

POEMs

Patient-Oriented Evidence That Matters

Dapagliflozin in High-Risk Type 2 Diabetes Reduces Hospitalization for Heart Failure But Does Not Reduce Death, Myocardial Infarction, or Stroke

Clinical Question

Does dapagliflozin (Farxiga) improve cardiovascular outcomes in patients with type 2 diabetes mellitus and cardiovascular disease?

Bottom Line

The only cardiovascular benefit to treatment with dapagliflozin was a reduction in the likelihood of hospitalization; 125 patients would need to be treated for 10 years to prevent one hospitalization. For patients with type 2 diabetes and heart failure, that might tip the scales in favor of dapagliflozin (or another sodium glucose co-transporter 2 [SGLT2] inhibitor) as a second or third drug choice. The researchers promote a reduction in the composite of cardiovascular death or hospitalization for heart failure, but there is no reduction in cardiovascular death. This composite is good marketing, but bad science. (Level of Evidence = 1b)

Synopsis

Dapagliflozin is one of several SGLT2 inhibitors that induce glucosuria to lower blood glucose levels. In the current study, researchers identified patients 40 years or older with type 2 diabetes and established cardiovascular disease or men who were 55 years or older (60 or older for women) with one or more cardiovascular risk factors in addition to age. Patients had to have an A1C level between 6.5% and 12% and creatinine clearance of at least 60 mL per minute per 1.73 m² (1 mL per second per m²). After a four-

to-eight-week placebo run-in period, approximately 25% of the patients who were initially enrolled were excluded, largely because they did not meet the laboratory criteria (although the stated purpose of the run-in period in the study protocol document was to identify nonadherent patients). Patients could receive other medications to treat their diabetes at the discretion of their physician.

A total of 17,160 patients were randomized to receive dapagliflozin, 10 mg, or placebo. Groups were balanced, with a mean age of 64 years, a mean body mass index of 32 kg per m², with 41% of patients having cardiovascular disease, and 59% having multiple risk factors. They were contacted regularly and followed up for a median of 4.2 years. The primary outcome was the composite of cardiovascular death, acute myocardial infarction, or ischemic stroke. There was no difference between groups for the primary outcome or for secondary individual outcomes of cardiovascular death, all-cause mortality, ischemic stroke, or myocardial infarction. There were significantly fewer hospitalizations due to heart failure in the intervention group (2.5% vs. 3.3%; number needed to treat [NNT] = 125 over four years) and fewer patients with progression of renal disease in the intervention group (1.5% vs. 2.8%; NNT = 77 over four years). The authors highlight the composite outcome of cardiovascular death or hospitalization for heart failure, an outcome not prespecified in their protocol, and one that makes no sense scientifically because there was no difference in cardiovascular deaths—all of the benefit in this composite outcome was due to fewer heart failure admissions. Nevertheless, this is the featured outcome in the figures and abstract. Patients given dapagliflozin had more genital infections serious enough to

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discontinue the study medicine or be classified as severe (0.8% vs. 0.1%) and more episodes of diabetic ketoacidosis (0.3% vs. 0.1%).

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (any)

Reference: *Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347-357.*

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More Evidence Against Antibiotics for Acute Asthma Exacerbations

Clinical Question

Does the use of antibiotics in patients hospitalized with an asthma exacerbation result in better outcomes?

Bottom Line

Antibiotics do not benefit patients hospitalized with an asthma exacerbation. Evidence from this study suggests worse outcomes with antibiotic use, including a longer hospital stay, higher costs, and greater risk of diarrhea. Antibiotic use was not associated with a decreased risk of treatment failure. Although findings were not unexpected, it is surprising that almost one-half of the patients in this study were receiving antibiotics, despite current guidelines. (Level of Evidence = 2b)

Synopsis

Although current evidence does not support the use of antibiotics for the management of acute asthma exacerbations, patients continue to receive them. Using an administrative database that includes 543 nonteaching hospitals in the United States, the investigators identified patients who were hospitalized during a two-year period with a principal diagnosis of asthma being treated with systemic corticosteroids. Those with a potential indication for

antibiotic treatment, such as a secondary diagnosis of chronic obstructive pulmonary disease, were excluded, leaving a total of 19,811 patients. The median age of the cohort was 46 years, and 73% were women. The exposure of interest was the use of antibiotics within the first two days of hospitalization for a minimum of two days, which was noted in 44% of the overall cohort. The comparison was the subset of patients who either did not receive any antibiotics or did not receive antibiotics within the first two days. The primary outcome was hospital length of stay. Patients treated with early antibiotics were older and more likely to be white. They were also more likely to have comorbidities, including congestive heart failure, diabetes mellitus, and renal failure. The most common antibiotic class used was macrolides. In a propensity-matched cohort of 13,666 patients, exposure to early antibiotics was associated with a longer length of stay (four days vs. three days) and higher hospitalization costs (\$4,776 vs. \$3,641). The risks of treatment failure and 30-day mortality were similar in the two groups. In a sensitivity analysis that compared patients who received early antibiotics with those who received no antibiotics at all, the risk of diarrhea was 2.6 times higher. However, in patients treated only with macrolides compared with those treated with other antibiotics, the incidence of antibiotic-related diarrhea was lower (1.1% vs. 2.0%; $P < .001$).

Study design: Cohort (retrospective)

Funding source: Unknown/not stated

Setting: Inpatient (any location) with outpatient follow-up

Reference: *Stefan MS, Shieh M, Spitzer KA, et al. Association of antibiotic treatment with outcomes in patients hospitalized for an asthma exacerbation treated with systemic corticosteroids. JAMA Intern Med. 2019;179(3):333-339.*

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