COMMENTARY

Deciphering the Effects of Semaglutide Across the Glycemic Spectrum

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Ameliorating progression of prediabetes to type 2 diabetes, and consequently reducing the risk of cardiovascular disease (CVD) (1), has been the focus of much research. While many modalities for type 2 diabetes prevention have been studied, including behavioral interventions (2,3) and use of medications (4–7), each has limitations. Since a significant proportion of people in the prediabetes range never progress to type 2 diabetes, some have argued the benefits of intervening are unclear (8,9). Indeed, most large-scale prevention studies have shown no benefit on future CVD risk (3–6), and only one small study has shown a long-term reduction in CVD risk (10). In the current era of highly efficacious glucose-lowering treatments, the composite effects of glucagon-like peptide 1 (GLP-1) agonists on weight and insulin secretion open the door to medical interventions that could reduce progression to type 2 diabetes (7). What remains unclear is whether this effect is sustainable and, if so, whether it reduces future CVD events and/or mortality while at the same time being cost-effective.

In the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) study, people with overweight and obesity (BMI >27 kg/m^2), a history of prior CVD, and without diabetes were randomized to receive 2.4 mg semaglutide or placebo (11). After 40 months of follow-up, a 20% reduction in the risk of major adverse cardiovascular events (MACE), a composite outcome of death from CVD, nonfatal myocardial infarction, or nonfatal stroke, was observed in the semaglutide group (11). SELECT followed the results of the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6), a similar study performed in people with type 2 diabetes and known CVD that showed a reduction of 26% in the same outcome (12). Thus, across the spectrum of glycemia, semaglutide reduces the risk of MACE in those with established CVD.

Given that two-thirds of SELECT participants met criteria for prediabetes, several important questions remain. Was the observed reduction in CVD risk driven by improvements in HbA_{1c}? How did glycemia change over the study, and were changes independent of baseline HbA_{1c} or weight reduction? Did semaglutide help prevent the development of type 2 diabetes? These questions are explored in two informative articles from the SELECT investigators in this issue of the *Diabetes Care* (13,14).

The analysis by Ildiko et al. (13) investigated the effect of semaglutide on CVD risk reduction across the range of baseline HbA_{1c}. The 17,604 SELECT participants were categorized into three baseline HbA_{1c} categories, comprising approximately a third in each group. Irrespective of baseline HbA_{1c} category, similarly reduced hazards of MACE events were observed: 18% for HbA_{1c} $<5.7\%$, 23% for HbA_{1c} 5.7% to $<6.0\%$, and 19% for HbA_{1c} 6.0% to $<6.5\%$. A time-to-event analysis incorporating baseline HbA_{1c} as a continuous covariate showed no significant effect of HbA_{1c} on progression to outcomes. Lastly, the beneficial effects of semaglutide occurred independently of whether HbA_{1c} decreased or increased by >0.3 percentage points or remained unchanged.

In contrast, studies in type 2 diabetes, such as Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (15) and Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) (16), have shown CVD risk reduction is partially dependent on baseline HbA_{1c}.

In people with diabetes, the wider range of glycemia may mean that the insulin-dependent effects of GLP-1 are dominant, making glucose lowering a key mediator. Conversely, in the narrower normoglycemic/prediabetes range, the non–glucose-dependent effects might predominate. As changes in many other cardiometabolic risk factors have been noted with semaglutide in SELECT (11,17,18), a mediation analysis that accounts for changes in body weight and anthropometry, cholesterol, blood pressure, C-reactive protein, and renal function would be of interest.

The second analysis by Kahn et al. (14) sought to better understand the effects of semaglutide on glycemia over 156 weeks of follow-up. There was a clear effect of

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semaglutide to lower glycemia, but importantly HbA_{1c} increased over time at a similar rate in both semaglutide and placebo arms, indicating a clear progressive loss of β-cell function. When considering regression, semaglutide demonstrated benefit; about a third of participants had normoglycemia at baseline, and after 3 years of semaglutide treatment nearly 70% were normoglycemic, while with placebo the proportion was unchanged. Analyzing progression to type 2 diabetes at 3 years, 3.5% of those randomized to semaglutide had developed diabetes versus 12.0% in the placebo arm, a 73% risk reduction. In the cohort that was most hyperglycemic at baseline (HbA_{1c} 6.0% to <6.5%), the respective proportions were 7.4% and 27.8% (a similar risk reduction).

A third of the effects on regression and progression were found to be mediated by the magnitude of weight loss, but notably, semaglutide did not slow the rate of progression, it just occurred in a lower proportion (like the SCALE study of liraglutide [7]). Furthermore, since progression was greatest in those with the highest HbA_{1c} at baseline, it seems weight loss was not enough to mitigate the development of diabetes. A crucial missing element is understanding the change in the β-cell's insulin secretion capability and its relationship to progression and remission. Beneficial effects on HbA_{1c} were observed even in participants who did not lose weight, highlighting the significance of semaglutide's role in enhancing insulin secretion.

Taken together, both analyses extend our understanding of the effects of semaglutide in people without diabetes across a range of HbA_{1c}. What do these findings mean in practice? With the important caveat that these findings relate to individuals with established CVD, it is increasingly evident that the benefits of GLP-1 receptor agonists extend far beyond those initially observed in type 2 diabetes and are mediated via multiple mechanisms—be it weight loss, glucose lowering, or other pathways.

There will be a broader role for GLP-1 agonists in cardiovascular risk management, and the latest analysis of renal outcomes in those with and without type 2 diabetes demonstrates its multisystem effects (17,19). These agents will likely be used more holistically than specifically for weight or glucose lowering; this might include a role in prevention of type 2 diabetes and, gazing further into the future, perhaps even in the prevention of multimorbidity.

For now, broader use in at-risk populations seems to be low-hanging fruit. People with early-onset type 2 diabetes, for example (children and adults diagnosed at <40 years of age), have excess cardiovascular morbidity and reduced life expectancy (20). The presentation is associated with an adverse cardiometabolic profile with severe obesity and faster β-cell failure. Might aggressive treatment with GLP-1 agonists at diagnosis reduce mortality in the long term?

The use of GLP-1 agonists for type 2 diabetes prevention is controversial; whether this would prove to be cost-effective is unclear, as are the questions of when, would, or could treatment be stopped. There also remains a gap in understanding: while some individuals progress to type 2 diabetes, many others will not, even without intervention. Perhaps a focus on those with prediabetes who are the most hyperglycemic (HbA_{1c} >6.0%) is needed. Studying effects across a range of BMIs could additionally help fill the knowledge gap for those who develop type 2 diabetes at leaner body mass.

It is clearly not feasible, cost-effective, or likely safe to treat large swathes of the population with GLP-1 agonists, so the next phase of research must, in part, be focused on identifying the subgroups of people at highest risk. SELECT recruited participants who were predominantly male (70%) and of White ethnicity (~80%). Generalizability of findings to female sex and other ancestry groups is limited, and some ancestry-specific differences are already observed; Asian participants were leaner and lost less weight, for example (18). With four out of five people with type 2 diabetes living in low- and middle-income countries (21), regions where deaths from CVD now outnumber deaths from communicable disease, studies in diverse ancestries and resource settings are needed.

In conclusion, the fast-evolving field of incretin-based therapeutics continues to surprise and surpass expectations. We must now focus on diversifying populations studied through age, sex, BMI, and ancestry, be more precise about stratifying those at risk, and ensure affordability and equitable implementation of these therapeutics.

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