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REVIEW

Oral glucagon-like peptide-1 receptor agonists and combinations of entero-pancreatic hormones as treatments for adults with type 2 diabetes: where are we now?

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ABSTRACT

Introduction: Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have changed the landscape of type 2 diabetes (T2D) management due to their cardio-renal benefits, their glucose-lowering efficacy and weight loss (WL) maintenance. However, the response to GLP-1 RA monotherapy is heterogeneous. Additionally, the majority of GLP-1 RAs are injectable treatments. Oral GLP-1 RAs and injectable combinations of GLP-1 with other entero-pancreatic hormones (glucose-dependent insulinotropic polypeptide (GIP), glucagon and amylin) are under development for T2D and obesity management.

Areas covered: Herein, we review the data on (i) oral GLP-1 RAs (oral semaglutide 25/50 mg and orforglipron) and (ii) dual/triple agonists (tirzepatide, cagrilintide 2.4 mg/semaglutide 2.4 mg, survodutide, mazdutide, retatrutide) that have recently completed phase 3 trials for T2D or are currently in phase 3 clinical trials. Tirzepatide is the first approved dual agonist (GLP-1/GIP) for T2D and obesity management.

Expert opinion: We are in a new era in T2D management where entero-pancreatic hormone-based treatments can result in ≥15% WL and euglycemia for many people with T2D. Multiple molecules with different mechanisms of action are under development for T2D, obesity and other metabolic complications. Data on their cardio-renal benefits, long-term efficacy and safety as well as their cost-effectiveness will better inform their position in treatment algorithms.

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1. Introduction

Type 2 diabetes (T2D) is a chronic disease affecting more than half a billion people worldwide – its prevalence has almost doubled since 1990 and it is estimated that by 2050 over 1.3 billion people will live with T2D, posing a major public health challenge with substantial impact on healthcare systems, patients and their families [1]. Obesity is the strongest risk factor for T2D and the obesity epidemic is heavily contributed to the rise of T2D prevalence, especially the increased rates of young-onset T2D [2]. For example, in the UK, approximately 60% of adults with a diagnosis of T2D and age 16–39 years old are living with obesity [3].

Obesity and T2D share key pathophysiological mechanisms and are both associated with increased risk for (i) metabolic complications [such as hypertension, dyslipidemia, obstructive sleep apnea (OSA) and metabolic-dysfunction associated steatotic liver disease (MASLD)] and (ii) cardiovascular disease [2,4]. Among individuals with T2D, obesity increases mortality risk by sevenfold when also increases the risk for micro- and macrovascular complications, suggesting that the co-existence of obesity with T2D accelerate the disease process [5–7].

Intensive glycemic control in the early stages of T2D can reduce the subsequent risk of microvascular complications; yet its impact on macrovascular outcomes is less clear and takes time to become evident [8,9]. On the other hand, for many people with overweight/obesity and T2D, a weight-centric approach has recently been proposed in the ADA/EASD 2022 guidelines [9]. Weight loss (WL) of 10–15% or more in people with T2D and obesity can have a disease-modifying effect leading to diabetes remission, but also results in improvement in quality of life and multiple risk factors for cardiometabolic disease [9]. Moreover, prospective observational data from bariatric surgery (SOS study) suggest that ≥ 15% mean WL and weight maintenance over a period of 15 years in people with T2D and obesity could lead not only in long-term diabetes remission for a significant proportion of them (around 30%), but also in reduction of micro- and macrovascular complications compared to the control group [10,11].

Despite that sleeve gastrectomy and gastric bypass, the two most commonly performed bariatric procedures today, can result in sustained long-term WL ≥ 20–25% in people with obesity and T2D and in multiple cardiometabolic benefits, bariatric surgery is an intervention which is not scalable in population level and people can be hesitant to this option due to the risk of postoperative complications [12,13]. On the other hand, intensive lifestyle interventions could be implemented

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Article highlights

- Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are an established treatment for type 2 diabetes (T2D) with proven cardio-renal and metabolic benefits, but they are administered predominantly via injections. Moreover, the response to GLP-1 RA is heterogeneous and a proportion of people with T2D will not achieve the individualized glycemic, metabolic and WL targets.
- For people who do not prefer injectable treatments, a number of oral GLP-1 RAs are currently under development for T2D and obesity, with high doses of oral semaglutide (25 and 50 mg) demonstrating good tolerability and higher efficacy than oral semaglutide 14 mg in phase 3 trials. Orforglipron, an oral, non-peptide, GLP-1 RA is also undergoing phase 3 trials as treatment for T2D and obesity.
- Additionally, injectable combinations of GLP-1 with other entero-pancreatic hormones with different mechanisms of actions [glucose-dependent insulinotropic polypeptide (GIP), glucagon and amylin] are under development as dual or triple agonists for T2D and/or obesity, aiming to enhance further the efficacy and metabolic benefits of GLP-1 RAs.
- Tirzepatide (5, 10 and 15 mg doses) is the first dual GLP-1 and GIP RA approved for T2D and chronic weight management with up to 2.6% mean HbA1c reduction, 15.7% mean weight loss (WL) and good safety and tolerability profile. Multiple other dual and triple agonists are currently in phase 3 trials for T2D and/or obesity including the combination of the amylin agonist cagrilintide 2.4 mg with the GLP-1 receptor agonist (RA) semaglutide 2.4 mg (CagriSema), the dual GLP-1/glucagon RAs survodutide and mazdutide as well as the triple agonist (GLP-1/GIP/glucagon) retatrutide.
- Numerous novel pharmacotherapies based on entero-pancreatic hormones may be approved over the next years for T2D and obesity. These pharmacotherapies will provide the opportunity for individualized treatment plans aiming to help many people with T2D to achieve euglycemia together with ≥ 10% WL and even ≥ 15% WL, with subsequent improvements in multiple metabolic complications and their overall health.
- Some of these novel molecules may have direct effects on body composition and on specific metabolic complications (e.g. multi-agonists targeting glucagon receptor appear to have direct effect on liver fat reduction). The cardio-renal and metabolic benefits of each of the novel molecules for people with T2D, their long-term safety and efficacy, as well as their cost-effectiveness for different populations and different times of initiation during the T2D continuum will need to be evaluated further over the next years.

easier and result in up to 10% mean WL; however, there is large heterogeneity in response and long-term weight maintenance is challenging due to compensatory increases in appetite and reduction in energy expenditure during the WL state [14–16].

The glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have changed the landscape of T2D management over the last years, due to their cardio-renal benefits in high cardiovascular risk populations, but also due to their glucose-lowering effects and the clinically important and sustained WL. The efficacy of the injectable GLP-1 RAs semaglutide and liraglutide in inducing WL and weight maintenance through appetite reduction has led to clinical trials assessing higher doses of these molecules as treatments for obesity and both semaglutide 2.4 mg once weekly and liraglutide 3 mg once daily have now received approval for chronic weight management [17,18]. However, the efficacy of GLP-1 RAs, especially on WL, can vary between individuals – for example, even with subcutaneous semaglutide 2.4 mg once weekly (currently, the most efficacious approved GLP-1 RA monotherapy for chronic weight management), only 46% of people with overweight/obesity and T2D will achieve ≥ 10% WL and 68% will achieve an HbA1c ≤ 6.5% [19]. Additionally, a proportion of people are not able to tolerate the higher doses of GLP-1 RAs due to dose-dependent adverse events making even more difficult for them to achieve the individualized metabolic and WL targets [17,20].

Looking for the next step in the treatment for T2D and overweight/obesity, combinations of GLP-1 with other entero-pancreatic hormones with diverse metabolic actions, such as glucose-dependent insulinotropic peptide (GIP), glucagon, and amylin (Figure 1) are currently under development with the potential of achieving euglycemia together with ≥ 10% and even ≥ 15% WL for many people living with T2D. Tirzepatide, a dual GLP-1 and GIP RA became the first combination of entero-pancreatic hormones approved for T2D management (2022) and chronic weight management (2023) (Figure 2) [21,22]. In addition, a number of oral GLP-1 RAs are under development to offer an alternative option to people reluctant to injectable treatments, with early data for some of them suggesting similar efficacy in glycemia and WL to injectable GLP-1 RAs [17,23].

Here, we will review the data on safety and efficacy of (i) oral GLP-1 RAs and (ii) injectable combinations of entero-pancreatic hormone therapies that have recently completed or undergoing phase 3 trials as treatments for people with T2D. We will also discuss the potential implications and challenges that the new pharmacotherapies may bring in T2D and obesity management.

2. Oral GLP-1 receptor agonists

GLP-1 is a 30 amino-acid peptide primarily secreted from the ileum as response to food intake and exerts glucose-lowering effect by augmenting glucose-dependent insulin secretion, suppressing glucagon release and slowing gastric emptying (Figure 1) [24]. Moreover, GLP-1 reduces appetite and food intake [25].

Currently, GLP-1 RAs are predominantly administered via injections as the oral delivery of peptide therapeutics has been historically limited due to challenges in bioavailability. An oral form of semaglutide has been developed over the past years with the use of an absorption enhancer, with the medication needed to be taken in the morning, on an empty stomach and with maximum 120 ml of water to ensure adequate drug absorption, as its bioavailability ranges between 0.4% and 1% [26].

2.1. Oral semaglutide

Oral semaglutide in doses up to 14 mg once daily gained approval as T2D treatment by the Food and Drug Administration (FDA) in September 2019 based on the results of the phase 3 trials of the PIONEER program (up to 1.4% HbA1c reduction and up to 4.4 kg WL in the global trials) and become the first approved oral GLP-1 RA [26].

Recently, the safety and efficacy of higher doses of oral semaglutide (25 and 50 mg) once daily for people with T2D have been assessed in the phase 3 PIONEER-PLUS trial, where oral semaglutide at doses of 25 and 50 mg was compared to the approved 14 mg oral semaglutide for 68 weeks (Table 1) [23]. Oral semaglutide 50 mg resulted in mean HbA1c reduction of 2.1% and mean WL of 9.8% compared to 1.3% HbA1c reduction and 5.4% WL with oral semaglutide 14 mg (Table 2,

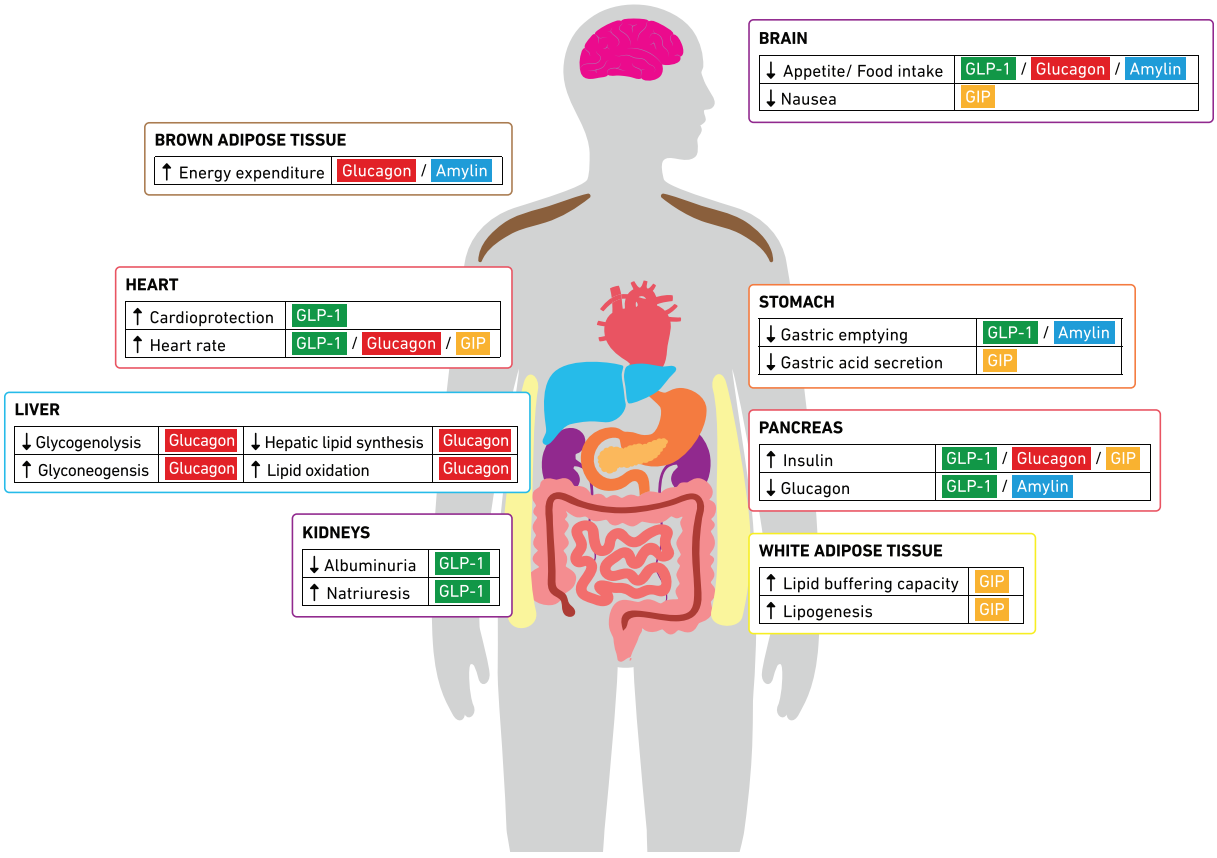

Figure 1. Actions of entero-pancreatic hormones on different organs.
GIP: glucose-dependent insulinotropic polypeptide, GLP-1: glucagon-like peptide-1.

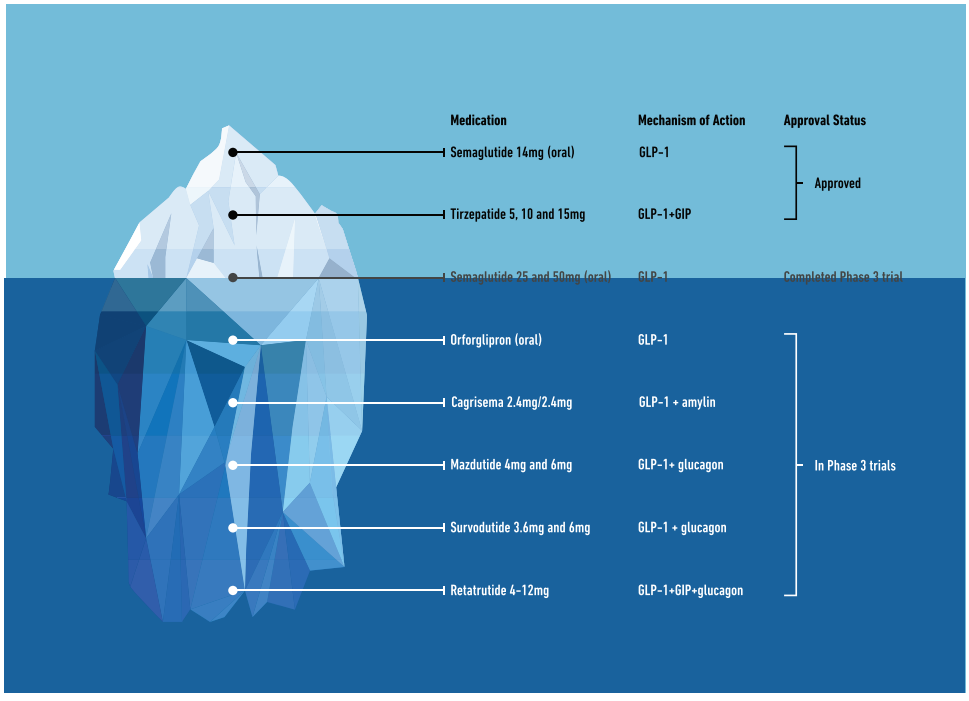

Figure 2. Approved molecules and those in the pipeline (currently undergoing phase 3 trials) for type 2 diabetes and/or obesity.
GIP: glucose-dependent insulinotropic polypeptide, GLP-1: glucagon-like peptide-1.

Figure 3) [23]. Approximately 55% of participants on oral semaglutide 50 mg achieved an HbA1c ≤ 6.5% (compared to 32% on oral semaglutide 14 mg) and 42% achieved ≥ 10% WL (vs 16% on oral semaglutide 14 mg) [23].

Adverse events (AEs) in PIONEER-PLUS study were primarily gastrointestinal (nausea, diarrhea, vomiting and constipation), occurring more frequently in higher dosage groups [23]. AEs leading to treatment discontinuation were experienced by 13% of people on oral semaglutide 50 mg vs 10% on oral semaglutide 14 mg (Table 2). During PIONEER-PLUS, less than 0.3% (4/1602) of participants across the three groups of oral semaglutide experienced pancreatitis and ≈ 1% of participants (16/1602) experienced gallbladder-related disorders [23].

The PIONEER-6 study confirmed the cardiovascular safety of oral semaglutide 14 mg for people with T2D and established cardiovascular disease (non-inferiority study) [27], when the ongoing SOUL study (NCT0391432) investigates whether oral semaglutide 14 mg will reduce major adverse cardiovascular events in people with T2D and established cardiovascular disease and/or chronic kidney disease (superiority study) [28].

2.2. Orforglipron

Orforglipron, an oral, non-peptide, G-protein biased GLP-1 RA (resulting in lower activation of the beta-arrestin pathway) is currently under development for the treatment of T2D and obesity [29]. Orforglipron is a small molecule and may offer a less burdensome administration for individuals with T2D compared to the oral semaglutide as it has minimal dosing requirements (i.e it does not require to be taken on an empty stomach) [30].

In a phase 2 trial, the safety and efficacy of multiple doses of orforglipton once daily (ranging from 3 mg to 45 mg) were assessed [30]. After 26 weeks of treatment, the mean change in HbA1c with orforglipron ranged from −1.19% to −2.10% (maximum effect with orgorglipron 45 mg) compared to −0.43% with placebo and −1.10% with dulaglutide 1.5 mg once weekly (Table 3, Figure 3) [30]. Moreover, mean body weight reduced by 9.6% with orforglipron 45 mg, compared to −2.2% with placebo and −4% with dulaglutide 1.5 mg. The AE profile associated with orforglipron closely resembled that of other GLP-1 RAs in similar stages of development with 12%-19% of participants discontinuing the medication due to AEs. The majority of AEs were gastrointestinal, they were typically of mild to moderate severity, they were associated with dose escalation and were more present in the rapid dose escalation groups [30].

A program of phase 3 trials (ACHIEVE, Figure 4) assessing extensively the safety and efficacy of oral orforglipron in people with T2D is ongoing. Moreover, orforglipron is under assessment as treatment for obesity and the ATTAIN-2 trial (NCT05872620, phase 3 trial) will investigate the safety and efficacy of once daily oral orforglipron compared with placebo in adults with obesity/overweight and T2D.

2.3. Other oral GLP-1 RAs not progressed to phase 3 trials

A plethora of oral GLP-1 RA is under development, but not all of them will progress to approval for T2D and/or obesity. For example, the development of lotiglipron, an oral, non-peptide, GLP-1 RA for T2D and obesity has been stopped in early phase clinical trials, as its administration was associated with elevated transaminases and concerns regarding potential liver toxicity.

Moreover, danuglipron, another oral, non-peptide, G-protein biased GLP-1 RA will not advance into phase 3 studies at the twice daily formulation trialed in phase 2 studies for T2D and obesity due to high discontinuation rates related to AEs [31]. More specifically, in people with T2D, the safety and efficacy of multiple doses of danuglipron (ranging from 2.5 mg twice daily to 120 mg twice daily) were assessed in a phase 2b study [32]. After 16 weeks of treatment, danuglipron 120 mg twice daily resulted in a mean HbA1c reduction of 1.2% compared to no change from baseline with placebo and 4.6 kg WL vs. 0.43 kg WL with placebo [32]. However, 34% of participants at danuglipron 120 mg twice daily discontinued the medication due to AEs, with most common AEs being gastrointestinal. Discontinuation rates were even higher (greater than 50% across all doses) in a phase 2 study assessing danuglipron as obesity treatment in people without diabetes in doses ranging from 40 mg twice daily up to 200 mg twice daily [31]. A modified release formulation of danuglipron, which is administered once daily is currently under investigation to improve tolerability [31].

2.4. The future of oral GLP-1 RAs

From patient perspective, oral therapies are generally associated with improved convenience, acceptance and adherence compared to injectable treatments, hence a significant opportunity exists for entero-pancreatic hormone-based oral molecules [33]. Oral semaglutide, a peptide-based treatment which acts on the GLP-1 receptor similar to the native GLP-1 peptide, appears to have similar efficacy to semaglutide 2.4 mg once weekly at the dose of 50 mg once daily. However, despite that oral semaglutide has addressed some of the burdens associated with injectable treatments, it requires a complex dosing regimen involving food and water restrictions. The development of small molecules which interact with the GLP-1 receptor slightly different compared to native GLP-1 (biased toward G protein activation over β-arrestin recruitment at the GLP-1 receptor) hold potential for less burdensome administration and improved efficacy. Orforglipron is the first small molecule GLP-1 RA reaching phase 3 trials after demonstrating good efficacy and safety in early phase clinical trials. Moreover, small molecules may be easier to produce compared to peptide treatments and as a result their supply may be easier scalable to meet the constantly increasing demand for obesity pharmacotherapies [34]. Other oral, small molecules, GLP-1 RA are currently in early phase clinical trials, whilst oral combinations of entero-pancreatic hormones are also in development [20].

3. Combination of entero-pancreatic hormones

Apart from oral GLP-1 RAs, numerous entero-pancreatic hormones with diverse metabolic actions are currently under investigation in combination with GLP-1 RA, aiming to enhance and complement the metabolic effects of GLP-1 RAs (predominantly as injectable treatments). Tirzepatide (injectable, once weekly) is the first dual agonist (acting on GLP-1 and GIP receptors) approved for T2D and/or obesity management [21,35]. Multiple

Table 1. Baseline characteristics and summary of trial designs of the pipeline for type 2 diabetes medications.

Medications	Comparator	No. of participants	Background treatment(s) and additional intervention	Duration of trial; randomization ratio	Primary outcome	Mean age	Baseline diabetes characteristics	Baseline weight and BMI
Phase 3 studies								
Oral Semaglutide 25, 50 mg (PIONEER-PLUS) [23]	Oral semaglutide 14 mg	1606	Background treatment: any oral glucose-lowering agent except DPP-4i or GLP-1RA	68 weeks; 1:1:1	Change from baseline in HbA1c at 52 weeks	57.6–58.8 yr	Mean baseline HbA1c: 8.9–9% Mean diabetes duration: 8.9–9.7 yr	Mean baseline weight: 96.1–96.6 kg Mean baseline BMI: 33.7–34.1 kg/m^2
Tirzepatide 5, 10, 15 mg (SURPASS-1) [41]	Placebo	478	Background treatment: diet and exercise	40 weeks; 1:1:1:1	Change from baseline in HbA1c at 40 weeks	52.9–55.8 yr	Mean baseline HbA1c: 7.85–8.05% Mean diabetes duration: 4.5–4.9 yr	Mean baseline weight: 84.8-87 kg Mean baseline BMI: 31.5–32.2 kg/m^2
Tirzepatide 5, 10, 15 mg (SURPASS-2) [40]	Semaglutide 1 mg	1879	Background treatment: metformin	40 weeks; 1:1:1:1	Change from baseline in HbA1c at 40 weeks	55.9–57.2 yr	Mean baseline HbA1c: 8.25–8.32% Mean diabetes duration: 8.3–9.1 yr	Mean baseline weight: 92.5–94.8 kg Mean baseline BMI: 33.8–34.5 kg/m^2
Tirzepatide 5, 10, 15 mg (SURPASS-3) [44]	Insulin degludec (once daily)	1444	Background treatment: metformin ± SGLT-2i	52 weeks; 1:1:1:1	Change from baseline in HbA1c at 52 weeks	57.2–57.5 yr	Mean baseline HbA1c: 8.12–8.21% Mean diabetes duration: 8.1–8.5 yr	Mean baseline weight: 93.8–94.9 kg Mean baseline BMI: 33.4–33.6 kg/m^2
Tirzepatide 5, 10, 15 mg (SURPASS-4) [45]	Insulin glargine (once daily)	2002	Background treatment: at least 1 and no more than 3 types of oral antihyperglycemic drugs (metformin, SGLT-2 inhibitors, and/or sulfonylureas)	Up to 104 weeks; 1:1:1:3	Change from baseline in HbA1c at 52 weeks	62.9–63.8 yr	Mean baseline HbA1c: 8.50–8.59% Mean diabetes duration: 9.8–10.7 yr	Mean baseline weight: 90–90.6 kg Mean baseline BMI: 32.5–32.8 kg/m^2
Tirzepatide 5, 10, 15 mg (SURPASS-5) [43]	Placebo	475	Background treatment: insulin glargine ± metformin	40 weeks; 1:1:1:1	Change from baseline in HbA1c at 40 weeks	60–62 yr	Mean baseline HbA1c: 8.23–8.37% Mean diabetes duration: 12.9–14.1 yr	Mean baseline weight: 94.1–96.3 kg Mean baseline BMI: 33.2–33.6 kg/m^2
Tirzepatide 5, 10, 15 mg (SURPASS-6) [42]	Insulin lispro	1428	Background treatment: insulin glargine ± metformin	52 weeks; 1:1:1:3	Change from baseline in HbA1c at 52 weeks	58–59.6 yr	Mean baseline HbA1c: 8.74–8.80% Mean diabetes duration: 13.4–14 yr	Mean baseline weight: 89.1–91.7 kg Mean baseline BMI: 33–33.5 kg/m^2
Tirzepatide 10, 15 mg (SURMOUNT-2) [53]	Placebo	2539	Lifestyle intervention: 500 kcal/day deficit diet + advise for 150 mins/week physical activity. Background treatment: any oral glucose-lowering agent except DPP-4i or GLP-1RA	72 weeks; 1:1:1	1) Percentage change in bodyweight from baseline to week 72 2) Weight reduction ≥ 5% at week 72	53.6–54.7 yr	Mean baseline HbA1c: 7.89–8.07% Mean diabetes duration: 8–8.8 yr	Mean baseline weight: 99.6–100.9 kg Mean baseline BMI: 35.7–36.6 kg/m^2
Phase 2 studies								
Orfoglipron 3, 12, 24, 36*, 45*mg/day [30]	vs (i) dulaglutide 1.5 mg vs (ii) placebo	383	Background treatment: diet and exercise ± metformin	26 weeks; 5:5:5:5:5:3:3:3:3	Change from baseline in HbA1c at week 26	57.4–60.5 yr	Mean baseline HbA1c: 8–8.2% Mean diabetes duration: 5–7.9 yr	Mean baseline weight: 98.5–104.6 kg Mean baseline BMI: 34.1–36.4 kg/m^2
CagriSema 2.4 mg/2.4 mg [64]	vs (i) semaglutide 2.4 mg vs (ii) cagrilintide 2.4 mg	92	Background treatment: metformin ± SGLT2i	32 weeks; 1:1:1	Change from baseline in HbA1c at week 32	56–62 yr	Mean baseline HbA1c: 8.1–8.6% Mean diabetes duration: 6.4–10.7 yr	Mean baseline weight: 104.3–107.4 kg Mean baseline BMI: 34.4–36.2 kg/m^2

(*Continued*)

Table 1. (Continued).

Medications	Comparator	No. of participants	Background treatment(s) and additional intervention	Duration of trial; randomization ratio	Primary outcome	Mean age	Baseline diabetes characteristics	Baseline weight and BMI
Survodutide 0.3, 0.9, 1.2, 1.8**, 2.7 mg [73]	vs (i) semaglutide 1.0 mg vs (ii)placebo	411	Background treatment: stable dose of metformin	16 weeks 1:1:1:1:1:1:1:1	Change from baseline in HbA1c at week 16	55.3–59.6 yr	Mean baseline HbA1c: 7.89–8.18% Mean diabetes duration: 6.1–8.8 yr	Mean baseline weight: 93–100.1 kg Mean baseline BMI: 33–34.9 kg/m^2
Mazdutide 3, 4.5,6 mg [72]	vs (i) dulaglutide 1.5 mg vs (ii) placebo	252	Background treatment: with or without metformin and/or diet and exercise.	20 weeks; 1:1:1:1:1	Change from baseline in HbA1c at week 20	52.5–54.4 yr	Mean baseline HbA1c: 7.94–8.16% Mean diabetes duration: 3.3–4.4 yr	Mean baseline weight: 72.3–78.1 kg Mean baseline BMI: 26.7–28 kg/m^2
Retatrutide 0.5, 4†, 8†, 12 mg† [77]	vs (i) dulaglutide 1.5 mg vs (ii) placebo	281	Background treatment: diet and exercise ± metformin	36 weeks; 2:2:1:1:1:2:2	Change from baseline in HbA1c at week 24	53.8–57.7 yr	Mean baseline HbA1c: 8.1–8.4% Mean diabetes duration: 7.2–10.5 yr	Mean baseline weight: 93.1–108.3 kg Mean baseline BMI: 33.8–36.3 kg/m^2

NA = data not available; HbA1c = glycosylated hemoglobin; BMI = body mass index; SGLT2i = sodium-dependent glucose cotransporter 2 inhibitor; DPP-4i = dipeptidyl peptidase IV inhibitor; yr: years. * Different dose-escalation schemes were used for 36 and 45 mg – slow and rapid dose escalation to final doses, ** both once weekly and twice weekly dosing were trialed, † different dose-escalation schemes were used for doses 4, 8 and 12 mg.

other dual and triple agonists are currently undergoing late phase clinical trials as treatments for T2D and/or obesity (Figure 2).

3.1. GLP-1 and GIP agonists

GIP is a peptide produced by K cells in the duodenum and upper jejunum in response to food intake. The main role of GIP is to stimulate insulin secretion in a glucose-dependent manner [36]. In people with T2D, GIP stimulates glucagon secretion and the GIP ability to stimulate insulin secretion and improve glycemia is impaired. Other GIP actions include reduction of nausea, stimulation of lipogenesis, inhibition of lipolysis and enhancement of the lipid-buffering capacity (Figure 1) [37].

Studies in animals have also shown an anorexigenic effect of the GIP and in preclinical studies, the simultaneous activation of GLP-1 and GIP receptors leads to enhanced glucose-lowering effects and more WL compared to activating either receptor alone [21,38,39].

Tirzepatide, a unimolecular dual agonist of GLP-1 and GIP receptors, has been approved for T2D management at the doses of 5, 10 and 15 mg once-weekly based on findings from the phase 3 SURPASS program [40–45]. In these clinical trials, tirzepatide resulted in HbA1c reduction up to 2.6%, with 70–94% of participants achieving HbA1c ≤ 6.5% with tirzepatide 15 mg (Table 2, Figure 3). Mean WL ranged from −11.7 kg to −12.9 kg with tirzepatide 15 mg at 52 weeks and up to 43% of people with T2D achieved ≥ 15% WL, even if tirzepatide was not combined with a lifestyle intervention at SURPASS programme. Tirzepatide was more effective in improving glycemia, reducing weight and improving multiple cardiometabolic risk factors (blood pressure, waist circumference and lipids) compared to placebo and other glucose-lowering agents, including semaglutide 1 mg, insulin glargine, insulin degludec and insulin lispro across the T2D spectrum [21].

In the SURPASS-2 study, after 40 weeks of treatment, a composite outcome of (1) an HbA1c ≤ 6.5% together with (2) ≥15% WL and (3) without episodes of hypoglycemia (defined as blood glucose <54 mg/dl or severe hypoglycemia) was achieved by 38% of participants at the tirzepatide 15 mg group compared to 7% at the semaglutide 1 mg group, demonstrating the potential of tirzepatide to improve further the current management of people with T2D and obesity compared to the currently licensed doses of GLP-1 RAs for T2D management [40,46]. Mechanistic studies have also shown that in people with T2D, tirzepatide 15 mg improved more insulin secretion and insulin sensitivity and decreased glucagon secretion compared to semaglutide 1 mg and placebo [47]. Moreover, tirzepatide 15 mg reduced the appetite and food intake compared to placebo in an ad libitum lunch (after 28 weeks of treatment) [47]. The molecular mechanisms leading to more WL and glycemia improvement with tirzepatide compared to GLP-1 RAs are still under investigation, however tirzepatide appears to have a greater degree of engagement for the GIP receptor compared to GLP-1 receptor and it also acts as biased GLP-1 RA [48].

In SURPASS-6, people with inadequately controlled T2D on basal insulin were initiated either on tirzepatide once weekly or on insulin lispro (rapid-acting insulin) three times per day. After 52

Table 2. Efficacy and safety data for completed phase 3 trials in people with type 2 diabetes.

Trial Name	PIONEER PLUS [23]	SURPASS-1 [41]	SURPASS-2 [40]	SURPASS-3 [44]	SURPASS-4 [45]	SURPASS-5 [43]	SURPASS-6 [42]	SURMOUNT-2 [53]
Medication	**Oral semaglutide 25, 50 mg**	**Tirzepatide 5 mg, 10 mg, 15 mg**	**Tirzepatide5 mg, 10 mg, 15 mg**	**Tirzepatide 5 mg, 10 mg, 15 mg**	**Tirzepatide 5 mg, 10 mg, 15 mg**	**Tirzepatide 5 mg, 10 mg, 15 mg**	**Tirzepatide 5 mg, 10 mg, 15 mg**	**Tirzepatide 10 mg, 15 mg**
Route and frequency	Oral, OD	SC, OW	SC, OW	SC, OW	SC, OW	SC, OW	SC, OW	SC, OW
Comparator	**vs 14 mg oral semaglutide**	**vs placebo**	**vs semaglutide 1 mg**	**vs insulin degludec**	**vs insulin glargine**	**vs placebo**	**vs insulin lispro**	**vs placebo**
MOA	GLP-1	GLP-1 + GIP	GLP-1 + GIP	GLP-1 + GIP	GLP-1 + GIP	GLP-1 + GIP	GLP-1 + GIP	GLP-1 + GIP
Trial Duration (weeks)	68	40	40	52	52	40	52	72
Participants	1070 vs 536	363 vs 115	1409 vs 469	1077 vs 360	995 vs 1000	355 vs 120	717 vs 708	623 vs 315
Background therapy	Any oral glucose-lowering agent except DPP-4i or GLP-1RA	Diet and exercise	Metformin	Metformin ± SGLT-2i	Metformin ± SGLT-2i ± SU	Insulin glargine ± metformin	Insulin glargine ± metformin	Any oral glucose-lowering agent except DPP-4i or GLP-1RA
Diabetes duration (years)	8.9–9.7	4.5–4.9	8.3–9.1	8.1–8.5	9.8–10.7	12.9–14.1	13.4–14	8–8.8
Baseline BMI (kg/m^2)	33.7–34.1	31.5–32.2	33.8–34.5	33.4–33.6	32.5–32.8	33.2–33.6	33–33.5	35.7–36.6
Main efficacy outcomes								
HbA1c change (%)	−1.7% to −2.1% vs 1.3%	−1.87% to −2.07% vs + 0.04%	−2.09% to −2.46% vs −1.86%	−1.93% to −2.37% vs −1.34%	−2.24% to −2.58% vs −1.44%	−2.23% to −2.59% vs −0.93%	−2.05% to −2.46% vs −1.16%	−2.14% to −2.22% vs −0.16%
HbA1c ≤ 6.5%	42–56% vs 32%	81–86% vs 10%	74–87% vs 66%	71–85% vs 44%	66–81% vs 32%	80–95% vs 17%	49–70% vs 22%	84–87% vs 16%
HbA1c < 7%	58–70% vs 50%	87–92% vs 19%	85–92% vs 81%	82–93% vs 61%	81–91% vs 51%	93–97% vs 34%	61–80% vs 37%	90–91% vs 29%
Weight change	−8.0% to −9.8% vs −5.4%	−7.9% to −11.0% vs −0.9%	−8.5% to −13.1% vs −6.7%	−7.5 kg to −12.9 kg vs +2.3 kg	−7.1 kg to −11.7 kg vs +1.9 kg	−6.2 kg to −10.9 kg vs +1.7 kg	−6.9 kg to −12.0 kg vs +3.8 kg	−13.4% to −15.7% vs −3.3%
≥5% WL	63–73% vs 47%	67–78% vs 14%	69–86% vs 58%	66–88% vs 6%	63–85% vs 8%	54–85% vs 6%	64–83% vs 6%	82–86% vs 31%
≥10% WL	34–42% vs 16%	31–47% vs 1%	36–65% vs 25%	37–69% vs 3%	36–66% vs 2%	23–51% vs 1%	33–61% vs 2%	63–70% vs 9%
≥15% WL	NA	13–27% vs 0%	15–40% vs 9%	13–43% vs 0%	14–37% vs < 1%	7–32% vs 0%	14–41% vs 0%	41–52% vs 3%
SBP change (mmHg)	−5.0 to −6.3 vs −4.2*	−4.7 to −5.2 vs −2.0*	−4.8 to −6.5 vs −3.6*	−4.9 to −5.5 vs + 0.5*	−0.6 to −6.0 vs + 3.6*	−6.1 to −12.6 vs −1.7*	−5.9 to −9.0 vs −0.4*	−6.3 vs −1.2
DBP change (mmHg)	−2.3 to −2.7 vs −2.4*	−2.9 to −3.4 vs −1.4*	−1.9 to −2.9 vs −1.0*	−1.9 to −2.5 vs + 0.4*	−1.0 to −1.2 vs + 1.0*	−2.0 to −4.5 vs −2.1*	−1.0 to −3.3 vs −0.4*	−2.5 vs −0.3
Main safety outcomes								
Any AE	79–80% vs 76%	64–69% vs 66%	64–69% vs 64%	61–73% vs 54%	71–77% vs 68%	68–78% vs 68%	70–75% vs 56%	71–78% vs 76%
SAE	8–11% vs 10%	1–4% vs 3%	5–7% vs 3%	6–8% vs 6%	12–17% vs 19%	8–11% vs 8%	6% vs 11%	6–9% vs 7%
AE leading to discontinuation	12–13% vs 10%	3–7% vs 3%	6–9% vs 4%	7–11% vs 1%	9–11% vs 5%	6–11% vs 3%	4–9% vs 2%	4–7% vs 4%

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide; GCG = glucagon; PO = oral; SC = subcutaneous; OD = once daily; OW = once-weekly; MOA = mechanism of action; BMI = body mass index; AEs = adverse events; SAEs = serious adverse events; DPP-4i = dipeptidyl peptidase IV inhibitor; RA = receptor analogue; WL = weight loss; SBP = systolic blood pressure; DBP = diastolic blood pressure; plb = placebo; NA = data not available. *safety analysis set. Data presented as mean change (for continuous data) or proportion of participants (%, for categorical data) and as efficacy estimand, unless stated otherwise.

weeks, initiation of tirzepatide resulted in 2.1% HbA1c reduction (vs 1.1% HbA1c reduction with insulin lispro) with marked reduction in the dose of basal insulin, lower risk of hypoglycemia and 12.2 kg more WL compared to insulin lispro (9 kg WL with tirzepatide compared to 3.2 kg weight gain with insulin lispro) [42].

Tirzepatide 10 mg and 15 mg resulted also in a relative reduction in liver fat content by 40–47% compared to 11% with insulin glargine in people with T2D, in a substudy of SURPASS-3 [49]. Additionally, in an exploratory post hoc analysis of SURPASS-4 study, tirzepatide delayed the decline in the estimated glomerular filtration rate (eGFR) and reduced the urine albumin-to-creatinine ratio compared with insulin glargine in people with T2D and high cardiovascular risk (mean eGFR was 81 mL/min/1.73 m^2 and median urine albumin creatinine ratio 15 mg/g at baseline) [49,50]. A pre-specified cardiovascular meta-analysis from SURPASS programme studies showed that there is no excess cardiovascular risk with tirzepatide use [51], however the ongoing SURPASS-CVOT (NCT04255433) will provide evidence on the definitive impact of tirzepatide on cardiovascular disease in people with T2D (Figure 4).

In the phase 3 SURMOUNT program, tirzepatide was also assessed as treatment for obesity and was combined with different intensity lifestyle programmes [52]. In people with obesity and T2D (SURMOUNT-2 trial), tirzepatide 10 and 15 mg once weekly combined with a moderate intensity lifestyle intervention led to a mean HbA1c reduction of up to −2.1%,

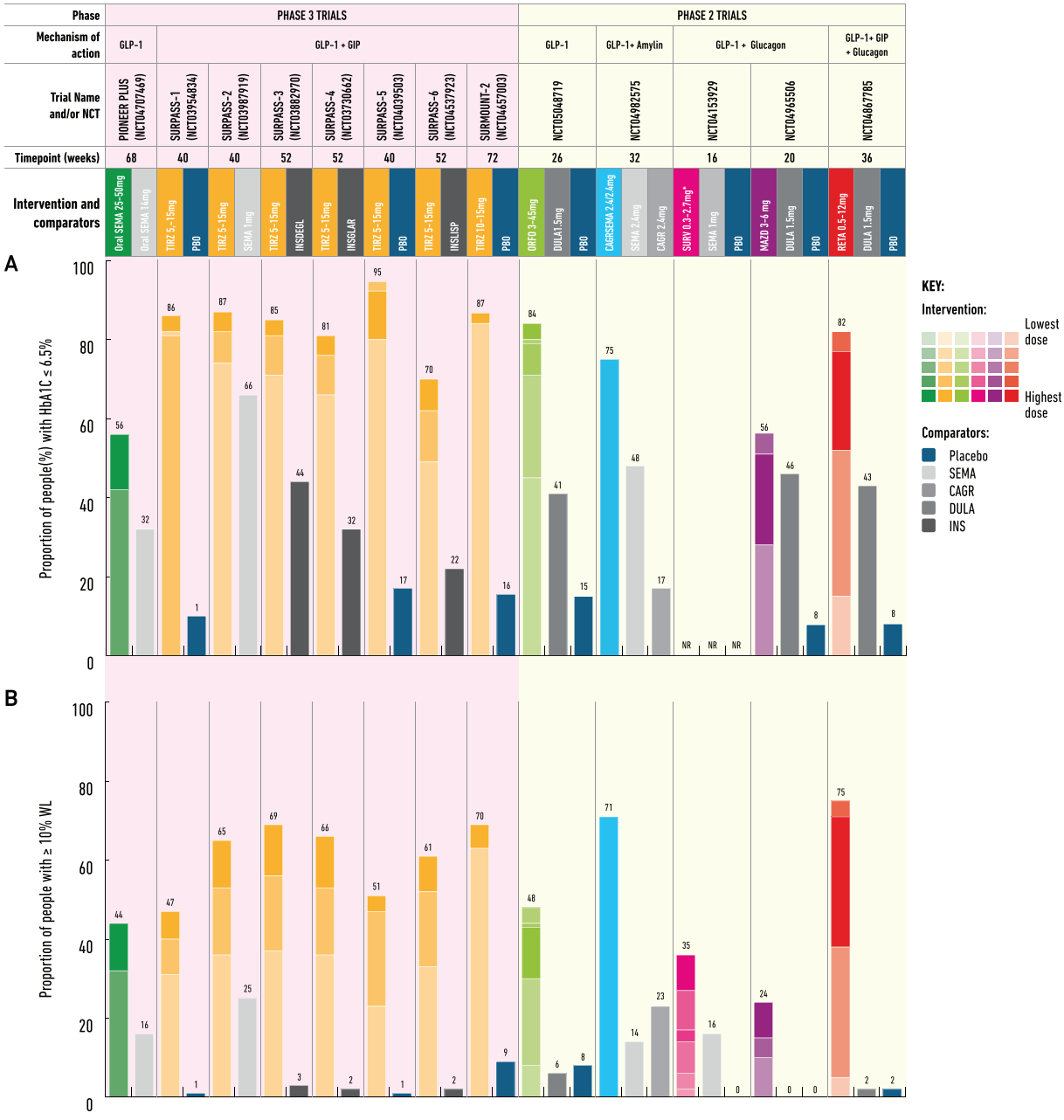

Figure 3. Efficacy results with the novel molecules on HbA1C and WL from phase 3 and phase 2 clinical trials in people with type 2 diabetes.

CAGR: cagrilintide, CAGRISEMA: cagrilintide/semaglutide, DULA: dulaglutide, GIP: glucose-dependent insulinotropic polypeptide, GLP-1: Glucagon-like peptide-1, HbA1c: glycated hemoglobin, INSDEGL: insulin degludec, INSGLAR: insulin glargine, INSLISP: insulin lispro, MAZD: mazdutide, ORFO: orforglipron, PLB: placebo, RETA: retatrutide, SEMA: semaglutide, SURV: survodutide, TIRZ: tirzepatide, WL: weight loss, NR: data not reported/not available.

Table 3. Efficacy and safety data for completed phase 2 trials in people with type 2 diabetes.

Medication	Orfoglipron 3, 12, 24, 36*, 45*mg [30]	CagriSema 2.4 mg/2.4 mg [64]	Survodutide^ 0.3, 0.9, 1.2, 1.8, 2.7 mg [73]	Mazdutide^ 3, 4.5, 6 mg [72]	Retatrutide 0.5, 4†, 8†, 12 mg† [77]
Route and frequency	PO, OD	SC, OW	SC, 0.3, 0.9, 1.8, 2.7 OW or 1.2, 1.8 mg BW	SC, OW	SC, OW
Comparator	**vs (i) dulaglutide 1.5 mg vs (ii) placebo**	**vs (i) semaglutide 2.4 mg vs (ii) cagrilintide 2.4 mg**	**vs (i) semaglutide 1 mg vs (ii) placebo**	**vs (i) dulaglutide 1.5 mg vs (ii) placebo**	**vs (i) dulaglutide 1.5 mg vs (ii) placebo**
MOA	GLP-1	GLP-1 + Amylin	GLP-1 + Glucagon	GLP-1 + Glucagon	GLP-1 + GIP + Glucagon
Trial Duration (weeks)	26	32	16	20	36
Participants	278 vs (i) 50 vs (ii) 55	31 vs (i) 31 vs (ii) 30	302 vs (i) 50 vs (ii) 59	149 vs (i) 50 vs (ii) 51	184 vs (i) 46 vs (ii) 45
Background therapy	Diet and exercise± metformin	Metformin ± SGLT2i.	Metformin	± Metformin and/or diet and exercise.	diet and exercise± metformin
Diabetes duration (years)	5–7.9	6.4–10.7	6.1–8.8	3.3–4.4	7.2–10.5
Baseline BMI (kg/m^2)	34.1–36.4	34.4–36.2	33.4–34.9	26.7–28	33.8–36.3
Main efficacy outcomes					
HbA1c change (%)	−1.19 to −2.1 vs (i) −1.1 vs (ii) −0.4	−2.20 vs (i) −1.8 vs (ii) −0.9	−0.91 to −1.71 vs (i) −1.46 vs (ii) −0.25	−1.41 to −1.67 vs (i) −1.35 vs (ii) −0.03	−0.54 to −2.16 vs (i) −1.36 vs (ii) −0.30
HbA1c ≤ 6.5%	45–84% vs (i) 41% vs (ii) 15%	75% vs (i) 48% vs (ii) 17%	NA	28%-56% vs (i) 46% vs (ii) 8%	15%-82% vs (i) 43% vs (ii) 8%
HbA1c < 7%	65–96% vs (i) 64% vs (ii) 24%	89% vs (i) 69% vs (ii) 33%	NA	54%-74% vs (i) 60% vs (ii) 18%	37%-82% vs (i) 60% vs (ii) 22%
Weight change	−3.7% to −10.0% vs (i) −4.0% vs (ii) −2.2%	−15.6% vs (i) −5.1% vs (ii) −8.1%	−1.9% to −9.0% vs (i) −5.4% vs (ii) −1.2%	−4.1% to −7.1% vs (i) −2.7% vs (ii) −1.4%	−3.3% to −16.9% vs (i) −2.0% vs (ii) −3.0%
≥5% WL	33–81% vs (i) 35% vs (ii) 22%	NA	8%-57% vs (i) 38% vs (ii) 7%	24%-57% vs (i) 18% vs (ii) 10%	32%-94% vs (i) 17% vs (ii) 25%
≥10% WL	8–48% vs (i) 6% vs (ii) 8%	71% vs (i) 14% vs (ii) 23%	2%-35% vs (i) 16% vs (ii) 0%	10%-25% vs (i) 0% vs (ii) 0%	5%-75% vs (i) 2% vs (ii) 2%
≥15% WL	0–24% vs (i) 2% vs (ii) 2%	54% vs (i) 0% vs (ii) 7%	NA	NA	0%-63% vs (i) 0% vs (ii) 2%
SBP change (mmHg)	−6.7 to −8.7 vs (i) −7.9 vs (ii) −5.5	−13.0 vs (i) +1.0 vs (ii) −2.5**	NA	−6.1 to −8.9 vs (i) −3.5 vs (ii) −1.3	−2.8 to −8.8 vs (i) −1.5 vs (ii) +1.5**
DBP change (mmHg)	−1.1 to −2.3 vs (i) −2.5 vs (ii) −1.8	−4.5 vs (i) 0 vs (ii) −0.1**	NA	−1.6 to −4.5 vs (i) −1.9 vs (ii) −0.8	−1.6 to −3.9 vs (i) 0 vs (ii) −1.2**
Main safety outcomes					
Any AE	62–89% vs (i) 56% vs (ii) 62%	68% vs (i) 71% vs (ii) 80%	66–86% vs (i) 52% vs (ii) 53%	76–84% vs (i) 76% vs (ii) 65%	55–79% vs (i) 67% vs (ii) 62%
SAE	0–11% vs (i) 2% vs (ii) 6%	0% vs (i) 6% vs (ii) 13%	2–8% vs (i) 0% vs (ii) 5%	0–6% vs (i) 8% vs (ii) 8%	4–8% vs (i) 2% vs (ii) 7%
AE leading to discontinuation	12–19% vs (i) 4% vs (ii) 6%	0% vs (i) 3% vs (ii) 0%	8–30% vs (i) 4% vs (ii) 5%	0% vs (i) 1% vs (ii) 0%	0–17% vs (i) 2% vs (ii) 4%

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide; GCG = glucagon; PO = oral; SC = subcutaneous; OD = once daily; OW = once-weekly; BW = twice weekly; MOA = mechanism of action; BMI = body mass index; AEs = adverse events; SAEs = serious adverse events; WL = weight loss; SBP = systolic blood pressure; DBP = diastolic blood pressure; NA = data not available. Data presented as mean change (for continuous data) or proportion of participants (%, for categorical data) and as efficacy estimand unless stated otherwise; ^ efficacy estimand not available, so primary analysis is presented;* different dose-escalation schemes were used for 36 and 45 mg – slow and rapid dose escalation to final doses; **data presented from safety analysis; † different dose-escalation schemes were used for doses 4, 8 and 12 mg.

with 84–87% of the participants achieving HbA1c ≤ 6.5% [53]. At the tirzepatide 15 mg group, 52% of participants achieved ≥ 15% WL compared to 2.6% at the placebo group [53].

The most commonly reported AEs were mild-to-moderate nausea, diarrhea, and vomiting, which generally improved over time. There was no increased risk of hypoglycemia in people with T2D, except when tirzepatide was combined with sulfonylurea or insulin [54]. A reduction of 20–30% of basal insulin dose at the time of tirzepatide initiation has taken place in SURPASS trials to reduce the risk of hypoglycemia [42,45]. AEs leading to treatment discontinuation were ranging between 3–11% with tirzepatide at SURPASS programme and SURMOUNT-2 study. Across a pool of nine phase 2 and phase 3 clinical trials in people with T2D, acute pancreatitis was reported in 0.24% of participants with tirzepatide vs 0.13% with the comparators and acute gallbladder adverse events were reported in 1.1% of participants with tirzepatide vs 0.6% with the comparators [55].

Multiple phase 4 studies are currently ongoing with tirzepatide (Figure 4), including the SURPASS SWITCH (Figure 4), a study investigating the safety and efficacy of swapping dulaglutide 1.5 mg to tirzepatide compared to titration of dulaglutide to higher doses. Tirzepatide is also currently assessed as treatment for numerous metabolic complications that are frequently related to diabetes and obesity such as heart failure with preserved ejection fraction (HFpEF, NCT04847557), chronic kidney disease (CKD, NCT05536804) and metabolic-dysfunction associated steatohepatitis (MASH, NCT04166773). A recent press release from Eli-Lilly revealed the primary outcome results for the phase 2 SYNERGY-NASH trial (assessing the impact of tirzepatide in people with histologically proven MASH and stage 2 or 3 fibrosis) – 52–74% of participants achieved MASH resolution with no worsening of fibrosis at 52 weeks with tirzepatide 5, 10, and 15 mg (maximum effect with tirzepatide 15 mg) compared to 13% of participants with placebo [56]. However, data on improvement in fibrosis stage with tirzepatide for the participants in SYNERGY-NASH trial is not yet available.

It is worth mentioning that different doses and dosing schemes of the injectable GLP-1 RA semaglutide have also demonstrated benefits for a number of metabolic complications that tirzepatide is currently assessed for (such as HFpEF, CKD and MASH). In people with MASH (with and without diabetes), semaglutide 0.4 mg once daily for 72 weeks demonstrated that 59% of them could achieve MASH resolution with no worsening of fibrosis compared to placebo, however there was not improvement in fibrosis stage [57]. Further details for the benefits of semaglutide in people with CKD and HFpEF are discussed in section 2.2 [58,59].

3.2. GLP-1 and amylin

Amylin is a pancreatic hormone secreted by β-cells in response to food intake. It slows down the gastric emptying and inhibits the glucagon secretion – both these actions improve glycemia [60]. Amylin also increases satiety and reduces food intake through actions on the area postrema at the brainstem, and the reduction in food intake is not accompanied by the expected decrease in energy expenditure [61].

Cagrilintide, a once weekly administered amylin analogue, is currently under investigation as treatment for obesity. In a phase 2 study, cagrilintide in doses ranging from 0.3 mg to 4.5 mg resulted in up to 10.8% WL in people with overweight/obesity without diabetes compared to 9% with the GLP-1 RA liraglutide 3 mg and 3% WL with placebo [62].

The mechanisms leading to glycemic improvement and WL with the amylin RAs have several overlapping pharmacological effects with the GLP-1 RAs (including a marked reduction in food intake, delay of gastric emptying and inhibition of glucagon secretion), however amylin RAs and GLP-1 RAs act also in different sites and through different mechanisms of action [63]. Combinations of GLP-1 RA with amylin RA are under investigation for treatment of T2D and/or obesity, aiming to enhance the effect of GLP-1 RA [60,64]. Indeed, experimental studies in animals have shown that combining a GLP-1 RA and an amylin RA exert a synergistic suppression of food intake [65]. Moreover, studies in high fat diet fed rats have shown that the combination of the GLP-1 RA liraglutide with a dual amylin and calcitonin receptor agonist (DACRA) results not only in more WL, but also in improvement in glycemia compared to liraglutide monotherapy and DACRA monotherapy, demonstrating the potential for combining GLP-1 RA with amylin RA in T2D management [66].

In a phase 2 study, the co-administration of cagrilintide 2.4 mg and semaglutide 2.4 mg (cagrisema) once weekly for 32 weeks led to HbA1c reduction of −2.2% compared to −0.9% observed with cagrilintide 2.4 mg once weekly monotherapy and −1.8% with semaglutide 2.4 mg once weekly monotherapy [64]. Data from continuous glucose monitoring demonstrates also that at week 32, time in range (defined as 3.9–10.0 mmol/L [70–180 mg/dL]) was 89% with cagrisema compared to 76% with semaglutide 2.4 mg and 72% with cagrilintide 2.4 mg. Additionally, cagrisema led to 15.6% WL compared to 5.1% WL with semaglutide 2.4 mg monotherapy and 8.1% with cagrilintide 2.4 mg monotherapy [64].

Gastrointestinal AEs were more commonly seen with cagrisema compared to the monotherapies, however the serious adverse events (SAEs) and the AEs leading to treatment discontinuation were similar between groups [64].

Cagrisema is currently being evaluated in a series of phase 3 trials as treatment for T2D (REIMAGINE programme) and/or obesity (REDEFINE programme). REIMAGINE-2 is the first study from the phase 3 programme assessing cagrisema as treatment for T2D, when REDEFINE-2 will evaluate the use of cagrisema in people with overweight/obesity and T2D (Figure 4). Additionally, the REDEFINE-3 will assess the impact of cagrisema on cardiovascular events in people with and without T2D and preexisting cardiovascular disease.

3.3. GLP-1 and glucagon

Glucagon, is a 29-amino acid peptide hormone produced by the pancreatic α-cells, and its role in increasing hepatic glucose production through glycogenolysis and gluconeogenesis is well described (43). Glucagon agonism reduces also food intake and increases energy expenditure, stimulates lipolysis, and in in vivo models decreases muscle protein synthesis [67–

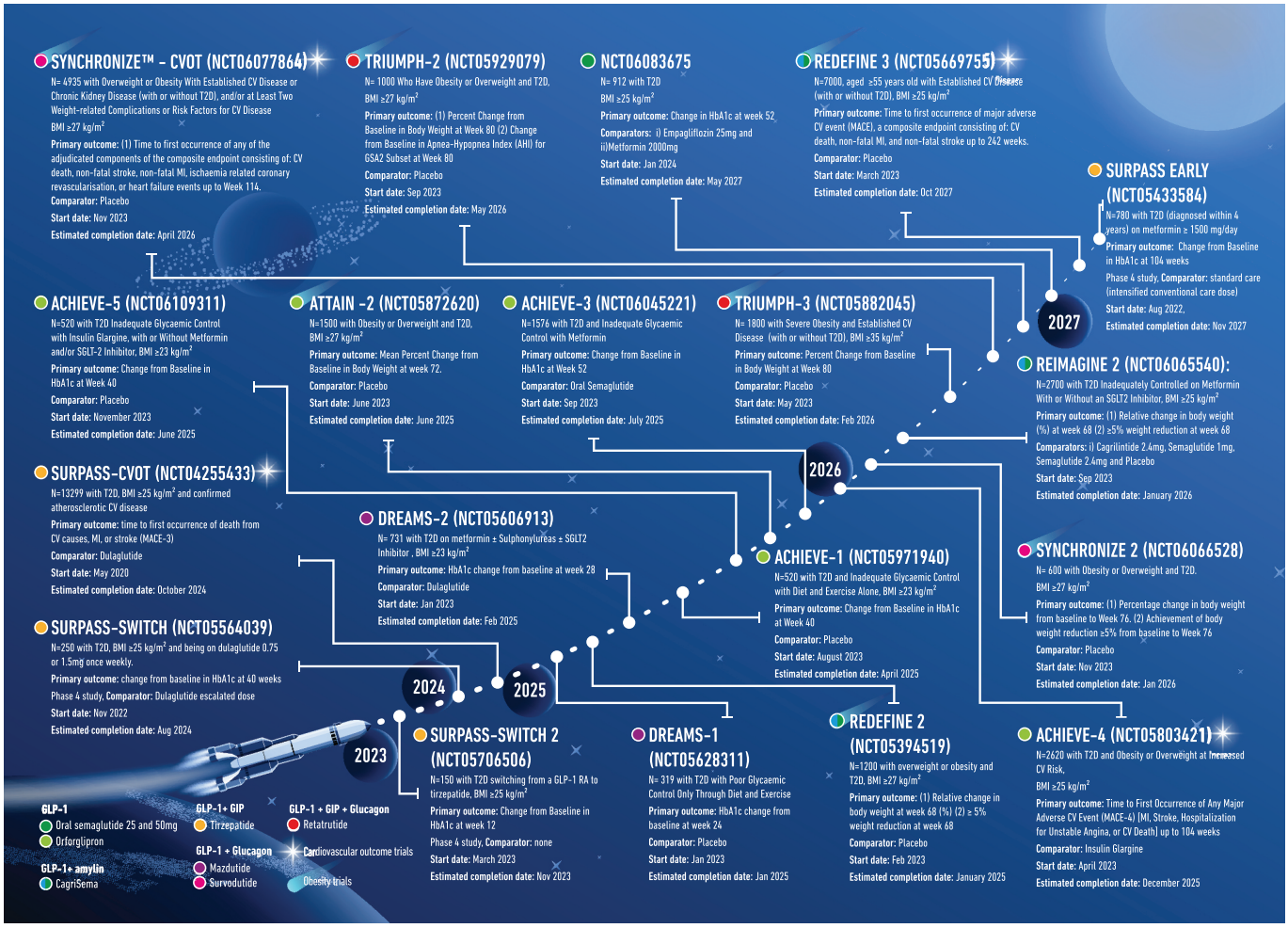

Figure 4. The journey of evidence for the novel molecules for type 2 diabetes and/or obesity – the ongoing phase 3 and phase 4 clinical trials.

BMI: body mass index, CV: cardiovascular, GLP-1: glucagon-like peptide-1, HbA1c: glycated hemoglobin, MACE: Major Adverse Cardiovascular Event, MI: myocardial infarction, RA: Receptor Agonist, SGLT-2: sodium glucose-cotransporter-2, T2D: type 2 diabetes.

69]. Moreover, glucagon agonism increases hepatic fatty acid oxidation and reduces hepatic lipid accumulation, improves mitochondrial function and reduces oxidative stress, suggesting that it may represent a potential treatment approach for MASLD and MASH [70].

In experimental human studies, the co-administration of GLP-1 and glucagon have shown three advantages over GLP-1 RA alone: (a) a synergistic reduction in food intake, (b) increased energy expenditure, countering the tendency to reduce resting energy expenditure with WL, and (c) a neutral effect on glycemia, offering the potential for improved long-term glycaemic control with WL [67,71]. Based on these findings and promising data from experimental models, a number of dual agonists acting on both glucagon and GLP-1 receptors have been developed (with different ratios of GLP-1 vs glucagon receptors agonism) and some of them have progressed in clinical trials as potential treatments for T2D, obesity and/or MASH. Currently, mazdutide and survodutide appear the most promising options in improving glycemia together with achieving clinically important WL, and both these molecules are undergoing phase 3 studies for T2D and/or obesity.

3.3.1. Mazdutide

Mazdutide, is a once weekly dual GLP-1 and glucagon RA. A phase 2 trial of 20 weeks duration assessed the safety and efficacy of three different doses of mazdutide (3, 4.5 and 6 mg) in a Chinese population with T2D [72]. The mean HbA1c change ranged from −1.41% to −1.67% with mazdutide (maximum efficacy with mazdutide 4.5 mg) compared to −1.35% with dulaglutide and + 0.03% with placebo. There was also a dose-dependent effect on body weight, with mazdutide 6 mg achieving mean WL 7.1%, compared to 2.7% WL with dulaglutide and 1.4% WL with placebo. Mazdutide improved also cardiometabolic risk factors such as waist circumference, blood pressure and lipids. The SAEs with mazdutide were similar to the dulaglutide and placebo groups with no participant discontinuing mazdutide due to AEs. Phase 3 trials (DREAMS-1 and DREAMS-2) are currently ongoing, assessing mazdutide 4 mg and 6 mg as treatment for T2D in Chinese population (Figure 4).

3.3.2. Survodutide

Survodutide is another dual glucagon/GLP-1 RA which has completed a phase 2 trial in people with T2D, assessing the

safety and efficacy of multiple doses of survodutide (ranging from 0.3 mg to 2.7 mg once weekly and 1.2 mg and 1.8 mg twice weekly) [73]. After 16 weeks of treatment, the mean HbA1c reduction ranged from −0.91% to −1.71% (maximum effect with survodutide 1.8 mg once weekly) compared with −1.46% with semaglutide 1 mg and −0.25% with placebo [73]. In this phase 2 trial, the mean WL with survodutide was up to −8.95% (with survodutide 1.8 mg twice weekly) compared to 5.4% WL with semaglutide 1 mg and 1.3% WL with placebo [73].

Most common AEs with survodutide were gastrointestinal and in total 15.9% of participants experienced AEs leading to treatment discontinuation at survodutide groups (discontinuation rate ranged from 7.8% with survodutide 1.2 mg twice weekly to 30% with survodutide 2.7 mg once weekly) compared to 4% with semaglutide 1 mg and 5.1% in the placebo group [73].

Survodutide (3.6 mg and 6 mg once weekly) is currently undergoing phase 3 trials as treatment for obesity (SYNCHRONIZE programme) and the SYNCHRONIZE-2 study will assess the efficacy and safety of survodutide in people with overweight/obesity and T2D. Moreover, a phase 2 study in adults with MASH and liver fibrosis with and without diabetes is ongoing (NCT04771273).

There are also other dual GLP-1/glucagon co-agonists under assessment as treatments for obesity and/or MASH (pemvidutide, efinopegdutide); however, these molecules did not demonstrate a clinically important effect in HbA1c in early phase clinical trials in people with T2D [74,75].

3.4. Triple receptor activation: GLP-1, GIP and Glucagon

Triple agonists targeting concurrently the GLP-1, GIP and glucagon receptors could potentially result in better glycemic control and WL compared to the dual GLP-1/GIP agonist tirzepatide and the dual GLP-1/glucagon co-agonists. Indeed, in preclinical studies, retatrutide, a novel triple agonist acting on all GLP-1, GIP and glucagon receptors led to greater WL and better glucose levels compared to tirzepatide [76].

Retatrutide is administered once weekly and in a phase 2 clinical trial, 36 weeks of treatment with retatrutide (doses ranged from 0.5 mg to 12 mg) resulted in up to −2.2% HbA1c reduction (with retatrutide 12 mg once weekly) compared to −1.4% with dulaglutide 1.5 mg and −0.3% with placebo [77]. A dose-dependent reduction in bodyweight up to 16.9% with retatrutide 12 mg was also observed compared with 3% WL with placebo and 2% WL with dulaglutide 1.5 mg [77]. Marked improvements in waist circumference (mean reduction up to −13.2 cm), systolic (mean reduction up to −8.8 mmHg) and diastolic (mean reduction up to −3.9 mmHg) blood pressure as well as in triglycerides (up to −35%) were observed with retatrutide compared to baseline.

Mild-to-moderate gastrointestinal AEs were reported in 35% of participants at the retatrutide group, 35% at the dulaglutide 1.5 mg group and 13% at the placebo group [77]. AEs leading to treatment discontinuation were experienced by up to 17% of participants at the retatrutide groups compared to 2% with dulaglutide and 4% with placebo (Table 3).

Currently, retatrutide is being assessed as treatment for obesity in a programme of phase 3 trials (TRIUMPH) and TRIUMPH-2 (NCT05929079) aims to assess the efficacy and safety of retatrutide in people with overweight/obesity and T2D.

4. Conclusion

Tirzepatide, a dual GLP-1/GIP RA, marks a new era in T2D management where HbA1c ≤ 6.5% together with ≥ 15% WL and improvement in multiple cardiometabolic risk factors is a feasible target across the T2D spectrum with pharmacotherapy. Multiple other molecules with different routes of administration (such as oral GLP-1 RAs) and/or different mechanisms of action (such as injectable combinations of entero-pancreatic hormones) have shown promising data in early phase clinical trials and are currently undergoing phase 3 trials as treatments for T2D, obesity and other metabolic complications (e.c MASH, HFpEF) with some of them having the potential to induce even more WL and/or metabolic benefits compared to tirzepatide. Data on the cardio-renal and metabolic outcomes, the long-term efficacy and safety as well as the cost-effectiveness for each of the novel pharmacotherapies will allow clinicians to offer better individualized care for people with T2D and will also provide a better understanding of their potential position at the T2D treatment guidelines.

5. Expert opinion

Tirzepatide is the first approved combination of entero-pancreatic hormones for T2D and chronic weight management and it has already incorporated in the ADA/EASD 2022 guidelines for management of hyperglycemia in T2D. Numerous other molecules based on entero-pancreatic hormones with different mechanisms of action and routes of administration are also in phase 3 clinical trials as treatments for T2D and/or obesity. The potential availability of multiple effective treatments that could achieve euglycemia together with double digit WL over the next years will provide the opportunity to clinicians to individualize their treatment choice based on patient preference, characteristics and underlying comorbidities, the safety profile of the medication and the treatment response [20]. However, a number of knowledge gaps will need to be addressed over the next years in order to fully understand the benefits and risks of the novel entero-pancreatic hormone based treatments for T2D and/or obesity.

5.1. Long-term safety and efficacy of novel pharmacotherapies

The phase 3 trials which are currently taking place and may lead to the approval of multiple molecules over the next years (Figures 2 and 4) for T2D and/or obesity will provide important information on their safety, the appropriate dose escalation schemes and their full potential regarding efficacy. Discontinuation rates due to AEs in phase 2 trials were above 15% for the higher doses of orforglipron and

retatrutide and approached 30% with survodutide 2.7 mg once weekly (Table 3). Modifications in doses and titration schemes for some of these molecules will take place in phase 3 trials and this may improve their tolerability. Moreover, the phase 3 trials will help us understand better the efficacy and safety of the novel molecules, as the phase 2 trials in people with T2D had relatively short follow-up (ranging from 16 weeks for survodutide to 36 weeks for retatrutide), without evidence for WL plateau at the end of these studies.

Another important aspect requiring further investigation is the cardiovascular safety and efficacy of the new entero-pancreatic hormone based treatments. Currently, the ADA/EASD 2022 guidelines for management of hyperglycemia in T2D recommend tirzepatide as a treatment with very high efficacy in improving glycemia and achieving clinically important WL, but in people with established/high risk of cardiovascular disease the use of sodium glucose co-transporters-2 inhibitors (SGLT-2i) or GLP-1 RAs with known cardiovascular benefits is recommended, as limited data is available on the cardiovascular safety of tirzepatide [9]. The SURPASS CVOT study will provide definitive evidence on the cardiovascular safety and efficacy of tirzepatide compared to dulaglutide 1.5 mg (non-inferiority study), a glucose-lowering agent with known cardioprotective effect [78]. Additionally, clinical trials on the cardiovascular safety and/or benefits of oral GLP-1 RAs in people with T2D (SOUL for oral semaglutide 14 mg and ACHIEVE-4 for orforglipron) are ongoing, when the REDEFINE-3 and SYNCHRONIZE-CVOT will assess the impact of cagrisema and survodutide, respectively (both combinations of entero-pancreatic hormones) in populations with obesity (with and without T2D) and established cardiovascular disease.

The cardiovascular outcome trials will also provide long-term efficacy and safety data with the novel molecules for T2D and/or obesity, as the phase 3 trials for pharmacotherapies with primary outcome glycemia or WL have usually follow-up up to 2 years [45,79]. For the novel molecules with GLP-1 receptor agonism actions, long-term data on AEs of special interest for GLP-1 RAs, such as pancreatitis and gallbladder-related events will be important to establish their safety. GLP-1 RAs use has been associated with approximately 1.4 times increased risk of gallbladder and biliary diseases, especially when used at higher doses and for longer duration [80,81]. Although achieving substantial WL is associated with increased risk for gallbladder-related events, mechanisms beyond WL may also be involved with GLP-1 RAs use [80]. On the other hand, the association of GLP-1 RAs with the occurrence of acute pancreatitis is a matter of controversy [80]. A recent meta-analysis from eleven randomized, placebo-controlled, cardiovascular outcome trials with substantial GLP-1 RA exposure time did not indicate a significantly elevated risk of acute pancreatitis with GLP-1 RA use [82]. Moreover, as the WL achieved with some of the novel pharmacotherapies such as tirzepatide, cagrisema and retatrutide may approach that of bariatric surgery, we will also need to evaluate whether long-term nutrition-related complications seen after bariatric surgery such as increased risk of osteoporosis, fractures and nutrient deficiencies will also present with pharmacotherapies [83–85].

5.2. Impact of novel pharmacotherapies on metabolic complications related to T2D and/or obesity

A significant proportion of people with T2D have also other underlying metabolic and/or mechanical complications such as HFpEF, OSA, MASLD, CKD and knee osteoarthritis which could be improved with ≥ 10–15% WL, a feasible target with the novel T2D pharmacotherapies [86]. Ectopic fat deposition to the heart, kidneys and liver appears to contribute to the development of some of these complications and a number of the new molecules have direct and weight-independent actions on ectopic fat and may further enhance the potential for individualized treatment choices based on underlying comorbidities [20]. More specifically, in people with MASLD, the dual GLP-1/glucagon RAs achieve more liver fat reduction compared to GLP-1 RA alone after similar weight loss, likely due to direct action of glucagon on hepatic lipid oxidation [87]. Nevertheless, GLP-1 RAs such as liraglutide 1.8 mg once daily and semaglutide 2.4 mg once weekly have demonstrated their benefits in MASH resolution compared to placebo, without however improvement in fibrosis [57,88]. Currently, there is lack of data on the potential benefits of dual GLP-1/glucagon RAs or the triple agonist retatrutide on liver histology in people with MASH, but phase 2 trials assessing changes in liver histology with some of these pharmacotherapies are ongoing (NCT04771273, NCT05877547).

In people with CKD and/or heart failure, SGLT-2i have shown remarkable benefits (independent of diabetes status) and are currently recommended as first line glucose-lowering treatments for these populations with T2D [9,89]. However, emerging evidence suggest that some GLP-1 RAs have also benefits in people with HFpEF and CKD. The FLOW study assessed the effect of semaglutide 1 mg compared to placebo on the progression of renal impairment in people with T2D and CKD – the composite primary endpoint was time to first kidney failure (persistent eGFR <15 ml/min/1.73 m^2 or initiation of chronic kidney replacement therapy), persistent ≥ 50% reduction in eGFR or death from kidney or cardiovascular causes – this trial has been stopped early due to efficacy after an interim analysis which met certain pre-specified criteria [90]. In people with HFpEF and obesity (with and without diabetes), semaglutide 2.4 mg once weekly for 52 weeks improved symptoms, physical function, exercise function and bodyweight compared to placebo (STEP HFpEF and STEP HFpEF DM clinical trials) [59,91]. For people without diabetes, the mean WL with semaglutide 2.4 mg once weekly at 52 weeks was 13.3% (vs 2.6% WL with placebo, STEP HFpEF trial), when for people with T2D mean WL with semaglutide 2.4 mg was 9.8% (vs 3.6% WL with placebo, STEP HFpEF DM trial) [59,91]. GLP-1 RAs reduce epicardial fat which is associated with increased risk of HFpEF and they may also impact on perinephric fat, suggesting the potential of weight-independent mechanisms on the effect of semaglutide on CKD and HFpEF [92,93]. Whether the novel GLP-1 based molecules (either oral GLP-1 RAs or those based on combinations of GLP-1 with other entero-pancreatic hormones) will also have similar impact on these metabolic complications will need to be assessed in future studies.

5.3. Timing of treatment initiation with the novel pharmacotherapies in different populations during the T2D continuum

The ideal timing for initiation of the novel treatments based on individual's characteristics and comorbidities will also require further investigation over the next years. For people with severe obesity and T2D, the evidence from bariatric surgery suggests that the earlier after the T2D diagnosis that marked and sustained WL is achieved, the more is the long-term benefit in terms of sustained euglycemia and reduction of the risk for micro- and macrovascular complications [11]. Moreover, a recent cohort study of people newly diagnosed with T2D and 10 years of survival data found that an HbA1c ≥ 6.5% (≥48 mmol/mol) for the 1st year after diagnosis was associated with worse outcomes (micro- and macrovascular complications), suggesting also that an early and intensive treatment for people newly diagnosed with T2D may reduce the long-term risk for diabetes complications and mortality [94]. This may be particularly important in young-onset T2D where higher rates of obesity, more rapid deterioration in blood glucose levels and earlier development of diabetes complications have been observed [9,95]. Nevertheless, the cost-effectiveness of initiating treatment with the novel molecules for T2D in different populations and at different time points during the disease continuum will require further assessment [96]. The ongoing SURPASS EARLY study will provide over the next years data on the benefits of early tirzepatide initiation (as second line, after metformin) compared to standard care using gradual escalation of glucose-lowering treatments (NCT05433584).

5.4. Potential risks and considerations with the novel pharmacotherapies for T2D

The lean muscle mass loss is of particular interest with the new pharmacotherapies for T2D, especially for people with increased risk of sarcopenia (such as elderly, frail populations with T2D and those from Asian background) [97]. For example, 72 weeks of treatment with tirzepatide in people with obesity (without diabetes, SURMOUNT-1 trial), resulted in an overall improvement of the total fat mass: total lean mass ratio, but there was a 10.9% reduction of total lean mass at the end of the study [22]. Adequate nutrition with focus on protein intake and support for resistance exercise during the rapid WL phase, as well as slower dose titration schemes in high risk populations (to try and control the WL rate) may help people preserve their lean muscle mass and optimize further the physical function and body composition. Additionally, understanding the impact of each novel molecule on body composition will help us to determine the optimal strategies for integrating them with various lifestyle interventions. For example glucagon agonism has a suppressive effect on circulating amino-acids and whether the novel dual and triple agonists targeting the glucagon receptor impact negatively on lean muscle mass will need further research [77,98].

It should be noted that the majority of the phase 3 and phase 2 trials in people with T2D have been performed in populations with obesity, as the mean baseline BMI for the global studies included in this review was ranging between 32 and 36 kg/m^2 (only exception the mazdutide study that included Chinese population only). As a result, the efficacy of the novel medications on lean people with T2D has not been adequately studied.

Long-term glycemic control is important for reducing the risk of microvascular complications, although transient worsening of retinopathy or neuropathy may occur during glucose control intensification. In SUSTAIN-6, treatment with semaglutide 1 mg led to the development of retinopathy-related complications in more people (3%) compared to placebo (1.8%) and the risk was higher for people with a history of proliferative or non-proliferative diabetic retinopathy at baseline, with higher baseline HbA1c and longer diabetes duration [99,100]. The magnitude and the rapidity of HbA1c reduction during the first few months after semaglutide 1 mg initiation has been suggested as the main underlying mechanism for the increased risk of retinopathy with this treatment. Data from SURPASS-2 study suggest that glycemic and WL targets were achieved significantly quicker with tirzepatide (at all the three doses, 5, 10 and 15 mg) compared to semaglutide 1 mg (for example time to reach HbA1c < 7% was 8.1 weeks for tirzepatide doses vs 12 weeks for semaglutide 1 mg) and this will be likely the case with the majority of the novel entero-pancreatic hormone-based therapies [101]. People with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy and macular edema have not been studied in the SURPASS program and in studies with other novel agents, so we need to be cautious on initiation of treatment in these populations, especially in those with uncontrolled glycemia. Slower titration of medication doses, retinal screening before treatment initiation and close monitoring from ophthalmology team may be required for this population. Similarly, the novel agents that include GLP-1 receptor agonism should be used with caution for those with a history of pancreatitis as this population has been excluded from the studies with the novel agents.

In summary, apart from tirzepatide, there is a large pipeline of novel molecules with different mechanisms of action that have either completed phase 3 trials and awaiting approval (oral semaglutide 25 and 50 mg) or currently undergoing phase 3 trials for T2D management, obesity and/or metabolic complications (orforglipron, cagrisema, survodutide, mazdutide and retatrutide). Understanding better the full therapeutic potential of these molecules, but also the potential risks associated with their use in different populations through data from clinical trials and real-world evidence will give the opportunity to clinicians to develop personalized treatment plans for people with T2D.

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