Circulation

IN DEPTH

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

Nikolaus Marx, MD; Mansoor Husain, MD; Michael Lehrke, MD; Subodh Verma, MD, PhD; Naveed Sattar, FMedSci, PhD

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

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Nikolaus Marx, MD, Department of Internal Medicine I (Cardiology), University Hospital Aachen, RWTH Aachen University, Pauwelsstraße 30, D-52074 Aachen, Germany. Email nmarx@ukaachen.de

For Sources of Funding and Disclosures, see page 1891.

Circulation is available at www.ahajournals.org/journal/circ

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://clinicaltrials.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

	General aspects		Pharmacokinetics		
GLP-1 receptor agonists	Doses*	Administration	TTP	Elimination half-life	Reference
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://clinicaltrials.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://clinicaltrials.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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.