POEMs

Aliskiren Worsens Outcomes in High-Risk Patients with Diabetes

Clinical Question

In patients with diabetes mellitus and renal or heart disease, does the direct renin inhibitor aliskiren (Tekturna) improve outcomes?

Bottom Line

Aliskiren increases the likelihood of adverse cardiovascular outcomes in patients with diabetes and kidney or heart disease, and cannot be recommended. (Level of Evidence = 1b)

Synopsis

In this study, more than 8,500 patients older than 35 years with type 2 diabetes who also had evidence of microalbuminuria, macroalbuminuria, or coronary artery disease were randomized to receive aliskiren or placebo. The drug was initially given in a daily dosage of 150 mg and was increased to 300 mg if tolerated. The mean age of participants was 64 years, 32% were women, 13% were smokers, and the average A1C level was 7.8. Groups were balanced at the start of the study, and follow-up was good (with a mean follow-up of 2.8 years and less than 3% lost). The study was stopped after the second interim analysis because of an increase in the likelihood of the primary composite outcome among patients in the aliskiren group. This composite included cardiovascular death, cardiac arrest, myocardial infarction, stroke, unplanned hospitalization for heart failure, end-stage renal disease or death due to renal failure, or doubling of serum creatinine levels. This occurred in 18.3% of the aliskiren group and 17.1% of the placebo group (hazard ratio = 1.08; 95% confidence interval, 0.98 to 1.2). The only individual end point with a statistically significant difference between groups was cardiac arrest (0.4% for aliskiren vs. 0.2% for placebo; P = .04; number needed to harm = 500). However, the trend for all other outcomes but two (doubling of serum creatinine and unplanned hospitalization for heart failure) favored the placebo group. Hyperkalemia and hypotension were among the most common reasons that the drug was discontinued, and were significantly more common in patients taking aliskiren.

Reference

Parving HH, Brenner BM, McMurray JJ, et al.; ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. *2012;367(23):2204-2213.*

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Concealed

Setting: Outpatient (any)

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Testosterone Does Not Improve Sildenafil Effectiveness

Clinical Question

Does testosterone supplementation improve the response to sildenafil (Viagra) in men with erectile dysfunction and low testosterone levels?

Bottom Line

Boosting low testosterone levels into the normal range did not further improve the effectiveness of sildenafil in men with erectile dysfunction. The researchers did not determine whether testosterone replacement alone is as effective as sildenafil for the treatment of erectile dysfunction. (Level of Evidence = 1b)

Synopsis

These researchers identified, through advertisements and through referrals from specialty clinics, 140 men with erectile dysfunction and low serum testosterone levels (i.e., total testosterone level less than 330 ng per dL [11.45 nmol per L] or free testosterone level less than 50 pg per mL [173.35 pmol per L]). The men, 40 to 70 years of age, were tested to find the optimal dose of sildenafil before being randomized, using concealed allocation, to receive testosterone 1% gel or placebo gel, in addition to continuing sildenafil. Testosterone levels were tested two weeks after the start of treatment, and the dose was titrated up or down to achieve normal levels. Sildenafil, used alone, improved erectile function in men in both groups. Intention-to-treat and on-protocol analyses found that the addition of testosterone did not significantly improve erectile function compared with the placebo. Testosterone did not affect the frequency of sexual encounters, percentage of successful sexual intercourse, sexual desire, quality-of-life scores, or marital intimacy scores.

Reference

Spitzer M, Basaria S, Travison TG, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. Ann Intern Med. *2012;157(10):681-691.*

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

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Vitamin D Does Not Reduce Knee Pain from Osteoarthritis

Clinical Question

Does vitamin D supplementation reduce knee pain in adults with osteoarthritis?

Bottom Line

Vitamin D supplementation at a dose targeted to reach a 25-hydroxyvitamin D plasma level greater than 36 ng per mL for two years did not reduce symptomatic knee pain in adults with osteoarthritis. (Level of Evidence = 1b)

Synopsis

Another trial of supplemental vitamin D not able to show any clinical benefit—when will this medical fad run its course? These investigators identified adults 45 years or older who met standardized international criteria for knee osteoarthritis based on clinical and radiology findings. Patients randomly received (concealed allocation assignment) 2,000 IU oral cholecalciferol or matched placebo daily, with optional subsequent increments of 2,000 IU at four, eight, and 12 months, targeted to reach a 25-hydroxyvitamin D plasma level between 36 and 100 ng per mL (89.9 and 249.6 nmol per L). No supplemental calcium was given, but all patients received advice on optimal dietary calcium intake. Individuals assessing outcomes using standard pain rating scales and magnetic resonance imaging remained masked to treatment group assignment. Complete follow-up occurred for 85% of participants at 24 months.

Using intention-to-treat analysis, significantly more patients assigned to the active supplement group achieved the target plasma level of 25-hydroxyvitamin D compared with the placebo group (61.3% vs. 8.3%, respectively). However, there was no significant difference in reduction of knee pain between the two treatment groups. There were also no significant between-group differences based on magnetic resonance imaging studies in cartilage thickness or bone marrow lesion size. At 16 months, significantly more patients in the supplemental group reported increased use of nonsteroidal anti-inflammatory drugs than in the placebo group (40% vs. 22%; number needed to treat = 5.6). The study was 80% powered to detect a predetermined clinically significant difference in pain reduction between the two treatment groups.

Reference

McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. JAMA. *2013;309(2):155-162.* ▶

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

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D-dimer vs. Ultrasonography for DVT: Use Prediction Rule

Clinical Question

Is D-dimer testing always necessary in patients with possible deep venous thrombosis (DVT)?

Bottom Line

Use the Wells criteria to determine the likelihood of deep venous thrombosis; patients at moderate to high risk should go straight to ultrasonography. Patients at low risk should have D-dimer testing, followed by ultrasonography only if the results are positive. This approach decreases the use of D-dimer testing, as well as the need for ultrasonography, while producing the same clinical results. (Level of Evidence = 1b)

Synopsis

The Canadian researchers enrolled 1,732 consecutive patients presenting with a suspected first DVT. The patients were randomly assigned, using concealed allocation, to receive usual testing or selective testing. In the usual testing group, all patients had D-dimer testing; if positive, the affected leg was examined by ultrasonography. In the selective testing group, patients were evaluated based on their pretest probability of DVT, calculated using the Wells clinical prediction rule. Patients at low or moderate risk of DVT underwent D-dimer testing and, if results were positive, had ultrasonography evaluation. Patients with high probability, and all inpatients, underwent ultrasonography without initial D-dimer testing.

All study participants were followed for three months, and clinical results were similar in both groups. The selective testing approach decreased D-dimer testing in one of every five patients (21.8 percentage points; 95% confidence interval, 19.1 to 24.8) and decreased the overall proportion who required ultrasonography by 7.6 percentage points (95% confidence interval, 2.9 to 12.2).

Reference

Linkins LA, Bates SM, Lang E, et al. Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. Ann Intern Med. *2013;158(2):93-100.*

Study design: Diagnostic test evaluation

Funding source: Foundation

Allocation: Concealed

Setting: Outpatient (any)

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