Is Metformin a 'Drug for All Diseases'?

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As a front-line treatment for type 2 diabetes, metformin is among the most widely prescribed drugs in the United States. In 2021 alone, clinicians wrote more than 91 million orders for the medication — up from 40 million 2004.

But is metformin just getting started? Emerging evidence suggests the drug may be effective for a much broader range of conditions beyond managing high blood glucose, including various cancers, obesity, liver disease, cardiovascular, neurodegenerative, and renal diseases. As the evidence for diverse uses accumulates, many trials have launched, with researchers looking to expand metformin's indications and validate or explore new directions.

Metformin's long history as a pharmaceutical includes an herbal ancestry, recognition in 1918 for its ability to lower blood glucose, being cast aside because of toxicity fears in the 1930s, rediscovery and synthesis in Europe in the 1940s, the first reported use for diabetes in 1957, and approval in the United States in 1994.

The drug has maintained its place as the preferred first-line treatment for type 2 diabetes since 2011, when it was first included in the World Health Organization's essential medicines list.

"The focus hitherto has been primarily on its insulin sensitization effects," Akshay Jain, MD, a clinical and research endocrinologist at TLC Diabetes and Endocrinology, in Surrey, British Columbia, Canada, told *Medscape Medical News*.

Akshay Jain, MD

"The recent surge of renewed interest is in part related to its postulated effects on multiple other receptors," he said. "In my mind, the metformin data on coronary artery disease reduction and cancer-protective effects have come farther along than other disease states."

Cardiovascular Outcomes

Gregory G. Schwartz, MD, PhD, chief of the cardiology section at Rocky Mountain Regional VA Medical Center and professor of medicine at the University of Colorado School of Medicine in Aurora, Colorado, is leading the VA-IMPACT trial. Despite metformin's long history and widespread use, he said his study is the first placebo-controlled cardiovascular outcomes trial of the drug.

Gregory G. Schwartz, MD, PhD

Launched in 2023, the study tests the hypothesis that metformin reduces the risk for death or nonfatal ischemic cardiovascular events in patients with prediabetes and established coronary, cerebrovascular, or peripheral artery disease, Schwartz said. The trial is being conducted at roughly 40 VA medical centers, with a planned enrollment of 7410 patients. The estimated completion date is March 2029.

"The principal mechanism of action of metformin is through activation of AMP [adenosine monophosphate]–activated protein kinase, a central pathway in metabolic regulation, cell protection, and survival," Schwartz explained. "Experimental data have demonstrated attenuated development of atherosclerosis, reduced myocardial infarct size, improved endothelial function, and antiarrhythmic actions — none of those dependent on the presence of diabetes."

Schwartz and his colleagues decided to test their hypothesis in people with prediabetes, rather than diabetes, to create a "true placebo-controlled comparison," he said.

"If patients with type 2 diabetes had been chosen, there would be potential for confounding because a placebo group would require more treatment with other active antihyperglycemic medications to achieve the same degree of glycemic control as a metformin group," Schwartz said.

"If proven efficacious in the VA-IMPACT trial, metformin could provide an inexpensive, generally safe, and well-tolerated approach to reduce cardiovascular morbidity and mortality in a large segment of the population," Schwartz added. "Perhaps the old dog can learn some new tricks."

Other recruiting trials looking at cardiovascular-related outcomes include Met-PEF, LIMIT, and Metformin as an Adjunctive Therapy to Catheter Ablation in Atrial Fibrillation.

Reducing Cancer Risks

Sai Yendamuri, MD, chair of the Department of Thoracic Surgery and director of the Thoracic Surgery Laboratory at Roswell Park Comprehensive Cancer Center in Buffalo, New York, is leading a phase 2 trial exploring whether metformin can prevent lung cancer in people with overweight or obesity who are at a high risk for the malignancy.

The study, which has accrued about 60% of its estimated enrollment, also will assess whether metformin can reprogram participants' immune systems, with a view toward reducing the activity of regulatory T cells that are linked to development of tumors.

"In our preclinical and retrospective clinical data, we found that metformin had anticancer effects but only if the patients were overweight," Yendamuri said. "In mice, we find that obesity increases regulatory T-cell function, which suppresses the immune system of the lungs. This effect is reversed by metformin." The team is conducting the current study to examine if this happens in patients, as well. Results are expected next year.

Research is underway in other tumor types, including oral and endometrial, and brain cancers.

Preventing Alzheimer's Disease

Cognitive function — or at least delaying its erosion — represents another front for metformin. José A. Luchsinger, MD, MPH, vice-chair for clinical and epidemiological research and director of the section on geriatrics, gerontology, and aging at Columbia University Irving Medical Center in New York City, is heading a phase 2/3 randomized controlled trial assessing the ability of the drug to prevent Alzheimer's disease.

The study investigators hope to enroll 326 men and women aged 55-90 years with early and late mild cognitive impairment, overweight or obesity, and no diabetes.

"The hypothesis is that improving insulin and glucose levels can lead to lowering the risk of Alzheimer's disease," Luchsinger said. Recruitment should be complete by the end of 2024 and results are expected in late 2026.

Similar studies are underway in Europe and Asia.

Other areas of investigation, while tantalizing, are mostly in early stages, although bolstered by preclinical and mechanistic studies. The authors of a recent review on the potential mechanisms of action of metformin and existing evidence of the drug's effectiveness — or lack thereof — in treating diseases other than diabetes, wrote: "Collectively, these data raise the question: Is metformin a drug for all diseases? It remains unclear as to whether all of these putative beneficial effects are secondary to its actions as an antihyperglycemic and insulin-sensitizing drug, or result from other cellular actions, including inhibition of mTOR (mammalian target for rapamycin), or direct antiviral actions."

Off-Label Uses

Metformin currently is approved by the US Food and Drug Administration only for the treatment of type 2 diabetes, although it is also the only antidiabetic medication for prediabetes currently recommended by the American Diabetes Association.

Some studies currently are looking at its use in a variety of off-label indications, including obesity, gestational diabetes, weight gain from antipsychotics, and polycystic ovary syndrome.

For the most part, metformin is considered a safe drug, but it is not risk-free, Jain cautioned.

"Although it would certainly be helpful to see if this inexpensive medication that's universally available can help in disease states, one shouldn't overlook the potential risk of adverse effects, such as gastrointestinal, potential vitamin B12 deficiency, blunting of skeletal muscle development and the rare risk of lactic acidosis in those with kidney impairment," he said.

"Similarly, with recent reports of the carcinogenic potential of certain formulations of long-acting metformin that contained NDMA [N-nitrosodimethylamine], it would be imperative that these kinks are removed before we incorporate metformin as the gift that keeps giving."

Jain reported financial relationships with Abbott, Amgen, Boehringer Ingelheim, Dexcom, Eli Lilly, Janssen, Medtronic, Merck, and Novo Nordisk. Sai Yendamuri disclosed serving on the scientific advisory board member of Karkinos Healthcare and research funding from Lumeda for the metformin study. Luchsinger reported receiving donated metformin and matching placebo from EMD Serono, a subsidiary of Merck, for the MAP study. Schwartz received research support from the US Department of Veterans Affairs as National Chair of the VA-IMPACT trial.

Marilynn Larkin, MA, is an award-winning medical writer and editor whose work has appeared in numerous publications, including Medscape Medical News *and its sister publication* MDedge, The Lancet *(where she was a former contributing editor),* Reuters Health*, and* Scientific American*.*