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Incretin-based therapies for the management of cardiometabolic disease in the clinic: Past, present, and future

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Abstract

Among newer classes of drugs for type 2 diabetes mellitus (T2DM), glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are incretin-based agents that lower both blood sugar levels and promote weight loss. They do so by activating pancreatic GLP-1 receptors (GLP-1R) to promote glucose-dependent insulin release and inhibit glucagon secretion. They also act on receptors in the brain and gastrointestinal tract to suppress appetite, slow gastric emptying, and delay glucose absorption. Phase 3 clinical trials have shown that GLP-1 RAs improve cardiovascular outcomes in the setting of T2DM or overweight/obesity in people who have, or are at high risk of having atherosclerotic cardiovascular disease. This is largely driven by reductions in ischemic events, although emerging evidence also supports benefits in other cardiovascular conditions, such as heart failure with preserved ejection fraction. The success of GLP-1 RAs has also seen the evolution of other incretin therapies. Tirzepatide has emerged as a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA, with more striking effects on glycemic control and weight reduction than those achieved by isolated GLP-1R agonism alone. This consists of lowering glycated hemoglobin levels by more than

2% and weight loss exceeding 15% from baseline. Here, we review the pharmacological properties of GLP-1 RAs and tirzepatide and discuss their clinical effectiveness for T2DM and overweight/obesity, including their ability to reduce adverse cardiovascular outcomes. We also delve into the mechanistic basis for these cardioprotective effects and consider the next steps in implementing existing and future incretin-based therapies for the broader management of cardiometabolic disease.

KEYWORDS
atherosclerosis, diabetes, incretins, obesity, tirzepatide

1 | INTRODUCTION

Metabolic disorders, such as type 2 diabetes mellitus (T2DM) and overweight/obesity, are among the most important modifiable risk factors for cardiovascular disease (CVD).[1] CVD represents a significant and increasing public health burden, with a projected global mortality of 23.4 million people in 2030, representing an increase of 31.5% from 2017.[2] The rising global prevalence of CVD is compounded both by aging populations and the linked pandemics of overweight/obesity and T2DM. By 2030, it is forecast that 1.025 billion adults will be obese (BMI ≥ 30 kg/m^2) (Figure 1A,B).[3] In parallel, rates of T2DM are also surging and are predicted to increase from a worldwide prevalence of 151 million people in 2000 to 643 million by 2030 (Figure 1C,D).[4] CVD is the commonest cause of death in T2DM and cardiovascular deaths related to metabolic disease are expected to reach an annual prevalence of 16.5 million globally by 2029 (Figure 1E,F).[5,6] These concerning trends have continued despite a growing armory of antidiabetic and obesity therapies with proven efficacy, such as sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) and incretin-based drugs, beginning with glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Therefore, there still exists a need for more effective therapies. One novel agent that has been developed following the arrival of GLP-1 RAs is tirzepatide, which is a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR)/GLP-1 receptor (GLP-1R), or dual incretin, agonist. Results from the first wave of SURPASS studies in T2DM[7–11] and SURMOUNT trials in overweight/obesity[12] suggest that in addition to its effects on glucose lowering and weight loss, tirzepatide may also exert cardiovascular outcome benefits.[13]

Here, we review the continually evolving field of incretin therapies for T2DM and overweight/obesity, extending from the initial experience with GLP-1 RAs to the more potent effects of dual incretin agonism with tirzepatide. We focus specifically on how both types of drugs affect cardiovascular outcomes and describe the proposed mechanisms underlying these observations. Finally, we discuss the next wave of treatments in this space and consider key questions and challenges that should be addressed to optimize the effectiveness and safety of these agents as they are used more widely for cardiometabolic disease moving forward.

2 | PUBLIC HEALTH BURDEN OF CVD, OVERWEIGHT/OBESITY, AND T2DM

The rising worldwide burden of CVD is compounded both by aging populations and the pandemics of T2DM and overweight/obesity. The prevalence rates of T2DM and obesity differ geographically, and within many countries are disproportionally higher among those who are socioeconomically disadvantaged, live in rural and remote

communities and are of certain ethnic groups.[14,15] The increased prevalence in these demographics coincides with elevated rates of both atherosclerotic and nonatherosclerotic CVD.[14,15] Australian data from 2018 to 2019 report that 60% of the population were overweight with BMI > 27 kg/m^2 or obese, and 5.2% had T2DM.[14,16] Similarly, rates of obesity are rapidly rising in the United States, where up to 75% are now considered overweight or obese,[17] with projections that half the adult population will have a BMI ≥ 30 kg/m^2 by 2030.[18] This trend is also emerging in

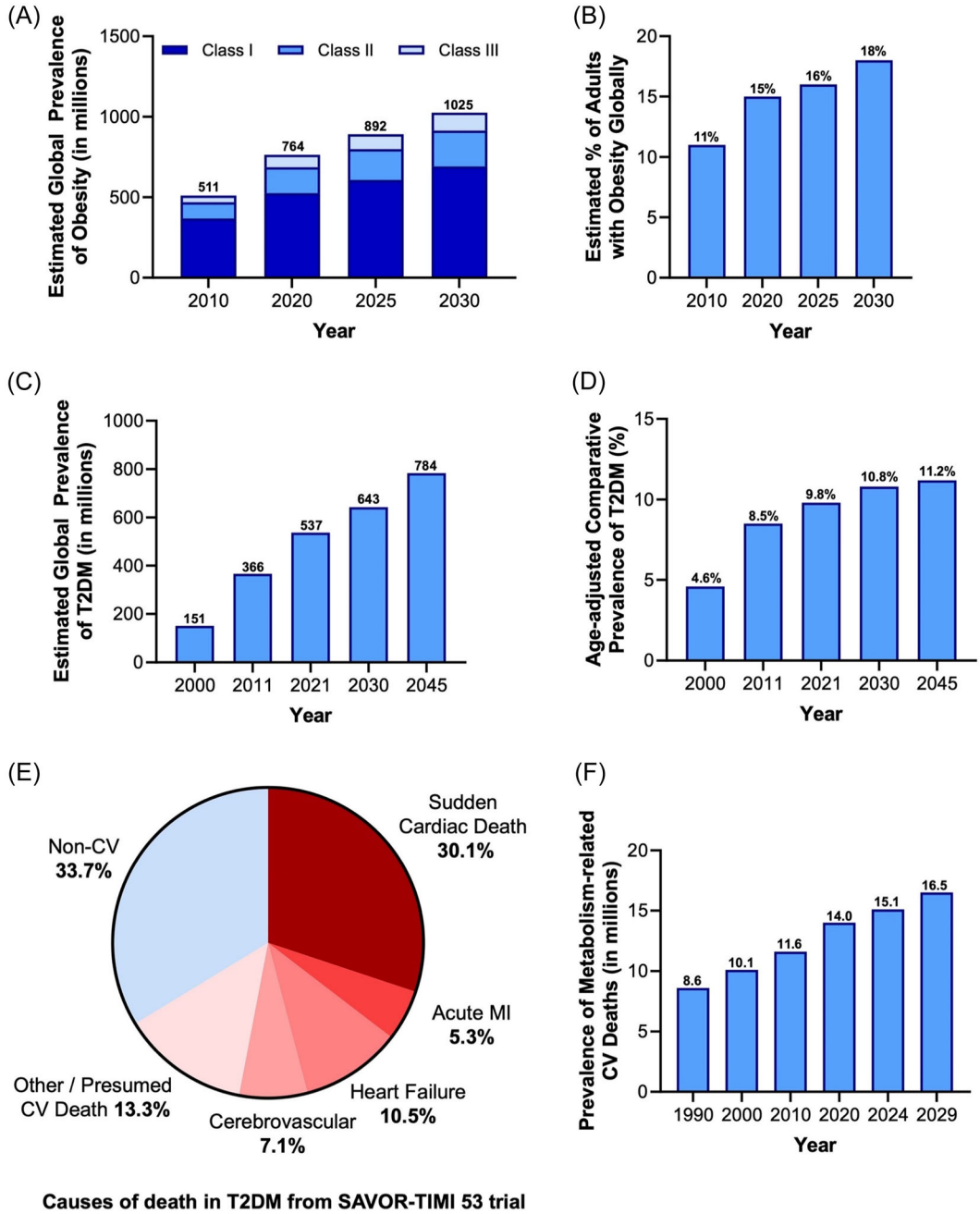

FIGURE 1 (See caption on next page).

regions where obesity has not traditionally been prevalent; for example, in Southeast Asia where rates are expected to double between 2010 and 2030.[19]

Given that two-thirds of all obesity-related deaths are due to CVD, and that almost a third of people with T2DM suffer from CVD, it follows that the rising prevalence of these two conditions will have major implications for the mortality, morbidity, and health economic burden associated with CVD globally over the next decade.[20,21] Among the many mechanisms by which T2DM and obesity lead to cardiovascular complications, key contributors are heightened states of inflammation, oxidative stress, dyslipidemia and hypertension, which are all known to promote accelerated growth and destabilization of atherosclerotic plaques across different vascular territories,[22,23] as well as imposing increased risk of myocardial fibrosis, heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF) and arrhythmias, such as atrial fibrillation (AF).

3 | UNMET TREATMENT NEEDS FOR PATIENTS WITH T2DM AND OVERWEIGHT/OBESITY

Despite the roles that overweight/obesity and T2DM play in the pathogenesis of different types of CVD, treatments aimed at addressing these risk factors have only recently been shown to reduce adverse cardiovascular outcomes. Dietary and lifestyle interventions have typically achieved only modest sustained effects on weight loss of <5% in most randomized trials, while early generations of drugs (e.g., orlistat) have been associated with up to 10% weight loss but are hampered by limiting side effects.[24,25] Concerning T2DM, the traditional glucocentric approach to treatment with agents such as metformin, sulfonylureas, and insulin failed to reduce macrovascular complications. In fact, in the ACCORD trial, intensive glucose lowering was associated with *increased* cardiovascular and total mortality when compared to a more permissive approach to glycemia control.[26,27] In 2008, the goalposts changed for new pharmacotherapies in T2DM when the US Food and Drug Association (FDA) mandated that new classes of diabetic drugs be evaluated for cardiovascular outcomes to ensure adequate safety. From this, two major classes of agents emerged at an inflection point for the T2DM field, achieving not only adequate safety but also benefits in cardiovascular outcomes. These were SGLT2 inhibitors and incretin-based drugs, beginning with GLP-1 RAs. In the case of GLP-1 RAs, these agents have subsequently shown dual utility for glucose-lowering in T2DM and weight reduction in overweight/obesity. In both settings, GLP-1 RAs offer demonstrable cardiovascular protection with 12%–26% reductions in major adverse cardiovascular events (MACE),[28–30] depending on the individual agent trialed and the specific clinical context. In contrast to SGLT2 inhibitors which mediate most of their cardioprotective benefit through the prevention of heart failure and slowing of chronic kidney disease, GLP-1 RAs appear to modify atherosclerotic and ischemic endpoints, such as stroke and myocardial infarction (MI),[29] although data for other salutary effects are also emerging.[31]

FIGURE 1 Global trends in obesity, T2DM and cardiovascular disease. (A) Graph depicts the estimated global prevalence of obesity from 2010 to 2030, with obesity stratified into class 1 (body mass index [BMI] 30–34.9 kg/m^2), class 2 (BMI 35–39.9 kg/m^2), and class 3 (BMI ≥ 40 kg/m^2). (B) Graph shows estimated percentage of adults with obesity worldwide from 2010 to 2030. Data extracted from Lobstein et al.[3] (C) Trend in estimated global prevalence of type 2 diabetes mellitus (T2DM) from 2000 to 2045. (D) Graph summarises age-adjusted comparative prevalence of T2DM from 2000 to 2045. Data extracted from International Diabetes Federation.[4] (E) Pie-chart shows breakdown of causes of death in the SAVOR-TIMI 53 trial, which enrolled 16,492 patients with T2DM who had either established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors. Two-thirds (66.3%) of the 798 deaths that occurred after a median of 2.1 years follow-up were due to one of five cardiovascular (CV) causes. One-third (33.7%) of deaths were from non-CV causes, including malignancy (13.9%) and infection (9.3%). Adapted from Cavallari et al.[5] (F) Graph depicts the prevalence of metabolism-related CV deaths from 1990 to 2029. Data extracted from Wang et al.[6] [Color figure can be viewed at wileyonlinelibrary.com]

While GLP-1 RAs are now recommended cornerstone therapies for patients with T2DM at high cardiovascular risk, real-world uptake continues to lag, with recent US data indicating their use in only 3.9% of eligible patients.[32] Even among individuals who are appropriately prescribed these drugs, cardiovascular event rates remain unacceptably high. For example, in the LEADER trial comparing liraglutide and placebo, 13% of participants with T2DM in the active treatment arm still experienced a new cardiovascular event over a median follow-up of 3.8 years.[28] Considering the spiralling upward trends in T2DM and obesity globally, more effective therapies are still required.

4 | BIOLOGICAL BASIS OF INCRETIN THERAPIES

Incretins are a family of hormones released from the gut postprandially that regulate insulin secretion in response to a meal, accounting for ~65% of postprandial insulin secretion by pancreatic beta (β) cells in health.[33] GIP and GLP-1 are the two known incretin hormones. GLP-1 is a 30-amino acid peptide produced in enteroendocrine L-cells of the small intestine and ascending colon. It exists in two main forms: (1) biologically active GLP-1 (7–36) amide which has a terminally amidated carboxyl group and comprises over 80% of GLP-1 in humans and (2) GLP-1 (7–37).[34] Once released into circulation, GLP-1 binds to specific GLP-1R, expressed on cells of the pancreas, gastrointestinal tract, kidney, heart, and brain.[35,36] Ligand–receptor binding on pancreatic β-cells exerts an insulinotropic effect through two main mechanisms: (1) GLP-1 increases insulin synthesis by stimulating β-cell proliferation through increased intracellular cyclic adenosine monophosphate (cAMP) signaling and upregulation of the β-cell transcription factor, pancreatic duodenal homeobox-1 protein and (2) GLP-1 increases insulin release through similar cAMP signaling leading to a rise in intracellular calcium ion levels.[34] Figure 2 expands on the intracellular signaling pathways of GLP-1 in β-pancreatic cells. Furthermore, GLP-1 also binds to its receptor on pancreatic alpha (α) cells to exert a glucagonostatic effect, inhibiting glucagon secretion under both normoglycemic and hyperglycemic conditions.[34] In addition to these canonical actions on pancreatic secretion of insulin and glucagon, binding of GLP-1 to receptors in the hypothalamus results in increased satiety, while in the gastrointestinal system, it leads to decreased gastrointestinal motility, gastric emptying, and appetite.[33,34]

Endogenous GLP-1 (7–36) has a very short half-life of only 1–2 min in peripheral blood and is rapidly degraded by dipeptidyl peptidase 4 (DPP-4) to GLP-1 (9–36) amide, which has no direct insulinotropic effects. Despite this, GLP-1 (7–36) exerts direct cardioprotective effects by maintaining cardiomyocyte and endothelial cell health.[38] Other preclinical research has demonstrated that both GLP-1 (7–36) and its metabolic byproduct, GLP-1 (9–36), exert direct and indirect cardioprotective effects by promoting endothelium-dependent vasodilation and increasing cardiomyocyte uptake of glucose which, in the setting of acute MI, may help attenuate infarct size.[39] In the clinical setting, parenteral infusion of GLP-1 (7–36) has also been shown to improve myocardial function and left ventricular ejection fraction in patients with chronic heart failure.[40] These findings suggest that native GLP-1 plays an important, albeit incompletely understood role in preserving cardiovascular health, laying the groundwork for investigating the cardiovascular benefits of GLP-1 RAs and tirzepatide.

GIP is a 42-amino acid peptide produced by enteroendocrine K-cells of the duodenum and proximal jejunum in response to detecting intestinal glucose via sodium/glucose cotransporter 1. The GIP receptor (GIPR) is a class II G-protein coupled receptor expressed in similar amounts on both pancreatic α- and β-cells.[33,41] Studies with exogenously administered GIP have illustrated that this incretin can regulate blood glucose levels (BGLs) in both hypoglycemic and hyperglycemic states, by binding to pancreatic α-cells to promote glucagon secretion in the former, and pancreatic β-cells to promote insulin secretion in the latter. However, endogenous GIP is predominantly secreted postprandially in only the hyperglycemic state.[42] GIP is also responsible for enhancing alanine-stimulated glucagon secretion by pancreatic α-cells, leading to further insulin secretion through signaling between α- and β-cells in pancreatic islets.[11]

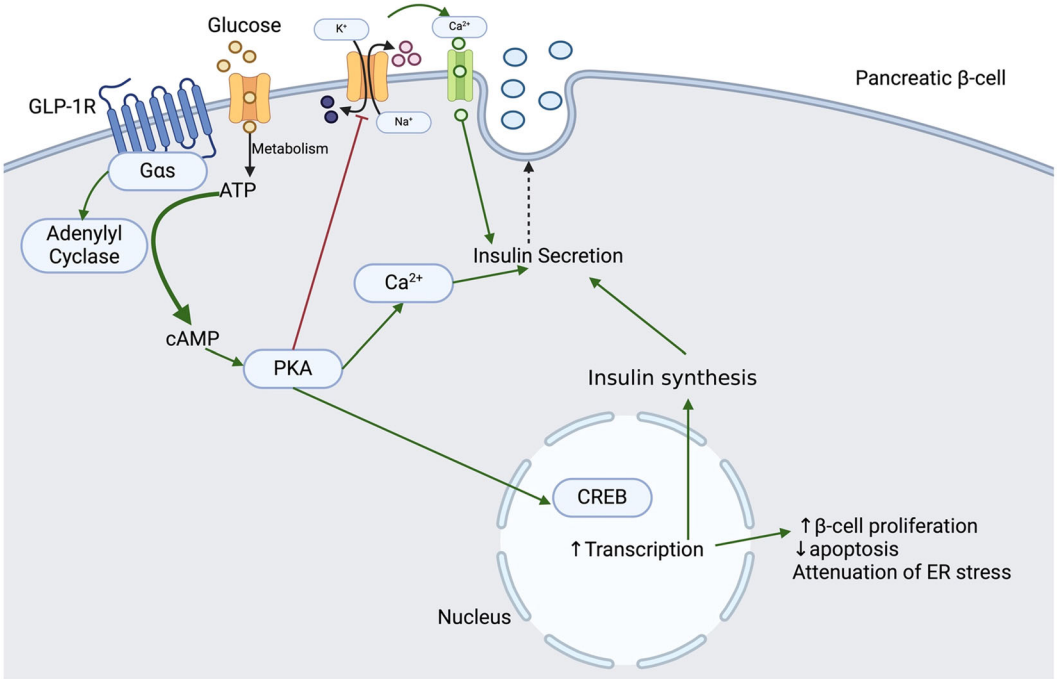

FIGURE 2 Signaling mechanisms of GLP-1 in pancreatic β-cells. Scheme depicting the intracellular signaling pathway of glucagon-like peptide 1 (GLP-1) in pancreatic beta (β) cells. GLP-1 binding to the GLP-1 receptor (GLP-1R) activates the G alpha subunit (Gαs), which subsequently phosphorylates and activates adenylyl cyclase. Adenylyl cyclase converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) which then activates protein kinase A (PKA). Protein kinase A inhibits potassium (K^+) ATP channels, leading to membrane depolarization, influx of extracellular calcium (Ca^{2+}) and finally insulin secretion. PKA also activates cAMP response element binding protein (CREB) in the nucleus which induces transcription of key genes that: (1) promote β-cell proliferation, (2) inhibit β-cell apoptosis, (3) promote insulin synthesis and (4) attenuate endoplasmic reticulum (ER) stress, protecting cellular health. Figure created using www.biorender.com and Adapted from Mayendraraj et al.[37] [Color figure can be viewed at wileyonlinelibrary.com]

Interestingly, although the secretion of GIP can also be triggered by ingestion of fat, it does not exert insulinotropic effects in that setting.[33] This is because insulin secretion mediated by GIP is strictly glucose-dependent.[33] However, it is a key player in lipid metabolism. Fatty acid-mediated GIP secretion promotes lipogenesis through direct GIP-GIPR binding on adipocytes and (in the presence of glucose) increased insulin secretion leading to anabolic conditions.[43] The GIPR is also expressed in the central nervous system (CNS), and studies in obese people have found that increased endogenous GIP activity in the CNS plays a role in propagating leptin resistance and obesity.[44] This is contrasted by the effect of long-acting GIP agonists shown to have significant antiobesity effects.[45] The paradoxical effect of exogenous GIP may be because chronic GIP agonism induces downregulation and desensitization of the GIPR, thereby mimicking antagonism and positively impacting metabolic homeostasis.[45]

Endogenous GIP has been shown to exert numerous cardiovascular effects in studies of healthy subjects. GIP stimulates endothelial cells of the hepatic portal vein to secrete nitric oxide (NO), which can help counteract portal hypertension.[46] It also promotes arterial vasodilation and confers anti-inflammatory and antiproliferative effects on endothelium to protect against adverse arterial remodeling.[46] Furthermore, GIP may exert atheroprotective effects by inhibiting cholesterol uptake by macrophages and subsequent foam cell formation, and was found to reduce

atherosclerosis formation in Apolipoprotein E knockout (*Apoe*$^{-/-}$) mice fed an atherogenic diet.[46] Therefore, both GLP-1 and GIP exert pleiotropic actions that may benefit cardiovascular health.

5 | ROLE OF INCRETINS IN T2DM AND OVERWEIGHT/OBESITY

5.1 | T2DM

The incretin effect, mediated by GIP and GLP-1, is considerably reduced in people with T2DM.[47] In healthy individuals, GIP is thought to be the more dominant incretin; however, under hyperglycemic conditions in T2DM the effect of GIP is significantly reduced.[48] Hyperglycemic clamp experiments comparing the incretin effect of GIP and GLP-1 found that GIP's ability to augment insulin secretion was more than halved in patients with T2DM compared to controls, whereas GLP-1's incretin effect was mostly preserved.[49] Furthermore, studies monitoring secretion of immunoreactive GIP in response to oral glucose showed that GIP secretion is largely preserved in mild T2DM.[50–52] Therefore, the loss of GIP incretin effect in T2DM is due to a qualitative defect in GIP's insulinotropic action rather than a quantitative defect in its secretion. This is potentially due to rapid desensitization of GIPR under hyperglycemic conditions.[53]

The pathogenesis of obesity and T2DM are closely intertwined and GIP's role in promoting postprandial lipid metabolism may also contribute to development of T2DM. Excess GIP secretion plays a role in diet-induced obesity.[54] Obesity, in turn, promotes insulin resistance and T2DM by releasing free fatty acids and adipokines from adipocytes, impairing the insulin-mediated activation of insulin receptor substrate 1 and glucose cotransporter 4 activity.[54] This inhibits insulin signaling and subsequent glucose uptake by muscle and adipose cells.[54] In this way, although GIP secretion is largely preserved in T2DM patients or elevated in those with high BMI, its ensuing effect on the actions of insulin is significantly reduced.[55] Because it was recognized in the 1980s–90s that the insulinotropic actions of GIP are lost under hyperglycemia, interest in GIP agonism for therapeutic glucose-lowering waned substantially for the next decade.[49,56] However, it is now known that near-normalization of hyperglycemia by insulin can partially restore GIP's insulinotropic activity,[57] suggesting that the loss of its activity in T2DM is reversible.

Hyperglycemic clamp experiments have demonstrated that, unlike GIP, GLP-1 retains its insulinotropic actions in mild T2DM and lowers glucagon concentrations to a similar extent as that achieved during hyperglycemia in healthy individuals.[49] As with GIP, GLP-1 secretion in T2DM also appears preserved.[58] Taken together, poor insulin secretion in people with T2DM despite unchanged levels of GIP and GLP-1 secretion suggests that the impaired incretin effect is due to the impaired insulinotropic action of GIP with GLP-1 being insufficient to maintain physiologic insulin levels. Notably, there may be downregulation of GLP-1R expression on β-cells in T2DM, which can lead to some GLP-1 resistance.[59] Like β-cell dysfunction in T2DM, pancreatic α-cell function is also disrupted, with patients with T2DM exhibiting elevated glucagon levels under postprandial conditions.[60] This can be explained by the fact that, unlike β-cells, α-cells remain sensitive to incretins in T2DM, so GLP-1 stimulates glucagon release irrespective of the glycemic state due to loss of insulin-mediated α-cell inhibition.[60]

5.2 | Overweight/obesity

Overweight/obesity is associated with impaired secretion and functioning of incretin hormones. In overweight individuals, leptin resistance and dysfunctional ghrelin secretion are hypothesized to impair physiological GLP-1 signaling, leading to increased hedonic feeding and reward-related pathway activation. This drives hyperphagia and increased appetite.[61,62] In contrast, endogenous GIP secretion is upregulated in obesity. Excess GIP secretion in response to fatty foods contributes to diet-induced obesity, by promoting leptin inhibition and lipogenesis.[44]

Furthermore, murine studies suggest that inhibition of the GIPR is protective against obesity, as GIPR knock-out mice do not become obese when fed a high-fat diet—possibly due to increased lipolysis and lipoprotein lipase activity.[63,64]

6 | GLP-1 RAS IN T2DM AND OVERWEIGHT/OBESITY

6.1 | T2DM

Despite the pivotal role that endogenous GLP-1 plays in regulating body weight and glycemia, its short half-life due to rapid degradation by DPP-4 precludes its therapeutic use.[65] This prompted the development of GLP-1 RAs with longer half-lives, which reach plasma levels up to 40 times higher than endogenous GLP-1.[33,66] The first synthetic GLP-1 RA for T2DM was exendin-4 (exenatide), which was FDA approved in 2005.[67] Exenatide exhibited ~50% homology to native GLP-1, was resistant to cleavage by DPP-4 and had a half-life of 3.3–4 h, allowing it to be administered subcutaneously twice daily.[68] Lixisenatide was then developed, based on slight modifications to exenatide, so that it could be administered subcutaneously once daily despite a half-life of only 2.6 h.[23] Exenatide and lixisenatide, among other short-acting GLP-1 RAs, act through multiple mechanisms, including insulin secretion, glucagon suppression, and by delaying gastric emptying, which sharply lower postprandial glucose levels in people with T2DM.[69,70] Over time, longer-acting GLP-1 RAs were formulated with greater resemblance to native GLP-1 and higher affinity for GLP-1R on pancreatic β-cells, stimulating insulin secretion and leading to sustained lowering of fasting BGLs.[70]

The difference in mechanisms of action between short and long-acting GLP-1 RAs is due to continuous activation of the GLP-1R by long-acting agents, which can lead to tachyphylaxis in the delay of gastric emptying.[70] The first long-acting GLP-1 RA, liraglutide, became commercially available in 2009–10 and featured the addition of a fatty acid chain which facilitated binding to albumin.[39,66] This modification impaired DPP-4 degradation, extending the drug's half-life to 12 h and making it more suitable for once-daily subcutaneous injection.[23] Other long-acting GLP-1 RAs have since been developed, including albiglutide, dulaglutide, and semaglutide. Table 1 compares the pharmacological properties of GLP1-RAs and other newly developed incretin agonists.

Both short and long-acting GLP-1 RAs are effective for glycemic control, with long-acting agents being more effective for the long-term management of T2DM, based on greater and more consistent reductions in HbA1c levels.[71] Landmark trials of dulaglutide, albiglutide, and semaglutide in T2DM demonstrated that they lower HbAlc from baseline by averages of 0.9% (1.5 mg dulaglutide), 1.6% (30 mg albiglutide), and 1.1% (1.0 mg semaglutide).[72–74] Similarly, 1.8 mg liraglutide reduced HbA1c by a mean of 1.3% more than placebo when added to insulin, irrespective of concurrent use of metformin.[75]

6.2 | Overweight/obesity

Some GLP-1 RAs were also found to cause weight loss when used for T2DM. The first wave of agents in this class, namely exenatide, lixisenatide, and albiglutide, resulted in a modest weight reduction of 1%–3%. However, newer, longer-acting agents have had a more pronounced effect.[76] Among these, liraglutide (up to 3.0 mg daily) was the first GLP-1 RA approved by the FDA in 2014 for weight management, followed by semaglutide (up to 2.4 mg weekly) in 2021.[77] In the Phase 3a SCALE program, comprising five randomized, controlled studies of liraglutide for weight management among participants with and without T2DM, the range of weight loss achieved across all doses (1.2, 1.8, 2.4, and 3.0 mg) was 4.8–7.2 kg.[78] Furthermore, ~60% of participants on liraglutide achieved the generally accepted criterion of clinically significant weight loss (CSWL) of ≥5%, which was higher than the placebo comparator.[78]

TABLE 1 Pharmaceutical properties of incretin agonists.

Generic name	Brand name	Formulation	Administration	Dosing	Elimination half-life
GLP-1 Receptor Agonists					
Albiglutide	Tanzeum®	Two altered GLP-1 molecules bound to albumin	s.c., once weekly	30 and 50 mg	5.7–6.8 d
Dulaglutide	Trulicity®	Two altered GLP-1 molecules bound to Fc region of human IgG 4	s.c., once weekly	0.75 and 1.5 mg	4.7–5.5 d
Efpeglenatide	FDA approval pending	Modeled on exendin with conjugation of exendin chain to Fc portion of IgG4	s.c., once weekly	4 and 6 mg	135–180 h
Exenatide	Byetta®	Natural peptide (extendin-4) obtained from saliva of the lizard *Heloderma suspectum*	s.c., twice daily	5 and 10 μg	3.3–4.0 h
Exenatide ER	Bydureon Bcise®	A 39-amino acid synthetic peptide modeled on exendin-4	s.c., once weekly	2 mg	3.3–4.0 h
Liraglutide	Victoza®	Free fatty acid side chain attached to modified GLP-1 (97% homology)	s.c., once weekly	0.6, 1.2, and 1.8 mg	12.6–14.3 h
Lixisenatide	Adlyxinc®	Exenatide plus a poly-lysine tail	s.c., once weekly	10 and 20 μg	2.6 h
Semaglutide (s.c.)	Ozempic®	Modified mammalian GLP-1 (94% homology) with a hydrophilic spacer and a C18 fatty di-acid side chain attached	s.c., once weekly	0.5 and 1.0 mg,	7.6 d
Semaglutide (oral)	Rybelsus®	Modified mammalian GLP-1 (94% homology) with a hydrophilic spacer and a C18 fatty di-acid side chain attached SNAC for enhanced stomach absorption	Oral, once daily	3, 7, and 14 mg	7.6 d
Incretin-based multi-agonists					
Tirzepatide	Mounjaro®	A 39-amino acid peptide, sharing 9-amino acids homologous to GIP and 10-amino acids homologous to both GIP and GLP-1 This sequence is conjugated with a C20 fatty di-acid moiety via a lysine residue in position 20. Two non-coded amino acid residues (Aib, α-amino isobutyric acid) are present at positions 2 and 13	s.c., once weekly	2.5, 5, 7.5, 10, and 15 mg	5 d
Retatrutide	FDA approval pending	A single peptide conjugated to a fatty di-acid moiety	s.c., once weekly	1–12 mg	6 d

Abbreviations: d, daily; Fc region, fragment crystallizable region; FDA, Food and Drug Administration; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide; h, hours; IgG4, immunoglobulin G4; s.c., subcutaneous; SNAC, sodium salcaprozate.

In the landmark SUSTAIN 6 trial, the use of semaglutide for T2DM achieved mean body weight 2.9 kg lower than placebo at a dose of 0.5 mg weekly, and 4.3 kg lower at 1 mg weekly.[29] At the 2.4 mg weekly dose in STEP 2, the semaglutide group had an average weight reduction of 6.2 percentage points more than placebo.[79] Moreover, almost 70% of participants on semaglutide had ≥5% weight loss from baseline. These results highlight the effectiveness of GLP-1 RAs for weight management in patients with and without T2DM.[79]

7 | GLP-1 RAS AND CARDIOVASCULAR OUTCOMES

7.1 | T2DM

The 2008 FDA mandate that all new diabetic drugs undergo evaluation for cardiovascular outcomes has resulted in a large body of phase 3 data showing that not only are GLP-1 RAs safe from a cardiovascular perspective, but they also confer significant cardiovascular benefits (Table 2).[28–30,80–84] These have been consistent for most of the individual agents studied and, unlike SGLT2 inhibitors, have been predominantly driven by reductions in the ischemic endpoints of nonfatal MI and stroke, along with cardiovascular death.[65] In their respective clinical trials for the indication of T2DM and high cardiovascular risk, dulaglutide, albiglutide, and semaglutide each significantly reduced these cardiovascular complications compared to placebo.[29,82,83] In the REWIND (dulaglutide) and LEADER (liraglutide) studies, active drug reduced the primary composite MACE endpoint by 12% (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.79–0.99, $p = 0.026$) and 13% (HR: 0.87, 95% CI: 0.78–0.97, $p < 0.001$ for noninferiority and $p < 0.01$ for superiority) relative to placebo, respectively.[28,83] Subsequently, SUSTAIN 6 showed a relative reduction of 26% for three-point MACE (nonfatal MI, stroke, cardiovascular death) when subcutaneous semaglutide (up to 1 mg weekly) was compared against placebo.[29,30] Notably, this appeared to be driven by fewer cases of stroke (HR: 0.61, 95% CI: 0.38–0.99, $p = 0.04$), with a nonsignificant trend for reduced risk of nonfatal MI (HR: 0.74, 95% CI: 0.51–1.08, $p = 0.12$). However, there was no difference in cardiovascular death (HR: 0.98, 95% CI: 0.65–1.48, $p = 0.92$) over 104 weeks of follow-up.[29]

In PIONEER 6, oral semaglutide was tested at up to 14 mg daily and resulted in 21% reduction in a similar composite MACE outcome.[30] This reached statistical significance for noninferiority compared to placebo, but not for the prespecified superiority requirement. Secondary analysis of the individual components of MACE also suggested reduction in cardiovascular mortality (HR: 0.49, 95% CI: 0.27–0.92) over median follow-up of 15.9 months.[30] Therefore, while PIONEER 6 demonstrated cardiovascular safety, it was not powered to assess the cardiovascular efficacy of oral semaglutide, which will be formally addressed in the Semaglutide CardiOvascular oUtcomes (SOUL) study.[85] Other noteworthy surrogate effects of semaglutide compared to placebo in SUSTAIN 6 and PIONEER 6 were: (1) reductions in systolic blood pressure by ~2.6 mmHg; (2) average weight reduction of 4.3 and 3.4 kg, respectively; and (3) average increases in heart rate by 2.5 and 4 bpm, respectively.[29,30]

Support for the reduction of cardiovascular event rates by GLP-1 RAs in T2DM has also been consolidated through meta-analysis. One such study analyzed 60,080 participants enrolled into eight major trials for lixisenatide (ELIXA), liraglutide (LEADER), semaglutide (SUSTAIN 6 and PIONER 6), exenatide ER (EXSCEL), dulaglutide (REWIND), efpeglenatide (AMPLITUDE-O), and albiglutide (Harmony Outcomes), and found a 14% relative reduction in MACE (HR: 0.86, 95% CI: 0.80–0.93, $p < 0.0001$).[86]

7.2 | Overweight/obesity

Recently, the SELECT trial also reported cardiovascular outcome benefits for semaglutide in nondiabetic individuals who are overweight or obese and have established atherosclerotic CVD. This double-blind, phase 3 trial randomized 17,604 participants (72.5% male, mean age 61.6 years, mean BMI 33.3 kg/m^2) to placebo or semaglutide (up to

TABLE 2 Cardiovascular outcome trials with GLP-1 RAs versus placebo.

Trial	Active intervention	Sample size	% with ASCVD	Median treatment duration	Mean HbA1c change in active arm	Primary CVD endpoint	Primary result
ELIXA (2015)[80]	Lixisenatide 20 μg s.c. daily	6068	100%	25 months	−0.27%	First occurrence CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina	HR 1.02 95% CI 0.89–1.17 $p < 0.001$ noninferiority $p = 0.81$ superiority
LEADER (2016)[28]	Liraglutide 1.8 mg s.c. daily	9341	82.1%	3.8 years	−0.40%	First occurrence CV death, nonfatal MI, or nonfatal stroke	HR 0.87 95% CI 0.78–0.97 $p < 0.001$ noninferiority $p = 0.01$ superiority
SUSTAIN 6 (2016)[29]	Semaglutide 0.5 or 1 mg s.c. weekly	3297	0.5 mg: IHD 59.7% MI 32.2% HF 24.3% CVA 10.8% 1.0 mg: IHD 60.2% MI 32.1% HF 21.9% CVA 10.8%	109 weeks	0.5 mg: -0.66% 1.0 mg: -1.05%	First occurrence CV death, nonfatal MI, or nonfatal stroke	HR 0.74 95% CI 0.58- 0.95 $p < 0.001$ non- inferiority $p = 0.02$ superiority
EXSCEL (2017)[81]	Exenatide ER 2 mg s.c. weekly	14,752	73.3%	3.2 years	−0.53%	First occurrence CV death, nonfatal MI, or nonfatal stroke	HR 0.91 95% CI 0.83–1.00 $p < 0.001$ noninferiority $p = 0.06$ superiority
Harmony Outcomes (2018)[82]	Albiglutide 30–50 mg s.c. weekly	9463	31.5%	1.65 years	−0.52%	First occurrence CV death, nonfatal MI, or nonfatal stroke	HR 0.78 95% CI 0.68–9.0 $p < 0.0001$ noninferiority $p < 0.006$ superiority

(Continues)

TABLE 2 (Continued)

Trial	Active intervention	Sample size	% with ASCVD	Median treatment duration	Mean HbA1c change in active arm	Primary CVD endpoint	Primary result
REWIND (2019)[83]	Dulaglutide 1.5 mg s.c. weekly	9901	IHD 70% MI 47% HF 20% CVA 17% PAD 25%	5.4 years	−0.61%	First occurrence CV death, nonfatal MI, or nonfatal stroke	HR 0.88 95% CI 0.79–0.99 $p = 0.026$ superiority
PIONEER 6 (2019)[30]	Semaglutide 14 mg oral daily	3183	84.9%	15.9 months	−1.0 pct points	First occurrence CV death, nonfatal MI, or nonfatal stroke	HR 0.79 95% CI 0.57–1.11 $p < 0.001$ noninferiority $p = 0.17$ superiority
AMPLITUDE-O (2021)[84]	Efpeglenatide 4 mg or 6 mg s.c. weekly	4076	89.1%	1.81 years	−1.24%	First occurrence CV death, nonfatal MI, or nonfatal stroke	HR 0.75 95% CI 0.58–0.92 $p < 0.001$ noninferiority $p = 0.007$ superiority

Note: Trials: AMPLITUDE-O, Effect of Efpeglenatide on Cardiovascular Outcomes; ELIXA, Evaluation of LIXisenatide in Acute coronary syndrome; EXSCEL, EXenatide Study of Cardiovascular Event Lowering Trial; Harmony Outcomes, Effect of Albiglutide, When Added to Standard Blood Glucose; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PIONEER 6, Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND, Researching cardiovascular Events with a Weekly INcretin in Diabetes; SUSTAIN 6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; CVA, ischemic cerebrovascular accident; HbA1c, Hemoglobin A1c; HF, heart failure; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; PAD, peripheral artery disease; pct points, percentage points; s.c., subcutaneous.

2.4 mg subcutaneous weekly).[87,88] Semaglutide was associated with 20% relative reduction in MACE (HR: 0.80, 95% CI: 0.72–0.90, $p < 0.001$) and a nonsignificant 15% reduction in cardiovascular death. It also reduced the heart failure composite endpoint (HR: 0.82, 95% CI: 0.71–0.96) and had favorable effects compared to placebo on multiple metabolic parameters, including weight loss (estimated treatment difference of −8.5%), systolic blood pressure (−3.3 mmHg), triglyceride levels (−15%), and HbA1c (−0.3%).[89] The results of this landmark study align with previous observational data that showed significant cardiovascular event reduction associated with weight loss of ~20%–30% achieved through bariatric surgery.[90]

7.3 | Heart failure

The benefits of targeting weight loss with semaglutide have also been demonstrated in patients with obesity and HFpEF in the STEP-HFpEF study.[31] In this trial, 529 participants were randomized 1:1 to receive 2.4 mg semaglutide or placebo for 52 weeks. The dual primary endpoints were change in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and percentage change in body weight. The KCCQ-CSS increased by 16.6 points in the semaglutide group compared to 8.7 points in those allocated placebo (estimated difference 7.8 points, $p < 0.001$), while weight reduced by an average of 13.3% with semaglutide compared to 2.6% with placebo ($p < 0.001$).[31] Semaglutide also improved the secondary endpoint of 6-min walking distance (mean +21.5 m *vs.* +1.2 m with placebo, $p < 0.001$). Finally, it was associated with greater reductions in systolic blood pressure and blood levels of C-reactive protein (CRP) and NT-pro-brain natriuretic peptide, with fewer serious adverse events than the placebo group. Although not powered for clinical outcomes, there were also numerically fewer heart failure events among participants on semaglutide.[31]

8 | MECHANISTIC BASIS FOR CARDIOVASCULAR BENEFITS OF GLP-1 RAS

Figure 3 summarizes different organ-targeted effects of GLP-1 RAs that are relevant to T2DM, overweight/obesity, and CVD. While GLP-1 RAs exert favorable actions on glycemia, systolic blood pressure, weight, and serum concentrations of low-density lipoprotein cholesterol (LDL-C) and triglycerides, it is unlikely these effects on traditional risk factors fully account for the scope of cardiovascular outcome benefits.[91–93] Consequently, preclinical and clinical studies have sought to elucidate additional cardioprotective mechanisms of action.[65] Consistent evidence now shows that GLP-1 RAs exert pleiotropic anti-inflammatory and antiatherosclerotic effects, even at relatively low doses.[65] For example, semaglutide reduced atherosclerotic plaque formation in aortas of *Apoe*$^{-/-}$ mice, in association with reduced messenger RNA expression of key inflammatory and osteogenic proteins, such as interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), and osteopontin (OPN).[94] In humans, liraglutide reduced serum CRP levels by 30.5% compared to placebo, further building the case that GLP-1 RAs have anti-inflammatory properties.[95] It was also associated with modest reductions of interleukin 1-beta (IL-b) and TNF-α,[96] and reduced macrophage uptake of oxidized-LDL, thereby inhibiting foam cell accumulation in arterial plaques.[97]

GLP-1 RAs also impart direct actions on vascular endothelial cells, expressing GLP-1R. This may result in higher expression of endothelial nitric oxide synthase (eNOS), promoting vasodilation, and lower expression of intercellular adhesion molecule-1 (ICAM-1), inhibiting leukocyte recruitment to the vasculature.[98,99] In addition, GLP-1 RAs inhibit phosphorylation of AKT-Thr308 in vascular smooth muscle cells,[98] a key kinase that promotes cell growth and survival. This downregulates the expression of matrix metalloproteinase (MMPs), which may help stabilize plaque by increasing plaque fibrous cap thickness.[98,100]

Although there appear to be several mechanisms whereby GLP-1 RAs exert athero-protective effects to lower ischemic risk, there is still a lack of direct proof for their antiatherosclerotic activity in human studies.

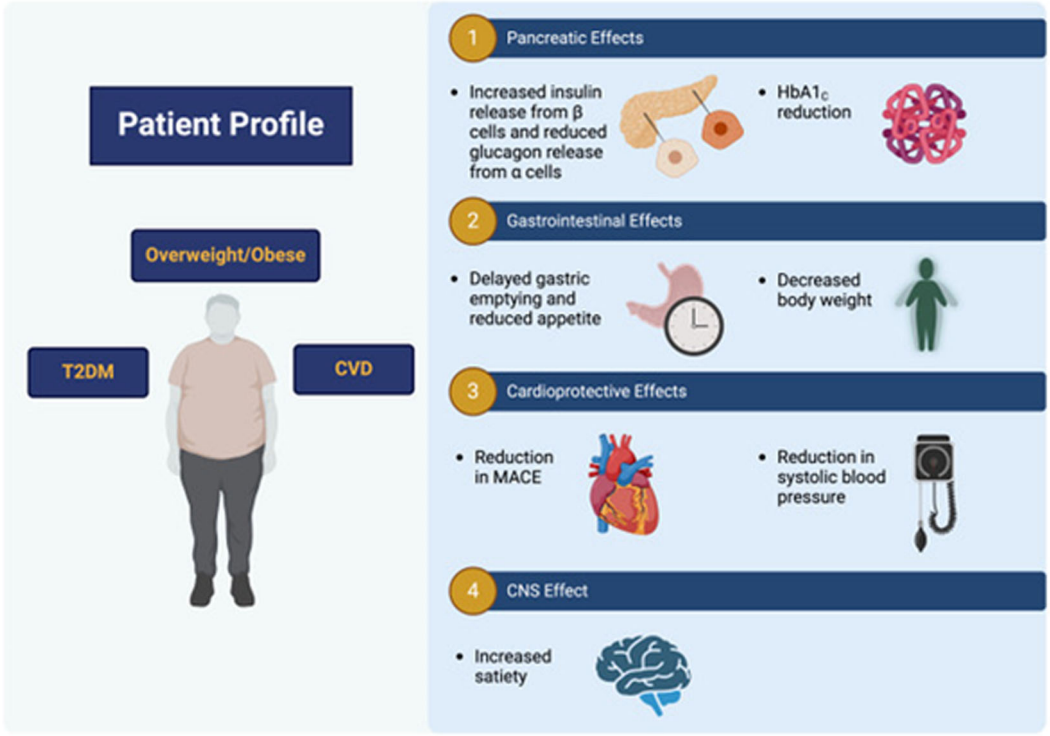

FIGURE 3 Organ-targeted effects of GLP-1 RAs. Schematic showing the different organ-targeted effects that glucagon-like peptide 1 receptor agonists (GLP-1 RAs) exert in the management of overweight/obesity, type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). These include: (1) pancreatic effects, consisting of increased insulin release from beta (β) cells, reduced glucagon release from alpha (α) cells and glucose lowering, as measured by reduction in Hemoglobin A1c (HbA1c) levels; (2) gastrointestinal effects, including delayed gastric emptying and reduced appetite; (3) cardioprotective effects in the form of reduced major adverse cardiovascular events (MACE) and systolic blood pressure; and (4) increased satiety mediated through the central nervous system (CNS). Figure created using www.biorender.com. [Color figure can be viewed at wileyonlinelibrary.com]

The Semaglutide Treatment Effect on Atherosclerosis Progression (STOP) study used computed tomography coronary angiography (CTCA) to measure calcified and noncalcified coronary plaque at baseline and after 52 weeks in 140 participants with T2DM randomized to once weekly semaglutide or placebo.[101] Although not yet in peer-reviewed form at the time of writing, results presented at the 2022 American Heart Association ASM found no significant difference in the primary endpoint of change in calcified or noncalcified plaque volume between the two groups.[101] However, exploratory analysis suggested a greater conversion of noncalcified to calcified plaque with semaglutide, which may represent a "plaque stabilization" effect. Meanwhile, the placebo-controlled LIRAFLAME study also failed to show a benefit of liraglutide on arterial inflammation in patients with T2DM, as measured by change in [^{18}F]-fluorodeoxyglucose positron emission tomography.[102]

The capacity of GLP-1 RAs to reduce ischemic events could also be mediated by direct cardioprotective, in addition to vasculoprotective, effects. For example, these agents can attenuate myocardial ischemia and infarction by counteracting oxidative stress.[39] As discussed above, evidence from STEP-HFpEF also supports that GLP-1 RAs may exert benefits in nonatherosclerotic CVD, at least in obesity.[31] Preclinical results also point to potential effects in AF. Daily dosing with subcutaneous liraglutide reduced atrial fibrosis in hyperglycemic *db*/*db* mice, with less

susceptibility to AF episodes, which were also of shorter duration when they occurred compared to control.[103] Outcomes of clinical studies that address arrhythmic burden, including AF, are now awaited.

9 | SAFETY OF GLP-1 RAS

Gastrointestinal adverse events are common with GLP-1 RAs.[104] Nausea and diarrhea affect ~25% and ~12% of patients respectively, while vomiting, abdominal pain, and dyspepsia occur in up to 10%.[91] Upper gastrointestinal effects (e.g., nausea and vomiting) are likely due to slowing of the stomach and proximal small intestine.[105] Meanwhile, the mechanisms behind lower gastrointestinal effects, such as constipation and diarrhea, are unclear. Importantly, gastrointestinal side effects are common early in treatment and tend to subside over time.[104] Therefore, GLP-1 RAs are usually introduced at low doses and then steadily up-titrated to a maximum tolerated dose.

A handful of GLP-1 RA outcome trials observed an increased risk for diabetic retinopathy; however, none were designed to provide robust estimates of this endpoint, and the methodology for ascertainment varied. More recent evaluation suggests that the magnitude and rapidity of HbA1c reduction may drive the risk of retinopathy, rather than a GLP-1 RA-specific class effect.[106] While we await results from the placebo-controlled FOCUS trial, which will serially evaluate retinal changes from semaglutide (NCT03811561), it is recommended that all patients have their retinopathy status monitored while intensifying glucose-lowering treatment.[29] The use of GLP-1 RAs for at least 1 year is also associated with an increased risk of thyroid cancer,[107] such that they are contraindicated if there is a prior or family history of this. There has also been conjecture about whether GLP-1 RAs confer increased risk of pancreatitis.[108] Those with prior pancreatitis and obese people on GLP-1 RAs for weight loss appear to be most vulnerable.[109] Given their overall frequency, the different adverse effects of GLP-1 RA pose a real-world challenge for long-term patient adherence, which is problematic given that the benefits of these agents depend on their continued use.

Concerns have also arisen around the significant impact that GLP-1 signaling has on gastric emptying. Intravenous GLP-1 delays gastric emptying in a dose-dependent manner, such that its action to delay emptying may outweigh its insulinotropic effects on health.[110] Intermittent and continuous infusions of GLP-1 appear to impair gastric emptying to a comparative extent.[111] However, the evidence base is low quality as the large randomized trials involving GLP1-RAs have tracked gastric emptying using suboptimal techniques, such as paracetamol absorption, or not at all.[112] This is important to consider, as employing the 'gold standard' technique of scintigraphy shows that while both short-acting (exenatide bidaily and lixisenatide) and long-acting (liraglutide, exenatide once weekly and subcutaneous semaglutide) GLP-1 RAs delay gastric emptying, the magnitude of delay is greater with the short-acting agents.[113–116] The effect of dulaglutide and oral semaglutide on gastric emptying has not yet been evaluated, to the best our knowledge. Cases of GLP-1 RA-induced gastroparesis have also now been reported.[117] The prolonged gastric retention of contents induced by GLP-1 RAs poses two potential issues:

(1) Perioperative aspiration risk: The American Society of Anesthesiologists, in recognition of this, published a press release in June 2023 on the preoperative management of people using GLP-1 RAs. They advised that "for patients on daily dosing, consider holding GLP-1 agonists on the day of the procedure/surgery. For patients on weekly dosing, consider holding GLP-1 agonists a week before the procedure/surgery."[118] The effects of long-acting GLP-1 RAs on gastric retention may last longer than a week, and it is likely this recommendation will be revised in the future.
(2) Risk of hypoglycemia: People with diabetes who have developed gastroparesis (e.g., from diabetic autonomic neuropathy) require lower postprandial insulin doses compared with those with normal gastric emptying.[119] There is a concern that delayed gastric emptying in GLP-1 RA-treated individuals may cause mismatch between

glucose absorption and insulin delivery and predispose to hypoglycemia, especially in those concomitantly treated with insulin or sulfonylureas.[120]

10 | DEVELOPMENT OF INCRETIN CO-AGONISTS

Building from the success of GLP-1 RAs, there have been concerted efforts to advance the field of incretin-based pharmacotherapy for metabolic disease.[121] This has led to development of the dual GIPR/GLP-1R agonist, tirzepatide. As the first dual incretin agonist, tirzepatide holds great promise in the treatment of T2DM and overweight/obesity. It achieves its effects on glucose lowering and weight loss via its binding to both GIPR and GLP-1R, generating intracellular signaling cascades.[122] Tracer displacement and cAMP generation studies have demonstrated that it has the same affinity for the GIPR as native GIP but binds to the GLP-1R with five times weaker affinity than native GLP-1.[122] This preference for GIPR activation is thought to enable higher dosing of tirzepatide, without proportionally increasing the risk of gastrointestinal intolerance associated with high doses of GLP-1 RAs.[122] Figure 4 depicts tirzepatide's primary structure alongside that of GIP, GLP-1 and GLP-1 RAs, while Figure 5 provides an overview of tirzepatide's dual GIPR/GLP-1R agonist effects.

11 | MECHANISMS OF ACTION OF TIRZEPATIDE: FOCUS ON GIP

The co-agonism of GLP-1 and GIP results in significantly greater blood glucose and weight reduction than for GLP-1R agonism alone,[8,121] likely via multiple mechanisms. However, the specific role that activation of GIP plays, especially for weight loss, remains unclear because preclinical evidence suggests that it may have a weight gain effect.[123] For example, GIP accelerates lipoprotein lipase activity in a dose-dependent manner in cultured pre-adipocytes[63] and induces fatty acid incorporation into adipose tissues in obese Zucker rats.[124] Moreover, mice deficient in the GIPR are lean and resistant to weight gain after increased dietary caloric intake.[64]

Relatively few clinical studies have focused on the actions of GIP over the past three decades, especially when compared to GLP-1.[125] Animal studies report that GIP agonists reduce nausea and vomiting [126] and have proposed that this is mediated centrally via GIP receptors in the brain.[127] However, it is not known if this applies to humans. Complicating our understanding of how tirzepatide works is the fact that combining GLP-1R agonism with a GIP "antagonist" (rather than GIP agonist, as for tirzepatide) improved glycemia and reduced weight in an early phase clinical study.[128] Therefore, GIP agonism and GIP antagonism appear to have similar effects. Clearly, there is still much to learn about how the co-agonism of GIPR and GLP-1R mediates synergistic benefits on glucose and weight.

12 | CLINICAL TRIAL RESULTS FOR TIRZEPATIDE

Tirzepatide's effects on glycemia in T2DM and weight management in overweight/obesity have been evaluated respectively in the SURPASS and SURMOUNT clinical trial programs, together with its cardiovascular safety profile.

12.1 | T2DM: SURPASS trials

The SURPASS program has studied the effectiveness and safety of tirzepatide in T2DM. It encompasses the SURPASS-1 to 6 trials, SURPASS-J mono and combo studies in Japanese populations, SURPASS-AP in Asian-Pacific patients and SURPASS-CVOT, an ongoing cardiovascular outcomes trial.[13] Across all studies, tirzepatide was

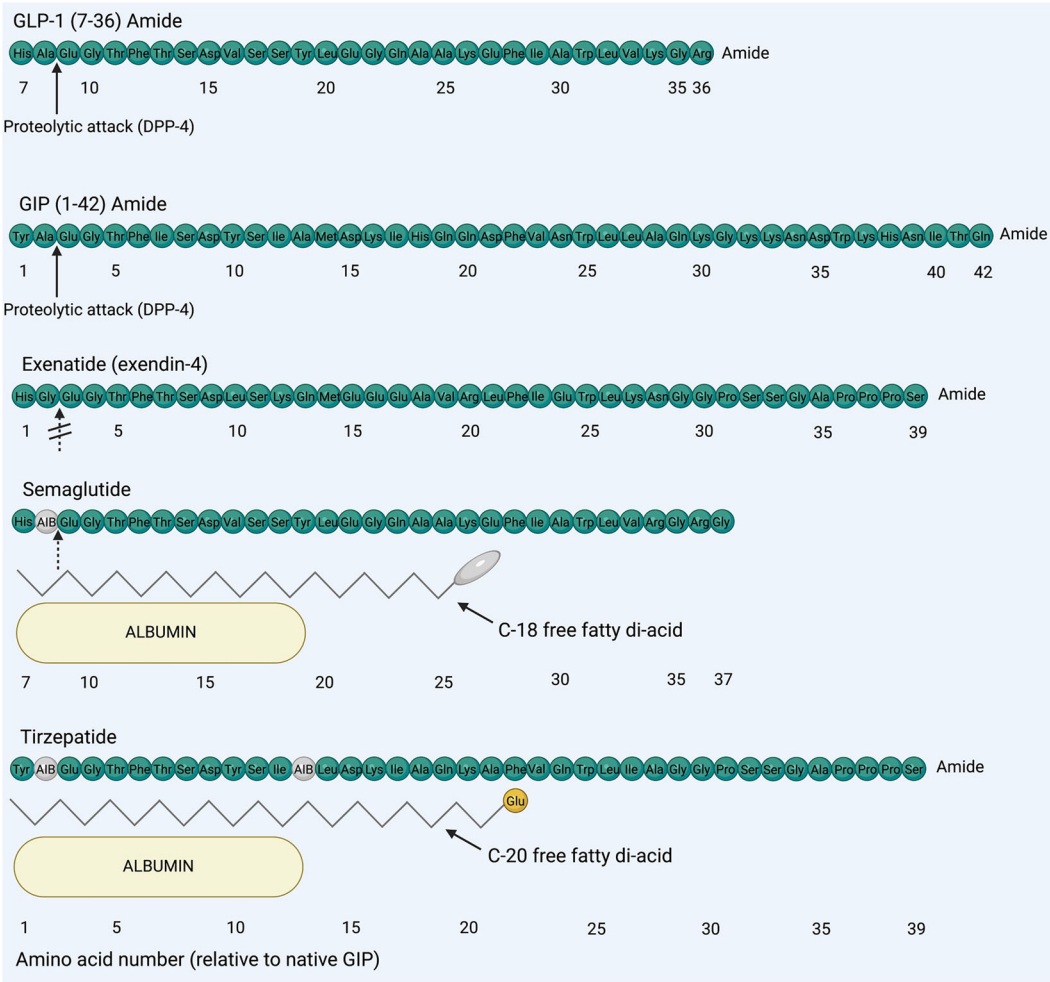

FIGURE 4 Primary structures of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and tirzepatide. Schematic shows tirzepatide's primary structure alongside those of GIP, GLP-1 (7–36) which is cleaved via DPP-4 to GLP-1 (9–36) and exenatide and semaglutide. Tirzepatide is a 39-amino acid linear polypeptide which is conjugated with a C-20 free fatty di-acid moiety at lysine position 20. It contains two noncoded amino acid residues (Aib, α-amino isobutyric acid) at positions 2 and 13. These residues contribute to tirzepatide's long-half life and high affinity to albumin. Figure created using www.biorender.com and Adapted from Nauck and D'Alessio.[13] [Color figure can be viewed at wileyonlinelibrary.com]

studied at three doses of 5, 10, and 15 mg per week, with the initiation of treatment at 2.5 mg weekly and dose escalation at 4-week intervals, as tolerated.[13] Table 3 summarizes the major results from SURPASS-1 to 5.

SURPASS-1 was a placebo-controlled, dose-comparison study in which tirzepatide was studied over 40 weeks in 478 participants with T2DM and mean baseline HbA1c 7.9%.[7] Tirzepatide significantly reduced HbA1c (−1.87% to −2.07%) across all doses versus placebo.[7] Furthermore, depending on dose, 31%–52% of the participants randomized to active drug achieved normoglycemia (HbA_{1c} < 5.7%) compared to only 1% of placebo recipients.[7] These compelling results demonstrate the glucose-lowering potency of tirzepatide, which also induced a dose-dependent reduction of body weight in the order of 7–9.5 kg.[7]

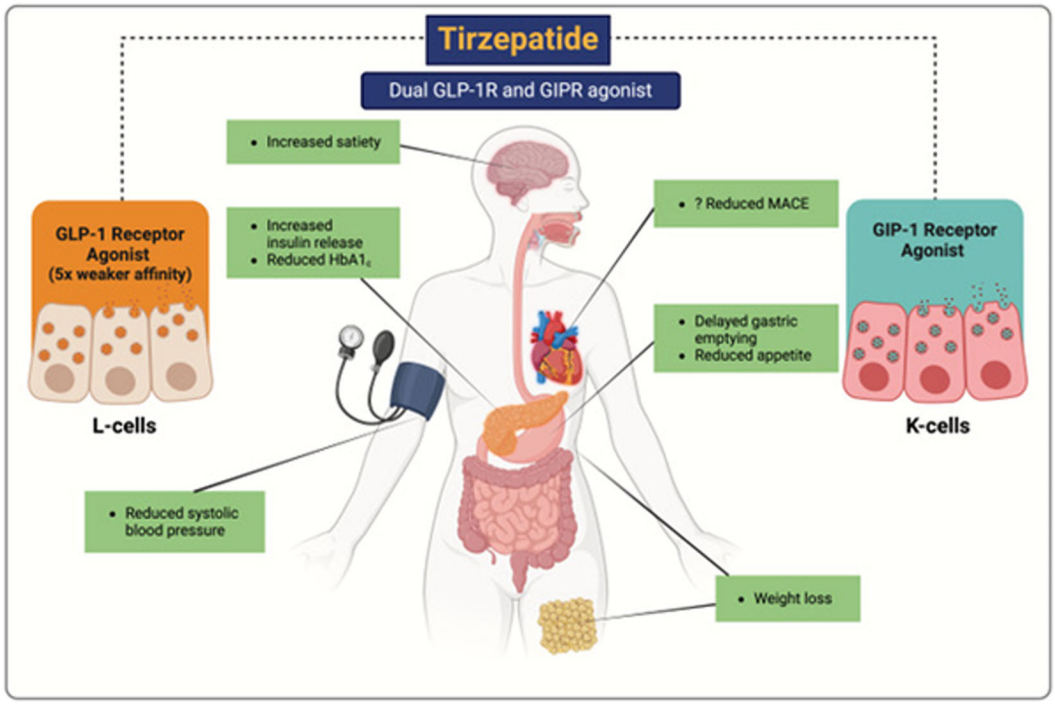

FIGURE 5 Tirzepatide's dual receptor agonist effects. Schematic showing tirzepatide's dual receptor agonist actions, mediated through both the glucagon-like peptide 1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR). Relevant effects of tirzepatide in the context of type 2 diabetes mellitus and/or overweight/obesity include: increased satiety, delayed gastric emptying and reduced appetite, weight loss, increased insulin release, and reduction of Hemoglobin A1c (HbA1c). Tirzepatide has also been found to reduce systolic blood pressure and is currently being investigated for its ability to reduce major adverse cardiovascular events (MACE) in the setting of atherosclerotic cardiovascular disease. Figure created using www.biorender.com. [Color figure can be viewed at wileyonlinelibrary.com]

SURPASS-2 then compared the same three doses of tirzepatide against 1 mg semaglutide in 1879 participants with T2DM who were already on metformin (randomization 1:1:1:1).[8] Tirzepatide was superior to semaglutide for HbA1c lowering and weight reduction. This was further supported by a recent network meta-analysis of 22 randomized controlled trials comprising n = 18,472 participants with T2DM. Preliminary data, presented at the 2023 annual European Association for the Study of Diabetes (EASD), showed that tirzepatide 15 mg was most efficacious at reducing HbA1c compared to placebo (mean difference of −2.00%), followed by tirzepatide 10 mg (−1.86%) and then semaglutide 2.0 mg (−1.62%). Furthermore, in this meta-analysis, each of the three doses of tirzepatide (5, 10, and 15 mg) assessed were more effective for weight reduction than the corresponding "low," "medium," and "high" doses of semaglutide (0.5, 1, and 2 mg).[129]

SURPASS-3 compared once weekly tirzepatide to daily insulin degludec as an adjunct to metformin in sub-optimally controlled T2DM (HbA1c 7.0%–10.5%). In this trial, 1444 participants were randomized to the aforementioned doses of tirzepatide or insulin degludec with a 52-week treatment period.[9] All tirzepatide groups displayed significantly greater reductions in HbA1c from baseline compared to insulin. Furthermore, a larger proportion of participants on tirzepatide achieved the target Hb1Ac of less than 7.0% compared to the insulin group (82-93% vs. 61%).

SURPASS-4 compared tirzepatide and insulin glargine in adults with high cardiovascular risk and T2DM (HbA1c 7.5%–10.5%) who were already on other glucose-lowering medications (e.g., metformin, sulfonylurea

TABLE 3 Tirzepatide for type 2 diabetes mellitus: SURPASS-1 to 5 trials.

Trial	Interventions	Sample size	Mean baseline HbA1c	Treatment duration	Mean HbA1c changes	Mean change in body weight (kg and % where available)
SURPASS-1[7]	Tirzepatide 5, 10, 15 mg Placebo	478	7.94%	40 weeks	T 5 mg: −1.87% T 10 mg: −1.89% T 15 mg: −2.07% Placebo: +0.04%	T 5 mg: −7.0 kg, −7.9% T 10 mg: −7.8 kg, −9.3% T 15 mg: −9.4 kg, −11.0% Placebo: −0.7 kg, −0.9%
SURPASS-2[8]	Tirzepatide 5, 10, 15 mg Semaglutide 1 mg	1879	8.28%	40 weeks	T 5 mg: −2.01 pct pts T 10 mg: −2.24 pct pts T 15 mg: −2.30 pct pts S 1 mg: −1.86 pct pts	T 5 mg: −7.6 kg, −8.5% T 10 mg: −9.3 kg, −11.0% T 15 mg: −11.2 kg, −13.1% S 1 mg: −5.7 kg, −6.7%
SURPASS-3[9]	Tirzepatide 5, 10, 15 mg Insulin degludec	1444	8.17%	52 weeks	T 5 mg: −1.93% T 10 mg: −2.20% T 15 mg: −2.37% Insulin: −1.34%	T 5 mg: −7.5 kg T 10 mg: −10.7 kg T 15 mg: −12.9 kg Insulin: +2.3 kg
SURPASS-4[10]	Tirzepatide 5, 10, 15 mg Insulin glargine	2002	8.52%	52 weeks	T 5 mg: −2.24% T 10 mg: −2.43% T 15 mg: −2.58% Insulin: −1.44%	T 5 mg: −7.1 kg, −8.1% T 10 mg: −9.5 kg, −10.7% T 15 mg: −11.7 kg, −13.0% Insulin: +1.9 kg, +2.2%
SURPASS-5[11]	Tirzepatide 5, 10, 15 mg + insulin glargine Placebo + insulin glargine	475	8.29%–8.39%	40 weeks	T 5 mg: −2.11% T 10 mg: −2.40% T 15 mg: −2.34% Placebo: −0.86%	T 5 mg: −5.4 kg T 10 mg: −7.5 kg T 15 mg: −8.8 kg Placebo: +1.6 kg

Abbreviations: pct pts, Percentage points; S, Semaglutide; T, Tirzepatide.

or SGLT2 inhibitors).[10] This study randomized 1995 participants to receive tirzepatide (5, 10, and 15 mg) or insulin glargine in a 1:1:1:3 ratio. At 52 weeks, the 10 and 15 mg tirzepatide groups achieved mean HbA1c reductions of 2.43% and 2.58%, respectively, compared to 1.44% for glargine. Nausea, diarrhea, decreased appetite, and vomiting were more frequent with tirzepatide but most cases were mild to moderate and occurred during dose escalation. Importantly, tirzepatide was associated with less hypoglycemia than glargine, and no increase in adjudicated MACE-4 events, indicating satisfactory cardiovascular safety.

SURPASS-5 studied tirzepatide in combination with insulin glargine for 475 patients with T2DM and suboptimal glycemic control (HbA1c 7.0%–10.5%).[11] Participants were randomized 1:1:1:1 to the standard doses of tirzepatide or placebo. By 40 weeks, the active treatment arms achieved both marked lowering of HbA1c and weight reduction compared to placebo. The magnitude of weight loss ranged from 5.4 to 8.8 kg for the different doses of tirzepatide. This is still considerable given the background use of insulin, which itself, is typically associated with weight gain.

12.2 | Overweight/obesity: SURMOUNT trials

The SURMOUNT program includes four global, phase 3, double-blind, randomized, placebo-controlled studies, SURMOUNT-1 to 4. Each of these studied different doses of tirzepatide (5, 10, and 15 mg weekly) in overweight/obese individuals who had at least one weight-related complication, not including diabetes.[12] The placebo groups in these studies received weight loss advice around dietary and lifestyle modifications. Table 4 summarizes the key findings from SURMOUNT-1 to 4.

SURMOUNT-1 investigated 2359 participants and found that over 72 weeks, the mean percentage weight change from baseline was −15.0%, −19.5%, and −20.9% for 5, 10, and 15 mg tirzepatide, respectively, compared to −3.1% for placebo.[12] Moreover, the percentage of participants who achieved ≥5% weight reduction was 85%, 89%, and 91% in the three tirzepatide groups versus 35% with placebo. Tirzepatide recipients achieving ≥20% weight reduction in the same groups were 30%, 50%, and 57%. Additional effects of tirzepatide included: (1) mean reductions in waist circumference of 14.0 cm (for 5 mg), 17.7 cm (10 mg), and 18.5 cm (15 mg) compared to 4.0 cm with placebo; (2) mean reduction in total body fat mass of 33.9% overall versus 8.2% with placebo, as measured by dual-energy X-ray absorptiometry; and (3) improved physical function and greater control of cardiometabolic risk factors. Pooled analysis of the three tirzepatide groups also showed a greater mean increase in the Short Form-36 physical function score of 3.6 points compared to 1.7 points for placebo. Meanwhile, 95.3% of pre-diabetic participants (defined as having HbA1c 5.7%–6.4%) allocated to tirzepatide returned to normoglycemia by the end of the study, compared to 61.9% in the placebo group. Finally, tirzepatide resulted in reductions in systolic blood pressure (−7.2 vs. −1.0 mmHg with placebo), triglycerides (−24.8% vs. −5.6%), total cholesterol (−4.8% vs. −1.8%), LDL-C (−5.8% vs. −1.7%), very low-density lipoprotein-cholesterol (VLDL-C) (−24.4% vs. −4.8%) and an increase in high-density lipoprotein-cholesterol (HDL-C) (+8.0% vs. +0.7%).[12]

SURMOUNT-2 randomized 938 participants with T2DM to weekly tirzepatide 10 mg, tirzepatide 15 mg or placebo over a 72-week follow-up period. Tirzepatide 15 mg resulted in the largest body weight reduction (−14.7%), followed by tirzepatide 10 mg (−12.8%) and placebo (−3.2%). Therefore, both doses were superior to placebo with estimated treatment differences of −9.6 and −11.6 percentage points for 10 and 15 mg, respectively. Meanwhile, HbA1c was reduced to a similar extent with both 10 mg (−1.55%) and 15 mg (−1.57%).[130]

SURMOUNT-3 enrolled 806 participants who underwent a 12-week lifestyle intervention lead-in period consisting of a low-calorie diet, exercise, and counseling sessions.[131] The 579 individuals who achieved at least 5% weight loss by this were then randomized to once weekly placebo or 15 mg tirzepatide for another 72 weeks. From the time of randomization, the mean change in body weight was −21.1% with tirzepatide versus +3.3% with placebo, giving an estimated treatment difference of −24.5 percentage points ($p < 0.001$).[131] Tirzepatide also achieved greater reductions in waist circumference compared to placebo (−14.8%), systolic blood pressure

TABLE 4 Tirzepatide for overweight/obesity: SURMOUNT-1 to 4 trials.

Trial	Interventions	Sample size	Mean baseline body weight and BMI	Treatment duration	Mean change in body weight (kg and %)
SURMOUNT-1[12]	Tirzepatide 5, 10, and 15 mg Placebo	2539	104.8 kg BMI of 38.0	72 weeks	T 5 mg: −16.1 kg, −15·0% T 10 mg: −22.2 kg, −19.5% T 15 mg: −23.6 kg, −20.9% Placebo: −2.4 kg, −2.4%
SURMOUNT-2[130]	Tirzepatide 10 and 15 mg Placebo	938	100.7 kg BMI of 36.1	40 weeks	T 10 mg: −12.9 kg, −12.8% T 15 mg: −14.8 kg, −14.7% Placebo: −3.2 kg, −3.2%
SURMOUNT-3[131]	Tirzepatide 10 or 15 mg (maximum tolerated dose) Placebo	579	101.9 kg BMI of 35.9	72 weeks	T 10 or 15 mg: −18.4% Placebo: −2.5%
SURMOUNT-4[132]	Tirzepatide 10 or 15 mg (maximum tolerated dose) Placebo	670	107.3 kg BMI of 38.4	52 weeks	T 10 or 15 mg: −4.7 kg, −5.5% Placebo: +11.1 kg, +14.0%

Abbreviations: BMI, body mass index; T, Tirzepatide.

(−9.2 mmHg), LDL-C (−11.5%), VLDL-C (−27.8%), triglycerides (−28.0%), and a greater increase in HDL-C (+11.4%).[131]

SURMOUNT-4 recruited 783 participants with obesity/overweight but not T2DM to open-label tirzepatide during an initial 36-week run-in phase, before then randomizing 1:1 to tirzepatide or placebo for the next 52 weeks. Mean weight loss was 20.9% during run-in, with an additional 6.7% weight loss in the group that continued active therapy compared to 14.8% weight gain in those changed to placebo ($p < 0.001$).[132] Over 88 weeks, 97.3% of participants on tirzepatide achieved ≥5% weight reduction, compared to 70.3% on placebo. Weight reduction of at least 20% was achieved by 69.5% on tirzepatide and only 12.6% on placebo.[132]

Collectively, these impressive data from the SURMOUNT program highlight that tirzepatide is capable of rapid and substantial weight reduction with accompanying benefits on cardiometabolic risk parameters. However, as is the case with GLP-1 RAs, discontinuation of the drug results in regain of lost weight.[133] Further results from SURMOUNT-5 are awaited to compare the weight loss benefits of tirzepatide and semaglutide in overweight/obese patients who do not have diabetes (NCT05822830).

13 | TIRZEPATIDE AND CARDIOVASCULAR OUTCOMES

Beyond its ability to improve glycemic control and induce weight loss, tirzepatide is also expected to exert cardiovascular benefits.[13] SURPASS-4 provided preliminary evidence of its safe cardiovascular profile, and moreover, suggested a trend for reduced four-point MACE (MI, angina, stroke, all-cause death) with a HR of 0.74 (95% CI: 0.51–1.08) compared to placebo over a median of 52 weeks follow-up.[10] This signal was strongest for the highest dose of 15 mg, which was associated with a HR of 0.50 (95% CI: 0.26–0.95). Further insights into tirzepatide's impact on cardiovascular outcomes among patients with T2DM were provided by a recent meta-analysis of 7215 participants recruited into the SURPASS-1 to 5 trials. In contrast to the comparator groups in these studies, tirzepatide had a nonsignificant HR of 0.80 (95% CI: 0.51–1.08, $p = 0.18$) for MACE-4 events, with HRs of 0.90 (95% CI: 0.50–1.61) for cardiovascular death, 0.76 (95% CI: 0.45–1.26) for nonfatal MI, 0.81 (95% CI: 0.39–1.68) for nonfatal stroke and 0.46 (95% CI: 0.15–1.41) for hospitalization for unstable angina.[134] This analysis also concluded that the upper bounds of confidence for the HR of MACE-3 (MI, stroke, and all-cause death) and MACE-4 were both below 1.3,[13,134] indicating that tirzepatide is safe for clinical use from a cardiovascular perspective, in line with FDA requirements.

Table 5 illustrates how tirzepatide's use in both T2DM and overweight/obesity has also been accompanied by improvements in the atherogenic lipid signature in plasma. In SURPASS-1, this consisted of dose-dependent mean reductions in plasma triglyceride concentrations of 18.5%–21.0% and LDL-C by 6.7%–12.4%, while HDL-C increased by 4.8%–7.5%.[7] These changes were all significantly greater than those in the placebo group. SURPASS-2 also found that tirzepatide's effects on triglycerides, VLDL-C, and HDL-C were greater than for semaglutide at each of the three doses studied, although this did not apply to total cholesterol or LDL-C.[8] Limited available data from pooled randomized trials suggest reductions in systolic blood pressure between 4 and 6 mmHg for different doses.[135] Tirzepatide's effects on blood pressure and lipids would be expected to have flow-on benefits for reducing clinical outcomes from atherosclerotic and non-atherosclerotic CVD, although this needs to be formally evaluated in ongoing phase 3 trials (see below).

14 | THE MECHANISTIC BASIS FOR CARDIOVASCULAR BENEFITS FROM TIRZEPATIDE

Despite a lack of mechanistic studies in human populations, murine experiments have provided signs of tirzepatide's multifaceted cardiovascular protective properties (Figure 6). In female *Apoe**3-Leiden CETP mice with diet-induced hyperlipidemia, administering a GIPR/GLP-1R co-agonist increased plasma triglyceride clearance

TABLE 5 Tirzepatide's effects on lipids in SURPASS-1 to 5 trials.

Trial	Mean % change Triglycerides	Mean % change Total cholesterol	Mean % change HDL-C	Mean % change LDL-C	Mean % change VLDL-C
SURPASS-1[7]	T 5 mg: −18.5%	T 5 mg: −5.5%	T 5 mg: +4.8%	T 5 mg: −6.7%	N/A
	T 10 mg: −18.2%	T 10 mg: −6.3%	T 10 mg: +3.2%	T 10 mg: −7.6%	
	T 15 mg: −21.0%	T 15 mg: −8.4%	T 15 mg: +7.5%	T 15 mg: −12.4%	
	Placebo: +4.7%	Placebo: −0.8%	Placebo: −3.8%	Placebo: −1.6%	
SURPASS-2[8]	T 5 mg: −19.0%	T 5 mg: −5.5%	T 5 mg: +6.8%	T 5 mg: −7.7%	T 5 mg: −17.5%
	T 10 mg: −24.1%	T 10 mg: −6.0%	T 10 mg: +7.9%	T 10 mg: −5.6%	T 10 mg: −23.1%
	T 15 mg: −24.8%	T 15 mg: −6.3%	T 15 mg: +7.1%	T 15 mg: −5.2%	T 15 mg: −23.7%
	S 1 mg: −11.5%	S 1 mg: −4.8%	S 1 mg: +4.4%	S 1 mg: −6.4%	S 1 mg: −11.1%
SURPASS-3[9]	T 5 mg: −15.4%	T 5 mg: −4.25%	T 5 mg: +5.49%	T 5 mg: −6.01%	T 5 mg: −14.2%
	T 10 mg: −26.7%	T 10 mg: −5.81%	T 10 mg: +10.22%	T 10 mg: −5.70%	T 10 mg: −25.2%
	T 15 mg: −25.2%	T 15 mg: −5.69%	T 15 mg: +10.20%	T 15 mg: −6.55%	T 15 mg: −23.8%
	Ins degludec: −12.2%	Ins degludec: −2.92%	Ins degludec: +1.03%	Ins degludec: −2.71%	Ins degludec: −10.6%
SURPASS-4[10]	T 5 mg: −16.3%	T 5 mg: −5.1%	T 5 mg: +6.7%	T 5 mg: −6.8%	T 5 mg: −15.7%
	T 10 mg: −20.1%	T 10 mg: −5.5%	T 10 mg: +9.7%	T 10 mg: −8.3%	T 10 mg: −19.5%
	T 15 mg: −22.5%	T 15 mg: −5.6%	T 15 mg: +10.8%	T 15 mg: −7.9%	T 15 mg: −21.8%
	Ins glargine: −6.4%	Ins glargine: 0%	Ins glargine: +2.9%	Ins glargine: +1.4%	Ins glargine: −5.7%
SURPASS-5[11]	T 5 mg: −15.2%	T 5 mg: −8.8%	T 5 mg: +2.1%	T 5 mg: −8.9%	T 5 mg: −15.1%
	T 10 mg: −19.3%	T 10 mg: −10.3%	T 10 mg: +1.8%	T 10 mg: −12.8%	T 10 mg: −18.7%
	T 15 mg: −24.9%	T 15 mg: −12.9%	T 15 mg: +0.9%	T 15 mg: −15.5%	T 15 mg: −24.1%
	Placebo: −6.8%	Placebo: −0.4%	Placebo: +1.7%	Placebo: +2.8%	Placebo: −5.5%

Abbreviations: HDL-C, high-density lipoprotein-cholesterol; Ins, insulin; LDL-C, low-density lipoprotein-cholesterol; N/A, not available; S, semaglutide; T, tirzepatide; VLDL-C, very low-density lipoprotein-cholesterol.

compared to the control group.[136] This was mediated via increased VLDL-derived fatty acid uptake by adipose tissue and increased liver uptake of VLDL remnants.[136] Combined GIPR/GLP-1R agonism also decreased the rate of VLDL-C production by 33% compared to control. Reduction of excess circulating VLDL and LDL available for oxidization and enzymatic modification may lead to decreased deposition of apolipoprotein B-containing cholesterol in the sub-endothelial compartment of arteries, which in turn would help reduce atherosclerosis. Indeed, this signal was seen in the study of *Apoe**3-Leiden CETP mice, where GIPR/GLP-1R agonism resulted in a nonsignificant 22% reduction in plaque size.[136] Interestingly, this effect was not achieved in mice receiving only GLP-1 or GIP receptor monoagonists.[136]

Mechanistic studies have also shown that tirzepatide attenuates other mediators of atherogenesis. In a phase 2b clinical study comparing once weekly tirzepatide at 1, 5, 10, or 15 mg against dulaglutide 1.5 mg or placebo in T2DM, tirzepatide achieved dose-dependent reductions in circulating levels of the pro-atherosclerotic adhesion molecule, ICAM-1 and high-sensitivity CRP after just 4 weeks.[137] Although the above results hint at its potential for modifying atherosclerosis, serial plaque imaging studies are required to demonstrate its actions on coronary and non-coronary atherosclerosis.[138,139]

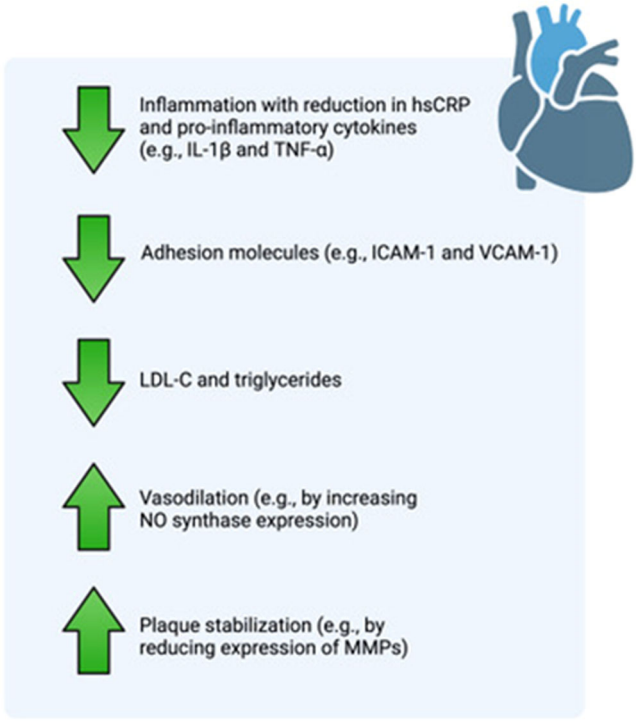

FIGURE 6 Proposed mechanisms underlying the potential cardioprotective effects of tirzepatide. Among numerous mechanisms that are expected to mediate cardiovascular protective effects, tirzepatide has been shown to: (i) reduce systemic levels of inflammation, as evidenced by reductions in circulating concentrations of high-sensitivity C-reactive protein (hsCRP) and proinflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α); (ii) reduce vascular cell expression of intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1); (iii) decrease blood concentrations of low-density lipoprotein-cholesterol (LDL-C) and triglycerides; (iv) promote vascular dilation by upregulating expression of nitric oxide (NO) synthetase; and v) downregulate expression of matrix metalloproteinases (MMPs) in atherosclerotic plaques, thereby potentially improving fibrous cap thickness to stabilize plaque. Figure created using www.biorender.com. [Color figure can be viewed at wileyonlinelibrary.com]

15 | SAFETY OF TIRZEPATIDE

Tirzepatide was approved by the FDA in May 2022 as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.[140] It does not require dosage adjustments in the presence of hepatic or renal impairment. Not surprisingly, it shares many of the gastrointestinal adverse effects of GLP-1 RAs. Nausea and diarrhea occur in ~25% of patients and vomiting and headaches in ~13%–15%.[141] Reduced appetite is also common because tirzepatide suppresses hunger and increases satiety by acting directly on the CNS and as a byproduct of delayed gastric emptying.[141] These effects are commonest soon after starting the drug and can be minimized by smaller, more gradual dosage escalations.[141] In severe cases, tirzepatide's gastrointestinal effects may also cause acute kidney injury secondary to dehydration. Other reported adverse effects include sinus tachycardia, hypersensitivity reactions, acute cholecystitis/cholelithiasis, and pancreatitis.[142,143] Given the nature of glucose-dependent glucose lowering, tirzepatide does not inherently cause hypoglycemia. However, SURPASS-5 demonstrated that in the presence of co-administered insulin, it does confer a higher risk of severe hypoglycemia than placebo.[11]

Tirzepatide also has the potential for long-term effects on nutritional uptake. An 18-week study of 55 obese participants randomized 1:1 to 15 mg tirzepatide or placebo found that it substantially decreased appetite, as

measured during fasting and standardized mixed meal tolerance testing.[144] Food cravings and preference were also measured via the Food Craving Inventory and Food Preference Questionnaire at baseline and 18 weeks, and identified that tirzepatide reduced preference for sweets, carbohydrates, starches, and fast-food fats, but not fruit and vegetables, compared to placebo. On the surface, this effect seems favorable. Indeed, in addition to achieving weight loss, tirzepatide was associated with beneficial effects on body composition in SURMOUNT-1, with percentage reductions in total fat mass that were threefold higher than that of lean mass after 72 weeks.[145] These proportions of fat:lean muscle loss are similar to those accompanied by effective dietary, lifestyle, and surgical treatments for obesity.[146] However, it remains to be seen if there will be longer-term adverse consequences of reduced dietary intake, such as nutritional or vitamin deficiencies, sarcopenia, or osteoporosis. It is well-established that T2DM itself carries an increased risk of fractures.[147] While some GLP-1 RAs in T2DM (e.g., exenatide, dulaglutide) are thought to positively affect bone mineral density,[148] data with tirzepatide is still lacking.

16 | FUTURE DIRECTIONS

16.1 | Ongoing studies

Although the SURPASS and SURMOUNT programs have shown the beneficial effects of tirzepatide on glycemic control and weight loss over follow-up periods of up to 72 weeks, its longer-term effects still need to be determined. Its potential cardiovascular benefits are also being explored in dedicated outcome trials in diabetic and overweight/obese participants with established CVD or high cardiovascular risk (Table 6). SURPASS-CVOT (NCT04255433) has enrolled 13,299 participants with T2DM and CVD and will compare tirzepatide and dulaglutide for cardiovascular events.[149] Baseline characteristics include mean age 64.1 years, diabetes duration ~15 years, HbA1c 8.4%, and BMI 32.6 kg/m^2. Meanwhile, SURMOUNT-MMO is a placebo-controlled, multinational phase 3 trial that is recruiting overweight/obese participants without diabetes, who have atherosclerotic CVD (secondary prevention) or an enriched risk profile (primary prevention). The primary outcome is a cardiovascular composite of all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, and heart failure. It will be evaluated over a 5-year period with results expected in 2027 (NCT05556512).

As described earlier, future mechanistic studies using different plaque imaging modalities will help understand how GLP-1 RAs and tirzepatide work on the atherosclerotic substrate in coronary, cerebrovascular and peripheral arterial disease. Similarly, the impact of these agents remains to be fully determined in patients with nonatherosclerotic CVD, such as HFpEF, HFrEF, and AF, for which there is already literature showing the benefits of weight loss from lifestyle interventions.[150,151] On the back of semaglutide's use in the STEP-HFpEF study, the SUMMIT trial (NCT04847557) will now examine the safety and efficacy of tirzepatide against placebo in 700 obese individuals with HFpEF but not diabetes.

16.2 | Next generation of therapeutics

Tirzepatide's superiority over its mono-agonist counterparts represents a significant milestone in the evolution of incretin-based therapies and has sparked the development of additional multi-agonistic medications as the next generation of therapeutics for metabolic disease. One such medication that has shown promise is retatrutide, a triple GIP/GLP-1/glucagon receptor agonist. In a recently completed phase 2 study, 338 obese adults were randomized to once-weekly subcutaneous retatrutide at doses up to 12 mg (starting at 2 mg) or placebo for 48 weeks.[152] At 24 weeks, retatrutide resulted in dose-dependent reductions in body weight of up to 24.2% with 12 mg compared to 2.1% with placebo. Moreover, the proportions of participants achieving 5%, 10%, or 15% weight loss were far greater than for placebo, with 83% of those on 12 mg achieving at least 15% weight loss by

TABLE 6 Examples of ongoing clinical trials with tirzepatide.

Trial name	Study design	Status	Estimated completion date	Primary outcome measure	Sample size
A study of Tirzepatide in participants with Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT) NCT04847557	Phase 3 Double-blind Randomized Placebo-controlled	Recruiting	June 2024	Composite of all-cause mortality, heart failure, 6-min walk test distance, and Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) category	700
A study of Tirzepatide compared with Dulaglutide on Major Cardiovascular Events in participants with Type 2 Diabetes (SURPASS-CVOT) NCT04255433	Phase 3 Double-blind Randomized	Completed recruiting	October 2024	Time to first occurrence of death from cardiovascular causes, myocardial infarction, or stroke (MACE-3)	13,299
A study of Tirzepatide in participants with Overweight or Obesity and Chronic Kidney Disease with or without Type 2 Diabetes (TREASURE-CKD) NCT05536804	Phase 2 Double-blind Randomized Placebo-controlled	Recruiting	November 2025	Change in kidney oxygenation from baseline	140
Effect of Tirzepatide on Progression of Coronary Atherosclerosis using MDCT (T-PLAQUE) NCT05708859	Double-blind Randomized Placebo-controlled	Not yet recruiting	February 2026	Reduction of total noncalcified coronary plaque volume from baseline	120
A study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults with Obesity (SURMOUNT-MMO) NCT05556512	Phase 3 Double-blind Randomized Placebo-controlled	Recruiting	October 2027	Time to first occurrence of all-cause death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or heart failure events	15,000

Abbreviation: MACE, Major Adverse Cardiovascular Events.

48 weeks, and 100% of those on 8 or 12 mg achieving at least 5% weight loss.[152] Dose-dependent effects on heart rate were also reported, along with gastrointestinal side effects.[152] The glucose-lowering activity of retatrutide in T2DM has also been demonstrated in another phase 2 study, where it achieved mean HbA1c reductions of 1.88% with fast escalation of the 8 mg dose, 1.99% for slow escalation of 8 mg, and 2.02% for 12 mg, outperforming both placebo and 1.5 mg dulaglutide, which achieved a 1.41% reduction.[153] These results were accompanied by mean weight loss of 16%–17% after just 36 weeks on the 8 and 12 mg doses. Although mild-moderate gastrointestinal side-effects were reported in 35% of retatrutide recipients overall, there were no cases of severe hypoglycemia or death. The long-term safety profile and tolerability of more potent incretin-based therapies, like retatrutide, still need to be determined.

Other multi-agonists have also shown promise, with phase 2 trials of GLP-1 and glucagon co-agonists, such as survodutide (BI 456906), having demonstrated significant dose-dependent reductions in weight (up to 18.7% with once weekly survodutide 0.6 to 4.8 mg vs 2% with placebo) and HbA1c (up to 1.9% with 1.8 mg twice weekly survodutide vs 1.5% with 1 mg semaglutide).[154] Moreover, dual agonism of GLP-1 with other entero-pancreatic hormones, such as amylin, are also being evaluated. Amycretin is an example of an oral GLP-1/amylin co-agonist that is currently in early-phase clinical trial (NCT05369390).

Given the complex interplay between CVD, obesity, and T2DM, GLP-1 analogs have also been combined with lipid-lowering medications, most notably proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies.[155] Once such fusion molecule, dubbed MEDI4166, has been assessed in a 5-week phase 1 double-blinded study where 63 participants were randomized 3:1 to once weekly subcutaneous MEDI4166 (50, 200, or 400 mg) or placebo. Although MEDI4166 resulted in significant but modest dose-dependent decreases in LDL-C compared to placebo, it did not produce a clinically relevant reduction in plasma glucose concentration after mixed-tolerance test.[155]

Many current incretin-based therapies for metabolic disease are given subcutaneously and some patients may be reluctant to use injectable medications. Therefore, there is growing interest in the development of oral GLP-1 RAs, as exemplified by oral semaglutide which has been evaluated in the PIONEER clinical trial program.[156] However, patient preference to take oral medication may be counterbalanced by the need for more frequent dosing with this administration route, which is a known deterrent to long-term compliance.

16.3 | Special considerations

Despite the already established benefits of incretin analogs in T2DM and overweight/obesity, several important considerations exist for their long-term implementation into broader clinical practice. Due to unprecedented demand, the last 2 years have seen a global shortage, limiting continuous access to GLP-1 RAs, with supplies of these agents not expected to catch up to an increasing market demand until at least late 2024. This has important implications for maintaining consistent levels of glycemic control in people with T2DM and sustained weight loss in those who take these medications for weight loss. To our knowledge, the short-term consequences of these interruptions to GLP-1 RA treatment (e.g., on diabetic complications including cardiovascular events) have yet to be formally measured and represent an important area of future research that may shape the viability of both existing and future therapeutics.

As the pandemics of T2DM and obesity continue to grow, it is only expected that the demand for incretin-based agents will also soar. It is therefore already worth anticipating the impact that current, and any future, global shortages in access to GLP-1 RAs will have on the implementation and uptake of novel incretin agents, including tirzepatide, when it becomes approved for use across the globe. The current recommendation regarding a single missed dose of tirzepatide is that patients should administer their next dose as soon as possible, preferably within 4 days of the missed dose.[157] If more than 4 days have passed, they are advised to skip the dose and administer the drug on the next scheduled day. If one or two doses are missed, then tirzepatide should be resumed at the same dose as was previously taken; but if three or more doses have lapsed, then it should be recommenced at 5 mg once weekly.[157]

The recent shortages have also highlighted the need to prioritize the availability of these agents to people with T2DM in preference to those without T2DM for weight management. For example, in Australia access to GLP-1 RAs was already partly subsidized by the government for individuals with suboptimal control of T2DM but requires full private payment for those without diabetes using the treatment for weight management. During this extended period of limited and interrupted supply, Australian pharmacies have been instructed to further restrict access to patients with a diabetes indication only. The recent shortages and high demand of incretin agonists highlight the need to have as much therapeutic choice in the market as possible, including newer agents that require less frequent dosing. A suitable analogy for this is the advent of lipid-lowering RNA-therapeutics, that can be given monthly in the case of antisense oligonucleotides or 6-monthly for small interfering RNAs (siRNAs).[158]

Supply issues aside, the lack of reimbursement for these agents is likely to amplify already inequitable access to efficacious weight management care. Socioeconomically disadvantaged communities around the world are disproportionately affected by obesity and its physical and mental health consequences. Yet in most countries, these people will not have the financial means to access incretin-based pharmacotherapies unless there are changes to existing public and private health insurance models to cover their considerable costs. Therefore, the efficacy of any future incretin-based therapies should be weighed alongside their potential cost and accessibility.

As emphasized earlier, our current understanding is that these agents' glycemic and weight loss benefits require continued use. The experience from clinical trials and real-world practice is that lost weight is often entirely regained within 12 months after GLP-1 RAs or tirzepatide are discontinued.[133] The very long-term effects of these drugs on nutritional status, bone, and muscle health still need to be established, along with the impact they will have on societal trends (e.g., eating and exercise habits) and nonhealth industries. Beyond better understanding of the broader cardiovascular impact and the responsible mechanisms of action, including effects on atherosclerosis, thrombosis, vascular and myocardial function and arrhythmogenic substrate, future research may also wish to explore the degree to which these actions are also contingent on uninterrupted, long-term use. For example, it remains to be seen whether taking incretin-based therapies for even the short or intermediate term could induce epigenetic changes that have longer-lasting positive health consequences even after treatment is stopped. In a similar vein, one might speculate about how they could impact other age-related diseases (e.g., dementia) that share similar metabolic risk factors with CVD.

17 | CONCLUSION

Despite current therapies, the burden of CVD in patients with T2DM and overweight/obesity continues to grow. The last decade has seen the emergence of new therapies that act on incretin receptors to achieve better metabolic control and unprecedented amounts of pharmacological weight loss. This began with single agonist GLP-1 RAs and has rapidly evolved into the potent dual agonist agent, tirzepatide, with triple agonist therapy also on the horizon. There is already growing evidence that tirzepatide's dual-agonist actions give it significant advantages over its single agonist predecessors, with results from the SURPASS and SURMOUNT studies highlighting major therapeutic benefits in the treatment of T2DM and obesity. In the wake of the cardiovascular benefits shown for semaglutide, there is expectation that tirzepatide and other new therapies in this space may achieve even greater cardiovascular event reduction. There is still much to understand about the scope of benefit they may achieve in both atherosclerotic and non-atherosclerotic CVD and the mechanisms by which this is mediated. However, as these agents will likely be lifelong therapies, it is imperative that we continue to learn about their long-term safety.

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CONFLICT OF INTEREST STATEMENT

James P. Psaltis, Mau T. Nguyen, Richard Le, and Christina A. Bursill have nothing to declare. Jessica A. Marathe has received speaking honoraria from Novartis. Chinmay S. Marathe has received speaking honoraria from Boehringer Ingelheim, Novo Nordisk, and Eli Lilly. Adam J. Nelson has received consulting fees or speaking honoraria from Amgen, Boehringer Ingelheim, GSK, Lilly, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, and VAXXINITY. Peter J. Psaltis has received consulting fees from Amgen, Eli Lilly, and Esperion and speaker honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck Schering-Plough, Novartis, Novo Nordisk, Pfizer, and Sanofi.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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Dr. Jessica A. Marathe (MBBS, BMedSc (Hons), GradCertRes, PhD, FRACP) is an interventional cardiologist based at the Royal Adelaide Hospital, Clinical Research Fellow at the South Australian Health and Medical Research Institute (SAHMRI), and Senior Clinical Lecturer at the University of Adelaide. She undertook her speciality and subspecialty training in Australia and was awarded her PhD in 2022. She has an interest in cardiometabolic health, actively practising to improve outcomes for patients who have inter-related conditions (particularly in indigenous populations), and has research interests in diabetes (including incretin physiology) and associated metabolic conditions.

Dr. Mau T. Nguyen (BMedSci (Hons 1), MBBS, MBiostat) is a cardiology physician trainee at the Royal Adelaide Hospital, Adelaide, Australia, and a PhD candidate at the University of Adelaide and South Australian Health and Medical Research Institute (SAHMRI). He has a broad interest in basic and clinical research including novel mediators of atherosclerotic coronary artery disease. His PhD project is investigating the role of autophagic flux in the development and progression of coronary atherosclerosis. He is also involved in projects looking at improving the quality of care delivered to patients presenting with acute coronary syndrome.

Mr. Richard Le (BClinSci, MD4, Flinders University) is a 4th and final year postgraduate medical student who is passionate about cardiometabolic health and research. He volunteers for lab-based research projects within the Heart and Vascular Research Centre at the South Australian Health and Medical Research Institute (SAHMRI). He is also involved in several clinical trials such as the RAPIDx AI trial, which explores the use of an AI-based decision support tool for improved detection and diagnosis of acute coronary syndrome within South Australian emergency departments. He is also involved in the ACT-2 trial, which investigates the appropriateness of early invasive coronary angiography in patients with myocardial injury and type 2 myocardial infarction. Richard is the current Chair of the South Australian committee of Doctors for the Environment Australia (DEA). He holds a special interest in the intersection between climate change and human health, especially the effect of extreme weather events on cardiovascular and metabolic health outcomes.

A/Prof. Christina A. Bursill (BSc (Hons 1) PhD, Adelaide University; Postdoc, Oxford University, UK) is a leader in cardiovascular biology recognised for her expertize in the biology and mechanisms of atherosclerotic plaques and angiogenesis. She is Co-director of the Vascular Research Centre at the South Australian Health and Medical Research Institute (SAHMRI) and has held two National Heart Foundation (NHF) Fellowships. A/Prof Bursill has received >$AU4.5 million in competitive research funding in the last 4 years and has published >100 manuscripts and supervised >15 PhD students to completion. A/Prof Bursill cochairs the South Australian Cardiovascular Research network and is a board member for the International Atherosclerosis Society. She is a past board member (Treasurer) of the Australian Cardiovascular Alliance (ACvA) and is a past-President of the Australian Atherosclerosis Society. A/Prof Bursill spent five years as postdoctoral fellow at Oxford University in the Departments of Cardiovascular Medicine and the Sir Willian Dunn School of Pathology where her project focused on understanding the role of chemokines in atherosclerotic plaque biology. She then returned to Australia to lead the Immunobiology Group at the Heart Research Institute, Sydney, where she uncovered novel vasculo-protective effects of high-density lipoproteins. More recently at SAHMRI, her group is testing nanoparticles that identify and prevent atherosclerotic plaque, as well as pursuing novel therapeutic strategies to inhibit newly identified targets of atherosclerosis.

Dr. Chinmay S. Marathe (MBBS, PhD, FRACP) is a consultant diabetologist/endocrinologist and mid-career researcher based at the Royal Adelaide Hospital and University of Adelaide, Adelaide, Australia. He undertook his specialist training in diabetes and endocrinology in Australia, followed by postdoctoral training in the United Kingdom (King's College London). His PhD thesis (2016, University of Adelaide) explored the relationships between gastric emptying, glycaemic, and the incretin effect in health and diabetes and was awarded by a Dean's Commendation and the Royal Australasian College of Physicians' Trainee Research Award. Dr. Marathe is an expert in gut-based incretin physiology having published over 50 papers in the area and continues to be actively involved in research involving diabetes and incretins, currently supervising five higher research degree students in these areas of interest, and having gained >$AU2 million dollars in research funding in the area.

A/Professor Adam J. Nelson (MBBS, MPH, MBA, PhD, FRACP, FCSANZ) is an early career academic cardiologist, trialist and outcomes researcher from Adelaide, Australia. He has an established track record in systems improvement, quality of care and implementation science with clinical and academic interests in diabetes, obesity and dyslipidaemia. A/Prof Nelson is considered a key opinion leader regarding diabetes, obesity, and cardiovascular disease having authored consensus statements, manuscripts, and book chapters, as well as receiving international faculty meetings to the American Diabetes Association, European Association for the Study of Diabetes and Diabetes Malaysia, among others. A/Prof Nelson was the highest-ranked candidate for a National Heart Foundation of Australia post-doctoral fellowship in 2021, is a chief investigator on multiple Category 1 grants and has generated >$AU8 million in project funding. He has published over 150 manuscripts (113 in last 5 years) with over 4,500 cumulative citations and has an H-index of 35.

A/Professor Peter J. Psaltis (MBBS Hons, PhD, FRACP, FCSANZ, FESC) is an academic interventional cardiologist and vascular biologist, who holds Faculty positions at the South Australian Health and Medical Research Institute (SAHMRI), Central Adelaide Local Health Network and the University of Adelaide. He is the Deputy Director of SAHMRI, co-leads its largest research department, the Lifelong Health Theme (> 310 researchers), and leads its Heart and Vascular Program. He is also Head of Interventional Coronary Services in the Department of Cardiology, Royal Adelaide Hospital. Among other leadership positions, A/Prof Psaltis is Past-President of the Australian Atherosclerosis Society, co-chair of the SA Aboriginal Heart and Stroke Leadership Group, co-chair of the South Australian Cardiovascular Research Network, and serves on the board of the Australian Cardiovascular Alliance and Scientific Committee of the Cardiac Society of Australia and New Zealand. He has expertize across all three disciplines of basic, translational, and clinical research and leads bench-to-bedside projects spanning topics of developmental macrophage biology, vascular stem cells, inflammatory regulation of atherosclerosis, pharmacological modification of atherosclerosis, coronary plaque imaging, the modeling of biomechanical forces in coronary arteries and cardiometabolic disease. He currently holds a Level 3 Australian National Heart Foundation Future Leader Fellowship and has received >$AUD24 million of peer-reviewed grant funding. He has published over 200 manuscripts and has graduated 13 PhD students. A/Prof. Psaltis was/is the Australian national lead of the CLEAR Outcomes (Esperion) and SURMOUNT-MMO (Eli Lilly) clinical trials.

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