MARCH 2020

Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

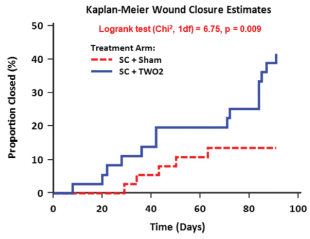
Global Mechanisms Proposed for Cardioprotective Effects of SGLT2 Inhibitors

The beneficial effects of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in type 2 diabetes are mostly attributed to their ability to enhance glucose excretion and lower hyperglycemia. But they can also promote positive cardiovascular outcomes. Less clear is quite how they manage to achieve the effects, and although many hypothetical mechanisms exist, they only partly explain what might be going on. Avogaro et al. (**p. 501**) attempt to bring the different strands of evidence together and propose a hypothesis that suggests SGLT2i might modify the trajectory of cell responses to high glucose levels from one of defense to dormancy. They suggest this might be the mechanism that explains the cardiac and renal protective effects of SGLT2i treatments. On that basis they call for dedicated studies to test the hypothesis to ultimately gather the support needed for human studies. They explain that high blood glucose is effectively a toxic environment that likely shifts cell responses to a state of defense characterized by immune responses, anabolic metabolism, inflammation, adiposity, and also cardiovascular events. In contrast, they suggest that switching to a dormancy program would curtail many of these issues and that evidence suggests that SGLT2i may actually be able to force this switch—effectively explaining the positive cardiorenal outcomes of the trials. They acknowledge that most of the cited evidence comes from animal studies but suggest that, together with the more limited human data, the evidence points towards SGLT2i having a dormancy effect at a cellular level. Commenting further, author Angelo Avogaro told us: "There is still a lot to be understood about what SGLT2i do to humans beyond their glycosuric effects. Many hypotheses have been proposed, but we found it fascinating that they may switch the milieu of the cells to a state similar to that observed in mammalian animals during hibernation. If this is the case, this evolutionary hypothesis should be rigorously tested in future studies."

Avogaro et al. Reinterpreting cardiorenal protection of renal sodium–glucose cotransporter 2 inhibitors via cellular life history reprogramming. Diabetes Care 2020;43:501–507

Oxygen Therapy Improves Diabetic Ulcer Wound Healing: RCT Data

Treating diabetic foot ulcers for 12 weeks with a topical wound oxygen therapy in addition to standard care increases the likelihood that they heal, according to Frykberg et al. (**p. 616**). Specifically, they found that the therapy resulted in a >4.5-fold increased likelihood of healing compared with placebo and notably could be administered at home by patients. The results come from a double-blind randomized controlled trial (RCT) that compared an oxygen treatment approach (Topical Wound Oxygen [TWO2]) or placebo (circulating air) delivered via a device called a HyperBox (AOTI Ltd., Galway, Ireland). Both approaches were applied on top of standard care for wounds, which were long-standing and had not healed prior to the trial. The company-sponsored trial was stopped early (as planned) after the active treatment showed clear success in healing wounds compared with placebo. Seventy-three individuals had been enrolled up to that point. The primary outcome was the percentage of ulcers achieving 100% healing at 12 weeks. The authors found that the active treatment had a closure rate of nearly 42%, while the placebo had a closure rate of 13.5%. This resulted in an odds ratio of ~4.5, which was statistically significant, and it increased to 6.0 once ulcer grade was accounted for. Additionally, more than half of ulcers were closed at 12 months after the active treatment but only about one-quarter following placebo. Quality of life measures also improved more following the active treatment. There were high compliance rates in both groups, and no device-related adverse events were experienced in either group. Commenting further, author Robert Frykberg told us: "We believe that in this rather robust double-blinded RCT we have clearly demonstrated the positive effects of cyclical, pressurized topical oxygen therapy in the healing of chronic diabetic foot ulcers. Accordingly, we now have the evidence required to recommend the use of this therapy as an adjunct to good standard care for the management of difficult-to-heal diabetic foot ulcers."



Kaplan-Meier curve showing the separation between placebo (SC + Sham) and active therapy (SC + TWO2) study groups throughout the 12-week trial. SC, standard care.

Frykberg et al. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical Topical Wound Oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO2 study. Diabetes Care 2020;43:616–624

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"A Bidirectional Relationship": Severe Hypoglycemia and Cardiovascular Events

Certain individuals with type 2 diabetes may have an increased risk for severe hypoglycemia following a cardiovascular event, according to Standl et al. (**p. 643**). But these same individuals may also have an increased risk for cardiovascular events following severe hypoglycemia—effectively suggesting the existence of a bidirectional relationship and consequently the existence of a potential "frailty" phenotype. The findings come from a post hoc analysis of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial that originally looked at the cardiovascular safety of exenatide in patients with type 2 diabetes. Using fully adjusted models, Standl et al. found that following a severe hypoglycemic event, hazard ratios (all $P < 0.05$) were 1.83 (95% CI 1.38–2.42) for all-cause mortality, 1.60 (1.11–2.30) for cardiovascular death, and 2.09 (1.37–3.17) for hospitalization due to heart failure. In terms of the reverse relationship, they found that numerous cardiovascular events were all associated with a subsequent increased risk for severe hypoglycemia events. In this case all associations were statistically significant. They also note that the elevated risks in terms of both directions were approximately constant over time, except for the risk of all-cause death. This was increased fivefold close to a severe hypoglycemic event and gradually decreased over the subsequent 2 years to about normal levels. Taken together, the findings suggest that certain individuals with type 2 diabetes have significantly increased risks for hypoglycemia and cardiovascular events, whichever order they occur in. The authors go on to explain some of the potential mechanisms but quite rightly note that any associations in such a cohort study do not prove a causal relationship. Commenting further, author Eberhard Standl told us: "Our study should help to better recognize those with type 2 diabetes at high dual risk of severe hypoglycemia and cardiovascular events. This is clinically important, as they need special attention. On the one hand, one needs to deal with the complex comorbidities, but on the other, one has to reconsider the often high doses or even the use of insulin therapy, as there might be now alternate treatment options."

Standl et al. Confirming the bidirectional nature of the association between severe hypoglycemic and cardiovascular events in type 2 diabetes: insights from EXSCEL. Diabetes Care 2020;43:643–652

Artificial Pancreas and a Combination of Rapid Insulin/Pramlintide Improves Glucose Control

An artificial pancreas system that delivers rapid insulin and pramlintide can improve glucose control in individuals with type 1 diabetes according to Haidar et al. (**p. 597**). During inpatient care, the approach improved control during the daytime—a period when users still experience periods of hyperglycemia even when they use artificial pancreas but with insulin alone. As a result of the study, the authors propose that further studies are now warranted in free-living outpatient settings. The conclusions are the result of a randomized crossover study that compared three artificial pancreas setups that delivered rapid insulin alone, rapid insulin with pramlintide, and regular insulin with pramlintide. Twenty-eight individuals with type 1 diabetes were randomly assigned to the treatments during three separate 24-hour inpatient visits. The primary outcome was time in range of 3.9–10.0 mmol/L for blood glucose. The authors found that compared to rapid insulin alone, where time in range was 74%, the rapid insulin/pramlintide combination resulted in 84% time in range, which was significantly higher. For the regular insulin/pramlintide combination, time in range was 69%, which was not significantly different from rapid insulin alone. Other parameters that changed included reduced mean glucose, reduced time spent above range, and reduced glucose variance. Notably, nearly all the improvements seen with the rapid insulin/pramlintide combination were seen during the day. In terms of adverse events, there were 13 hypoglycemia events that required treatment with the rapid insulin alone approach, 12 with the rapid insulin/pramlintide combination, and 18 with the regular insulin/pramlintide combination. There were also a small number of gastrointestinal complaints following meals with the combinations but not with insulin alone. Notably, a very high proportion of the individuals in the study said that if a coformulation of rapid insulin and pramlintide was available commercially, they would use it.

Haidar et al. A novel dual-hormone insulin-and-pramlintide artificial pancreas for type 1 diabetes: a randomized controlled crossover trial. Diabetes 2020;43:597–606

https://doi.org/10.2337/dc20-ti03