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Moving Beyond Weight Loss: a Focus on the SELECT Trial and its Impact on Cardiovascular Health in Obesity Management

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Obesity is a well-established chronic disease that significantly impacts 1 in 4 adults and 1 in 10 children across Canada. Its prevalence continues to escalate, paralleled by an increase in its associated comorbidities such as diabetes, heart disease, and metabolic dysfunction-associated steatotic liver disease (MASLD). In order to address this complex challenge, the Canadian obesity clinical practice guidelines outlined three, safe and effective treatment strategies including; behavioural/psychological therapy, pharmacotherapy, and bariatric surgery. However, as treatments advance and their efficacy improve, most notably in pharmacotherapy, the landscape of obesity management is undergoing a profound shift in treatment goals. The conventional benchmark of success, primarily focused on weight reduction, is gradually evolving towards a more comprehensive approach centred on improving health outcomes. This change in narrative is redefining success of obesity treatment by shifting emphasis away from weight loss to seeing objective improvement in comorbidities related to adipocyte dysfunction. Hopefully, these changes result in improving access to obesity treatments, individualizing treatment options to specific patients, and reducing stigma and bias associated with obesity management.

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Cardiovascular disease and its risk factors are amongst the most common comorbidities for those with a BMI>30. However, despite its high prevalence and poor health outcomes, most obesity treatments have shown a trend toward improving cardiovascular risk factors but have not yet shown a reduction in major adverse cardiovascular events (MACE). The Look AHEAD trial focused on intensive lifestyle interventions (ILI) in those with overweight or obesity with type 2 diabetes and its impact on cardiovascular disease (CVD) and it did not show a significant difference in CVD outcomes. This may be a result of poor efficacy of treatment, generally yielding a sustained weight loss of less than 10%. Bariatric surgery, yielding an average weight loss of 25%, was the only obesity treatment to date to show a significant reduction in overall mortality as seen in the Swedish Obesity Study. Cardiovascular outcome trials (CVOTs) in obesity treatments have started to make headlines as the newer, more effective obesity medications have started to show benefit in hard outcomes like cardiovascular disease for the first time. We will review the landmark trial for **Semaglu-**

tide and Cardiovascular Outcomes in Obesity without Diabetes (SELECT) as this is the landmark trial for the first obesity medication to show cardiovascular benefit.

The SELECT trial was published in the *New England Journal of Medicine* in Nov 2023 and marked significant advancement in cardiovascular risk management for individuals with overeweight or obesity but without diabetes. This trial was a multi-centre, double-blind, randomized, placebo-controlled study. Its primary aim was to assess the efficacy of semaglutide 2.4mg, a weekly subcutaneous GLP-1 receptor agonist, in reducing major cardiovascular events. Participants in this study were 45 years of age or older with a BMI of 27 or higher, and all had preexisting cardiovascular disease. Patients were excluded from the trial if they had a previous diagnosis of Type 1 or Type 2 diabetes, an HbA1c level above 6.5%, had taken any glucose-lowering agents in the past 90 days, or had NYHA Class IV heart failure. 17604 patients were enrolled in the study with a mean follow-up time of 39.8 months. This qualifies as the largest and longest obesity pharmacotherapy clinical trial to date. The demographic of patients enrolled in the SELECT trial were predominantly male participants (72.3%), older than average (61.6 years) and a mainly white ethnicity (84%). This demographic is likely to be significantly different from most patient populations across Canada and has been a criticism of the study. The mean BMI was 33.3 kg/m^2 with most patients having prediabetes (66.4%). Patients were randomly assigned to receive either weekly subcutaneous injections of semaglutide (2.4 mg) or a placebo. The primary endpoint was a composite of MACE including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

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The trial's results were impressive and had significant impact: Patients treated with semaglutide experienced a 20% reduction in the risk of MACE compared to those who received the placebo (HR 0.80 (95% CI: 0.72; 0.90) p<0.001). All three components of MACE, death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke contributed to this outcome. Specifically, to note was a 15% reduction in cardiovascular death, although this was not statistically significant (HR 0.85 (95% CI: 0.71 ;1.01) p=0.07), see Figure 1.

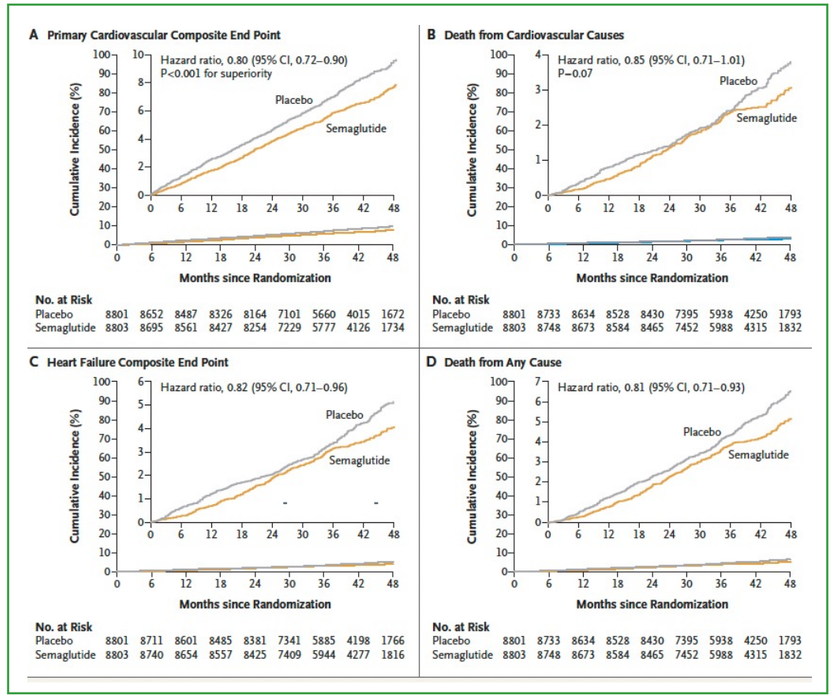

Figure 1 Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points[5]

At week 52, 66% of semaglutide-treated patients with baseline glycated hemoglobin levels of ≥5.7% achieved levels of <5.7%, compared to only 19.8% in the placebo group, showing a significant benefit for diabetes prevention. Additionally, semaglutide showed marked improvements over placebo in body weight reduction (-9.4%, -8.51% placebo subtracted), waist circumference decrease (-6.53 cm), and reductions in systolic and diastolic blood pressure, alongside favourable changes in cholesterol and triglyceride levels. Most significant is the fact that these changes are seen on top of high rates of statin, anti-hypertensive and disease modifying therapy use for established CVD. The trial maintained a high completion rate, with 17,061 patients (96.9%) reaching the end of the study, either through attending the final trial visit or due to mortality.

Serious adverse events fortunately occurred less frequently in the semaglutide group (33.4%) compared to the placebo group (36.4%), with a statistically significant difference. Adverse events leading to the discontinuation of the trial product were twice as high with semaglutide (16.6%) than placebo (8.2%), particularly due to gastrointestinal and nervous system disorders. This is important as the higher rates of discontinuation may make it difficult to adhere to this medication long term despite its positive benefits. Gallbladder-related disorders were slightly more common with semaglutide. Importantly, the incidence of malignant neoplasms, acute pancreatitis, acute kidney failure and psychiatric disorders was comparable between the two groups. This was a key finding as it helps to reassure us of the safety profile of semaglutide, through standardized clinical trial protocol, in a large group of high risk patients over many years. Importantly, there was no unexpected safety findings in the SELECT trial (see table 4 for details).

The mechanism of reduction of cardiovascular events with semaglutide is still largely unknown. Certainly, the MACE curve diverged early in the course of treatment in favour of semaglutide, long before significant weight loss was seen (weight plateau occurred ~52 weeks), making it unlikely that weight loss alone is the sole mechanism of benefit. However, other non-surgical obesity treatments have failed to yield this degree of weight loss and previous studies have shown that a 10% weight reduction can decrease cardiovascular risk. There was significant improvement in cardiometabolic risk factors including blood pressure, cholesterol and waist circumference therefore the cardiovascular risk reduction with semaglutide could be attributed to both the early physiological changes and improvement of adipocyte dysfunction through weight reduction. In the subgroup analysis of MACE outcomes across all BMI categories, semaglutide showed greater reduction in MACE vs placebo regardless of obesity class, however, MACE reduction was greater for those with a BMI of 35 or less. There was a 37.8% reduction in high sensitivity C-reactive protein, an inflammatory marker in CVD, statin therapy. GLP1 receptor agonists have been shown to reduce inflammation, improve ventricular function and plaque stability in preclinical trials[5].

Event	Semaglutide (N=8803)	Placebo (N=8801)	P Value†
	no. of patients (%)		
Serious adverse events‡	2941 (33.4)	3204 (36.4)	<0.001
Cardiac disorders	1008 (11.5)	1184 (13.5)	<0.001
Infections and infestations	624 (7.1)	738 (8.4)	0.001
Nervous system disorders	444 (5.0)	496 (5.6)	0.08
Surgical and medical procedures	433 (4.9)	548 (6.2)	<0.001
Neoplasms benign, malignant, and unspecified	405 (4.6)	402 (4.6)	0.94
Gastrointestinal disorders	342 (3.9)	323 (3.7)	0.48
Adverse events leading to permanent discontinuation of trial product, irrespective of seriousness‡	1461 (16.6)	718 (8.2)	<0.001
Gastrointestinal disorders	880 (10.0)	172 (2.0)	<0.001
Nervous system disorders	124 (1.4)	92 (1.0)	0.03
Metabolism and nutrition disorders	108 (1.2)	27 (0.3)	<0.001
General disorders and administration-site conditions	105 (1.2)	47 (0.5)	<0.001
Neoplasms benign, malignant, and unspecified	80 (0.9)	105 (1.2)	0.07
Infections and infestations	75 (0.9)	84 (1.0)	0.47
Prespecified adverse events of special interest, irrespective of seriousness§			
Covid-19–related events	2108 (23.9)	2150 (24.4)	0.46
Malignant neoplasms	422 (4.8)	418 (4.7)	0.92
Gallbladder-related disorders	246 (2.8)	203 (2.3)	0.04
Acute kidney failure	171 (1.9)	200 (2.3)	0.13
Acute pancreatitis¶	17 (0.2)	24 (0.3)	0.28

Table 4 Investigator-Reported Adverse Events[5]

The SELECT trial findings pave the way for a more tailored, patient-centric approach to obesity treatment, advancing past current treatment with only modest outcomes.

In summary, the SELECT trial signifies a paradigm shift in obesity management, particularly for individuals with obesity but without diabetes. It also underscores another effective tool for the secondary prevention of CVD, on top of the current standard of care. The SELECT trial findings pave the way for a more tailored, patient-centric approach to obesity treatment, advancing past current treatment with only modest outcomes. Semaglutide's success in this landmark trial advocates for its consideration as a first-line therapy for obesity in those with concomitant CVD. Moreover, the trial's rigorous methodology and comprehensive data collection offer a robust foundation for future pharmacological advances, emphasizing the importance of personalized and outcome-focused treatment strategies. Of note, other obesity pharmacotherapy agents such as the dual GLP1/GIP agonist, Tirzepatide is following suit with its own CVOT – SURMOUNT-MMO, which is evaluating both primary and secondary prevention of cardiovascular events in obesity and is due to be completed in 2027. As obesity continues to be a global health challenge, the SELECT trial's insights are not merely encouraging—they are indicative of a new direction in chronic disease management where the benefits extend beyond weight loss, into the realm of overall health improvement and quality of life improvement.

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