Medical Xpress

Which diabetes meds are best for reducing heart attack and stroke risk?

August 28 2024, by Eva Cornman

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Almost 500 million adults around the world are living with type 2 diabetes, and over 200 million of those take metformin, an oral medication that reduces blood sugar (glucose) levels. Despite

metformin's widespread use, many type 2 diabetes patients eventually require second-line medications to maintain control of their blood sugar levels when metformin's efficacy fades.

But these second-line medications can impact more than just blood sugar . Growing evidence suggests that these treatments could benefit type 2 diabetes patients who also have cardiovascular disease by reducing their risk for heart attack and stroke.

Despite these known positive effects, the main second-line diabetes medications—older drugs such as sulfonylureas (SUs) and dipeptidyl peptidase-4s (DPP-4s), and newer drugs including glucagon-like peptide-1 (GLP-1RAs) analogs and sodium-glucose cotransporter 2 (SGLT-2is) inhibitors—have never been compared against each other for their cardiovascular benefits.

"The challenge now, for clinicians, is to decide which therapy to use in a patient, especially those with an elevated risk of cardiovascular adverse events," says Rohan Khera, MD, MS, assistant professor of medicine (cardiovascular medicine) and director of the Cardiovascular Data Science (CarDS) Lab at Yale School of Medicine (YSM), and assistant professor of biostatistics (health informatics) at the Yale School of Public Health.

"Some of the older drugs were never even tested for whether they were safe and effective or actually improve cardiovascular risk, and the newer drugs were never compared head-to-head."

Khera, his co-principal investigator Marc Suchard, MD, Ph.D., at UCLA, and CarDS Lab members Arya Aminorroaya, MD, MPH; Lovedeep Dhingra, MBBS; Phyllis Thangaraj, MD, Ph.D.; and Aline Pedroso Camargos, Ph.D., along with a large international team of scientists, published the first study directly comparing these second-line

diabetes drugs and their cardiovascular benefits in the *Journal of the American College of Cardiology* on August 26.

The study draws from 10 international datasets and spans nearly two decades of data from almost 1.5 million patients with type 2 diabetes and cardiovascular disease. The study, Khera says, is exciting not only for its clinically relevant findings, but also for the rigorous scientific methods that the team used.

Newer second-line diabetes medications reduce cardiovascular risk better than older ones

Using datasets from the United States, Germany, Spain, and the United Kingdom, Khera and his team compared how well each of the four different second-line diabetes medication classes reduced adverse cardiovascular events, including heart attack, stroke, and death, among type 2 diabetes patients with cardiovascular disease.

They found that the newer SGLT-2i and GLP-1RA drugs were the most effective at reducing cardiovascular risk, while the older sulfonylurea drugs were the least effective: SGLT-2is and GLP-1RAs had 24% and 28% lower risk for cardiovascular events than sulfonylureas, respectively.

Sulfonylureas, such as glipizide and glimepiride, are among the most commonly used second-line diabetes medications, and Khera believes this finding should be taken into clinical consideration, especially since the newer drugs contain blood glucose levels as effectively as the old and have lower risk for adverse side effects such as hypoglycemia and weight gain.

"The older generation drugs do seem to be inferior on cardiovascular

risk reduction," he says. "I think that's an important key takeaway while we make these decisions in practice, especially among those who have high risk, whether continued use of some of the old drugs is appropriate."

Scientific rigor in comparative effectiveness research

It's not just the study's clinical findings that were significant. The scientific methodology of the study was equally important, Khera says.

Khera and his collaborators performed a "comparative effectiveness study," a research method that compares evidence of the benefits and harms of different treatment methods.

Unlike a clinical trial, for which scientists control the conditions of the experiment, a comparative effectiveness study is a type of observational research, which means that there tend to be more "confounding" variables, such as treatment timing or treatment choices and availability, that could influence the results.

Khera's study used some of the most advanced methods in comparative effectiveness research to account for some of those confounding factors. For one, by using multiple datasets from across the world, they established a large enough sample size to help reduce scientific bias.

"The value of including a multinational collaborative like this is that, one, you get large enough sample sizes so that you are not underpowered," Khera says. "Second, it ensures that there is enough variation in practice across sites that some of the challenges that occur with confounding factors, such as who should get the drug, is different at each site."

Additionally, Khera and his team emulated what a clinical trial in this

domain would look like by only including patients at the point of when they started a second-line drug. They also used "federated analysis," an approach where the collaborating institutions mapped their datasets onto a standard structure that allowed them to run the analyses locally, and not face any complications or privacy issues associated with sharing health data across sites.

The team also applied rigorous statistical testing by checking the data to see whether the drugs were statistically associated with completely unrelated outcomes.

For example, if the researchers had found an association between taking a particular diabetes medication and having abnormal posture, then they would not have been able to confidently say that participants taking the medication were less likely to experience adverse cardiovascular events.

All of the team's methodology, programming codes, and results were made available to the public for other scientists to use and adapt for their own research. By performing this study with such scientific rigor and transparency, Khera hopes he has set an example for future comparative effectiveness research—a type of research that he believes could be vitally important when making suggestions for clinical practice.

"We need more studies like these that are done more rigorously, and we need to find a mechanism to incorporate them when the FDA and other guidelines make determinations on what should be recommended," Khera says.

"This can change practice, but how much it does depends on our trust in this domain of work. I think we have to build trust in the principles so that, in the absence of other studies, we can rely on these data as the best available, ensuring they are robust and reliable enough to guide our decisions."

More information: Rohan Khera et al, Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes, *Journal of the American College of Cardiology* (2024). DOI: 10.1016/j.jacc.2024.05.069

Provided by Yale University