GOAL: GUIDANCE ORIENTED APPROACH TO LEARNING
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Unit No. 6

SEMAGLUTIDE: HEART OF THE MATTER (SUSTAIN-6 AND PIONEER-6)

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ABSTRACT

T2 diabetes has long been recognised as a major and exponentially growing global public health concern. Asia is no exception. Cardiovascular adverse events remain the leading cause of morbidity and mortality in T2 diabetics. There is an urgent need for effective therapies to improve cardiovascular outcomes and glucagon-like peptide-1 receptor agonists. Semaglutide is a potent glucagon-like peptide-1 analogue with the exclusive advantage of being available in both subcutaneous and oral formulations. The cardiovascular safety of each of these formulations was assessed in the SUSTAIN-6 and PIONEER-6 trials and the observed benefits has led to the approval of both the subcutaneous and oral formulations as an adjunct to diet and lifestyle measures in high-risk patients with Type 2 diabetes.

Keywords: Semaglutide, Glucagon-like peptide-1 (GLP-1), cardiovascular outcomes, T2 diabetes, Obesity,

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INTRODUCTION AND BACKGROUND

Diabetes mellitus is a major public health problem worldwide, as 10 percent of adults have the disease, which corresponded to 463 million individuals in the world in 2019.[1] By 2045, this number will rise to 700 million.[1] Type 2 diabetes (T2D) accounts for 90 percent of the cases and the majority of these patients do not have easy access to healthcare facilities for timely diagnosis or treatment. The prevalence of T2D is rapidly increasing in three regions of the world: South America, Asia, and Eastern Europe. Multi-ethnic Singapore, which comprises predominantly Chinese, Malay. and Indian races. typifies the greater susceptibility of the Asian genotype to T2D. Coupled with the ageing population that Singapore faces, the prevalence of diabetes and its complications is expected to present an enormous prospective health burden, which the Ministry of Health has publicly acknowledged. The prevalence of T2D has rapidly increased from 2 percent in 1975 to 11 percent in 2010,[2] and this trend is projected to reach one in six adults by 2050. T2D is commonly associated with clinical conditions that are implicated in worse prognosis, increased mortality, and negative impacts on patient health-related quality of life, such as obesity and cardiovascular disease (CVD). Increased adiposity is the strongest risk factor for developing T2D.

Obesity increases the risk of death in patients with T2D, with an estimated 20 percent increase in mortality risk for each 5 kg/m^2 increase in BMI.[3] Furthermore, this association has a direct linear relationship, with the lowest mortality risk described among patients with BMI equal to 22.5-24.9 kg/m^2. Weight loss with diet and physical activity can prevent or reverse T2D.[4] The DIRECT trial reported that a weight loss of approximately 15 kg can lead to T2D remission in approximately 80 percent of patients with obesity and T2D.[5] However, most drug classes involved in T2D therapy promote weight gain (insulin, sulfonylureas, and others). Therefore, it is important that anti-hyperglycaemic therapies do not increase weight and ideally promote weight loss.

CVD is the leading cause of mortality in patients with T2D.[6,7] Controlling blood sugar is an extremely important practice to avoid or delay chronic diabetic complications. According to the United Kingdom Prospective Diabetes Study (UKPDS), a decrease of 1 percent in glycated haemoglobin (HbA1c) results in a 21 percent reduction in the risk of any endpoint related to diabetes, 21 percent in the risk of death related to diabetes, 14 percent in the risk of myocardial infarction, and 37 percent in the risk of microvascular complications.[8]

GLUCAGON LIKE PEPTIDE-1 (GLP-1)

Following food consumption, the gastrointestinal tract (GIT) naturally releases several hormones collectively called incretins.[9] GLP-1 is one of the incretins family that stimulates pancreatic cells to secrete insulin and suppress glucagon release. Gastric emptying is also delayed. GLP-1 receptors (GLP-1r) are mainly expressed in the pancreas, bowels, and the central nervous system, and to a lesser degree in the heart, lungs, kidneys, vasculature, and peripheral nervous system. In the central nervous system, GLP-1 acts as a neurotransmitter responsible for mediating signalling satiety pathways via the brainstem-hypothalamus.[10] Peripherally, GLP-1 reduces energy intake and affects all components of appetite regulation including increased satiety and fullness, and decreased hunger and prospective food consumption.[11] The latter attribute assists with weight loss. Collectively, these mechanisms of action of GLP-1 have been harnessed and manufactured analogues have been consistently proven as efficacious treatments for T2 diabetes.

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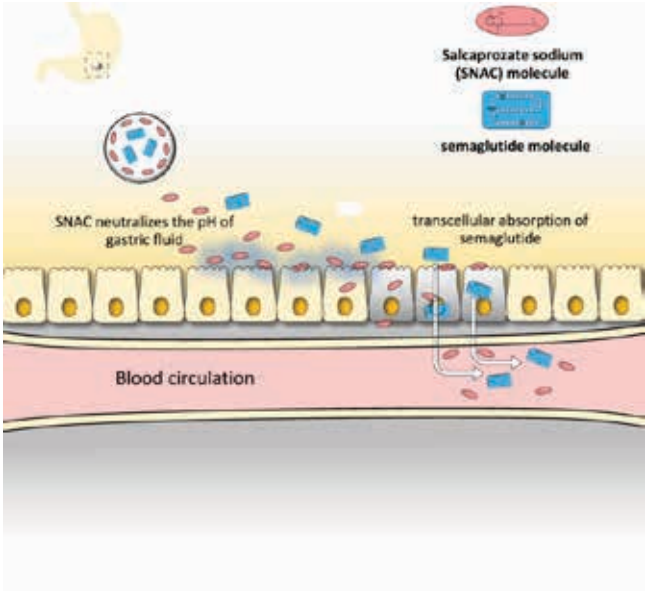
SEMAGLUTIDE

The short half-life of human GLP-1 resulting from degradation by DPP-4 raised challenges for pharmaceutical use in the clinical setting where a constantly high and stable plasma level is required. Semaglutide is a potent glucagon-like peptide-1 (GLP-1) analogue with a 94 percent degree of homology to human GLP-1.[12] Three key structural differences provide the extended pharmacokinetics of this drug: namely, the substitution of Ala with Aib at position 8 that increases enzymatic (DPP4) stability; attachment of a linker; and C18 di-acid chain at position 26 that provides strong binding to albumin and substitution of Lys with Arg at position 34 that prevents C18 fatty acid-binding at the wrong site.[12] Two formulations have been approved by the FDA – subcutaneously once weekly, and an oral administration once daily. The latter provides an option for T2D patients who are unwilling to self-administer an injectable agent and might also confer benefits for longer-term adherence. It needs to be taken 30 minutes prior to eating food or other medications, on an empty stomach.[12]

The co-formulation of semaglutide with sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC), a transcellular permeation enhancer, ensures the bioavailability of the oral formulation (refer to **Figure 1).** In association with semaglutide, SNAC has a predominantly transcellular transit mode via the gastric epithelium, where absorption occurs 60-140 minutes after ingesting a tablet containing 10 mg of semaglutide and 300 mg of SNAC in humans.[13] SNAC probably also attenuates semaglutide proteolytic digestion as it increases the local gastric pH.

Figure 1. Mechanism of absorption of semaglutide and SNAC co-formulation tablet: After digestion, the tablet is rapidly eroded and releases high concentrated amount of SNAC. SNAC neutralises the acidic environment in the stomach by which semaglutide is protected from enzymatic degradation. In addition, SNAC also enhances semaglutide absorption via transcellular pathway.[13]

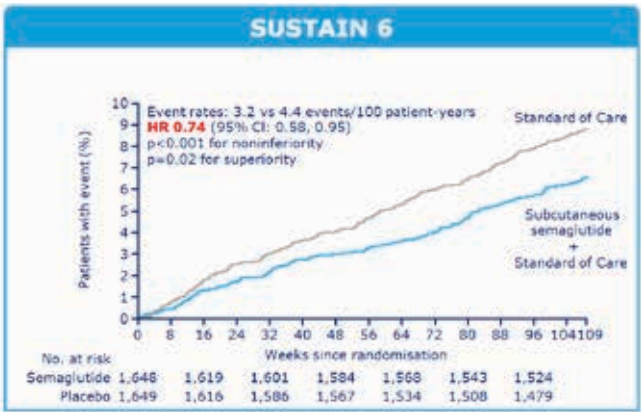


CARDIOVASCULAR OUTCOME TRIALS

Two large phase 3 cardiovascular outcomes trials, SUSTAIN-6[14] AND PIONEER-6,[15] investigated once weekly subcutaneous and oral semaglutide formulations, respectively, versus placebo on major adverse cardiac events in patients with type 2 diabetes and high CV risk. All participants had a baseline HbA1c >7 percent. The primary endpoint was time from randomisation to first occurrence of an adjudicated 3-component composite MACE endpoint defined as CV death, non-fatal myocardial infarction (MI), or non-fatal stroke.

The majority of patients in both trials were enrolled based on established cardiovascular disease and/or chronic kidney disease (CKD) (refer to **Table 1**). A substantial proportion of patients were 65 years of age or older. Background therapy, including glucose-lowering treatments, was in accordance with the standards of care commonly used in the T2D population.

Table 1. Key points regarding baseline characteristics and study outcomes for the major cardiovascular outcomes in the SUSTAIN-6 and PIONEER-6 Trials



SUSTAIN-6 recruited 3,297 patients and the overall CV risk reduction was 26 percent (refer to **Figure 2**) over a median observation time of 2.1 years. This risk reduction was observed with both the 0.5 mg dose (HR 0.77, 95 percent CI 0.55, 1.08) and 1 mg dose (HR 0.71, 95 percent CI 0.49, 1.02). The benefit of subcutaneous semaglutide was driven by fewer non-fatal myocardial infarctions and non-fatal strokes. There was no difference in cardiovascular deaths and all-cause mortality was not reduced. The MACE results were similar across multiple sub-groups, including those with established cardiovascular disease and chronic kidney disease. A meta-analysis that compiled data from the SUSTAIN-6 trial showed that CV benefits were associated with decreases in HbA1c and body weight (ref 10). HbA1c was reduced by 0.7 percent in the 0.5 mg dose versus placebo and 1.0 percent in the 1.0 mg dose, both of which were statistically significant (p<0.001).

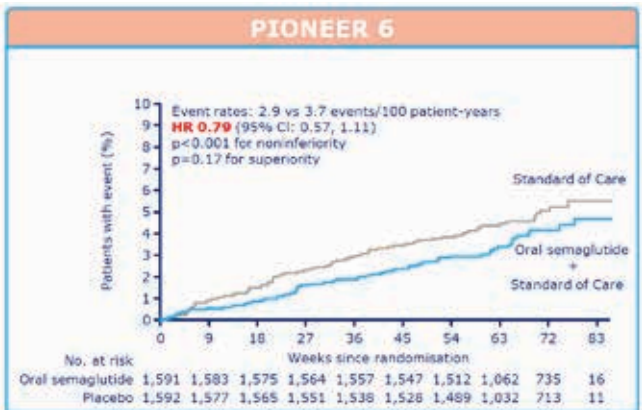
Figure 2. Primary CV Outcome Result in SUSTAIN-6

Variable	SUSTAIN 6 (2013-2016)		PIONEER 6 (2017-2019)	
	Semaglutide (N=1648)	Placebo (N=1649)	Semaglutide (N=1591)	Placebo (N=1592)
Median exposure, y	2.1	2.1	1.3	1.3
Mean age, y	64.6	64.6	66	66
Diabetes duration, y	14.2	13.6	14.7	15.1
Baseline HbA1c, %	8.7	8.7	8.2	8.2
History of CVD or CKD, %	83	83	84.9	84.5
eGFR, mL/min/1.73m² (<60 ml/min, %)	76 (28.5%)		74 (27%)	
MACE	108 (6.6%) 3.24/100PY	146 (8.9%) 4.4/100PY	61 (3.8%) 2.9/100PY	76 (4.8%) 3.7/100PY
	HR 0.74 (0.58-0.95)		HR 0.79 (0.57-1.11)	
CV death	44 (2.7%) 1.29/100PY	46 (2.8%) 1.35/100PY	15 (0.9%) 0.7/100PY	30 (1.9%) 1.4/100PY
	HR 0.98 (0.65-1.48)		HR 0.49 (0.27-0.92)	
Nonfatal MI	47 (2.9%) 1.40/100PY	64 (3.9%) 1.92/100PY	37 (2.3%) 1.8/100PY	31 (1.9%) 1.5/100PY
	HR 0.74 (0.51-1.08)		HR 1.18 (0.73-1.90)	
Nonfatal stroke	27 (1.6%) 0.8/100PY	44 (2.7%) 1.31/100PY	12 (0.8%) 0.6/100PY	16 (1.0%) 0.8/100PY
	HR 0.61 (0.38-0.99)		HR 0.74 (0.35-1.57)	
All-cause death	62 (3.8%) 1.82/100PY	60 (3.6%) 1.76/100PY	23 (1.4%) 1.1/100PY	45 (2.8%) 2.2/100PY
	HR 1.05 (0.74-1.50)		HR 0.51 (0.31-0.84)	
Expanded MACE	199 (12.1%) 6.17/100PY	264 (16.0%) 8.36/100PY	83 (5.2%) 4.0/100PY	100 (6.3%) 4.9/100PY
	HR 0.74 (0.62-0.89)		HR 0.82 (0.61-1.10)	
Hospitalization for UAP	22 (1.3%) 0.65/100PY	27 (1.6%) 0.80/100PY	11 (0.7%) 0.5/100PY	7 (0.4%) 0.3/100PY
	HR 0.82 (0.47-1.44)		HR 1.56 (0.60-4.01)	
Hospitalization for HF	59 (3.6%) 1.76/100PY	54 (3.3%) 1.61/100PY	21 (1.3%) 1.0/100PY	24 (1.5%) 1.2/100PY
	HR 1.11 (0.77-1.61)		HR 0.86 (0.48-1.55)	
New or worsening nephropathy	62 (3.8%) 1.86/100PY	100 (6.1%) 3.06/100PY	NR	NR
	HR 0.64 (0.46-88)		NR	

The headline SUSTAIN-6 result was consistent with other CV outcome trials evaluating other subcutaneously administered GLP1ra such as dulaglutide and liraglutide, where significant CV risk reduction also manifested when compared to placebo.[16,17]

In PIONEER-6, the overall risk reduction with 14 mg oral semaglutide was 21 percent (refer to **Figure 3**) over a median observation time of 1.8 years but was not statistically significant. The risk difference was driven by fewer CV deaths and non-fatal strokes, but more patients experienced non-fatal myocardial infarction with semaglutide. In addition, a statistically significant reduction in all-cause mortality was observed with oral semaglutide.

Figure 3. Primary CV Outcome Result in PIONEER-6



In both SUSTAIN 6 and PIONEER 6 trials, semaglutide was associated with a favourable impact on systolic blood pressure (SBP) (placebo-controlled reduction in SBP of 1.3 and 2.6 mmHg with 0.5 and 1mg dose in SUSTAIN 6; 2.6 mmHg reduction in PIONEER 6), weight loss (placebo-controlled weight loss of 2.9 and 4.3 kg with 0.5 and 1 mg dose in SUSTAIN 6; 3.4 kg weight loss in PIONEER 6), and glycaemic control (placebo-controlled reduction in HbA1c of 0.7 percent and 1.0 percent with 0.5 and 1 mg dose in SUSTAIN 6; 0.7 percent reduction in PIONEER 6). The mean pulse rate increased by 2 and 2.5 bpm with 0.5 and 1.0 mg dose of semaglutide in SUSTAIN 6, and by 4 bpm in PIONEER 6.

SAFETY OF SEMAGLUTIDE

Gastrointestinal-adverse events (nausea, abdominal cramps, diarrhoea) were the most frequently reported adverse drug reactions with semaglutide.[18] The risk of severe hypoglycaemia was low, typically increased in conjunction with sulphonylureas or insulin therapy. No increased risk of pancreatitis, pancreatic cancer, or thyroid medullary cancer was observed, although the duration of exposure was limited. One new safety finding emerged from SUSTAIN 6 – there was an increased risk of diabetic retinopathy complications primarily in patients with pre-existing diabetic retinopathy (HR 1.76, 95 percent CI 1.11, 2.78). The available data suggest that this might be associated with pronounced improvement in glycaemic control as seen with insulin therapy. Despite patients with proliferative diabetic retinopathy being excluded from PIONEER 6, a 0.8 percent increase in diabetic retinopathy was observed with oral semaglutide.[9] A dedicated ophthalmic trial (FOCUS) with a treatment duration of five years will assess the long-term effect of semaglutide on diabetic retinopathy development and progression.[19]

FUTURE DIRECTIONS FOR CV OUTCOMES OF SEMAGLUTIDE

The risk reduction in MACE in SUSTAIN 6 was supported by the favourable outcome in PIONEER 6, thereby providing independent confirmation. No difference in safety outcomes were observed across the trials. However, there are important differences in individual CV outcomes among the two trials, which require further reflection. For example, with the exception of stroke findings, there are inconsistencies among the two trials with regards to impact on CV death and all-cause mortality (favourable impact in PIONEER-6), non-fatal MI and UAP (favourable impact in SUSTAIN-6), and hospitalisation for heart failure (favourable impact in PIONEER-6). The discordance on the individual endpoints despite similar pharmacokinetic exposure challenges the argument of consistent exposure-response relationship. Following the confirmation that subcutaneous semaglutide is associated with CV safety and preliminarily, even some evidence of benefit, a definitive CV outcome trial is ongoing to assess the effects of subcutaneous semaglutide on CV events in patients at high CV risk who are overweight or obese. In the ongoing Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial, approximately 17,500 people with pre-existing CVD and with overweight or obesity (body mass index ≥27 kg/m^2) but *without diabetes* will receive either

subcutaneous semaglutide (up to 2.4 mg) or placebo in addition to standard care for up to five years.[20] Furthermore, the finding that a drug reduces all-cause mortality without impacting the incidence of non-fatal myocardial infarction merits further study and the longer-term SOUL trial will further inform about CV outcomes with oral semaglutide versus placebo.[21]

CONCLUSION AND THE PLACE OF GLP1RA IN THE GUIDELINES FOR PATIENTS WITH TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

The American Diabetes Association's *Standards of Medical Care in Diabetes—2019* recommend GLP-1 receptor agonists with proven cardiovascular benefit as one of the two preferred options for add-on therapy in patients with type 2 diabetes and established atherosclerotic cardiovascular disease after metformin and lifestyle intervention.[22] Both subcutaneous and oral semaglutide are now commonly prescribed for patients who have T2 diabetes despite treatment with other anti-hyperglycaemic medications and as an adjunct to diet and exercise, especially for patients who are overweight or obese and have a previous history of cardiovascular disease or with multiple risk factors for cardiovascular disease.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 2019. 9th edition. https://www.diabetesatlas.org/en/
2. Phan TP, Alkema L, Tai ES, Tan KH, Yang Q, Lim WY, Teo YY, Cheng CY, Wang X, Wong TY, Chia KS, Cook AR. Forecasting the burden of type 2 diabetes in Singapore using a demographic epidemiological model of Singapore. BMJ Open Diabetes Res Care. 2014 Jun 11;2(1):e000012. doi: 10.1136/bmjdrc-2013-000012. PMID: 25452860; PMCID: PMC4212579.
3. Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, Manson JE, Hu FB. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med. 2014 Jan 16;370(3):233-44. doi: 10.1056/NEJMoa1304501. Erratum in: N Engl J Med. 2014 Apr 3;370(14):1368. PMID: 24428469; PMCID: PMC3966911.
4. Magkos F, Hjorth MF, Astrup A. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2020 Oct;16(10):545-555. doi: 10.1038/s41574-020-0381-5. Epub 2020 Jul 20. PMID: 32690918.
5. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018 Feb 10;391(10120):541-551. doi: 10.1016/S0140-6736(17)33102-1. Epub 2017 Dec 5. PMID: 29221645.
6. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018 Jun 8;17(1):83. doi: 10.1186/s12933-018-0728-6. PMID: 29884191; PMCID: PMC5994068.
7. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. Circulation. 2016 Jun 14;133(24):2459-502. doi: 10.1161/CIRCULATIONAHA.116.022194. PMID: 27297342; PMCID: PMC4910510.
8. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405-12. doi: 10.1136/bmj.321.7258.405. PMID: 10938048; PMCID: PMC27454.
9. Holst JJ. The incretin system in healthy humans: The role of GIP and GLP-1. Metabolism. 2019 Jul;96:46-55. doi: 10.1016/j.metabol.2019.04.014. Epub 2019 Apr 25. PMID: 31029770.
10. Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. Nature. 1996 Jan 4;379(6560):69-72. doi: 10.1038/379069a0. PMID: 8538742.
11. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998 Feb 1;101(3):515-20. doi: 10.1172/JCI990. PMID: 9449682; PMCID: PMC508592.
12. Kalra S, Sahay R. A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus. Diabetes Ther. 2020 Sep;11(9):1965-1982. doi: 10.1007/s13300-020-00894-y. Epub 2020 Jul 28. PMID: 32725484; PMCID: PMC7434819.
13. Pearson S, Kietsiriroje N, Ajjan RA. Oral Semaglutide In The Management Of Type 2 Diabetes: A Report On The Evidence To Date. Diabetes Metab Syndr Obes. 2019 Dec 2;12:2515-2529. doi: 10.2147/DMSO.S229802. PMID: 31819577; PMCID: PMC6897065.
14. Marso SP, Holst AG, Vilsbøll T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2017 Mar 2;376(9):891-2. doi: 10.1056/NEJMc1615712. PMID: 28249135.
15. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019 Aug 29;381(9):841-851. doi: 10.1056/NEJMoa1901118. Epub 2019 Jun 11. PMID: 31185157.
16. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019 Jul 13;394(10193):121-130. doi: 10.1016/S0140-6736(19)31149-3. Epub 2019 Jun 9. PMID: 31189511.
17. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. PMID: 27295427; PMCID: PMC4985288.
18. Del Olmo-Garcia MI, Merino-Torres JF. GLP-1 Receptor Agonists and Cardiovascular Disease in Patients with Type 2 Diabetes. J Diabetes Res. 2018 Apr 2;2018:4020492. doi: 10.1155/2018/4020492. PMID: 29805980; PMCID: PMC5902002.
19. A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes (FOCUS). Available at: https://clinicaltrials.gov/ct2/show/NCT03811561. Accessed March 5 2022.
20. Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, et al. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. Am Heart J. 2020 Nov;229:61-69. doi: 10.1016/j.ahj.2020.07.008. Epub 2020 Jul 17. PMID: 32916609.
21. A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL). Available at: https://clinicaltrials.gov/ct2/show/NCT03914326. Accessed March 5 2022.
22. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020 Feb;43(2):487-493. doi: 10.2337/dci19-0066. Epub 2019 Dec 19. Erratum in: Diabetes Care. 2020 Jul;43(7):1670. PMID: 31857443; PMCID: PMC6971782.

LEARNING POINTS

- **The incretin effect refers to the amplification of insulin secretion after oral glucose intake. It is essential for glucose tolerance and is partly mediated by glucagon-like peptide-1 (GLP-1), which is secreted by the intestinal epithelial cells and its actions in the gastrointestinal tract.**
- **Semaglutide is a potent glucagon-like peptide-1 analogue, with a very high degree of homology to the human peptide with the exclusive advantage of being available in both subcutaneous and oral formulations.**
- **The cardiovascular safety of both subcutaneous and oral administration of semaglutide was confirmed in the SUSTAIN-6 and PIONEER-6 randomised control trials in patients with Type 2 diabetes and established cardiovascular and chronic kidney disease, maintained on current standard of care. This led to their approval to reduce cardiovascular risk as an adjunct to diet and lifestyle.**