

Insulin analogues provide marginal, if any, benefit

Clinical question Are insulin analogues safer and/or more effective than older insulins?

Bottom line Insulin analogues have few, if any, benefits over regular insulin and NPH insulin, and in some cases perform worse. An accompanying cost-effectiveness analysis found that the cost per quality-adjusted life-year ranged from a low of \$22,500 for insulin aspart in patients with type 2 diabetes mellitus (T2DM) to \$643,000 for insulin glargine. (Level of evidence = 1a)

Synopsis Although widely used and heavily promoted, the benefit of insulin analogues is uncertain. The analogues include insulin lispro or aspart (given instead of regular insulin), and insulin glargine or detemir (given instead of NPH insulin). This careful meta-analysis searched the literature for randomized controlled trials comparing insulin analogues with their older counterparts for type 1 diabetes mellitus (T1DM), T2DM, and gestational diabetes mellitus. The authors looked at both disease-oriented outcomes (ie, glycated hemoglobin [A1C]) and patient-oriented outcomes (hypoglycemia), although not a single study reported diabetic complications or mortality. A total of 68 studies of short-acting insulins and 49 studies of long-acting insulins was found. Independent reviewers extracted data and assessed the studies for quality; most studies were of poor quality (Jadad score = 2 or 3 out of 5), most were short duration (less than 1 year, in some cases just a few months), and most were open label. The authors found only small benefits in terms of glycemic control for adults with T1DM between insulin analogues and their older counterparts (range of improvement in A1C of -0.06% to -0.13%). A single study of insulin detemir plus insulin aspart versus NPH plus regular insulin showed a whopping -0.23% benefit in A1C. In children and adolescents with T1DM, there was no benefit at all. There were

inconsistent benefits generally favoring insulin analogues regarding the rates of severe and nocturnal hypoglycemia, with relative risks in the range of 0.5 to 0.9. For patients with T2DM, glycemic control was not improved with insulin analogues. In fact, in one study comparing insulin glargine with NPH insulin, A1C was 0.28% higher with the analogue; three studies comparing insulin detemir with NPH insulin in patients who were also using oral drugs similarly found higher A1C in the analogue groups. Nocturnal hypoglycemia was somewhat less common in patients with T2DM who were taking long-acting insulin analogues compared with those taking NPH insulin. Studies of short-acting insulin analogues compared with regular insulin in pregnant women found no differences.

Singh SR, Ahmad F, Lal A, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ*. 2009;180(4):385-397.

Aspirin benefits uncertain in patients with PAD

Clinical question Is aspirin useful in reducing the risk of cardiovascular events in adults with peripheral artery disease (PAD)?

Bottom line Aspirin alone or in combination with dipyridamole significantly reduces the risk of nonfatal stroke in adults with PAD. There was no significant association between aspirin alone or aspirin with dipyridamole in reducing the risk of MI, cardiovascular mortality, major bleeding events, or all-cause mortality. (Level of evidence = 1a)

Synopsis Various guidelines recommend aspirin for patients with PAD. These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, The Cochrane Registry of Controlled Trials, Science Citation Index, bibliographies of retrieved trials, and abstracts from major scientific meetings for randomized trials investigating the effect of aspirin alone or aspirin with dipyridamole on cardiovascular event rates in patients with PAD. Two individ-

uals independently evaluated potential studies for inclusion criteria and methodologic quality. Discrepancies were resolved by consensus agreement. Study quality was assessed using standard Jadad criteria; resulting scores ranged from 2 to 5 (0 = low quality; 5 = high quality). Eighteen trials (n = 5,269) met inclusion criteria with follow-up durations of 10 days to 6.7 years. Aspirin doses ranged from 100 mg/d to 1,500 mg/d. Treatment with aspirin alone or with dipyridamole was associated with a statistically significant reduction in the risk of nonfatal stroke (number needed to treat = 79; 95% CI, 47-234). There was no significant association between aspirin alone or aspirin with dipyridamole in reducing the risk of MI, cardiovascular mortality, major bleeding events, or all-cause mortality. Formal analyses found no evidence for publication bias or significant heterogeneity of the results.

Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease. A meta-analysis of randomized trials. *JAMA*. 2009;301(18):1909-1919.

High false-positive rate seen with repeated, multimodal screening for cancers

Clinical question When patients undergo repeated screenings for multiple cancers, how often do false-positive results occur?

Bottom line Almost half the healthy adults undergoing repeated multimodal cancer screening will have at least one false-positive result by the time they have had 14 screening procedures. Many people seem to believe there is no harm in screening; however, these results are a sobering reminder that screening healthy populations may not be so benign. (Level of evidence = 1b)

Synopsis These authors report data from patients aged 55 to 74 years who represented the intervention wing of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Women in this wing were offered annual can-

cer antigen 125 testing and transvaginal ultrasonography for ovarian cancer for 4 years, chest radiography for lung cancer at baseline and yearly for 2 years in nonsmokers or 3 years in smokers, and flexible sigmoidoscopy for colorectal cancer at baseline and at 3 or 5 years. Men were offered the same tests for lung and colorectal cancers, and also received annual digital rectal examinations and prostate-specific antigen blood tests for 4 years. The investigators declared a false-positive result if a screening test result was abnormal, but the cancer went undiagnosed after 3 years of follow-up. At the end of 3 years of follow-up, each patient could have had up to 14 screening tests. Among the 68,436 patients, more than 40% had at least one false-positive result. Approximately 33% of the women and 50% of men had at least one false-positive. Approximately 3% had minimally invasive diagnostic procedures, 16% underwent moderately invasive procedures, and nearly 2% underwent major surgery. Flexible sigmoidoscopy and chest radiography, for men and for women, were the tests yielding the highest rates of false-positive results. This study did not include screening mammography. Adding mammography to the above would increase the number of false-positive results and invasive procedures for women.

Croswell JM, Kramer BS, Kreimer AR, et al. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. *Ann Fam Med*. 2009;7(3):212-222.

BP lowering by any means is beneficial for most patients

Clinical question What is the relationship between antihypertensive choice, BP lowering, and outcomes in patients with normal and elevated BP, and those with and without coronary heart disease?

Bottom line In a very sophisticated and complex meta-meta-analysis, we can put together the following picture of pharmacologic treatment of BP: (1) It's the degree of BP that matters; all

drugs are equivalent in decreasing coronary heart disease (CHD) and stroke at a given reduction in BP; (2) beta-blockers are better, at least in the first few years, than other medicines in patients who have had a coronary event; (3) lowering BP is beneficial in patients with and without CHD, though the effect will be greater in the latter group; (4) in patients at high risk, lowering BP is effective even in patients without hypertension; (5) in older patients, three drugs used at half their normal doses prevent outcomes to a greater extent than a single drug at its full dose. (Level of evidence = 1a)

Synopsis The authors assembled data from 147 studies evaluating the outcomes of BP lowering by drug therapy in a total of 464,000 patients. The studies were found by searching three databases, previous review articles, and citation lists of retrieved articles. Two authors independently extracted the data, using only data from randomized, controlled trials evaluating the effect of BP treatment on CHD events and stroke. Here's where the authors were very creative: They compared the results in the studies with results obtained from epidemiologic studies and trials of drug doses and BP response to extrapolate a dose-response between the drugs and BP and to determine the relationship between cardiovascular mortality and BP lowering. Their goal? To extrapolate from existing data the relationship between lower doses of medication (and the resulting lesser effect on BP lowering) and patient-oriented outcomes. They had five outcomes from this analysis: (1) As long as BP is lowered, it doesn't matter how. All medications are equivalent in decreasing CHD events and stroke at a given reduction in BP. (2) Beta-blockers work better than other medications in preventing CHD events in patients with a history of CHD for the first few years after an infarction, reducing subsequent events by 29%, as compared with a 15% decrease with BP lowering with other

medicines. (3) BP lowering is equally effective in preventing CHD and stroke in patients with and without a history of cardiovascular disease, though the absolute risk reduction is greater with secondary prevention because the absolute risk is higher in these patients. (4) The effect on event reduction is due to the relative BP lowering and not due to some other, non-BP effect of drug therapy. (5) BP lowering is helpful for anyone at high risk of CHD or stroke; reducing BP is effective from any initial level (even "normal"), down to 110 mm Hg systolic and 70 mm Hg diastolic. (6) In patients aged 60 to 69 years with hypertension, using three drugs at half their standard doses produces a greater reduction in outcomes than using one drug at its usual dose.

Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiologic studies. *BMJ*. 2009;338:b1665.

Blunt abdominal trauma score predicts absence of organ injury in children

Clinical question Does a scoring system using clinical, laboratory, and radiographic criteria reliably predict the absence of organ injury in children with blunt abdominal trauma?

Bottom line This unvalidated scoring system, which includes clinical, laboratory, and ultrasound results, is fairly sensitive in identifying children with blunt abdominal trauma who are unlikely to have organ injury. (Level of evidence = 2b)

Synopsis Consecutive children suffering from blunt abdominal trauma underwent a standard work-up consisting of blood and urine tests and abdominal ultrasound. The children who did not have normal (or nearly normal) test results or an abnormal ultrasound underwent a contrast CT of the abdomen. All patients were admitted to the hospital, either for treatment or for observation for at least 24 hours. Children who were doing well were sent home, those

with persistent pain had a CT if they hadn't had one in the emergency department. A pediatric radiologist interpreted all ultrasound and CT images, although the authors do not report if the radiologist was aware of any of the other clinical data. The diagnosis of organ injury was based on the presence of abnormal CT findings. The absence of injury was based on a normal CT. For children who did not have a CT because their initial workup was normal, the absence of injury was based on whether they were pain free at 24 hours. The authors played a variety of statistical games to identify factors in children unlikely to have organ injury. They developed a scoring system and used receiver operating characteristic curves to identify cutoff points for the scoring system. Thirty children had organ injury and 116 did not. To use the score, assign 4 points for abnormal ultrasound; 2 points for each of the following: abdominal pain, peritoneal irritation, hemodynamic instability, AST above 60 IU/L, ALT above 25 IU/L; 1 point for each of the following: WBC count more than 9.5 grams/L, LDH higher than 330 IU/L, lipase higher than 30 IU/L, creatinine higher than 50 g/L. A score of 7 or less was 91% sensitive and 84% specific (positive likelihood ratio = 5.7; negative likelihood ratio = 0.11). In other words, when the score was 7 or less, the child was unlikely to have organ injury. This score needs to be independently validated.

Karam O, Sanchez O, Chardot C, La Scala G. Blunt abdominal trauma in children: a score to predict the absence of organ injury. *J Pediatr*. 2009;154(6):912-917.

American Pain Society guidelines for low back pain

Clinical question What treatments for low back pain are effective?

Bottom line Patients with persistent nonradicular low back pain should be offered interdisciplinary rehabilitation, but no facet joint injections, prolotherapy, or intradiscal steroid injections. Patients with radicular symptoms do

better in the short term with procedures, but long-term data are lacking. (Level of evidence = 1a)

Synopsis These authors used systematic reviews conducted by the Oregon Evidence-based Practice Center, funded by the Agency for Healthcare Research and Quality, to inform the guideline. All members of the panel were required to disclose conflicts of interest and recuse themselves from relevant votes. For therapeutic interventions, they used a grading scheme based on the United States Preventive Services Task Force (grade appears in brackets).

The following is a summary of their key recommendations for patients with nonradicular back pain: (1) Do not perform a provocative discogram because of its poor diagnostic accuracy. The authors found insufficient evidence to recommend other diagnostic interventions, such as selective nerve blocks, facet blocks, and so forth, whether or not radicular symptoms are present (strong recommendation based on moderate quality evidence). (2) For patients with persisting symptoms after "usual care," consider interdisciplinary rehabilitation (rehabilitation integrated with psychological and/or social/occupational evaluation) [B]. (3) Patients with persistent pain should not receive facet joint corticosteroid injections, prolotherapy, or intradiscal corticosteroid injections because these have not been found to be more effective than sham therapies [D]. (4) The authors found fair evidence that spinal fusion is more effective than usual nonsurgical care in patients with degenerative changes, but the surgery is no more effective than intensive rehabilitation [B]. (5) Patients with presumed facet-joint pain do not benefit from facet-joint injection with steroids [D]. (6) The authors found fair evidence that artificial disc replacement improves 2-year clinical outcomes in patients with single-level degenerative disc disease [B], but insufficient data for longer-term outcomes [I]. (7) The authors found insufficient data to com-

ment on botulinum toxin, local injections, epidural steroids, facet blocks, radiofrequency denervation, various intradiscal thermal treatments, spinal cord stimulation, or intrathecal therapy [I].

The following is a summary of the key recommendations for patients with radicular back pain or symptomatic spinal stenosis: (1) Discectomy (open or micro) is effective for the short-term (3 months) relief for patients with prolapsed disc [B]. (2) Laminectomy (with or without fusion) provides intermediate relief (1-2 years) in patients with symptomatic spinal stenosis [B]. (3) Chemonucleolysis is better than placebo but worse than surgery in patients with prolapsed discs [B]. (4) Epidural steroid injections provide short-term (3 months) relief in patients with prolapsed discs [B]. (5) Spinal cord stimulation is effective in patients with persistent radicular symptoms after surgery [B].

Grading scheme: **A**, Strongly recommended. The panel found good evidence that the intervention improves health outcomes and concludes that benefits substantially outweigh harms. **B**, Recommended. The panel found at least fair evidence that the intervention improves health outcomes and concludes that benefits moderately outweigh harms, or that benefits are small but there are no significant harms, costs, or burdens associated with the intervention. **C**, No recommendation for or against. The panel found at least fair evidence that the intervention can improve health outcomes but concludes that benefits only slightly outweigh harms, or the balance of benefits and harms is too close to justify a general recommendation. **D**, Recommendation against. The panel found at least fair evidence that the intervention is ineffective or that harms outweighs benefits. **I**, Insufficient evidence to recommend for or against. Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

Chou R, Loeser JD, Owens DK, et al; American Pain Society Low Back Pain Guideline Panel. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society. *Spine*. 2009;34(10):1066-1077.

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