



How do these 3 diabetes agents compare in reducing mortality?

A meta-analysis reveals that there may be advantages associated with SGLT-2 inhibitors and GLP-1 agonists that are not associated with DPP-4 inhibitors.

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PRACTICE CHANGER

Consider adding a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide 1 (GLP-1) agonist to the treatment regimen of patients with poorly controlled type 2 diabetes—especially those with higher CV risk. Doing so can reduce all-cause and cardiovascular (CV) mortality¹

STRENGTH OF RECOMMENDATION

B: Based on a network meta-analysis of 236 randomized controlled trials.

Zheng S, Roddick A, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2018;319:1580-1591.

ILLUSTRATIVE CASE

A 64-year-old man with type 2 diabetes mellitus (T2DM) presents for a follow-up visit. His point-of-care hemoglobin A1c is 9.5%, and he is currently taking only metformin 1000 mg bid. You are considering adding an SGLT-2 inhibitor, a GLP-1 agonist, or a dipeptidyl peptidase 4 (DPP-4) inhibitor to his treatment regimen. Which do you choose to better control his diabetes and reduce his all-cause and cardiovascular (CV) mortality risk?

Over the past several years, the number of patients with T2DM has continued to climb. In the United States, approximately 30 million people, or 1 of every 11, now struggles to reduce their blood sugar.² As prevalence of the disease has increased,

so has the number of medications available that are aimed at lowering blood sugar and improving diabetes control.² In particular, the introduction of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors over the past several years has produced an area of some clinical ambiguity, due to the lack of randomized controlled trials (RCTs) comparing their efficacy.

The “American Diabetes Association Standards of Medical Care in Diabetes” points specifically to the potential roles of the SGLT-2 inhibitors empagliflozin and canagliflozin, and the GLP-1 agonist liraglutide, as agents that should be added to metformin and lifestyle modification in patients with established atherosclerotic CV disease. They cite data indicating that these drugs reduce major adverse CV events and CV mortality in this population.³ Deciding among these 3 medications, however, is left to providers and patients. For dual therapy in patients with T2DM without CV disease who remain hyperglycemic despite metformin and lifestyle modifications, SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors are recommended equally, with the choice among them to be determined by “consideration of drug-specific effects and patient factors.”³

The National Institute for Health and Care Excellence (NICE) guidelines on T2DM management list both SGLT-2 inhibitors and DPP-4 inhibitors among the potential options for intensifying therapy after metformin.⁴ The American Association of Clinical Endocrinologists and the American

➤ When compared to placebo or no treatment, the use of SGLT-2 inhibitors or GLP-1 agonists is associated with lower all-cause mortality and lower CV mortality than is the use of DPP-4 inhibitors.

College of Endocrinology guidelines do include a hierarchical recommendation to try a GLP-1 agonist first, followed by an SGLT-2 inhibitor, followed by a DPP-4 inhibitor, after metformin and lifestyle modifications—although the difference in strength of recommendations for these classes is noted to be small.⁵

STUDY SUMMARY

SGLT-2s, GLP-1s are associated with better mortality outcomes than DPP-4s

Zheng and colleagues performed a network meta-analysis of 236 RCTs involving 176,310 patients to compare the clinical efficacy of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors to reduce all-cause mortality and CV endpoints in patients with T2DM. The authors analyzed English-language RCTs that followed patients with T2DM for at least 12 weeks and compared SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors to one another, to placebo, or to no treatment.

A majority of the patients in both the intervention and control groups were taking additional diabetes medications, such as metformin, prior to enrollment and during the trials. About half of the patients analyzed were enrolled in trials that specifically evaluated patients at elevated CV risk, which is notable because patients with higher CV risk ultimately derived the most benefit from the treatments studied.

The primary outcome was all-cause mortality. Secondary outcomes were CV mortality, heart failure (HF) events, myocardial infarction (MI), unstable angina, and stroke, as well as the safety outcomes of hypoglycemia and adverse events (any events, serious events, and those leading to study withdrawal).

■ **Results.** Compared with the patients in the control groups (placebo or no treatment), patients in both the SGLT-2 inhibitor and GLP-1 agonist groups had decreased all-cause mortality (SGLT-2 inhibitor group, hazard ratio [HR]=0.80; 95% credible interval [CrI], 0.71-0.89; absolute risk difference [RD]= -1%; number needed to treat [NNT]=100; GLP-1 agonist group, HR=0.88; 95% CrI, 0.81-0.94; absolute RD= -0.6%; NNT=167). Patients in the DPP-4 inhibitor group did not have a

difference in mortality compared with the control groups (HR=1.02; 95% CrI, 0.94-1.11; absolute RD=0.1%). Both the SGLT-2 inhibitor (HR=0.78; 95% CrI, 0.68-0.90; absolute RD= -0.9%; NNT=111) and GLP-1 agonist (HR=0.86; 95% CrI, 0.77-0.96; absolute RD= -0.5%; NNT=200) groups had reduced all-cause mortality when compared with the DPP-4 inhibitor group.

■ **CV endpoints.** Similarly, the SGLT-2 inhibitor (HR=0.79; 95% CrI, 0.69-0.91; absolute RD= -0.8%; NNT=125) and GLP-1 agonist (HR=0.85; CrI, 95% 0.77-0.94; absolute RD= -0.5%; NNT=200) groups had a reduction in CV mortality compared with the control groups, while those in the DPP-4 inhibitor group experienced no effect. Additionally, those taking SGLT-2 inhibitors had lower rates of HF events (HR=0.62; 95% CrI, 0.54-0.72; absolute RD= -1.1%; NNT=91) and MIs (HR=0.86; 95% CrI, 0.77-0.97; absolute RD= -0.6%; NNT=167) than those in the control groups. They also had lower rates of HF than those taking GLP-1 agonists (HR=0.67; 95% CrI, 0.57 to 0.80; absolute RD= -0.9; NNT=111) or DPP-4 inhibitors (HR=0.55; 95% CrI, 0.46-0.67; absolute RD= -1.1%; NNT=91). Neither the GLP-1 agonist groups nor the DPP-4 inhibitor groups saw lower rates of HF or MI than the control groups.

■ **Adverse effects.** DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors were all associated with a small increased risk for hypoglycemia compared with the control groups, but there were no significant differences between drug classes. All agents resulted in an increased risk for adverse events leading to trial withdrawal compared with the control groups (GLP-1 agonists, HR=2; 95% CrI, 1.70-2.37; absolute RD=4.7%; number needed to harm [NNH]=21; SGLT-2 inhibitors, HR=1.8; 95% CrI, 1.44-2.25; absolute RD=5.8%; NNH=17; and DPP-4 inhibitors, HR=1.93; 95% CrI, 1.59-2.35; absolute RD=3.1%; NNH=32).

When compared with the control groups, the SGLT-2 inhibitor group was associated with an increased risk for genital infection (relative risk [RR]=4.19; 95% confidence interval [CI], 3.45-5.09; absolute RD=6%; NNH=16), but not of urinary tract infection or lower limb amputation, although the authors

noted high heterogeneity among studies with regard to the limb amputation outcome. DPP-4 inhibitors were associated with an increased risk for acute pancreatitis (RR=1.58; 95% CI, 1.04-2.39; absolute RD=0.1%; NNH=1000) compared with control groups.

WHAT'S NEW

SGLT-2s: Lower mortality, fewer heart failure events

This meta-analysis concludes that when compared with placebo or no treatment, the use of SGLT-2 inhibitors or GLP-1 agonists is associated with lower all-cause mortality and lower CV mortality than is the use of DPP-4 inhibitors. Additionally, SGLT-2 inhibitors are associated with lower rates of HF events than GLP-1 agonists or DPP-4 inhibitors.

CAVEATS

A lack of head-to-head RCTs

This study was a network meta-analysis that included many trials, the majority of which compared SGLT-1 inhibitors, GLP-1 agonists, and DPP-4 inhibitors with controls rather than to one another. Thus, the findings are not derived from a robust base of head-to-head RCTs involving the 3 classes of medication.

However, there was relatively low heterogeneity among the studies included (I²=12), which lends strength to the meta-analysis.⁶ Patients with the highest baseline CV risk likely gleaned the greatest benefits from these treatments and may have driven much of the observed mortality reduction. This may limit the generalizability of the results to people with low CV risk. The comparative effectiveness and risk for adverse effects among individual medications within each class is unknown because

the analysis was completed by drug class in order to adequately power the study to detect treatment effects.

CHALLENGES TO IMPLEMENTATION

Cost, adverse effects, and formulation may represent challenges

The cost of SGLT-2 inhibitors and GLP-1 agonists may present challenges to patients wishing to use these options. Additionally, the increased risk for genital infections with SGLT-2 inhibitors, and of overall adverse effects (many of which were gastrointestinal) with GLP-1 agonists, must be considered. Lastly, the injectable formulation of GLP-1 agonists may present a barrier to patients' ability and willingness to effectively administer these agents.

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For another diabetes-related PURL, see “Bariatric surgery + medical therapy: Effective Tx for T2DM?” on page 102.



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