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Review

Semaglutide: Review and Place in Therapy for Adults With Type 2 Diabetes

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Key Messages

- Semaglutide is a glucagon-like peptide-1 receptor agonist that was approved in Canada for the treatment of type 2 diabetes on January 4, 2018.
- Semaglutide is superior to placebo and sitagliptin, exenatide extended-release, dulaglutide and insulin glargine for reduction of glycated hemoglobin levels and weight.
- SUSTAIN 6 trial data confirmed noninferiority based on significant reductions in major cardiovascular events with semaglutide vs. placebo.

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ABSTRACT

Guidelines increasingly highlight the importance of multifactorial management in type 2 diabetes, in contrast to the more traditional focus on glycemic control. Semaglutide, a recently approved glucagon-like peptide-1 receptor agonist, is indicated in Canada for adults with type 2 diabetes to improve glycemic control as monotherapy with diet and exercise when metformin is inappropriate or as an add-on to either metformin alone or metformin plus a sulfonylurea or basal insulin. The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trial program for semaglutide comprises 6 pivotal global phase 3a trials (SUSTAIN 1 through 6) and 2 Japanese phase 3a trials. Phase 3b trials include SUSTAIN 7, and SUSTAIN 8 and 9 (both ongoing). Results from the completed trials support the superiority of semaglutide for reduction of glycated hemoglobin levels and weight loss vs. placebo as well as active comparators, including sitagliptin, exenatide extended-release, dulaglutide and insulin glargine. SUSTAIN 6 trial data confirmed cardiovascular safety and demonstrated significant reductions in major cardiovascular events with semaglutide vs. placebo, an outcome that confirmed the noninferiority of semaglutide. The robust and sustained effects of semaglutide on glycated hemoglobin levels and weight loss vs. comparators, as well as its safety and possible cardiovascular benefit, address an unmet need in the treatment of type 2 diabetes. This article overviews data from across the semaglutide clinical trial program, including efficacy and safety results and findings from post hoc analyses. The potential place of semaglutide in clinical practice is discussed.

Mots clés :
cardiovasculaire
agoniste des récepteurs GLP–1 (*glucagon-like peptide–1*)
semaglutide
études SUSTAIN
diabète de type 2
perte de poids

RÉSUMÉ

Les lignes directrices insistent de plus en plus sur l'importance de la prise en charge multifactorielle du diabète de type 2 que sur l'importance généralement accordée à la régulation de la glycémie. Le semaglutide, un agoniste des récepteurs GLP–1 (*glucagon-like peptide–1*) récemment approuvé au Canada, est indiqué en monothérapie associée à un régime alimentaire et la pratique d'une activité physique chez les adultes atteints de diabète de type 2 pour mieux réguler leur glycémie, lorsque la metformine est inappropriée, ou en traitement d'appoint à la metformine seule, ou à la metformine et une sulfonylurée, ou à l'insuline basale. Le programme d'études cliniques SUSTAIN (The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) sur le semaglutide regroupe 6 études

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pivots internationales de phase IIIa (SUSTAIN, de 1 à 6) et 2 études japonaises de phase IIIa. Les études de phase IIIb sont les suivantes : l'étude SUSTAIN 7, et les études SUSTAIN 8 et 9 (qui sont en cours). Les résultats des études complétées confirment la supériorité du semaglutide par rapport au placebo et aux comparateurs actifs, dont la sitagliptine, l'exénatide à libération prolongée, le dulaglutide et l'insuline glargine, dans la réduction des concentrations de l'hémoglobine glyquée et la perte de poids. Les données de l'étude SUSTAIN 6 ont confirmé l'innocuité cardiovasculaire du semaglutide (*vs* le placebo) et démontré qu'il réduisait de manière significative les événements cardiovasculaires majeurs. Ces résultats confirment la non-infériorité du semaglutide. Les effets importants et prolongés du semaglutide, leur innocuité et leurs avantages cardiovasculaires potentiels par rapport aux comparateurs sur les concentrations de l'hémoglobine glyquée et la perte de poids répondent à un besoin non comblé dans le traitement du diabète de type 2. Le présent article donne un aperçu des données de l'ensemble du programme d'études cliniques sur le semaglutide, y compris les résultats sur l'efficacité et l'innocuité, et les conclusions des analyses *post-hoc*. Nous traitons de l'utilisation potentielle du semaglutide en pratique clinique.

Introduction

The focus of type 2 diabetes management has traditionally been on glycemic control, but the importance of multifactorial management is now highlighted in treatment guidelines. This approach includes the optimization of cardiovascular (CV) risk factors, including hyperglycemia, overweight/obesity, hypertension and dyslipidemia (1–4). Recent guidelines also recommend prioritizing antihyperglycemic agents with demonstrated CV outcome benefit in patients with clinical CV disease (CVD) (3,4).

Despite the range of available treatments for type 2 diabetes, recommended targets are not attained by many patients, leaving them at risk for serious complications (5–7). In the Diabetes Mellitus Status in Canada study, only half of the 5,123 patients with type 2 diabetes surveyed had met the glycated hemoglobin (A1C) level target of ≤7.0%, despite most (87%) being on at least 1 antihyperglycemic agent (6). Similarly, in the US-based National Health and Nutrition Examination Survey, only 52.2% of people with self-reported diabetes had met an A1C target of <7.0% in 2011 through 2014 (7). Another key target is weight control. The vast majority (≥85%) of people with diabetes are overweight or obese (8), and the risk of having an A1C level ≥7.0% is greater than in those of normal weight (9).

Addressing CVD risk as part of diabetes management has also been an important focus. People with diabetes are at a 2- to 4-fold increased risk for CVD compared to those without diabetes, and CV events are more likely to occur at an earlier age (10,11). Although the precise role of glycemic control in CVD risk reduction remains to be elucidated (12), a recent observational study showed that there is a greater risk for a CV event with increasing A1C level (13). However, other factors contribute to CV risk, as demonstrated in the INTERHEART study involving approximately 30,000 individuals worldwide. Multivariate analysis revealed an increased risk for myocardial infarction (MI) with diabetes (OR 95% CI 2.37 [2.07 to 2.71]); abdominal obesity (OR 95% CI 1.62 [1.45 to 1.80]) for the highest vs. lowest tertile of waist/hip ratio); hypertension (OR 95% CI 1.91 [1.74 to 2.10]); and dyslipidemia (raised apolipoprotein B and A1 ratio (OR 95% CI 3.25 [2.81 to 3.76]) for the highest vs. the lowest quintile) (14).

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that reduces hyperglycemia through stimulation of glucose-induced insulin secretion, inhibition of glucagon secretion, reduction of hepatic glucose production, slowing of gastric emptying and, possibly, increase of pancreatic beta cell growth and differentiation (15). Currently approved GLP-1 receptor agonists (GLP-1RAs) include the exendin-based therapies (exenatide/exenatide extended-release and lixisenatide) and human GLP-1 analogs (albiglutide [to be withdrawn in 2018] (16), dulaglutide, liraglutide and semaglutide (17,18)). Hypoglycemia is not an expected side effect of GLP-1RA agents because of their glucose-dependent mode of action (2). Gastrointestinal (GI) adverse events (AEs), such as diarrhea, nausea and vomiting, are associated with this class of agents (19).

Head-to-head studies of GLP-1RAs have shown similar decreases in A1C levels from baseline with liraglutide 1.8 mg and dulaglutide 1.5 mg (–1.36% vs. –1.42% at 26 weeks; p<0.0001 for noninferiority), and they have reported that liraglutide 1.8 mg reduces A1C levels to a greater extent than exenatide twice daily (–1.12% vs. –0.79% at 26 weeks; p<0.0001); lixisenatide (–0.51% vs. –0.32% at 28 days; p<0.01); albiglutide (–0.99% vs. –0.78% at 32 weeks) (p=0.0846 for noninferiority of albiglutide vs. liraglutide), or exenatide extended release (–1.48% vs. –1.28% at week 26; p=0.02) (20,21). Compared with exenatide twice daily, noninferiority criteria were met with lixisenatide (–0.96% vs. –0.79% at 24 weeks; 0.033 to 0.297), a greater reduction from baseline was observed with dulaglutide 0.75 mg (–0.99% vs. –1.30% at 26 weeks; p<0.001), and dulaglutide 1.5 mg (–0.99% vs. –1.51% at 26 weeks; p<0.001), and a significantly greater reduction in A1C levels was observed with exenatide extended-release in 3 studies (–0.9% vs. –1.6% at 24 weeks; p<0.0001; and –1.12% vs. –1.43% at 26 weeks; p<0.001; and –1.5% vs. –1.9% at 30 weeks; p=0.0023) (20,21). Head-to-head studies of GLP-1RAs vs. active comparators have suggested that exenatide twice daily results in a reduction in weight from baseline vs. lixisenatide (–3.98 kg vs. –2.96 kg at 24 weeks; 95% CI 0.456 to 1.581), a significant reduction vs. dulaglutide 0.75 mg (–1.07 kg vs. +0.2 kg at 26 weeks; p<0.001); a similar (–3.6 kg vs. –3.7 kg at 30 weeks; p=0.89) and (–1.4 kg vs. –2.3 kg at 24 weeks; 95% CI –1.9 to 0.01) or a significant reduction vs. exenatide extended-release (–2.45 kg vs. –1.63 kg at 26 weeks; p<0.001) and a similar reduction compared with liraglutide 1.8 mg (–2.87 kg vs. –3.24 kg at 26 weeks; p=0.2235) and dulaglutide 1.5 mg (–1.07 kg vs. –1.30 kg at 26 weeks; p=0.474) (20,21). Liraglutide 1.8 mg demonstrated a significant reduction in weight from baseline vs. exenatide extended-release (–3.57 kg vs. –2.68 kg at 26 weeks; p=0.0005); dulaglutide 1.5 mg (–3.61 kg vs. –2.90 kg at 26 weeks; p=0.011); and lixisenatide (–2.4 kg vs. –1.6 kg at 28 days; p<0.01) (20,21).

Trials of GLP-1RAs designed to investigate CV endpoints reported CV safety, although not efficacy, with lixisenatide in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) or exenatide extended-release in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial (22,23), respectively, compared with placebo. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, liraglutide was found to have a beneficial effect on CV-related outcomes, including the primary composite endpoint of first occurrence of death from CV causes, nonfatal myocardial infarction (MI) or nonfatal stroke, as well as CV death and all-cause mortality, compared with placebo, in people at high CV risk, following a 3.8-year median follow up (24). The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) study of the CV effects of dulaglutide

(NCT01394952) (25) and the HARMONY outcomes trial with albiglutide (NCT02465515) are ongoing (16). The Semaglutide Unabated Sustainability In Treatment of Type 2 Diabetes (SUSTAIN) clinical trial program was designed to investigate semaglutide, a GLP-1RA administered once weekly by subcutaneous (s.c.) injection, and included efficacy and safety trials as well as a CV outcomes trial (CVOT) (26–34).

The SUSTAIN clinical trial program included 5 controlled, phase 3a trials (SUSTAIN 1 through 5), which compared semaglutide with placebo (as monotherapy or add-on to basal insulin) or with the antihyperglycemic agents sitagliptin, exenatide extended-release and insulin glargine (26–30). Two Japanese phase 3a trials were also conducted (31,32). The SUSTAIN 6 phase 3a trial investigated the safety, efficacy and long-term CV outcomes with semaglutide vs. placebo in adults with type 2 diabetes at high risk for CV events (33). The phase 3b SUSTAIN 7 trial was a head-to-head comparison of semaglutide vs. dulaglutide (34).

Semaglutide was approved in Canada on January 4, 2018 (17), in the United States on December 5, 2017 (35) and by the European Medicines Agency in early 2018 (36), and it is approved (37) or under review by several other regulatory agencies (38). This article communicates practical information for health-care professionals about the GLP-1RA semaglutide, the findings from the semaglutide clinical trial program, including the efficacy and safety results, and the implications of results from comparative studies and a CVOT. It also provides health-care professionals with insights concerning the place of semaglutide in the management of type 2 diabetes.

Pharmacology

The semaglutide molecule has >90% homology to human GLP-1 and, structurally, 3 main modifications in comparison with human GLP-1 (39,40): 1) at peptide position 8, alanine was substituted with alpha-aminoisobutyric acid to disrupt the dipeptidyl peptidase 4 cleavage site and extend its systemic half-life, in comparison with native GLP-1; 2) a linker and C18 diacid chain was attached at peptide position 26, resulting in higher binding affinity for albumin (semaglutide has a 5.6-fold increased affinity for albumin compared with liraglutide, which has a shorter diacid chain), and the linker structure impacts the affinity of semaglutide for binding to the GLP-1 receptor; 3) at peptide position 34, lysine was substituted with arginine to ensure that acylation correctly occurs at Lys^{26}.

Once-weekly dosing of semaglutide was established in preclinical and pharmacokinetic studies of adults with type 2 diabetes (39–42). The half-life of semaglutide was approximately 7 days (165 h to 184 h) (40). Exposure of semaglutide was similar for individuals with or without renal or hepatic impairment (43,44). Semaglutide excretion occurs in both urine (primarily, in which approximately 3% of the dose is excreted as intact semaglutide) and in feces (45).

Phase 3 Efficacy and Safety Trials: SUSTAIN 1–5 and SUSTAIN 7

Methods and baseline characteristics

In the Phase 3 SUSTAIN 1 through 5 and SUSTAIN 7 trials, 5,098 subjects with type 2 diabetes were randomized to receive semaglutide (0.5 mg or 1.0 mg s.c. once weekly) or comparators and were exposed to at least 1 dose of treatment (i.e. modified intention-to-treat population) (26–30,34) (Table 1).

Inclusion and exclusion criteria were similar across the SUSTAIN 1 through 5 (26–30) and SUSTAIN 7 trials (34). Participants were ≥18 years of age and had type 2 diabetes, with baseline A1C levels of 7.0% to 10.0% (53 to 86 mmol/mol) in SUSTAIN 1, 4, 5 and 7.0% to 10.5% (53 to 91 mmol/mol) in SUSTAIN 2, 3 and 7. Exclusion criteria included personal histories of chronic or idiopathic acute pancreatitis, personal or family histories of medullary thyroid carcinoma/multiple endocrine neoplasia type 2 or a calcitonin level ≥50 ng/L, an acute coronary or cerebrovascular event within 90 days prior to randomization (or, for SUSTAIN 7, MI, stroke or hospitalization for unstable angina and/or transient ischemic attack within 180 days prior to screening), heart failure (New York Heart Association class IV) or any known proliferative retinopathy or maculopathy requiring acute treatment in the opinion of the investigator.

Baseline characteristics (mean) were similar across the SUSTAIN 1 through 5 and SUSTAIN 7 trials; the mean duration of type 2 diabetes varied across trials (26–30,34) (Table 1).

Table 1
Overview of the phase 3 SUSTAIN 1 through 5 and SUSTAIN 7 trials

	SUSTAIN 1 (Ref 26)	SUSTAIN 2 (Ref 27)	SUSTAIN 3 (Ref 28)	SUSTAIN 4 (Ref 29)	SUSTAIN 5 (Ref 30)	SUSTAIN 7 (Ref 34)	
	Semaglutide (0.5 mg and 1.0 mg) vs. placebo	Semaglutide (0.5 mg and 1.0 mg) vs. sitagliptin (100 mg)	Semaglutide (1.0 mg) vs. exenatide ER (2.0 mg)	Semaglutide (0.5 mg and 1.0 mg) vs. IGlar*	Semaglutide (0.5 mg and 1.0 mg) vs. placebo	Semaglutide (0.5 mg) vs. dulaglutide (0.75 mg)	Semaglutide (1.0 mg) vs. dulaglutide (1.5 mg)
Background therapy	n/a, drug-naive	Add-on to MET, TZD, MET/TZD	Add-on to 1 to 2 OADs (MET/SU/TZDs)	Add-on to MET±SU	Add-on to basal insulin±MET	Add-on to MET	
Total randomized, n	388	1,231	813	1,089	397	1,201	
mITT population, n	387	1,225	809	1,082	396	1,199	
Treatment duration, weeks	30	56	56	30	30	40	
Primary endpoint	A1C	A1C	A1C	A1C	A1C	A1C	
Age at baseline,† years	53.7	55.1	56.6	56.5	58.8	56	
A1C at baseline,† %	8.1	8.1	8.3	8.2	8.4	8.2	
BW at baseline,† kg	91.9	89.5	95.8	93.4	91.7	95.2	
Duration of type 2 diabetes,† years	4.2	6.6	9.2	8.6	13.3	7.4	

Note: See references (26–30,34).

A1C, glycated hemoglobin; BW, body weight; *ER,* extended-release; *IGlar,* insulin glargine; *MET,* metformin; *mITT,* modified intention-to-treat population; *OAD,* oral antidiabetic drug; s.c., subcutaneous; *SU,* sulfonylurea; *TZD,* thiazolidinedione.

* IGlar (titrated to target) once daily.

† Mean value. Subjects with type 2 diabetes in the mITT population were those randomized to receive semaglutide (0.5 mg or 1.0 mg s.c. once weekly) or comparators and were exposed to at least 1 dose of treatment (mITT).

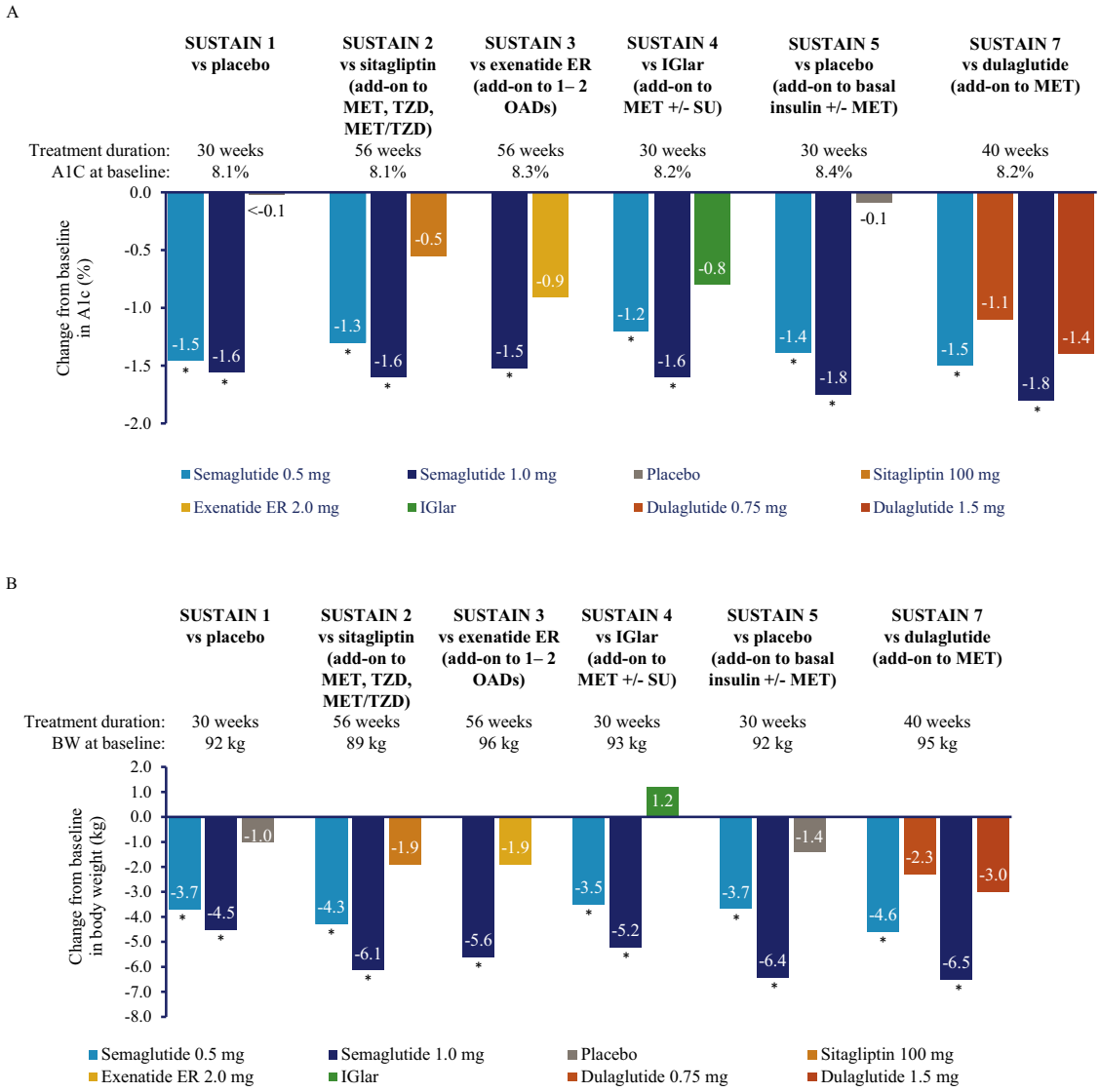


Figure 1. (A) Change in glycated hemoglobin (A1C) levels with semaglutide vs. comparators across the SUSTAIN 1 through 5 and SUSTAIN 7 trials (34,47). *p<0.0001 vs. comparator. Calculated using estimated means from a mixed model for repeated measurements analysis using "on-treatment without rescue medication" data from subjects in the full analysis set. (B) Change in body weight with semaglutide vs. comparators across the SUSTAIN 1 through 5 and SUSTAIN 7 trials (34,47). *p<0.0001 vs. comparator. Calculated using estimated means from a mixed model for repeated measurements analysis using "on-treatment without rescue medication" data from subjects in the full analysis set. *BW,* body weight; *ER,* extended-release; *IGlar,* insulin glargine; *MET,* metformin; *OAD,* oral antidiabetic drug; *SU,* sulfonylurea; *TZD,* thiazolidinedione. Adapted with permission from *Drugs of the Future* 2017;42(8):479. Copyright © 2017 Clarivate Analytics DOI: 10.1358/dof.2017.042.08.2653526.

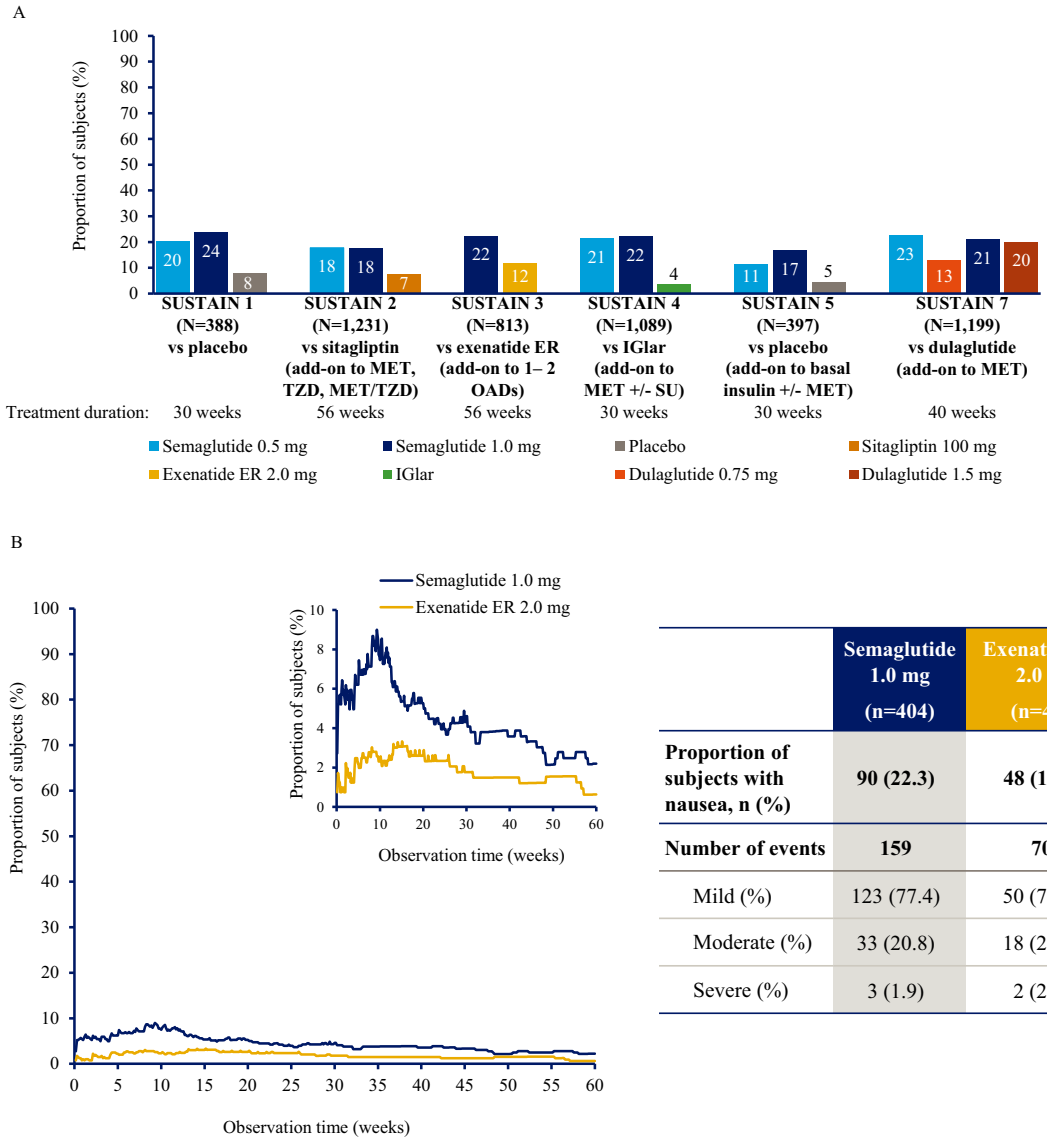
Effect on glycemic control

By the end of treatment, a significant reduction in mean A1C levels was demonstrated with semaglutide: 0.5 mg and 1.0 mg vs. all comparators across the 5 SUSTAIN trials (26–30,46) and in SUSTAIN 7 (34) (all p<0.0001; Figure 1a). A1C reduction from baseline ranged from 1.2% to 1.5% with the 0.5 mg dose and from 1.5% to 1.8% with the 1.0 mg dose, with the 1.0 mg dose decreasing A1C 0.1% to 0.4% more than the 0.5 mg dose (Figure 1a) (34,47). The target A1C of <7.0% was achieved by up to 78.7% of subjects in the semaglutide groups, compared with up to 24.8% in the placebo (p<0.0001) and 66.6% in the active comparator groups (p≤0.0021) (26–30,34,48). The target A1C of ≤6.5% was met by up to 66.7% of subjects in the semaglutide groups, compared with up to 13.2% with placebo, and up to 47.2% with active comparators (all p<0.0001) (26–30,34,48). Up to 74.3% of the subjects receiving semaglutide achieved the composite endpoint of A1C <7.0% without severe/blood glucose-confirmed symptomatic hypoglycemia or weight gain—a significantly greater proportion than those receiving placebo or active comparator (≤58.4%; all p≤0.0001) (26–30,34).

A significant reduction in fasting plasma glucose was demonstrated with semaglutide 1.0 mg vs. all comparators (all p≤0.0005) by the end of treatment and with the 0.5 mg semaglutide dose in the SUSTAIN 1, 2 and 5 trials (all p≤0.0002; note that SUSTAIN 3 did not include the 0.5 mg dose) (26–30,34,49).

Effect on body weight

Statistically significant reductions in weight were found with semaglutide 0.5 mg and 1.0 mg vs. all comparators (p<0.0001) (Figure 1b) (26–30,34,47). Weight loss from baseline ranged from 3.5 to 4.6 kg with the 0.5 mg dose and from 4.5 to 6.5 kg with the 1.0 mg dose, with the 1.0 mg dose lowering weight by 0.8 to 2.7 kg more than the 0.5 mg dose (Figure 1b) (26–30,34,47). Weight loss observed in the groups receiving semaglutide 1.0 mg was 2-fold or greater than that observed in the placebo or active comparator



	Semaglutide 1.0 mg (n=404)	Exenatide ER 2.0 mg (n=405)
Proportion of subjects with nausea, n (%)	**90 (22.3)**	**48 (11.9)**
Number of events	**159**	**70**
Mild (%)	123 (77.4)	50 (71.4)
Moderate (%)	33 (20.8)	18 (25.7)
Severe (%)	3 (1.9)	2 (2.8)

Figure 2. (A) Proportion of subjects reporting nausea with semaglutide vs. comparators across the SUSTAIN 1 through 5 and SUSTAIN 7 trials (26–30,34). Adverse event proportions are based on the total percentage of subjects experiencing at least 1 event. (B) Occurrence of nausea over time and by severity in the SUSTAIN 3 trial (28). SUSTAIN 3 was selected as a representative study from the SUSTAIN trials, which all show similar results. Figure at left: "on-treatment" summary of adverse events. Events are shown until the scheduled follow-up visit. Table at right: treatment-emergent adverse events include events collected from first exposure to the follow-up visit scheduled 5 weeks (+7-day visit window) after the last trial product dose (42 days). Semaglutide was escalated from a starting dose of 0.25 mg, and the dose was doubled every 4 weeks until the trial dose was achieved. © 2018 by the American Diabetes Association® Diabetes Care 2018 Feb; 41(2):258-266. Reprinted with permission from the American Diabetes Association®. *ER,* extended-release; *IGlar,* insulin glargine; *MET,* metformin; *OAD,* oral antidiabetic drug; *SU,* sulfonylurea; *TZD,* thiazolidinedione.

groups (26–30,34,47) (Figure 1b) and, although weight reduction was apparent with semaglutide in the SUSTAIN 4 trial, weight gain was found in the insulin glargine group (Figure 1b) (29,47). Up to 65.7% of subjects in both semaglutide dose groups achieved weight-loss responses of ≥5%, compared with up to 11.3% with placebo and up to 30.2% with active comparators (all p<0.0001) (26–30,34). Up to 26.7% of subjects in both semaglutide groups achieved weight-loss responses of ≥10% compared with up to 3.0% with placebo (p≤0.05) and up to 7.7% with active comparators (all p≤0.0002) (26–30,34).

Adverse and serious adverse events

The proportion of subjects reporting serious AEs in the SUSTAIN 1 through 5 and SUSTAIN 7 trials, respectively, was similar in the semaglutide 0.5 mg and 1.0 mg groups (6.3%; 84/1332 and 7.3%; 127/1734, respectively) vs. comparators (6.4%; 131/2032) (26–30,34). The AE profile for semaglutide 0.5 mg and 1.0 mg groups was generally consistent with that noted with other GLP-1RAs and the proportion of subjects reporting an event (70.3%, 936/1332 and 70.5%, 1223/1734, respectively) was similar to, or higher than, comparators (68.4%; 1389/2032), mainly because of a higher proportion of subjects who experienced gastrointestinal (GI) disorders with semaglutide (26–30,34). GI disturbances, particularly nausea, were the most common type of AEs experienced with semaglutide (Figure 2a) (26–30,34). The proportion of subjects reporting nausea ranged from 11.4% to 23.8% with the semaglutide 0.5 mg and 1.0 mg doses, compared with 4.5% to 7.8% with placebo and 3.6% to 20.1% with active comparators (26–30,34). The proportion of subjects reporting nausea was similar to or slightly greater with the 1.0 mg dose than with the 0.5 mg dose (Figure 2a) (26–30,34). Nausea was mainly mild to moderate in severity and usually decreased over time (26–30,34) (Figure 2b).

The number of confirmed malignant neoplasms across the SUSTAIN 1 through 5 trials was low, and in SUSTAIN 7, the events (n=11) were evenly distributed between the semaglutide and dulaglutide groups (26,27,29,34,50). No events of medullary thyroid carcinoma were observed with semaglutide (34,50), nor was there any effect of semaglutide on calcitonin levels (26,27,29,34,50). Few subjects had increased calcitonin levels, and levels >50 ng/L and >100 ng/L were comparable to those found with comparators (26,27,29,34,50).

Cholelithiasis was reported more frequently in the semaglutide 0.5 mg (n=6) and 1.0 mg groups (n=16) vs. pooled comparators (n=8) across the SUSTAIN 1 through 5 trials (26–30) and with similar frequency with semaglutide (n=0 for 0.5 mg and n=2 for 1.0 mg, respectively) and dulaglutide (n=1 for 0.75 mg and n=2 for 1.5 mg, respectively) in SUSTAIN 7 (34). Most cholelithiasis events were nonserious, and the absolute risk was low (34,50) (Novo Nordisk, data on file).

The number of pancreatitis-related events across the SUSTAIN 1 through 5 trials was low and was comparable to semaglutide, placebo or active comparator (semaglutide 0.5 mg [n=5] and 1.0 mg groups [n=3] vs. placebo [n=0] or active comparator groups [n=3, all with exenatide extended release]) (26–30). In SUSTAIN 7, there were no confirmed cases of pancreatitis with either semaglutide or dulaglutide (34).

The proportion of subjects across the SUSTAIN 1 through 5 and in the SUSTAIN 7 trials that discontinued treatment due to AEs was up to 8.1% with semaglutide 0.5 mg and up to 10.0% with semaglutide 1.0 mg, compared with up to 7.2% with both placebo and active comparators, with the difference from comparators being due mainly to GI AEs with semaglutide (26–30,34). In correspondence with the dose-response effects on GI AEs, there was generally a higher proportion of premature treatment discontinuation in subjects who had received semaglutide 1.0 mg vs. 0.5 mg.

Further Findings Based on SUSTAIN Trials 1 Through 5 Post Hoc Analyses

Data from the SUSTAIN 1 through 5 trials were assessed to evaluate semaglutide vs. comparators within baseline categories of body mass index (BMI) (<25, 25 to 30, 30 to 35, ≥35 kg/m^2) (51) or A1C levels (≤7.5, 7.5 to 8.0, 8.0 to 8.5, 8.5 to 9.0 and >9.0%) (46). Across the 5 trials and within each baseline BMI category, a greater reduction in body weight was reported with semaglutide 0.5 mg and 1.0 mg vs. comparators (BMI <25 kg/m^2: –2.0 to –6.3 kg vs. –0.5 to +1.4 kg; BMI 25 to 30 kg/m^2: –2.5 to –5.1 kg vs. –1.4 to +1.5 kg; BMI 30 to 35 kg/m^2: –3.0 to –6.6 kg vs. –2.0 to +1.2 kg; BMI ≥35 kg/m^2; –3.6 to –7.9 kg vs.–3.7 to +0.8 kg). Regardless of baseline A1C levels, a greater improvement in A1C levels was evident with semaglutide (–0.7% to –2.8%) vs. all comparators (–1.8 to +0.6%) (46). Subjects with higher baseline A1C values experienced greater reductions in A1C levels (46).

A minor component of the weight loss (0.07 to 0.5 kg) with semaglutide vs. comparators was attributed to nausea and vomiting in SUSTAIN 1 through 5, and weight loss with semaglutide was significantly greater than with comparators in subjects who did or did not experience these GI AEs (p<0.001) (52).

In the SUSTAIN 1 through 5 trials, a significantly greater proportion of subjects achieved the clinically meaningful composite endpoint of ≥1.0% A1C reduction and ≥5% weight loss with semaglutide 1.0 mg (38% to 56%) or 0.5 mg (25% to 35%) vs. comparators (2% to 13%) (all p<0.0001) (53). Similarly, a significantly greater proportion of subjects achieved the composite endpoint of A1C <7.0% with no weight gain or severe/blood glucose-confirmed symptomatic hypoglycemia or moderate/severe GI AEs with semaglutide 1.0 mg (46% to 64%) or 0.5 mg (40% to 55%) vs. comparators (7% to 25%) (all p<0.0001) (54).

Two network meta-analyses compared semaglutide trial results with those for the sodium glucose cotransporter-2 inhibitors (SGLT2is) empagliflozin, canagliflozin and dapagliflozin in individuals with type 2 diabetes inadequately controlled on 1 to 2 oral antidiabetes drugs (OADs) (55) or metformin monotherapy (56). These analyses suggested that, after 26 weeks of treatment, semaglutide is superior to SGLT2is in regard to A1C level reductions and weight loss, with a significantly greater reduction found in A1C levels with semaglutide 0.5 mg (mean difference in change from baseline [MD]: –0.4% to –0.8%) and 1.0 mg (MD: –0.7 to –1.1%). A significantly greater reduction in body weight (MD: –0.9 to –2.3 kg) was also observed with semaglutide 1.0 mg, in comparison with SGLT2i while, in general, no difference was evident with the semaglutide 0.5 mg dose vs. SGLT2i (55,56). SUSTAIN 8, the ongoing phase 3b trial in which semaglutide is being compared with the SGLT2i canagliflozin, should provide more robust data.

Phase 3 CV Outcomes Trial: SUSTAIN 6

Methods

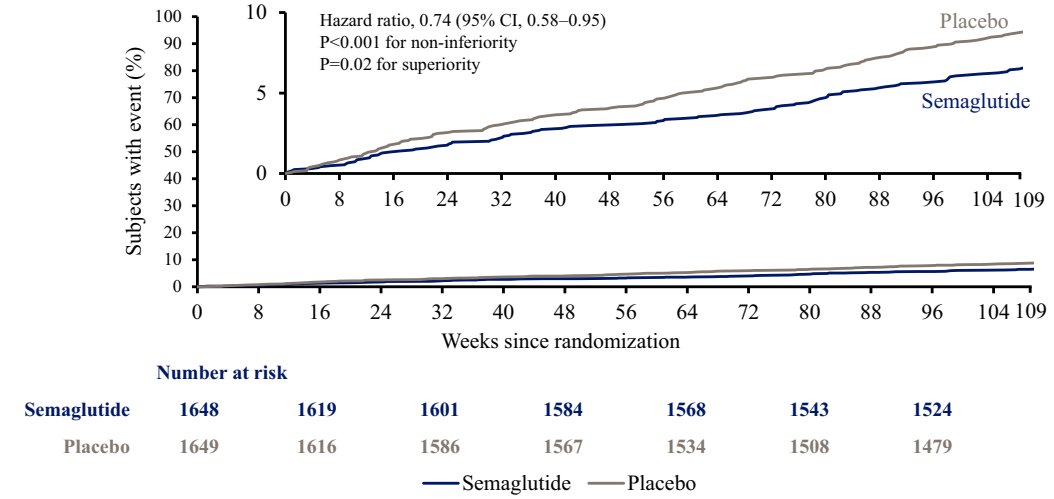
SUSTAIN 6 compared the long-term safety and efficacy of semaglutide with placebo during 2 years in adults with type 2 diabetes at high risk for CV events (33). Subjects were ≥50 years of age who had established CVD (prior cardio-, cerebro- or peripheral vascular disease, chronic heart failure; New York Heart Association Classes II and III) or had chronic kidney disease stage 3 or higher or were ≥60 years of age with at least one CV risk factor (33). Of the 3,297 subjects randomized, 17% were in the primary prevention (CV risk factor) strata and 83% in the secondary prevention strata (33).

Subjects were randomized to receive semaglutide (0.5 mg and 1.0 mg s.c. once weekly) or placebo, in addition to standard of care (i.e. as add-on to 0 to 2 OADs±basal or premixed insulin) (33). The primary endpoint was time to first occurrence of a major adverse CV event—i.e. death from CV causes, nonfatal MI or nonfatal stroke. The data were analyzed for noninferiority (the prespecified number of events was ≥122 in 3,260 patients). Superiority testing was not part of the prespecified analysis because the trial was powered for noninferiority.

Efficacy and safety data

A 26% reduction was observed in the composite outcome of CV death, nonfatal MI or nonfatal stroke, occurring in 6.6% of semaglutide-treated subjects vs. 8.9% of those receiving placebo (HR 0.74; 95% CI 0.58 to 0.95; p<0.001 for noninferiority; p=0.02 for superiority, not prespecified) (Figure 3a) (33). Compared with placebo, a significantly lower proportion of semaglutide-treated subjects experienced nonfatal stroke (p=0.04), with no significant difference found in nonfatal MI (p=0.12) or CV death (p=0.92) (33). There was no significant difference between semaglutide and placebo in regard to the occurrence of all-cause mortality or hospitalization for heart failure (Figure 3b) (33). Revascularization occurred in a significantly lower proportion of semaglutide-treated subjects vs. placebo (p=0.003) (Figure 3b) (33). The expanded composite CV outcome (i.e. major adverse cardiac event, revascularization or hospitalization for unstable angina or heart failure) was reported in a significantly lower proportion of subjects treated with semaglutide vs. placebo (p=0.002) (Figure 3b) (33). In a prespecified subgroup analysis, a benefit in the primary outcome (28% risk reduction) was demonstrated for subjects in the secondary prevention strata. Although there was no statistical heterogeneity among subjects with or without CVD for the primary outcome (p value for interaction=0.49), the HR for the primary prevention subgroup was 1.00

A



B

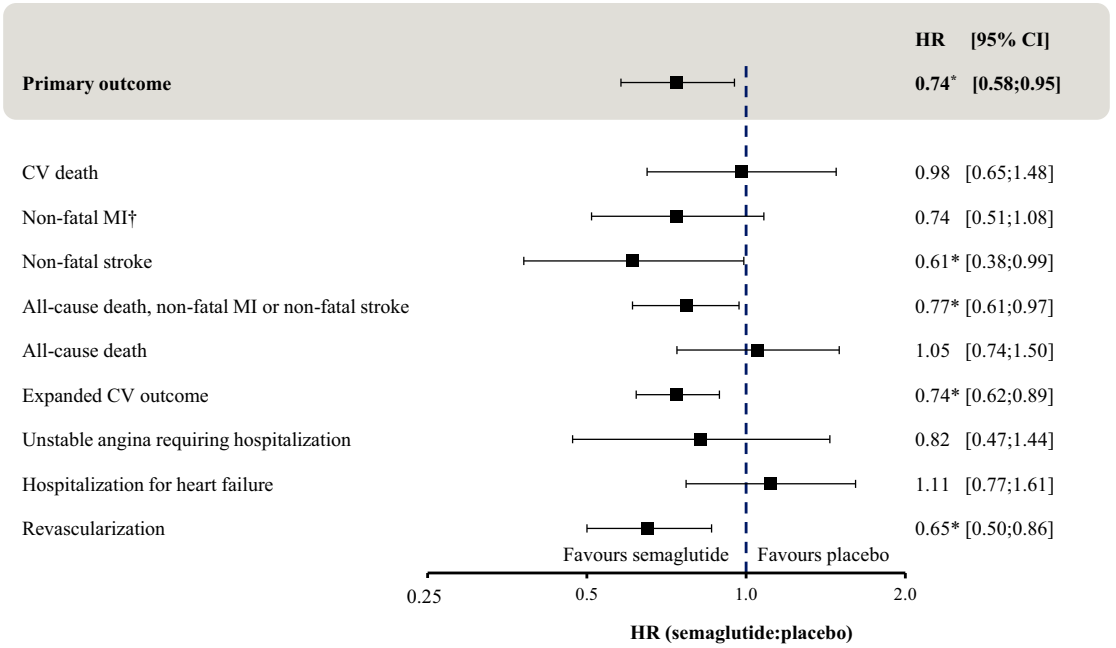


Figure 3. (A) Primary cardiovascular outcome results in the SUSTAIN 6 trial. Time to first occurrence of CV death or nonfatal MI/stroke (33). Events: 108 semaglutide; 146 placebo. Incidence rate per 100 patient years of risk time (time from randomization until first event or censoring): 3.24 semaglutide; 4.44 placebo. Relative risk reduction: 26% lower risk for the primary composite outcome of death from CV causes, nonfatal MI or nonfatal stroke with semaglutide vs. placebo. p value for superiority not prespecified. Kaplan-Meier plot for first event adjudication committee-confirmed CV death, nonfatal MI and nonfatal stroke using in-trial data from subjects in the full analysis set. From *The New England Journal of Medicine*, Marso, SP, Bain SC, Consoli, A et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. 375:1834–44. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. (B) Summary of cardiovascular outcomes in the SUSTAIN 6 trial (33). *Indicates significance (p<0.05). Values are estimated HRs with 95% CIs using in-trial data from subjects in the full analysis set. †Nonfatal MI includes 4 (0.2%) silent MIs in the semaglutide group and 7 (0.4%) in the placebo group. Adapted from Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44. *CI,* confidence interval; *CV,* cardiovascular; *HR,* hazard ratio; *MI,* myocardial infarction.

(95% CI 0.41 to 2.46), and this subgroup accounted for only 7.5% of all primary outcome events, precluding any definitive opinion about the CV benefit in the primary prevention strata (33).

In comparison with placebo, a significantly greater reduction in A1C levels was observed with semaglutide 0.5 mg and 1.0 mg (–0.7% and –1.0%, respectively; p<0.001) and in body weight (–2.9 kg and –4.3 kg, respectively; p<0.001) (33). Reduction in systolic blood pressure was also significantly greater with semaglutide 1.0 mg vs. placebo (–2.6 mmHg; p<0.001) (33).

The proportion of subjects with new or worsening nephropathy complications was significantly lower in the pooled semaglutide groups (3.8%) compared with placebo (6.1%) (HR 0.64; 95% CI 0.46 to 0.88; p=0.005), driven by a reduction in new-onset macroalbuminuria (33). Diabetic retinopathy (DR) complications (vitreous hemorrhage, blindness or the need for treatment with an intravitreal agent or photocoagulation) were found in more subjects in the semaglutide groups (n=50; 3.0%), compared with the placebo group (n=29; 1.8%) (HR 1.76; 95% CI 1.11 to 2.78; p=0.02) (33). Subjects with histories of DR at baseline were more likely to experience retinopathy complications (absolute risk: 8.2% with semaglutide and 5.2% with placebo) vs. those without (0.7% with semaglutide and 0.4% with placebo) (35,57,58). In contrast, no

statistically significant difference in the development of DR complications was observed with semaglutide vs. placebo in those without preexisting retinopathy at baseline (59). With the exception of DR complications, a similar safety profile was observed for semaglutide in SUSTAIN 6 as in the other SUSTAIN trials.

Discussion

Semaglutide can be used to improve glycemic control in adults with type 2 diabetes (17). Advantages of semaglutide include its robust and sustained effects on A1C levels and weight loss vs. comparators across a spectrum of background therapies, as well as CV safety vs. placebo (26–30,33,34). The SUSTAIN 6 CVOT in adults with type 2 diabetes at high risk for CV events demonstrated a 26% reduction in the primary (composite) outcome of CV death, nonfatal MI or nonfatal stroke compared with placebo (HR 0.74; 95% CI 0.58 to 0.95; $p<0.001$ for noninferiority; $p=0.02$ for superiority, not prespecified) (33). Although the SUSTAIN 6 trial was not powered to show superiority, the treatment effect of semaglutide and the accrual of more events than estimated meant that a post hoc sensitivity analysis demonstrated a significantly lower risk for the primary outcome in subjects in the semaglutide vs. the placebo group, thereby raising the possibility of CV benefit of semaglutide (33).

Glycemic equipoise (i.e. similar A1C values in the experimental and comparator arms) (60) was not achieved in the SUSTAIN 6 trial (33). Rather, the reduction in A1C values was significantly greater in the semaglutide 0.5 mg and 1.0 mg groups compared with placebo (resulting in A1C values of 7.6% and 7.3% vs. 8.3%, respectively) (33). Lack of glycemic equipoise has been proposed as a limitation of CVOTs because of the difficulty in establishing whether a demonstrated CV safety/benefit has arisen independently from improved glycemia (60). However, a recent commentary on the LEADER trial highlighted that, due to the pleiotropic actions of liraglutide, positive CVOT results could arise from the multiple beneficial CV effects ascribed to this agent, rather than simply from a lack of glycemic equipoise (60). The pleiotropic effects of GLP-1RAs as a class have been well documented (61). The robust lowering of A1C levels with semaglutide may have contributed to the CV results in SUSTAIN 6, in addition to other pleiotropic effects. Furthermore, the significant reduction in the numbers of revascularizations with semaglutide treatment compared with placebo in SUSTAIN 6 is interesting, especially considering the nonsignificant decrease in risk for nonfatal MI and no change in risk for CV death (33). Such findings may suggest a protective mechanism, perhaps linked to the metabolic effects of semaglutide treatment, as hypothesized elsewhere (62).

In SUSTAIN 1 through 5 and SUSTAIN 7, in contrast to SUSTAIN 6, no increase in DR complications was evident in the semaglutide groups vs. comparators (26–30,34,59). A pooled analysis of the SUSTAIN 1 through 5 and the 2 Japanese trials did not show a difference in DR complications between semaglutide and comparators (59). One possible explanation for the discrepancy in DR findings between SUSTAIN 6 and other SUSTAIN trials is the difference in exclusion criteria and baseline demographics (59). The SUSTAIN 1 through 5 and SUSTAIN 7 trials (though not SUSTAIN 6) excluded subjects with baseline A1C levels >10.0/10.5% or any known proliferative retinopathy or maculopathy requiring acute treatment in the opinion of the investigator. Accordingly, subjects in the SUSTAIN 6 trial were more likely than those in SUSTAIN 1 through 5 and SUSTAIN 7 to be older and taking insulin prior to or at the time of the event and to have longer-duration diabetes, higher baseline A1C levels and higher rates of preexisting DR, all of which are risk factors associated with DR (26–30,34,59). Methodologic considerations may also have contributed to the DR complication findings in SUSTAIN 6, including how retinopathy was assessed (58). In the LEADER trial, a nonsignificant trend was found in the incidence of adjudicated DR complications with liraglutide compared with placebo ($p=0.33$), and no clinically relevant difference in the incidence of DR complications was reported in the EXSCEL study, in which exenatide was compared with placebo (23,24). The increase in DR risk in SUSTAIN 6 could be attributed to the rapid improvement and large decline in A1C levels, especially in those with preexisting retinopathy and poor glycemic control (59). Previous studies have suggested that a rapid improvement in glycemic control in patients with preexisting retinopathy may result in a temporary worsening of DR (59). In the Diabetes Control and Complications Trial (DCCT), intensive glycemic control in persons with type 1 diabetes demonstrated that despite early transient worsening, retinopathy outcomes were similar or more favourable than conventional treatment in the long term (63). The SUSTAIN 6 trial duration was too short to detect a possible long-term benefit for retinopathy. Diabetes Canada guidelines recommend screening all adults with type 2 diabetes for retinopathy at diagnosis and every 1 to 2 years thereafter or monitoring for progression at least annually in individuals in whom retinopathy is already present (64).

Ongoing investigations within the SUSTAIN clinical trial program include SUSTAIN 8 (NCT03136484) (65), to compare semaglutide and the SGLT2i canagliflozin (as add-on to metformin) over 52 weeks, and SUSTAIN 9 (NCT03086330) (66), to compare semaglutide with placebo (as add-on to SGLT2i) over 30 weeks in subjects with type 2 diabetes. A well-powered CV outcomes trial, prespecified for superiority testing, would help to establish the overall CV benefit of semaglutide.

Semaglutide in the Overall Management of Type 2 Diabetes

GLP-1RAs are 1 of several second-line treatment options in Canadian and international guidelines (2,3,67,68) and are associated with efficacious glucose lowering, weight loss and low risk for hypoglycemia (2,20,21,69). Diabetes Canada guidelines for 2018 recommend incretin agents and/or SGLT2 inhibitors over insulin secretagogues, insulin and thiazolidinediones as add-on agents in people without clinical CVD, if lower risk for hypoglycemia and/or weight gain are priorities (67). The costs associated with GLP-1RA agents are generally within the higher range in comparison with other classes of agents (2,3,68,70), but they should be considered within the context of clinical benefits (17). Results suggest that semaglutide has better efficacy for glycemic control and weight loss than most other antihyperglycemic agents, and it seems to be the most efficacious in the GLP-R1A class for achieving A1C reductions and weight loss (26–30,33,34). Current guidelines recommend prioritizing the use of an antihyperglycemic agent with demonstrated CV superiority in patients with clinical CVD (3,4). Although there may be a possible CV benefit with semaglutide in those with established CVD, determining a benefit in patients without clinical CVD requires further study.

Semaglutide dosing is started at 0.25 mg s.c. once weekly for 4 weeks, then 0.5 mg s.c. once weekly for at least 4 weeks, followed by dose escalation to 1.0 mg once weekly if further glycemic control is required (17). It is administered once weekly at any time of day (with or without meals) (17). As with other GLP-1RAs, gradual dose escalation may help to reduce the risk for GI AEs. The occurrence of nausea, vomiting and diarrhea is more common at the start of therapy but generally decreases over time (17).

Semaglutide can be used in elderly patients (age ≥65 years) because no differences in overall safety and efficacy were found, nor was there a need for dose adjustment, compared with younger individuals. However, a greater sensitivity in some older individuals cannot be ruled out, and data are limited in older patients (age

>75 years) (17). Semaglutide has not been investigated in individuals <18 years of age. No dose adjustment is needed in patients with mild, moderate or severe renal impairment, but caution should be exercised in cases of severe renal impairment because of limited experience with its use, and semaglutide is not recommended in end-stage renal disease (17). Semaglutide should be used with caution in patients with hepatic insufficiency, again because of limited experience with its use (17).

Semaglutide is a welcome addition to the antihyperglycemic agent armamentarium in type 2 diabetes, offering robust A1C lowering and weight loss across a variety of background therapies, as well as CV safety and convenient once-weekly dosing, and it may have a possible CV benefit in those with established CVD. It can be used across a spectrum of patients with type 2 diabetes, both in primary and secondary prevention, as monotherapy with diet and exercise when metformin is inappropriate, or as a first-line add-on to metformin alone or as an add-on to metformin plus sulfonylurea or basal insulin. Semaglutide can also be considered a preferred first injectable option in the management of type 2 diabetes. The additional possible benefit of CV risk reduction in patients with established CVD makes it an excellent option for these high-risk patients.

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Author Contributions

All authors actively contributed to manuscript preparation. The final submitted manuscript was approved by all authors, who made the decision to submit the manuscript for publication. The authors assume responsibility for the accuracy and completeness of the data.

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