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CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

# GLP-1 Receptor Agonists: A Review of Success & Safety



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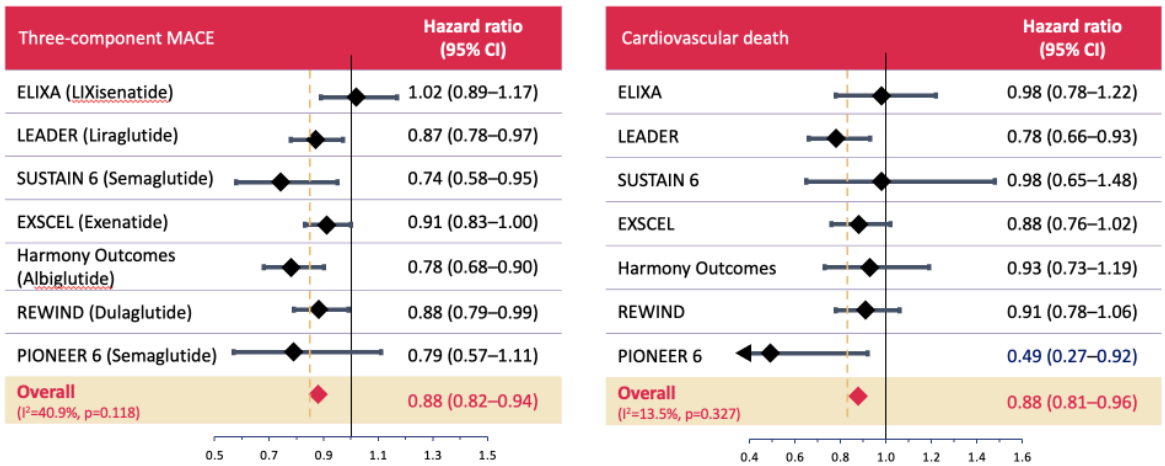
GLP-1 receptor agonists (GLP-1RA) have established themselves as a highly effective treatment option for patients affected with diabetes and/or obesity. Semaglutide is approved in Canada for the treatment of type 2 diabetes (T2D), available as the weekly subcutaneous injection, Ozempic®, and as the daily oral tablet, Rybelsus®. Semglutide is also approved for the treatment of obesity, as the weekly subcutaneous injection, Wegovy®, but this product is not yet available in Canada due to overwhelming demand in other countries. Evident metabolic benefits including a potent reduction in HbA1c and body weight have already been demonstrated leading to growing utilization of GLP-1RA. However, as any class of medications becomes increasingly popular, an expectant rise in safety concerns becomes an important subject for discussion amongst healthcare professionals and patients.

**large CV outcomes trials (CVOT) have been conducted for all GLP-1RA and CV safety has already been established (Figure 1)**

**Figure 1:** GLP-1 RAs: Risk of 3-point MACE and CV death




MACE, major adverse cardiovascular event; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; CI, confidence interval.

Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet Diabetes & Endocrinology*. 2019;0(0). doi:10.1016/S2213-8587(19)30249-9

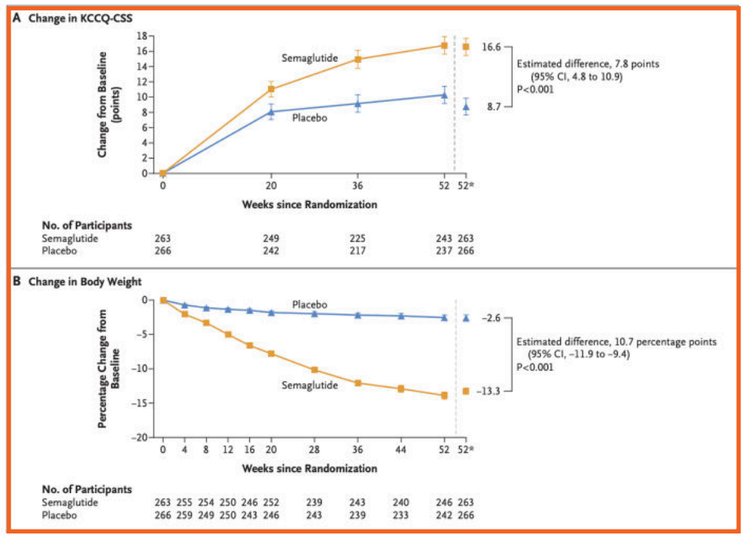
**For patients affected with obesity, the SELECT trial's topline results revealed that subcutaneous semaglutide showed a 20% MACE reduction**

## Mandated Safety Trials Showing Us Clear Cardiovascular Benefits

As new classes of diabetes medications emerge, safety concerns usually begin with those at high-risk for cardiovascular (CV) disease. Since 2008, the FDA mandates that all new agents for the treatment of diabetes must demonstrate CV safety. As such, large CV outcomes trials (CVOT) have been conducted for all GLP-1RA and CV safety has already been estab¬lished (Figure 1). Liraglutide (Victoza®) not only reduced major adverse cardiovascular events (MACE) by 13% in the LEADER study, but also decreased CV and all-cause mortality by 22% and 15%, respectively. Subcuta¬neous semaglutide reduced MACE by 26% in the SUSTAIN-6 trial. Cardiovascular safety was demonstrated with oral semaglutide in the PIONEER-6 trial, though the much larger SOUL trial is designed to show CV superiority, and these results should be available next year. These trials have enrolled participants predominantly with established CV disease (secondary prevention). The REWIND trial demonstrated a 12% reduction in MACE with dulaglutide (Trulicity®) with a majority (69%) of subjects only at high-risk of CV disease (primary prevention).

For patients affected with obesity, the SELECT trial's topline results revealed that subcutaneous semaglutide showed a 20% MACE reduction meeting superiority, and all three MACE components contributed. The publication was not available during the writing of this article but will soon be featured as a separate Clinical Practice Update issue. Also, a very recently published STEP HFpEF trial showed us the benefits of subcutaneous semaglutide amongst participants affected with obesity and heart failure with preserved ejection fraction (Figure 2). Participants' symptoms and physical limitation related to heart failure were evaluated using the Kansas City Cardiomyopathy Questionnaire clinical summary score over 52 weeks (KCCQ-CSS, with higher scores indicating fewer symptoms and physical limitation). A statistically significant estimated difference in mean change in the KCCQ-CSS of 7.8 points (p<0.001) favoured the group receiving subcutaneous semaglutide over placebo. Not surprisingly, mean percentage change in body weight was –13.3% with semaglutide and –2.6% with placebo (p<0.001). Greater improvements in exercise function using the mean change in the 6-minute walk test also favoured semaglutide over placebo (21.5m vs. 1.2m, p<0.001). Lastly, an exploratory analysis evaluating adjudicated events of hospitalization for heart failure or an urgent visit favoured semaglutide over placebo (1 participant vs. 12 participants, hazard ratio 0.08).

**Figure 2:** Changes from Baseline to Week 52 in the Dual Primary End Points




Kosiborod, Mikhail N., et al. "Semaglutide in patients with heart failure with preserved ejection fraction and obesity." New England Journal of Medicine 389.12 (2023): 1069-1084.

The CV benefits of semaglutide amongst patients affected with type 2 diabetes and/or obesity is not entirely well understood. Some may be due to the observed reduction in body weight, but there may be other atherogenic mechanisms that have not yet been proven. Thus far, GLP-1RA trials that were meant to evaluate safety have all demonstrated CV benefits.

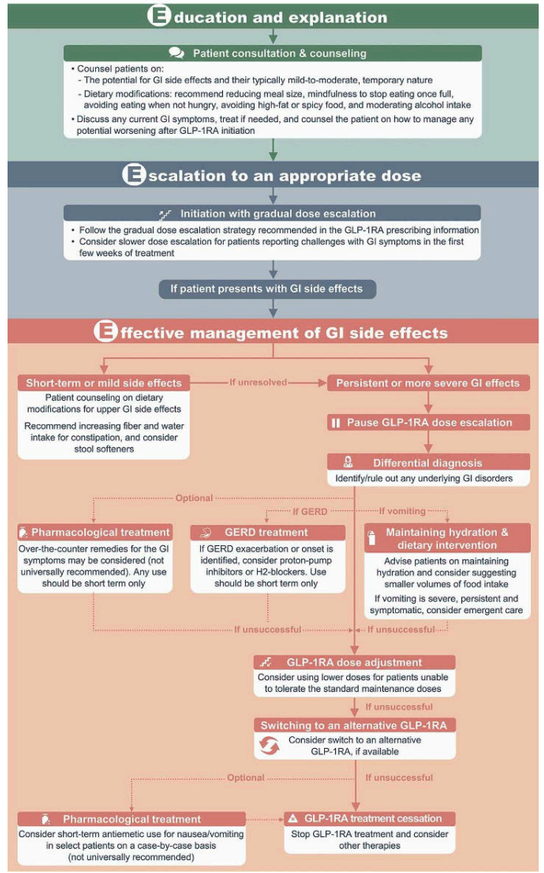
## What is Gastroparesis?

The adverse effects of GLP-1RA are usually gastrointestinal (GI), and are most commonly observed following treatment initiation and dose escalation.

**In most cases, temporarily reducing or discontinuing GLP-1RA will alleviate symptoms amongst those affected**

These include nausea, vomiting and diarrhea, and less frequently, constipation, dyspepsia, and eructation. For most, these adverse effects are mild and transient in nature. However, anecdotal reports in mainstream media of "stomach paralysis" associated with both semaglutide and tirzepatide (a dual GLP/GIP agonist) have raised recent concerns amongst patients and providers. It is important to recognize that delayed gastric emptying is an intended effect of GLP-1RA leading to reduced postprandial hyperglycemia, increased satiety, and weight loss. Further, autonomic neuropathy is one of least recognized complications of T2D and is often associated with diabetic gastroparesis. Given the widespread use of GLP-1RA, a patient with undiagnosed or mild diabetic gastroparesis may experience undesirable or worsening GI adverse effects after starting a GLP-1RA. In most cases, temporarily reducing or discontinuing GLP-1RA will alleviate symptoms amongst those affected. It is also worth noting that gastroparesis, and even the use of prokinetic agents, are not contraindications for GLP-1RA. Counselling about expectant effects of GLP-1RA is of critical importance (Figure 3). Other strategies to minimize adverse effects amongst all patients starting GLP-1RA include consuming smaller meal portions, increasing fluid intake, and avoiding fried, fatty, or spicy foods.

**Figure 3:** Managing the Gastrointestinal Side Effects of GLP-1 Receptor Agonists




Wharton, S et al. "Managing the Gastrointestinal Side Effects of GLP-1 Receptor Agonists in Obesity: Recommendations for Clinical Practice." Postgraduate Medicine 134, no. 1 (January 2, 2022): 14–19.

Initial concerns of pancreatitis and pancreatic cancer associated with GLP-1RA have not been observed in clinical trial programs for both type 2 diabetes and obesity. Animal models initially suggesting a risk of medullary thyroid cancer (MTC) have also not been observed in humans. These agents remain contraindicated with a personal or family history of MTC or MEN2. The incidence of gallstones with GLP-1RA use is higher compared to placebo in recent observational studies. While the mechanism has not been well-defined, gallstones are also reported amongst patients experiencing significant weight loss, including following bariatric surgery. For T2D, hypoglycemia with GLP-1RA is observed only when these agents are combined with sulphonylureas or insulin, and the risk remains relatively low overall. For obesity, the incidence of hypoglycemia with GLP-1RA is negligible and comparable to placebo.

Safety ties into the mantra that all physicians and healthcare professionals abide by which is to avoid harm for our patients: be it from disease progression or adverse effects from medications. There are a variety of pharmacologic options in our toolkit for the treatment of T2D and obesity. GLP-1RA possess many positive benefits, including robust A1C lowering, weight loss, and CV benefits. Counselling ensures success, especially when mitigating some of the more commonly associated GI adverse effects. And for those apprehensive about using a subcutaneous injection, oral semaglutide is a viable alternative. Today, we can better individualize therapy leading to greater benefits for our patients affected with metabolic disease.

CLINICAL PRACTICE UPDATE IN

# ENDOCRINOLOGY & DIABETES

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back to our in-person format

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agenda

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|---|---|
| **8:00-8:30am** | Continental Breakfast & Registration |
| **8:30-8:45am** | Welcome & Introductions |
| **8:45-9:15am** | **High-Dose GLP-1R Agonists for T2D, Obesity or NASH**<br>Dr. Ron Goldenberg |
| **9:15-9:45am** | **Insulins: Basals, Biosimilars & Beyond**<br>Dr. Megha Poddar |
| **9:45-10:15am** | **New Evidence for Continuous Glucose Monitoring in T2D**<br>Dr. Ronnie Aronson |
| **10:15-10:45am** | Panel Discussion & Questions |
| **10:45-11:15am** | Snack Break / Exhibit Booths |
| **11:15-11:45am** | **A New Look: Lipid Disorders, Surrogate Markers & Novel Agents**<br>Dr. Alex Abitbol |
| **11:45-12:15pm** | **Diabetes Remission: Is it Ready for Prime Time?**<br>Dr. Harpreet Bajaj |
| **12:15-12:45pm** | Panel Discussion & Questions |
| **12:45-1:00pm** | Closing Remarks & Evaluations |

✱ **PLEASE RSVP VIA:** **FAX:** 416.645.2931 or **EMAIL:** rsvp@LMC.ca or **QR CODE:**

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