

# Experts Highlight How GLP-1s Have Revolutionized Management of T2D and Obesity

LAURA JOSZT, MA

In the past few years, glucagon-like peptide-1 (GLP-1) receptor agonists have revolutionized the treatment of patients with type 2 diabetes (T2D) and obesity, and the cardiometabolic space has “exploded,” according to speakers at an Institute for Value-Based Medicine (IVBM) event hosted by *The American Journal of Managed Care* and Cleveland Clinic.

Nearly 12% of Americans have diabetes and another 38% have prediabetes,<sup>1</sup> which could turn into T2D within 5 years, according to the CDC.<sup>2</sup> Furthermore, 70% of individuals in the US are overweight or obese.<sup>3</sup> These statistics highlight the need for treatments, said Diana Isaacs, PharmD, BCPS, BCACP, BC-ADM, CDCES, director of education and training in diabetes technology at Cleveland Clinic.

In this landscape, the introduction of incretin therapies such as semaglutide and liraglutide (both GLP-1s) and the GLP-1/gastric inhibitory polypeptide (GIP) tirzepatide for diabetes and weight loss has been very exciting, noted Isaacs, who chaired the IVBM event.

The introduction of GLP-1s has “ushered in a new generation of managing diabetes beyond just chasing glucose,” Kevin Malloy, PharmD, BCPS, BC-ADM, CDCES, endocrinology clinical pharmacist at Cleveland Clinic, said during his presentation.

He discussed the physiological role of GLP-1 and its relevance to diabetes management, highlighting that GLP-1 receptor stimulation increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, decelerates gastric emptying, and increases satiety while decreasing prospective food consumption.

The first GLP-1 receptor agonist was exenatide (Byetta, Bydureon), followed by lixisenatide, liraglutide (Victoza), dulaglutide (Trulicity), and semaglutide (Ozempic, Rybelsus, Wegovy). In addition, albiglutide was approved in 2014 but removed from the market in 2017.<sup>4,5</sup> These agents have been

not only effective at lowering glucose, but they also carry a low risk of hypoglycemia and have been linked to weight loss.

In 2017, the therapy selected for patients with T2D was “really dealer’s choice,” Malloy said. Physicians would consider what patients could afford and what would get their glucose to the goal level.

“It didn’t matter [whether] your patient had cardiovascular disease or heart failure [or] chronic kidney disease, [you would] just pick whatever gets their glucose to goal and then call it a day,” he said.

Managing diabetes is different today because, in addition to targeting glucose, physicians are managing patients’ cardio-metabolic-renal risk. The evolution of GLP-1s beyond just glucose-lowering agents came from the cardiovascular outcome trials, which all showed a trend of the agents lowering cardiovascular risk. Results of the phase 3 REWIND trial (NCT01394952) for dulaglutide even showed primary prevention of cardiovascular events.<sup>6</sup>

GLP-1s have “ushered in a new age of diabetes management,” Malloy said. “We’re no longer just chasing glucose and [hemoglobin] A<sub>1c</sub> [HbA<sub>1c</sub>]. We are providing full comprehensive care to patients and reducing their cardio, renal, and metabolic risk.”

Now the role of GLP-1s is expanding to weight-related comorbidities. Obesity takes a significant toll on a patient’s lifespan and healthy years of life lost, explained Yael Mauer, MD, MPH, staff physician in the Department of Endocrinology, Diabetes, and Metabolism at Cleveland Clinic. People tend to think obesity affects cardiometabolic health only when it’s severe, but there are risks even for people with overweight.

A disease-simulation model found that a man between the ages of 20 and 39 years with overweight will lose 2.7 years of life and 5.9 years of healthy life.<sup>7</sup> Meanwhile, that same patient

with severe obesity will lose 8.4 years of life and 18.8 years of healthy life. And women are affected even more. By 2030, half of adults will have obesity and nearly one-fourth will have severe obesity, which is expected to become the most common body mass index (BMI) category for women, non-Hispanic Black adults, and low-income adults.<sup>8</sup>

There are no recent guidelines from major endocrine societies in terms of obesity pharmacotherapy, although they are in the works, Mauer said. Among the antiobesity medications approved are the GLP-1s semaglutide and liraglutide, as well as the GLP-1/GIP receptor agonist tirzepatide (Mounjaro, Zepbound). In addition, phentermine-topiramate extended release (ER), naltrexone-bupropion ER, sympathomimetics, and orlistat (Xenical, Alli) are approved.

Mauer highlighted 3 phase 3 incretin therapy trials, all of which excluded patients with diabetes. In the STEP 1 trial (NCT03548935), 1961 patients with a BMI of at least 27 were randomly assigned to receive semaglutide or placebo.<sup>9</sup> More than half of patients on semaglutide lost 15% or more of their body weight compared with 5% of patients on placebo.

In the SELECT trial (NCT03574597), 17,000 patients with a BMI of at least 27 with established cardiovascular disease received either semaglutide or placebo in addition to standard of care.<sup>10</sup> Patients on semaglutide had a major adverse cardiovascular event (MACE) reduction of approximately 20%. MACE occurred in approximately 6.5% of patients on semaglutide compared with 8% of patients on placebo.

Finally, in the SURMOUNT-1 trial (NCT04184622), 2539 adults with a BMI of at least 27 and at least 1 weight-related complication received either tirzepatide (5 mg, 10 mg, or 15 mg) or placebo.<sup>11</sup> In the tirzepatide groups, the mean percentage change in weight was between -15% and -20.9% compared with -3.1% for the placebo group.

“We have to look at patients with obesity in the context of all of their cardiovascular disease,” Mauer said. He added that these study results show “the incretin therapies can significantly improve weight and bring cardiovascular benefits.”

Robert Zimmerman, MD, a specialist in the Department of Endocrinology, Diabetes, and Metabolism at Cleveland Clinic, looked into the future of a therapy for T2D and obesity. He highlighted that researchers are looking at higher doses of oral semaglutide, as well as new therapies including orforglipron and retatrutide.

The phase 3 OASIS 1 trial (NCT05035095) evaluated oral semaglutide 50 mg,<sup>12</sup> which is a much higher dose than the 14 mg currently available. Research results show that patients can achieve a weight reduction of approximately 15%, which is similar to injectable products, Zimmerman said. However, vomiting is associated with the higher dose.

The phase 3 PIONEER PLUS trial (NCT04707469) looked at oral semaglutide 25 mg and 50 mg vs 14 mg in adults with T2D, and it found a greater decrease in HbA<sub>1c</sub> for the higher dose and a lower efficacy with the 14-mg dose.<sup>13</sup> For patients with T2D, the 14-mg dose results in an approximate 4% reduction in weight vs 6% with the 25-mg dose and 8% with the 50-mg dose. However, Zimmerman noted that the percentage of patients with vomiting was less than in OASIS 1.

Another agent being investigated is orforglipron, an oral nonpeptide GLP-1, which has been studied in a phase 2 trial (NCT05051579) in patients with obesity or overweight plus at least 1 weight-related coexisting condition.<sup>14</sup> After 36 weeks, participants had an average body weight reduction of approximately 15%. Vomiting occurred less often than it did with the highest dose of oral semaglutide. Orforglipron also reduced HbA<sub>1c</sub> by approximately 2.1%.

“This is very exciting that we again have another oral GLP-1 agonist that is possibly going to become available for us that will help us both with weight reduction and glycemic control,” Zimmerman said.

Cagrilintide in combination with semaglutide (CagriSema) is a multiagonist compound being investigated in patients with T2D.<sup>15</sup> From baseline, CagriSema reduced HbA<sub>1c</sub> by approximately 2.2% compared with 1.8% for semaglutide alone and 0.8% for cagrilintide alone in a phase 2 trial (NCT04982575). Furthermore, the average reduction in body weight was approximately 15%, which again was higher than with either agent alone.

“This is very exciting that we’re going to start seeing with these combination products much greater efficacy at weight loss and control of diabetes,” Zimmerman said. “But weight loss, in particular, in patients [who] have type 2 diabetes is going to be much, much better.”

Finally, he covered retatrutide, a GLP-1/GIP receptor agonist that is being studied in a phase 2 trial (NCT04867785) in multiple doses in patients with T2D with overweight or obesity.<sup>16</sup> The agent reduced HbA<sub>1c</sub> by 2.2% and body weight by 17%. The benefit of this agent is that the GIP receptor agonist seems to reduce the amount of vomiting and gastrointestinal adverse effects seen with other GLP-1 agents, Zimmerman pointed out.

However, despite the promise of these agents, cost and availability remain barriers. “The hope is that more patients will have access to these agents when supplies increase and costs come down,” he said.

With the increasing use of GLP-1s and sodium-glucose cotransporter 2 (SGLT2) inhibitors, there are more questions about their use in pregnancy, said Stacey Ehrenberg, MD, maternal-fetal medicine specialist and director of diabetes in

pregnancy at Cleveland Clinic. Slightly more than one-third of women with a new diagnosis of diabetes are of reproductive age,<sup>17</sup> with many women of reproductive age now meeting the criteria for starting GLP-1s and SGLT2s outside of pregnancy. In addition, an increasing number of pregnant patients have T2D and sequelae from it, she said.

Recent research results have shown that the use of GLP-1s and other noninsulin antidiabetic therapies is increasing in pregnancy, which is exciting to Ehrenberg. Despite the lack of data on the use of these therapies in pregnancy, their use does mean pregnant patients have their HbA<sub>1c</sub> under control, which helps prevent complications.

When HbA<sub>1c</sub> and BMI increase, there can be complications such as an increased risk of miscarriage, preterm labor, hypertensive disorders, stillbirth, cesarean deliveries, and labor complications. In addition, there has been more research showing the lifelong effects on children born to women who did not have their blood glucose well controlled. There are increased complications for the newborn in the short term after delivery, including respiratory distress, jaundice, hypoglycemia, and metabolic complications that can lead to stays in the neonatal intensive care unit.

Although results of some animal studies have shown potential risks, human data are still limited. Ehrenberg noted that most data come from case reports of very small numbers of participants. One study looked at 3 patients with exposure to GLP-1s in pregnancy and others with exposure to SGLT2s. But she said the findings were “not enough to hang my hat on when you look at the total... It’s not something that I can really feel confident explaining data based off of this to my patients.”

Similarly, with research into lactation, only results from animal studies of GLP-1s were available, and the findings varied from safe to nonsafe levels, highlighting the need for human studies to evaluate this better.

However, according to results of a recent study of the teratogenic risk of periconception exposure to second-line noninsulin antidiabetic medications, the rates of malformations or cardiac malformations for noninsulin medications were no different than insulin,<sup>18</sup> which is the gold standard in pregnancy because it is definitively known that it does not cross the placenta. The study included a cohort of more than 3.5 million participants in 6 countries, evaluating use of metformin, insulin, sulfonylureas, dipeptidyl-peptidase-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists before pregnancy or within the first trimester. The study findings indicate that any malformations were a result of patients’ underlying comorbidities and not the medications.

“I love that these medications can be used in pregnancy, or leading up to pregnancy, to optimize [patients’] care, and then take them off of it when we recognize they’re pregnant, or in the first trimester,” Ehrenberg said.

Finally, M. Cecilia Lansang, MD, MPH, director of diabetes technology in the Department of Endocrinology at Cleveland Clinic, discussed the use of continuous glucose monitoring (CGM) to support medication titration.

She ran through the types of devices available and the differences between them, including an OTC device that is already approved and could be available this summer. She also highlighted that CGM tools are becoming more accurate.<sup>19</sup>

The CGM data create a report called the ambulatory glucose profile, which can be used to identify patterns to inform medication changes. “When we want to home in on patterns of behavior that we can improve on or maybe what medications we want to escalate or deescalate, then we probably want to look at the individual readings,” Lansang said.

For instance, for a patient who is hypoglycemic, the first thing to do is deescalate medication, even if that means their HbA<sub>1c</sub> rises a little, she said. Because hypoglycemia is associated with cardiovascular risks, she would put that patient on a GLP-1.

“If you see something that’s actionable, then let’s do something about it,” Lansang said.

**Author Information:** Ms Joszt is an employee of MJH Life Sciences, parent company of the publisher of *The American Journal of Accountable Care*.

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