**SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications**

**Emily Brown1,2, Hiddo JL Heerspink**3**, Daniel J Cuthbertson1,2, John PH Wilding1,2**

1Department of Metabolic and Cardiovascular Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom

2Liverpool University Hospitals NHS Foundation Trust, Longmoor Lane, Liverpool L9 7AL

3Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands.

**Corresponding author & address for reprints:**

Professor Dan Cuthbertson

3rd floor Clinical Sciences Centre,

Liverpool University Hospitals NHS Foundation Trust,

Longmoor Lane,

Liverpool, L9 7AL

**E-mail:** dan.cuthbertson@liv.ac.uk

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**Summary**

Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are used in patients with type 2 diabetes (T2D) as glucose lowering therapies with the additional benefits of concomitant weight loss and blood pressure reduction. Data from cardiovascular outcome trials have highlighted these drugs confer protection against major cardiovascular disease in those with established atherosclerotic cardiovascular disease (~10-20% relative risk reduction), hospitalisation for heart failure (~30-40% reduction) and against progression of chronic kidney disease They have also been associated with reductions in cardiovascular and all-cause mortality (up to 20%). Thus, these drugs are now second-line or even arguably first line glucose-lowering therapies in patients with cardiorenal disease irrespective of glycaemic control. There is now compelling data for their benefits for a range of other clinical indications, even in the absence of T2D, most recently for GLP-1 RAs in patients with overweight and obesity with weight-related co-morbidities. We present data to highlight the clinical populations most likely to benefit from treatment with either agent, as well as advice around adverse effects and safety.

**Key Considerations for Prescribers**

* SGLT2 inhibitors are a group of oral medications whereas GLP-1 RAs are generally injectable therapies. Oral semaglutide is the first oral GLP-1 RA available.
* **SGLT2 inhibitors:**
* All SGLT2 inhibitors can be initiated if eGFR >60 ml/min/1.73m2. Discontinue if eGFR <45 ml/min/1.73m2 (canagliflozin may be continued until eGFR <30 in certain circumstances).
* Close monitoring for genital mycotic infections and volume depletion.
* Carefully monitor for lower limb ulceration. Consider stopping if a patient develops lower limb complications, at least until the condition has resolved.
* Counsel on the risk of diabetic ketoacidosis (DKA). Test for raised ketones in patients with typical symptoms, even if plasma glucose levels near-normal. Discontinue during acute illness or surgical intervention.
* Contraindicated in pregnancy (reproductive toxicity in animal studies)/breastfeeding (limited animal studies only).
* **GLP-1 RAs:**
* Common side effects are gastrointestinal upset; hypoglycaemia risk is increased with concomitant sulphonylureas and insulin use. Avoid in patients with previous pancreatitis.
* Ensure retinopathy screening performed prior to initiation (semaglutide only).
* Contraindicated in pregnancy/breastfeeding (based on limited animal studies only) and personal/family history of MEN2 or medullary thyroid cancer.
* For patients with established cardiovascular disease the level of evidence is greatest for GLP-1 RAs; for patients with heart failure, SGLT2 inhibitors are favoured. Increasingly used first-line in these patient sub-groups.
* Treatment deintensification of other glucose lowering agents (insulin, sulphonylureas) or diuretics, particularly in the elderly, is recommended to avoid hypoglycaemia and hypovolaemia.
* Represents the most effective pharmacotherapy currently available for patients with overweight and obesity and weight-related co-morbidities.

**Introduction**

Type 2 diabetes (T2D) carries with it a major disease burden, including cardiovascular disease (CVD) and renal/chronic kidney disease (CKD). While intensive glucose control reduces microvascular complications in type 1 (T1D) and T2D, trials of glucose lowering therapies have shown variable impact on CVD (possible harm with some drugs and others showing no benefit). Regulatory requirements for cardiovascular outcome trials (CVOTs) for newer glucose-lowering therapies has yielded exciting and surprising outcomes for sodium-glucose cotransporter type 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Beyond metabolic efficacy and cardiovascular safety, they confer cardiorenal protection and particularly for SGLT2 inhibitors can prevent and treat heart failure (HF). Considering their dual effect on body weight and glycaemic control, combining these two classes is attractive in T2D but there is emerging evidence of multiple benefits for a range of clinical indications in patients without T2D. This review will describe and compare the evidence around the SGLT2 inhibitors and GLP-1 RAs individually and highlight their combination.

**Search strategy and selection criteria**

We obtained citations for this publication through searches of Pubmed from inception to January 12, 2021, using both MeSh and free text terms to identify relevant articles. We reviewed guidelines for the management of T2D and CVD published by American Diabetes Association, European Association for the Study of Diabetes and European Society of Cardiology. We also searched ClinicalTrials.gov and conference abstracts for additional eligible studies and trial information. We supplemented this with articles from the authors “personal databases” and reviewed relevant references cited in retrieved articles and review articles.

**SGLT2 inhibitors**

***Summary of key drugs in class***There are currently 5 oral SGLT2 inhibitors available in the EU. Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are approved by the European Medicines Agency (EMA) and the Federal Drug Administration (FDA) while sotagliflozin (an SGLT1/2 inhibitor with 20:1 selectivity for SGLT2) is approved only by the EMA for use in T1D. Several other SGLT2 inhibitors, approved in Japan, will not be discussed further. There are modest differences in pharmacology, but all are orally bioavailable and have circulating half-lives suitable for once daily administration.

***Mechanism of action*** SGLT2 inhibitors are inhibitors of renal glucose reabsorption resulting in significant glycosuria. Most compounds are highly selective (200-2500x) for SGLT2 located in the renal proximal tubules, but some also inhibit SGLT1, located in the kidneys and gut.1-3 At therapeutic doses, about 60-100g of glucose is excreted in the urine, thus directly removing glucose from the systemic circulation and lowering blood glucose. This simple mode of action of increased urinary glucose excretion and an osmotic diuresis is associated with multiple and complex secondary effects which are not explored further in this manuscript.

***Glycaemic, weight and blood pressure benefits*** Clinical development of all SGLT2 inhibitors demonstrated their glucose-lowering efficacy; reductions in glycated haemoglobin (HbA1c) of 0.5-0.9% (5-9 mmol/mol) after 12 months of treatment, largely independent of baseline treatment. As expected from the glucoretic effect, body weight reduced by ~2 kg, and systolic and diastolic blood pressure also significantly reduced by ~2.5-5 and 1-2 mmHg respectively.4 Currently, SGLT2 inhibitors should not be initiated in patients with an eGFR <60ml/min/1.73m2 and should be discontinued with and eGFR <45ml/min/1.73m2 due to a diminished glucose lowering effect. However, recently the FDA and EMA have approved continued use of canagliflozin in patients with a urinary albumin-to-creatinine ratio (UACR) >300mg/g and eGFR <30 ml/min/1.73m2 until renal replacement therapy due to its renoprotective benefits.

***Adverse effects*** Polyuria due to diuresis, and fungal genital infections, affects up to 10 % of women and 2-3% of men; these can be treated with standard antifungal therapy (topical/systemic fluconazole). Although most only occur on initiation, in some patients this requires treatment discontinuation. Recent meta-analyses and observational studies suggest there is no increased risk of bacterial urinary tract infections,5,6 and similarly for pyelonephritis, background risk is similar to that seen in other patients with T2D. These drugs are best avoided in those patients with recurrent infections. Spontaneous event reporting has led to concern regarding Fournier’s gangrene7, although in large RCTs (CREDENCE, DAPA-CKD, DECLARE, EMPA-REG and VERTIS)8-12, there was no increased risk. Diabetic ketoacidosis (DKA) also emerged as a rare adverse event (<0.1%) from spontaneous reporting and subsequently confirmed in several large RCTs, particularly in patients with T1D. Risk factors include concomitant insulin use, intercurrent illness and emergency or major elective surgery. Other concerns include hypotension, possibly leading to falls and acute kidney injury (AKI), secondary to diuresis. Data from RCTs and propensity-matched analyses of real-world data do not support increased risk of AKI.13,14 Minor changes in phosphate metabolism and parathyroid hormones may increase risk of fractures although the risk seems low and confined to canagliflozin. Finally, a higher rate of lower extremity amputations with canagliflozin in the CANVAS trials15, leading to guidance to avoid SGLT2 inhibitors in people at high risk of amputation, was not subsequently seen in other CVOTs or CREDENCE.8

**Impact of SGLT2 inhibitors on cardiorenal outcomes in T2D** Four randomised controlled CVOTs and a renal outcomes trial with SGLT2 inhibitors in people with T2D are summarised in Table 1.8-10,15

***Cardiovascular benefits*** Data from the CVOTs reveals several clear themes (Figure 1 and Supplementary Figure 1): a 30% reduction in hospitalisation for heart failure (HHF) is seen with all the drugs in the class, independent of background CVD/known history of HF. Event rates, and thus numbers needed to treat (NNT) depend on background risk. There is also a reduction in HF-related and arrythmia-related deaths. Further analysis of DECLARE data has also shown a reduction in atrial fibrillation, a finding not yet confirmed in a dedicated RCT.16 Results from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-reduced) strongly support use of SGLT2 inhibitors in the treatment of patients with T2D and established HF (with reduced ejection fraction, HFrEF). 17,18 DAPA-HF demonstrated a 26% reduction in worsening HFrEF/CV death with a median duration of follow up of 1.5 years.17 Findings from The Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) and Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease (SCORED) extended these findings to patients with recently decompensated HF and CKD (suggesting early SGLT2 initiation maybe helpful) although both trials were terminated early due to the COVID-19 pandemic.19,20

***Observational data of cardiovascular effects of SGLT2 inhibitors*** ‘Real world’ outcomes with SGLT2 inhibitors, using large datasets from health insurance databases and national health systems from multiple countries (CVD-REAL 1,2,3, THIN, EASEL, EMPRISE) (Supplementary Table 1)21-24, provide reassurance that the reductions in HHF, mortality and preservation of renal function are reproducible in routine clinical practice.

***Renal benefits*** Secondary/exploratory analyses from the above studiessuggested renal benefits (slower decline in eGFR) with less end-stage renal disease (Table 1 and Supplementary Figure 2). CREDENCE, the first renal outcome trial of a diabetes medication, recruited ~ 4500 patients with T2D and CKD with proteinuria (eGFR of 30-90 mL min–1 [1.73 m]–2 andUACR of 300–5000 mg/g.8 The study confirmed renoprotection (30% reduction) in composite renal outcome and CV protection in this group. The licenses for canagliflozin in the US and EU have been updated to reflect these findings, now indicated for the treatment of diabetic kidney disease with eGFR > 30 ml/min/1.73m2. The results of the DAPA-CKD trial extended these findings to a broader population of patients with CKD, demonstrating renoprotective effects of the SGLT2 inhibitor dapagliflozin in patients with CKD, with or without T2D.12,25

**Use of SGLT2 inhibitors as treatment adjunct in T1D** For people with T1D in Europe, but not the USA, dapagliflozin and sotagliflozin have been approved for patients with sub-optimal control on insulin and a BMI of >27kg/m2 based on safety and efficacy data from the phase 3 DEPICT and TANDEM clinical programmes respectively. Pooled analysis from these clinical programmes supported the EMA decision to limit their use to those with a BMI >27kg/m2 due to lower rates of DKA. Meta-analysis data has demonstrated the benefits of adjunctive SGLT2 use in T1D with evidence of improved glycaemic control, smaller glucose excursions and weight loss without increasing hypoglycaemia risk.26 Safety concerns about DKA should be addressed with a commitment to monitor blood glucose and ketone levels. SGLT2 inhibitors should be avoided in poorly compliant patients or those with recurrent DKA and discontinued during acute illness or surgical intervention.

**Clinical use of SGLT2 inhibitors in patients without diabetes**

***Cardiovascular and renal benefits in patients without diabetes*** There have been no completed dedicated CVOTs or renal endpoint trials which have exclusively included patients without T2D. Following on from the CREDENCE study, the effect of SGLT2 inhibitors in non-diabetic kidney disease is of interest given the common pathophysiological pathways in CKD.8 DAPA-CKD examined the effects of dapagliflozin on CKD in patients with and without T2D.12 One other large clinical trial with renal specific endpoints, EMPA-KIDNEY (NCT03594110) has been initiated in people with and without T2D, with non-proteinuric kidney disease, *i.e.* those with eGFR <45 ml/min/1.73m2, with or without albuminuria.

***Treatment of heart failure with reduced ejection fraction (HFrEF)*** The results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-reduced) strongly support the use of an SGLT2 inhibitor in the treatment of patients with established HF (with reduced ejection fraction, HFrEF) with reductions in worsening HFrEF/CV death with or without T2D.17,18 Significantly 45-55% of patients did not have a history of T2D at baseline. The benefits were similar in patients with and without diabetes, suggesting benefits are independent of glycaemia. Post-hoc analysis of two CVOTs suggest that the same benefits are not seen in patients with HF with preserved EF (HFpEF)27,28, and we await the results of dedicated studies in this patient group (NCT03057951 and NCT03619213). Interestingly, dapagliflozin also reduced the risk of new onset of T2D by 32% (HR 0.68; 95% CI 0.50-0.94), compared to those receiving placebo, amongst at risk patients with pre-diabetes; a similar effect size to that seen with metformin in diabetes prevention studies (~31%). In the SOLOIST-WHF study, in which all patients had T2D, benefits were consistent in those with HFrEF *and* HFpEF.19 Following results from DAPA-HF, the FDA and EU regulators have approved use of dapagliflozin to reduce the risk of CV death or worsening HF in patients with HFrEF, with and without T2D.

**Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)**

***Summary of key drugs in class*** Several GLP-1 RAs are currently approved for use in T2D: exenatide, liraglutide, lixisenatide, dulaglutide and semaglutide.29 All are administered as subcutaneous injections although oral semaglutide is available. These molecules were developed based on the structure of either gila monster salivary peptide, exendin-4 or human GLP-1, with biological properties (half-life and dosing interval) reflective of key structural modifications to the amino acid sequence conferring resistance to DPP-4 degradation; half-livesvary between 2-3 h and several days. These molecular differences translate to distinct clinical effects.

*Short-acting RAs* The short-acting GLP-1 RAs (including b.d./weekly exenatide and lixisenatide) are structurally based on exendin 4 with 90-97% sequence homology. Relative to long-acting GLP-1 RAs, they have a more pronounced slowing of gastric emptying and a lesser effect on insulin secretion, more potently affecting post-prandial (*versus* fasting) plasma glucose concentrations.

*Long-acting RAs* These other GLP-1 RAs have a distinct mechanism of action with a lesser effect on gastric emptying, predominantly by increasing insulin and decreasing glucagon secretion. Thus, long-acting GLP-1 RAs more profoundly impact fasting (*versus* post-prandial) and on 24-hour glucose profiles.

***Mechanism of action*** GLP-1is a gut-derived peptide secreted from intestinal epithelial L-cells, in response to nutrients, particularly glucose and fat. GLP-1 has physiological actions on multiple target organs. It is an incretin, augmenting glucose-stimulated insulin secretion by pancreatic β-cells while additionally stimulating β-cell neogenesis and inhibiting apoptosis and reduces glucagon secretion from α-cells (shown in rodent models). Insulin secretion is only increased above ~3.5 mmol/l glucose hence GLP-1 does not induce hypoglycaemia. GLP-1 also acts on the hypothalamus to promote satiety and reduce food intake. Other sites of GLP-1 action include the stomach (inhibiting gastric emptying), adipose tissue, skeletal muscle (enhancing glucose disposal) and in the heart.30

***Glycaemic, weight and blood pressure effects*** Each GLP-1 RA have been studied as monotherapy or in combination with other glucose-lowering therapies, and irrespective of differences in study design, duration and patient characteristics demonstrate consistent efficacy in lowering HbA1c, weight and blood pressure (2-3 mmHg) with a small increase in heart rate (summarised in Table 231-42). Longer acting GLP-1 RAs and more recent weekly preparations, seem to more potently lower glucose, and cause less gastrointestinal upset with no clinically significant difference in weight loss.43 The PIONEER programme highlights use of oral semaglutide across a wide range of patients, compared with liraglutide (PIONEER 4), with similar reductions in HbA1c but greater weight loss.42

Liraglutide is the most studied GLP1-RA in the real world with one systematic review of uncontrolled observational data suggesting after 6 months mean change in HbA1c was -0.9% to -2.2% with a mean change in absolute weight from baseline of -1.3 to -8.65 kg.44 UK real world data might be biased by application of ‘stopping rules’ which stipulate thresholds of changes in HbA1c and weight when treatment with a GLP-1 RA should be discontinued.

***Combination with insulin***RCT data also supports combination therapy of a GLP1-RA with basal insulin, considering insulin’s contribution to weight gain and hypoglycaemia. Several fixed-ratio combination products of GLP-1 RAs and basal insulin are available in a single injection/device (insulin degludec with liraglutide (iDegLira) and insulin glargine with lixisenatide (iGlarLixi)).

***Adverse effects*** The most common adverse effects are gastrointestinal, particularly nausea (25-60%) and vomiting (5-15%); generally of mild-moderate severity decreasing over time, with lower rates of discontinuation for gastrointestinal upset (5-10%). Occasionally, there may be injection-site reactions, headache and nasopharyngitis.Due to their glucose-dependent mechanism of action, they have minimal risk of hypoglycaemia except when used with sulphonylureas or insulin.

*Pancreatitis and pancreatic/hepatobiliary disease* The risk of acute pancreatitis and pancreatic carcinoma is higher in people with T2D who are obese than non-obese controls, irrespective of treatment. Reassuringly, the risk of acute pancreatitis and cancer does not appear to be higher in patients receiving GLP-1 RAs than in those receiving other forms of anti-diabetes treatments.45 These drugs are associated with an increased risk of bile duct and gallbladder disease and so patients are more likely to undergo cholecystectomy46; patients should be counselled accordingly.

*Medullary thyroid carcinoma* Concerns about C-cell proliferation and formation of medullary thyroid carcinomas (MTC) seen in rodent studies are not borne out in clinical trials (normal human thyroid tissue has low/absent GLP1 receptor expression). Nonetheless patients at risk of MTC should not be prescribed GLP1-RAs.

*Diabetic ketoacidosis* (DKA) DKA has been reported in patients with T2D on a combination of a GLP-1 RAs and insulin, when concomitant insulin was either rapidly reduced or discontinued. Insulin reductions should be undertaken in a cautious stepwise manner, with capillary blood glucose monitoring (MHRA guidance, June 2019).

*Retinopathy* In SUSTAIN-6, higher than expected rates of diabetic retinopathy complications occurred with semaglutide (3%) compared to placebo (1.8%).47 Rapid improvement in glucose control has been associated with temporary worsening of diabetic retinopathy, but a direct effect of semaglutide cannot be excluded. The trials in the phase 3a programme were not designed for systematic evaluation of retinopathy progression unlike endpoints such as ETDRS (Early Treatment Diabetic Retinopathy Study) assessing both severity and changes over time. Clinical trials studying the long-term effects of GLP-1 RAs are underway (NCT03811561).

**Impact of GLP-1 receptor agonists on cardiorenal outcomes in type 2 diabetes**

Despite the different structure and duration of action of the various GLP-1 RAs, results of various studies, in heterogenous patient populations, have amassed significant evidence to demonstrate the clear role of GLP-1 RAs in cardiovascular, renal and stroke protection and their impact on mortality in patients with T2D (summarised in Table 3 and Online Supplementary Figure 3).

***Cardiovascular benefits*** Of seven CVOT trials, ELIXA was the first major CVOT with a GLP-1 RA, examining the short-acting agent lixisenatide in patients with T2D and acute coronary syndrome.48 While it demonstrated cardiovascular safety, it did not demonstrate benefit. In contrast, all of the subsequent GLP-1 CVOTs have shown benefit in reducing the risk of CV events *vs.* standard care (Figure 1).47,49-53

A recent meta-analysis of cardiovascular and kidney outcomes in the seven GLP1-RA CVOTs, with a combined total of 56,004 participants confirmed GLP-1 RA treatment reduces MACE and all-cause mortality by 12% (HR 0.88; 95% CI 0.82,0.94 and 95% CI, 0.83,0.95 respectively.54 Importantly, there was also demonstration of a reduction in HHF by 9% (HR 0.91, 95% CI 0.83,0.99).

***Stroke protection*** GLP-1 RAs may also exert neuroprotective effects with some CVOT data demonstrating reductions in stroke. A recent systematic review and meta-analysis of 5 multi-centre, randomised, placebo-controlled trials (ELIXA, LEADER, SUSTAIN, EXSCEL and HARMONY) demonstrated a 13% reduction in the risk of total stroke from GLP-1 treatment (risk ratio 0.87; 95% CI 0.78,0.98) although no protection when only fatal stroke was included.55 An exploratory analysis of outcomes in the REWIND trial indicates that dulaglutide may reduce the incidence but not severity of ischaemic stroke (3.2 % stroke with dulaglutide *vs*. 4.1% with placebo); a 24% risk reduction with dulaglutide. No effects were seen on haemorrhagic stroke.56

***Renal benefits*** The goal of renoprotection is to slow loss of functional nephrons, preserving glomerular and tubular function to delay the onset of end-stage kidney disease and renal death. Microalbuminuria is often the earliest clinical manifestation of diabetic kidney disease and predictive of progression. Surrogate measures include emergence and progression of proteinuria (normal, micro- and macroalbuminuria), decline in eGFR (often assessed by persistent doubling of serum creatinine/eGFR<45ml/min/1.73m2) or a need for continuous renal replacement. Unlike SGLT2 inhibitors, there have been no dedicated renal primary outcome studies with GLP1-RAs, with all evidence regarding their renoprotective effect derived from analysis of results from secondary outcome measures or exploratory analyses in CVOTs using UACR and eGFR measurements. Despite this caveat, many of the CVOTs have demonstrated favourable renal outcomes. In ELIXA, lixisenatide reduced progression of UACR in macroalbuminuric patients and is associated with a lower risk of new onset macroalbuminuria; it did not change eGFR decline.57 In LEADER and SUSTAIN 6, treatment with liraglutide and semaglutide reduced the risk of CKD development and progression, benefits mainly driven by reduction in new onset microalbuminuria.47,49 HARMONY, EXSCEL and PIONEER 6 did not assess renal outcomes. In the AWARD-7 trial, dulaglutide was accompanied by UACR reduction and preservation of renal function compared to insulin glargine, most evident in patients with macroalbuminuria and CKD stages 3b and 4.58 A recent meta-analysis of kidney outcomes in the seven GLP1-RA CVOTs, with a combined total of 56,004 participants confirmed GLP1-RA treatment reduced a broad composite renal outcome by 17% (HR 0.83, 95% CI 0.78,0.89).54 These data suggest GLP-1 RAs may be particularly effective in patients with established CKD. The ongoing FLOW trial (NCT03819153), investigating the effect of semaglutide versus placebo on renal outcomes in patients with (T2D) and CKD, will provide further therapeutic and mechanistic insight. Further mechanistic studies of the effects of GLP-1 RAs on CKD progression are required.

**Use of GLP-1 receptor agonists as treatment adjunct in T1D** Few high-quality studies have assessed safety and efficacy of GLP-1 RAs, as adjunctive therapy, in patients with T1D. The efficacy and safety of liraglutide as add-on to insulin treatment in overweight patients with T1D has been evaluated.Despite modest impact on HbA1c (mean 0.15–0.2% reduction), reductions in weight (−6.8 kg) and insulin requirements were seen with liraglutide.59 However, rates of symptomatic hypoglycaemia and hyperglycaemia with ketosis increased significantly.There may be a subgroup of overweight/obese patients with T1D who would most benefit from adjunctive GLP-1 RA therapy.

**GLP1 receptor agonists in obesity/prediabetes** Liraglutide 3.0 mg (Saxenda®; Novo Nordisk), has been approved for weight management in multiple countries, as an adjunct to a reduced‐calorie diet and increased physical activity. The Satiety and Clinical Adiposity Liraglutide Evidence (SCALE) phase 3 clinical development programme investigated the safety and efficacy of liraglutide 3.0mg (once daily subcutaneous injection) in people with and without T2D; subjects experienced a dose-dependent mean weight loss 5.7%-9.2% (6.0-8.8 kg) *versus* between 0.2% -3.1% (0.2-3.0 kg) with placebo (on diet and exercise alone).60-62 In the 3 year assessment of the SCALE Obesity and Prediabetes trial le Roux *et al* examined whether 3.0mg liraglutide reduced progression of T2D in overweight or obese individuals with pre-diabetes.63 With liraglutide, a 4.6kg placebo-subtracted weight loss reduction (50% of patients lost >5% weight) was associated with regression from prediabetes to normoglycaemia in 66% of individuals (36% regression with placebo). The magnitude of risk reduction of T2D is consistent with findings from other diabetes prevention studies.

Semaglutide is also being evaluated as a treatment for obesity, with or without weight-related complications, in the STEP programme. Most recently, STEP 1, a phase 3 trial, evaluated the use of once-weekly Semaglutide (2.4 mg subcutaneously) in 1961 adults with obesity (BMI>30kg/m2) or overweight (BMI >27kg/m2), with ≥1 weight-related co-morbidity who did not have diabetes. The mean reduction in body weight from baseline after 68 weeks was 14.9% in the semaglutide group *vs*. 2.4% with placebo; estimated treatment difference of 12.4 % (95% confidence interval [CI]11.5,13.4), or 12.7 kg (95% CI, 11.7,13.7). There was an associated improvement both in cardiometabolic risk factors and in participant-reported physical functioning with semaglutide.64 Four further trials will examine weight loss in T2D and if weight loss can be sustained over a longer period of time (NCT03552757, NCT03611582, NCT03548987, NCT03693430). The question as to whether benefits in CVD are also seen in people without T2D is being evaluated in the ongoing SELECT trial (NCT03574597).

**Non-alcoholic fatty liver disease (NAFLD)** There are currently no licensed therapies for NAFLD/NASH but even modest weight loss (~8kg) in patients with T2D substantially reduces hepatic steatosis (~80%), concomitantly improving hepatic insulin resistance.65 RCTs with SGLT2 inhibitors and GLP-1 RAs have demonstrated improved liver enzymes and reductions in liver fat in patients with T2D, but only GLP-1 RAs (liraglutide and semaglutide) have demonstrated reversal/improvements of the histological features of NAFLD.66-69

**Efficacy studies comparing SGLT2 inhibitors and GLP-1 receptor agonists**

In DURATION 8, comparing dapagliflozin 10 mg with exenatide 2mg once weekly, there were similar reductions in HbA1c (1.4-1.6%) but greater reductions in body weight with dapagliflozin.70 In SUSTAIN 8, comparing subcutaneous semaglutide 1.0 mg once weekly with canagliflozin 300mg: semaglutide was superior to canagliflozin in lowering both HbA1c and body weight (−4.7 *vs*. −3.8 kg) after 52 weeks.71 Finally, in PIONEER 2, comparing oral semaglutide 14mg with empagliflozin 25m semaglutide demonstrated greater potency in glucose lowering but no difference in weight.72 Thus GLP-1 RAs may be considered the most potent agents to simultaneously lower HbA1c and body weight.

***Cardiovascular and renal benefits: comparison with SGLT2 inhibitors and GLP-1 receptor agonists*** Several meta-analyses have been published on these drug classes for primary and secondary prevention of cardiovascular and renal outcomes in T2D 73,74 attempting to reconcile what patient characteristics (e.g. presence/absence of atherosclerotic cardiovascular disease (ASCVD), history of HF or baseline renal function) benefit from cardiorenal protection. Furthermore, recognising important differences in mechanisms of action, attempts have been made to compare and contrast the relative distinct clinical benefits of SGLT2 inhibitors and GLP1-RAs.

Incorporating data from 34,322 patients in EMPA-REG, OUTCOME, CANVAS and DECLARE-TIMI 58, the clinical benefits of SGLT2 inhibitors are in reducing the risk of a 3-point MACE (MI, stroke or cardiovascular death) only in those with established CVD and not in those with multiple risk factors. However, the risk reduction in HHF and progression in renal disease were evident regardless of presence of ASCVD or HF at baseline.74 Using data from these three studies combined with 5 GLP1-RA studies, incorporating data from 77,242 patients, similar reductions in MACE (~11-12%) were seen with both drug classes, with the treatment effects restricted to those with established ASCVD. However, the GLP1-RA did not influence HHF and while both GLP1-RA and SGLT2 inhibitors reduced the risk of progression of kidney disease including macroalbuminuria, only SGLT2 inhibitors reduced the risk of worsening eGFR, end-stage kidney disease or renal death.73 These data have important clinical implications in decision making when selecting the best therapeutic options for patients.

**Current position in treatment algorithms** The position of SGLT2 inhibitors and GLP-1 RAs as glucose-lowering therapies in treatment algorithms in people with T2D has been updated reflecting results of these CVOTs. 75-77 In 2019 the European Society for Cardiology (ESC), in collaboration with the European Association for the Study of Diabetes (EASD), published updated guidelines on diabetes, prediabetes and CVD. SGLT2 inhibitors and GLP-1 RAs were positioned as first-line in treatment naïve patients with existing CVD/high risk, *irrespective* of HbA1c. If an SGLT2 inhibitor or GLP-1 RA is considered suitable, treatment should be prioritised according to existing evidence such that GLP-1 RAs should be considered in patients with T2D and those at high risk/with established CVD and SGLT2 inhibitors considered for patients with HFrEF or CKD (with/without established CVD). In this rapidly evolving area, evidence for the management of certain subgroups may change. Caution should be used when comparisons are made between individual trials due to differences in trial design, baseline characteristics and endpoints (notably renal).

**Combination therapy**

Overall, the evidence supports combination therapy with a GLP-1 RA and SGLT2 inhibitor with additive benefits of glycaemic improvement and weight loss reflecting distinct and complementary mechanisms of action (Table 4).70,78,79 Further studies are necessary to elucidate their combined effects on metabolic and cardiorenal disease (Table 5).

***Glycaemic control and weight loss* benefits** DURATION-8 randomised patients on maximal metformin to dapagliflozin alone, exenatide alone, or dapagliflozin plus exenatide for 28 weeks. The reduction in HbA1c with combination (–2·0%) was less than additive compared to dapagliflozin (- 1.4%) or exenatide (-1.6%) alone.70 The results of AWARD-10 supports the sequential addition of these two agents.78. In DURATION-8, the weight loss with combination (- 3.41kg) was similar to that achieved with dapagliflozin (-1.54kg) and exenatide (-2.19kg) monotherapy.70 These benefits may be extended to people without T2D with the phase 2 RCT examining the effects of dual therapy with dapagliflozin and exenatide weekly in obese adults without T2D. After 24 weeks, for dapagliflozin/exenatide versus placebo: the difference in body weight change was −4.13 kg (95% confidence interval −6.44, −1.81; *P* < .001).80

***Blood pressure and lipid profile benefits*** In DURATION-8, exenatide plus dapagliflozin treatment (−4.3 ± 0.8 mmHg) was associated with a significantly greater reduction in systolic blood pressure from baseline to week 28 compared with exenatide once weekly (−1.2 ± 0.8 mm Hg; P = .005) or dapagliflozin (−1.8 ± 0.8 mm Hg; P = .022) in the overall population.70 No significant differences between groups were noted for diastolic blood pressure or lipid measurements.

***NAFLD/NASH*** Post-hoc analysis of DURATION-8 examined the effects of treatment on NAFLD. Greater improvements in liver enzymes and non-invasive biomarkers of hepatic steatosis were seen with combination therapy compared to monotherapy after 28 weeks.81 Prospective studies in people with or without T2D are needed.

***Cardiorenal benefits*** Both drug classes reduce body weight, HbA1c and other intermediate markers of cardiorenal health (blood pressure, UACR or eGFR). The cardiovascular risk reduction seen with SGLT2 inhibition is partly explained by the glycosuric effect and associated plasma volume reduction, whilst the benefits of GLP-1 RAs relate to potentially complementary anti-atherogenic mechanisms.

**Future Directions**

Newer formulations of GLP-1 RAs are becoming available. Implantable GLP1-RAs have recently been evaluated82,83 but the most encouraging is use of oral semaglutide with compelling clinical data. GLP1 may also be one of several key peptide hormone receptors that can be targeted with novel co-peptides targeting GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors simultaneously in phase 2 and phase 3 trials.84 Evidence regarding combination therapy will continue to add to this data-rich, rapidly evolving, therapeutic area.

With the benefits observed in CVOTs on risk of CVD, HF and CKD in people with T2D, both drug classes have evolved from use as additional glucose-lowering therapies in T2D, used at a later stage in treatment algorithms, to being used first line in selected patients (with ASCVD, HF and CKD) in T2D and with increasingly expanding indications in T1D, obesity, cardiorenal disease and NAFLD without T2D. Ongoing studies are evaluating the cardiorenal benefits of SGLT2 inhibitors and GLP-1 RAs in different populations compared with previous CVOTs.

**Declarations**

**Conflicts of Interest**

EB is currently supported by a grant funded to the University of Liverpool by Astra Zeneca and has received support for attendance at educational meetings by Sanofi and Astra Zeneca. HJLH reports grants and other from Janssen R&D, grants and other from Astra Zeneca, during the conduct of the study; grants and other from Abbvie, grants and other from Boehringer Ingelheim, other from Chinook, other from CSL Pharma, other from Gilead, other from Merck, other from MundiPharma, other from Mitsubishi Tanabe, other from Retrophin, other from Novo Nordisk, other from Bayer, outside the submitted work. DJC has competing interests with AstraZeneca,Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly, Pfizer & Novo Nordisk. JPHW has acted as a consultant, received institutional grants and given lectures on behalf of pharmaceutical companies developing or marketing medicines used for the treatment of diabetes and obesity, specifically Astellas, AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Eli Lilly, Novo Nordisk, Napp, Mundipharma, Orexigen, Rhythm Pharmaceuticals, Sanofi & Takeda, Wilmington Healthcare.

**Authors’ contributions** All authors made substantial contributions to the conception and development of this article. EB and DJC produced the first draft and led on subsequent drafts in collaboration with all of the co-authors and coordinated revisions in response to reviewers. All authors agreed on the final version to be published.

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**Figure 1** Cardiovascular outcomes from the key CVOTs with **(A)** SGLT2 inhibitors *vs.* placebo (white bars) **(B)** GLP-1 receptor agonists *vs.* placebo (white bars). Data are shown as incidence per 1000 patient years; \*\*\* <0.05 *vs.* placebo. HR (95% CI) values are shown.Caution should be used when comparisons are made between individual trials due to differences in trial design and baseline characteristics.

**Table 1** Summary of the major randomised controlled, cardiovascular outcome trials (CVOTs) with SGLT2 inhibitors in type 2 diabetes. Primary outcome measure was **3-point MACE**: non-fatal MI, non-fatal stroke or death from cardiovascular (CV) causes or **4-point MACE:** composite endpoint of CV death, myocardial infarction, stroke or hospitalisation for unstable angina. **HHF,** hospitalisation for heart failure; **MI,** myocardial infarction**; ESKD,** end-stage kidney disease; **RRT,** renal replacement therapy; **RRD,** renal related death; **Cr,** creatinine. \*Remaining participants with CV risk factors.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial**  |  | **EMPA-REG10** | **DECLARE-TIMI9** | **CANVAS15** | **VERTIS11**  | **CREDENCE8** |
|  |  | **Empagliflozin *vs.* placebo**n=7,020 | **Dapagliflozin *vs.* placebo**n=17,160 | **Canagliflozin *vs.* placebo**n=10,142 | **Ertugliflozin *vs.* placebo**n=8,246 | **Canagliflozin *vs.*** **placebo**n=4,401 |
| **Main inclusion criteria (type 2 diabetes+)** |  | Established CVD, eGFR>30 | Established CVD (40.6%)\*Multiple cardiovascular risk factors (59.4%) | Established CVD  | Age >40 yearsEstablished CVD | Albuminuric CKD: (eGFR 30 to <90 and ACR >300 to 5000 mg/g) |
| **Key CV outcomes** (Event rate per 1000 patient years) | **Treatment arm** |  |  |  |  |  |
| MACE | PlaceboSGLT2 inhibitorHR (95% CI) | 43.937.4**0.86 (0.74, 0.99)** | 24.222.60.93 (0.84, 1.03) | 31.526.9**0.86 (0.75, 0.97)** | 40.039.00.97 (0.85, 1.11) | 48.738.7**0.80 (0.67, 0.95)** |
| CV death | PlaceboSGLT2 inhibitorHR (95% CI) | 20.212.4**0.62 (0.49, 0.77)** | 7.17.00.98 (0.82, 1.17) | 12.811.60.87 (0.72, 1.06) | 19180.92 (0.77, 1.11) | 24.419.00.78 (0.61, 1.00) |
| CV death or HHF | PlaceboSGLT2 inhibitorHR (95% CI) | 30.119.7**0.66 (0.55, 0.79)** | 14.712.2**0.83 (0.73, 0.95)** | 20.816.3**0.78 (0.67, 0.91)** | 27.023.00.88 (0.75, 1.03) | 45.431.5**0.69 (0.57, 0.83)** |
| All-cause mortality | PlaceboSGLT2 inhibitorHR (95% CI) | 28.619.4**0.68 (0.57, 0.82)** | 16.415.10.93 (0.82, 1.04) | 19.517.30.87 (0.74, 1.01) | 26.024.00.93 (0.80, 1.08) | 35.029.00.83 (0.68, 1.02) |
| HHF | PlaceboSGLT2 inhibitorHR (95% CI) | 14.59.4**0.65 (0.50, 0.85)** | 8.56.2**0.73 (0.61, 0.88)** | 8.75.5**0.67 (0.52, 0.87)** | 11.07.0**0.70 (0.54, 0.90)** | 25.315.7**0.61 (0.4, 0.80)** |
| MI | PlaceboSGLT2 inhibitorHR (95% CI) | 19.316.80.87 (0.70, 1.09) | 13.211.70.89 (0.77, 1.01) | 12.611.20.89 (0.73, 1.09) | 17.018.01.04 (0.86, 1.26) | - |
| Stroke  | PlaceboSGLT2 inhibitorHR (95% CI) | 10.512.31.18 (0.89, 1.56) | 6.86.91.01 (0.84, 1.21) | 9.67.90.87 (0.69, 1.09) | 9.010.01.06 (0.82, 1.37) | - |
| **Key renal outcomes** | **Treatment arm** |  |  |  |  |  |
|  | PlaceboSGLT2 inhibitorHR (95% CI) | Doubling of serum Cr and eGFR≤45, RRT or RRD11.56.3**0.54 (0.40, 0.75)** | >40 % reduction to eGFR<60, ESKD or RRD7.03.7**0.53 (0.43, 0.66)**  | Progression of albuminuria128.789.4**0.73 (0.67, 0.79)** | RRD, dialysis/transplant or doubling serum Cr12.09.00.81 (0.63, 1.04) | ESKD, doubling of serum Cr or renal/cardiovascular death61.243.2**0.70 (0.59, 0.82)** |
|  | PlaceboSGLT2 inhibitorHR (95% CI) | Incident/worsening nephropathy76.047.8**0.61 (0.53, 0.70)** | **-** | 40% reduction in eGFR, RRT or RRD9.05.5**0.60 (0.47, 0.77)** | - | ESKD29.420.4**0.68 (0.54, 0.86)** |
|  | PlaceboSGLT2 inhibitorHR (95% CI) | Initiation of RRT2.11.0**0.45 (0.21, 0.97)** | **-** | - | - | Dialysis, renal transplant or RRD18.613.6**0.72 (0.54, 0.97)** |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study name** | **Treatment arms** | **Duration (weeks)** | **Inclusion criteria** | **Change in HbA1c** | **Change in weight (kg)** |
| **DURATION 1**31 | Exenatide 10mcg b.d. *vs.* Exenatide 2mg weekly | 30 | Therapy with diet/exercise, or with 1–2 OADs (metformin, SU and/or TZD) HbA1c 7.1–11.0% | -1.5 % *vs.* -1.9%(p=0.0023) | -3.6 *vs.* -3.7(NS) |
| **DURATION 5**32 | Exenatide 2mg weekly *vs.* Exenatide 10mcg b.d.  | 24 | Drug-naïve, treated with one or more oral medication | -1.6% *vs.* -0.9% | -2.3 *vs.* -1.4 (NS) |
| **DURATION 6**33 | Exenatide 2mg weekly *vs.* liraglutide 1.8mg o.d. | 26 | Lifestyle modification and oral anti-diabetes medication  | -1.28% *vs.* 1.48%(p=0.2) | -2.68 *vs.* -3.57 (p=0.0005) |
| **LEAD 6**34 | Exenatide 10 mcg b.d. *vs.* liraglutide 1.8 mg o.d. | 26 | Maximally tolerated doses of metformin, SU or both  | -0.79 *vs.* -1.2 (p<0.0001) | -2.87 *vs.* -3.24(NS) |
| **GET GOAL X**35 | Lixisenatide 20 mcg weekly *vs.* exenatide 10mcg b.d.  | 24 | Inadequately controlled with metformin, HbA1c 7-10% | -0.79 *vs.* 0.96(NS) | -2.96 *vs.* -3.98 |
| **HARMONY 7**36 | Albiglutide once weekly vs. liraglutide once daily  | 32 | Inadequately controlled, BMI 20-45 kg/m2 | -0.78 *vs.* -0.99 | -0.64 vs. -2.16(p<0.0001) |
| **AWARD 1**37 | Dulaglutide 0.75 mg *vs.* 1.5 mg weekly *vs.* exenatide 10mcg bd | 26 | Inadequately controlled HbA1c 7-11% on monotherapy or 7-10% on combination, BMI 23-45 kg/m2 | -1.30 *vs.* -1.51 *vs.* -0.99 | 0.2 *vs*. -1.30 *vs.* -1.07 (p<0.001) |
| **AWARD 6**38 | Dulaglutide 1.5 mg weekly *vs.* liraglutide 1.8 mg o.d. | 26 | Inadequately controlled HbA1c 7-10% on metformin, BMI<45 kg/m2 | -1.42 vs. -1.36(p<0.0001, non- inferiority) | -2.9 *vs.* 3.61 |
| **SUSTAIN 3**40 | Semaglutide weekly vs. exenatide 2mg weekly | 56 | HbA1c 7-10.5%, one or two oral agents  | -1.5 *vs.* -0.9 | -5.6 *vs.* 1.9 |
| **SUSTAIN 10**39 | Semaglutide weekly *vs.* liraglutide once daily | 30 | HbA1c 7-10.5%, on 1-3 oral agents | -1.7 *vs.* 1.0 | -5.8 *vs.* 1.9 |
| **SUSTAIN 7**41 | Semaglutide 0.5 mg *vs.* dulaglutide 0.75 mg *vs.* semaglutide 1.0 mg *vs.* dulaglutide 1.5mg | 40 | Inadequately controlled HbA1c 7-10.5% on metformin | -1.5 *vs.* 1.1 *vs.* 1.8 vs. 1.4 | -4.6 *vs.* 2.3 *vs.*6.5 *vs.* 3.0 |
| **PIONEER-4**42 | Oral semaglutide 14mg *vs.* liraglutide 1.8 mg | 52 | Metformin treatment with/without an sGLT2 inhibitor | -1.2 vs. -0.9 | -4.4 vs. -3.1 |

**Table 2** Phase 3, randomised controlled, head-to head comparisons of GLP-1 receptor agonists (subcutaneous and oral) in type 2 diabetes.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial**  |  | **ELIXA** (2015)48 | **LEADER**(2016)49 | **SUSTAIN-647** | **EXSCEL**85 | **HARMONY51**(2018) | **REWIND86** | **PIONEER-687** |
|  |  | **Lixisenatide *vs.* placebo**n= 6,068 | **Liraglutide *vs.* placebo**n=9,340 | **Semaglutide *vs.* placebo**n= 3,297 | **Exenatide QW *vs.* placebo**n= 14,752 | **Albiglutide *vs.* placebo****n=9,463** | **Dulaglutide *vs.* placebo****n=9,901** | **Semaglutide (oral) *vs.* placebo****n=3,183** |
| **Main inclusion criteria (type 2 diabetes+)** |  | Acute coronary event <180 days before screening | Established CVD, CKD or HF>50y (72.5%) **OR** with at least one known risk factor age >60 years  | Established CVD (73.1%)\* **OR**Multiple cardiovascular risk factors | Age >40 years and atherosclerotic CVD | Age>50 years, previous CV event, evidence of CVD (31.5%)\* **OR** multiple cardiovascular risk factors | Age >50 years and CVD (84.7%)\* **OR** age>60 years and at least one CV risk factor  |
| **Treatment arm****(Event rate per 1000 patient years)** |  |  |  |  |  |  |  |  |
| MACE | PlaceboGLP-1 RAHR (95% CI) | 63.064.01.02 (0.89, 1.17) | 39.034.0**0.87 (0.78, 0.97)** | 44.432.4**0.74 (0.58, 0.95)** | 40.037.00.91 (0.83, 1.00) | 58.745.7**0.78 (0.68, 0.90)** | 26.623.5**0.88 (0.79, 0.99)** | 37290.79 (0.57, 1.11)  |
| CV death | PlaceboGLP-1 RAHR (95% CI) | 23.024.00.98 (0.78, 1.22) | 16.012.0**0.78 (0.66, 0.93)**  | 13.512.90.98 (0.65, 1.48) | 15.014.00.88 (0.76, 0.97) | 17.216.10.93 (0.73, 1.19) | 13.412.20.91 (0.78, 1.06) | 14.07.00.49 (0.27, 0.92) |
| All-cause mortality | PlaceboGLP-1 RAHR (95% CI) | 31330.94 (0.78, 1.13) | 25.021.0**0.85 (0.74, 0.97)** | 17.618.21.05 (0.74, 1.50) | 23.020.00.86 (0.77, 0.97) | 25.624.40.95 (0.79, 1.16) | 22.920.60.90 (0.80, 1.01) | 22110.51 (0.31, 0.84) |
| HHF | PlaceboGLP-1 RAHR (95% CI) | 18.019.00.96 (0.75, 1.23) | 14.012.00.87 (0.73, 1.05) | 16.117.61.11 (0.77, 1.61) | 10.09.00.94 (0.78, 1.13) | - | 8.98.30.93 (0.77, 1.12) | 12100.86 (0.48, 1.55) |
| MI | PlaceboGLP-1 RAHR (95% CI) | 42.042.01.03 (0.87, 1.22) | 19.016.0**0.86 (0.73, 1.00)** | 19.214.00.74 (0.51, 1.48) § | 21.021.00.97 (0.85, 1.10) | 32.624.3**0.75 (0.61, 0.90)** | 9.18.70.96 (0.79, 1.15) | 15181.18 (0.73, 1.90)§ |
| Stroke  | PlaceboGLP-1 RAHR (95% CI) | 10.09.01.12 (0.79, 1.58) | 11.010.00.86 (0.71, 1.06) | 13.18.0**0.61 (0.38, 0.99)** § | 0.85 (0.70, 1.03) | 14.512.50.86 (0.66, 1.14) | 8.16.2**0.76 (0.62, 0.94)** | 860.74 (0.35, 1.57)§ |
| **Key renal outcomes** | **Treatment arm****(Event rate per 1000 patient years)** |  |  |  |  |  |  |  |
|  | PlaceboGLP-1 RAHR (95% CI) | - | New macroalbuminuria, doubling of serum Cr and eGFR≤45, RRT or RRD19.015.0**0.78 (0.67, 0.92)** | New macroalbuminuria, doubling of serum Cr and eGFR≤45, RRT30.618.6**0.64 (0.46, 0.88)** | 40% reduction in eGFR, RRT, RRD--0.87 (0.73, 1.04) | **-** | New macroalbuminuria, >30 % reduction of eGFR, or RRT40.734.7**0.85 (0.77, 0.93)** | - |
|  | PlaceboGLP-1 RAHR (95% CI) | - | New macroalbuminuria12.19.0**0.74 (0.60, 0.91)** | New macroalbuminuria 24.713.1**0.54 (0.37, 0.77)** | New macroalbuminuria--0.87 (0.70, 1.07) | **-** | New macroalbuminuria22.917.6**0.77 (0.68, 0.87)** |  |

**Table** **3** Summary of the major randomised controlled, cardiovascular outcome trials (CVOTs) with GLP-1 receptor agonists in type 2 diabetes. Primary outcome measure was **3-point MACE**: non-fatal MI, non-fatal stroke or death from cardiovascular (CV) causes or **4-point MACE:** composite endpoint of CV death, myocardial infarction, stroke or hospitalisation for unstable angina. **HHF,** hospitalisation for heart failure; **MI,** myocardial infarction**; ESKD,** end-stage kidney disease; **RRT,** renal replacement therapy; **RRD,** renal related death; **Cr,** creatinine. \*Remaining participants with CV risk factors § nonfatal stroke or MI

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial** | **DURATION-870** | **AWARD-1078** | **SUSTAIN-979** |
|  |  |  |  |
| **History** | Type 2 diabetes, HbA1c 8-12%, 28 weeks | Type 2 diabetes, HbA1c 8-12%, 24 weeks | Type 2 diabetes, HbA1c 7-10%30 weeks |
| **Treatment** | Exenatide QW + Dapagliflozin (n=228) | Dapagliflozin + placebo(n=230) | Exenatide QW + placebo(n=227) | Dulaglutide 1.5mg + SGLT2 inhibitor (n=142) | Dulaglutide 0.75mg + SGLT2 inhibitor (n=140) | Placebo + SGLT2 inhibitor (n=140) | Semaglutide QW + SGLT2 inhibitor (n=151) | Placebo + SGLT2 inhibitor(n= 151) |
| **Baseline****HbA1c (%)** | 9.3 (1.1) | 9.3 (1.0) | 9.3 (1.1) | 8.04 (0.65) | 8.04 (0.61) | 8.05 (0.66) | 8.0 (0.8) | 8.1 (0.8) |
| **HbA1c****change (%)** | -2.0 (-2.2, -1.8) | -1.4 (-1.6, -1.2) | -1.6 (-1.8, -1.4) | -1.34 (0.06)\* | -1.21 (0.06)\*  | -0.54 (0.06)\* | -1.5 (0.06)\* | -0.1 (0.07)\* |
| **Weight****change (kg)** | -3.55 (-4.12, -2.99) | -2.22 (-2.78, -1.66) | -1.56 (-2.13, -0.98) | -3.1 (0.3)\* | -2.6 (0.3)\* | -2.1 (0.3)\* | -4.7 (0.32) | -0.9 (0.31)\* |

**Table 4** Randomised, placebo-controlled trials with combination of an SGLT2 inhibitor and GLP-1 receptor agonist in type 2 diabetes. Data are mean (SD), least-squares mean (95% CI) unless otherwise specified. \* mean (SE).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Drug** | **Follow up (weeks)** | **n** | **History** | **Primary outcome** | **Estimated end date** |
| **DECADE** (2017-004709-42) | Exenatide QW + Dapagliflozin | 6 | 17 | Type 2 diabetes, HbA1c ≥ 7.5% and <10%, eGFR > 30 ml/min/1.73m2, urine albumin:creatinine ratio >3.5mg/mmol  | Change in urine albumin:creatinine ratio | 2020 |
| **DECREASE** (NCT03361098) | Exenatide BD + Dapagliflozin | 16 | 64 | Type 2 diabetes, HbA1c 7.5–10%, BMI 30-40 kg/m2  | Difference in neuronal activity in central reward and satiety circuits (BOLD)  | Unknown |
| **EXENDA** (NCT03007329) | Exenatide QW+ Dapagliflozin | 24 | 90 | Type 2 diabetes, HbA1c >=6.5% and <=11%, BMI>=25 kg/m2 | Change in liver fat (%)  | Completed(Results awaited) |
| **RESILIENT**(2015-005242-60) | Exenatide QW + Dapagliflozin | 32 | 120 | Type 2 diabetes, HbA1c >=6.5% and <=11%, BMI 30-50 kg/m2  | Change in total body fat mass (%)  | 2021 |
| **DEXBASU** (2017-001454-33) | Exenatide QW + Dapagliflozin | 24 | 56 | Type 2 diabetes, HbA1c ≥ 7.0 - ≤ 10.0%, BMI of ≥ 35.0 - ≤ 42.5 kg/m2. | Proportion achieving a BMI ≤ 35.0 kg/m2 or a BMI ≤ 40.0 kg/m2 plus an HbA1c ≤ 6.0% | 2020 |
| Effect of GLP-1 RA, Exenatide on Glucosuria Induced Elevation in Endogenous Glucose Production (NCT02981069) | Exenatide BD/QW + Dapagliflozin | 16 | 80 | Type 2 diabetes, > 7.0%- < 10.0%, BMI of 25- 35 kg/m2 | Change in EGP | 2021 |
| **Table 5** Ongoing randomised controlled trials with combination of an SGLT2 inhibitor and GLP-1 receptor agonist.BD, twice daily; BMI, body mass index; BOLD, Blood-oxygen-level-dependent; DEXA, Dual energy x-ray absorptiometry; EGP, endogenous glucose production; QW, once weekly. |

**References**

1. Brown E, Rajeev SP, Cuthbertson DJ, Wilding JPH. A review of the mechanism of action, metabolic profile and haemodynamic effects of sodium-glucose co-transporter-2 inhibitors. *Diabetes Obes Metab* 2019; **21**: 9-18.

2. Wilding JP. The role of the kidneys in glucose homeostasis in type 2 diabetes: clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. *Metabolism* 2014; **63**: 1228-37.

3. Yakovleva T, Sokolov V, Chu L, et al. Comparison of the urinary glucose excretion contributions of SGLT2 and SGLT1: A quantitative systems pharmacology analysis in healthy individuals and patients with type 2 diabetes treated with SGLT2 inhibitors. *Diabetes, Obesity and Metabolism* 2019; **21**: 2684-93.

4. Hussein H, Zaccardi F, Khunti K, et al. Efficacy and tolerability of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: A systematic review and network meta-analysis. *Diabetes Obes Metab* 2020; **22**: 1035-46.

5. Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. *Ann Intern Med* 2019; **171**: 248-56.

6. Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2017; **19**: 348-55.

7. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier Gangrene Associated With Sodium–Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing CasesFournier Gangrene Associated With Sodium–Glucose Cotransporter-2 Inhibitors. *Annals of Internal Medicine* 2019; **170**: 764-9.

8. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019; **380**: 2295-306.

9. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019; **380**: 347-57.

10. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 2117-28.

11. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med* 2020; **383**: 1425-35.

12. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; **383**: 1436-46.

13. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2019; **7**: 845-54.

14. Cahn A, Melzer-Cohen C, Pollack R, Chodick G, Shalev V. Acute renal outcomes with sodium-glucose co-transporter-2 inhibitors: Real-world data analysis. *Diabetes Obes Metab* 2019; **21**: 340-8.

15. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 644-57.

16. Zelniker TA, Bonaca MP, Furtado R, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: Insights from the DECLARE-TIMI 58 Trial. *Circulation* 2020; **141**: 1227-34.

17. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**: 1995-2008.

18. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**: 1413-24.

19. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2020. (Online ahead of print).

20. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med* 2020. (Online ahead of print).

21. Kosiborod M, Cavender MA, Fu AZ, et al. Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study. *Circulation* 2017; **136**: 249-59.

22. Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL 2 Study. *J Am Coll Cardiol* 2018; **71**: 2628-39.

23. Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol* 2020; **8**: 27-35.

24. Birkeland KI, Jorgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. *Lancet Diabetes Endocrinol* 2017; **17**: 30258-9.

25. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol* 2021; **9**: 22-31.

26. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: Systematic review and meta-analysis of randomized controlled trials. *Diab Obes Metab* 2018; **20**: 1755-61.

27. Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation* 2019; **139**: 2528-36.

28. Figtree GA, Rådholm K, Barrett TD, et al. Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus. *Circulation* 2019; **139**: 2591-3.

29. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. *Diab Obes Metab* 2016; **18**: 317-32.

30. Lim GE, Brubaker PL. Glucagon-Like Peptide 1 Secretion by the L-Cell. The View From Within. *Diabetes* 2006; **55**: S70-S7.

31. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet (London, England)* 2008; **372**: 1240-50.

32. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *The Journal of clinical endocrinology and metabolism* 2011; **96**: 1301-10.

33. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet (London, England)* 2013; **381**: 117-24.

34. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; **374**: 39-47.

35. Rosenstock J, Raccah D, Koranyi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care* 2013; **36**: 2945-51.

36. Pratley RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol* 2014; **2**: 289-97.

37. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 2014; **37**: 2159-67.

38. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 2014; **384**: 1349-57.

39. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2019; **46**: 100-9.

40. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. *Diabetes Care* 2018; **41**: 258-66.

41. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018; **6**: 275-86.

42. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet (London, England)* 2019; **394**: 39-50.

43. Nauck MA, Meier JJ. Management of endocrine disease: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? *Eur J Endocrinol* 2019; **181**: R211-r34.

44. Ostawal A, Mocevic E, Kragh N, Xu W. Clinical Effectiveness of Liraglutide in Type 2 Diabetes Treatment in the Real-World Setting: A Systematic Literature Review. *Diabetes Ther* 2016; **7**: 411-38.

45. Storgaard H, Cold F, Gluud LL, Vilsboll T, Knop FK. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. *Diabetes Obes Metab* 2017; **19**: 906-8.

46. Faillie JL, Yu OH, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of Bile Duct and Gallbladder Diseases With the Use of Incretin-Based Drugs in Patients With Type 2 Diabetes Mellitus. *JAMA Intern Med* 2016; **176**: 1474-81.

47. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **374**: 1834-44.

48. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med* 2015; **373**: 2247-57.

49. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 311-22.

50. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2017; **38**: 1228-39.

51. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet (London, England)* 2018; **392**: 1519-29.

52. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet (London, England)* 2019; **394**: 121-30.

53. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2019; **381**: 841-51.

54. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; **7**: 776-85.

55. Barkas F, Elisaf M, Milionis H. Protection against stroke with glucagon-like peptide 1 receptor agonists: a systematic review and meta-analysis. *Eur J Neurol* 2019; **26**: 559-65.

56. Gerstein HC, Hart R, Colhoun HM, et al. The effect of dulaglutide on stroke: an exploratory analysis of the REWIND trial. *Lancet Diabetes Endocrinol* 2020; **8**: 106-14.

57. Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018; **6**: 859-69.

58. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; **6**: 605-17.

59. Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2016; **4**: 221-32.

60. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med* 2015; **373**: 11-22.

61. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. *Jama* 2015; **314**: 687-99.

62. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes* 2016; **40**: 1310-19.

63. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet (London, England)*; **389**: 1399-409.

64. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med* 2021.

65. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 2005; **54**: 603-8.

66. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet (London, England)* 2016; **387**: 679-90.

67. Kuchay MS, Krishan S, Mishra SK, et al. Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial). *Diabetes Care* 2018; **41**: 1801-8.

68. Eriksson JW, Lundkvist P, Jansson PA, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. *Diabetologia* 2018; **61**: 1923-34.

69. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *New England Journal of Medicine* 2020. (Online ahead of print).

70. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2016; **4**: 1004-16.

71. Lingvay I, Catarig AM, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019; **7**: 834-44.

72. Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care* 2019; **42**: 2272-81.

73. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Co-Transporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials. *Circulation* 2019; **139**: 2022-31.

74. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet (London, England)* 2019; **393**: 31-9.

75. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020; **43**: 487-93.

76. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; **41**: 2669-701.

77. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41**: 255-323.

78. Ludvik B, Frias JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018; **6**: 370-81.

79. Zinman B, Bhosekar V, Busch R, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; **7**: 356-67.

80. Lundkvist P, Sjostrom CD, Amini S, Pereira MJ, Johnsson E, Eriksson JW. Dapagliflozin once-daily and exenatide once-weekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. *Diabetes Obes Metab* 2017; **19**: 49-60.

81. Gastaldelli A, Repetto E, Guja C, et al. Exenatide and dapagliflozin combination improves markers of liver steatosis and fibrosis in patients with type 2 diabetes. *Diabetes Obes Metab* 2020; **22**: 393-403.

82. Henry RR, Rosenstock J, Logan DK, Alessi TR, Luskey K, Baron MA. Randomized Trial of Continuous Subcutaneous Delivery of Exenatide by ITCA 650 Versus Twice-Daily Exenatide Injections in Metformin-Treated Type 2 Diabetes. *Diabetes Care* 2013; **36**: 2559-65.

83. Rosenstock J, Buse JB, Azeem R, et al. Efficacy and Safety of ITCA 650, a Novel Drug-Device GLP-1 Receptor Agonist, in Type 2 Diabetes Uncontrolled With Oral Antidiabetes Drugs: The FREEDOM-1 Trial. *Diabetes Care* 2017; **41**: 333-40.

84. Frias JP, Bastyr EJ, 3rd, Vignati L, et al. The Sustained Effects of a Dual GIP/GLP-1 Receptor Agonist, NNC0090-2746, in Patients with Type 2 Diabetes. *Cell Metab* 2017; **26**: 343-52.e2.

85. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 1228-39.

86. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394**: 121-30.

87. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2019; **381**: 841-51.