No Clear Survival or Cardiovascular Benefits Seen Among Diabetes Drugs shown in large metastudy

Eight different diabetes drug classes examined in a meta-analysis failed to demonstrate improved cardiovascular or all-cause mortality compared with placebo.

Researchers analyzed 301 randomized clinical trials of patients with type 2 diabetes, and found that, metformin outperformed some other drug classes for its effect on hemoglobin A1c levels, there were no significant differences in mortality -- including when placebo was included as a drug class.

Of all the classes, sodium-glucose cotransporter-2 (SGLT2) drugs were associated with the lowest odds of hypoglycemia when added to metformin (odds ratio 0.12, 95% CI 0.008-0.18; risk difference -22%), but when added to both metformin and sulfonylurea, glucagon-like peptide-1 receptor agonists had the lowest odds (OR 0.60, 95% CI 0.39-0.94; risk difference 10%), according to lead author Suetonia Palmer, PhD, at the University of Otago Christchurch in New Zealand.

Palmer and colleagues published their findings on Tuesday in the *Journal of the American Medical Association*.

"A central finding in this meta-analysis was that despite more than 300 available clinical trials involving nearly 120,000 adults and 1.4 million patient-months of treatment, there was limited evidence that any glucose-lowering drug stratified by coexisting treatment prolonged life expectancy or prevented cardiovascular disease," the authors wrote.

Four classes of drugs were associated with higher HbA1c levels when compared to metformin:

- Sulfonylurea (standardized mean difference 0.18, 95% CI 0.01-0.34)
- Thiazolidinedione (0.16, 95% CI 0.00-0.31)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (0.33, 95% CI 0.13-0.52)
- α-Glucosidase inhibitor (0.35, 95% CI 0.12-0.58)

In addition, of all the drugs, sulfonylurea (OR 3.13, 95% CI 2.39-4.12; risk difference 10%, 95% CI 7%-13%) and basal insulin (OR 17.9, 95% CI 1.97-162; RD 10%, 95% CI 0.08%-20%) were associated with the highest risk of hypoglycemia.

Most (177) of the trials were of drugs given as monotherapy; in 109 trials the drugs were given as an add-on to metformin, and 29 trials of drugs added to metformin plus sulfonylurea. There were nearly 120,000 patients included in the trials in total.

There was no evidence of differences in the association between the drug classes with serious adverse events, myocardial infarction, or stroke. However, "Considerable uncertainty about the association of drug treatment with cardiovascular mortality existed within trial evidence, largely because of few events in most available studies," the authors warned.

All of the trials included in the study were randomized and lasted at least 24 weeks. In addition to the classes already mentioned, meglitinide was also included, as was placebo. Only trials that had publicly available data as of March 21, 2016 were included in the meta-analysis. Cardiovascular mortality was the primary end-point, and all-cause mortality, myocardial infarction, stroke, HbA1c levels, and treatment failure were secondary end-points. Safety end-points were also included.

All of the monotherapies were associated with lower HbA1c levels versus placebo, but thiazolidinedione, DPP-4 inhibitors, and α-glucosidase inhibitors were associated with higher HbA1c levels compared with metformin. Placebo was most associated with treatment failure (OR versus metformin 3.83, 95% CI 2.88-5.10; RD 11%), and GLP-1 receptor agonist monotherapy was associated with a lower body weight compared with metformin.
There were no data for basal insulin and GLP-1 receptor agonists as a monotherapy for cardiovascular mortality. For dual therapies, all classes were associated with lower odds of hypoglycemia than metformin plus sulfonylurea; the GLP-1 class was ranked best in avoiding hypoglycemia, and thiazolidinediones were ranked worst.

The risk of bias was classified as either high or unclear for most of the trials for reasons including random sequence generation (208 trials), concealment of treatment allocation (232 trials), masking outcome assessment (281 trials), and selective reporting of outcomes (172 trials). In 63% of the trials, the trial sponsor was involved in authorship, data management, or both.

The authors wrote that their findings are consistent with guidelines from the American Diabetes Association, which recommend that metformin monotherapy be used for the initial treatment of patients with type 2 diabetes. "Based on this review, clinicians and patients may prefer to avoid sulfonylureas or basal insulin for patients who wish to minimize hypoglycemia, choose GLP-1 receptor agonists when weight management is a priority, or consider SGLT-2 inhibitors based on their favorable combined safety and efficacy profile," the authors wrote. Two recent studies, EMPA-REG and LEADER, have shown two diabetes drugs to be associated with lower mortality. But the authors added that neither of those trials analyzed treatment as a monotherapy or added to metformin. "Future trials might prioritize comparisons of SGLT-2 inhibitors against metformin or added to metformin to compare specific dual-therapy regimens," wrote Palmer and colleagues.

Relatively few studies reported cardiovascular mortality and most of those had zero or very few events, which is a limitation to the meta-analysis, they added. The authors didn't examine triple therapy treatments, and the analysis was not adjusted for baseline kidney function. Most of the studies were relatively short-term and were conducted in higher-income countries.
Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes

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ABSTRACT

Importance Numerous glucose-lowering drugs are used to treat type 2 diabetes.

Objective To estimate the relative efficacy and safety associated with glucose-lowering drugs including insulin.

Data Sources Cochrane Library Central Register of Controlled Trials, MEDLINE, and EMBASE databases through March 21, 2016.

Study Selection Randomized clinical trials of 24 weeks’ or longer duration.

Data Extraction and Synthesis Random-effects network meta-analysis.

Main Outcomes and Measures The primary outcome was cardiovascular mortality. Secondary outcomes included all-cause mortality, serious adverse events, myocardial infarction, stroke, hemoglobin A1c (HbA1c) level, treatment failure (rescue treatment or lack of efficacy), hypoglycemia, and body weight.

Results A total of 301 clinical trials (1 417 367 patient-months) were included; 177 trials (56 598 patients) of drugs given as monotherapy; 109 trials (53 030 patients) of drugs added to metformin (dual therapy); and 29 trials (10 598 patients) of drugs added to metformin and sulfonylurea (triple therapy). There were no significant differences in associations between any drug class as monotherapy, dual therapy, or triple therapy with odds of cardiovascular or all-cause mortality. Compared with metformin, sulfonylurea (standardized mean difference [SMD], 0.18 [95% CI, 0.01 to 0.34]), thiazolidinedione (SMD, 0.16 [95% CI, 0.00 to 0.31]), DPP-4 inhibitor (SMD, 0.33 [95% CI, 0.13 to 0.52]), and α-glucosidase inhibitor (SMD, 0.35 [95% CI, 0.12 to 0.58]) monotherapy were associated with higher HbA1c levels. Sulfonylurea (odds ratio [OR], 3.13 [95% CI, 2.39 to 4.12]; risk difference [RD], 10% [95% CI, 7% to 13%]) and basal insulin (OR, 17.9 [95% CI, 1.97 to 162]; RD, 10% [95% CI, 0.08% to 20%]) were associated with greatest odds of hypoglycemia. When added to metformin, drugs were associated with similar HbA1c levels, while SGLT-2 inhibitors offered the lowest odds of hypoglycemia (OR, 0.12 [95% CI, 0.08 to 0.18]; RD, −22% [−27% to
When added to metformin and sulfonylurea, GLP-1 receptor agonists were associated with the lowest odds of hypoglycemia (OR, 0.60 [95% CI, 0.39 to 0.94]; RD, −10% [95% CI, −18% to −2%]).

Conclusions and Relevance Among adults with type 2 diabetes, there were no significant differences in the associations between any of 9 available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality. Metformin was associated with lower or no significant difference in HbA1c levels compared with any other drug classes. All drugs were estimated to be effective when added to metformin. These findings are consistent with American Diabetes Association recommendations for using metformin monotherapy as initial treatment for patients with type 2 diabetes and selection of additional therapies based on patient-specific considerations.