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GLP-1 Receptor Agonists in Obesity and Type 2 Diabetes: A Narrative Review of Clinical Effectiveness, Safety, And Future Directions

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Abstract- Background: ***Since they were first discovered as a glucose-lowering drug, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have developed into drugs with significant impacts on weight loss and cardiorenal protection in the treatment of type 2 diabetes mellitus. This huge increase in evidence coupled with the emergence of dual incretin agonism calls for a comprehensive integration.***

Objective: ***To assess the clinical efficacy of the GLP-1 RAs and the dual GLP-1 and GIP receptor agonist tirzepatide in the domains of glycaemic, weight and cardiorenal clinical outcomes in type 2 diabetes and obesity; to review their safety profile; and to suggest future directions for the use of the class.***

Methods: ***This review is written in the fashion of a narrative review, combining data from 20 landmark and key { }randomized controlled trials (RCTs) and meta-analyses from cardiovascular outcome trials (CVOTs), weight-management trials and head-to-head comparisons published from 2016 to 2023.***

Results: ***All GLP-1 RAs have a proven ability to lower HbA1c consistently and to decrease body weight, and some agents have been proven to decrease major adverse cardiovascular events and renal outcomes in type 2 diabetes. Semaglutide is associated with reduction in cardiovascular events in obesity without diabetes and tirzepatide has had unprecedented reduction in glycaemic and weight status in head-to-head and placebo-controlled trials. The gastrointestinal side effect profile prevails, and low intrinsic hypoglycaemia risk.***

Conclusion: ***GLP-1 RAs and dual incretin agonists have come into a new role in the management of type 2 diabetes and obesity providing metabolic and cardiorenal benefit. New product development activities involve oral formulations, new multi-agonists and new indications that are not related to glycaemia and weight.***

Keywords: ***GLP-1 Receptor Agonists, Type 2 Diabetes, Obesity, Tirzepatide, Semaglutide, Cardiovascular Outcomes, Narrative Review***

I. INTRODUCTION

Diabetes (DM) mellitus of type 2 and obesity are the most prominent chronic disease challenges of the twenty first century, and their link in pathogenesis and effect on cardiovascular and renal health. Historically, the focus of therapy for type 2diabetes has been glycaemic control at the expense of increasing weight and there was little evidence that there was a relationship between cardiovascular outcomes and glycaemic control. This has changed in recent years with the introduction of a therapeutic class of new glucose-lowering agents known for their glucagon-like peptide-1 receptor (GLP-1) activity that not only help to lower glucose but also have beneficial effects on body weight and for some GLP-1 RAs cardiovascular and renal protection. This metabolic and cardiorenal benefit of the two are among the most significant recent therapeutic developments in diabetic medicine.

The impact these agents have to deal with is vast. Type 2 diabetes is an ever-increasing burden in developed countries, paralleling the increase in obesity, and insulin resistance, which is a major pathophysiological mechanism found in both, and chronic low-grade inflammation, are key common mechanisms. These costs are borne disproportionately due to cardiovascular disease (CVD), which is the leading cause of death in Type 2 Diabetes, and due to diabetic kidney disease (DKD) which is one of the main risk factors for end-stage renal failure. Traditionally, the available glucose-lowering medications aimed only at the biochemical defect of hyperglycaemia without any effects downstream of the disorder on these cardiorenal glucose side effects, and some of them (such as insulin and the Sulphonylureas) covered the disadvantages of weight gain and hypoglycaemia.

Thus there was not only glycaemic power effect but power to change natural history of the cardiometabolic disease complex.

L-cells in the intestine make an incretin hormone, GLP-1, in response to taking food into the body. It increases insulin production when there is some basal glucose production, reduces the glucagon, slows gastric emptying and has an influence on the pathways of the central nervous system, increasing feelings of fullness. The physiological effects are pharmacologically targets of GLP-1 RAs and their insulinotropic effect is glucose dependent, offering a significant advantage over insulin and sulfonylureas in its intrinsic hypoglycaemic properties. These mechanisms are translated into clinical benefit with evidence from a comprehensive programme of randomized controlled trials (RCTs) that has been performed.

There have been a number of pivot points along the path of the class. The first was the proof – in separate dedicated cardiovascular outcome trials that GLP-1 RAs could be beneficial in reducing MACE in people with type 2 diabetes, starting with liraglutide and semaglutide (Marso et al., 2016; Bain et al., 2016). The second is that any weight loss that these drugs cause, at the higher doses at least, is clinically significant and can be used as a treatment to combat obesity. Recently though, the third inflection has occurred, with the emergence of dual incretin agonism (DIA) therapy, typified by tirzepatide which has demonstrated glycaemic and weight reduction effects that are superior to those of selective GLP-1 RAs (Frías et al., 2021; Jastreboff et al., 2022).

This narrative review aims to bring together the current evidence as a single reference for using GLP-1 RAs and dual incretin agonists for type 2 diabetes and obesity. In a section structured around three themes, it discusses the clinical effectiveness of these agents in glycaemic, weight and cardiorenal outcomes, their safety and tolerability and future directions in an "evolving class of agents. Instead of a systematic approach, a narrative approach is used as the objective is to integrate across the uneventful and different outcomes and indications rather than to pool quantitatively.

1.1 Scope and Aims

The aim of the review includes the syntheses of head-to-head trials, class-level syntheses, weight-management trials, cardiovascular outcome trials, reviews of the key randomised controlled trials (RCTs), and meta-analyses that have influenced clinical practice. It discusses the selective GLP-1 RAs liraglutide; semaglutide; dulaglutide and albiglutide and GIP/GLP-1 dual receptor agonist tirzepatide. Three goals guide the synthesis: evaluation of clinical effectiveness in each of the primary outcome areas, description of the safety profile and determination of directions of progress of the class.

II. METHODS

2.1 Review approach

It was a narrative review which is appropriate for integrative synthesis of evidence for a variety of outcomes, indications and agents. The narrative review does not attempt to answer any one quantitative question but brings together the key trial evidence to shape the narrative of the class's effectiveness, safety, evolution, etc. Sources have been chosen for their key role in clinical practice and in the formulation of clinical practice guidelines.

2.2 Evidence Sources

Twenty sources of evidence were synthesised, including dedicated cardiovascular outcome trials (CVOTs) of the GLP-1s, semaglutide trials as part of the SURPASS programme in type 2 diabetes, SUSTAIN and SURMOUNT programmes in weight management, head-to-head comparisons (such as SUSTAIN 7 and SURPASS-2), renal-outcome analyses, two class-level systematic reviews and meta-analyses of cardiovascular, mortality, and kidney outcomes. All these sources cover the three glycaemic, weight and cardiorenal areas which essentially characterise the clinical profile of the class.

2.3 Synthesis structure

Evidence is synthesized in terms of themes. After an overview of mechanism (Figure 1), glycaemic effectiveness, weight loss, cardiovascular and renal outcomes are discussed in sequence followed by a

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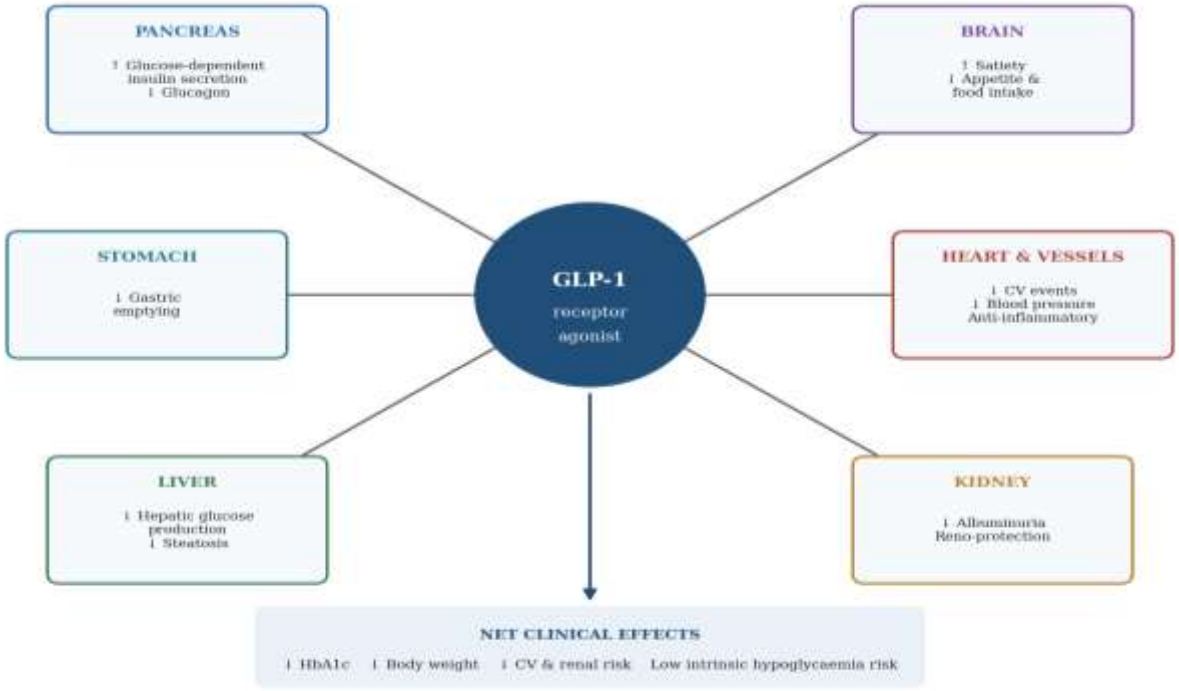
discussion on safety and what the future may hold. The trial evidence was summarised into two tables: Table 1 shows a summary of the pivotal RCTs by agent, population and main study outcomes and Table 2 combines cardiovascular and renal outcomes from cardiovascular outcome trials and meta-analyses.

Fig 1: Mechanisms of Action and Multi-Organ Effects of GLP-1 Receptor Agonists



III. THE MECHANISTIC BASIS OF GLP-1 RECEPTOR AGONISM IS DISCUSSED

Understanding clinical effect of GLP-1 RAs is best understood due to their physiology, which is summarised in Figure 1. GLP-1 is an incretin that is secreted from L-cells in the gut after feeding that acts through the GLP-1 receptor expressed in various organs. It can simultaneously benefit two of the key aspects of type 2 diabetes – by enhancing glucose-dependent insulin secretion and by reducing inappropriate glucagon secretion – in the pancreatic islet. The Glucose-dependence of the insulinotropic effect is also pharmacologically significant: insulin is only released when glucose is raised, this means that there is a low risk of hypoglycaemia from the drug itself as compared to the insulin and sulfonylureas which can cause hypoglycaemia.

In addition to the islet, GLP-1 receptor agonism has been shown to slow gastric emptying, thus reducing excess post prandial glucose and satiety, and has effects on various appetite regulating areas of the hypothalamus and brainstem controlling energy intake. The principle way by which the class has been so significant to obesity is by weight loss (primary central action). Weight loss effects are dependent on dose, meaning that there is a greater effect at a higher weight-loss dosage than what has been historically used in a glycaemic control study. Artificial experiments also clarify the favourable effects of GLP-1 receptor agonism on blood pressure, vascular inflammation, and atherogenesis that have been observed in the cardiovascular system as well as effects on slowing renal function decline and reduction in albuminuria in the kidney.

The latest development in terms of mechanisms is the combination of GIP along with GLP-1 receptor

agonism in one drug. The other main incretin hormone, GIP, is a co-agonist with GLP-1 in tirzepatide, which may lead to complementary/synergistic glycaemic and weight effects compared to those seen with selective GLP-1 receptor agonists (Frías et al., 2021). This two-in-one combination is setting a new direction in incretins therapy, and is part of the focus on future directions later in this review.

As students learn more about the pharmacology of the class, they will gain insight into the class's application. Each of the GLP-1 RAs has distinct molecular makeup, duration of action and route of administration from a daily injection injection to a weekly one and, in the case of semaglutide, an oral formulation. These differences in drug behavior probably account for clinically relevant differences in efficacy, toxicity and ease of use. For those with a longer receptor effect than the shorter acting agents, once-weekly agents like semaglutide, dulaglutide and tirzepatide deliver more profound, durable glycaemic and weight reduction and are better to adhere to, thanks to its dosing convenience. The upward trend in dose – evidenced by the higher dose versions of semaglutide in diabetes and obesity is indicative of the progressive optimisation of the dose, which demonstrates the recognition that the effects of receptor agonism are dose dependent and that early versions of these agents were sub-optimal in utilising the full benefits of the receptor agonism mechanism.
This is due to the class' mechanistic activity, which includes multiple targets in the pancreas, gut, brain, cardiovascular system, liver and kidney and which has made it very difficult for older therapies in single target trials to be matched. It also delineates the typical adverse effect profile, that adverse effects seen in clinical practice tend to be mediated by similar mechanisms as those that mediate benefit - the delayed gastric emptying and central effects of satiety and weight loss, such that benefit and adverse effect are mechanistically connected, to a degree. In summary, this all-encompassing account where DNA proteins are involved in a unified way, and illustrated in Figure 1, constitutes the context in which the clinical pieces of evidence discussed below can be best understood.

IV. CLINICAL EFFECTIVENESS: GLYCAEMIC CONTROL

GLP-1 RAs are clearly indicated for the treatment of type 2 diabetes and these drugs have undertaken the trial programme with consistent clinically significant HbA1c reductions. The cardiovascular outcome trials, though its purpose was mainly to ascertain cardiovascular safety and benefit, have all reported glycaemic improvement, while the specific efficacy trials have measured this quite precisely. The efficacy of leniardum in reducing HbA1c compared with dulaglutide was established during the head-to-head SUSTAIN 7 trial with once-weekly use of semaglutide demonstrating superior glycaemic control, and thus, leniardum belongs to one of the more potent selective GLP-1 RAs to reduce HbA1c (Pratley et al., 2018).

With the introduction of tirzepatide, the goal line got extended. When tirzepatide was compared with the other drugs evaluated in the SURPASS programme, it reduced HbA1c more than them in each background treatment and disease stage. Tirzepatide monotherapy significantly lowered HbA1c compared to placebo that was not well controlled by diet and exercise when it was used in the SURPASS-1 study (Rosenstock et al., 2021). The results of the head-to-head SURPASS-2 trial in these initial analyses put a new benchmark on the table regarding the potential of incretin-based therapy, as once-weekly semaglutide was a very effective agent in that study and all three doses of tirzepatide proved to be superior (Frías et al., 2021). Results from SURPASS-3 indicated greater efficacy of SURPASS as an add-on to metformin vs titrated insulin degludec in patients with type 2 diabetes who had inadequate glycemic control, as well as results from SURPASS-4, which showed greater efficacy compared to insulin glargine treatment in patients with elevated cardiovascular risk.

Thus Tirzepatide was also effective when combined with other insulin treatment. In SURPASS-5, the combination of tirzepatide and optical titration of insulin glargine showed efficacy beyond placebo in patients with more complex, insulin-treated diabetes even among those who were more advanced and had

insulin-treated diabetes (Dahl et al., 2022). Similarly, optimisation of doses has also lengthened the glycaemic effect of semaglutide: in SUSTAIN FORTE, a dose transition from 1mg to 2mg of once weekly semaglutide resulted in greater HbA1c reduction as well as a similar safety signal, providing a new opportunity for those needing more intensive glycaemic control (Frías et al., 2021). Put together, these trials put a clear order of glycaemic potency in place: dual action, at the top, followed by the high dose Semaglutide.

Single Point Summary (SPS) to highlight for implementation in clinical practice. Firstly, the HbA1C improvement obtained by the most effective drugs is enough to get a significant percentage of patients to glycemic goals that were previously only reached with insulin therapy or complicated dose adjustment strategies; and without the weight gain and hypoglycemia that was previously associated with intensification of insulin therapy. Second, the longevity of glycaemic control seems better than for many of the older drugs; this is due to the long-lived receptor effects under glycaemic control seen with the long acting agents, and also weight loss, which enhances insulin sensitivity. Third, the wide range of efficacy demonstrated in each of these patient populations (whether used as monotherapy, combination with metformin, combination with insulin, and across a range of disease duration), gives support for the flexible use of these agents at different stages of the treatment pathway, instead of in a single line of therapy.

The glycaemic superiority of tirzepatide over semaglutide in SURPASS-2 is of special interest as it directly compares the 2 most effective incretin based agents available (Frías et al., 2021). The consistent superiority of tirzepatide irrespective of dose and the same results seen when compared with various products across the SURPASS programme lend strong support for dual GIP/GLP-1 agonism to provide additional glycaemic benefits beyond selective GLP-1 receptor agonism. This discovery raises expectations and has changed the therapeutic paradigm of incretin-related glucose-lowering, and has implications in the obesity indication as well, which does follow the same trend of increasing potency.

4.1 Summary of Key Trials

Table 1 summarizes the key trials assessed in this review, including the agents, populations treated, comparison agents, and primary outcomes for each of those trials by glycaemic, weight and cardiorenal outcome, respectively. It illustrates the wide spectrum of evidence and the trend of increasing the number of indications from GLP-1 receptor agonism to dual incretins agonism and from glycaemic to weight and cardiorenal indications.

Table 1: Pivotal randomised controlled trials of GLP-1 receptor agonists and the dual GIP/GLP-1 agonist tirzepatide

Trial / source	Agent	Population	Principal outcomes
LEADER (Marso, Daniels, et al., 2016)	Liraglutide	T2D with high CV risk	Reduced major adverse CV events; reduced CV and all-cause mortality.
SUSTAIN-6 (Marso, Bain, et al., 2016)	Semaglutide (SC)	T2D with high CV risk	Reduced major adverse CV events; reduced non-fatal stroke.
PIONEER 6 (Husain et al., 2019)	Oral semaglutide	T2D with high CV risk	CV safety confirmed; reduced CV mortality (secondary).
REWIND (Gerstein et al., 2019)	Dulaglutide	T2D, broad CV risk	Reduced major adverse CV events across primary and secondary prevention.
SUSTAIN 7 (Pratley et al., 2018)	Semaglutide vs dulaglutide	T2D on metformin	Superior HbA1c and weight reduction with semaglutide.
SURPASS-1–	Tirzepatide	T2D, various	Superior HbA1c and weight vs placebo,

Trial / source	Agent	Population	Principal outcomes
SURPASS-5		backgrounds	semaglutide, insulin (Rosenstock et al., 2021; Frías et al., 2021; Ludvik et al., 2021; Del Prato et al., 2021; Dahl et al., 2022).
STEP 1 / STEP 4 (Wilding et al., 2021; Rubino et al., 2021)	Semaglutide 2.4 mg	Overweight/obesity without diabetes	Substantial weight loss; maintenance with continued treatment.
SURMOUNT-1 / -2 (Jastreboff et al., 2022; Garvey et al., 2023)	Tirzepatide	Obesity ± T2D	Unprecedented weight reduction vs placebo.
SELECT (Lincoff et al., 2023)	Semaglutide	Obesity without diabetes, established CVD	Reduced major adverse CV events.

V. CLINICAL EFFECTIVENESS - REDUCING WEIGHTS

What was originally a welcome secondary benefit seen when GLP-1 RAs were evaluated in the field of diabetes, is now a target for its use. These agents have been appreciated for their ability to yield clinically relevant and maintained weight reductions and led to the establishment of specific programmes for the development of obesity drugs that have dramatically changed an area that has suffered from suboptimal and only short-term effective pharmaceutical treatments.

The pivotal demonstration was with STEP programme for semaglutide. In STEP 1, weight loss with once-weekly semaglutide 2.4 mg was about 15% in adults with overweight or obesity (not diabetes) which was similar to maximal weight loss seen with bariatric surgery, and greater than previous medications (Wilding et al., 2021). In STEP 4, sustained weight loss with SEM was compared with such a rebound with CE in group 2 (placebo), suggesting that obesity is a chronic condition that requires an ongoing therapy, while treatment with SEM will lead to a prolonged result (Rubino et al., 2021). This discovery has significant implications for the way that obesity medications are thought of and funded.

Tirzepatide took the weight-loss baton one step further. In the SURMOUNT-1 study, tirzepatide resulted in mean weight losses significantly more than placebo in adults with obesity, not diabetic, with the top dose of tirzepatide plummeting differences with bariatric surgery to the lowest levels ever seen (Jastreboff et al., 2022). In view of diabetes tends to

dull the impact of weight loss, the SURMOUNT-2 trial specifically focused on tirzepatide in an obesity and type 2 diabetes (T2D) population, thus demonstrating clinically important weight loss in a more treatment-resistant patient cohort (Garvey et al., 2023). The STEP and SURMOUNT programmes have paved the way for today's obesity treatment with incretin agonist-based drugs, with the combined action of a dual agonist remaining the most effective. This reduction in weight is not just a number; it has a lot of significance for patients' well-being. The impact of these agents on weight loss improves glycaemia, blood pressure, lipid profiles, and reduces the burden of obesity associated comorbidity; with an understanding of a considerable cardiovascular impact, partly due to the weights achieved. The combination of weight loss and cardiovascular benefit as seen most recently in the obesity population, in the SELECT trial is an innovative paradigm shift that attempts to redefine obesity treatment as a strategy to protect the cardiovascular system.

One of the most salient conceptual implications of this evidence is the uptake of obesity from a one-shot, discrete surgery mentality into a chronic,

relapse-prone concept of the disease that can be managed for a long time through long-term pharmacotherapy. The upshot of this evidence is the reframing of obesity as a chronic and relapse-prone disease with long-term pharmacologic management being the way to go about controlling the disease. The view on treating obesity only by modifying lifestyle activities and using pharmacotherapy only in the margins, and sometimes as an unsafe option, has prevailed for a long time in the twentieth century. Given the newly demonstrated safety and enduring weight loss effects of incretins, however, the perception of obesity treatment as "like crack is different" has been swept away, paving the way for obesity pharmacotherapy to become comparable to treatment of other chronic diseases. The STEP 4 finding, that when treatment was ceased, the weight came back: it is a 'chronic disease' phenomenon, similar to increases in blood pressure due to the withdrawal of antihypertensive drugs. The STEP 4 finding that weight rebound occurred after treatment cessation reinforces a chronic disease model: increases in BP upon removal of antihypertensives; increases in weight upon removal of modulation of appetite. This awareness has important implications for the length of therapy and for the way funding is designed in health systems, which should plan for a prolonged treatment over a longer span of time with therapy episodic.

This is clinically instructive as there is a difference in effect magnitude between some agents and populations. There is evidence of the added value of dual incretin agonism over selective GLP-1 receptor agonism in terms of weight loss in the SURMOUNT and STEP programmes, respectively, suggesting that this is a case of dual agonism being beneficial for the obesity indication (Jastreboff et al., 2022; Wilding et al., 2021). “Attenuated effects of weight loss in those with diabetes” was seen consistently across obesity pharmacologies, and is a specific subpopulation that has not seen consistent investigation of obesity pharmacology and is directly addressed in the SURMOUNT-2 trial, highlighting the need to understand effects of these agents in specific populations in which they will be used, and not cross-pollinate (Garvey et al., 2023). In the clinical applications, these fine distinctions are relevant for selecting the agent and dose appropriate for a given individual.

5.1 This section covers Clinical Effectiveness: Cardiovascular and Renal Outcomes.
One of the most significant properties of the GLP-1 RA class is that a number of members of the class offers cardioprotection and nephroprotection. This benefit put glucose lowering agents into a new realm: that of disease-modifying cardiometabolic therapies and, as a consequence of this, the new class of diabetes treatment guidelines was developed, focusing on agents that demonstrate cardiovascular benefit in the patient population that is at risk for cardiovascular disease.

The foundation were laid in the course of the cardiovascular outcome trials. In the LEADER trial, treatment with liraglutide led to a reduction in the frequency of major adverse cardiovascular events and cardiovascular and all-cause mortality in individuals with type 2 diabetes who had a high cardiovascular risk score levels (Marso, Daniels, et al., 2016). In the SUSTAIN-6 trial, subcutaneous semaglutide was shown to be effective for both reducing major adverse cardiovascular events and reducing non-fatal stroke (Marso, Bain, et al., 2016). The results from the REWIND trial further added to the evidence base since it contained a cohort with a large number of patients with no previously diagnosed cardiovascular disease, suggesting that a wider population might benefit from the cardiovascular effects of dulaglutide begining through primary prevention and also to secondary prevention (Gerstein et al., 2019).

The oral formulation of semaglutide was assessed for cardiovascular safety in another trial, PIONEER 6, which confirmed cardiovascular safety and additionally found that use of the oral version led to a reduction in cardiovascular death, suggesting that cardiovascular safety of the class could be maintained in an orally administered agent (Husain et al., 2019). Not all of the agents in the class offered the same degree of benefit and, as was the case with albiglutide (which was tested in the Harmony Outcomes trial), the improvements in the drug's efficacy could be a reason for its availability, but not just the only one (Hernandez et al., 2018).

A groundbreaking addition to the cardiovascular proof of benefit was the SELECT trial which looked at the cardiovascular results of semaglutide in the people with overweight or obesity who were not diabetic, who also had established cardiovascular disease. By showing a benefit of preventing cardiovascular events in this non-diabetic population of patients with obesity, SELECT demonstrated that the cardiovascular benefit of the GLP-1 RA class is independent of glucose reduction. Select establishes for the first time that a GLP-1 RA could offer a cardiovascular benefit in the absence of diabetes and in the setting of obesity. This finding has significant implications as the suggestion is that these could have a therapeutic role in cardiovascular prevention in the obese population in general.

Renal results have been similar to the cardiovascular results. A pre-planned analysis of the LEADER trial showed that liraglutide is reno-protective and caused a reduction in the development of DKA, the most important being a decrease in the onset of persistent macroalbuminuria (Mann et al., 2017). This renal signal has been since confirmed and validated at the class level through the meta-analysis and is the topic of particular renal-results trials, surpassing the scope of the present sources.

Despite the cardiovascular benefits, the mechanism of the class is still not well understood and most likely multifactorial. The blood vessels and heart muscle, blood pressure lowering, changes in lipid metabolism, anti-inflammatory properties and the metabolic changes associated with a reduction in weight and improvement in glycaemia are likely all contributing factors. The benefit seen in the trials (notably in the reduction in atherosclerotic events like stroke and myocardial infarction) suggests a cardiovascular effect resulting from anti-atherosclerotic activity, unlike agents that have primarily an effect on reducing heart failure and renal events. Weight reduction was an evident feature of cardiovascular protection in an obese cohort in SELECT, which provided clarification on the relative effect of weight loss on cardiovascular outcomes, but showed that cardiovascular outcomes seemed to extend upstream to weight loss — suggesting direct mechanisms outcomes (Lincoff et al., 2023).

The implications for the treatment of these important clinical findings of the cardiorenal evidence are all over the map. As the cardiovascular outcome trials were conducted in patients with increased cardiovascular risk, the absolute risk reduction achieved in this study can be appreciated in patients with the highest cardiovascular risk. Because a majority of REWIND participants were not known to have cardiovascular disease, benefits generalizable to primary prevention (Gerstein et al., 2019). Combined, the trials confirm a paradigm shift from glycaemic control towards the more general reduction of cardiometabolic risk where use of the glucose-lowering interventions is based partly on their cardiovascular and renal safety and effectiveness.

VI. CLASS LEVEL SYNTHESES OF HUMAN OUTCOMES OF HEART/KIDNEY

The cardiovascular outcomes, all-cause mortality and kidney outcomes compared between the class, have been synthesized by two systematic reviews and two meta-analyses. Two systematic reviews and two meta-analyses have been conducted to summarise the cardiovascular outcomes, all-cause mortality and kidney outcomes of the class. The previous cardiovascular outcome trial (CVOT) meta-analysis showed that the group of GLP-1 RAs were shown to reduce major adverse cardiovascular events, cardiovascular mortality, all-cause mortality, and kidney outcomes in patients with type 2 diabetes (T2D) (Kristensen et al., 2019). These findings were reinforced with an updated and expanded meta-analysis which included more trials and showed consistent cardiovascular and renal benefit across trials and with increasing class level (Sattar et al., 2021). CV outcomes from the individual CV outcome trials and these meta-analyses are summarised in Tab. 2.

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Table 2: Cardiovascular and renal outcomes across GLP-1 receptor agonist outcome trials and class level meta-analyses

Source	Agent / scope	Outcome focus	Key finding
Marso, Daniels, et al. (2016)	Liraglutide	MACE; mortality	Reduced MACE, CV death, and all-cause mortality.
Marso, Bain, et al. (2016)	Semaglutide (SC)	MACE	Reduced MACE, driven notably by reduced non-fatal stroke.
Gerstein et al. (2019)	Dulaglutide	MACE	Reduced MACE across primary and secondary prevention.
Husain et al. (2019)	Oral semaglutide	CV safety	CV safety confirmed; reduced CV death (secondary).
Hernandez et al. (2018)	Albiglutide	MACE	Reduced MACE (agent later withdrawn commercially).
Lincoff et al. (2023)	Semaglutide	MACE in obesity, no diabetes	Reduced MACE in obesity with established CVD.
Mann et al. (2017)	Liraglutide	Renal outcomes	Reduced new macroalbuminuria; slowed nephropathy.
Kristensen et al. (2019)	Class meta-analysis	CV, mortality, kidney	Class-level reductions across MACE, mortality, kidney outcomes.
Sattar et al. (2021)	Class meta-analysis	CV, mortality, kidney	Updated analysis confirming and strengthening class benefit.

VII. SAFETY AND TOLERABILITY

In general, the safety profile of GLP-1 RAs is good, and contributed greatly to the popularity of the class. The most common side-effect is gastrointestinal (nausea, vomiting, diarrhoea and constipation) and is a result of the same mechanisms described as responsible for its therapeutic effects: Most importantly, a delayed gastrointestinal emptying and central action. The effects are usually mild to moderate, dose dependent and are usually most severe at the start of dosing (when the dose is being escalated) and taper off the longer the treatment continues. The latter is the typical approach to gradually reduce the dose of treatment and is the cause for not sticking to treatment, being the major reason in both the standard treatment programmes (Frías et al., 2021; Jastreboff et al., 2022).

One of the most important features of safety is that of the low intrinsic risk of hypoglycaemia of the class. The diabetes-lowering effects of GLP-1 receptor agonism (the insulinotropic activity) is glucose-

dependent, so these do not cause hypoglycaemia in people receiving these agents as monotherapy, or in

combination with agents with low hypoglycaemia potential. But the use of these agents is useful in the context of insulin use especially (Dahl et al., 2022) while insulin dose reduction is recommended in GLP-1 RAs. Especially in elderly people and in the patient who is at high risk from hypoglycaemia.

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VIII. WHERE THERE ARE OTHER SAFETY CONCERNS THEY HAVE BEEN EXPLORED THROUGHOUT THE TRIAL PROGRAMME

Theoretically, the use of vitamin A has a risk of pancreatic and thyroid neoplasia, as well as pancreatitis, which have been monitored, but with no evidence of them being more likely in vitamin-A use than at the class level (Kristensen et al., 2019; Sattar et al., 2021). Little improvement in heart rate has been seen with the class with the effect seen as relatively trivial in respect to the benefit to the heart. Both experimental groups (tirzepatide vs selective GLP-1 RA) had the same dose-dependent efficacy across the glycemic effect and the most frequent adverse events were digestive effects, which were demonstrated across the efficacy programmes, SURPASS and SURMOUNT.Safety profile was generally similar in the 2 programmes, gastrointestinal events being the most common adverse events and no dose related events being of major concern in either; efficacy dose levels were satisfactory, with similar results in both programmes. Overall, there is good knowledge and safety of the class; in terms of tolerability the class profile is acceptable, and favorable compared to the other alternatives used in diabetes and obesity.

Tolerability adherence relationships are quite important in practice. As the gastrointestinal side-effects are most likely to occur during dose-step up and to diminish over time, the treatment initiation will be most critical to long-term success. Slow titration to achieve rational levels, patient education about typical side effect (short-term) can help with chances of persistence with this early phase. To not change from one gastrointestinal agent to another, or change dose of the drug/subclass of drugs, but maintain a therapeutic relationship if gastrointestinal effects are troublesome. Multiple therapy options and formulations (including oral) provide flexibility in therapy to accommodate the tolerability and patient preference for therapy, likely resulting in increased rates of product adherence in the ‘real-world'.

8.1 Intrachievement and Interachievement (Significant Connections)

We can put together a consistent narrative on relative effectiveness within and across classes and to alternatives where there are multiple head-to-head and placebocontrolled comparisons. Semaglutide was the most effective selective GLP-1 RA directly tested for glycaemic effect to be superior, in SUSTAIN 7 (Pratley et al., 2018), compared to dulaglutide, and was also superior for weight, effects of which are also directly tested in SUSTAIN 7. When introduced, the dual agonist then set a new benchmark for efficacy superiority with regard to glycaemic control in SURPASS-2 and weight loss in SURMOUNT-1 over other GLP-1/GLP-2 combination drugs, such as semaglutide, which cement its position at the top of the escalating effectiveness of incretins as class (Frías et al, 2021; Jastreboff et al, 2022).

When compared to comparators that are older, both GLP-1 RAs and tirzepatide have proven to have some benefits beyond glycaemic potency. In the SURPASS trials, tirzepatide was superior to basal insulin degludec and insulin glargine for glycaemic control, and was also superior to these other types of insulin for producing weight loss (which other basal insulins did not produce) while not inducing the weight gain that other basal insulins did, and not carrying with it the burden of hypoglycaemia that insulin does (Ludvik et al., 2021; Del Prato et al., 2021). With their superior glycaemic control, weight reduction, low level of hypoglycaemia risk, they have changed the treatment landscape for type 2 diabetes to the extent that many people are now at the front of the treatment line-up being treated with incretins, instead of insulin.

It is the cardiorenal evidence that further helps to position therapy. To date, there are 3 GLP-1 RAs that have been demonstrated to have cardiovascular and renal benefits beyond glycaemic control, thus guidelines are recommending GLP-1 RAs that were shown to be beneficial on the CV system in T2D even when it is not for glycaemic control. In these cases of cardiovascular prevention in the obese population without diabetes, the SELECT result is beginning to raise questions about simply using glycaemia as the only indication for use when using

these therapies. This has planted doubt regarding exclusivity based on glycaemia for the use of these drugs for cardiovascular prevention in the obese population without diabetes (Lincoff et al., 2023). The class is thus making a transition, from a "glucose-centric" to a" cardiometabolic risk-centric" paradigm of use.

In this dynamic context, there are various factors to consider when deciding on which to use. Both potency and the specific direction (glycaemic effect or weight loss) that favour each agent for glycaemic and weight responses is consistent; however, the extent of cardiovascular and renal effects' supporting evidence varies, and specific agents supporting cardiorenal protection should be selected based on the strongest evidence of a beneficial outcome. Weight loss is a key consideration factor, as is whether they have existing problems such as cardiovascular or renal disease; gastrointestinal effects; whether they prefer to take pills or shots; or cost or access issues; all play a role in the decision. The vast spectrum of classes including daily and weekly IM's, an oral agent and now a dual agent, provide a therapy that can now be customized to these unique situations to a greater extent than in the past. This individualisation will likely grow more complex as they obtain more comparative and as outcomes are gathered.

IX. DISCUSSION & FUTURE DIRECTIONS

Whilst the evidence that has been synthesised in this review identifies one class of agents, which have completely changed the way that type 2 diabetes and obesity are managed. There are three themes which are prominent. First, GLP-1 RAs have a broad range of activity: glycaemic effect, weight loss and cardiorenal protection; none of which has been seen with other glucose-lowering treatments. That's because there has been a limit on how much benefit you can achieve since dual incretin agonism began, since, to date, every head-to-head and every placebo-controlled trial that has been conducted has shown tirzepatide to be more effective than GLP-1s. For the third, the association of cardiovascular benefit in people with obesity – who do not suffer from diabetes – has separated the cardioprotective effects of the class from its glucose-lowering therapy, and this might lead to a significant increase in its indications.

These developments need to be understood in the context of the history. The emergence of GLP-1 receptor agonists as a class of drugs to treat cardiometabolic diseases is an example of a broader trend towards using outcome-oriented drugs in the treatment of these disorders. Compared to the traditional approval and prescription criteria of glycaemic reductions, measured by Haemoglobin A1c (HbA1c), which have long been the basis of approval for a large proportion of the glucose lowering drugs introduced, the new criteria for approval stems from the evidence set, which is largely contributed by cardiovascular outcome trials, all of which demand evidence of benefit on the hard clinical outcomes reviewed. The effects of the GLP-1 receptor agonists not only meet this criterion, but exceed it not only in terms of benefits for glycaemic parameters, but also in regards to glycaemic, weight, cardiovascular and renal parameters all at once. In doing that, they've changed the way that obesity and diabetes are treated and now how any diabetes and obesity therapies are evaluated, and most importantly they have reinforced the central concept of the treatment of OBs as the treatment of CM risk.

Based on these observations, some suggestions for future research, development and incubation are forwarded. Oral formulations, of which oral-semaglutide is the first to be shown to be cardiovascular safe, will help address the lack of treatment option as an oral preparation, greatly improving access and adherence to this class of treatment, which is currently injectable (oral-semaglutide), and the cardiovascular safety seen in PIONEER 6 suggests that benefits can be maintained when delivered via mouth (Husain et al., 2019). The positive results of dual GIP/GLP-1 agonism also have spurred the development of other multi-agonist molecules, such as "triple" agonists that also have glucagon receptor activity for even longer action. The extension to the indications is a second important area – and these agents could be used for cardiovascular prevention in obesity, where continued process of discovery is enquiry into these

agents in heart failure, chronic kidney disease, metabolic liver disease and other areas associated with adiposity and metabolic dysfunction.

Each of the above opportunities will send representatives with challenges. These agents are not cheap and the resulting burden on accessing it is significant, especially since obesity is a chronic disease and the weight gain that occurred after the agents were taken off the market confirms that after the agents are no longer used, weight can be regained as shown in STEP 4 (Rubino et al., 2021). Issues of benefit post-shutdown and methods of managing weight in the post-therapy phase as well as the long term safety of life-long therapy will need to continue to be monitored. When it comes to gastrointestinal tolerability the class, although tolerable, has some limitations in regards to how effective it will be in real life and strategies will need to be implemented to overcome this. Ethically, and as a policy, the equitable distribution of these transformative therapies with respect to both resource level in the health system and access to the patient populations along with their respective needs is a problem of similar size to the clinical promise of these therapies.
The future is certainly most dynamic with regards to extension of indications. The cardiovascular protection seen in obesity without any history of diabetes (on the original glycaemic remit) is a template of conditions to which indices might expand, due to the biological argument for this in conditions associated with adiposity and metabolic dysfunctions (Lincoff et al., 2023). That means studies taking place that are seeing health impacts on compromised heart health, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnoea and even neurodegenerative and addictive diseases where incretin signalling may be implicated are continuing. If this work of investigation carries during and if it pays off, the class of GLP-1 receptor agonists might end up playing an even bigger role in medicine than it was originally intended to play in diabetes it can be used as a platform to treat a wide variety of cardiometabolic and related diseases.

What isn't quite as benign is the fact that the molecules are evolving as well. The development of selective GLP-1 receptor agonism to dual GIP/GLP-1 agents has shown that two incretins together can be beneficial over one alone and this era of triple combinations with glucagon receptor activity is now in the works, with the intent of further improving weight loss and metabolic effects. Better formulation, including better, more convenient forms (oral) and longer acting products will help aid adherence and accessibility. The development story of the molecules included in the review here was indeed a process of transformation, but not an end it is a process that is ongoing and the next few years will witness more effective molecules and a better understanding of how to deploy these molecules throughout the cardiometabolic disease landscape.

X. CONCLUSION

GLP-1 receptor agonists have revolutionized the care of type 2 diabetes and obesity and insulin sensitizers are set to be invaluable as well, as is the development of the new dual GIP/GLP-1 receptor agonist, tirzepatide. In a large programme of RCTs, these agents have proven to have a significant and consistent effect on glycated Hb, body weight and for some, clinically important benefits on major adverse cardiovascular events and renal outcomes. Building off the concept of leptin resistance, relying on GLP-1 activity, GLP-1 being used to gain cardiovascular benefit in those with obesity (as opposed to diabetes), and superior glycaemic and weight-loss effects of GLP-1, notably tirzepatide compared to selective GLP-1 activity is an unprecedented progression of therapy. Classes have an excellent safety profile, with a generally good characterisation of gastrointestinal side effects being the predominant side effects and a low intrinsic risk for hypoglycaemia. GLP-1 receptor agonists will continue to play a key role in cardiometabolic medicine as the class continues to expand (via oral forms, novel multi-agonists and indications beyond glycaemia and weight) into the future. To realize their promise will be also require additional scientific progress as well as solving issues around access, cost and equity that will go alongside therapies of this transformative potential.

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