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In This Issue of *Diabetes Care*

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Consensus Report on Diabetic Ketoacidosis and Adjunctive SGLT Inhibitor Therapy in Type 1 Diabetes

With the promise of sodium–glucose cotransporter (SGLT) inhibitors being very real for adults with type 1 diabetes, Danne et al. (**p. 1147**) report an international consensus on what can practically be done to safely use the drugs, specifically in relation to diabetic ketoacidosis (DKA). Initially setting out the clinical data on the use of the drugs in the context of type 1 diabetes, they describe trial evidence that demonstrate reductions in HbA_{1c} and improved glucose variability. There were also consistent reductions in weight, blood pressure, and overall insulin use. Less consistently, the trials reportedly show no overall increases in the incidence of hypoglycemia, which might be expected in the context of reductions in HbA_{1c}. On the issue of DKA and SGLT inhibitors, Danne et al. discuss the possible mechanisms involved, the diagnosis of DKA, and approaches to prevent and treat DKA. They touch on the importance of ketone monitoring, making recommendations on how best patients might approach the issue, and when discontinuing therapy might be right to avoid DKA. The authors also cover the issue of patient and clinician education and the outstanding research questions that would move forward the use of SGLT inhibitors in type 1 diabetes, potentially also with regulatory approval. Notably, they point to research that is needed in the real world and also call for clinical evaluation of the guidance they give. With the recent limited regulatory approval in Japan and Europe of three different SGLT inhibitors for select adults with type 1 diabetes, this may be possible on a wider scale. Commenting further on the research, author John B. Buse said: "In trials and with off-label use, patients with type 1 diabetes often experience meaningful improvements in glycemic control, weight, blood pressure, and quality of life with SGLT inhibitors. DKA is a life-threatening risk of SGLT inhibitors that can be mitigated with appropriate patient selection and patient and provider education. We hope this paper is useful in that regard."

Danne et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium–glucose cotransporter (SGLT) inhibitors. Diabetes Care 2019;42:1147–1154

Dapagliflozin Improves Glucose Outcomes in Type 1 Diabetes

A pooled analysis of continuous glucose monitoring (CGM) data from the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1 and DEPICT-2) trials suggests that dapagliflozin can reduce glucose and glycemic variability in patients with type 1 diabetes. According to Mathieu et al. (**p. 1081**), the effect was achieved without increasing readings in the range that would indicate hypoglycemia. As a result, they suggest that treatment with the drug on top of adjustable insulin might improve treatment adherence and reduce risk of complications, while noting that concerns in relation to diabetic ketoacidosis remain. The conclusions come from a post hoc analysis of the DEPICT trials and specifically the CGM data that was collected at various time points during the two studies. Both trials were phase 3, double blind, placebo controlled, ran for 24 weeks, and included ~800 participants with type 1 diabetes. After pooling the data from both studies, the authors report that both dapagliflozin dosing groups (either 5 mg or 10 mg) spent more time in the target glucose range over 24 h compared with placebo. Increases from baseline in terms of time spent in the target range was from ~6.5% and ~9.0% while placebo was reduced by ~2.6%. In terms of hypoglycemia, there were no differences between either dose of the drug and placebo in terms of time spent below 3.9 or 3.0 mmol/L. Additionally, both doses of dapagliflozin resulted in reductions in HbA_{1c} of just under 0.5%. Author Chantal Mathieu told *Diabetes Care*: "What was interesting to see when doing this analysis was the consistent effect throughout the two studies on variability of glucose values, as expressed by a reduction in MAGE (mean amplitude of glycemic excursion), but we were particularly impressed by the substantial increase in time in range. Adding dapagliflozin 5 mg or 10 mg to intensive insulin therapy in people living with type 1 diabetes increased the daily time in range by 2 h and 2.3 h compared with a decrease of 0.2 h in the placebo-treated people."

Mathieu et al. Glucose variables in type 1 diabetes studies with dapagliflozin: pooled analysis of continuous glucose monitoring data from DEPICT-1 and -2. Diabetes Care 2019;42:1081–1087

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Bluetooth-Enabled Insulin Pen Cap and Insulin Dose Adherence

A Bluetooth-enabled insulin pen cap that transmits dosing activity to a smartphone can be used to objectively assess dosing of insulin and adherence, according to Munshi et al. (**p. 1129**). The study involved two groups of individuals with diabetes: one aged 18–35 years with type 1 diabetes and the other aged ≥65 years with either type 1 or type 2 diabetes on two or more insulin injections per day. All participants were then provided with basal and bolus insulin pens in combination with the Bluetooth cap and smartphone app that transmitted data to a web portal. They were also provided with a continuous glucose monitoring device if they were not already using one for the first 14-day period. Munshi et al. found that overall the setup could detect nonadherence in approximately one-quarter of bolus doses and just over one-third of basal insulin doses. Based on tertiles, the most adherent participants achieved 85% dose adherence compared with 49% in the least adherent tertile. That corresponded to achieved HbA_{1c} levels in the most adherent tertile of ~7.7%, while those in the least adherent managed ~8.6%. Notably, no participant achieved 100% adherent dosing. While acknowledging some limitations with the study, they suggest that the information available via the cap and app should be useful for both patients and clinicians in making treatment decisions. According to author Medha Munshi: "Our study is the first to show the usability of this technology by both younger and older adults. The results also show that objective assessment of adherence to dosing and timing of insulin injection had an impact on glycemic control. Although we believe that the factors affecting the adherence may be different in younger and older age-groups, larger studies are needed to clearly define these factors. The next step would be to do intervention trials using this technology to improve glycemic control and other patient-related outcomes."

Munshi et al. Nonadherence to insulin therapy detected by Bluetooth-enabled pen cap is associated with poor glycemic control. Diabetes Care 2019;42:1129–1131

Anti-GAD Antibodies Identify Young-Onset Type 2 Diabetes Patients With an Altered Prognosis

GAD antibodies appear to determine the complications experienced by individuals with young-onset type 2 diabetes according to Luk et al. (**p. 1042**). Specifically, the complications appear to differ from those experienced by similar individuals who were anti-GAD antibody negative and also individuals with type 1 diabetes. As a result, the authors suggest that anti-GAD positivity indicates there is a group of patients with diabetes that have a different prognosis that should be treated carefully and accordingly. The conclusions come from a study of ~1,500 individuals with diabetes enrolled in the Hong Kong Diabetes Register where they were followed over a number of years for incident cardiovascular disease, end-stage renal disease (ESRD), hypoglycemia, and all-cause mortality. The individuals were only included if their status for anti-GAD antibodies had been determined and there was a follow-up of parameters such as insulin use and HbA_{1c}. The authors report that just over 8% of individuals with type 2 diabetes were GAD antibody positive. Compared with antibody-negative individuals, those who were positive had a lower hazard for cardiovascular disease, a higher hazard for severe hypoglycemia, and similar hazards for ESRD and mortality. Compared with individuals with type 1 diabetes, the antibody-positive individuals only had increased hazard for ESRD. The authors also looked at the incident use of insulin across the groups and found that antibody-positive individuals with type 2 diabetes had glycemic responses to insulin that were much stronger than in individuals without the GAD antibodies. They suggest this supports the use of insulin at a much earlier stage, particularly when oral antihyperglycemic drugs are not effective. However, they caution that this risks hypoglycemia and so warrants close monitoring and vigilance during any treatment escalation. Overall, they suggest that testing for such antibodies, irrespective of metabolic phenotype, will inform of risks and should guide treatment decisions.

Luk et al. Diabetes-related complications and mortality in patients with young-onset latent autoimmune diabetes: a 14-year analysis of the prospective Hong Kong Diabetes Register. Diabetes Care 2019;42:1042–1050

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