

A SELECTION OF TEN READINGS ON TOPICS RELATED TO GOAL: GUIDANCE ORIENTED APPROACH TO LEARNING

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Selection of readings made by A/Prof Goh Lee Gan

READING 1 – SAFETY OF SEMAGLUTIDE

Smits MM,¹ Van Raalte DH.¹ Safety of Semaglutide. Front Endocrinol (Lausanne). 2021 Jul 7;12:645563. PMID: 34305810.

URL: doi: 10.3389/fendo.2021.645563. PMID: 34305810.

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ABSTRACT

The glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide is the most recently approved agent of this drug class, and the only GLP-1RA currently available as both subcutaneous and oral formulation. While GLP-1RAs effectively improve glycaemic control and cause weight loss, potential safety concerns have arisen over the years. For semaglutide, such concerns have been addressed in the extensive phase 3 registration trials including cardiovascular outcome trials for both subcutaneous (SUSTAIN: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) and oral (PIONEER: Peptide InnOvation for the Early diabetes tReatment) semaglutide and are being studied in further trials and registries, including real world data studies. In the current review, we discuss the occurrence of adverse events associated with semaglutide focusing on hypoglycaemia, gastrointestinal side effects, pancreatic safety (pancreatitis and pancreatic cancer), thyroid cancer, gallbladder events, cardiovascular aspects, acute kidney injury, diabetic retinopathy (DRP) complications, and injection-site and allergic reactions, and where available, we highlight potential underlying mechanisms. Furthermore, we discuss whether effects are specific for semaglutide or a class effect. We conclude that semaglutide induces mostly mild-to-moderate and transient gastrointestinal disturbances and increases the risk of biliary disease (cholelithiasis). No unexpected safety issues have arisen to date, and the established safety profile for semaglutide is similar to that of other GLP-1RAs where definitive conclusions for pancreatic and thyroid cancer cannot be drawn at this point due to low incidence of these conditions. Due to its potent glucose-lowering effect, patients at risk for deterioration of existing DRP should be carefully monitored if treated with semaglutide, particularly if also treated with insulin. Given the beneficial metabolic and cardiovascular actions of semaglutide, and the low risk for severe adverse events, semaglutide has an overall favourable risk/benefit profile for patient with type 2 diabetes.

READING 2 – EFFICACY OF SEMAGLUTIDE

Meier JJ.¹ Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation. Front Endocrinol (Lausanne). 2021 Jun 25;12:645617. PMID: 34248838

URL: doi: 10.3389/fendo.2021.645617. PMID: 34248838.

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ABSTRACT

Despite the benefits of early and effective glycaemic control in the management of type 2 diabetes (T2D), achieving glycated haemoglobin (HbA1c) targets is challenging in some patients. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide effective reductions in HbA1c and body weight. Semaglutide is the only GLP-1RA that is available in both an injectable and oral formulation. The efficacy of once-weekly subcutaneous semaglutide and once-daily oral semaglutide has been investigated in the global SUSTAIN and PIONEER phase 3 clinical trial programmes in a range of clinical settings, including early T2D managed with diet and exercise only, more established T2D uncontrolled on one to three oral antidiabetic drugs, and advanced disease treated with insulin. Across the SUSTAIN program, once-weekly subcutaneous semaglutide 1.0 mg reduced HbA1c by 1.5-1.8 percent after 30-56 weeks, which was significantly more than sitagliptin,

liraglutide, exenatide extended release, dulaglutide, canagliflozin, or insulin glargine. Across the PIONEER program, once-daily oral semaglutide 14 mg reduced HbA1c by 1.0-1.4 percent, significantly more than sitagliptin or empagliflozin, and to a similar extent as liraglutide after 26 weeks. In addition, subcutaneous semaglutide reduced body weight significantly more than all active comparators tested, while oral semaglutide reduced body weight more than sitagliptin and liraglutide, and to a similar extent as empagliflozin. Neither formulation of semaglutide has been associated with an increased risk of hypoglycaemia and both improve various measures of health-related quality of life. Semaglutide offers the benefits of a highly effective GLP-1RA in both injectable and oral formulations. Selection of the most appropriate formulation can be made on an individual basis to best suit the patient's preferences and needs.

READING 3 – DRUG THERAPY IN OBESITY, CURRENT AND EMERGING TREATMENTS

Williams DM,¹ Nawaz A,² Evans M.² Drug Therapy in Obesity: A Review of Current and Emerging Treatments. *Diabetes Ther.* 2020 Jun;11(6):1199-1216. PMID: 32297119.

URL: doi: 10.1007/s13300-020-00816-y. PMID: 32297119.

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ABSTRACT

As the prevalence of obesity continues to increase at an alarming rate worldwide, the personal and economic burden of obesity-related complications become ever more important. Whilst dietary and lifestyle measures remain the fundamental focus of the patient to counter obesity, more frequently pharmacological and/or surgical interventions are required. Nevertheless, these therapies are often limited by weight loss efficacy, side effects, surgical risks, and frequently obesity relapse. Currently, only five drug therapies are approved for the specific treatment of obesity. However, our understanding of the pathophysiology of obesity and of gut hormones has developed precipitously over the last 20-30 years. As a result, there has been a recent movement to create and use analogues that manipulate these gut hormones to support weight loss. In this article we review the efficacy of the currently approved drug therapies and discuss future potential drug mechanisms and early clinical trial results exploring these budding avenues. We discuss the use of glucagon-like peptide-1 (GLP-1) analogues as monotherapy and unimolecular dual or triple agonists that exploit the GLP-1 receptor and/or the gastric inhibitory peptide (GIP) receptor and/or the glucagon receptor. We also explore the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors, amylin mimetics, leptin analogues, ghrelin antagonists and centrally-acting agents to suppress appetite (neuropeptide Y (NPY) antagonists, melanocortin-4 receptor (MC4R) agonists and cannabinoid-1 receptor antagonists). Whilst further evidence is required to support their clinical use, preclinical and early clinical trial results are encouraging.

READING 4 – GLP-1 RECEPTER AGONISTS AND CARDIORENAL OUTCOMES: UPDATED META-ANALYSIS

Giugliano D,^{#,1,2} Scappaticcio L,^{#,3,4} Longo M,^{#,3,4} Caruso P,^{3,4} Maiorino MI,⁵ Bellastella G,³ Ceriello A,⁶ Chiodini P,⁷ Esposito K.^{4,5} **GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol.* 2021 Sep 15;20(1):189. PMID: 34526024.**

URL: doi: 10.1186/s12933-021-01366-8. PMID: 34526024.

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ABSTRACT

BACKGROUND: A meta-analysis is presented of cardiovascular outcome trials (CVOTs) comparing glucagon-like peptide-1 receptor agonists (GLP-1RA) versus placebo on cardiorenal outcomes in patients with type 2 diabetes mellitus (T2DM). **METHODS:** We did an electronic search up to 30 June 30 2021 for eligible trials. We did a meta-analysis of available trial data using a random-effects model to calculate overall hazard ratios (HRs) and 95 percent CI (confidence intervals). We included data from eight CVOTs and 60,080 patients (72.4 percent with established cardiovascular disease). **RESULTS:** GLP-1RA reduced major cardiovascular events (MACE) by 14 percent (HR=0.86, 95 percent CI 0.79-0.94, P=0.006) with a non-significant heterogeneity between subgroups of patients with and without cardiovascular disease (P=0.127). GLP-1RA also reduced the risk of cardiovascular death by 13 percent (P=0.016), non-fatal stroke by 16 percent (P=0.007), hospitalisation for heart failure by 10 percent (P=0.023), all-cause mortality by 12 percent (P=0.012), and the broad composite kidney outcome by 17 percent (P=0.012), which was driven by a reduction in macroalbuminuria only (HR=0.74, 0.67-0.82, P<0.001).

CONCLUSIONS: GLP-1RA have moderate benefits on MACE, and reduce hospitalisation for heart failure and all-cause mortality. They also have robust benefits on reducing the incidence of macroalbuminuria.

READING 5 – ORAL SEMAGLUTIDE: NEW WEIGHT LOSS DRUG

Singh G,¹ Krauthamer M,² Bjalme-Evans M.³ Wegovy (semaglutide): a new weight loss drug for chronic weight management J Investig Med. 2022 Jan;70(1):5-13. PMID: 34706925.

URL: doi: 10.1136/jim-2021-001952. PMID: 34706925.

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ABSTRACT

Obesity is a growing epidemic within the USA. Because weight gain is associated with an increased risk of developing life-threatening comorbidities, such as hypertension or type 2 diabetes, there is great interest in developing non-invasive pharmacotherapeutics to help combat obesity. Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of antidiabetic medications that have shown promise in encouraging glycaemic control and promoting weight loss in patients with or without type 2 diabetes. This literature review summarises and discusses the weight loss results from the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes), PIONEER (Peptide Innovation for Early Diabetes Treatment), and STEP (Semaglutide Treatment Effect in People with Obesity) clinical trial programmes. The SUSTAIN and PIONEER clinical trials studied the use of 1.0 mg, once-weekly, subcutaneous, and oral semaglutide (a new GLP-1 homologue), respectively, on participants with type 2 diabetes. The STEP trial examined the effects of 2.4 mg, once-weekly, subcutaneous semaglutide on patients with obesity. Trial data and other pertinent articles were obtained via database search through the US National Library of Medicine Clinical Trials and the National Center for Biotechnology Information. All three clinical trials demonstrated that semaglutide (injected or oral) has superior efficacy compared with placebo and other antidiabetic medications in weight reduction, which led to Food and Drug Administration approval of Wegovy (semaglutide) for weight loss.

READING 6 – USE OF SUBCUTANEOUS AND ORAL SEMAGLUTIDE

Gallwitz B,¹ Giorgino F.² Clinical Perspectives on the Use of Subcutaneous and Oral Formulations of Semaglutide. Front Endocrinol (Lausanne). 2021 Jun 29;12:645507. PMID: 34267725.

URL: doi: 10.3389/fendo.2021.645507. PMID: 34267725.

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ABSTRACT

Early and effective glycaemic control can prevent or delay the complications associated with type 2 diabetes (T2D). The benefits of glucagon-like peptide-1 receptor agonists (GLP-1RAs) are becoming increasingly recognised and they now feature prominently in international T2D treatment recommendations and guidelines across the disease continuum. However, despite providing effective glycaemic control, weight loss, and a low risk of hypoglycaemia, GLP-1RAs are currently underutilised in clinical practice. The long-acting GLP-1RA, semaglutide, is available for once-weekly injection and in a new once-daily oral formulation. Semaglutide is an advantageous choice for the treatment of T2D since it has greater efficacy in reducing glycated haemoglobin and body weight compared with other GLP-1RAs, has demonstrated benefits in reducing major adverse cardiovascular events, and has a favourable profile in special populations (e.g., patients with hepatic impairment or renal impairment). The oral formulation represents a useful option to help improve acceptance and adherence compared with injectable formulations for patients with a preference for oral therapy and may lead to earlier and broader use of GLP-1RAs in the T2D treatment trajectory. Oral semaglutide should be taken on an empty stomach, which may influence the choice of formulation. As with most GLP-1RAs, initial dose escalation of semaglutide is required for both formulations to mitigate gastrointestinal adverse events. There are also specific dose instructions to follow with oral semaglutide to ensure sufficient gastric absorption. The evidence base surrounding the clinical use of semaglutide is being further expanded with trials investigating effects on diabetic retinopathy, cardiovascular outcomes, and on the common T2D comorbidities of obesity, chronic kidney disease, and non-alcoholic steatohepatitis. These will provide further information about whether the benefits of semaglutide extend to these other indications.

READING 7 – ADVANCES IN GLP-1 RA: FOCUS ON ORAL SEMAGLUTIDE

Eliaschewitz FG,¹ Canani LH.² **Advances in GLP-1 treatment: focus on oral semaglutide. *Diabetol Metab Syndr.* 2021 Sep 15;13(1):99. PMID: 34526121**

URL: doi: 10.1186/s13098-021-00713-9. PMID: 34526121.

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ABSTRACT

BACKGROUND: There is currently a large arsenal of antidiabetic drugs available to treat type 2 diabetes (T2D). However, this is a serious chronic disease that affects millions of adults worldwide and is responsible for severe complications, comorbidities, and low quality of life when uncontrolled due mainly to delays in initiating treatment or inadequate therapy. This review article aims to clarify the therapeutic role of the oral formulation of the glucagon-like peptide 1 receptor agonist (GLP-1 RA) semaglutide in treating typical T2D patients. The discussion focuses on metabolic, glycaemic, and weight alteration effects and the safety of the therapy with this drug.

MAIN TEXT: Therapy with glucagon-like peptide 1 receptor agonist (GLP-1 RA) promotes strategic changes in the pathophysiological pathway of T2D and improves the secretion of glucagon and insulin, which results in a reduction in blood glucose levels and the promotion of weight loss. Until recently, the only route for semaglutide administration was parenteral. However, an oral formulation of GLP-1 RA was recently developed and approved by the Brazilian Health Regulatory Agency (ANVISA) and the Food and Drug Administration (FDA) based on the Peptide Innovation for Early Diabetes Treatment (PIONEER) programme results. A sequence of 10 clinical studies compared oral semaglutide with placebo or active standard-of-care medications (empagliflozin 25 mg, sitagliptin 100 mg, or liraglutide 1.8 mg) in different T2D populations.

CONCLUSIONS: Oral semaglutide effectively reduces glycated hemoglobin (HbA1c) levels and body weight in a broad spectrum of patients with T2D and shows cardiovascular safety. Oral semaglutide broadens therapy options and facilitates the adoption of earlier GLP-1 RA treatment once T2D patients present low rates of treatment discontinuation. The main adverse events reported were related to the gastrointestinal tract, common to GLP-1 RA class drugs.

READING 8 – SEMAGLUTIDE IN DIABESITY TREATMENT

Tilincă MC,^{1,2} Tiuca RA,^{3,4} Niculas C,⁵ Varga A,^{6,7} Tilea I.^{1,7} **Future perspectives in diabetes treatment: Semaglutide, a glucagon-like peptide 1 receptor agonist (Review). *Exp Ther Med.* 2021 Oct;22(4):1167. PMID: 34504612**

URL: doi: 10.3892/etm.2021.10601. PMID: 34504612

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ABSTRACT

Given their endemic prevalence in the past decades, obesity and type 2 diabetes mellitus (T2DM) have become major sanitary burdens with an important economic impact. Novel treatment options have been designed with the aim of

reducing the numerous complications associated with these metabolic disorders as well as reducing morbidity and mortality and improving the quality of life of those who suffer from these disorders. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are among the most modern therapeutics that target “diabesity”, a term used to describe the pathophysiological link between obesity and T2DM. Their glucose-lowering effects are mainly attributed to glucose-dependent insulin secretion, glucagon inhibition, and decreased gastric emptying. Given the effects on the central nervous system, GLP-1 RA usage may lead to body weight reduction. GLP-1 RAs are classified based on their pharmacokinetic properties as short- and long-acting agents, with both types being administered by subcutaneous injection. The latest agent from this drug class approved for use in T2DM is semaglutide, a long-acting compound that is the only GLP-1 RA available as an oral pill. The present narrative review highlights the most recently published data on the effects and safety of semaglutide in diabetic obesity, while also emphasising its cardiovascular benefits and potential side effects. In addition, an overview of the role of semaglutide in the treatment of non-diabetic obesity is provided.

READING 9 – SEMAGLUTIDE, ORAL GLP-1 RA FOR CARDIOVASCULAR BENEFITS FOR MANAGEMENT OF T2DM

Mahapatra MK,¹ Karuppasamy M,² Sahoo BM.³ Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. *Rev Endocr Metab Disord.* 2022 Jan 7:1-19. PMID: 34993760.

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ABSTRACT

Semaglutide, a glucagon like peptide-1 (GLP-1) receptor agonist, is available as monotherapy in both subcutaneous as well as oral dosage form (first approved oral GLP-1 receptor agonist). It has been approved as a second-line treatment option for better glycaemic control in type 2 diabetes and currently under scrutiny for anti-obesity purpose. Semaglutide has been proved to be safe in adults and elderly patients with renal or hepatic disorders demanding no dose modification. Cardiovascular (CV) outcome trials established that it can reduce various CV risk factors in patients with established CV disorders. Semaglutide is well tolerated with no risk of hypoglycaemia in monotherapy but suffers from gastrointestinal adverse effects. A large population affected with COVID-19 infection were diabetic, therefore the use of semaglutide in diabetes as well as CV patients would be beneficial in the maintenance of the healthcare system during this pandemic situation. Hence, this peptidic drug can be truly considered quintessential in GLP-1 agonists for management of type 2 diabetes.

READING 10 – ORAL SEMAGLUTIDE FOR T2DM

Kim HS,^{1,2} Jung CH.^{1,2} Oral Semaglutide, the First Ingestible Glucagon-Like Peptide-1 Receptor Agonist: Could It Be a Magic Bullet for Type 2 Diabetes? *Int J Mol Sci.* 2021 Sep 14;22(18):9936. PMID: 34576096.

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ABSTRACT

The gastrointestinal tract secretes gut hormones in response to food consumption, and some of these stimulate insulin secretion. Glucagon-like peptide-1 (GLP-1) is an incretin peptide hormone released from the lower digestive tract that stimulates insulin secretion, suppresses glucagon secretion, and decreases hunger. GLP-1 receptor agonist (GLP-1RA) mimics the action of endogenous GLP-1, consequently reversing hyperglycaemia and causing weight reduction, demonstrating its efficacy as an antidiabetic and antiobesity agent. Previously restricted to injection only, the invention of the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino) caprylate resulted in the development of oral semaglutide, the first ingestible GLP-1RA. Oral semaglutide demonstrated its efficacy in glycaemic management and body weight loss with a low risk of hypoglycaemia as a monotherapy and in combination with other hypoglycaemic medications in its clinical trial programmes named Peptide Innovation for Early Diabetes Treatment. Consistent with other injectable GLP-1RAs, gastrointestinal side effects were often reported. Additionally, cardiovascular safety was established by demonstrating that oral semaglutide was not inferior to a placebo in terms of cardiovascular outcomes. Thus oral semaglutide represents a novel treatment option that is particularly well-suited for patients with type 2 diabetes and/or obesity.