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Review

# Prevention of cardiorenal complications in people with type 2 diabetes and obesity

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## SUMMARY

Traditional approaches to prevention of the complications of type 2 diabetes (T2D) and obesity have focused on reduction of blood glucose and body weight. The development of new classes of medications, together with evidence from dietary weight loss and bariatric surgery trials, provides new options for prevention of heart failure, chronic kidney disease, myocardial infarction, stroke, metabolic liver disease, cancer, T2D, and neurodegenerative disorders. Here I review evidence for use of lifestyle modification, SGLT-2 inhibitors, GLP-1 receptor agonists, selective mineralocorticoid receptor antagonists, and bariatric surgery, for prevention of cardiorenal and metabolic complications in people with T2D or obesity, highlighting the contributions of weight loss, as well as weight loss-independent mechanisms of action. Collectively, the evidence supports a tailored approach to selection of therapeutic interventions for T2D and obesity based on the likelihood of developing specific complications, rather than a stepwise approach focused exclusively on glycemic or weight control.

## INTRODUCTION

The global burden of cardiometabolic disease contributes substantially to excess disability, and increased rates of death from heart disease, kidney failure, cerebrovascular disease, and cancer, with important contributions from poorly controlled type 2 diabetes (T2D) and obesity.[1–3] Although all-cause mortality (ACM) for people with T2D has decreased in high-income countries from 1995 to 2016,[4] a substantial residual risk of increased disability and mortality requires ongoing attention.[2,3] Moreover, the global burden of disability and excess mortality attributable to an increased body mass index (BMI) has increased from 1990 to 2017.[5] Analysis of the relationship between changes in body weight and the risk of 13 obesity-related complications over ~7.3 years of follow-up in subjects with a BMI >30 kg/m$^2$ enrolled in the UK Clinical Practice Research Datalink GOLD database revealed considerable metabolic benefit (lower rates of T2D, dyslipidemia, and hypertension) of weight loss in individuals with lower baseline BMI, with reductions in cardiovascular disease (CVD) risk leveling off after 10% weight loss.[6] Conversely, the relative risk of obesity-related complications increased with subsequent weight gain. Interestingly, the risk of heart failure and atrial fibrillation was reduced to a greater extent in subjects with higher baseline BMI and greater weight loss, whereas the risk of depression was not reduced with weight loss across a range of BMI.[6]

The recognition that double-digit weight loss (achievable with bariatric surgery, diet and newer GLP-1-based medicines) may be associated with remission of T2D and a substantial reduction of T2D-associated complications[7] has refined treatment goals for T2D beyond reduction of A1c, with new emphasis on weight loss (Figure 1) as a primary goal for reduction of diabetes-associated complications.[8] Simultaneously, weight loss-independent reductions in rates of CVD including heart failure, chronic kidney disease (CKD), and all-cause and cardiovascular mortality have been achieved using SGLT-2 inhibitors (SGLT2is),[9] and reductions in major adverse cardiovascular events (MACE), including stroke, as well as decreases in cardiovascular and all-cause mortality are reported with GLP-1R agonists (GLP-1RAs)[9,10] even with GLP-1RAs that produce modest weight loss.[11] Moreover, mineralocorticoid blockade with finerenone attenuated progression of diabetic kidney disease (DKD) and reduced rates of MACE plus hospitalization for heart failure in people with T2D,[12] and use of pioglitazone reduced rates of stroke and myocardial infarction (MI) in people with insulin resistance and a history of transient ischemic attacks or ischemic stroke.[13] Collectively, these observations support a refinement of traditional treatment goals (historically focused on reduction of A1c for T2D, weight loss for obesity, and control of blood pressure and renin angiotensin system [RAS] blockade to reduce kidney disease) to a more tailored approach targeting reduction of the major complications of chronic metabolic disease (Figure 2). Here I review the evidence for reducing the complications of cardiorenal disorders in people with T2D and obesity.

## REDUCTION IN ALL-CAUSE MORTALITY

The results of clinical trials studying lifestyle intervention in people with T2D highlight challenges with traditional approaches to improve health and reduce excess mortality. Intensive lifestyle intervention (ILI) in the Look AHEAD (Action for Health in Diabetes) trial, a combination of sustained counseling to optimize nutrition, diet, and exercise, was not associated with reduction

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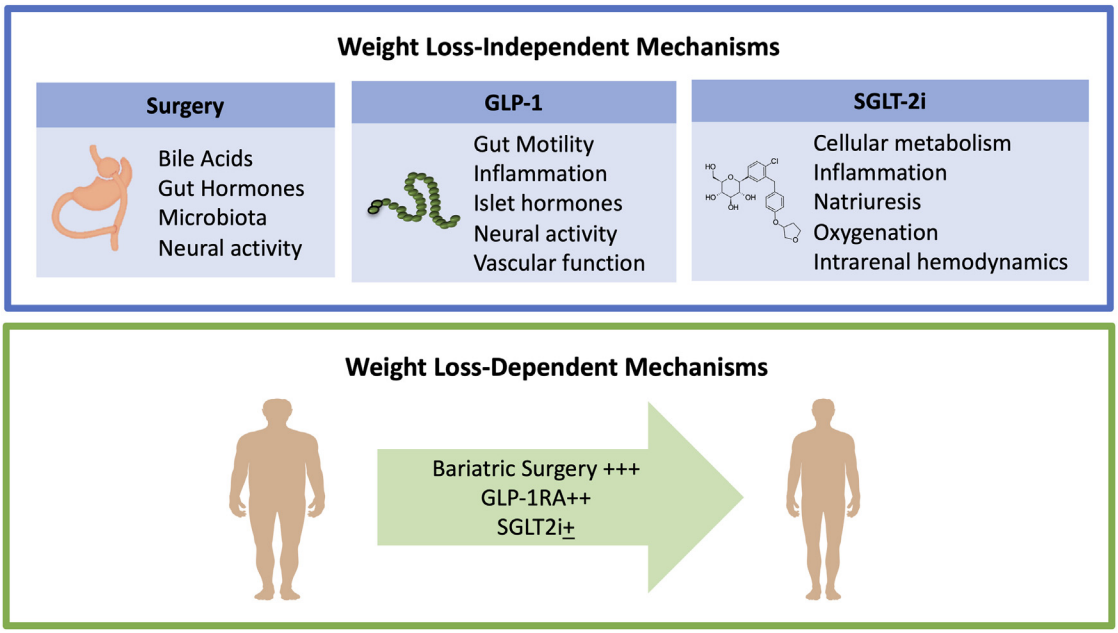


**Figure 1. Comparison of bariatric surgery, GLP-1-based medicines, and SGLT-2 for weight loss-dependent versus weight loss-independent mechanisms that contribute to reduction of diabetes- and obesity-associated complications**

in rates of ACM in individuals with overweight or obesity and T2D after 9.6 years, despite ~6% weight loss, compared to 3.5% for subjects in the control arm who received diabetes support and education.[14] Similarly, long-term follow-up of adults with prediabetes at high risk of developing T2D in the Diabetes Prevention Program over a median period of 21 years demonstrated no reductions in mortality associated with metformin or lifestyle intervention; however, event rates are lower in this population relative to rates in people with T2D.[15] However, in Look AHEAD, rates of moderate to severe disability were reduced (6% versus 6.8% per year, in the ILI versus control group, respectively) and disability-free years were increased in subjects randomized to ILI, with a 0.8- to 0.9-year delay in the onset of moderate to severe disability in the ILI cohort.[16] More prolonged follow-up of Look AHEAD trial participants did not reveal differences in mortality; however, subjects with >10% weight loss after ILI at 1 year had a 21% reduction in mortality after 16.7 years of follow-up.[17] A genetic predisposition to higher BMI did not predict the extent of weight loss or regain in Look AHEAD participants.[18]

A meta-analysis of trials comparing ACM in subjects after metabolic surgery compared with matched controls demonstrated a reduction in hazard ratio (HR) of death of 0.49 and a longer median life expectancy of 6.1 years relative to usual non-surgical care, with greater benefits observed for people

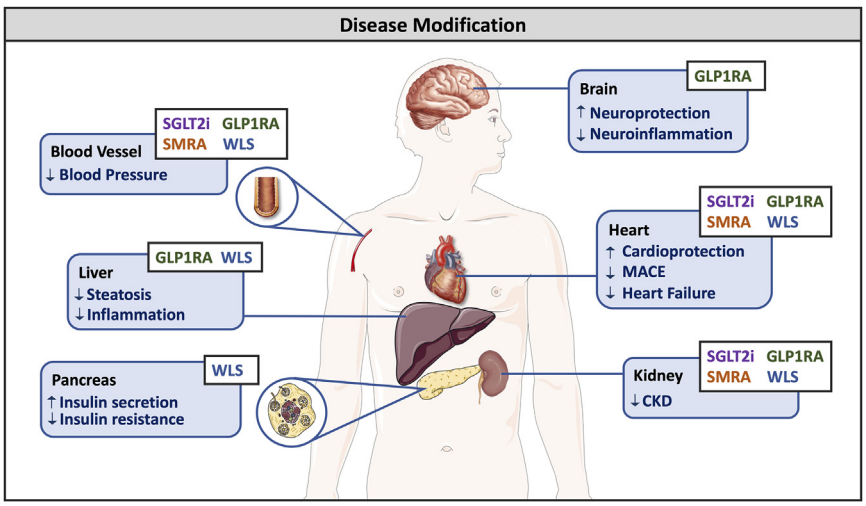


**Figure 2. Reduction of end organ complications and disease modification achieved with weight loss versus SGLT-2is and selective mineralocorticoid inhibition versus GLP-1 receptor agonists**

CKD, chronic kidney disease; SGLT2i, SGLT-2 inhibitors; GLP1RA, GLP-1 receptor agonists; SMRA, selective mineralocorticoid receptor antagonism; WLS, weight loss surgery.

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with T2D.[19] These observations translated into a number needed to treat to prevent one death over 10 years of 8.4 for adults with diabetes versus 29.8 for individuals without diabetes.[19] A reduction in ACM was detected at a threshold of 5% weight loss after 4.9 years in subjects treated with bariatric surgery, whereas 20% weight loss was required to detect a reduction in ACM in the non-surgical control group.[20] Similarly, analysis of outcomes in 6,910 individuals with T2D and a BMI >35 kg/m$^2$ undergoing bariatric surgery in Ontario (mean age 52, 71.6% female) with a median follow-up period of 4.6 years revealed a reduction in death rates relative to non-surgical controls, with an HR of 0.52, primarily driven by a 68% decrease in cardiovascular mortality.[21] The mortality benefits were most notable in subjects >55 years old with a duration of T2D of <15 years.

While the majority of subjects experience considerable benefit after metabolic surgery, 23% of individuals in the Scandinavian Obesity Surgery Registry met at least one definition of surgical treatment failure based on insufficient weight loss, associated with a higher incidence of T2D, and persistent dyslipidemia and hypertension assessed 5 years after surgery.[22] The durability of bariatric surgery benefits has been assessed in follow-up of several long-term cohorts. Among 281 subjects treated with Roux-en-Y gastric bypass (RYGB) and assessed more than 10 years later, mean weight loss from baseline was 24%, and remission rates were 54.2%, 34.1%, 52.4%, and 50% for T2D, hypertension, dyslipidemia, and obstructive sleep apnea, respectively.[23] Beyond weight loss, mechanisms underlying the metabolic benefits of bariatric surgery may include increased levels of bile acids, alteration in levels of branched-chain amino acids, changes in neural innervation or gut microbiota, and increased circulating levels of gut peptides (Figure 1).[24,25]

Studies in people with CVD or CKD demonstrate that SGLT2is frequently reduce ACM[9,26,27] in people with or without T2D with an overall HR of 0.86.[28] Similarly, the use of GLP-1RAs in people with T2D is associated with a reduction (~12%) in ACM in cardiovascular outcome trials (CVOTs)[10,29] and a 19% reduction in people with overweight or obesity.[30] Excluding people with pre-existing heart failure with reduced ejection fraction (HFrEF), the use of the selective mineralocorticoid receptor antagonist finerenone in people with T2D and CKD was also associated with a reduction in ACM.[31]

## TYPE 2 DIABETES REMISSION

Remission of T2D is defined as an HbA1c of <6.5% after at least 3 months following cessation of glucose-lowering therapies.[32] The Diabetes Remission Clinical Trial (DIRECT) enrolled subjects with T2D diagnosed within the previous 6 years, aged 20–65 years, with a BMI of 27–45 kg/m$^2$, with individuals randomized to a series of interventions including withdrawal of medicines for T2D and hypertension, total diet replacement using a low-energy diet (59% carbohydrate, 13% fat, 26% protein, and 2% fiber) for 3–5 months, stepped reintroduction of food over several weeks, and periodic sessions of structured support.[33] Remission of T2D was observed in 46% of subjects randomized to a weight management program (versus 4% in the control group) in primary care at 1 year of follow-up. After 2 years, with data reported for 86% of initial trial subjects, mean body weight loss was 7.6 versus 2.3 kg lower from baseline in the intervention versus control group, respectively; 60% of subjects in the intervention arm were not taking glucose-lowering agents, versus 16% of control subjects.[34] Weight loss was more sustained in the dietary intervention group, with 24% of subjects maintaining at least 10% weight loss at 24 months. The rates of diabetes remission were proportional to the extent of weight loss, reported in 5% of subjects with less than 5 kg weight loss, versus 64% of subjects who had maintained at least 10 kg weight loss.[34] Recovery of β cell function (first-phase insulin response to glucose) was predominantly detected in subjects reporting remission of T2D.[35] A retrospective analysis of rates of diabetes remission in 1,903 male Japanese subjects enrolled in the Panasonic health care database with new-onset T2D between 2013 and 2018 (mean baseline BMI of 26.3 kg/m$^2$) revealed that 32.5% of subjects experienced remission of T2D within 5 years of plan enrollment. For every 1 kg of weight loss over the 5-year study period, the rate of T2D remission increased by 6%.[36] Consistent with these findings, the extent of weight loss and starting HbA1c was directly related to the likelihood of T2D remission in 39,676 Japanese subjects seen in specialist diabetes clinics and followed over time.[37]

Improvement in β cell function is detectable within several weeks to months after medical or surgical weight loss and correlates with the induction and maintenance of diabetes remission.[38] Remission of T2D after metabolic surgery is more common in younger subjects with a shorter history of T2D, preserved β cell function, lower requirements for insulin, and better glucose control.[39,40] Among 5,928 people treated with RYGB or vertical sleeve gastrectomy (VSG), over an average follow-up period of 5.9 years, 71% of subjects achieved remission of T2D, with a mean time to remission of 1 year.[41] Beyond a weight loss threshold of 20%, little additional benefit is seen in rates of diabetes remission.[41] Remission of T2D achieved at 5 years (HbA1c at <6% without glucose-lowering medicines) with bariatric surgery is generally proportional to the degree of weight loss achieved[42] but may not be fully explained by the extent of weight loss alone.[24,43] A shorter duration of T2D, better glycemic control, and lower levels of ceramides (an indirect readout of insulin resistance) may contribute to weight loss-independent prediction of diabetes remission.[44] Among subjects randomized to lifestyle intervention versus RYGB or VSG and reassessed after 1 year, diabetes remission (HbA1c < 6.5%) was reported in 68% and 65% of subjects after RYGB and VSG, respectively, versus only 6% of the lifestyle control group.[45] The Alliance of Randomized Trials of Medicine versus Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D) examined rates of diabetes remission 3 years after metabolic surgery (RYGB, VSG, and gastric banding) in pooled data from 4 separate randomized controlled trials (RCTs), revealing greater remission rates after surgery (n = 195) versus non-surgical controls (n = 121) (37.5% versus 2.6%, respectively).[46] After surgery, fewer subjects required medication to control blood pressure, diabetes, or dyslipidemia.

Weight loss is generally greater following RYGB relative to VSG or laparoscopic gastric banding (LGB), and this difference is sometimes associated with higher remission rates (up to 27% higher remission in a single-center RCT) for T2D,[47] as well as greater reductions in rates of dyslipidemia, obstructive sleep apnea, and gastroesophageal reflux disease.[39,48] However, in the STAMPEDE trial, subjects with a mean duration of

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diabetes of 8.4 ± 5.2 years, 44% requiring insulin at baseline, randomized to RYGB versus VSG, exhibited similar rates of diabetes remission (29% versus 23%, respectively, p = 0.07 versus 5% in the medical therapy alone control arm) and modest differences in weight loss (−23% versus −19%) after 5 years of follow-up.[49] Nonetheless, even after controlling for weight loss, remission of T2D may be up to 4-fold higher after RYGB relative to LGB and 1.5-fold more common after sleeve gastrectomy relative to LGB.[39,50] The extent of weight loss achieved using GLP-1RA or bariatric surgery (either RYGB or VSG) is attenuated in people with T2D and overweight or obesity,[51–53] although the mechanisms accounting for differential weight loss in people with diabetes are not clearly understood. Bariatric surgery is highly effective in older subjects >65 years old; however, rates of diabetes remission and reduction in rates of hypertension, dyslipidemia, and reflux disease are lower in older subjects when assessed 3 years after surgery for RYGB or VSG.[54]

## GLP-1-BASED MEDICINES AND OUTCOMES IN PEOPLE WITH OBESITY

3 mg liraglutide once daily was the first GLP-1RA approved for the treatment of overweight or obesity in 2014.[55] The number of cardiovascular events in the phase 3 Satiety and Clinical Adiposity—Liraglutide Evidence (SCALE) program for obesity among 5,908 trial participants was too low (8 events in people randomized to liraglutide, 10 in the control group, HR 0.42 favoring liraglutide) to make conclusions about the potential safety versus benefit of liraglutide therapy in this population.[56] Although long-term follow-up of people achieving weight loss with modern GLP-1RA therapy is limited, participants in the Semaglutide Treatment Effect in People with Obesity (STEP)-5 trial sustained a mean weight loss of 15.2% after 104 weeks, with 61.8% of trial subjects achieving a mean weight loss of >10% of therapy.[57] A meta-analysis of the cardiovascular safety of the 4,582 subjects enrolled in the STEP(1–4) trials examining the actions of 2.4 mg semaglutide once weekly in people with obesity reported a decreased risk of pooled major or minor cardiovascular disorders in subjects randomized to semaglutide (HR 0.7), although the number of MACE was too small to infer conclusions.[58]

The cardiovascular safety of semaglutide was examined in 17,604 people with overweight or obesity without T2D (72% male) in the Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) trial, with a primary outcome of the time to first report of 3-point MACE. Eligibility criteria included age >45, with at least one prior MI, stroke, diagnosis of symptomatic peripheral artery disease, arterial revascularization, or amputation due to atherosclerotic vascular disease.[59] Exclusion criteria included known type 1 or type 2 diabetes or an HbA1c of >6.5%. At trial enrollment, the average BMI was 33.3 kg/m$^2$, with 28.5% of the population classified as overweight. A previous history of MI (76.3%) was the most common antecedent reported cardiovascular event, while 24.3% of participants had a previous diagnosis of heart failure.[59] Prediabetes was present in 64.5% of subjects, with a mean HbA1c in the trial population of 5.78%. Mean weight loss on semaglutide was 9.3 kg 104 weeks after randomization, and this difference was maintained more than 4 years after randomization. The SELECT trial demonstrated a 20% reduction in 3-point MACE in subjects with obesity treated with once-weekly semaglutide with a mean duration of exposure of 34.2 + 13.7 months.[30]

## CHILDHOOD AND ADOLESCENT OBESITY

Childhood obesity is associated with increased mortality and higher rates of anxiety, depression, T2D, and autoimmune and CVD. Substantial weight loss attenuates but may not fully reverse many of these co-morbidities.[60] Much less information is available on the long-term benefits and risks of weight loss medications versus bariatric surgery for children and adolescents. Analysis of outcomes in 96 individuals treated with bariatric surgery before the age of 21 (mean age 18.8) revealed sustained reductions in body weight and improvements in co-morbidities such as dyslipidemia, asthma, hypertension, sleep apnea, and reflux disease when reassessed at a mean follow-up period of 14.2 years.[61] Consistent with these findings, sustained substantial improvements in resolution of T2D, dyslipidemia, and hypertension were observed in follow-up up to 10 years of 2,504 children and adolescents with class II/III obesity who underwent VSG, with very low rates of adverse events.[62] Comparison of the outcomes of RYGB in 161 adolescents versus 396 adults 5 years after surgery revealed similar weight loss (36%); however, rates of remission of T2D (86% versus 53%) and hypertension (68% versus 41%) were greater in adolescents, relative to adults, respectively.[63] The pivotal trial for approval of 2.4 mg semaglutide once weekly in adolescents 12–18 years of age demonstrated 16.1% weight loss in subjects (134) randomized to semaglutide, versus 0.6% weight gain in 64 placebo-treated subjects.[64] Guidelines from the American Academy of Pediatrics have endorsed a comprehensive approach to the diagnosis, evaluation, and treatment of obesity in children and adolescents.[65] These guidelines support the use of bariatric surgery, as well as weight loss medicines, including GLP-1RAs such as semaglutide and tirzepatide, for the management of obesity, while recognizing gaps in our understanding of the durability and long-term safety of these interventions.

## CARDIOVASCULAR DISEASE, WEIGHT LOSS, AND THERAPEUTIC OPTIONS

Interrogation of health records for adults receiving primary care at Geisinger Health System revealed that subjects with sustained weight loss >5% over 2 years, reflecting the impact of diet and exercise but not surgery, exhibited lower rates of new-onset T2D, hypertension, and dyslipidemia, relative to control subjects without weight loss or with weight regain, with the magnitude of the benefit proportional to the degree of weight loss.[66] Individuals enrolled in the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION)–Cambridge trial with new-onset T2D experiencing >5% weight loss (n = 241/725) within the first year of diabetes diagnosis exhibited improved metabolic control and a reduced likelihood of developing CVD, defined as a broad range of cardiovascular events and cardiovascular death (HR 0.52) assessed after 10 years of follow-up.[67]

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### Weight loss

Two years of (25%) calorie restriction in male and female subjects (BMI range 22–27.9 kg/m$^2$, age 21–50) produced a mean weight loss of 7.5 kg and a reduction of cardiometabolic risk factors including blood pressure, LDL cholesterol, and C-reactive protein.[68] Participants in the Look AHEAD trial with at least 10% weight loss in the first year had a 21% lower risk of the primary outcome, a composite of death from cardiovascular causes, non-fatal acute MI, non-fatal stroke, or admission to hospital for angina.[69] Similarly, rates of the secondary outcome in this subgroup, which included the primary composite indicators plus coronary artery bypass grafting, carotid endarterectomy, percutaneous coronary intervention, hospitalization for congestive heart failure, peripheral vascular disease, or total mortality, were reduced by 24%. Although rates of heart failure alone were not different in the ILI versus control groups in Look AHEAD, individuals rated as moderately or highly fit exhibited a 40% and 77% lower rate of heart failure with preserved ejection fraction (HFpEF), respectively, over a follow-up period of 12.4 years.[70] In studies of people with T2D treated with glucose-lowering agents in CVOTs, a decrease in bodyweight of 1 kg was associated with a 9% (3.9%–8.0%) relative decrease in the risk of heart failure.[71]

### Bariatric surgery

A retrospective single-center cohort analysis of people with T2D (HbA1c > 6.5%) and obesity (BMI > 30 kg/m$^2$) who underwent metabolic surgery revealed a lower cumulative incidence rate of MACE (30.8% versus 47.7%) after 8 years of follow-up in the surgical versus non-surgical control group.[72] Consistent with these findings, ACM at 8 years was lower after surgery versus non-surgical controls (10% versus 17.8%, respectively). Retrospective propensity-matched analyses of individuals treated with bariatric surgery versus non-surgical controls followed for 4.9 years demonstrated weight loss-independent benefits of bariatric surgery on rates of MACE, with weight loss thresholds for reduction in MACE of ~10% in the surgical versus 20% in the control cohort.[20] In the same cohort, ACM was reduced after 5% weight loss in the surgical group, and after 20% weight loss in the non-surgical control group.[20] In a propensity-matched retrospective analysis of hospitalized subjects in the US from 2007 to 2014, mortality rates were lower in individuals with a history of bariatric surgery after MI (1.85% versus 3.03%) and stroke (1.43% versus 2.74%), and duration of hospital stay was shorter, relative to non-surgical controls, otherwise matched for metabolic parameters, including BMI.[73] Substantial weight loss, achieved predominantly in subjects with obesity without clinically apparent heart failure undergoing bariatric surgery, has been associated with improvement in a range of hemodynamic parameters, including reductions in heart rate, mean arterial blood pressure, resting oxygen consumption, pulmonary capillary wedge pressure, and pulmonary artery pressure.[74]

## SGLT2is AND REDUCTION OF CVD

SGLT2is produce weight loss of ~2–3 kg in people with or without T2D, although the contribution of weight loss to achieving cardiorenal benefit remains uncertain.[9,75] The EMPA-REG outcome study evaluated the safety of empagliflozin or placebo in 7,020 people with T2D observed for a median follow-up time of 3.1 years. Empagliflozin reduced the rates of MACE, cardiovascular death, ACM, and hospitalization for heart failure.[26] Similar benefits, albeit with some heterogeneity across trials likely reflecting trial design and study size and populations, were detected in evaluation of the cardiovascular safety of dapagliflozin,[76] canagliflozin,[77] and to a lesser extent, ertugliflozin.[78] Notably, reduction in hospitalization for heart failure represents a consistent feature observed across all of the CVOTs assessing SGLT2i safety in people with T2D.[9]

Empagliflozin reduced the time to hospitalization for heart failure or cardiovascular death across a wide range of BMIs in subjects with HFrEF in EMPEROR-Reduced. This benefit was dissociated from weight loss, as the presence of more than 5% weight loss was associated with an increased risk of ACM.[79] Comparable benefits were observed in 4,744 subjects with (42%) or without T2D, with class II–IV HFrEF, randomized to dapagliflozin (10 mg daily) versus placebo, and followed for a median duration of 18.2 months.[80] Similarly, both empagliflozin and dapagliflozin, administered at doses of 10 mg once daily, reduced the rates of hospitalization and/or cardiovascular death (HR 0.79 and 0.82 for empagliflozin and dapagliflozin, respectively) in subjects with or without T2D with HFpEF (>40%).[81,82] Heart failure is more common in people with obesity; however, the reduction in hospitalization for heart failure events observed with SGLT2is is seen across a wide range of BMIs,[83] with dapagliflozin achieving great symptomatic relief in people with higher BMIs in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial.

## GLP-1R AGONISTS AND CVD

Long-acting GLP-1RAs such as liraglutide, albiglutide, semaglutide, dulaglutide, and efpeglenatide reduce the incidence of the MACE composite outcome in people with T2D studied in CVOTs.[11,29,84–86] Some heterogeneity is evident across trials, as reduction of rates of either stroke, MI, or cardiovascular death has been observed in some but not all trials.[10] While the majority of subjects enrolled in the GLP-1RA CVOTs have established CVD, 31.5% of participants in the REWIND trial had a history of established CVD at the time of trial enrollment, with reduction of MACE in this population suggesting an opportunity for early use of GLP-1RAs in primary prevention for individuals at risk for CVD.[85] Similar findings, namely a reduction in rates of MACE, were reported in post-hoc analysis of the PIONEER-6 and SUSTAIN-6 trials implicating a cardiovascular benefit for semaglutide in people with T2D across a broad spectrum of cardiovascular risk.[87] Whether ongoing treatment with GLP-1RAs reduces mortality in people actively experiencing MI or stroke is uncertain.

Analysis of pooled data from the GLP-1RA CVOTs reveals a reduction in hospitalization for heart failure of ~11%.[10] The longer time period, generally at least 1 year, required for detection of reduced rates of MACE in the GLP-1RA CVOTs in T2D is consistent with a reduction in atherosclerosis, rather than a more acute hemodynamic effect as may be evident in the SGLT2i trials.[9,88] Dedicated trials are underway examining the safety and benefit of GLP-1RAs in people with T2D and peripheral arterial disease (NCT04560998). Compared with GLP-1RAs,

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use of SGLT-2is from 2013 to 2020 was not associated with an increased risk of amputations in new users within the Veterans Health Care Administration database.[89] Two trials are examining the effects of 2.4 mg semaglutide once weekly in people with obesity (BMI, 30 m/kg$^2$) with or without T2D and HFpEF, over 52 weeks, with randomization stratified by BMI.[90] The primary outcomes in the STEP HFpEF trial include a change in a composite heart failure outcome score, as well as weight loss. Analysis of 529 subjects with HFpEF, median body weight and BMI of 105.1 kg and 37.0, respectively, randomized to treatment with 2.4 mg semaglutide once weekly versus placebo demonstrated a significant reduction in the Kansas City Cardiomyopathy Questionnaire (KCCQ-CSS) clinical summary score in semaglutide-treated subjects after 1 year of treatment, associated with a 13.3% reduction in body weight.[91] Improvements in secondary outcomes included favorable changes in the 6-min walk distance and a reduction in a hierarchical composite endpoint that included death, heart failure events, the KCCQ, the 6-min walk test, and plasma levels of C-reactive protein.[91] The benefits achieved with semaglutide therapy were detected across a range of BMIs, independent of the starting ejection fraction,[92] and directly proportionate to the extent of weight loss achieved.[93]

Consistent with these findings, the cardiorenal benefits of liraglutide and semaglutide were also detected across a range of BMIs in people with T2D.[94] Importantly, in some GLP-1RA CVOTs, such as the HARMONY Outcomes trial studying the safety of albiglutide, the incidence of MACE was reduced by 22% over a median follow-up period of 1.6 years, with an HR of 0.75 for MI, yet the mean weight loss at 16 months was only 0.83 kg in subjects randomized to albiglutide.[11] Hence, data from preclinical and clinical studies indicate that the cardioprotective actions of GLP-1RAs are not strictly dependent on weight loss or the presence of T2D.[88,95] Importantly, analysis of subgroups from the AMPLITUDE-O CVOT examining the cardiovascular safety of the GLP-1RA efpeglenatide revealed that the cardioprotective benefits of efpeglenatide were detected with or without concomitant use of SGLT2is.[96] Consistent with these findings, analysis of real-world data from primary care databases demonstrated a lower HR for incident heart disease in people with T2D treated with combined use of SGLT2is and GLP-1RAs, relative to reduction in risk achieved with either agent alone.[97] Although GLP-1RAs and, to a lesser extent, SGLT2is reduce body weight in CVOTs, the reduction in cardiovascular events seen with both these agents was independent of changes in body weight.[75]

## THIAZOLIDINEDIONES AND SELECTIVE MINERALOCORTICOID ANTAGONISTS

While utilization of thiazolidinediones for the treatment of T2D has not accelerated due to complications associated with fluid retention, bone and eye disease, and heart failure, analysis of outcomes in 3,876 subjects with a recent ischemic stroke or transient ischemic attack and insulin resistance revealed reduced rates of stroke or MI after 4.8 years of follow-up in individuals randomized to 45 mg pioglitazone once daily.[13] Nevertheless, pioglitazone therapy was associated with weight gain, edema, and clinically significant bone fractures. The effect of pioglitazone on people with T2D and preexisting macrovascular disease was studied in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study.[98] Subjects randomized to pioglitazone exhibited a reduction in the rate of the primary composite outcome, ACM, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and above-ankle amputation.

The non-steroidal mineralocorticoid antagonist finerenone reduced the time to the cardiovascular composite outcome of cardiovascular death, MI, stroke, or hospitalization for heart failure in people with T2D and DKD, eGFR $\geq$25 to <75 mL per min per 1.73 m$^2$, concomitantly treated with RAS blockade, in the FIDELIO-DKD trial.[99] The beneficial effects of finerenone were evident in subjects with or without a prior history of CVD, and finerenone also reduced the rate of new-onset heart failure.[100] Similar benefits in reduction of 4-point MACE, driven primarily by reduced rates of hospitalization for heart failure (HR 0.71), were seen in a population of subjects with an expanded entry range of eGFR 25 to 90 mL per minute per 1.73 m$^2$.[101]

## KIDNEY FUNCTION AND DISEASE

Rates of eGFR decline are lower after bariatric surgery in people with obesity or T2D, even in subjects with reduced eGFR < 30 mL/min/1.73 m$^2$; however, separating out the contributions of weight loss from potential weight loss-independent mechanisms is challenging.[102] Rates of new non-fatal renal events (dialysis or transplantation) were 42% lower in people with T2D and severe obesity after bariatric surgery (median follow-up period of 4.6 years).[21]

SGLT-2is reduce the rates of subsequent renal events (rates of eGFR decline or renal-related death) in people with CKD, in the presence or absence of T2D.[103] Importantly, use of SGLT-2is reduced the rates of eGFR decline and the extent of microalbumin excretion in people with T2D with normal eGFR and ACR, providing cardiorenal protection across a broad range of baseline kidney function.[104,105] Subjects with CKD randomized to empagliflozin exhibited a reduction in CKD progression or cardiovascular death over a mean follow-up period of 2 years (HR 0.72), without between-group differences in ACM, or a composite outcome of hospitalization for heart failure or death from cardiovascular causes.[103] Similarly, treatment of patients with CKD, defined as an eGFR of 25–75 mL/min/1.73m$^2$ and a urinary albumin-to-creatinine ratio of 200–5,000, with dapagliflozin over a median period of 2.4 years significantly reduced the primary composite outcome of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes, with similar findings evident in people with or without T2D.[106]

FIDELIO-DKD randomized 5,734 individuals with T2D and stage 2–4 CKD to receive finerenone, a non-selective mineralocorticoid antagonist, or placebo, on top of standard of care (renin-angiotensin system blockade) over a median follow-up period of 2.6 years. Finerenone reduced the rate of the composite endpoint of kidney failure, a decrease of at least 40% in eGFR, or renal-related death (HR 0.82).[12] In a separate study analyzing 7,437 subjects with a broader range of eGFR (FIGARO-DKD), finerenone also reduced the rate of the cardiovascular composite endpoint (HR 0.87) consisting of cardiovascular death, non-fatal

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MI, nonfatal stroke, or hospitalization for heart failure, over a mean follow-up period of 3.4 years,[101] primarily driven by reduced rates of hospitalization for heart failure (HR 0.71).[101] Finerenone also improved all heart failure-related outcomes, including death, in the FIGARO-DKD trial.[100] In contrast, there was no difference in rates of the secondary outcome, a composite of renal failure, 40% decline in eGFR, and renal-related death. Of the subjects enrolled in FIDELIO-DKD, 394 (6.9%) were receiving GLP-1RAs at baseline, and there was no difference in the relative improvement of CV and renal outcomes without or without GLP-1RA therapy.[107] Similarly, 6.7% of subjects in FIGARO-CKD and FIDELIO-DKD received an SGLT2i at baseline and 1,113 (8.5%) initiated one during the trial; however, the cardiorenal benefits of finerenone were maintained in the presence or absence of concomitant SGLT-2 use.[107]

GLP-1RAs reduce albumin excretion in clinical trials of people with T2D; however, there is limited definitive evidence supporting a decrease in rates of end-stage renal failure, need for dialysis, or transplantation.[9,10] The rate of decline of eGFR has been reported to be reduced in people with T2D in CVOTs treated with either dulaglutide or semaglutide.[108,109] The renal effects of 1 mg semaglutide once weekly were examined in the FLOW trial, which enrolled 3,534 people with T2D at risk for DKD (50 $\geq$ eGFR $\leq$ 75 mL/min/1.73 $m^2$, 300 > urine albumin-to-creatinine ratio [UACR] < 5,000 mg/g or 25 $\geq$ eGFR < 50 mL/min/1.73 $m^2$ and 100 > UACR < 5,000 mg/g).[110] Mean age at enrollment was 66.6 years, eGFR of 47 mL/min/1.73 $m^2$, and duration of T2D 17.4 years. The primary composite outcome included persistent eGFR decline $\geq$50%, end-stage renal disease, death from kidney disease, or death from CVD. The FLOW trial was stopped early on October 10, 2023, for efficacy, with trial results to be released in 2024.

## METABOLIC LIVER DISEASE

Following bariatric surgery for 180 people living with severe obesity (66% female, 71% with T2D) and biopsy-proven nonalcoholic steatohepatitis (NASH), resolution of NASH was detected within 1 year in 84% of biopsies, with resolution of fibrosis generally not evident by 1 year of follow-up. Resolution of NASH without worsening fibrosis was observed in 84% of liver histology assessments 5 years after surgery, with resolution of fibrosis detected in 56% of subjects.[111] A single-center randomized trial compared the effectiveness of VSG versus RYGB in 100 subjects, 65% female, mean BMI 42 kg/$m^2$. At 1 year of follow-up, liver fat decreased significantly in both groups, and the enhanced liver fibrosis score was stable in 77% of subjects but deteriorated in 18% of trial participants, with no differences between VSG versus RYGB groups.[112] Consistent with these findings, subjects with advanced NASH were evaluated with a liver biopsy at 6 ± 3 years after surgery, revealing substantial histological improvement in 29% of people, resolution of NASH without progression of fibrosis in 74%, yet persistence of advanced fibrosis in 47% of study subjects.[113] The degree of weight loss correlated with the extent of histological improvement.

Analysis of outcomes in 1,158 individuals with obesity and biopsy-proven NASH and fibrosis without cirrhosis demonstrated that rates of adverse liver outcomes (a composite endpoint encompassing complications of liver disease, cancer, transplantation, and death) after 10 years were lower (2.3% versus 9.6%) in the surgical (n = 650) versus non-surgical (n = 508) control group, respectively.[114] Similarly, rates of MACE at 10 years of follow-up were also lower (8.5% versus 15.7%) in the bariatric surgery versus control group, respectively.

A multi-center trial compared liver outcomes in 288 participants with biopsy-proven NASH randomized to an ILI (n = 96 [33%]), RYGB (n = 96 [33%]), or VSG (n = 96 [33%]). Histological resolution of NASH without worsening of fibrosis was detected in the intent-to-treat analysis after 1 year in 16% of the lifestyle group, versus 56% and 57% for RYGB and VSG groups, respectively.[45] Notably, improvement in fibrosis without worsening of NASH was detected in the cohorts randomized to surgery, but not in the group treated with lifestyle intervention. However, the majority of study subjects had minimal to moderate (stages F1 and F2) fibrosis. The extent of NASH resolution was fairly proportional to the degree of weight loss up to 20%; however, weight loss greater than 20% did not confer additional benefits on liver outcomes; the probability of achieving the primary endpoint was greater in individuals without T2D.[45]

SGLT2is reduce liver fat and biomarkers of liver disease in people with T2D[115]; however, whether these agents reduce NASH and fibrosis has not been examined in large prospective studies. A randomized trial examined the efficacy of 1.8 mg of the GLP-1RA liraglutide daily (n = 26) versus placebo (n = 26) over 48 weeks, in subjects ages 18–70, mean BMI 25 kg/$m^2$, with or without T2D, with biopsies done before and after treatment.[116] Liraglutide-treated subjects experienced a 5.5% reduction in body weight. Resolution of NASH without worsening of fibrosis was detected in 39% versus 9% of individuals in the liraglutide versus placebo cohorts, respectively. The efficacy of a range of doses of once-daily semaglutide versus placebo was assessed in 320 randomized subjects with biopsy-confirmed NASH and stages F1–F3 fibrosis over 72 weeks. A greater proportion of semaglutide-treated subjects achieved resolution of NASH without worsening of fibrosis, and mean weight loss reported was 13% in the group treated with 0.4 mg semaglutide once daily.[117] However, the relative improvement in fibrosis was not different in the semaglutide- versus placebo-treated groups. 2.4 mg semaglutide once weekly is currently being evaluated in 1,200 subjects with NASH enrolled in the ESSENCE trial (NCT04822181).

## COGNITIVE FUNCTION, NEURODEGENERATIVE DISORDERS, AND DEMENTIA

Weight gain and obesity have been linked to increased risk for cognitive impairment in sequential assessments of 14,691 individuals (mean age 53 at baseline) enrolled in the Singapore Chinese Health Study.[118] Consistent with these findings, T2D and, to a lesser extent, obesity were identified as risk factors for development of dementia following analysis of 9,017 subjects >65 years old in the Swedish Twin registry study.[119] Nevertheless, identification of healthy diets that meaningfully reduce the rates of cognitive impairment has been challenging.[120] Assessments of cognitive function using the NIH cognitive toolbox were carried out in 1,002 participants in the LOOK AHEAD trials ~10.9 years after randomization to ILI versus conventional management, with no overall differences in cognitive function

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detected between groups.[121] A single blinded trial of twice-daily exenatide in people with Parkinson's disease (n = 20 on exenatide, versus 24 in the control group) demonstrated improvements in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) across both motor and cognitive measures after 12 months.[122] An RCT of subjects with Parkinson's disease with the GLP-1RA exenatide once weekly (n = 32) for 48 weeks followed by a 12-week washout period demonstrated improvements in Parkinson's disease activity scale at 60 weeks (off medication), whereas control subjects (n = 30) exhibited a deterioration in scores.[123] A larger, longer trial of exenatide once weekly in people with Parkinson's disease is currently underway, with an expected duration of 96 weeks.[124]

Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution Test (DSST) in the REWIND cardiovascular outcomes trial assessing the safety of once-weekly dulaglutide in 8,828 evaluable participants with T2D over a median follow-up period of 5.4 years. The extent of impairment of cognitive function was reduced in subjects randomized to dulaglutide (HR 0.86).[125] Interrogation of pooled data from three randomized GLP-1RA CVOTs (9,340 subjects in the LEADER trial, 3,297 in SUSTAIN-6, and 3,183 in PIONEER 6[9]) and a nationwide Danish registry of people with T2D demonstrated lower rates of dementia in the clinical trial data (HR 0.47) and in the registry cohort (HR 0.89 for each 1-year increase in GLP-1RA exposure).[126]

Whether bariatric surgery reduces the risk of subsequent cognitive impairment is unclear. Analysis of the Utah Bariatric Surgery Registry using electronic medical record data identified 17,026 individuals treated with surgery and 34,052 non-surgical controls, followed for a median period of 10.5 years, and revealed an increased risk of dementia in the surgical cohort (NR 1.3).[127] On the other hand, longitudinal assessment of cognitive function in 50 individuals with severe obesity (mean preoperative BMI 46.6) enrolled in the Longitudinal Assessment of Bariatric Surgery cohort revealed sustained improvements in executive functions and short-term memory after 3 years of follow-up.[128] In a larger, yet shorter study, 146 individuals with a BMI > 35 enrolled in the BARICO (Bariatric Surgery Rijnstate and Radboudumc Neuroimaging and Cognition in Obesity) study were studied before and 6 months after surgery. Subjects evaluated after surgery exhibited lower biomarkers of inflammation, reduced depressive symptoms, and higher levels of physical activity.[129] Cognitive function, assessed using standardized neuropsychological testing, improved (at least a 20% change from baseline) in 43.8% of subjects, and was associated with lower levels of leptin and CRP and generalized improvements in overall health, ranging from reduced use of medication for T2D and hypertension to greater physical activity, and reduced rates of depression.[129]

## CANCER

While CVD has historically accounted for substantial morbidity and mortality in people with T2D and obesity, cancer has emerged as a dominant contributor to metabolic disease-associated mortality.[130,131] Longitudinal analysis of 2,645,885 individuals aged $\geq$40 years in Catalonia, Spain, for $\sim$9 years revealed that the duration, extent, and age of onset of obesity were associated with an increased risk of 12 cancer types.[132] Rates of cancer were 16% lower in 5,145 adults with overweight or obesity and T2D randomized to ILI with a median follow-up of 11 years in LOOK-AHEAD, yet these differences were not significant, due to the low event rates and the size of the study population.[133] In the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study, cancer was the leading cause of death over 21 years of follow-up; however, subjects initially randomized to the metformin or ILI arms did not exhibit reductions in cancer-specific, cardiovascular, or ACM, despite lower rates of incident T2D.[15]

Rates of 13 different obesity-associated cancers[134] were lower in 5,053 adults with a BMI > 35 who underwent bariatric surgery (RYGB and VSG) between 2004 and 2017, relative to rates in non-surgical controls (n = 25,265), with a median follow-up of 6.1 years (2.9% versus 4.9%), respectively.[135] Cancer-related mortality was also lower (0.8% versus 1.4%) in the surgical versus the non-surgical cohort, respectively. Although long-term data from randomized studies are limited, there is little evidence linking use of SGLT2is or GLP-1RAs in people with T2D to an imbalance of cancer. The use of GLP-1RAs for the treatment of T2D reduces incidence rates of prostate, lung, and colon cancer; however, reports of new thyroid cancers are increased in some,[136] but not all,[137] studies. Use of modern GLP-1RAs in people with obesity is not yet associated with sufficient real-world exposure to inform cancer risk; however, sustained weight loss might be expected to reduce the incidence of obesity-associated cancers.

## REPRODUCTIVE OUTCOMES AND PREGNANCY

Complete remission of polycystic ovary syndrome (PCOS), defined as resumption of normal menses for 6 consecutive cycles and/or achievement of pregnancy, has been reported for women electing treatment with bariatric surgery, relative to improvements achieved in control subjects treated with metformin alone.[138] The final post-intervention BMI was the primary determinant of achieving remission for both study arms. A retrospective analysis compared perinatal outcomes in 1,591 pregnancies after bariatric surgery from January 2012 through December 2018 with outcomes in 7,955 non-surgical controls.[139] Surgery was associated with reduced rates of preeclampsia (HR 0.72), gestational diabetes or impaired fasting glucose (HR 0.73), and large for gestational age babies (HR 0.56) and an increased risk of small for gestational age babies (HR 1.51).

The use of GLP-1RAs in women with obesity to optimize pregnancy outcomes has not been systematically examined. 3 mg liraglutide once daily reduces body weight and circulating androgen levels in women with PCOS[140]; however, whether GLP-1RAs produce improvements in clinically meaningful outcomes in women with infertility remains uncertain. A small study of 28 women with obesity, PCOS, and infertility randomized to metformin with or without 3 mg liraglutide once daily for 12 weeks prior to ovarian stimulation and/or embryo transfer demonstrated that combination therapy was associated with higher rates of fertilization and pregnancy.[141] GLP-1RAs are not indicated for use in pregnancy; hence, careful monitoring is required in women with PCOS who may be treated with GLP-1RAs.

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## BODY COMPOSITION AND MUSCULOSKELETAL OUTCOMES

Multiple studies reveal bone loss in people after bariatric surgery, after both VSG and RYGB, despite supplementation with calcium and vitamin D,[142] with the extent of bone loss and fracture rates higher after RYGB than VSG.[143–145] In a randomized prospective study of people with T2D and obesity assessed 1 year after surgery, bone density declined at multiple sites (femoral neck, total hip, and lumbar spine) after both RYGB (n = 54, 63% female, 50% postmenopausal) and VSG (n = 55, 80% female, 46% postmenopausal)[145]; the decline in bone density and increase in circulating levels of markers of bone turnover are greater after RYGB and not proportional to differences in weight loss. Retrospective analysis of fractures following bariatric surgery after at least 5 years of follow-up (surgery eligibility defined as BMI 40 or greater, more than 100 lb. overweight, or BMI of 35 or greater and at least 1 or more obesity-related comorbidities) revealed an overall reduction in relative fracture risk at multiple sites in both men and women.[146] Fewer fractures were reported in the cohort undergoing VSG relative to RYGB and non-operated surgery-eligible matched control subjects (16,371 subjects in each observational cohort). A meta-analysis of available studies showed higher rates of fracture for both RYGB and VSG, with relatively greater fracture rates (2-fold increase in wrist and hip fractures) seen after RYGB.[147] As is the case with many interventions that produce weight loss, lean mass is also reduced following bariatric surgery, but the relative proportion of lean mass post-surgery is often increased due to greater loss of fat mass.[148]

Treatment with GLP-1RAs and SGLT2is is associated with a generalized reduction in adipose tissue, including visceral fat mass,[149] and to a lesser extent, depending on the extent of weight loss,[150] a reduction in lean mass in people with T2D or obesity.[75,151,152] It is unclear if the reduction in lean mass is associated with clinically meaningful changes in muscle strength in some populations. Whether combining regimens incorporating aerobic exercise and resistance training together with GLP-1RA therapy might mitigate the extent of loss of fat-free mass is not yet clear.[153] Compared to subjects with weight loss secondary to non-pharmaceutical weight loss intervention alone treated with 3 mg liraglutide once weekly for 16 weeks (12.2 versus 9.7 kg weight loss, liraglutide versus control), no additional differences were detected in loss of fat-free mass (assessed by dual-energy X-ray absorptiometry) in either cohort.[153] Treatment of subjects with T2D, mean BMI 38.8, with semaglutide (0.5–1 mg once weekly) for 26 weeks produced >5% weight loss (mean 9.9 kg) in most trial participants, a modest reduction in muscle mass, but no change in grip strength.[154] Similarly, physical functioning, as assessed by SF-36 and IWQOL-Lite-CT instruments, improved in people with obesity and semaglutide-induced weight loss in the STEP-1 trial, despite modest reductions in lean body mass; however, the relative proportion of lean body mass was increased after semaglutide therapy.[155]

GLP-1 acts on calcitonin-producing thyroid C cells to indirectly modulate bone turnover in rats and mice, but not in humans.[156,157] Despite warnings in prescribing information about the risk of medullary thyroid cancer, an imbalance of MTC with GLP-1RAs has not been described in RCTs or real-world data, and a registry is ongoing.[158] There is little evidence from clinical trial or real-world data for changes in bone density or fracture rates after treatment with GLP-1RAs,[159] although limited long-term data are available.[160] Similarly, fracture rates (mean duration of follow-up <1 year) were similar and not increased in people with T2D treated with either SGLT2i, a DPP-4 inhibitor, or a GLP-1RA in a propensity matched analysis of subjects starting a new glucose-lowering agent enrolled in a Medicare database.[161]

## MISCELLANEOUS OUTCOMES

Among subjects positive for SARS-CoV-2 infection studied up to March 1, 2021, individuals with a history of metabolic surgery between January 1, 2004, and December 31, 2017, exhibited lower rates of hospitalization and reduced severity of COVID-19 infection (encompassing intensive care unit admission, need for supplemental oxygen, and death), compared to non-surgical matched controls.[162] The efficacy of the SGLT2i dapagliflozin was examined in an RCT in 1,250 people with acute SARS-CoV-2 infection requiring hospitalization and a background history of cardiometabolic disease. 10 mg dapagliflozin once daily for 30 days did not improve outcomes of organ dysfunction or death; however, it was well tolerated, with no imbalance of adverse events.[163] Post hoc analysis of the DECLARE-TIM58 cardiovascular outcomes trial demonstrated that randomization to dapagliflozin was associated with reduced rates of hospitalization for any cause, including events not directly attributed to cardiac, kidney, or metabolic causes.[164]

The extent of weight loss has been correlated with proportional improvement and reduction of intracranial pressures in women with obesity and idiopathic intracranial hypertension (IIH), with 24% weight loss achieving normalization of pressures.[165] Interestingly, an RCT evaluating the effects of exenatide in adult women with obesity and IIH demonstrated a meaningful reduction in intracranial pressures after 12 weeks of treatment, without significant changes in body weight.[166] The severity of sleep apnea is reduced in people with T2D treated with liraglutide in combination with continuous positive airway pressure (CPAP) for 3 months,[167] as well as in people with obesity not using CPAP who were treated with 3 mg liraglutide daily for 32 weeks.[168] SGLT2is may reduce the rates of a new diagnosis of sleep apnea in people with T2D; however, the small number of events in these analyses precludes definitive conclusions.

## SAFETY OF INTERVENTIONS

Bariatric surgery may be associated with postoperative complications, including stricture and infection, dumping syndrome and hypoglycemia, gastroesophageal reflux, vitamin deficiencies, metabolic bone disease and fractures, and less commonly, increased rates of alcohol dependence.[169] SGLT-2is have been associated with urogenital infections, euglycemic ketoacidosis, and hypovolemia, whereas selective mineralocorticoid receptor antagonists may cause hyperkalemia.[170] GLP-1RAs cause gastrointestinal side effects and an increased risk of gall stones, and rarely, dehydration may predispose individuals to risk of acute kidney injury.[171] An imbalance of pancreatitis or pancreatic cancer has not been detected in adjudicated

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clinical trials or in real-world registry data with GLP-1RAs. A registry for incident medullary thyroid cancer was established in 2010, based on a theoretical risk from animal data, and continues to accrue cases.[158]

## CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS: TOWARD PERSONALIZED MEDICINE

The preponderance of data examining renal and cardiovascular outcomes stems from trials in people with T2D. Remarkably, the precise mechanisms linking SGLT-2 inhibition or GLP-1R agonism continue to be debated (Figures 1 and 2)[9] and are challenging to elucidate in human studies. Some of the striking metabolic improvements associated with bariatric surgery in people with T2D appear rapidly prior to the development of weight loss,[172] whereas over several months, the improvements in insulin sensitivity, β cell function, and reduction of glycemia are mimicked by adherence to a low-calorie diet to achieve a similar degree of weight loss (Figure 1).[173] A single-center study of MACE in individuals followed for ∼10.2 years after RYGB or VSG revealed a correlation between the extent of weight loss achieved and the reduction in MACE.[174] The relative importance of weight loss for other long-term benefits of metabolic surgery, including reductions in the rates of cancer in people with T2D and/or obesity, is less clear (Figure 1).[175] For many individuals, the long-term safety and outcome data associated with bariatric surgery make this a compelling choice.

Recommendations that distinguish between preferential use of selective mineralocorticoid antagonists versus SGLT2is versus GLP-1RAs or bariatric surgery are limited by the lack of evidence from outcome trials directly comparing these interventions. SGLT2is and SMRAs may be preferred for HFrEF and prevention of CKD, whereas GLP-1RAs may preferentially reduce rates of stroke, attenuate the progression of non-alcoholic fatty liver disease, and provide greater weight loss, relative to other medical therapies. Bariatric surgery provides a one-and-done definitive option for many individuals living with obesity, with or without poorly control T2D, and reduces rates of many of the chronic complications of T2D and obesity, yet is not as easily scalable on a population-wide basis. With a slew of newer GLP-1-based medicines under development that are likely to enable 20%+ weight loss, the opportunity to compare these agents, assessing long-term outcomes achieved with bariatric surgery versus GLP-1-based medicines in a prospective randomized trial, may be on the horizon.

The majority of the people with T2D studied in CVOTs examining the safety of GLP-1RAs, selective mineralocorticoid antagonists such as finerenone, or SGLT2is to date had a BMI >30.[9,10,12] However, the cardioprotective benefits of these agents are not tightly correlated with the extent of weight loss in people with T2D or obesity (Figure 1).[9,11,30] Furthermore, the cardiovascular benefits of SGLT2is and GLP-1RAs are preserved across a range of BMIs, ages, sexes, baseline HbA1c, eGFR, and the presence or absence of pre-existing renal or CVD.[176] With respect to understanding determinants of successful weight loss with GLP-1RAs, baseline characteristics did not predict achievement of weight loss thresholds with liraglutide after 56 weeks in the SCALE-Teens trial.[177] Similarly, the time to event analysis in the SELECT trial suggests a weight loss-independent benefit of semaglutide on the reduction of the primary outcome in people with obesity and CVD.[30] On the other hand, the benefits of semaglutide in the STEP-HFpEF trial seem directly proportional to the extent of weight loss.[91]

Current treatment approaches are based on clinical phenotyping, together with data from clinical trials supporting an evidence-based approach to selection of therapeutic agents. Although considerable effort has been expended to identify biomarkers or genetic variation indicative of differential response to therapeutic interventions, to date, these efforts have not yet yielded actionable results with clinically meaningful effect sizes. Common genetic variation in the gene encoding SGLT-2 (SLC5A2) has not yet been shown to influence the clinical responses to SGLT-2is.[178] Low-frequency genetic variation within the GLP1R and ARRB1 affecting 4% of the population identified a 30% greater reduction in HbA1c over 6 months, without impacting the extent of weight loss.[179] Furthermore, even less is known about genetic variation linked to preferential cardiorenal outcomes with the newer agents discussed herein. More data are needed to inform our understanding of whether these new interventions modify the risk of osteoporosis, frailty, and aging-related disorders. Furthermore, these agents have not been as extensively studied in outcome studies in populations with different ethnic backgrounds, limiting the generalizability of conclusions.

Finally, a range of new GLP-1-based medicines, ranging from oral small molecules to combination therapies to unimolecular multi-agonists, will require scrutiny to ascertain their safety and appropriate place in an expanding therapeutic armamentarium. The impact of the GIPR-GLP-1R co-agonist on reduction of HbA1c and body weight is unprecedented, and one anticipates that tirzepatide will exhibit a safety profile equal to or greater than that exhibited by unimolecular GLP-1RAs in ongoing safety trials. Small-molecule once-daily oral GLP-1RAs hold great promise, yet theoretical concerns surrounding off-target toxicity will need to be scrutinized in large phase 3 trials. Glucagon-containing medicines may be particularly effective for reducing hepatic fat, while preference will be given to GCGR-GLP-1R co-agonists or tri-agonists that robustly lower glycemia in people with dysglycemia or T2D. As glucagon exerts catabolic activity, ongoing scrutiny of functional muscle mass in individuals with substantial weight loss treated with GCGR agonists is warranted. Whether GIP or amylin-containing medicines will impact bone density, bone quality, or fractures is unknown. Furthermore, the substantial benefits attributed to GLP-1RAs, including reduction of MACE, HFpEF, DKD, and ACM, will require careful scrutiny as new GLP-1 medicines enter the clinic. Future advances in precision medicine incorporating information from biomarkers and genomics will hopefully improve the ability to individualize allocation of therapeutic interventions to prevent the complications of T2D and obesity in susceptible individuals.[180]

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## DECLARATION OF INTERESTS

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