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# Need an add-on to metformin? Consider this

Sulfonylureas have been the preferred add-on therapy to metformin for T2DM, but a study finds that DPP-4s have lower risks of death, CV events, and hypoglycemia.

**PRACTICE CHANGER**

Consider a dipeptidyl peptidase-4 inhibitor before a sulfonylurea for patients with type 2 diabetes mellitus who require therapy in addition to metformin.

Ou SM, Shih CJ, Chao PW, et al. Effects of clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. *Ann Intern Med.* 2015;163:663-672.<sup>1</sup>

**STRENGTH OF RECOMMENDATION**

**B:** Based on limited-quality, patient-oriented data from a high-quality, population-based cohort study.

**ILLUSTRATIVE CASE**

A 58-year-old woman with type 2 diabetes mellitus (T2DM) and heart failure returns to your office for follow-up of her T2DM. She has been on the maximum dose of metformin alone for the past 6 months, but her HbA1c is now 7.8%. She is keen to avoid injections. What do you recommend next?

**T**here is surprisingly little consensus about what to add to metformin for patients with T2DM who require a second agent to achieve their glycemic goal. Attainment of glycemic control earlier in the course of the disease may lead to reduced overall cardiovascular risk, so the choice of a second drug is an important one.<sup>2</sup> While metformin is well established as initial pharmacotherapy because of its proven mortality benefit, wide availability, and low cost, no second-choice

drug has amassed enough evidence of benefit to emerge as the add-on therapy of choice.

Furthermore, the professional societies and associations are of little assistance. Dual therapy recommendations from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes do not denote a specific preference, and while the American Association of Clinical Endocrinologists/American College of Endocrinology do suggest a hierarchy of choices, it is based upon expert consensus recommendation.<sup>3,4</sup>

## Sulfonylureas can cause hypoglycemia and weight gain

Options for add-on therapy include sulfonylureas, thiazolidines, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and insulin. Providers have frequently prescribed a sulfonylurea after metformin because such agents are low in cost, have long-term safety data, and are effective at lowering HbA1c. Sulfonylureas work by directly stimulating insulin secretion by pancreatic beta cells in a glucose-independent manner. But as a 2010 meta-analysis revealed, they carry significant risks of hypoglycemia (relative risk [RR]=4.57; 95% confidence interval [CI], 2.11-11.45) and weight gain (2.06 kg; 95% CI, 1.15-2.96) compared to placebo.<sup>5</sup>

DPP-4 inhibitors, on the other hand, work by inducing insulin secretion in a glu-

cose-dependent manner through an incretin mechanism. Combined with metformin, they provide glucose control similar to that achieved with the combination of a sulfonylurea and metformin.<sup>6</sup> DPP-4 inhibitors were initially found to be associated with fewer cardiovascular events and less hypoglycemia than sulfonylureas, but were subsequently linked to an increased risk of hospitalization for heart failure.<sup>7</sup>

This latest large observational study provides more evidence on the effects of DPP-4s when added to metformin.<sup>1</sup>

### STUDY SUMMARY

#### DPP-4s as effective as sulfonylureas with no increased risks

This population-based observational cohort study compared DPP-4 inhibitors and sulfonylureas when added to metformin for the treatment of T2DM.<sup>1</sup> Outcomes were all-cause mortality, major adverse cardiovascular events (MACEs; defined as hospitalization for ischemic stroke or myocardial infarction [MI]), and hospitalizations for either heart failure or hypoglycemia. Using the National Health Insurance Research Database in Taiwan, the study included data on over 70,000 patients ages 20 years and older with a diagnosis of T2DM. Individuals adherent to metformin were considered to be enrolled into the cohort on the day they began using either a DPP-4 inhibitor or a sulfonylurea, in addition to metformin.

The researchers collected additional data on the enrolled individuals regarding socioeconomic factors, urbanization, robustness of the local health care system, Charlson Comorbidity Index, adapted Diabetes Complications Severity Index, and other comorbidities and medications that could affect the outcomes of interest. Using these data, enrollees were matched by propensity score into 10,089 pairs consisting of a DPP-4 inhibitor user and a sulfonylurea user.

After a mean follow-up period of 2.8 years, the authors of the study used Cox regression analysis to evaluate the relative hazards of the outcomes. Subgroup analysis performed by age, sex, Charlson Comorbidity Index, hypertension, chronic kidney dis-

ease, hospitalization for heart failure, MI, and cerebrovascular disease yielded results similar to those of the primary analysis for each outcome. Additionally, similar results were obtained when the data were analyzed without propensity-score matching.

■ **The researchers found that** users of DPP-4 inhibitors—when compared to users of sulfonylureas—had a lower risk of all-cause mortality (366 vs 488 deaths; hazard ratio [HR]=0.63; 95% CI, 0.55-0.72; number needed to treat [NNT]=117), MACE (209 vs 282 events; HR=0.68; 95% CI, 0.55-0.83; NNT=191), ischemic stroke (144 vs 203 strokes; HR 0.64; 95% CI, 0.51-0.81; NNT=246), and hypoglycemia (89 vs 170 events; HR=0.43; 95% CI, 0.33-0.56; NNT=201). Further, there were no significant differences in either the number of MIs that occurred (69 vs 88 MIs; HR=0.75; 95% CI, 0.52-1.07) or in the number of hospitalizations for heart failure (100 vs 100 events; HR=0.78; 95% CI, 0.57-1.06) between users of DPP-4 inhibitors and those of sulfonylureas.

### WHAT'S NEW

#### Lower risks of death, CV events, and hypoglycemia

This study found that when added to metformin, DPP-4 inhibitors were associated with lower risks for all-cause mortality, cardiovascular events, and hypoglycemia when compared to sulfonylureas. Additionally, DPP-4 inhibitors did not increase the risk of hospitalization for heart failure. A recent multicenter observational study of nearly 1.5 million patients on the effects of incretin-based treatments, including both DPP-4 inhibitors and GLP-1 agonists, similarly found no increased risk of hospitalization for heart failure, with DPP-4 inhibitors compared to other combinations of oral T2DM agents.<sup>8</sup>

### CAVEATS

#### Did unmeasured confounders play a role?

Unmeasured confounders potentially bias all observational population cohort results. In this study, in particular, there may have been unmeasured, but significant, patient factors that providers used to choose diabetes medi-



**Combined with metformin, DPP-4s provide glucose control similar to that achieved with the combination of a sulfonylurea and metformin.**

cations. Also, the study did not evaluate diabetes control, although previous studies have shown similar glucose control between sulfonylureas and DPP-4 inhibitors when they were added to metformin.<sup>6</sup>

Another caveat is that the results from this study group may not be fully generalizable to other populations due to physiologic differences. People of Asian ancestry are at risk of developing T2DM at a lower body mass index than people of European ancestry, which could affect the outcomes of interest.<sup>9</sup>

Furthermore, the study did not evaluate outcomes based on whether patients were taking first-, second-, or third-generation sulfonylureas. Some sulfonylureas, such as glyburide, carry a higher risk of hypoglycemia, which could bias the results if a large number of patients were taking them.<sup>10</sup>

Lastly, the study only provides guidance when choosing between a sulfonylurea and a DPP-4 inhibitor for second-line pharmacotherapy. The GRADE trial, due to be completed in 2023, is comparing sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, and insulin as add-on medications to metformin, and may provide more data on which to base treatment decisions.<sup>11</sup>

**CHALLENGES TO IMPLEMENTATION**

**DPP-4s have a higher price tag than sulfonylureas**

Sulfonylureas and DPP-4 inhibitors are both available as generic medications, but the cost of DPP-4 inhibitors remains significantly higher.<sup>12</sup> Higher copays and deductibles could affect patient preference. Furthermore, for patients without health insurance, sulfonylureas are available on the discounted drug

lists of many major retailers, while DPP-4 inhibitors are not. **JFP**

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**Use of DPP-4s appears to have a lower risk of all-cause mortality, major adverse cardiovascular events, ischemic stroke, and hypoglycemia, compared to use of sulfonylureas.**

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