Sodium–glucose cotransporter 2 inhibitors for treating diabetes mellitus

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1 Sodium–glucose cotransporter 2 inhibitors are a new class of oral drugs for treating diabetes

Sodium–glucose cotransporter 2 inhibitors (SGLT2s) are typically prescribed as a second-line agent for adults with type 2 diabetes mellitus to improve glycemic control. They reduce tubular glucose reabsorption in the proximal tubule, thereby enhancing execretion of urinary glucose. This insulin-independent mechanism provides a modest reduction in hemoglobin A_{1c} (about 0.7%–1.0%), similar to other classes of oral drugs for treating diabetes, but with added benefits of lowering systolic blood pressure (by about 5 mm Hg) and weight loss (about 2 kg).[1]

2 Sodium–glucose cotransporter 2 inhibitors may reduce mortality in patients with type 2 diabetes at high risk for cardiovascular events

Based on a recent meta-analysis, SGLT2 inhibitors protected against cardiovascular death (relative risk [RR] 0.63, 95% confidence interval [CI] 0.51–0.77), heart failure (RR 0.65, 95% CI 0.50–0.85) and all-cause mortality (RR 0.71, 95% CI 0.61–0.83) in patients with preexisting cardiovascular disease.[2] These results were mainly driven by a trial that compared empagliflozin to placebo in patients at high risk for cardiovascular events.[2] It is unknown whether these findings apply to patients at lower risk. These drugs are also associated with increased low-density lipoprotein levels and an increased risk of nonfatal stroke (RR 1.30, 95% CI 1.00–1.68).[2]

3 Sodium–glucose cotransporter 2 inhibitors have a unique adverse-effect profile

Use of SGLT2 inhibitors is associated with a threefold increased risk of genital infection and may be associated with an increased risk of urinary tract infection, acute kidney injury and euglycemic diabetic ketoacidosis.[1,3] Among cases reported to the United States Food and Drug Administration, diabetic ketoacidosis typically occurred within six weeks of starting treatment, and patients presented with normal or mildly elevated levels of blood glucose.[3]

4 Sodium–glucose cotransporter 2 inhibitors should be used with caution in patients on insulin, insulin secretagogues and diuretics

Coadministration of SGLT2 inhibitors with insulin or insulin secretagogues increases the risk of hypoglycemia.[1] In addition, coadministration of SGLT2 inhibitors with diuretics may increase the risk of volume depletion.[4] Drug–drug interactions with other drugs (e.g., digoxin and rifampin) may also exist.[4]

5 Empagliflozin, dapagliflozin and canagliflozin are available in Canada

For patients with normal renal function, the initial dosages are dapagliflozin (5 mg daily), empagliflozin (10 mg daily) and canagliflozin (100 mg daily).[5] These drugs are more costly (about $80/month) than metformin ($8/month). They should not be prescribed for patients with renal impairment (i.e., renal function less than 60 mL/min/1.73 m^2 for dapagliflozin and less than 45 mL/min/1.73 m^2 for empagliflozin and canagliflozin).

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