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Metformin in Prediabetes: Time for a Proper CVOT Study?

Metformin may be able to reduce the risk of cardiovascular events in high-risk individuals with prediabetes, according to Sardu et al. (p. 1946). They also suggest that metformin can reduce coronary endothelial dysfunction but not the risk for developing full-on diabetes. The authors identified three groups of 86 individuals that varied according to having normoglycemia, prediabetes, or prediabetes with metformin for at least 6 months. They had variable levels of endothelial dysfunction at baseline. The composite major adverse cardiac events (MACE) outcome of cardiac death, myocardial infarction, and heart failure at 24 months of follow-up was highest in the prediabetes group, followed by the prediabetes group with metformin and the individuals with normoglycemia. The authors point out that the individuals involved had a very high risk for cardiovascular events and also that the development of diabetes was not particularly curtailed through the use of metformin. However, that is not the point of this trial—more individuals who took metformin during prediabetes had lower risk for cardiovascular events after 24 months even though they had high risk at baseline. The authors stress that this should be the impetus for larger and longer studies, which sounds like a call for cardiovascular outcome trials (CVOT) for metformin in prediabetes. Commenting more widely, author Celestino Sardu told *Diabetes Care*: “In our opinion, prediabetes is an important ischemic heart disease risk factor. The patients with prediabetes had worse prognosis and higher rates of adverse cardiovascular events as compared with normoglycemic patients. The study raises several questions for new investigations into individuals with prediabetes and ischemic heart disease and on the risk of developing diabetes. In this way, we raise a question: is it more important to take care of prediabetes with endothelial dysfunction and linked adverse cardiovascular events, or is it better to reduce the future risk of having patients with diabetes and already suffering from ischemic heart disease?”

Sardu et al. Effects of metformin therapy on coronary endothelial dysfunction in patients with prediabetes with stable angina and nonobstructive coronary artery stenosis: the CODYCE multicenter prospective study. *Diabetes Care* 2019;42:1946–1955

Sotagliflozin Renal Outcomes in Adults With Type 1 Diabetes: Time for a Renal Outcomes Trial?

An analysis by van Raalte et al. (p. 1921) of the first two inTandem trials of sotagliflozin suggests that the dual SGLT1/2 inhibitor is likely to confer renal protection in type 1 diabetes with effects in line with those seen with SGLT2 inhibitors in type 2 diabetes. Based on the analysis, they suggest that dedicated cardiorenal outcomes trials are now justifiable. Using a pooled analysis of data from the trials, the authors looked at a series of cardiorenal biomarkers in 1,575 individuals with type 1 diabetes who received 200 mg or 400 mg of sotagliflozin or placebo for 52 weeks. They found that in patients taking either dose of sotagliflozin, estimated glomerular filtration rate (eGFR) was significantly reduced compared with placebo at week 4, while eGFR in the 200 mg dose group remained significantly reduced at 52 weeks. Body weight, blood pressure, and uric acid were also significantly reduced with both doses while there were increases in serum albumin and hematocrit compared with placebo. They go on to detail how the effects of sotagliflozin align with those seen with SGLT2 inhibitors that are used in type 2 diabetes. Based on the outcomes, they propose that cardiorenal outcomes trials of the drug in type 1 diabetes are now justified. Commenting further, author David Cherney said: “We now know from the CREDENCE trial and from three cardiovascular safety trials that SGLT2 inhibitors have major cardiorenal protective effects in people with type 2 diabetes. Our analysis is therefore of potential importance because it is one of the first to explore the impact of an SGLT1/2 inhibitor on clinical parameters that have been associated with kidney and cardiovascular protection in previous studies. So, while our analysis gives us some exploratory insights and is very supportive of analogous physiological changes in type 1 versus type 2 diabetes, we ultimately need to plan and complete dedicated renal and cardiovascular outcome trials in patients with type 1 diabetes.”

van Raalte et al. The impact of sotagliflozin on renal function, albuminuria, blood pressure, and hematocrit in adults with type 1 diabetes. *Diabetes Care* 2019;42:1921–1929

Diabetes Increases Levels of Frailty in Older Individuals

Diabetes is associated with increased frailty in older individuals according to Aguayo et al. (p. 1903). They found that individuals with diabetes had frailty levels that were only reached in individuals without diabetes as much as a decade later. As a consequence, they highlight the relevance of a timely diagnosis of diabetes because of the accelerated frailty risks. The conclusions come from a study involving ~5,400 older individuals involved in the English Longitudinal Study of Ageing who were followed over a 10-year period. At baseline, they found that 35% of individuals were frail to some degree and 12% had diabetes. They also found that at any time after the age of 60 years, individuals with diabetes had increased levels of frailty compared with individuals without diabetes. Even after excluding individuals who had frailty at baseline, the relationship held, although frailty levels started at lower levels and progression was somewhat steeper. A model adjusted for a whole range of potential confounding showed that only diabetes remained associated with frailty in older age. The authors go on to explore some of the reasons for the association, with a picture emerging of a complex of pathways and potential determinants being involved. They even touch on the possibility that the inverse phenomenon—that frailty might be involved in the development of diabetes—could also be possible. Commenting more widely, author Gloria A. Aguayo told *Diabetes Care*: “This study analyzes frailty, a common condition of vulnerability in the older population, which increases the risk of death, disability, falls, and fractures. In 10 years of follow-up, we analyzed frailty every 2 years. Our results show an increase in the progression of frailty in individuals with diabetes compared with those without diabetes. We also found an association between slightly increased HbA_{1c} values and frailty progression. These results underline the relevance of diabetes screening to prevent the progression of frailty in older people.”

Aguayo et al. Prospective association among diabetes diagnosis, HbA_{1c}, glycemia, and frailty trajectories in an elderly population. *Diabetes Care* 2019;42:1903–1911

High Cardiometabolic Risk in Young Adults With Diabetes

The cardiometabolic risk profile of young adults with diabetes in the U.S. is explored by Saydah et al. (p. 1895), with the authors describing significantly elevated risk compared with young adults without diabetes and also older adults both with and without diabetes. Specifically, young adults with diabetes were almost twice as likely to have obesity, elevated lipids, or hypertension and much less likely to report having a healthy diet or leisure-time physical activity. As a result, they suggest efforts should be made to understand modifiable aspects to cut risk, as this would contribute to reducing future morbidity and mortality due to diabetes. The conclusions come from an analysis of the National Health and Nutrition Examination Survey (NHANES) and included data from just under 24,000 individuals (~11,000 younger adults aged 18–44 years, with the rest being older adults aged 45 years and above). They defined diabetes as self-report of diagnosis by a health care provider or HbA_{1c} >6.5% and compared cardiometabolic risk profiles between groups. Profiles consisted of adiposity, blood pressure, serum lipids, healthy eating, physical activity, and smoking status. They found that adults with diabetes in both age-groups had elevated levels of adiposity, hypertension, and cholesterol and engaged in less healthy eating and physical activity compared with individuals without diabetes. Virtually all of the risk factors measured in individuals with diabetes were significantly different from zero compared to individuals without diabetes. However, the differences in young adults between those with and without diabetes were much greater compared with the differences seen in older adults. While the study cannot determine causality, the authors suggest that such factors should be explored not least in an attempt to find modifiable behaviors to reduce future risk in the group. Commenting further, author Sharon H. Saydah told us: “Understanding the increase in modifiable risk factors among young adults with diabetes is an important step in working to reduce and prevent future diabetes-related morbidity and mortality.”

Saydah et al. The cardiometabolic risk profile of young adults with diabetes in the U.S. *Diabetes Care* 2019;42:1895–1902

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