POEMs

Fewer Deaths/Strokes/Revascularizations with Metformin Than Glipizide

Clinical Question

Does metformin (Glucophage) affect cardiovascular events in patients with type 2 diabetes mellitus?

Bottom Line

Over five years, treatment with metformin for three years, with other hypoglycemics as needed, reduced the likelihood of death, nonfatal stroke, or the need for vascularization compared with treatment beginning with glipizide (Glucotrol). Cardiovascular events were not individually reduced with metformin compared with glipizide. (Level of Evidence = 1b–)

Synopsis

These authors enrolled patients with type 2 diabetes and coronary artery disease, and followed them for a median of five years. The average age of all 304 patients was 63.3 years; 77% were men. After stopping current treatment (which included insulin in approximately 10% of the group), patients were randomized, with allocation concealment unknown, to receive 30 mg of glipizide daily or 1,500 mg of metformin daily, with additional treatment added as needed, to achieve an average A1C level of 7%. In each group, 25% of patients ended up receiving insulin in addition to the study drug. Using intention-to-treat analysis, the investigators compared the incidence of recurrent cardiovascular events in the two groups, including death, nonfatal stroke, or need for revascularization. After a median follow-up of five years, one or more events occurred in 35% of patients treated with glipizide and in 25% of patients treated with metformin (adjusted hazard ratio = 0.54; $P = .026$), which translates to a number needed to treat of 9.4 for five years. Death rates were not different between the two groups. This small study reinforces the findings from the long-ago study (*Diabetes.* 1970;19:747-830) that resulted in U.S. Food and Drug Administration warnings of an increased risk of cardiovascular events with sulfonylurea hypoglycemics.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Uncertain

Setting: Outpatient (any)

Reference: *Hong J, Zhang Y, Lai S, et al.; SPREAD-DIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease.* Diabetes Care. *2013;36(5):1304-1311.*

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No Effect of Vitamin D on Depressive Symptoms

Clinical Question

In patients with low vitamin D levels, does vitamin D supplementation improve symptoms of depression?

Bottom Line

Taken in aggregate, symptoms of depression do not improve in patients with low vitamin D levels when given vitamin D supplementation any more than when given placebo. There may be a benefit in patients with low vitamin D levels and mild to moderate depression. (Level of Evidence = 1b–)

Synopsis

This study was conducted in Norway, where researchers started by identifying patients ▶

with depressive symptoms and low vitamin D levels (< 22 ng per mL [< 55 nmol per L]). The authors excluded patients with severe depression (who were sent for treatment). The remaining 243 patients had a range of depression scores, although the percentage with mild to moderate depression was not reported. These patients were randomized, using concealed allocation, to receive oral placebo or cholecalciferol at a dosage of 40,000 IU weekly. After six months, vitamin D levels increased to normal in 97.5% of treated patients but in only 1.6% of the placebo group. However, there were significant improvements in depression scores in both groups, including an increase in global seasonality score, a measure of seasonal affective disorder. Patients with higher depression scores (who met the definition of depressive disorder) at the start of the study may have had a greater improvement in depression scores with treatment than patients receiving placebo, although this result needs to be confirmed by other studies.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (primary care)

Reference: *Kjærgaard M, Waterloo K, Wang CE, et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial.* Br J Psychiatry. *2012;201(5):360-368.*

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Pioglitazone Exposure Increases Bladder Cancer Risk

Clinical Question

Do adults with type 2 diabetes mellitus who are treated with pioglitazone (Actos) have an increased risk of bladder cancer?

Bottom Line

This review of all available data found a significantly increased risk of bladder cancer among adults with type 2 diabetes treated with pioglitazone. Pioglitazone also significantly increases the risk of heart failure, and there is minimal, if any, patient-oriented evidence of benefit from treatment (Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. *Cochrane Database Syst Rev.* 2006; [4]:CD006060). The French and German governments have suspended or strongly curtailed the use of pioglitazone. It lowers A1C levels, but I would not want my loved ones taking this stuff. (Level of Evidence = 2b)

Synopsis

Because of concern that pioglitazone is associated with an increased risk of bladder cancer, the French and German medicine agencies have suspended the use of pioglitazone or strongly advised physicians to stop prescribing it. The investigators thoroughly searched multiple databases (Medline, Embase, the Cochrane Register, the U.S. Food and Drug Administration website, and http://www.clinicaltrials.gov), reviewed bibliographic references of relevant articles, and contacted known researchers for longitudinal studies of patients who had type 2 diabetes with or without exposure to pioglitazone. Two authors independently performed the search and evaluated the methodologic rigor and the eligibility of individual trials. Disagreements were resolved by consensus discussion with a third reviewer. Observational and experimental trials were included, and sensitivity analyses were performed to assess the effect of study design and quality.

Six articles (N = 215,142) met inclusion criteria, including one large randomized controlled trial, one prospective cohort study, and four retrospective studies. The retrospective studies included reports from large population-based databases, including the French health care system, Kaiser Permanente Northern California, the Taiwanese national health system, and the United Kingdom general practice research database. Follow-up occurred for a median of 44 months. Compared with the nonexposed group, bladder cancer occurred significantly more often among patients exposed to pioglitazone (hazard ratio = 1.23; 95% confidence interval, 1.09 to 1.39; number needed to treat to harm = 20,903). The risk of bladder cancer was significantly increased with longer duration of pioglitazone use but not with increasing cumulative dosage.

Study design: Systematic review

Funding source: Self-funded or unfunded

Setting: Various (meta-analysis)

Reference: *Ferwana M, Firwana B, Hasan R, et al. Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies.* Diabet Med. *2013;30(9):1026-1032.*

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