MedicalXpress

Diabetes drug, metformin, lowers risk of heart disease deaths better than sulfonylureas

April 18 2016

A new analysis of 204 studies involving more than 1.4 million people suggests that metformin, the most frequently prescribed stand-alone drug for type 2 diabetes, reduces the relative risk of a patient dying from heart disease by about 30 to 40 percent compared to its closest competitor drug, sulfonylurea.

The study, designed to assess the comparative—not absolute or individual—benefits and risks of more than a dozen FDA-approved drugs for lowering blood sugar in type 2 diabetes, is described in the April 19, 2016 issue of the *Annals of Internal Medicine*. Diabetes now affects almost 10 percent of the U.S. population and poses a growing public health threat, and most people will eventually need drug treatment, the researchers say.

"Metformin looks like a clear winner," says Nisa Maruthur, M.D., M.H.S., assistant professor of medicine at the Johns Hopkins University School of Medicine. "This is likely the biggest bit of evidence to guide treatment of type 2 diabetes for the next two to three years."

Maruthur, the lead author on the meta-analysis, notes that cardiovascular fatalities—heart attacks and strokes—are major risks for people with uncontrolled blood sugar, but it has never been clear if one diabetes drug is better than another at lowering these fatalities. Other diabetes-related complications include blindness, kidney failure and limb amputations.

This review, Maruthur says, provides a much-needed update to two previous analyses, the last one published in 2011. Since then, researchers have published more than 100 new studies comparing the effectiveness of various blood sugar-lowering drugs, and several new drugs have also come on the market since the last report.

Of the total 204 studies analyzed, 50 spanned several continents, while others were conducted across Europe, Asia and the United States. Most of the studies were short term, with only 22 mostly observational studies lasting more than two years. Participants in the studies were generally overweight with uncontrolled blood sugar levels. Many studies excluded the elderly and those with significant health problems. Just shy of half of the studies made no mention of race or ethnicity. When researchers did report that information, only 10 to 30 percent of participants were nonwhite.

Maruthur says the new analysis not only looked at cardiovascular disease but also other drug effects, including glucose control, and common side effects, such as weight gain, hypoglycemia and gastrointestinal problems. Because the majority of patients with type 2 diabetes end up using multiple blood sugar-lowering drugs, Maruthur and her team also evaluated how the drugs performed when used alone or in combination. While some of the various studies' participants were on insulin, this injectable drug was only evaluated when used in combination with other drugs.

Among other findings, the new review revealed that DPP-4 inhibitors, a class of anti-diabetic drugs that were very new at the time of the 2011 review, were clearly less effective at lowering blood sugar levels compared to metformin and sulfonylureas.

In terms of side effects, a new class of drugs known as SGLT-2 inhibitors, which work by shuttling excess glucose out of the body

through urine, caused yeast infections in 10 percent of users, a side effect unique to this drug, Maruthur says. However, SGLT-2 inhibitors, along with another drug class known as GLP-1 receptor agonists, helped patients lose weight. Sulfonylureas, on the other hand, caused weight gain and resulted in the highest rates of hypoglycemia, or too-low blood sugar, among the oral medications.

Cautioning that such meta-analyses can be limited because of differences in research protocols and measurements across studies, Maruthur and her colleagues took steps to ensure that only studies using similar methods were combined. Also, they excluded from their analysis any studies that included patients taking additional, nonstudy diabetes drugs.

Overall, Maruthur says, the results indicate that metformin, which has been around since the late 1990s, works just as well, if not better, than sulfonylureas, which have been on the market since the late 1950s/1960s, and diabetes drugs that have appeared on the market more recently. She says the new findings are in line with the current recommendation that metformin be used as a first-line therapy. The real question arises, Maruthur says, when patients and doctors must choose a second drug to be used in combination with the metformin.

"The medications all have different benefits and side effects, so the choice of second-line medications must be based on an individual patient's preferences," Maruthur says.

Maruthur and her team's work will be published alongside the report they wrote for the Agency for Healthcare Research and Quality, the funding agency for the study, detailing the hundreds of studies included in Maruthur's analysis and an exhaustive summary. Both the American College of Physicians and the Veterans Association plan to use these publications to update their guidelines.

The cost of diabetes drugs is a major consideration when prescribing. While metformin is available as a relatively cheap generic, many newer drugs carry a hefty price tag. In 2014, per-person spending was higher for diabetes drugs for any other class of traditional drugs, in part because over half the prescriptions filled for diabetes were for nongenerics.

Provided by Johns Hopkins University School of Medicine