APRIL 2019

Diabetes Care®

In This Issue of *Diabetes Care*

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Higher Doses of Insulin in Long-term Therapy Associated With Cardiometabolic Risks in Type 1 Diabetes

A further analysis of the Diabetes Control and Complications Trial and the follow-up Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study by Braffett et al. (**p. 657**) suggests that over the long-term, higher insulin doses can be linked to adverse trends in several cardiometabolic risk factors but not with incident cardiovascular outcomes. The conclusions come from an analysis of ~30 years of follow-up data from the DCCT/EDIC studies. Just over 1,400 individuals with type 1 diabetes were initially assigned to receive intensive insulin therapy or conventional therapy and were then extensively monitored for various diabetes and cardiovascular outcomes over the years. The authors found that higher insulin doses were associated with a less favorable cardiovascular risk profile, including higher BMI, pulse rate, triglycerides, and lower HDL cholesterol. Conversely, higher insulin doses were also associated with lower diastolic blood pressure and lower LDL cholesterol. In terms of cardiovascular events, they found that in minimally adjusted models, a 0.1 unit per kg body weight per day increase in insulin dose conferred a 5%–6% increase in risk for cardiovascular events. However, there was no relationship between higher insulin dose and cardiovascular outcomes when they fully adjusted for all relevant risk factors. Commenting on behalf of the study group, authors Barbara H. Braffett and Samuel Dagogo-Jack said: "From 30 years of observation in the DCCT/EDIC study, our findings regarding insulin therapy clearly document an association between higher doses and adverse cardiometabolic risk profiles, most likely driven by weight gain. It is reassuring that our fully adjusted model does not show an independent association of insulin dose with cardiovascular disease events, indicating comprehensive concurrent management of cardiovascular disease risk factors with appropriate therapies is effective in patients with type 1 diabetes. Thus, necessary and appropriate doses of insulin for optimization of glycemic control are warranted to prevent diabetes complications; however, steps to prevent or manage insulin-associated weight gain are advisable."

Braffett et al. Association of insulin dose, cardiometabolic risk factors, and cardiovascular disease in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2019;42:657–664

Artificial Pancreas for Very Young Type 1 Diabetes Patients Takes a Step Forward

The ambition of creating a viable closed-loop insulin therapy system for the treatment of type 1 diabetes, otherwise known as the artificial pancreas (AP), has taken a step forward. Tauschmann et al. (**p. 594**) reveal the successful use of a version of the approach in free-living very young (1–7 years) children, with a convincing clinical outcome. The authors report that their approach appears to be feasible in young children and also appears to be safe from the perspective of avoiding hypoglycemia. Additionally, they also report that there is no tangible difference in using standard concentrations of insulin versus a diluted version in this population. They report an open-label, multicenter, crossover study that initially involved 24 very young individuals with type 1 diabetes who, along with their parents, agreed to use a tech combination that formed an operational AP. The study involved two 21-day periods of use, separated by a washout period with one period involving standard (U100) concentrations of insulin and the other a diluted version (U20). There were no real differences between the periods in terms of mean glucose levels and variability, the proportion of time spent within ranges, and the amount of insulin delivered in the periods. On the safety front, again there were no differences between the periods that could be tied to either the AP system or the different insulin doses. Commenting more widely on the study, author Roman Hovorka told *Diabetes Care*: "Managing diabetes in very young children places a huge burden on families due to highly fluctuating insulin needs during and between days. We showed that closed-loop insulin delivery is feasible, safe, and achieves excellent glucose control—especially overnight—helping families to live better lives. Diluting insulin for children with a total daily dose above 10 units per day does not change the outcomes. We are planning a longer and larger study based on these exciting observations."

Tauschmann et al. Home use of day-and-night hybrid closed-loop insulin delivery in very young children: a multicenter, 3-week, randomized trial. Diabetes Care 2019;42:594–600

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Metformin for Preventing Diabetes: Long-term Data Suggest Risk Reductions

While metformin is widely used to treat type 2 diabetes, there is also a school of thought (and guidelines) that it can be used to prevent diabetes developing in the first place. The Diabetes Prevention Program (DPP) and the follow-up Diabetes Prevention Program Outcomes Study (DPPOS) did demonstrate that metformin could reduce the risk of developing diabetes in certain circumstances. We now learn from the Diabetes Prevention Program Research Group (**p. 601**) that metformin continues to reduce the risk of developing diabetes in the long term (~15 years), and the effect of metformin on preventing type 2 diabetes may be enhanced in certain groups of individuals. The conclusions come from further analysis of the DPP and DPPOS where ~2,000 adults with a high risk for diabetes were initially randomly assigned to a masked placebo or 850-mg metformin twice daily. At the close of the DPP in 2001 and the opening of DPPOS in 2002, individuals on metformin continued unmasked, while placebo was discontinued. Regular monitoring with oral glucose tolerance tests and HbA_{1c} were used to track any diabetes developments. Based on hazard ratios and over 15 years of follow-up, the authors found that metformin reduced the incidence of diabetes by 17% or 36% according to whether glucose tests or HbA_{1c} were used to estimate diabetes risks. Turning to subgroups of individuals, they found that women with a history of gestational diabetes mellitus experienced much greater risk reductions due to metformin than women who had not experienced gestational diabetes mellitus. Metformin also had much greater effects when baseline glucose levels and HbA_{1c} were higher. As a result, they suggest the outcomes should help prioritize individuals with a high risk of diabetes who would benefit most from metformin prior to a diabetes diagnosis.

Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: Identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. Diabetes Care 2019;42:601–608

Insulin Pump Therapy Is Expensive and Overall Positive Benefits Are Still Not Clear

According to Toresson Grip et al. (**p. 545**), real-world data from Sweden suggest that insulin pump therapy for type 1 diabetes is associated with additional costs when compared with multiple daily injections of insulin. However, whether or not those costs bring extra benefits to users is not yet clear. They say that more time is still needed to fully assess the tangible and intangible benefits of the technology (as well as other more recent changes to therapy). The conclusions come from an analysis of the Swedish National Diabetes Register that included just over 14,000 individuals with type 1 diabetes, one-third of whom used insulin pumps and two-thirds who used multiple daily injections of insulin to control glucose. Longitudinal data were then extracted in relation to health care usage, treatments, and various other demographic factors. The authors found that mean annual costs associated with pump therapy were just under $13,000, while costs associated with multiple daily injections were just over $9,000. Breaking the numbers down, the research shows that the majority of costs associated with pump therapy were health care costs (73%), including medications and disposables. Equivalent health care costs made up 63% of total costs associated with multiple daily injections of insulin. Other costs that were higher with pump therapy included outpatient costs and dealing with complications. The research also highlights that low education, low income, and older age seem to be associated with higher costs. On health outcomes, the authors highlight that the number of events overall were low but that in some cases rates were higher in relation to pump use. Even so, they suggest that the 9 years of follow-up used in the analysis may not be enough to detect meaningful differences in treatment outcomes between the two approaches. As a result, while costs appear higher in relation to pump therapy, whether this translates to greater benefits for users is still not clear.

Toresson Grip et al. Real-world costs of continuous insulin pump therapy and multiple daily injections for type 1 diabetes: a population-based and propensity-matched cohort from the Swedish National Diabetes Register. Diabetes Care 2019;42:545–552

https://doi.org/10.2337/dc19-ti04