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

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SGLT2 inhibitors and GLP-1 receptor agonists are used in patients with type 2 diabetes as glucose lowering therapies, with additional benefits of weight loss and blood pressure reduction. Data from cardiovascular outcome trials have highlighted that these drugs confer protection against major cardiovascular disease in those with established atherosclerotic cardiovascular disease, reduce the risk of admission to hospital for heart failure, and reduce cardiovascular and all-cause mortality. Ongoing research using hard renal endpoints such as end stage kidney disease rather than surrogate markers might clarify the renoprotective benefits of both agents. When used for glucose lowering, SGLT2 inhibitors are most effective if the estimated glomerular filtration rate is more than 60 ml per min per 1.73m² at initiation and should be avoided where there is a risk of diabetic ketoacidosis. GLP-1 receptor agonists are contraindicated in those with a history of medullary thyroid cancer and used with caution in patients with a history of pancreatitis of a known cause. These drugs are now second-line, or even arguably first-line, glucose lowering therapies in patients with cardiorenal disease, irrespective of glycaemic control. If an SGLT2 inhibitor or GLP-1 receptor agonist is considered suitable in patients with type 2 diabetes, treatment should be prioritised according to existing evidence: GLP-1 receptor agonists should be considered in patients at a high risk of, or with established, cardiovascular disease and SGLT2 inhibitors considered for patients with heart failure (with reduced ejection fraction) or chronic kidney disease (with or without established cardiovascular disease). There is now compelling data on the benefits of these drugs for a range of other clinical indications even without type 2 diabetes, including for GLP-1 receptor agonists in patients with obesity and overweight with weight-related comorbidities.

Introduction

Type 2 diabetes has a major disease burden, including cardiovascular disease (CVD) and renal or chronic kidney disease (CKD). Although intensive glucose control reduces microvascular complications in type 1 and type 2 diabetes, trials of glucose lowering therapies have shown variable effects on CVD (possible harm with some drugs and other drugs showing no benefit). The regulatory requirements for cardiovascular outcome trials (CVOTs) for newer glucose lowering therapies has yielded

important and unexpected outcomes for SGLT2 inhibitors and GLP-1 receptor agonists. Aside from metabolic efficacy and cardiovascular safety, these drugs confer cardiorenal protection and, particularly for SGLT2 inhibitors, can prevent and treat heart failure. Considering their dual effect on bodyweight and glycaemic control, combining these two classes is attractive in type 2 diabetes, but there is emerging evidence of multiple benefits for a range of clinical indications in patients without type 2 diabetes. This Review will describe and compare the evidence around the SGLT2 inhibitors and GLP-1 receptor agonists individually and in combination.

Search strategy and selection criteria

We obtained citations for this publication through searches of PubMed up to May 12, 2021, with no lower limit set for the date, using both MeSH and free-text terms to identify relevant articles. The terms "glucagon-like peptide-1 receptor agonist" and "sodium glucose cotransporter 2 inhibitor" (including "exenatide", "lixisenatide", "albiglutide", "dulaglutide", "liraglutide", "semaglutide", "canagliflozin", "dapagliflozin", "empagliflozin", and "ertugliflozin") were searched for. We reviewed guidelines for the management of type 2 diabetes and cardiovascular disease published by the American Diabetes Association, European Association for the Study of Diabetes, and European Society of Cardiology. We also searched ClinicalTrials.gov, EudraCT, and conference abstracts for additional eligible studies and trial information. We supplemented this with articles from the personal databases of the authors of this paper and reviewed relevant references cited in retrieved articles and review articles. We restricted the search to human studies. We used no language restrictions.

SGLT2 inhibitors

Mechanism of action

SGLT2 inhibitors are inhibitors of renal glucose reabsorption resulting in substantial glycosuria. Most compounds are highly selective for SGLT2, which is located in the renal proximal tubules, 200–2500 times more selective than for SGLT1, which is located in the kidneys and gut.^{1–3} At therapeutic doses, approximately 60–100 g of glucose is excreted in the urine, thus directly removing glucose from the systemic circulation and lowering blood glucose. This simple method of action increases urinary glucose excretion and an osmotic diuresis is associated with multiple and complex secondary effects, which are not explored further in this Review.

Summary of key drugs in the class

There are five oral SGLT2 inhibitors available in Europe. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are approved by the European Medicines Agency

and the Federal Drug Administration, and sotagliflozin (an SGLT1 and 2 inhibitor with a 20:1 selectivity for SGLT2) is approved only by the European Medicines Agency for use in type 1 diabetes. Several other SGLT2 inhibitors, approved in Japan, will not be discussed further. There are modest differences in the pharmacology of these inhibitors, but all are orally bioavailable and have circulating half-lives suitable for administration once per day.

Glycaemic, weight, and blood pressure benefits

The clinical development of all SGLT2 inhibitors showed their glucose lowering efficacy, in that there were reductions in glycated haemoglobin (HbA_{1c}) 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, bodyweight reduced by approximately 2 kg, and there was a clinically significant reduction by approximately 2·5–5·0 mm Hg for systolic blood pressure

	EMPA-REG ¹⁰ (empagliflozin vs placebo, n=7020)	DECLARE-TIMI ⁹ (dapagliflozin vs placebo, n=17160)	CANVAS ¹⁵ (canagliflozin vs placebo, n=10142)	VERTIS ¹⁴ (ertugliflozin vs placebo, n=8246)	CREDENCE ⁸ (canagliflozin vs placebo, n=4401)
Main inclusion criteria	Established cardiovascular disease, eGFR >30 mL per min per 1·73 m ²	Established cardiovascular disease (40·6%) or multiple cardiovascular risk factors (59·4%)	Established cardiovascular disease	Aged older than 40 years, established cardiovascular disease	Albuminuric chronic kidney disease: eGFR 30 to <90 mL per min per 1·73 m ² and an albumin-to-creatinine ratio of >300 to ≤5000 mg/g
Key cardiovascular outcome: major adverse cardiovascular events					
Placebo	43·9	24·2	31·5	40·0	48·7
SGLT2 inhibitor	37·4	22·6	26·9	39·0	38·7
HR (95% CI)	0·86 (0·74–0·99)	0·93 (0·84–1·03)	0·86 (0·75–0·97)	0·97 (0·85–1·11)	0·80 (0·67–0·95)
Key cardiovascular outcome: cardiovascular death					
Placebo	20·2	7·1	12·8	19	24·4
SGLT2 inhibitor	12·4	7·0	11·6	18	19·0
HR (95% CI)	0·62 (0·49–0·77)	0·98 (0·82–1·17)	0·87 (0·72–1·06)	0·92 (0·77–1·11)	0·78 (0·61–1·00)
Key cardiovascular outcome: cardiovascular death or admission to hospital for heart failure					
Placebo	30·1	14·7	20·8	27·0	45·4
SGLT2 inhibitor	19·7	12·2	16·3	23·0	31·5
HR (95% CI)	0·66 (0·55–0·79)	0·83 (0·73–0·95)	0·78 (0·67–0·91)	0·88 (0·75–1·03)	0·69 (0·57–0·83)
Key cardiovascular outcome: all-cause mortality					
Placebo	28·6	16·4	19·5	26·0	35·0
SGLT2 inhibitor	19·4	15·1	17·3	24·0	29·0
HR (95% CI)	0·68 (0·57–0·82)	0·93 (0·82–1·04)	0·87 (0·74–1·01)	0·93 (0·80–1·08)	0·83 (0·68–1·02)
Key cardiovascular outcome: admission to hospital for heart failure					
Placebo	14·5	8·5	8·7	11·0	25·3
SGLT2 inhibitor	9·4	6·2	5·5	7·0	15·7
HR (95% CI)	0·65 (0·50–0·85)	0·73 (0·61–0·88)	0·67 (0·52–0·87)	0·70 (0·54–0·90)	0·61 (0·4–0·80)
Key cardiovascular outcome: myocardial infarction					
Placebo	19·3	13·2	12·6	17·0	..
SGLT2 inhibitor	16·8	11·7	11·2	18·0	..
HR (95% CI)	0·87 (0·70–1·09)	0·89 (0·77–1·01)	0·89 (0·73–1·09)	1·04 (0·86–1·26)	..
Key cardiovascular outcome: stroke					
Placebo	10·5	6·8	9·6	9·0	..
SGLT2 inhibitor	12·3	6·9	7·9	10·0	..
HR (95% CI)	1·18 (0·89–1·56)	1·01 (0·84–1·21)	0·87 (0·69–1·09)	1·06 (0·82–1·37)	..
Key renal outcome: doubling of serum creatinine and eGFR ≤45 mL per min per 1·73 m ² , renal replacement therapy, or renal-related death					
Placebo	11·5	..	..	..	..
SGLT2 inhibitor	6·3	..	..	..	..
HR (95% CI)	0·54 (0·40–0·75)	..	..	..	..
Key renal outcome: doubling serum creatinine, dialysis or transplant, or renal-related death					
Placebo	..	..	..	12·0	..
SGLT2 inhibitor	..	..	..	9·0	..
HR (95% CI)	..	..	..	0·81 (0·63–1·04)	..

(Table 1 continues on next page)

	EMPA-REG ¹⁰ (empagliflozin vs placebo, n=7020)	DECLARE-TIMI ⁹ (dapagliflozin vs placebo, n=17 160)	CANVAS ¹⁵ (canagliflozin vs placebo, n=10 142)	VERTIS ¹¹ (ertugliflozin vs placebo, n=8246)	CREDENCE ⁸ (canagliflozin vs placebo, n=4401)
(Continued from previous page)					
Key renal outcome: doubling of serum creatinine, end-stage kidney disease, or renal or cardiovascular death					
Placebo	..	..	..	..	61.2
SGLT2 inhibitor	..	..	..	..	43.2
HR (95% CI)	..	..	..	..	0.70 (0.59–0.82)
Key renal outcome: >40% reduction to eGFR <60 mL per min per 1.73 m ² , end-stage kidney disease, or renal or cardiovascular death					
Placebo	..	7.0	..	..	..
SGLT2 inhibitor	..	3.7	..	..	..
HR (95% CI)	..	0.53 (0.43–0.66)	..	..	..
Key renal outcome: 40% reduction in eGFR, renal replacement therapy, or renal-related death					
Placebo	..	..	9.0	..	..
SGLT2 inhibitor	..	..	5.5	..	..
HR (95% CI)	..	..	0.60 (0.47–0.77)	..	..
Key renal outcome: dialysis, renal transplant, or renal-related death					
Placebo	..	..	..	..	18.6
SGLT2 inhibitor	..	..	..	..	13.6
HR (95% CI)	..	..	..	..	0.72 (0.54–0.97)
Key renal outcome: progression of albuminuria					
Placebo	..	..	128.7	..	..
SGLT2 inhibitor	..	..	89.4	..	..
HR (95% CI)	..	..	0.73 (0.67–0.79)	..	..
Key renal outcome: incident or worsening nephropathy					
Placebo	76.0	..	..	..	..
SGLT2 inhibitor	47.8	..	..	..	..
HR (95% CI)	0.61 (0.53–0.70)	..	..	..	..
Key renal outcome: initiation of renal replacement therapy					
Placebo	2.1	..	..	..	..
SGLT2 inhibitor	1.0	..	..	..	..
HR (95% CI)	0.45 (0.21–0.97)	..	..	..	..
Key renal outcome: end-stage kidney disease					
Placebo	..	..	..	..	29.4
SGLT2 inhibitor	..	..	..	..	20.4
HR (95% CI)	..	..	..	..	0.68 (0.54–0.86)
Outcome shown as event rate per 1000 patient-years. Primary outcome measure was three-point MACE: non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes or four-point MACE: composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation where the primary diagnosis was unstable angina. eGFR=estimated glomerular filtration rate. HR=hazard ratio. MACE=major adverse cardiovascular events.					

Table 1: Summary of the major randomised controlled cardiovascular and renal outcome trials with SGLT2 inhibitors in type 2 diabetes

and 1–2 mm Hg for diastolic blood pressure.⁴ All SGLT2 inhibitors can be initiated if the estimated glomerular filtration rate (eGFR) is more than 60 mL per min per 1.73 m² and should be reviewed if the eGFR is less than 45 mL per min per 1.73 m² because of a diminished glucose lowering effect. The Federal Drug Administration and European Medicines Agency have approved the continued use of canagliflozin in patients with a urinary albumin-to-creatinine ratio (UACR) of 300 mg/g and eGFR of less than 30 mL per min per 1.73 m² until renal replacement therapy because of its renoprotective benefits. The dose adjustment recommendations should be referred to per the kidney functions and indications of use specific to the agent within the class.

Adverse effects

These include polyuria because of diuresis and fungal genital infections (treated with standard antifungal therapy, topical or systemic fluconazole) affecting up to 10% of women and 2–3% of men.⁵ Although most cases of polyuria only occur on initiation, in some patients this requires treatment discontinuation. Meta-analyses and observational studies suggest that there is no increased risk of bacterial urinary tract infections,^{5,6} including pyelonephritis, with background risk similar to that for other patients with type 2 diabetes. However, reviewing this therapy should be considered if the patient has had recurrent urinary tract infections. Spontaneous event reporting has led to concern regarding Fournier's

gangrene,⁷ although there was no increased risk in large randomised controlled trials (CREDENCE, DAPA-CKD, DECLARE, EMPA-REG, and VERTIS).^{8–12}

Diabetic ketoacidosis also emerged as a rare adverse event (<0·1%) from spontaneous reporting, subsequently supported in several large randomised controlled trials, particularly in patients with type 1 diabetes. 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, secondary to diuresis. Data from randomised controlled trials and propensity-matched analyses of real-world data do not support an increased risk of acute kidney injury from SGLT2 inhibitor use.^{13,14} Minor changes in phosphate metabolism and parathyroid hormones might increase the risk of fractures, although the risk seems low and confined to canagliflozin. Finally, a higher rate of leg amputations with canagliflozin in the CANVAS trials,¹⁵ prompting guidance to avoid SGLT2 inhibitors in people at a high risk of amputation, was not subsequently seen in other CVOTs or CREDENCE.⁸

Effect of SGLT2 inhibitors on cardiorenal outcomes in type 2 diabetes

Four randomised controlled CVOTs and a renal outcomes trial with SGLT2 inhibitors in people with type 2 diabetes are summarised in table 1.^{8–10,15}

Cardiovascular benefits

Data from the CVOTs reveal several clear themes (figure, appendix p 1): a 30% reduction in admission to hospital for heart failure (where the primary diagnosis is heart failure) is seen with all the drugs in the class, independent of a background of CVD or a known history of heart failure. Event rates, and thus numbers needed to treat, depend on background risk. There is also a reduction in heart failure-related and arrhythmia-related deaths. Further analysis of DECLARE data has also shown a reduction in atrial fibrillation, a finding not yet confirmed in a dedicated randomised controlled trial.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 the use of SGLT2 inhibitors in the treatment of patients with type 2 diabetes and established heart failure with reduced ejection fraction (HFrEF).^{17,18} DAPA-HF showed a 26% reduction in worsening HFrEF or cardiovascular 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 heart failure and CKD (suggesting that early SGLT2 initiation might be

helpful) although both trials were terminated early because of the COVID-19 pandemic.^{19,20}

Observational data of cardiovascular effects of SGLT2 inhibitors

So-called real-world outcomes with SGLT2 inhibitors, using large datasets from health insurance databases and national health systems from multiple countries (CVD-REAL 1, 2, and 3, THIN, EASEL, and EMPRISE; appendix p 1),^{21–24} provide reassurance that the reductions in admissions to hospital for heart failure, mortality, and preservation of renal function are reproducible in routine clinical practice.

Renal benefits

Secondary or exploratory analyses from the aforementioned studies suggested renal benefits (eg, a slower decline in eGFR) with less end-stage renal disease with SGLT2 inhibitors (table 1, appendix p 2). CREDENCE, the first renal outcome trial of a diabetes medication, recruited approximately 4500 patients with type 2 diabetes and CKD with proteinuria (eGFR of 30–90 mL per min per 1·73 m² and UACR of >300 mg/g and ≤5000 mg/g).⁸ The study confirmed renoprotection (30% reduction) in composite renal outcome and cardiovascular protection in this group. The licences for canagliflozin in the USA and Europe have been updated to reflect these findings, now indicated for the treatment of diabetic kidney disease with an eGFR of more than 30 mL per min per 1·73 m². The results of the DAPA-CKD trial extended these findings to a broader population of patients with CKD, showing the renoprotective effects of the SGLT2 inhibitor dapagliflozin in patients with CKD, with or without type 2 diabetes.^{12,25}

See Online for appendix

Use of SGLT2 inhibitors as treatment adjunct in type 1 diabetes

For people with type 1 diabetes in Europe, but not the USA, dapagliflozin and sotagliflozin have been approved for patients with a suboptimal control of insulin and a body mass index (BMI) of more than 27 kg/m² based on safety and efficacy data from the phase 3 DEPICT (dapagliflozin) and TANDEM (sotagliflozin) clinical programmes. Pooled analysis from these clinical programmes supported the European Medicines Agency decision to limit their use to those with a BMI of more than 27 kg/m² because of lower rates of diabetic ketoacidosis. Meta-analysis data has shown the benefits of adjunctive SGLT2 use in type 1 diabetes with evidence of improved glycaemic control, smaller glucose excursions, and weight loss without increasing hypoglycaemia risk.²⁶ Safety concerns about diabetic ketoacidosis should be addressed with a commitment to monitor blood glucose and ketone concentrations. SGLT2 inhibitors should be avoided in patients who are poorly compliant or those with recurrent diabetic ketoacidosis and should be discontinued during acute illness or surgical intervention.

Figure: Cardiovascular outcomes from the key cardiovascular outcome trials with (A) SGLT2 inhibitors versus placebo (grey bars) and (B) GLP-1 receptor agonists versus placebo (grey bars)

Data are shown as incidence per 1000 patient-years. HR=hazard ratio. MACE=major adverse cardiovascular events. * <0.05 versus placebo. Caution should be used when comparisons are made between individual trials because of differences in trial design and baseline characteristics.

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 that have exclusively included patients without type 2 diabetes. 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 type 2 diabetes.¹² One other large clinical trial with renal specific endpoints, EMPA-KIDNEY (NCT03594110), has been initiated in people with and without type 2 diabetes, with non-proteinuric kidney disease, in other words those with an eGFR of less than 45 mL per min per 1.73 m², with or without albuminuria.

Treatment of HFrEF

The results of the DAPA-HF and EMPEROR-reduced trials strongly support the use of an SGLT2 inhibitor in the treatment of patients with established HFrEF with reductions in worsening HFrEF or cardiovascular deaths with or without type 2 diabetes.^{17,18} Notably, 45–55% of patients did not have a history of type 2 diabetes at baseline.

The benefits were similar in patients with and without diabetes, suggesting that the benefits were independent of glycaemia. Post-hoc analysis of two CVOTs suggested that the same benefits are not seen in patients with heart failure with preserved ejection fraction,^{27,28} and the results of dedicated studies in this patient group are still awaited (NCT03057951 and NCT03619213). Notably, dapagliflozin also reduced the risk of new onset of type 2 diabetes by 32% (hazard ratio [HR] 0.68; 95% CI 0.50–0.94) compared with those receiving placebo among at risk patients with prediabetes; a similar effect size to that seen with metformin in diabetes prevention studies (approximately 31%). In the SOLOIST-WHF study, in which all patients had type 2 diabetes, the benefits were consistent in those with HFrEF and heart failure with preserved ejection fraction.¹⁹ After the results from DAPA-HF, the Federal Drug Administration and European regulators have approved the use of dapagliflozin to reduce the risk of cardiovascular death or worsening heart failure in patients with HFrEF, with and without type 2 diabetes.

GLP-1 receptor agonists

Mechanism of action

GLP-1 is 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, additionally stimulating β -cell neogenesis and inhibiting apoptosis, and reducing glucagon secretion from α -cells (shown in rodent models).²⁹ Insulin secretion is only increased above approximately 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

Summary of key drugs in class

Several GLP-1 receptor agonists are approved for use in type 2 diabetes: exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide.³¹ All are administered as subcutaneous injections, although oral semaglutide is available. These molecules were developed on the basis of the structure of either Gila monster (*Heloderma suspectum*) 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 dipeptidyl

peptidase-4 degradation; their half-lives vary between 2–3 h and several days. These molecular differences translate to distinct clinical effects.

The first type of receptor agonists, short-acting GLP-1 receptor agonists (including exenatide twice per day and lixisenatide once per day), are structurally based on exendin-4, with a 90–97% sequence homology. Relative to long-acting GLP-1 receptor agonists, these molecules have a more pronounced slowing of gastric emptying and a lesser effect on insulin secretion, more potently affecting post-prandial (vs fasting) plasma glucose concentrations.

The second type of receptor agonists, long-acting GLP-1 receptor agonists, 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 receptor agonists more profoundly affect fasting (vs post-prandial) and have a greater effect on 24-h glucose profiles.

Glycaemic, weight, and blood pressure effects

Each GLP-1 receptor agonist has been studied as a monotherapy or in combination with other glucose lowering therapies, and irrespective of differences in study design, duration, and patient characteristics, they

	Treatment groups	Duration (weeks)	Inclusion criteria	Change in HbA _{1c}	Change in weight (kg)
DURATION 1 ³²	Exenatide 10 µg twice per day vs exenatide 2 mg once per week	30	Therapy with diet and exercise, or with one to two oral antidiabetic drugs (metformin, sulfonylureas, or thiazolidinediones, or a combination) and HbA _{1c} 7.1–11.0%	–1.5% vs –1.9% (p=0.0023)	–3.6 vs –3.7 (NS)
DURATION 5 ³³	Exenatide 2 mg once per week vs exenatide 10 µg twice per day	24	Drug-naïve, given one or more oral medication	–1.6% vs –0.9%	–2.3 vs –1.4 (NS)
DURATION 6 ³⁴	Exenatide 2 mg once per week vs liraglutide 1.8 mg once per day	26	Lifestyle modification and oral anti-diabetes medications	–1.28% vs –1.48% (p=0.2)	–2.68 vs –3.57 (p=0.0005)
LEAD 6 ³⁵	Exenatide 10 µg twice per day vs liraglutide 1.8 mg once per day	26	Maximally tolerated doses of metformin, sulfonylureas, or both	–0.79 vs –1.12 (p<0.0001)	–2.87 vs –3.24 (NS)
GET GOAL X ³⁶	Lixisenatide 20 µg once per day vs exenatide 10 µg twice per day	24	Inadequately controlled with metformin, HbA _{1c} 7–10%	–0.79 vs –0.96 (NS)	–2.96 vs –3.98
HARMONY 7 ³⁷	Albiglutide once per week vs liraglutide once per day	32	Inadequately controlled, BMI 20–45 kg/m ²	–0.78 vs –0.99	–0.64 vs –2.16 (p<0.0001)
AWARD 1 ³⁸	Dulaglutide 0.75 mg vs 1.5 mg once per week vs exenatide 10 µg twice per day	26	Inadequately controlled HbA _{1c} 7–11% on monotherapy or 7–10% on combination, BMI 23–45 kg/m ²	–1.30 vs –1.51 vs –0.99	0.20 vs –1.30 vs –1.07 (p<0.001)
AWARD 6 ³⁹	Dulaglutide 1.5 mg once per week vs liraglutide 1.8 mg once per day	26	Inadequately controlled HbA _{1c} 7–10% on metformin, BMI <45 kg/m ²	–1.42 vs –1.36 (p<0.0001, non-inferiority)	–2.90 vs –3.61
SUSTAIN 3 ⁴⁰	Semaglutide once per week vs exenatide 2 mg once per week	56	HbA _{1c} 7.0–10.5%, on one or two oral agents	–1.5 vs –0.9	–5.6 vs –1.9
SUSTAIN 10 ⁴¹	Semaglutide once per week vs liraglutide once per day	30	HbA _{1c} 7.0–10.5%, on one to three oral agents	–1.7 vs –1.0	–5.8 vs –1.9
SUSTAIN 7 ⁴²	Semaglutide 0.5 mg vs dulaglutide 0.75 mg vs semaglutide 1.0 mg vs dulaglutide 1.5 mg, all once per week	40	Inadequately controlled HbA _{1c} 7.0–10.5% 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 ⁴³	Oral semaglutide 14 mg vs liraglutide 1.8 mg, all once per day	52	Metformin treatment with or without an SGLT2 inhibitor	–1.2 vs –0.9	–4.4 vs –3.1

NS=non-significant. BMI=body-mass index. HbA_{1c}=glycated haemoglobin.

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

show a consistent efficacy in lowering HbA_{1c}, weight, and blood pressure (2–3 mm Hg) with a small increase in heart rate (summarised in table 2).^{32–43} Longer acting GLP-1 receptor agonists and once per week preparations seem to more potently lower glucose and cause less gastrointestinal upset compared with shorter acting GLP-1 receptor agonists⁴⁴ with greater weight loss at higher doses of semaglutide and dulaglutide. The PIONEER programme highlights the use of oral semaglutide across a wide range of patients, compared with liraglutide (PIONEER 4), with similar reductions in HbA_{1c} but with slightly greater weight loss.⁴³

Liraglutide is the most studied GLP-1 receptor agonist in the real world, with one systematic review of uncontrolled observational data suggesting that after 6 months, there was a mean change in HbA_{1c} from –0.9% to –2.2% with a mean change in absolute weight from baseline of –1.3 to –8.65 kg.⁴⁵ UK real-world data might be biased by application of so-called stopping rules that stipulate thresholds of changes in HbA_{1c} and weight indicating when treatment with a GLP-1 receptor agonists should be discontinued.

Combination with insulin

Randomised controlled trial data also supports the combination therapy of a GLP-1 receptor agonist with basal insulin, considering insulin's contribution to weight gain and hypoglycaemia. Several fixed-ratio combination products of GLP-1 receptor agonists and basal insulin are available in a single injection or device (insulin degludec with liraglutide and insulin glargine with lixisenatide).

Adverse effects

The most common adverse effects of GLP-1 receptor agonists are gastrointestinal, particularly nausea (25–60%) and vomiting (5–15%); generally of mild to moderate severity, decreasing over time, with lower rates of discontinuation for gastrointestinal upset (5–10%). Occasionally, there might be injection-site reactions, headaches, and nasopharyngitis. Because of their glucose-dependent mechanism of action, these agonists have a minimal risk of hypoglycaemia except when used with sulfonylureas or insulin.

The risk of acute pancreatitis and pancreatic carcinoma is higher in people with type 2 diabetes who are obese than in 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 receptor agonists than in those receiving other forms of anti-diabetes treatments.⁴⁶ These drugs are associated with an increased risk of bile duct and gallbladder disease and so patients are more likely to undergo a cholecystectomy,⁴⁷ and so should be counselled accordingly.

Concerns about C-cell proliferation and formation of medullary thyroid carcinomas seen in rodent studies are not borne out in clinical trials (normal human thyroid

tissue has low or absent GLP-1 receptor expression). Nonetheless, patients at a risk of medullary thyroid carcinomas should not be prescribed GLP-1 receptor agonists.

Diabetic ketoacidosis has been reported in patients with type 2 diabetes on a combination of a GLP-1 receptor agonists 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.⁴⁸

In SUSTAIN-6, higher than expected rates of diabetic retinopathy complications occurred with semaglutide (3%) than placebo (1.8%).⁴⁹ Rapid improvement in glucose control has been associated with the temporary worsening of diabetic retinopathy, but a direct effect of semaglutide cannot be excluded. The trials in a phase 3a programme were not designed for systematic evaluation of retinopathy progression, unlike endpoints such as those in the Early Treatment Diabetic Retinopathy Study (ETDRS), which is assessing both severity and changes over time. Clinical trials studying the long-term effects of GLP-1 receptor agonists are underway (NCT03811561).

Effect 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 receptor agonists, the results of various studies in heterogeneous patient populations have amassed substantial evidence to show the clear role of GLP-1 receptor agonists in cardiovascular, renal, and stroke protection, and their effect on mortality in patients with type 2 diabetes (table 3, appendix p 3).

Cardiovascular benefits

Of seven CVOT trials, ELIXA was the first major CVOT with a GLP-1 receptor agonist, examining the short-acting agent lixisenatide in patients with type 2 diabetes and acute coronary syndrome.⁵⁰ Although this study showed cardiovascular safety, it did not indicate a benefit. In contrast, all subsequent GLP-1 CVOTs have shown benefit in reducing the risk of cardiovascular events versus standard care (figure).^{49,51,53,56–58}

One meta-analysis of cardiovascular and kidney outcomes in the seven GLP-1 receptor agonist CVOTs, with a combined total of 56 004 participants, substantiated that GLP-1 receptor agonist treatment reduces major adverse cardiovascular event (MACE) and all-cause mortality by 12% (HR 0.88; 95% CI 0.82–0.94 for MACE and 95% CI, 0.83–0.95 for all-cause mortality).⁵⁹ Importantly, admission to hospital for heart failure was also reduced by 9% (HR 0.91, 95% CI 0.83–0.99).

Stroke protection

GLP-1 receptor agonists might also exert neuroprotective effects, with some CVOT data showing reductions in stroke. A systematic review and meta-analysis of five multicentre, randomised, placebo-controlled trials

(ELIXA, LEADER, SUSTAIN, EXSCEL, and HARMONY) showed a 13% reduction in the risk of total stroke from GLP-1 treatment (risk ratio 0·87; 95% CI 0·78–0·98) but no protection when only fatal stroke was included.⁶⁰ An exploratory analysis of outcomes in the REWIND trial

indicates that dulaglutide might 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.⁶¹

	ELIXA (2015) ⁵⁰ (lixisenatide vs placebo, n=6068)	LEADER (2016) ⁵¹ (liraglutide vs placebo, n=9340)	SUSTAIN-6 (2016) ⁴⁹ (semaglutide vs placebo, n=3297)	EXSCEL (2017) ⁵² (exenatide once per week vs placebo, n=14 752)	HARMONY (2018) ⁵³ (albiglutide vs placebo, n=9463)	REWIND (2019) ⁵⁴ (dulaglutide vs placebo, n=9901)	PIONEER-6 (2019) ⁵⁵ (semaglutide [oral] vs placebo, n=3183)
Main inclusion criteria	Acute coronary event <180 days before screening	Established cardiovascular disease, chronic kidney disease, or heart failure at age >50 years (72·5%) or with at least one known risk factor at age >60 years	Established cardiovascular disease, chronic kidney disease, or heart failure at age >50 years (72·5%) or with at least one known risk factor at age >60 years	Established cardiovascular disease (73·1%) or multiple cardiovascular risk factors	Age >40 years and atherosclerotic cardiovascular disease	Age >50 years, previous cardiovascular event, evidence of cardiovascular disease (31·5%) or multiple cardiovascular risk factors	Age >50 years and cardiovascular disease (84·7%) or age >60 years and at least one cardiovascular risk factor
Key cardiovascular outcome: MACE							
Placebo	63·0	39·0	44·4	40·0	58·7	26·6	37
GLP-1 receptor agonist	64·0	34·0	32·4	37·0	45·7	23·5	29
HR (95% CI)	1·02 (0·89–1·17)	0·87 (0·78–0·97)	0·74 (0·58–0·95)	0·91 (0·83–1·00)	0·78 (0·68–0·90)	0·88 (0·79–0·99)	0·79 (0·57–1·11)
Key cardiovascular outcome: cardiovascular death							
Placebo	23·0	16·0	13·5	15·0	17·2	13·4	14·0
GLP-1 receptor agonist	24·0	12·0	12·9	14·0	16·1	12·2	7·0
HR (95% CI)	0·98 (0·78–1·22)	0·78 (0·66–0·93)	0·98 (0·65–1·48)	0·88 (0·76–0·97)	0·93 (0·73–1·19)	0·91 (0·78–1·06)	0·49 (0·27–0·92)
Key cardiovascular outcome: all-cause mortality							
Placebo	31	25·0	17·6	23·0	25·6	22·9	22
GLP-1 receptor agonist	33	21·0	18·2	20·0	24·4	20·6	11
HR (95% CI)	0·94 (0·78–1·13)	0·85 (0·74–0·97)	1·05 (0·74–1·50)	0·86 (0·77–0·97)	0·95 (0·79–1·16)	0·90 (0·80–1·01)	0·51 (0·31–0·84)
Key cardiovascular outcome: admission to hospital for heart failure							
Placebo	18·0	14·0	16·1	10·0	..	8·9	12
GLP-1 receptor agonist	19·0	12·0	17·6	9·0	..	8·3	10
HR (95% CI)	0·96 (0·75–1·23)	0·87 (0·73–1·05)	1·11 (0·77–1·61)	0·94 (0·78–1·13)	..	0·93 (0·77–1·12)	0·86 (0·48–1·55)
Key cardiovascular outcome: myocardial infarction							
Placebo	42·0	19·0	19·2	21·0	32·6	9·1	15
GLP-1 receptor agonist	42·0	16·0	14·0	21·0	24·3	8·7	18
HR (95% CI)	1·03 (0·87–1·22)	0·86 (0·73–1·00)	0·74 (0·51–1·48)†	0·97 (0·85–1·10)	0·75 (0·61–0·90)	0·96 (0·79–1·15)	1·18 (0·73–1·90)†
Key cardiovascular outcome: stroke							
Placebo	10·0	11·0	13·1	..	14·5	8·1	8
GLP-1 receptor agonist	9·0	10·0	8·0	..	12·5	6·2	6
HR (95% CI)	1·12 (0·79–1·58)	0·86 (0·71–1·06)	0·61 (0·38–0·99)†	0·85 (0·70–1·03)	0·86 (0·66–1·14)	0·76 (0·62–0·94)	0·74 (0·35–1·57)†
Key renal outcomes: new macroalbuminuria, doubling of serum creatinine and eGFR ≤45, renal replacement therapy, or renal-related death							
Placebo	..	19·0	..	..	..	..	..
GLP-1 receptor agonist	..	15·0	..	..	..	..	..
HR (95% CI)	..	0·78 (0·67–0·92)	..	..	..	..	..
Key renal outcomes: new macroalbuminuria, doubling of serum creatinine and eGFR ≤45, and renal replacement therapy							
Placebo	..	..	30·6	..	..	..	..
GLP-1 receptor agonist	..	..	18·6	..	..	..	..
HR (95% CI)	..	..	0·64 (0·46–0·88)	..	..	..	..

(Table 3 continues on next page)

	ELIXA (2015) ⁵⁰ (lixisenatide vs placebo, n=6068)	LEADER (2016) ⁵¹ (liraglutide vs placebo, n=9340)	SUSTAIN-6 (2016) ⁴⁹ (semaglutide vs placebo, n=3297)	EXSCEL (2017) ⁵² (exenatide once per week vs placebo, n=14 752)	HARMONY (2018) ⁵³ (albiglutide vs placebo, n=9463)	REWIND (2019) ⁵⁴ (dulaglutide vs placebo, n=9901)	PIONEER-6 (2019) ⁵⁵ (semaglutide [oral] vs placebo, n=3183)
(Continued from previous page)							
Key renal outcomes: new macroalbuminuria, >30% reduction of eGFR, or renal replacement therapy							
Placebo	..	..	..	..	..	40.7	..
GLP-1 receptor agonist	..	..	..	..	..	34.7	..
HR (95% CI)	..	..	..	0.87 (0.73–1.04)	..	0.85 (0.77–0.93)	..
Key renal outcomes: 40% reduction in eGFR, renal replacement therapy, or renal-related death							
Placebo	..	..	..	..	..	..	..
GLP-1 receptor agonist	..	..	..	..	..	..	..
HR (95% CI)	..	..	..	0.87 (0.73–1.04)	..	..	..
Key renal outcomes: new macroalbuminuria							
Placebo	..	12.1	24.7	..	..	22.9	..
GLP-1 receptor agonist	..	9.0	13.1	..	..	17.6	..
HR (95% CI)	..	0.74 (0.60–0.91)	0.54 (0.37–0.77)	0.87 (0.70–1.07)	..	0.77 (0.68–0.87)	..
Shown as event rate per 1000 patient-years. Primary outcome measure was three-point MACE: non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes or four-point MACE: composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. eGFR=estimated glomerular filtration rate. HR=hazard ratio. MACE=major adverse cardiovascular events. †Non-fatal stroke or myocardial infarction.							

Table 3: Summary of the major randomised, controlled, cardiovascular outcome trials with GLP-1 receptor agonists in type 2 diabetes

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 is predictive of progression. Surrogate measures include the emergence and progression of proteinuria (normal, microalbuminuria, and macroalbuminuria), a decline in eGFR (often assessed by a persistent doubling of serum creatinine or an eGFR of less than 45 mL per min per 1.73 m²), or a need for continuous renal replacement. Unlike SGLT2 inhibitors, there have been no dedicated renal primary outcome studies with GLP-1 receptor agonists, with all evidence regarding their renoprotective effect derived from the analysis of results from secondary outcome measures or exploratory analyses in CVOTs with the use of UACR and eGFR measurements. Despite this caveat, many CVOTs have shown favourable renal outcomes. In ELIXA, lixisenatide reduced the progression of UACR in patients who were macroalbuminuric and is associated with a lower risk of new onset macroalbuminuria; it did not change eGFR decline.⁶² In LEADER and SUSTAIN 6, treatment with liraglutide and semaglutide reduced the risk of CKD development and progression, benefits mainly driven by a reduction in new onset macroalbuminuria.^{49,51} HARMONY, EXSCEL, and PIONEER 6 did not assess renal outcomes. In the AWARD-7 trial, dulaglutide was accompanied by a UACR reduction and preservation of renal function compared with insulin glargine, most

evident in patients with macroalbuminuria and CKD stages 3b and 4.⁶³ A meta-analysis of kidney outcomes in the seven GLP-1 receptor agonist CVOTs, with a combined total of 56 004 participants, substantiated that GLP-1 receptor agonist treatment reduced a broad composite renal outcome by 17% (HR 0.83, 95% CI 0.78–0.89).⁵⁹ These data suggest that GLP-1 receptor agonists might 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 (type 2 diabetes) and CKD, will provide further therapeutic and mechanistic insight. Further mechanistic studies of the effects of GLP-1 receptor agonists on CKD progression are required.

Use of GLP-1 receptor agonists as treatment adjunct in type 1 diabetes

Few high-quality studies have assessed the safety and efficacy of GLP-1 receptor agonists as adjunctive therapy in patients with type 1 diabetes. The efficacy and safety of liraglutide as add-on to insulin treatment in patients with overweight and type 1 diabetes has been evaluated. Despite a modest effect on HbA_{1c} (mean, 0.15–0.20% reduction), reductions in weight (–6.8 kg) and insulin requirements were seen with liraglutide.⁶⁴ There might be a subgroup of patients with overweight and obesity with type 1 diabetes who would most benefit from adjunctive GLP-1 receptor agonist therapy but there is little evidence available.

GLP-1 receptor agonists in obesity and prediabetes

Liraglutide (3.0 mg), 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 3.0 mg liraglutide (once per day subcutaneous injection) in people with and without type 2 diabetes. Patients had a dose-dependent mean weight loss of 5.7–9.2% (6.0–8.8 kg) versus 0.2–3.1% (0.2–3.0 kg) with placebo (ie, on diet and exercise alone).^{65–67} In the 3 year assessment of the SCALE Obesity and Prediabetes trial, le Roux and colleagues⁶⁸ examined whether 3.0 mg liraglutide reduced the progression of type 2 diabetes in individuals who were overweight or obese with prediabetes. With liraglutide, a 4.6 kg placebo-subtracted weight loss reduction (50% of patients lost more than 5% weight) was associated with a regression from prediabetes to normoglycaemia in 66% of individuals (36% regression with placebo). The magnitude of risk reduction of type 2 diabetes 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. STEP 1, a phase 3 trial, evaluated the use of once per week semaglutide (2.4 mg subcutaneously) in 1961 adults with obesity (BMI >30 kg/m²) or overweight (BMI >27 kg/m²), with one or more patients with weight-related comorbidities who did not have diabetes. The mean reduction in bodyweight from baseline after 68 weeks was 14.9% in the semaglutide group versus 2.4% with placebo; the estimated treatment difference was 12.4% (95% 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.⁶⁹ Three other trials of semaglutide have also been published. STEP 2 (NCT03552757) showed additional weight loss with 2.4 mg semaglutide once per week (9.6% mean reduction in bodyweight from baseline after 68 weeks) in people

with diabetes compared with the approved 1 mg dose (7.0%) and placebo (3.4%).⁷⁰ Intensifying behavioural therapy in the STEP 3 (NCT03611582) resulted in similar weight loss to that seen in STEP 1 (16.0%).⁷¹ STEP 4 (NCT03548987) showed that stopping semaglutide treatment after 20 weeks led to weight regain, and in contrast, continuing for 68 weeks resulted in a 17.7% mean reduction in bodyweight from baseline.⁷² A further trial (STEP 5, NCT03693430) is investigating if weight loss can be sustained over a longer period of time.

The question as to whether benefits in CVD are also seen in people without type 2 diabetes is being evaluated in the ongoing SELECT trial (NCT03574597).

Non-alcoholic fatty liver disease (NAFLD)

There are currently no licensed therapies for NAFLD but even modest weight loss (approximately 8 kg) in patients with type 2 diabetes substantially reduces hepatic steatosis (by approximately 80%), concomitantly improving hepatic insulin resistance.⁷³ Randomised controlled trials with SGLT2 inhibitors and GLP-1 receptor agonists have shown improved liver enzymes and reductions in liver fat in patients with type 2 diabetes, but only GLP-1 receptor agonists (liraglutide and semaglutide) have shown reversal or improvements of the histological features of NAFLD.^{74–77}

Efficacy studies comparing SGLT2 inhibitors and GLP-1 receptor agonists

In DURATION 8, comparing dapagliflozin (10 mg once per day) with exenatide (2 mg once per week), there were similar reductions in HbA_{1c} (1.4–1.6%) but greater reductions in bodyweight with dapagliflozin.⁷⁸ In SUSTAIN 8, comparing subcutaneous semaglutide (1.0 mg once per week) with canagliflozin (300 mg once per day), semaglutide was superior to canagliflozin in lowering both HbA_{1c} and bodyweight (–4.7 kg vs –3.8 kg) after 52 weeks.⁷⁹ Finally, in PIONEER 2, comparing oral semaglutide (14 mg) with empagliflozin (25 mg), semaglutide showed a greater potency in glucose lowering but no difference in weight.⁸⁰ Thus, GLP-1 receptor agonists might be considered the most potent agents to simultaneously lower HbA_{1c} and bodyweight.

	DURATION-8 ⁷⁸			AWARD-10 ⁸⁶			SUSTAIN-9 ⁸⁷	
	Type 2 diabetes, HbA _{1c} 8–12%, 28 weeks follow-up			Type 2 diabetes, HbA _{1c} 8–12%, 24 weeks follow-up			Type 2 diabetes, HbA _{1c} 7–10%, 30 weeks follow-up	
	Exenatide once per week and dapagliflozin (n=228)	Dapagliflozin and placebo (n=230)	Exenatide once per week and placebo (n=227)	Dulaglutide 1.5 mg and SGLT2 inhibitor (n=142)	Dulaglutide 0.75 mg and SGLT2 inhibitor (n=140)	Placebo and SGLT2 inhibitor (n=140)	Semaglutide once per week and SGLT2 inhibitor (n=151)	Placebo and SGLT2 inhibitor (n=151)
Baseline HbA _{1c} (%)	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)
HbA _{1c} change (%)	–2.0 (–2.2 to –1.8)	–1.4 (–1.6 to –1.2)	–1.6 (–1.8 to –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 to –2.99)	–2.22 (–2.78 to –1.66)	–1.56 (–2.13 to –0.98)	–3.1 (0.3)*	–2.6 (0.3)*	–2.1 (0.3)*	–4.7 (0.32)	–0.9 (0.31)*

Data are mean (SD) or least-squares mean (95% CI) unless otherwise specified. HbA_{1c}=glycated haemoglobin. *Mean (SE).

Table 4: Randomised, placebo-controlled trials with combination of an SGLT2 inhibitor and GLP-1 receptor agonist in type 2 diabetes

Cardiovascular and renal benefits: comparison with SGLT2 inhibitors and GLP-1 receptor agonists

Several meta-analyses have been published on these drug classes for the primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes,^{81,82} attempting to reconcile which patient characteristics (eg, the presence or absence of atherosclerotic CVD, a history of heart failure, or baseline renal function) benefit from cardiorenal protection. Furthermore, recognising important differences in the mechanisms of action, attempts have been made to compare and contrast the relative distinct clinical benefits of SGLT2 inhibitors and GLP-1 receptor agonists.

Incorporating data from 34322 patients in the EMPA-REG, OUTCOME, CANVAS, and DECLARE-TIMI 58 trials, the clinical benefits of SGLT2 inhibitors are in reducing the risk of a three point MACE (myocardial infarction, stroke, or cardiovascular death) only in those with established CVD and not in those with multiple risk factors. However, the risk reduction in admission to hospital with heart failure and progression in renal disease were evident regardless of presence of atherosclerotic CVD or heart failure at baseline.⁸² Using data from these three studies combined with five GLP-1 receptor agonist studies, incorporating data from 77242 patients, similar reductions in MACE (approximately 11–12%) were seen with both drug classes, with the treatment effects restricted to those with established atherosclerotic CVD. However, the GLP-1 receptor agonist did not influence admission to hospital with heart failure and although both GLP-1 receptor agonist 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.⁸¹ 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 receptor agonists as glucose lowering therapies in treatment algorithms in people with type 2 diabetes has been updated reflecting results of these CVOTs.^{83–85} In 2019, the European Society for Cardiology in collaboration with the European Association for the Study of Diabetes published updated guidelines on diabetes, prediabetes, and CVD. SGLT2 inhibitors and GLP-1 receptor agonists were positioned as first-line treatment for naive patients with existing CVD or at a high risk of this, irrespective of HbA_{1c}. If an SGLT2 inhibitor or GLP-1 receptor agonist is considered suitable, treatment should be prioritised according to existing evidence such that GLP-1 receptor agonists should be considered in patients with type 2 diabetes and those at a high risk or with established CVD, and SGLT2 inhibitors considered for patients with HFrEF or CKD (with or without established CVD). In this rapidly evolving area, evidence for the management of some subgroups might change. Caution should be used when comparisons are made between individual trials because of differences in trial design, baseline characteristics, and endpoints (notably renal).

	Drug	Follow-up (weeks)	n	History	Primary outcome	Estimated end date
DECADE (2017-004709-42)	Exenatide once per week and dapagliflozin	6	17	Type 2 diabetes, HbA _{1c} ≥7.5% to <10%, estimated glomerular filtration rate >30 mL/min per 1.73 m ² , urine albumin-to-creatinine ratio >3.5 mg/mmol	Change in urine albumin-to-creatinine ratio	Unknown
DECREASE (NCT03361098)	Exenatide twice daily and dapagliflozin	16	64	Type 2 diabetes, HbA _{1c} 7.5 to 10%, BMI 30–40 kg/m ²	Difference in neuronal activity in central reward and satiety circuits (blood oxygen level dependent)	Unknown
COMBAT_T2_NASH (2019-001987-31)	Semaglutide once per week and empagliflozin	48	192	Type 2 diabetes, NASH with fibrosis (F1–F3), HbA _{1c} ≤9.5%, BMI ≤45 kg/m ²	Histological resolution of NASH without worsening of fibrosis	2023
RESILIENT (2015-005242-60)	Exenatide once per week and dapagliflozin	32	120	Type 2 diabetes, HbA _{1c} ≥6.5% to ≤11%, BMI 30–50 kg/m ²	Change in total body fat mass (%)	2021
DEXBASU (2017-001454-33)	Exenatide once per week and dapagliflozin	24	56	Type 2 diabetes, HbA _{1c} ≥7.0 to ≤10.0%, BMI of ≥35.0 to ≤42.5 kg/m ²	Proportion achieving a BMI ≤35.0 kg/m ² or a BMI ≤40.0 kg/m ² plus an HbA _{1c} ≤6.0%	Unknown
Effect of chronic exenatide therapy on beta cell function and insulin sensitivity in type 2 diabetes mellitus (NCT02981069)	Exenatide once per week and dapagliflozin	16	80	Type 2 diabetes, HbA _{1c} >7.0% and <10.0%, BMI of 25–35 kg/m ²	Change in endogenous glucose production	2021
NATRIURETIC (NCT04535960)	Liraglutide once per day and empagliflozin	12	36	Type 2 diabetes, estimated glomerular filtration rate ≥30 mL/min per 1.73 m ² , HbA _{1c} 7.0–12.0%, BMI 18.5–40.0 kg/m ²	Comparison of proximal tubular natriuresis	2022

BMI=body mass index. HbA_{1c}=glycated haemoglobin. NASH=non-alcoholic steatohepatitis.

Table 5: Ongoing randomised controlled trials with combination of an SGLT2 inhibitor and GLP-1 receptor agonist

Combination therapy

Overall, the evidence supports combination therapy with a GLP-1 receptor agonist and SGLT2 inhibitor with the additive benefits of glycaemic improvement and weight loss reflecting distinct and complementary mechanisms of action (table 4).^{78,86,87} Further studies are necessary to elucidate their combined effects on metabolic and cardiorenal disease (table 5).

Glycaemic control and weight loss benefits

DURATION-8 randomly assigned patients on maximal metformin to dapagliflozin alone, exenatide alone, or dapagliflozin plus exenatide for 28 weeks. The reduction in HbA_{1c} with combination (−2.0%) was less than additive compared with dapagliflozin (−1.4%) or exenatide (−1.6%) alone (table 4).⁷⁸ The results of AWARD-10 supports the sequential addition of these two agents.⁸⁶ In DURATION-8, the weight loss with combination (−3.41 kg) was greater than achieved with dapagliflozin (−1.54 kg) and exenatide (−2.19 kg) monotherapy.⁷⁸ These benefits might be extended to people without type 2 diabetes, with phase 2 randomised controlled trials examining the effects of dual therapy with dapagliflozin (10 mg, once per day) and exenatide (once per week) in obese adults without type 2 diabetes. After 24 weeks, for dapagliflozin and exenatide versus placebo, the difference in bodyweight change was −4.13 kg (95% CI, −6.44 to −1.81; $p < 0.001$).⁸⁸

Blood pressure and lipid profile benefits

In DURATION-8, exenatide plus dapagliflozin treatment (-4.3 ± 0.8 mm Hg) was associated with a significantly greater reduction in systolic blood pressure from baseline to week 28 compared with exenatide once per week (-1.2 ± 0.8 mm Hg; $p = 0.005$) or dapagliflozin (-1.8 ± 0.8 mm Hg; $p = 0.022$) in the overall population.⁷⁸ No significant differences between groups were noted for diastolic blood pressure or lipid measurements.

NAFLD

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 with monotherapy after 28 weeks.⁸⁹ In the EXENDA trial, a 24 week pilot trial, combined exenatide once per week and dapagliflozin had no additive effects on reduction of hepatocellular lipid compared with monotherapy, despite better glycaemic control.⁹⁰ Further prospective studies in people with or without type 2 diabetes are needed.

Cardiorenal benefits

Both drug classes reduce bodyweight, HbA_{1c}, 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

Panel: Key considerations for prescribers

Overview

- SGLT2 inhibitors are a group of oral medications whereas GLP-1 receptor agonists are generally injectable therapies. Oral semaglutide is the first oral GLP-1 receptor agonist available
- In people with type 2 diabetes, the evidence favours SGLT2 inhibitors for those with heart failure or chronic kidney disease, and GLP-1 receptor agonists for established cardiovascular disease. These are increasingly used as first-line treatments in these subgroups. GLP-1 receptor agonists are also the most effective pharmacotherapy currently available for some people with diabetes and overweight and obesity and weight-related comorbidities

SGLT2 inhibitors

- All SGLT2 inhibitors can be initiated if the estimated glomerular filtration rate is more than 60 mL per min per 1.73 m². The dose adjustment recommendations should be referred to per the kidney functions specific to the agent within the class. Further trial results might affect the licensed indications and dose adjustments
- Closely monitor 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, due to possible risk of amputation

- Counsel on the risk of diabetic ketoacidosis. Test capillary or venous blood ketones for raised ketones in patients with typical symptoms, even if plasma glucose concentrations are near normal. Discontinue during acute illness or surgical intervention
- Contraindicated in pregnancy (reproductive toxicity in animal studies) and breastfeeding (data from few animal studies only)

GLP-1 receptor agonists

- Gastrointestinal upset is a common side-effect.
- Hypoglycaemia risk is increased with concomitant sulfonylureas and insulin use. Treatment deintensification of these agents or of diuretics, particularly in older and frail individuals (approximately ≥ 65 years), is recommended to avoid hypoglycaemia and hypovolaemia
- Use with caution in patients with a history of treated pancreatitis of a known cause
- Ensure that retinopathy screening is done before initiation (for semaglutide only)
- Contraindicated in pregnancy and breastfeeding (based on few animal studies only) and a personal or family history of multiple endocrine neoplasia type 2 or medullary thyroid cancer

reduction, whereas the benefits of GLP-1 receptor agonists relate to potentially complementary anti-atherogenic mechanisms.

Future directions

Newer formulations of GLP-1 receptor agonists are becoming available. Implantable GLP1 receptor agonists have been evaluated,^{91,92} but the most encouraging is use of oral semaglutide, with compelling clinical data. GLP1 might also be one of several key peptide hormone receptors that can be targeted with novel co-peptides targeting GLP-1, glucose-dependent insulinotropic polypeptide, and glucagon receptors simultaneously in phase 2 and phase 3 trials.⁹³ 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, heart failure, and CKD in people with type 2 diabetes, both drug classes have evolved from their use as additional glucose lowering therapies in type 2 diabetes, used at a later stage in treatment algorithms, to being used first line in specific patients (with atherosclerotic CVD, heart failure, and CKD) in type 2 diabetes and with increasingly expanding indications in type 1 diabetes, obesity, cardiorenal disease, and NAFLD without type 2 diabetes (panel). Ongoing studies are evaluating the cardiorenal benefits of SGLT2 inhibitors and GLP-1 receptor agonists in different populations compared with previous CVOTs.

Contributors

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 the coauthors and coordinated revisions in response to reviewers. All authors agreed on the final version to be published.

Declaration of interests

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