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In This Issue of *Diabetes Care*

By Max Bingham, PhD

PIONEER 1 Full Results: Oral Semaglutide as Monotherapy Reduces HbA_{1c} and Weight

The full results of the phase 3a PIONEER 1 trial are published in this issue of *Diabetes Care* by Aroda et al. (**p. 1724**) with oral semaglutide showing, as expected, significant reductions in HbA_{1c} and body weight compared with placebo in adults with type 2 diabetes. The trial involved just over 700 individuals with type 2 diabetes randomized to three different daily doses or placebo. The primary endpoint was change from baseline to 26 weeks in HbA_{1c}. Change in weight over the same period was included as a secondary outcome. The study also used an estimand approach (see http://doi.org/10.1111/DOM.13804 for an explanation) to account for the effects of product discontinuation and the use of rescue medication in the trial. This fairly new approach was included to provide both regulators and clinicians with the highest quality data for their respective viewpoints. They found that under the trial product estimand, individuals treated with 3, 7, and 14 mg oral semaglutide experienced significant reductions in HbA_{1c} of 0.8, 1.3, and 1.5%, respectively, from a baseline of ~8.0%. Outcomes under the treatment policy estimand were very similar although effect sizes were smaller. In terms of body weight, significant weight loss was seen at the higher doses, and on safety, the authors report mild-to-moderate transient gastrointestinal events with oral semaglutide but that overall, safety was consistent with other glucagon-like peptide 1 (GLP-1) receptor agonists. Commenting further, author Vanita R. Aroda told *Diabetes Care*: "GLP-1 receptor agonists have traditionally only been available as injectable therapies, which may have presented a barrier to their use for some patients and providers. With completion of the oral semaglutide phase 3 PIONEER program, it is exciting to see the prospects of an oral GLP-1 agent that, at the 14-mg dose, for example, offers HbA_{1c} reductions of ~1.5% and weight loss of ~4 kg, and to consider that the availability of an oral GLP-1 receptor agonist may broaden the population that may benefit from this class of therapy."

Aroda et al. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. Diabetes Care 2019;42:1724–1732

Economic Burden Estimates Increased for Diabetes and Elevated Glucose Levels in U.S.

An update to the 2017 estimates of the economic burden of diabetes in the U.S. suggests that the costs involved, when categories of elevated blood glucose levels are included, now stand at $404 billion according to Dall et al. (**p. 1661**). This follows the American Diabetes Association's original estimates that were published in early 2018 (https://doi.org/10.2337/dci18-0007) that suggested the costs associated with diagnosed diabetes alone were $327 billion. Of the estimated costs, diagnosed diabetes remained at $327.2 billion, while undiagnosed diabetes accounted for $31.7 billion, prediabetes for $43.4 billion, and gestational diabetes mellitus for $1.6 billion. Compared with 2012 when the costs were estimated to be in the region of $322 billion, the new value represents a 13% increase in costs. With the inclusion of these extra categories, it now means that in 2017, the economic burden of elevated blood glucose and diabetes combined was $1,240 for each U.S. citizen. In addition, on a per-case basis, this indicated diagnosed diabetes had an economic burden of $13,240, gestational diabetes mellitus was $5,800, undiagnosed diabetes was $4,250, and prediabetes was $500. Author Timothy M. Dall commented further: "The hope that my coauthors and I have is that these economic burden estimates will inform and help galvanize support for policies and programs to better prevent and treat diabetes. Study findings illustrate the high cost of diabetes and elevated glucose to society overall, but also the high cost to the government, payers, employers, families, and especially to people living with diabetes. While our study attempts to put a dollar value on the burden of diabetes and elevated glucose levels in terms of higher health care costs and lost productivity, the true societal cost is much larger when one considers the impact of diabetes on reduced quality of life and early mortality for which one cannot easily place a dollar value."

Dall et al. The economic burden of elevated blood glucose levels in 2017: diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes. Diabetes Care 2019;42:1661–1668

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Clinical Implications of Heart Failure With Preserved Ejection Fraction in Diabetes

Heart failure with preserved ejection fraction (HFpEF) may be a clinical manifestation of microvascular rather than macrovascular complications in diabetes according to Tromp et al. (**p. 1792**). Moreover, microvascular complications are more common in individuals with diabetes and HFpEF than equivalent individuals with heart failure with reduced ejection fraction (HFrEF). The outcomes are the result of a study of 2,800 individuals with heart failure and diabetes who were prospectively enrolled from the Asian Sudden Cardiac Death In Heart Failure (ASIAN-HF) registry. Individuals were followed for up to 3 years and monitored for the prevalence of various microvascular complications of diabetes. The authors found that in their Asian cohort, individuals with diabetes and any microvascular complication were more likely to have had HFpEF than HFrEF (odds ratio 1.70 [95% CI 1.15–2.50]; *P* = 0.008). There was also an increased likelihood of having HFpEF when there were increasing numbers of microvascular complications. Such complications were also associated with more left ventricular hypertrophy and reduced quality of life. In terms of the primary composite outcome of all-cause death or hospitalization due to heart failure, the presence of microvascular complications of diabetes was associated with a hazard ratio of 1.35 (95% CI 1.04–1.76; *P* = 0.024) after adjusting for numerous factors. They go on to discuss certain limitations of the study, concluding that larger multiethnic studies are still needed to confirm the generalizability of the results. According to author Carolyn S.P. Lam: "Our findings call into question the assumption that 'diabetic heart disease' refers only to macrovascular coronary artery disease and HFrEF. In fact, HFpEF may be a microvascular manifestation of diabetes. The clinical implication is that in screening for microvascular complications of diabetes, beyond checking the eyes, kidneys, and nerves for retinopathy, nephropathy, and neuropathy, we should consider the heart and HFpEF."

Tromp et al. Microvascular disease in patients with diabetes with heart failure and reduced ejection versus preserved ejection fraction. Diabetes Care 2019;42:1792–1799

Microvascular Complication Risks Reduced After Reversal of Prediabetes

Perreault et al. (**p. 1809**) report that reversing prediabetes to normoglycemia through lifestyle interventions is associated with lower prevalence of microvascular complications. Specifically, they found that reductions in complications were primarily due to lower exposure to elevated glucose levels over time and that there is likely differential risk for subtypes of microvascular complications that begin in prediabetes glycemic ranges. The conclusions come from a post hoc analysis of the Diabetes Prevention Program (DPP) study and its follow-up outcomes study (DPPOS) and involved just over 2,000 individuals. The participants either managed to reverse prediabetes following lifestyle intervention or did not in the original DPP study. The authors also looked at microvascular outcomes over the following 15 years up to the beginning of 2014. They also looked at incidents of nephropathy, retinopathy, and neuropathy individually as well as an aggregate measure of all three. They found that returning to normoglycemia ever, as opposed to never, was associated with a lower prevalence of aggregate microvascular outcomes in models adjusted for a series of factors. In contrast, they found the association was lost in models additionally adjusted for either average HbA_{1c} in the follow-up period or diabetes status at the end of the follow-up, indicating that lower HbA_{1c} and lower diabetes risk likely explain the association. Similar associations could also be detected for nephropathy and retinopathy but not neuropathy. While cautioning about the exploratory and hypothesis generating nature of the analysis, the authors point out that guidelines are now appearing that suggest prediabetes be "treated" with lifestyle interventions that are very similar to those of diabetes. Consequently they question the use of "pre-" as a disease descriptor and suggest instead that prediabetes might simply be an early form of diabetes.

Perreault et al. Regression from prediabetes to normal glucose regulation and prevalence of microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). Diabetes Care 2019;42:1809–1815

https://doi.org/10.2337/dc19-ti09