Lifestyle changes, meds effective to prevent or delay Type 2 diabetes; no change in CVD

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A lifestyle intervention program of increased physical activity, healthy eating and aiming for weight loss of 7% or more, or taking the medication metformin were effective long-term to delay or prevent Type 2 diabetes in adults with prediabetes. Neither approach, however, reduced the risk of cardiovascular disease for study participants over 21 years of the study, according to the findings of the multicenter Diabetes Prevention Program Outcomes Study (DPPOS), published today in the American Heart Association's flagship, peer-reviewed journal *Circulation*.

Type 2 diabetes (T2D) is the most common form of diabetes, affecting more than 34 million people in the U.S., representing nearly 11% of the U.S. population, according to the U.S. Centers for Disease Control and Prevention's 2020 National Diabetes Statistics Report, and cardiovascular disease (CVD) is the leading cause of death and disability among people with T2D. Type 2 diabetes occurs when the body is unable to efficiently use the insulin it makes and the pancreas is unable to produce sufficient amounts of insulin. Adults with T2D are twice as likely to die from CVD—including heart attack, stroke or heart failure—compared to adults who do not have T2D. People with T2D often have other cardiovascular disease risk factors, including being overweight or having obesity, high blood pressure or high cholesterol.

The DPPOS evaluated 21-years of follow-up (through 2019) for the 3,234 adults who participated in the original, 3-year Diabetes Prevention Program (DPP) trial. This analysis of the DPPOS was focused on

determining whether the medication metformin or lifestyle intervention might reduce the risk of cardiovascular disease or the rate of major cardiac events such as heart attack, stroke or death due to cardiovascular disease.

"The risk of cardiovascular disease in people with prediabetes is increased, and CVD risk further increases over time after Type 2 diabetes develops and progresses," said Ronald B. Goldberg, M.D., chair of the writing group for the DPPOS and a professor of medicine, biochemistry and molecular biology in the division of diabetes, endocrinology and metabolism, and senior faculty member and co-director of the Diabetes Research Institute Clinical Laboratory at the University of Miami's Miller School of Medicine in Miami, Florida. "We were focused on assessing the impact of lifestyle or metformin interventions for prevention of Type 2 diabetes in people with prediabetes to reduce cardiovascular disease."

The DPP was a landmark, 27-center randomized trial across the U.S. from 1996-2001 to assess how to prevent or delay the onset of T2D in people with prediabetes. Study participants were screened and accepted in the DPP based upon these criteria: initially, a 2-hour glucose reading of 140-199 mg/dL on an oral glucose tolerance test; fasting glucose levels of 95-125 mg/dL; and body mass index of 24 kg/m^2 or higher.

A racially diverse group of 3,234 adults were studied in the original DPP for almost three years. The participants were an average age of 51 years, and nearly 70% of the participants were women. People in the intensive lifestyle intervention group (nutritional improvement and physical activity aimed at achieving a weight loss of 7%) reduced the incidence of developing T2D by 58%, and participants who took twice daily doses of metformin had a reduced incidence of 31% for T2D, when compared to people in the placebo group who received standard care, which included information about effective treatment and management of T2D

at the time of diagnosis.

The DPPOS began in 2002 and was open to all participants in the original DPP trial. The DPPOS enrolled almost 90% of the original study participants for up to 25 years of follow-up to assess the long-term impact of the interventions on the development of T2D and its complications. Due to the success of the lifestyle intervention, everyone in the study was offered enrollment in the lifestyle intervention through a group format during a one-year bridge period. The group who took metformin in the original DPP trial were able to continue take the medication during the DPPOS, and they were aware that they were taking metformin not the placebo. (The metformin and placebo groups were blinded in the original DPP, so participants did not know whether they were taking metformin or placebo during that time period.)

"From the beginning of the Diabetes Prevention Program, we were primarily interested in whether prevention of diabetes would lead to a reduction in the development of the complications that are caused by Type 2 diabetes—cardiovascular disease, kidney disease, retinopathy and neuropathy," said Goldberg. "Managing blood glucose levels is important, and we encourage interventions to prevent the long-term complications of Type 2 diabetes."

The DPPOS assessed cardiovascular disease outcomes in order to determine the effects of lifestyle and metformin interventions on participants' risk of having a non-fatal heart attack, stroke or death due to a cardiovascular occurrence, by comparing outcomes of each intervention group to the placebo group. Researchers reported results based on a median follow-up of 21 years, which included the average three-year follow-up period of the original DPP trial. The authors conducted a futility analysis of the cardiovascular outcomes, which resulted in ending the study prior to completing the planned 25-year follow-up.

Throughout the entire study, participants were screened annually with electrocardiogram testing; measures of their cardiovascular disease risk factors, including smoking, cholesterol levels and blood pressure levels; and body mass index measurements. The percentage of all participants taking blood pressure and cholesterol lowering medications increased over the duration of the study and was slightly lower among the participants in the lifestyle group versus the other two groups.

After an average 21 years of follow-up, researchers found no significant differences in the incidence of heart attacks, stroke or cardiovascular death among the three intervention groups. Specifically, the analysis found:

- There was a continued reduction or delay in the development of T2D for up to 15 years.
- The number of non-fatal heart attacks across each group was similar: 35 heart attacks occurred in the lifestyle intervention group; 46 in the metformin group; and 43 in the placebo group.
- Similarities were also found in the number of non-fatal strokes: 39 incidences of stroke in the lifestyle intervention group; 16 in the metformin-only group; and 28 in the placebo group.
- The number of deaths due to cardiovascular occurrences were low: 37 deaths among the lifestyle intervention participants; 39 in the metformin group; and 27 in the participants who took the placebo during the original DPP trial.

"The fact that neither a lifestyle intervention program nor metformin led to a decrease in cardiovascular disease among people with prediabetes may mean that these interventions have limited or no effectiveness in preventing cardiovascular disease, even though they are highly effective in preventing or delaying the development of Type 2 diabetes," said Goldberg. "It's important to note that most study participants also received treatment with cholesterol and blood pressure medications,

which are known to reduce CVD risk. Therefore, the low rate of development of cardiovascular disease found overall may have been due to these medications, which would make it difficult to identify a beneficial effect of lifestyle or metformin intervention. Future research to identify higher risk subgroups is needed to develop a more targeted approach to cardiovascular disease prevention in people with prediabetes and Type 2 diabetes."

There were several limitations to the study. The researchers selected a subgroup of people who met the criteria for prediabetes, however, these results are not generalizable to everyone with prediabetes. Additionally, the intensity of the lifestyle intervention was reduced after the initial DPP phase, and, over the 21-year study period, there was a gradual reduction in medication adherence by participants in the metformin group. There was also out-of-study metformin use in patients who were diagnosed with Type 2 diabetes, which may have diluted differences among the study groups. The high level of blood pressure and cholesterol medications prescribed by the participants' primary care team, as well as lower use of blood pressure medications in the lifestyle group, may have influenced results. There may have also been some under-estimation of cardiovascular events since some participants did not complete 21 years of follow-up.

"These long-term findings confirm the link between Type 2 diabetes and cardiovascular disease is complex and requires more research to understand it better," said the American Heart Association's Chief Medical Officer for Prevention Eduardo Sanchez, M.D., M.P.H., FAHA, FAAFP, and clinical lead for Know Diabetes by Heart, a collaborative initiative between the American Heart Association and the American Diabetes Association addressing the link between diabetes and cardiovascular disease. "However, these important results also tell us that lifestyle intervention is incredibly effective to delay or prevent Type 2 diabetes, which, itself, reduces the risk for cardiovascular disease. The

CDC estimates nearly 1 of every 3 adults in the U.S. has prediabetes, therefore, preventing or delaying Type 2 diabetes is a public health imperative to help extend and improve the lives of millions of people."

More information: Effects of Long-term Metformin and Lifestyle Interventions on Cardiovascular Events in the Diabetes Prevention Program and Its Outcome Study, *Circulation* (2022). DOI: 10.1161/CIRCULATIONAHA.121.056756

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