and the effect of the n-3 fatty acids was only seen with patients with pre-existing heart disease. In primary prevention trials, fibrates (fenofibrate, clofibrate, gemfibrozil) increased mortality, with 1 additional death in every 132 patients treated for an average 4.4 years (number needed to treat to harm=132; 95% confidence interval [CI], 69–662).

Many patients have to be treated with a statin to prevent 1 additional death; the number needed to treat for 3.3 years was 228 (95% CI, 123–2958). For patients with known heart disease, 50 patients (95% CI, 38–78) would have to be treated with a statin to prevent 1 additional death, and 44 patients (31–84) would need to be treated with fish oil to prevent 1 additional death, each over an average 4.4 years (excluding one low-quality study). Treatment with diet, resins (colestipol, cholestyramine), or niacin did not affect overall mortality.

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FAST TRACK

Only statins and n-3 fatty acids decreased overall mortality; many patients have to be treated with statins to prevent one death

Intermittent therapy effective for mild persistent asthma

Boushey HA, Sorkness CA, King TS, et al, for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005; 352:1519-1528.

■ Clinical Question

Does continuous therapy with anti-inflammatory drugs improve outcomes for patients with mild persistent asthma?

■ Bottom Line

Intermittent therapy, as measured by the outcomes that matter, is as effective as continuous therapy with oral zafirlukast or inhaled budesonide for patients with very mild but persistent asthma. Note that patients had a clear plan of action for when symptoms flared up: Begin inhaled budesonide in the "yellow zone," when symptoms initially worsen, and add prednisone 0.5 mg/kg if symptoms enter the "red zone," when breathlessness is present at rest or with activities of daily living. (LOE=1b)

Study Design

Randomized controlled trial (double-blinded)

Allocation

Uncertain

Setting

Outpatient (any)

Synopsis

One of the things for which primary care physicians are frequently criticized is a failure to treat asthma patients as intensively as is recommended by some guidelines. For example, adults with mild persistent asthma (defined as self-treatment with beta-agonist more than 2 days per week, nighttime awakenings related to asthma more than 2 days per month, or variability in the peak expira-

tory flow of 20% to 30%) should be taking chronic anti-inflammatory medications based on current National Heart, Lung, and Blood Institute guidelines. Or should they?

After an active run-in period, adults with this severity of asthma were randomized (allocation uncertain) to receive either 200 µg of inhaled budesonide (Pulmi-cort) twice daily, 20 mg of oral zafirlukast (Accolate) twice daily, or matching placebo. All groups could use rescue therapy with budesonide, as needed, according to a symptom guide, as well as inhaled albuterol (Salbutamol). They were followed-up for 1 year with a variety of symptoms scores and physiologic measures. Follow-up was good, with 199 of 225 patients completing the study.

After 1 year, patients in the placebo group (intermittent therapy only) performed slightly worse on a number of outcome measures, such as exhaled nitric oxide levels and the percentage of eosinophils in the sputum. There was no difference regarding the primary outcome of morning peak expiratory flow. If you understand the difference between patient- and disease-oriented outcomes, you should say to yourself, "Who cares?" More important, there was no clinically significant difference in the number of courses of budesonide or asthma control scores (0.1 to 0.2 on a 6-point scale), and no difference in quality-of-life scores.

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Make sure patients have a clear plan of action to deal with worsening symptoms

Intense diet, behavior, and physical activity intervention effective for obese children

Nemet D, Barkan S, Epstein Y, Friedland O, Kowen G, Eliakim A. Short- and long-term beneficial effects of a combined dietary-behavioral-physical activity intervention for the treatment of childhood obesity. *Pediatrics* 2005; 115:443–449.

■ Clinical Question

Can a specific program of diet and exercise cause a sustained weight loss in children?

■ Bottom Line

An intensive 3-month program of dietary counseling, a hypocaloric diet, and structured exercise can cause a weight loss in children that is sustained over 1 year. More important, the program seemed to increase the amount of exercise the children performed, and this increase was sustained after the intervention was discontinued. (LOE=2b)

Study Design

Randomized controlled trial (nonblinded)

Allocation

Uncertain

Setting

Outpatient (primary care)

Synopsis

The researchers conducting this study began with 54 obese children between the ages of 6 and 16 years. The children were randomly assigned either to a control group that received a single nutrition counseling session or to an active treatment group. Active treatment consisted of heavy-duty dietary and exercise modification for 3 months. It is not clear that allocation to treatment groups was concealed, and it is possible that children more likely to respond to treatment were preferentially enrolled.

The dietary intervention consisted of 6 meetings over a 3-month period with parents and the child. These counseling sessions focused on food choices, nutritional information, and behavior change. The children were placed on a diet of approximately 30% less than the reported intake or 15% less than the estimated daily required intake. The exercise program was conducted 2 hours per week by physicians who were former members of the Israeli national track and field team; it consisted of games focusing on endurance, with the children encouraged to add an extra 30 to 45 minutes of walking or other exercise per week. Analysis was per protocol and not by intention to treat, which is about the only way they could have done the analysis. After dropouts in the intervention period and in the subsequent 1-year follow-up, both groups dwindled to 20 patients each.

After 3 months of diet and exercise intervention, the children in the treatment group had lost an average 2.8 kg, whereas the children in the control group gained an average 1.1 kg. Body-mass index and body fat percentage also declined in the treated children. Over the 1 year of follow-up, children in the control group had gained an average 5.2 kg; the children in the treatment group gained an average 0.6 kg ($P<.05$). Body-mass index increased in the control group but decreased in the treated patients.

Other significant differences at 1 year included lower body fat, amount of exercise activity, and endurance time on a treadmill. Both groups reported a decrease in screen time (that is, time spent watching television or playing video games) from an average 4.5 to 4.8 hours per day to 3.3 to 3.4 hours per day 1 year later.

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The program seemed to increase the amount of exercise the children performed, even after the intervention was discontinued

Diagnosis unaffected by giving children narcotics for abdominal pain

Kokki H, Lintula H, Vanamo K, Heiskanen M, Eskelinen M. Oxycodone vs placebo in children with undifferentiated abdominal pain: a randomized, double-blind clinical trial of the effect of analgesia on diagnostic accuracy. *Arch Pediatr Adolesc Med* 2005; 159:320–325.

■ Clinical Question

Does giving a narcotic to children with abdominal pain obscure the surgical diagnosis?

■ Bottom Line

Giving analgesics to children with abdominal pain does not obscure the surgical diagnosis. We don't need to make kids suffer while waiting for a surgeon to evaluate their abdominal pain. (LOE=2b)

Study Design

Randomized controlled trial (double-blinded)

Allocation

Concealed

Setting

Emergency department

Synopsis

These researchers enrolled children aged 4 to 15 years who came to the emergency department with acute abdominal pain of less than 7 days' duration and had pain scores of 5 cm or higher on a 10-cm visual analog scale. The children were randomly assigned (concealed allocation) to receive oxycodone buccally (0.1 mg/kg) or placebo. The 63 children were asked to rate their pain every 30 minutes for up to 3.5 hours after treatment. One of 3 study surgeons evaluated each child, provided a provisional diagnosis (appendicitis, nonspecific abdominal pain, or other), a differential diagnosis, and initial management (observation or surgery), and assessed whether there was abdominal guarding. The same surgeon re-examined the patient 1 hour after the first dose of the study drug and provided the same assessments as at baseline.

Researchers contacted the children with non-specific abdominal pain 4 weeks later. The main outcomes were difference in pain intensity, the presence

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of abdominal guarding before and after medication, and the diagnostic accuracy between the oxycodone and placebo groups. The authors don't say whether these were assessed via intention to treat. The children receiving oxycodone began experiencing pain relief within the first 30 minutes. The diagnostic accuracy was not adversely affected by the administration of the drug. The study was powerful enough to detect modest differences in pain intensity.

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Aspirin prevents stroke, not MI, in women

Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005; 352:1293–1304.

■ Clinical Question

Does aspirin prevent cardiovascular disease in women?

■ Bottom Line

Aspirin reduces the risk of stroke and transient ischemic attack in women but does not reduce the risk of myocardial infarction (MI) or cardiovascular death. The reduction in strokes over 10 years (number needed to treat=444) must be balanced against an increase in serious gastrointestinal bleeds (number needed to treat to harm=553). No change was seen in this large, long study regarding all-cause mortality. (LOE=1b)

Study Design

Randomized controlled trial (double-blinded)

Allocation

Uncertain

Setting

Population-based

Synopsis

Most of the data on aspirin for the prevention of cardiovascular events comes from studies in men. The current study represents the largest and best evidence to date for women.

Women aged >45 years without a history of coronary artery disease, cerebrovascular disease, or cancer were initially enrolled in a 3-month placebo run-in period to establish compliance with the study protocol. Those who complied throughout the run-in period (n=39,876) were randomized (allocation not specified, but likely concealed) to receive either 100 mg aspirin daily or matching placebo. They were followed-up for a mean of 10 years, with 97% complete data on morbidity and 99% complete data on mortality: very impressive. The mean age was 55 years, and the 10-year risk of heart disease was <5% in 85% of the women. Groups were balanced at the start of the study; outcomes were blindly assessed; analysis was by intention to treat.

Women taking aspirin were less likely to have a stroke (1.1% vs 1.3%; P=.04; number needed to treat [NNT]=444 for 10 years) or transient ischemic attack (0.9% vs 1.2%; P=.01; NNT=384 for 10 years) than women taking placebo. However, there were no differences between groups in the likelihood of myocardial infarction (0.99% for aspirin and 0.97% for placebo) or death from cardiovascular causes (0.6% vs 0.63%), any major cardiovascular event (2.4% vs 2.6%), or any cause (3.1% vs 3.2%).

Gastrointestinal bleeds requiring transfusion were more common in the aspirin group (0.64% vs 0.46%; P=.02; number needed to treat to harm=553 for 10 years). The study was powered to have an 86% chance to detect a 25% reduction in the primary outcome of any major cardiovascular event. Review of the survival curve reveals a steady but small trend in favor of aspirin regarding the primary outcome. This apparent benefit, equivalent to a 5% to 10% relative reduction in all-cause mortality, was not statistically significant despite the study's large size. ■

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The reduction of strokes over 10 years must be balanced against an increase in serious GI bleeds