POEMs

Patient-Oriented Evidence That Matters

Older Treatments for Type 2 Diabetes Mellitus Do Not Affect Patient-Oriented Outcomes

Clinical Question

What treatments for type 2 diabetes mellitus decrease the likelihood of patient-oriented outcomes?

Bottom Line

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists reduce all-cause and cardiovascular mortality and other cardiac-related problems. Older treatments, including insulin, do not affect long-term outcomes. Metformin was not found to be more effective than standard treatment to prevent important outcomes, which is consistent with previous findings and may cause it to be removed as a cornerstone of treatment. (Level of Evidence = 1a–)

Synopsis

The investigators searched three databases, including Cochrane Central, and identified 816 English-language randomized controlled studies (N = 471,038) that compared two or more medications for type 2 diabetes. The researchers followed PRISMA criteria for reporting. Approximately one-fourth of the studies had a high risk of bias, usually from lack of masking (62%). The researchers conducted a network meta-analysis and compared all medications with one another by combining direct and indirect evidence across the studies. All the studies were short-term, with a median duration of six months. SGLT-2 inhibitors and GLP-1 receptor agonists reduced all-cause mortality to a small extent compared with usual treatment. They also reduced death due to cardiovascular causes, the likelihood of nonfatal myocardial infarction, and admission for heart failure. They have shown similar rates of adverse effects compared with usual care. Finerenone (Kerendia) probably reduces admissions for heart failure and end-stage kidney disease compared with usual care. Tirzepatide (Mounjaro) is associated with the greatest amount of weight loss.

The analysis clarifies which treatments do not have an overall benefit on patient-oriented outcomes. The older treatments, including insulin, do not affect mortality or hospitalizations, and thiazolidinediones increase the likelihood of being admitted for heart failure. Metformin, the cornerstone of treatment in most guidelines, may not have a benefit over standard treatment.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Foundation

Setting: Various (meta-analysis)

Reference: *Shi Q, Nong K, Vandvik PO, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials.* BMJ. *2023;381:e074068.*

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2023 AGS Update on Potentially Inappropriate Medication Use in Older Adults

Clinical Question

What medications do the American Geriatric Society (AGS) say are problematic for older adults?

Bottom Line

The 2023 AGS Beers Criteria provides many resources to assist in the rational prescribing of medications for older adults. The AGS panel encourages the judicious use of these resources to aid in shared decision-making. (Level of Evidence = 5)

Synopsis

The AGS convened a 12-person panel to evaluate systematic reviews and other evidence to update the 2019 AGS Beers Criteria. The panel used an iterative voting process to develop their final recommendations. One decision was to eliminate medications from the previous list that are rarely prescribed in the United States or are no longer on the market (such as flurazepam or reserpine). The list is fairly exhaustive, but the panel calls out a few noteworthy changes. For example, in their recommendations for using anticoagulants, the authors

recommend not using warfarin as initial therapy for adults with nonvalvular atrial fibrillation or for treating venous thromboembolic phenomena. The panel recommends avoiding aspirin for the primary prevention of cardiovascular disease, anticholinergic drugs, oral and transdermal estrogen, and sulfonylureas. The panel expanded the sections on drug-disease and drug-drug interactions. Recommendations for deprescribing medications on the list are also included. The panel attempted to address many limitations to their list. One significant limitation is the inability to distinguish between the potential harms in the frail patient and the potential harms, as well as benefits, in the healthy older adult. Physicians should use the list as a guide to therapeutic decisions, but not as an absolute mandate.

Study design: Practice guideline

Funding source: Self-funded or unfunded

Setting: Various (guideline)

Reference: *2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults.* J Am Geriatr Soc. *2023;71(7):2052-2081.*

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Testosterone Does Not Increase Major Adverse Cardiac Events, but Does Increase Risk of Atrial Fibrillation, Pulmonary Embolism, Acute Kidney Injury, and Arrhythmia

Clinical Question

Is transdermal testosterone replacement safe in men with known heart disease or at high risk of heart disease?

Bottom Line

Although the most serious cardiovascular (CV) events were not more common in high-risk men using testosterone gel, there were higher incidence rates of acute kidney injury, atrial fibrillation, nonfatal arrhythmias, and pulmonary embolism. Testosterone supplementation should be used with caution, if at all, in men with a history of these conditions. (Level of Evidence = 1b–)

Synopsis

Data regarding the safety of testosterone supplementation have been mixed, with some studies finding increased CV risk. The U.S. Food and Drug Administration, therefore, mandated that companies that sell these supplements perform a safety study. The researchers identified men, 45 to 80 years of age, with symptoms of hypogonadism and two fasting morning serum testosterone levels of less than 300 ng per dL (10.41 nmol per L). All of the patients had preexisting CV disease (55%) or were at increased risk of CV disease (45%). The patients were randomized to receive testosterone gel titrated to achieve a testosterone level of 350 to 750 ng per dL (12.15 to 26.03 nmol per L) or matching placebo gel with sham titrations. Testosterone was discontinued if the patient's serum level exceeded 750 ng per dL even at the lowest dose, or if hematocrit level exceeded 54%. Groups were balanced at baseline, with a mean age of 63 years, and 80% were White, 69% had diabetes mellitus, 93% had hypertension, and 90% had hyperlipidemia. Analysis was by intention to treat. The full study population included 5,204 patients; 5,198 received at least one dose of testosterone gel and were included in the safety population for the primary analysis. Patients were treated for a mean of approximately 22 months and followed for a mean of 33 months. There was no difference between groups in the primary safety outcome of major adverse cardiac events, which included CV death, nonfatal myocardial infarction, and nonfatal stroke (7.0% vs. 7.3%). There was also no difference for any of the components of the composite outcome, all-cause mortality, need for revascularization, or need for hospitalization. The authors did see an increase in the risk of nonfatal arrhythmia that warranted an intervention (5.2% vs. 3.0%; $P = .001$; number needed to harm [NNH] = 45 over 21 months), atrial fibrillation (3.5% vs. 2.4%; $P = .02$; NNH = 91 over 21 months), and acute kidney injury (2.3% vs. 1.5%; $P = .04$; NNH = 125 over 21 months). Improvement in symptoms was not reported. Pulmonary embolism was also more common with testosterone (0.92% vs. 0.46%). The authors did not report statistical significance for this outcome.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Lincoff AM, Bhasin S, Flevaris P, et al.; TRAVERSE Study Investigators. Cardiovascular safety of testosterone-replacement therapy.* N Engl J Med. *2023;389(2):107-117.*

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Adipose-Derived Stem Cell Injections Provide Borderline Meaningful Pain Relief in Adults With Degenerative Joint Disease of the Knee

Clinical Question

Are adipose-derived stem cell injections effective in adults with moderate degenerative joint disease of the knee?

Bottom Line

After six months, adults with moderate degenerative joint disease of the knee who received stem cell injections were

more likely to experience clinically meaningful improvements in pain and function than those who received saline injections. (Level of Evidence = 1b–)

Synopsis

The researchers from Korea enrolled adults with degenerative joint disease of the knee confirmed on radiography who had pain levels of at least 50 out of 100 on a visual analog scale and impaired function on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The authors reported that the minimum clinically important difference for these scores was 14 points and 9 points, respectively. They randomized patients (uncertain if the allocation was concealed) to receive ultrasound-guided injections of autologous adipose-derived stem cells (n = 131) or saline (n = 130) that were performed by a physician who was not part of the study. They cultured the stem cells for three weeks before injection (a practice currently not allowed in the United States). They evaluated changes in the visual analog scale and WOMAC only for the 252 patients who completed the six-month follow-up. After six months, both groups had clinically important improvements in pain, but the net difference (9.7 points) is less than the minimum clinically important difference. Similarly, both groups' function scores improved, but the net difference was only 5.4 points. More patients who received stem cell injections had clinically meaningful improvements in pain scores (68.6% vs. 53.3%; number needed to treat [NNT] = 7; 95% CI, 4 to 32) and in WOMAC scores (73.4% vs. 47.6%; NNT = 4; 95% CI, 3 to 8) than those who received placebo. Approximately one-third of the participants in each group experienced adverse events, which were mostly pain and swelling following the injections.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (specialty)

Reference: *Kim KI, Lee MC, Lee JH, et al. Clinical efficacy and safety of the intra-articular injection of autologous adipose-derived mesenchymal stem cells for knee osteoarthritis: a phase III, randomized, double-blind, placebo-controlled trial.* Am J Sports Med. *2023;51(9):2243-2253.*

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