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 for death, CV events, and hypoglycemia.

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PRACTICE CHANGER

For patients with type 2 diabetes mellitus (T2DM) who require therapy in addition to metformin, consider a dipeptidyl peptidase-4 (DPP-4) inhibitor before a sulfonylurea.

STRENGTH OF RECOMMENDATION

B: Based on limited-quality, patient-oriented data from a high-quality, population-based cohort study.[1]

A 58-year-old woman with T2DM and heart failure returns to your office for follow-up. She has been on the maximum dose of metformin alone for the past six months, but her A1C is now 7.8%. She wants to avoid injections. What do you recommend?

There is surprisingly little consensus about what to add to metformin for patients with T2DM who require a second agent to achieve their glycemic goal. Attaining glycemic control earlier in the course of the disease may lead to reduced overall cardiovascular (CV) risk, so the choice of a second drug is an important one.[2] While the proven mortality benefit, wide availability, and low cost of metformin make it well-established as initial pharmacotherapy, no second-choice drug has amassed enough evidence of benefit to become the add-on therapy of choice.

The professional societies are of little assistance; dual-therapy recommendations from the American Diabetes Association and the European Association for the Study of Diabetes do not specify a preference.[3] Although the American Association of Clinical Endocrinologists/American College of Endocrinology suggest a hierarchy of choices, it is based on expert consensus recommendations.[4]

A look at the options

Options for add-on therapy include sulfonylureas, thiazolidines, DPP-4 inhibitors, sodium glucose cotransporter 2 inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and insulin. Providers frequently prescribe sulfonylureas after metformin because they are low in cost, have long-term safety data, and are effective at lowering A1C. They work by directly stimulating insulin secretion via pancreatic ß-cells in a glucose-*independent* manner. But as a 2010 meta-analysis revealed, sulfonylureas carry significant risk for hypoglycemia (relative risk [RR], 4.57) and weight gain (average, 2.06 kg), compared to placebo.[5]

DPP-4 inhibitors, on the other hand, induce insulin secretion in a glucose-*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.[6] DPP-4 inhibitors were initially found to be associated with fewer CV events and less hypoglycemia than sulfonylureas but were subsequently linked to an increased risk for heart failure–related hospitalization.[7]

A recent study provides more data on the effects of DPP-4s added to metformin.[1]

STUDY SUMMARY

DPP-4s as effective, less risky

This observational cohort study compared DPP-4 inhibitors and sulfonylureas when

combined with metformin for the treatment of T2DM.[1] Outcomes were all-cause mortality, major adverse CV events (defined as hospitalization for ischemic stroke or myocardial infarction [MI]), and hospitalizations for either heart failure or hypoglycemia. The study included data from the National Health Insurance Research Database in Taiwan on more than 70,000 patients (ages 20 and older) with diagnosed T2DM. Individuals adherent to metformin were considered to be enrolled in 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 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. Participants were then matched by propensity score into 10,089 pairs, each consisting of one DPP-4 inhibitor user and one sulfonylurea user.

After mean follow-up of 2.8 years, the investigators used Cox regression analysis to evaluate the relative hazards of the outcomes. Subgroup analysis stratified by age, sex, Charlson Comorbidity Index, hypertension, chronic kidney disease, hospitalization for heart failure, MI, and cerebrovascular disease yielded results similar to those of the primary analysis for each outcome. Similar results were also obtained when the data were analyzed without propensity-score matching.

The researchers found that users of DPP-4 inhibitors—compared with those who used sulfonylureas—had a lower risk for all-cause mortality (366 vs 488 deaths; hazard ratio [HR], 0.63; number needed to treat [NNT], 117), major cardiac events (209 vs 282 events; HR, 0.68; NNT, 191), ischemic stroke (144 vs 203 strokes; HR, 0.64; NNT, 246), and hypoglycemia (89 vs 170 events; HR, 0.43; NNT, 201). There were no significant differences in the occurrence of MIs (69 vs 88 MIs; HR, 0.75) or the number of hospitalizations for heart failure (100 vs 100 events; HR, 0.78) between the two groups.

WHAT'S NEW

Lower risks for 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, CV events, and hypoglycemia when compared to sulfonylureas. Additionally, DPP-4 inhibitors did not increase the risk for heart failure hospitalization. A recent multicenter observational study of nearly 1.5 million patients on the effects of incretin-based treatments (including DPP-4 inhibitors and GLP-1 agonists) found no increased risk for heart failure hospitalization with DPP-4 inhibitors, compared to other combinations of oral T2DM agents.[8]

CAVEATS

Did unmeasured confounders play a role?

Unmeasured confounders potentially bias all observational population cohort results. In this particular study, there may have been unmeasured but significant patient factors that providers used to choose diabetes medications. Also, the study did not evaluate diabetes control, although previous studies have shown similar glucose control between sulfonylureas and DPP-4 inhibitors when added to metformin.[6]

Another caveat is that the results from this study group may not be generalizable to other populations due to physiologic differences. People of Asian ancestry are at risk for T2DM at a lower BMI than people of European ancestry, which could affect the outcomes of interest.[9]

Furthermore, the study did not evaluate outcomes based on whether patients were taking first-, second-, or third-generation sulfonylureas. Some sulfonylureas (eg, glyburide) carry a higher risk for hypoglycemia, which could bias the results.[10]

Lastly, the study only provides guidance when choosing between a sulfonylurea and a DPP-4 inhibitor for secondline 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;

it may provide more data on which to base treatment decisions.[11]

CHALLENGES TO IMPLEMENTATION

DPP-4s are more expensive

Sulfonylureas and DPP-4 inhibitors are both available as generic medications, but the cost of DPP-4 inhibitors remains significantly higher.[12] Higher copays and deductibles could affect patient preference. For patients without health insurance, sulfonylureas are available on the discounted drug lists of many major retailers, while DPP-4 inhibitors are not. **CR**

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