Two New Drug Classes Tied to Better Survival in Type 2 Diabetes

Marlene Busko
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Patients with type 2 diabetes who did not achieve adequate glycemic control with metformin had improved survival during follow-up if they received add-on therapy with a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide 1 (GLP-1) agonist rather than a dipeptidyl peptidase-4 (DPP-4) inhibitor or control (placebo or no treatment), in a network meta-analysis that indirectly compared these three drug classes.

Rates of heart failure and myocardial infarction (MI) were also lower in patients who received SGLT-2 inhibitors rather than controls.

But GLP-1 agonists were associated with a higher rate of (largely gastrointestinal) adverse events leading to withdrawal from the trials.

These findings, by Sean L Zheng, MB, from the National Heart and Lung Institute at Imperial College, London, UK, and colleagues were published April 17 in JAMA.

"Based on these findings, SGLT-2 inhibition and GLP-1 agonists may be preferred over DPP-4 inhibitors as add-on therapies to metformin," according to an accompanying video.

In fact, "of the three classes tested, SGLT-2 inhibition may be preferred over the incretin-based therapies based on their association with lower mortality and their favorable adverse event profile," Zheng and colleagues indicate.

However, they caution that SGLT-2 inhibitors were also associated with increased risk of genital infections, and canagliflozin, but not empagliflozin, was linked with a significant increase in lower-limb amputations. So "our analyses do not rule out the possibility of a clinically meaningful safety signal for SGLT-2 inhibitors and amputation," they warn.

On the other hand, DPP-4 inhibitors were linked with a greater risk of pancreatitis.

Thus, "careful treatment selection may be necessary to minimize these outcomes in at-risk patients," Zheng and colleagues advise. Moreover, because the network meta-analysis was an observational study, it cannot determine cause and effect, and the findings would have to be confirmed in further research.

Increasingly Prescribed, But Which Drug Class Is Best?

"The three drug classes assessed here are being increasingly prescribed," for type 2 diabetes, said Zheng in a statement by Imperial College, "yet until now there have been no clinical trials studying how these drugs compare to each other, and which type of drug could be the best option for patients."

He and his coauthors searched for studies published up until October 2017 and identified 236 randomized clinical trials in 176,310 patients.

There were 65 trials of SGLT-2 inhibitors, 83 trials of DPP-4 inhibitors, and 65 trials of GLP-1 agonists that compared these agents with a control, and 23 studies that directly compared two drug classes.

Zheng and colleagues aimed to investigate the rate of all-cause mortality (the primary outcome) as well as cardiovascular mortality, heart failure, MI, stroke, adverse events, and hypoglycemia, with use of the three drug classes.

Almost half of the patients came from nine cardiovascular outcome trials: EMPA-REG OUTCOME and CANVAS with SGLT-2 inhibitors; ELIXA, LEADER, SUSTAIN-6, and EXSCEL with GLP-1 agonists; and SAVOR-TIMI 53, EXAMINE, and TECOS with DPP-4 inhibitors.

Overall, during follow-up, patients who received an SGLT-2 inhibitor had a 1% absolute lower rate of death and a 0.8% lower rate of cardiovascular death than patients who received control therapy.

Patients who received a GLP-1 agonist, which are subcutaneously injected, had a "more modest" 0.6% lower risk of death and a 0.5% lower risk of cardiovascular death during follow-up than patients who received control therapy.

However, rates of these two outcomes were similar in patients who received a DPP-4 inhibitor or control therapy.
Expressed another way, patients who received an SGLT-2 inhibitor or a GLP-1 agonist were less likely to die of all causes during follow-up than patients who received control therapy (hazard ratio [HR], 0.80 and 0.88, respectively).

Similarly, patients who received an SGLT-2 inhibitor or a GLP-1 agonist were less likely to die of cardiovascular causes during follow-up than patients who received a DPP-4 inhibitor (HR, 0.78 and 0.0.86, respectively).

The researchers acknowledge a limitation is that they assume there are class effects on mortality. But while, for example, all-cause mortality during follow-up was reduced with GLP-1 agonists liraglutide (in LEADER) and semaglutide (in SUSTAIN-6) it was not with lixisenatide (in ELIXA) or exenatide (in EXSCEL).

Also, the trials may have been too short to detect cardiovascular mortality in patients at low cardiovascular risk, and the meta-analysis did not examine how glycemic control affected mortality.

"Crowded Market" of Second-Line Diabetes Drugs

Separately, an analysis of US sales figures for 2017 shows that sales of GLP-1 agonists rose by 32% in 2017 compared with 2016. Sales of SGLT-2 inhibitors grew by 24% during that time, but sales of DPP-4 inhibitors were flat.

The SGLT-2 inhibitor sales were likely boosted on the one hand by a new US indication for empagliflozin (Jardiance, Lilly/Boehringer Ingelheim), that of improving cardiovascular survival, but were probably diminished by a black-box warning mandated by the Food and Drug Administration for amputations for canagliflozin (Invokana, Janssen).

Meanwhile, Zheng and colleagues say their analysis will help inform patient–physician discussions.

"Our hope is that in the crowded market that is diabetes medications, patients and their doctors have the necessary information to allow them to make informed decisions about long-term treatment strategies," said Zheng.

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