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GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients With Type 2 Diabetes

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ABSTRACT: Patients with type 2 diabetes are at high risk for development of cardiovascular disease, including myocardial infarction, stroke, heart failure, and cardiovascular death. Multiple large cardiovascular outcome trials with novel glucose-lowering agents, namely SGLT2i (SGLT2 inhibitors) and GLP-1 RA (GLP-1 receptor agonists), have demonstrated robust and significant reductions of major adverse cardiovascular events and additional cardiovascular outcomes, such as hospitalizations for heart failure. This evidence has changed the landscape for treatment of patients with type 2 diabetes. Both diabetes and cardiology guidelines and professional societies have responded to this paradigm shift by including strong recommendations to use SGLT2i and/or GLP-1 RA, with evidence-based benefits to reduce cardiovascular risk in high-risk individuals with type 2 diabetes, independent of the need for additional glucose control. GLP-1 RA were initially developed as glucose-lowering drugs because activation of the GLP-1 receptor by these agents leads to a reduction in blood glucose and an improvement in postprandial glucose metabolism. By stimulating GLP-1R in hypothalamic neurons, GLP-1 RA additionally induce satiety and lead to weight loss. Data from cardiovascular outcome trials demonstrated a robust and consistent reduction in atherothrombotic events, particularly in patients with established atherosclerotic cardiovascular disease. Despite the consistent evidence of atherosclerotic cardiovascular disease benefit from these trials, the number of patients receiving these drugs remains low. This overview summarizes the experimental and clinical evidence of cardiovascular risk reduction offered by GLP-1 RA, and provides practical information on how these drugs should be implemented in the treatment of type 2 diabetes in the cardiology community.

Key Words: cardiovascular risk ■ diabetes ■ GLP-1 receptor agonists ■ incretin hormones ■ major cardiovascular events ■ myocardial infarction

People with type 2 diabetes (T2D) have an elevated risk of developing cardiovascular disease, including myocardial infarction (MI), heart failure (HF), peripheral artery disease, stroke, and cardiovascular death. Intensive glucose-lowering strategies failed to convincingly reduce cardiovascular morbidity and mortality in patients with diabetes at high cardiovascular risk,[1–3] although a meta-analysis of these trials did suggest a modest benefit on nonfatal MI.[4] Nevertheless, these data led for years to a perception among cardiologists that blood pressure control and low-density lipoprotein (LDL) cholesterol lowering were the only effective measures to reduce cardiovascular risk in people with T2D. Over the past several years, multiple large cardiovascular outcome trials (CVOTs) with novel glucose-lowering agents, namely SGLT2i (SGLT2 inhibitors) and GLP-1 RA (GLP-1 receptor agonists), have demonstrated robust and significant reductions of major adverse cardiovascular events (MACE) and additional cardiovascular outcomes, such as hospitalizations for HF (HHF). These beneficial effects on cardiovascular outcomes are thought to be largely independent of the glucose-lowering properties of these agents. The evidence from these CVOTs has changed the landscape for treatment of patients with T2D[5] with

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Nonstandard Abbreviations and Acronyms

AMPLITUDE-O	Effect of Efpeglenatide on Cardiovascular Outcomes
ASCVD	atherosclerotic cardiovascular disease
CRP	C-reactive protein
CVOT	cardiovascular outcome trial
DPP4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
ELIXA	Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010
ESKD	end-stage kidney disease
ESRD	end-stage renal disease
GIP	glucose-dependent insulinotropic polypeptide
GLP-1R	GLP-1 receptor
GLP-1 RA	GLP-1 receptor agonists
HARMONY OUTCOMES	Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus
HbA1c	hemoglobin A1c
HF	heart failure
HHF	hospitalizations for heart failure
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	major adverse cardiovascular events
MI	myocardial infarction
PIONEER-6	Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes
REWIND	Researching Cardiovascular Events With a Weekly Incretin in Diabetes
SGLT2i	SGLT2 inhibitors
SNAC	sodium N-(8-(2-hydroxybenzoyl) amino) caprylate
SOUL	Semaglutide Cardiovascular Outcomes Trial
SUSTAIN 6	Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
T2D	type 2 diabetes

a paradigm shift in both diabetes and cardiology guidelines. Now they include strong recommendations to use SGLT2i and GLP-1 RA with proven cardiovascular benefits to reduce cardiovascular risk in high-risk individuals with T2D, independent of baseline hemoglobin A1c (HbA1c).[6–8] On the basis of data from dedicated HF trials,[9–12] SGLT2i have emerged as an important treatment for patients with HF with both reduced and preserved ejection fractions. Despite the overwhelming evidence of cardiovascular benefit from large CVOTs, the number of patients receiving these lifesaving drugs remains low.[13–15] There may be several reasons for this: clinical inertia, a lack of knowledge in the cardiology community about the results of CVOTs, uncertainty in prescribing these agents, and concerns about potential side effects. To address these aspects, this overview summarizes the clinical and experimental evidence of cardiovascular risk reduction offered by GLP-1 RA and provides practical information on how these drugs should be implemented in the treatment of T2D in the cardiology community.

INCRETIN SYSTEM/BACKGROUND TO GLP-1 RA

Incretin System

GLP-1 is a small peptide hormone released from gastrointestinal L cells upon nutrient ingestion. It binds to the GLP-1R (GLP-1 receptor) and exhibits incretin effects that include glucose-dependent insulin secretion from pancreatic β cells, inhibition of glucagon release from pancreatic α cells, and the prolongation of gastric emptying. Together, these actions contribute to a reduction in blood glucose and an improvement in postprandial glucose metabolism. By stimulating GLP-1R–expressing hypothalamic neurons, GLP-1 also induces satiety and leads to weight loss. GLP-1 is generated through the cleavage of pre-proglucagon by convertase PC1/3, releasing equipotent peptides GLP-1(7-36 amide) and GLP-1(7-37). However, the half-life of GLP-1 is only a few minutes because of its cleavage by the ubiquitously expressed enzyme DPP4 (dipeptidyl peptidase-4) (see review[16]). Cleavage of the 2 N-terminal amino acids by DPP4 generates the metabolites GLP-1(9-36 amide) and GLP-1(9-37), which cannot activate GLP-1R. Thus, it no longer induces insulin secretion, but may still exhibit other GLP-1R–independent effects in the cardiovascular system.[17,18] In humans, the expression of the GLP-1R has been shown in various tissues, including pancreatic islet, lung, kidney, stomach, brain, endothelial cells, and smooth muscle cells, as well as specific atrial and ventricular cardiomyocytes.[19]

Incretin-Based Therapies

The potent action of the incretin hormone GLP-1 on glucose metabolism has led to the development of novel antidiabetic agents. Among them, DPP4 inhibitors prolong the half-life of GLP-1 by reducing DPP4 activity by about 80%, leading to an ~2-fold increase in GLP-1 plasma levels during postprandial periods. These

agents, including sitagliptin, vildagliptin, saxagliptin, and linagliptin, typically reduce HbA1c by 0.5% to 0.8%. Regardless of promising preclinical and mechanistic human studies on their antiatherothrombotic effects (see review[20]), consistent beneficial cardiovascular effects have not been established in large CVOTs.[21]

The second class of incretin-based drugs currently available for the treatment of patients with T2D is GLP-1 RA. Initially, exenatide (exendin-4), a GLP-1 mimetic found in the saliva of the Gila monster, was discovered. This peptide has 53% sequence homology with human GLP-1, cannot be cleaved by DPP4 and has been shown to be a full agonist of the GLP-1R. Subsequently, various GLP-1 RA were developed based on human GLP-1, such as liraglutide, semaglutide, and dulaglutide, etc. These GLP-1 RA reduce HbA1c ~0.8-1.5% (at doses now prescribed to patients with diabetes) and lead to additional weight loss.[22] In addition to their effect on postprandial glucose excursions, GLP-1 RA also reduce fasting plasma glucose.[23–25] Originally, these drugs were only available as injectable agents to be administered subcutaneously. However, recent technology has led to the development of an orally available GLP-1 RA with the coformulation of semaglutide and the absorption enhancer SNAC (sodium N-(8-(2-hydroxybenzoyl) amino) caprylate). This small fatty acid derivative, which promotes absorption across the gastric epithelium by causing a local increase of pH, leading to higher solubility and protection from proteolytic degradation,[26] has enabled oral bioavailability of the GLP-1 RA semaglutide. Table 1 summarizes the characteristics of currently approved GLP-1 RA.

To date, 3 of these drugs (liraglutide, semaglutide, and dulaglutide) are widely available with licensed indications for the prevention of cardiovascular disease. Although GLP-1 RA are more expensive than older glucose-lowering agents, recent cost-effectiveness analyses suggest that the added costs of treatment with GLP-1 RA in patients currently recommended for these drugs are offset by lower inpatient and outpatient care costs, resulting in budget neutrality against standard of care.[33]

Additional novel incretin-based glucose-lowering strategies include "dual" GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 RA, such as once-weekly tirzepatide. In people with T2D and elevated cardiovascular risk, tirzepatide, compared with insulin glargine, demonstrated greater and clinically meaningful HbA1c reduction with a lower incidence of hypoglycemia.[34] In addition, a meta-analysis of randomized phase II/III trials with tirzepatide versus placebo or GLP-1 RA has demonstrated significantly improved glycemic control and body weight,[35] whereas another predefined meta-analysis of cardiovascular outcomes suggested cardiovascular safety with a potential for cardiovascular benefit.[36] On the basis of these beneficial data on various risk factors, the combination of a GIP agonist with a GLP-1 RA is thought to be a promising approach to reduce cardiovascular events in high-risk patients. In May 2022, the US Food and Drug Administration approved tirzepatide injection to improve blood sugar control in adults with T2D as an addition to diet and exercise. The SURPASS-CVOT, a phase 3, randomized, double-blind, cardiovascular outcomes trial for tirzepatide assessing both noninferiority and superiority of tirzepatide versus dulaglutide (1.5 mg weekly), is ongoing and will provide data on the effect of tirzepatide on cardiovascular outcomes.[37]

CARDIOVASCULAR/KIDNEY EFFECTS OF GLP-1 RA IN CARDIOVASCULAR OUTCOME TRIALS

Effects on MACE

Eight CVOTs testing the benefits of GLP-1 RAs have now been published.[38–45] They have varying characteristics, as shown in Table 2. All but 1 trial used subcutaneously injected GLP-1 RA, with 5 of these being once-weekly injections, 2 daily injectables, and the last an oral preparation taken once daily (semaglutide 14 mg per day). A meta-analysis[46] of these 8 CVOTs revealed a 14% reduction in the primary outcome of the 3-component MACE (cardiovascular death, nonfatal MI, and nonfatal stroke; number needed to treat, 65), with moderate heterogeneity (Table 3). These results improve to a 15% reduction in MACE with low heterogeneity (14.9%) after removal of the ELIXA trial (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010). In this study, the sensitivity analyses supported the removal of ELIXA, with lixisenatide too short-acting for the once daily administration used in its CVOT.[38] The ongoing SOUL trial (Semaglutide Cardiovascular Outcomes Trial) compares the risk of MACE with oral semaglutide versus placebo in subjects with T2D at high risk of cardiovascular events (REGISTRATION: URL: https://clinical trials.gov; Unique Identifier: NCT03914326). This will address the current knowledge gap left by the PIONEER-6 safety study (Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) in which oral semaglutide failed reach statistically significant reductions in MACE compared with placebo (hazard ratio, 0.79 [95% CI, 0.57–1.11]; $P<0.001$ for noninferiority; $P=0.17$ for superiority).[44]

Effects on HF

The GLP-1 RA CVOTs included only a limited number of patients with a history HF, ranging from 12% to 24% of the population (New York Heart Association Class I–III, with Class IV patients excluded). Still, all GLP-1 RA had a neutral effect on risk of HHF (as

Table 1. Characteristics of Approved GLP-1 Receptor Agonists

GLP-1 receptor agonists	General aspects		Pharmacokinetics		Reference
	Doses*	Administration	TTP	Elimination half-life	
Exenatide BID	5 µg 10 µg	Twice daily	2.1–2.2 h	3.3–4.0 h	27
Liraglutide QD	0.6 mg 1.2 mg 1.8 mg	Once daily	11.0–13.8 h	12.6–14.3 h	28
Lixisenatide QD	10 µg 20 µg	Once daily	About 2 h	2.6 h	29
Dulaglutide QW	0.75 mg 1.5 mg 4.5 mg	Once weekly	48 h	4.7–5.5 h	30
Exenatide ER	2 mg	Once weekly	Not formally assessed†	3.3–4.0 h	27
Semaglutide SC	0.25 mg 0.5 mg 1.0 mg (2.4 mg)‡	Once weekly	24 h	5.7–6.7 d	31
Semaglutide oral	3 mg 7 mg 14 mg	Once daily	About 1–4 h	5.7–6.7 d	32

ER indicates extended release; and TTP, time to peak.
*For the initiation and up-titration, see Table 2.
†The onset of exenatide ER does not quickly lead to measurable concentrations; therefore, this has not been formally evaluated.
‡Semaglutide (2.4 mg once weekly) was approved by the Food and Drug Administration for obesity in patients without diabetes.

a predefined secondary end point) in the placebo-controlled randomized controlled trials despite increasing heart rate by 3 to 5 beats per minute. Two meta-analyses including the 8 CVOTs including 60 080 patients found HHF to be reduced by 10% to 11%.[46,47] This suggests that GLP-1 RA may also reduce HHF.[48] It is notable that the 2 trials with the most marked risk reductions in HHF, HARMONY OUTCOMES (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus), testing albiglutide versus placebo, and AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes), testing efpeglenatide versus placebo, also showed the greatest risk reductions in 3-point MACE, suggesting that antiatherosclerotic mechanisms may underlie some of the observed benefits on HHF, at least with the current tested doses of GLP-1 RAs. Of note, neither albiglutide nor efpeglenatide are currently available in the United States or European Union.

Dedicated studies on safety and efficacy of GLP-1 RA in patients with HF are missing. Only 2 small studies examined the effect of GLP-1 RA in patients with HF with reduced ejection fraction. In the placebo-controlled LIVE study in 241 patients with HF with reduced ejection fraction with and without diabetes, liraglutide treatment during 24 weeks did not change left ventricular ejection fraction, quality of life, or HF symptoms. However, patients in the liraglutide group exhibited a higher risk for cardiovascular events (sustained ventricular tachycardia, atrial fibrillation, or acute coronary syndromes; n=12 [10%] in the liraglutide group versus n=3 [3%] in the placebo group).[49] In the FIGHT study, 300 patients with HF with reduced ejection fraction and recent hospitalization for HF with and without diabetes were randomized to liraglutide or placebo. After 180 days, there was no difference in the primary end point of death, HF hospitalization, or change in NT-proBNP (N-terminal pro-B-type natriuretic peptide) between groups.[50]

Effect on Kidney Outcomes

Various GLP-1 RA have been shown to reduce albuminuria/ progression of albuminuria, an established surrogate parameter for worsening kidney function, and a meta-analysis of GLP-1 RA CVOTs suggests that a combined kidney outcome that includes progression of albuminuria was reduced by 21% to 22% (Table 3).[46] Only dulaglutide has been examined in chronic kidney disease (CKD) stages 3 to 4 in patients with T2D and demonstrated a slower estimated glomerular filtration rate (eGFR) decline compared with insulin glargine.[51] A recent pooled analysis of the SUSTAIN 6 trial (Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) and the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) suggests that semaglutide/liraglutide may provide kidney-protective effects, which seem to be more pronounced in patients with pre-existing CKD.[52] Still, the benefit of GLP-1 RA on kidney function and the risk of kidney failure has

Table 2. Baseline Characteristics and Use of Glucose-Lowering Agents Across Trials

	ELIXA (n=6068)	LEADER (n=9340)	SUSTAIN 6 (n=3297)	EXSCEL (n=14 752)	HARMONY OUTCOMES (n=9463)	REWIND (n=9903)	PIONEER-6 (n=3183)	AMPLITUDE-O (n=4076)
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide	Efpeglenatide
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Subcutaneous
Target dose	10 µg/d or 20 µg/d	1.8 mg/d	0.5 mg/wk or 1 mg/wk	2 mg/wk	30 mg/wk or 50 mg/wk	1.5 mg/wk	14 mg/d	4 mg/wk or 6 mg/d
Age, y	60±10	64±7	65±7	62±9	64±7	66±7	66±7	65±8
Sex								
Female	31%	36%	39%	38%	31%	46%	32%	33%
Male	69%	64%	61%	62%	69%	54%	68%	67%
BMI kg/m^2	30.1±5.6	32.5±6.3	32.8±6.2	32.7±6.4	32.3±5.9	32.3±5.7	32.3±6.5	32.7±6.2
Diabetes duration, y	9.2±8.2	12.8±8.0	13.9±8.1	13.1±8.3	14.2±8.8	10.5±7.2	14.9±8.5	15.4±8.8
HbA1c %	7.7±1.3	8.7±1.6	8.7±1.5	8.1±1.0	8.7±1.5	7.3±1.1	8.2±1.6	8.9±1.5
Established cardiovascular disease	100%	81%	83%	73%	100%	31%	85%	90%
History of heart failure	22%	18%	24%	16%	20%	9%	12%	18%
Systolic blood pressure (mm Hg)	129±17	136±18	136±17	135±17	135±17	137±17	136±18	135±16
eGFR, mL/min per 1.73 m^2*	78±21	80 (NR)	80 (61–92)	77 (61–92)	79±25	77±23	74±21	72±22

Numerical data are mean±SD or percentage, unless otherwise specified.

AMPLITUDE-O indicates Effect of Efpeglenatide on Cardiovascular Outcomes; BMI, body mass index; CVD, cardiovascular disease; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE001; HARMONY OUTCOMES, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; HbA1c, hemoglobin A1c; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; NR, not reported; PIONEER-6, Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SGLT2, sodium-glucose cotransporter-2; and SUSTAIN 6, Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

*eGFR data are median (interquartile range) for SUSTAIN 6 and EXSCEL.

yet to be confirmed. The ongoing FLOW trial is directly comparing once-weekly semaglutide subcutaneously versus placebo in patients with CKD, and its results are keenly anticipated (REGISTRATION: URL: https://clinical trials.gov; Unique Identifier: NCT03819153).

Ongoing Trials

On the basis of data from STEP-1, in which 2.4 mg of once weekly semaglutide subcutaneously plus lifestyle intervention was associated with sustained, clinically relevant reductions in body weight versus placebo,[53] semaglutide has been approved by the Food and Drug Administraton as a medication for chronic weight management in adults with obesity or who are overweight. The ongoing SELECT-trial randomized overweight participants (body mass index ≥27 kg/m^2) without T2D but with established CVD to semaglutide versus placebo and will assess whether this GLP-1 RA can reduce the primary composite cardiovascular end point of 3-point MACE[54] (REGISTRATION: URL: https://clinical trials.gov; Unique Identifier: NCT03574597). The results of this trial will extend our understanding of obesity management with GLP-1 RA and the effect of this class on cardiovascular risk reduction in patients without T2D.

MECHANISMS OF CARDIOVASCULAR RISK REDUCTION BY GLP-1 RA

Clinical data from large CVOTs in patients with T2D clearly show a reduction of cardiovascular morbidity and mortality by treatment with GLP-1 RA, as summarized in Effects on MACE above. A detailed analysis of the event curves with a separation of the curves after 12 to 18 months, as well as the fact that primary and secondary outcomes such as MI, stroke, cardiovascular death, and revascularization are reduced, suggest that the beneficial effects of GLP-1 RAs are mediated by a reduction of atherosclerosis-related events. Various mechanisms have been proposed to contribute to these results.

GLP-1 itself affects the pancreas, gut, and stomach as well as liver, adipose tissue, skeleton muscle, kidney, heart and vessels, and the immune system (see review[55]). Both DPP4 inhibitors and GLP-1 RA are GLP-1–based therapies. However, in contrast with GLP-1 RA, DPP4 inhibitors did not reduce MACE in large CVOTs. This difference may be a result of modest enhancement of DPP4 inhibitors and prolonged action of endogenous postprandial GLP-1 within the physiological range. Because GLP-1 RA achieve multiple-fold higher and near continuous pharmacological activation of the GLP-1R, the beneficial

Table 3. Summary Eesults of Meta-Analysis for MACE and Its Components as Reported by Sattar et al[46]

	Main analysis with all 8 CVOTs (HR; I^2)	Sensitivity analyses minus ELIXA (HR; I^2)
MACE	0.86 (0.80 to 0.93) 45%	0.85 (0.80 to 0.90) 15%
CV death	0.87 (0.80 to 0.94) 13%	0.85 (0.78 to 0.93) 12%
MI	0.90 (0.83 to 0.98) 27%	0.88 (0.81 to 0.96) 16%
All-cause mortality	0.88 (0.82 to 0.94) 10%	0.87 (0.81 to 0.94) 17%
Incident HHF	0.89 (0.82 to 0.98) 3%	0.88 (0.79 to 0.98) 12%
Kidney composite (+ albuminuria)	0.79 (0.73 to 0.87) 48%	0.78 (0.71 to 0.87) 57%
Worsening kidney function (eGFR)	0.86 (0.72 to 1.02) 43%	0.82 (0.69 to 0.98) 40%

CV indicates cardiovascular; CVOTs, cardiovascular outcome trials; eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE001; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

effects observed in CVOTs may depend on the supra-physiological effects only achieved by robust GLP-1 RA.

Effect of GLP-1 RA on Cardiovascular Risk Factors

All available GLP-1 RA have effects on cardiovascular risk factors. GLP-1 RA lead to a reduction in systolic blood pressure of 2 to 6 mm Hg, and blood pressure lowering has been discussed as a mediator of cardiovascular event reduction.[22] Previous data from trials in patients with hypertension suggest that blood pressure reduction leads to a significant reduction in MACE, with meta-analyses showing that a systolic blood pressure reduction of 10 mm Hg was associated with ~20% reduction of MACE. Therefore, the effect of GLP-1 RA on blood pressure in their CVOTs was rather modest. For example, the average reductions were only 1.2 mm Hg in LEADER and 1.7 mm Hg in REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes), making it unlikely that blood pressure alone can explain the observed cardiovascular benefits.[56] With respect to lipids, GLP-1 RA have been shown to modestly reduce total cholesterol, LDL cholesterol, and triglycerides, suggesting a potential beneficial effect.[57] Depending on the study population, GLP-1 RA lead to a reduction of HbA1c between 0.8% and 1.5%.[58] A meta-analysis of large CVOTs in patients with T2D and cardiovascular disease, such as ACCORD, ADVANCED, and VADT, showed an intensive versus a less stringent glucose-lowering strategy modestly reduced only nonfatal MI, but not cardiovascular death.[4] Thus, the glucose-lowering properties of GLP-1 RA can at best only partially explain the cardiovascular benefits observed. In addition, the metabolic effects of all currently commonly used GLP-1 RA lead to a modest reduction in weight between 2.5 and 4 kg, depending on the trial.[58,59] Such a weight reduction may contribute to the reduction of cardiovascular events. Previous data from the Look AHEAD trial[60] suggested a limited efficacy of modest body weight loss on cardiovascular risk reduction in patients with diabetes, but a subsequent post hoc reanalysis showed that those who lost >10% weight might have lower risk for future cardiovascular outcomes.[61] Of note, higher approved doses of semaglutide and tirzepatide demonstrate up to 10% to 20% weight loss in persons with and without diabetes, with lesser weight loss in people with diabetes.[62] Still, further trials are needed to support importance of weight loss per se, and we note that the ongoing STEP and SURPASS-CVOT trials may help determine to what extent weight loss contributes to cardiovascular benefits. Taken together, even the combination of these modest effects on classical cardiovascular risk factors may not entirely explain the beneficial results seen in the CVOTs of GLP-1 RA.

Additional Effects of GLP-1 RA on Atherosclerosis and Inflammation

Various experimental data in preclinical models of atherosclerosis have shown that GLP-1[63] and GLP-1 RA reduce atherosclerotic lesion development and progression by leading to more stabilized, less vulnerable plaques,[64,65] most likely by antiatherogenic and anti-inflammatory effects in endothelial cells, monocytes, and macrophages as well as vascular smooth muscle cells, which express GLP-1R.[19,64,66–70]

The hypothesis of anti-inflammatory properties of GLP-1 RA has been fostered by clinical data in small population of patients with liraglutide showing decreased production of TNF-α and interleukin-1 in isolated human peripheral blood mononuclear cells.[71] In addition, various GLP-1 RA have been shown to reduce systemic inflammation as measured by levels of CRP (C-reactive protein).[72,73]

Overall, the beneficial effects of GLP-1 RA on cardiovascular outcomes in high-risk patients with T2D are most likely explained by a combination of metabolic, vascular, antithrombotic and anti-inflammatory effects.

GUIDELINE RECOMMENDATIONS

On the basis of the results of multiple rigorous CVOTs, guidelines committees in both diabetes and cardiology have developed recommendations for the treatment of patients with T2D at high cardiovascular risk with GLP-1 RAs. The 2019 European Society of Cardiology guidelines on diabetes, prediabetes, and CVD recommend treatment with GLP-1 RA (or SGLT2i) in patients with T2D and atherosclerotic cardiovascular disease (ASCVD) or high/very high risk (high-risk patients, diabetes duration ≥10 years without target organ damage plus any other additional risk factor; very high–risk patients, diabetes and established CVD, evidence of target organ damage [proteinuria, eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy], 3 or more major risk factors, or early-onset type 1 diabetes [of long duration [>20 years]) to reduce cardiovascular events.

The 2020 report of the American College of Cardiology Solution Set Oversight Committee on novel therapies for cardiovascular risk reduction in patients with T2D recommends initiating a patient-clinician discussion about the use of an SGLT2i and/or a GLP-1 RA with demonstrated cardiovascular benefit for patients with T2D who have or who are at very high risk for clinical atherosclerotic cardiovascular disease, HF, and/or diabetic kidney disease.[74]

The 2022 American Diabetes Association "Standards of Medical Care in Diabetes" recommend treatment with GLP-1 RA or SGLT2i in T2D with ASCVD or high risk (such as patients ≥55 years of age with coronary, carotid, or lower-extremity artery stenosis >50% or left ventricular hypertrophy), independently of baseline HbA1c, individualized HbA1c target, or metformin use.[8]

PRACTICAL ASPECTS ON THE USE OF GLP-1 RA FOR THE CARDIOLOGIST

Patient Selection

On the basis of current guideline recommendations, SGLT2i and GLP-1 RA with proven cardiovascular benefit are recommended in patients with T2D and ASCVD or those at high risk of cardiovascular events. On the basis of the CVOT results discussed above, the group of GLP-1 RA with proven benefit include liraglutide, semaglutide subcutaneously, dulaglutide, albiglutide (currently not available in the United States or European Union), and efpeglenatide (currently not available in the United States or European Union). GLP-1 RA and SGLT2i differ with respect to the cardiovascular outcomes they reduce. As outlined in Effects on MACE above, GLP-1 RA mainly reduce ASCVD-associated outcomes such as MI, stroke, and cardiovascular death, whereas SGLT2i lead to a pronounced reduction in the risk of cardiovascular death and HHF, but also lower MI. Both classes of drugs exhibit beneficial effects on kidney outcomes: GLP-1 RA reduce albuminuria and may have modest effects (albeit with modest heterogeneity across trials) on "hard" kidney outcomes such as end-stage kidney disease (ESKD), decline in eGFR, or kidney death. Moreover, a meta-analysis of SGLT2i trials in T2D demonstrated a more robust and consistent reduction of ESKD in addition to effects on the decline of eGFR.[75]

These 2 drug classes have displayed additional variability in their effects on risk factors such as blood glucose, blood pressure, and weight. Both GLP-1 RA and SGLT2i improve HbA1c. In a systematic review and network meta-analysis, the long-acting GLP-1 RA semaglutide subcutaneously was more effective at lowering blood glucose at 24 weeks with a mean HbA1c reduction of 1.49%, whereas SGLT2i ertugliflozin showed a less pronounced effect within the same period (HbA1c lowering 0.84%).[76] Furthermore, both treatments reduced blood pressure in patients with T2D. In a meta-analysis, Hu et al concluded that GLP-1 RA and SGLT2i lower systolic blood pressure (by about 2.9 mm Hg and 4.3 mm Hg, respectively) and diastolic blood pressure (by about 0.9 mm Hg and 2.3 mm Hg, respectively).[77] In addition, long-acting GLP-1 RA have demonstrated a greater weight reduction than SGLT2i.[76] Of note, the benefits of GLP-1 RA have been demonstrated across a broad spectrum of ASCVD risk[78] and are beyond LDL cholesterol lowering,[79] blood pressure, and duration of diabetes.[80,81]

All of these aspects need to be taken into consideration when selecting patients for GLP-1 RA or SGLT2i to reduce their cardiovascular risk: GLP-1 RA have more consistent atherothrombotic benefits, whereas SGLT2i have better effects on HF and CKD. Without robust risk scores that help determine which future risks likely operate, clinicians need to make informed judgments on the basis of available evidence. For now, treatment with GLP-1 RA may be preferred for patients with ASCVD with a high risk of future stroke (eg, those after stroke or revascularization, or with evidence of significant artery narrowing in many beds [carotid, coronary, or peripheral]; Figure). They may also be favored when glycemia levels are more elevated or in patients with a much higher body mass index because GLP-1 RA have a more consistent weight loss effect with higher doses of some drugs (eg, semaglutide subcutaneously), yielding even greater weight loss. SGLT2i are preferred in patients with prevalent HF or CKD as well as in those with a high risk of HF, although how physicians best identify this latter group of patients remains unclear. Finally, because many patients have dual atherothrombotic and cardiorenal risks, these patients may also benefit from combination therapy with GLP-1 RA and SGLT2i.

Initiation of Therapy

Choice of Agent

Besides oral semaglutide, all currently available GLP-1 RA are administered as a subcutaneous injection

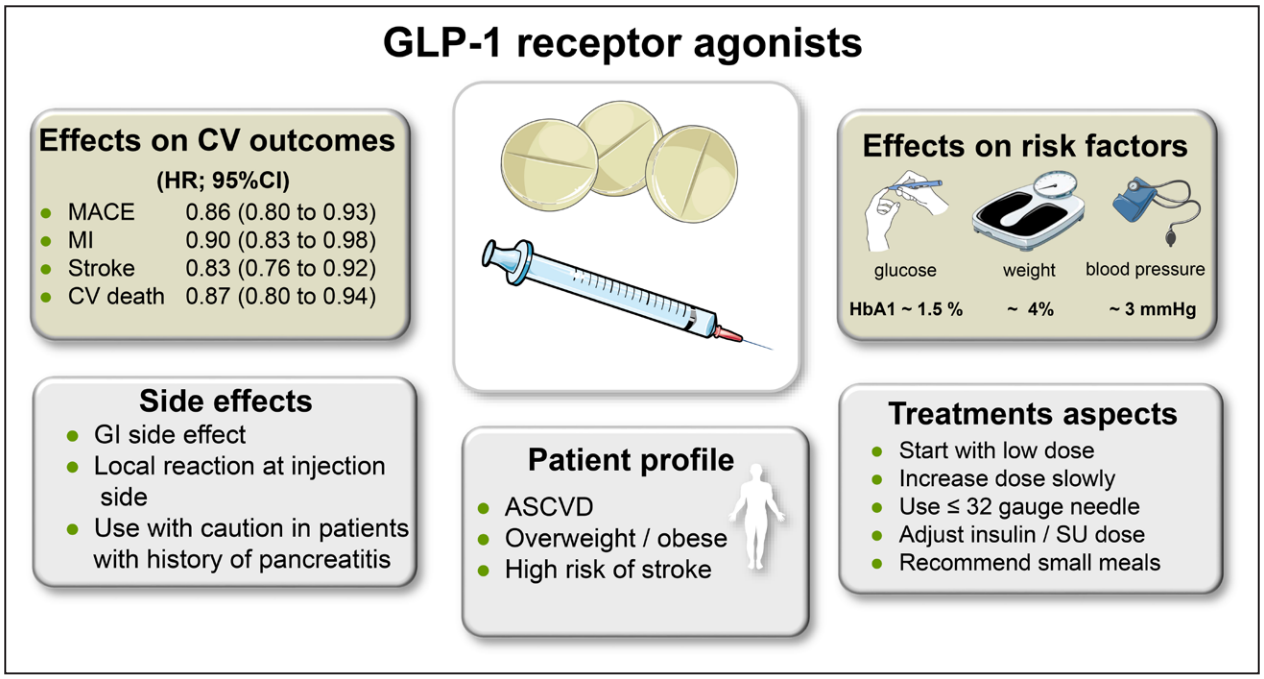

Figure. Effects of GLP-1 RA on CV risk factors/outcomes and practical aspects for the use of these agents.
Effects of GLP-1 RA on glucose control,[82] weight,[83] and blood pressure[77] are summarized in the respective articles. Data on the effects of GLP-1 RA on CV outcomes are taken from a meta-analysis of the 8 CVOTs conducted with GLP-1 RA.[46] Current guidelines recommend the following, presently available GLP-1 RA with proven CV benefit: liraglutide, semaglutide subcutaneously, and dulaglutide. ASCVD indicates atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcome trial; GLP-1 RA, GLP-1 receptor agonists; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

with different dose frequencies. As shown in Table 1, GLP-1 RA differ with respect to their half-life and frequency of injection. For the reduction of cardiovascular risk, a GLP-1 RA with proven cardiovascular benefit should be used; this group includes liraglutide, semaglutide subcutaneously, and dulaglutide (albiglutide and efpeglenatide are currently not available in the United States or European Union). Once-weekly injections with agents such as semaglutide or dulaglutide may be the preferred choice for many patients given the long-lasting effect and better tolerability in some patients.

Drug Administration

Usually, GLP-1 RA are injected by pens fitted with 32-gauge needles with minimal injection discomfort. In patients preferring oral medication, oral semaglutide can be prescribed, but patients need to be instructed that the tablet should be taken with up to half a glass of water (~120 mL; 4 fluid ounces) in the morning in a fasting state, and that they have to wait at least 30 minutes before eating, drinking, or taking any other oral medication. To reduce gastrointestinal side effects, all GLP-1 RA should be started at a low dose and titrated according to local product monographs (Table 4). If necessary, up-titration can be slowed to limit severity and frequency of side effects. Some patients may temporarily require lowering the dose of the respective GLP-1 RA until symptoms resolve.

Patient Counseling

Moreover, patient counseling may be helpful with advice on smaller meals, eating slowly, stopping before feeling full, and avoiding fatty or spicy foods as well as strongly flavored foods as they start and up-titrate GLP-1 RA. In addition, symptomatic treatment (proton pump inhibitors, etc) may help alleviate symptoms in some patients, but should only be used for short periods of time early on (Table 5).

Side Effects/Safety of GLP-1 RA

Gastrointestinal complaints are the most common side effects seen with GLP-1 RA, including nausea (25%–60%), vomiting (5%–15%), and diarrhea with nausea and vomiting being transient in most patients leading to discontinuation in 5% to 15% of participants in clinical trials.[84] The risk of hypoglycemia with GLP-1 RA is minimal unless these drugs are used in combination with agents that cause hypoglycemia, such as insulin or sulfonylureas, which should be stopped or their doses reduced when starting these patients on a GLP-1 RA. Clinical data suggest rare cases of gallbladder disease such a cholelithiasis with some GLP-1 RA.[85] Although some studies reported an increased risk of pancreatitis and pancreatic cancer with GLP-1 RA, this has not been observed in the large CVOT with an extensive follow-up of these agents. Furthermore, recent meta-analyses do not show a significant effect on these outcomes despite a numerically higher incidence of pancreatitis.[46,86] Still, patients should be counseled to report severe or

Table 4. Practical Recommendations for Initiation and Up-Titration of GLP-1 Receptor Agonists

GLP-1 receptor agonists	Initial dose	Up-titration doses	Discontinuation
Exenatide BID	5 µg twice daily for at least 1 month	Gradual increase to 10 µg	eGFR <15 mL/min or ESRD
Liraglutide QD	0.6 mg once daily for at least 1 week	May be increased to 1.2 mg after 1 week and to maximum 1.8 mg after 1 more week	eGFR <15 mL/min or ESRD
Lixisenatide QD	10 µg once daily for at least 2 weeks	Gradual increase to 20 µg	eGFR <15 mL/min or ESRD
Dulaglutide QW	0.75 mg once weekly	If needed, may be increased to 4.5 mg once weekly	eGFR <15 mL/min or ESRD
Exenatide ER	2.0 mg once weekly	…	eGFR <30 mL/min or ESRD
Semaglutide SC	0.25 mg for at least 1 month	After 0.25 mg initiation month, 0.50 mg for 1 further month and then 1.0 mg, if needed	eGFR <15 mL/min or ESRD
Semaglutide oral	3 mg for at least 1 month	Then increase the dose to 7 mg once daily after 1 additional month and then to 14 mg if needed	eGFR <15 mL/min or ESRD

eGFR indicates estimated glomerular filtration rate; ER, extended release; and ESRD, end-stage renal disease.

persisting abdominal pain. Notwithstanding a lack of established causality, GLP-1 RA are not recommended in patients with a history of pancreatitis. In addition, injection-site pruritus and erythema can occur, most notably with longer-acting medications in this class.[87] In contrast with other antihyperglycemic drugs such as metformin or SGLT2i, there are no special "sick day" rules to follow for GLP-1 RA.

Contraindications

GLP-1 RA are contraindicated in pregnancy and breastfeeding; some form of contraception is recommended in women of childbearing age. In addition, patients with severe gastrointestinal diseases such as gastroparesis and inflammatory bowel disease should avoid GLP-1 RA because of their effect of slowed gastric emptying and potential exacerbation of gastrointestinal symptoms. As mentioned in Side Effects/Safety of GLP-1 RA above, GLP-1 RA are contraindicated in patients with a history of pancreatitis. Experimental data in rodent models demonstrated that liraglutide stimulated calcitonin release and led to hyperplasia of thyroid gland C cells and tumors.[88] The effects in humans remain unclear, but GLP-1 RA are not recommended in patients with a personal or family history of multiple endocrine neoplasia 2A, multiple endocrine neoplasia 2B, or medullary thyroid cancer.[89]

Adjustment of Concomitant Glucose-Lowering Agents

With respect to concomitant glucose-lowering drugs in patients with T2D, various post hoc analyses have shown that the beneficial effects of GLP-1 RA are independent of metformin, the most often used first-line medication in this patient population.[42,90] Given that DPP4 inhibitors also act through GLP-1, these agents should be discontinued when starting GLP-1 RA. In addition, depending on the patient's baseline HbA1C and to limit the risk of hypoglycemia, it may be helpful to reduce the dose of concomitant insulin, eg, reduce basal insulin by 10% to 20% if HbA1c is <8%; moreover, sulfonylureas should be reduced in dose or stopped (Table 5).

So far, limited evidence exists on the combination therapy of SGLT2i and GLP-1 RA. Nevertheless, both clinical as well as experimental data suggest that these agents could have additive if not synergistic effects with respect to cardiovascular risk reduction. Recent subgroup analyses from the AMPLITUDE-O trial demonstrate an equal benefit of efpeglenatide versus placebo with respect to MACE in patients with and without baseline SGLT2i treatment.[45] Combination therapy could represent an interesting strategy to improve the prognosis of patients with T2D.[91] It is also important to acknowledge that the natural history of T2D may be such that some patients will continue to have poor glycemic (or body weight) control even after initiation of a SGLT2i or GLP-1 RA.

Table 5. Practical Recommendations and Patient Counseling

Potential concerns	Practical recommendation
Concomitant glucose-lowering medication	Stop DPP4 inhibitors Depending on HbA1C: stop or reduce dose insulin dose (~25%) or sulfonylurea to reduce risk of hypoglycemia
GI side effects (nausea, vomiting, etc)	Start with low dose and up-titrate slowly Consider symptomatic therapy (eg, proton pump inhibitor) Counsel patients on: – side effects only transient – small meals – eat slowly – stop before feeling full – avoid fatty, spicy, and strong-flavored foods
Injectable therapy	Use small needle (≤32 gauge) Fear of injection: consider oral available GLP-1 RA (semaglutide)
Laboratory controls	Kidney function: not necessary Pancreatic enzymes: – only if patient is symptomatic – levels increase on average by ~20% (no increased risk of acute pancreatitis in studies) Liver enzymes: not necessary

GI indicates gastrointestinal; and GLP-1 RA, GLP-1 receptor agonists.

This may occur particularly in response to declining renal function and the associated decline in glycemic efficacy of SGLT2i. Therefore, combination therapy with SGLT2i and GLP-1 RA may be required for reasons other than cardiovascular benefits.

Monitoring

GLP-1 RA are eliminated by the kidney, and dosing adjustments of GLP-1 agonists are not necessary in patients with hepatic or mild renal impairment. Extended-release exenatide should be discontinued at an eGFR <30 mL/min/m², whereas all other GLP-1 RA can be given until eGFR drops <15 mL/min/m². Although limited data exist for end-stage renal disease (ESRD), several studies have demonstrated the clinical utility of a variety of GLP-1 RA in patients on dialysis.[92–96]

COMPREHENSIVE CARDIOVASCULAR RISK REDUCTION IN PATIENTS WITH T2D

Various novel treatment strategies have led to a robust reduction in cardiovascular morbidity and mortality in patients with T2D,[97] but even today, patients with T2D still exhibit an ~2-fold increased risk of cardiovascular death compared with matched subjects without diabetes.[98] Given the high rate of undiagnosed diabetes in patients with CVD, cardiologists should screen all patients with CVD for the presence of diabetes. To this end, HbA1c and/or fasting plasma glucose should be measured in all patients with CVD.[6,99] Along with other strategies such as antiplatelet therapy, blood pressure, and lipid lowering, cardiologists should not miss the opportunity to implement evidence-based therapies to reduce cardiovascular risk in T2D and initiate GLP-1 RA and/or SGLT2i to avoid treatment delays and ensure that high-risk patients receive appropriate evidence-based treatment benefits as early as possible. In addition, cardiologists should refer these patients with CVD and newly diagnosed diabetes to an endocrinologist/diabetologist for help address other risks associated with diabetes, and in case of CKD (eg, eGFR <30 mL/min/m²) to a nephrologist, because these patients require a multidisciplinary approach to reduce disease burden and improve prognosis.

In conclusion, multiple trials have shown GLP-1 RA to reduce cardiovascular risk in patients with diabetes and ASCVD or high cardiovascular risk independent of HbA1c. Cardiologists should consequently consider the use of GLP-1 RA in respective patients as part of best medical care.

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