Cardiovascular outcomes in diabetic kidney disease: insights from recent clinical trials

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The prevalence of type 2 diabetes is catalyzing a pandemic in kidney disease, with ensuing cardiovascular complications. The effort to identify antidiabetic agents capable of promoting benefits that go beyond the bounds of glucose control has produced remarkable outcomes in recent cardiovascular outcomes trials in patients with type 2 diabetes mellitus, many of whom have diabetic kidney disease. Two novel antidiabetic drug classes, sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), improve cardiovascular outcomes in different ways, with SGLT2is reducing the risk of heart failure and cardiovascular death and GLP-1 RAs being associated with reduced risk of myocardial infarction and cardiovascular death. Further mechanistic studies and additional cardiovascular outcome trials are ongoing and are expected to determine whether these benefits are a result of class effect, as well as to delineate optimum timing for intervention and population target.

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When diabetes is associated with kidney disease, the cardiovascular (CV) risk increases substantially. It is known that a high proportion of patients with moderate chronic kidney disease (CKD) will never reach end stage owing to a prior fatal CV event. The current treatment strategies for the management of diabetic kidney disease and the prevention of CV mortality are based on conventional risk factor modification and the use of agents to antagonize the renin-angiotensin and sympathetic nervous systems; however, despite success, there is a pressing need for additional pharmacological treatments to abate the excess risk. This review will focus on describing the epidemiology of CV outcomes in diabetic kidney disease and will detail recent advances in type 2 diabetes mellitus (T2DM) treatment with CV impact, particularly sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Epidemiology of diabetic kidney disease and cardiovascular outcomes

Diabetes is an accelerating health and economic burden worldwide, with an estimated prevalence nearing 600 million by 2030 due to population aging, growth, and lifestyle changes associated with urbanization.¹ CV complications are the leading cause of morbidity and mortality in patients with diabetes, and diabetic kidney disease appears to predominantly account for the increased risk.^{2,3} The additive CV hazard between diabetes and CKD has been shown in many settings. Not only is this cohort of patients at increased risk of developing acute coronary syndrome, arrhythmias, and congestive heart failure; their risk of complications and mortality derived from these conditions is striking.^{4,5} Among medically treated patients with diabetes undergoing percutaneous coronary intervention (PCI), the presence of CKD has been associated with a significantly higher in-hospital and 1-year mortality rate, as well as longer hospital stays and higher rates of neurological, gastrointestinal, and pulmonary complications.⁵ Data from the Bypass Angioplasty Revascularization Investigation (BARI) study among patients with multivessel coronary artery disease undergoing revascularization show an increased risk of death among patients with CKD, independent of and additive to the risk associated with diabetes, reaching close to 70% in 7 years in this group.⁶ Both diabetes and CKD are risk factors for the development of atrial fibrillation^{7,8} and are associated with an increased risk of stroke with this arrhythmia.^{9,10} Given the notoriously high

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prevalence of bleeding in patients with impaired kidney function and the paucity of data from drug and procedure trials involving patients with a reduced estimated glomerular filtration rate, the balance between stroke prevention and the avoidance of bleeding in this group becomes especially challenging.^{11,12} When it comes to heart failure, diabetes is an independent risk factor for progression of disease, and regardless of the etiology, the concomitant presence of T2DM and CKD is associated with worse prognosis.^{13,14}

Conventional cardiovascular risk factor control

Traditional risk factor modification remains the cornerstone of treatment for patients with CKD and diabetes. The Kidney Disease: Improving Global Outcomes (KDIGO)¹⁵ and Kidney Disease Outcomes Quality Initiative (KDOQI)¹⁶ guidelines support the control of blood pressure (BP) and lipids to decrease the risk of CV mortality. For patients with urine albumin excretion < 30 mg in 24 hours, treatment is recommended to maintain a BP that is consistently no higher than 140 mm Hg systolic and 90 mm Hg diastolic (evidence grade 1B), while for patients with albumin excretion higher than 30 mg in 24 hours, the goal is to keep BP consistently no higher than 130 mm Hg systolic and 80 mm Hg diastolic (evidence grade 2D). The weak evidence level for the more strict control in the latter group derives from the lack of data from trials. The ACCORD trial in patients with diabetes¹⁷ failed to show a reduction in rates of fatal and nonfatal major CV events when comparing intensive therapy with the goals of maintaining systolic BP < 120 mm Hg and < 140 mm Hg. Conversely, the SPRINT trial in patients without diabetes¹⁸ showed a reduction in CV events and all-cause mortality among patients treated to a target systolic BP of 120 mm Hg compared with 140 mm Hg. Additionally, strict BP control in SPRINT was not associated with improved renal outcomes. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the preferred agents recommended by KDIGO and KDOQI when albumin excretion exceeds 30 mg in 24 hours (evidence grade 2D).

Strategies to reduce low-density lipoprotein cholesterol levels, such as statins or statin and ezetimibe combination, are recommended for patients with diabetes and CKD, including those who have undergone kidney transplantation (evidence grade 1B). Owing to lack of mortality benefit, statin therapy may not be started in patients treated with dialysis (evidence grade 1B); however, the risks and benefits of reducing nonfatal CV events need to be considered.

When it comes to smoking cessation, evidence is less established. Although multiple studies have tried to quantify the impact of smoking on progression of kidney dysfunction and consequent increased CV disease risk, methodologic issues have been relevant. A large cross-sectional study with 32,208 patients with T2DM with the goal of defining the prevalence and determinants of onset of albuminuria found smoking to be an independent risk factor for microalbuminuria.¹⁹ The impact of smoking exposure on CV

morbidity and mortality has been well documented in the population with CKD, both before dialysis and in those undergoing dialysis;²⁰ however, most studies included both patients with and those without diabetes. Despite the lack of prospective, randomized evidence specific for the cohort of patients with diabetic nephropathy, guidelines recommend providing smoking cessation counseling as an integral part of CKD treatment, regardless of the etiology.

Treatment of diabetes with the goal of reducing cardiovascular events

Until recently, there were no therapies for T2DM with proven CV benefits beyond the foundation of therapy with metformin and a strategy for glycemic control. Indeed, a decade ago the available treatment arsenal for diabetes was limited and included medications associated with weight gain, fluid retention, and hypoglycemia, effects that are deleterious to the CV system. In 2008, the regulatory guidance for the approval of new glucose-lowering medicines evolved to require large-scale CV outcome trials (CVOTs) with systematic assessment of overall and CV safety. The criteria to rule out excess CV risk were an upper bound of the 2-sided 95% confidence interval (CI) for the hazard ratio (HR) of major adverse cardiac events (MACEs) in the active treatment arm of <1.80 over the course of the trial and <1.30 at trial completion. Since then, several CVOTs have started; 4 of these, involving 2 SGLT2is and 2 GLP-1 RAs, have had positive primary composite outcomes for superiority against placebo: Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS), Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), and Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) (Tables 1–3).^{21–24} Additionally, the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial has been completed and has met its primary endpoint of noninferiority, as announced recently; results are due to be disclosed in the near future.²⁵

Empagliflozin is one of the SGLT2is approved for use in the USA, along with canagliflozin and dapagliflozin, while ertugliflozin is currently under review by the US Food and Drug Administration (FDA) for approval. This class of medications works by targeting the sodium–glucose cotransporter 2 located at the S1 segment of the proximal tubule, inhibiting urinary glucose reclamation and thereby increasing glucosuria and lowering plasma glucose independently of insulin. By decreasing the reabsorption of glucose at the proximal tubule, SGLT2 inhibition also causes natriuresis, increasing the availability of sodium to the macula densa, which prevents excessive afferent arteriole dilation and reduces the single-nephron glomerular filtration rate, halting the vicious cycle responsible for hyperfiltration in diabetic kidney disease.^{26–28} Additionally, the natriuretic and osmotic diuretic effect of SGLT2 inhibition leads to an increase in

Table 1 | Selected phase 3 trials of sodium–glucose cotransporter 2 inhibitors measuring cardiovascular and renal outcomes

Trial	Drug	Study status	Sample size	Intervention	Primary outcome measured	Baseline HbA _{1c}	Baseline CV status	Baseline renal status	Hazard ratio (95% CI) and <i>P</i> value for primary composite endpoint
EMPA-REG OUTCOME ²¹	Empagliflozin	Completed	7020	Empagliflozin 10 mg versus empagliflozin 25 mg versus placebo	CV death, MI, or stroke	7.0%–10.0%	Pre-existing CVD: 75.6% with prior CAD; 23.3% with prior stroke; 20.8% with prior PAD; and 10% with prior HF	Excluded if GFR < 30 ml/min	0.86 (0.74–0.99) <i>P</i> = 0.04
DECLARE-TIMI 58 ^a	Dapagliflozin	Ongoing, estimated end date April 2019	25,880	Dapagliflozin 10 mg versus placebo	CV death, MI, or stroke	Not specified	High-risk CVD events	Not specified	
VERTIS CV ^b	Ertugliflozin	Ongoing, estimated end date June 2020	8000	Ertugliflozin 5 mg versus ertugliflozin 15 mg versus placebo	CV death, MI, or stroke	7.0%–10.5%	Pre-existing vascular disease such as CAD, stroke, or PAD	Not specified	
Integrated CANVAS ²⁴	Canagliflozin	Completed	4330	Canagliflozin 100 mg versus canagliflozin 300 mg versus placebo	CV death, MI, UA, or stroke	7.0%–10.5%	Pre-existing CVD or ≥ 2 risk factors for a CV event	Not specified	0.86 (0.75–0.97) <i>P</i> = 0.02 for superiority
CREDENCE ^c	Canagliflozin	Ongoing, estimated end date January 2020	4200	Canagliflozin 100 mg versus placebo	ESRD, serum creatinine doubling, renal/CV death	6.0%–12.0%	Not specified	Diabetic nephropathy present with UACR > 300 mg/g but < 5000 mg/g	

CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; UA, unstable angina; UACR, urine albumin/creatinine ratio.

^aAstraZeneca. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58). <https://clinicaltrials.gov/ct2/show/NCT01730534>.

^bMerck Sharp & Dohme Corp. Cardiovascular outcomes following ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease, The VERTIS CV Study (MK-8835-004). <https://clinicaltrials.gov/ct2/show/NCT01986881>.

^cJanssen Research & Development LLC. Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE). <https://clinicaltrials.gov/ct2/show/NCT02065791>.

Table 2 | Cardiovascular outcomes found on the EMPA-REG OUTCOME trial, LEADER trial, and CANVAS program

Cardiovascular outcome	EMPA-REG OUTCOME Trial ²¹			LEADER Trial ²²			CANVAS Program ²⁴		
	Annualized event rate with drug versus placebo (rate/1000 patient-years)	Hazard ratio (95% CI)	P value	Annualized event rate with drug versus placebo (rate/1000 patient-years)	Hazard ratio (95% CI)	P value	Annualized event rate with drug versus placebo (rate/1000 patient-years)	Hazard ratio (95% CI)	P value
Primary composite MACE	37.4 versus 43.9	0.87 (0.78–0.97)	0.01	34 versus 39	0.86 (0.74–0.99)	0.04	26.9 versus 31.5	0.86 (0.75–0.97)	0.02
Cardiovascular death	12.4 versus 20.2	0.78 (0.66–0.93)	0.007	12 versus 16	0.62 (0.49–0.77)	< 0.001	11.6 versus 12.8	0.87 (0.72–1.06)	N/A
Fatal or nonfatal MI	16.8 versus 19.3	0.86 (0.73–1.00)	0.046	16 versus 19	0.87 (0.7–1.09)	0.23	11.2 versus 12.6	0.89 (0.71–1.09)	N/A
Fatal or nonfatal stroke	12.3 versus 10.5	0.86 (0.71–1.06)	0.16	10 versus 11	1.18 (0.89–1.56)	0.26	7.9 versus 9.6	0.87 (0.69–1.09)	N/A
Hospitalization for unstable angina	10 versus 10	0.98 (0.76–1.26)	0.87	7 versus 7	0.99 (0.74–1.34)	0.97	N/A	N/A	N/A
Hospitalization for heart failure	9.4 versus 14.5	0.87 (0.73–1.05)	0.14	12 versus 14	0.65 (0.50–0.85)	0.002	5.5 versus 8.7	0.67 (0.52–0.87)	N/A

CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction; N/A, not available.

urine output and hematocrit^{29,30} and a decrease in body weight^{31–33} and systolic BP.^{32,34}

Results of the EMPA-REG OUTCOME trial were published in September 2015 and were received with much excitement. This was the first time an antihyperglycemic agent had shown a decrease in mortality when compared with placebo.²¹ Its unprecedented data on CV outcome involved a pooled 14% reduction in the primary composite outcome of 3-point MACE (CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) at a median follow-up of 3.1 years.²¹ A significant reduction in the risk of death from any cause, CV death, and hospitalization for heart failure was found, as detailed in Table 2. No differences were found between groups in the occurrence of MI or stroke. Later, data from the secondary outcome of this trial showed promising results on renal endpoints, as will be discussed further in other sections of this editorial.³⁵ In December 2016, empagliflozin became the first antidiabetic drug to receive FDA approval for an expanded indication to reduce the risk of CV death in adults with T2DM.³⁶

The CANVAS program results have recently been published.²⁴ The program was composed of 2 double-blind, randomized, placebo-controlled trials, CANVAS and CANVAS-R, analyzed jointly to address CV safety and kidney outcomes. It involved 10,142 patients, with a median follow-up time of 126.1 weeks. Analysis of the program showed a 14% reduction in the primary composite outcome of 3-point MACE with superiority against placebo (Tables 1 and 2). No significant differences were found between the canagliflozin and placebo groups when the individual components of the primary outcome were analyzed. Similar to the EMPA-REG OUTCOME trial, a significant reduction in the rate of heart failure exacerbation and negative renal outcomes was observed. Regarding safety, there was a higher risk of amputation involving toes, feet, or legs with canagliflozin when compared with placebo (HR 1.97; 95% CI 1.41–2.75), which is a new finding.

The mechanisms by which SGLT2is improve CV outcomes are still a matter of debate; however, given the fact that the outcome improvement in EMPA-REG OUTCOME was driven by a decrease in CV mortality and heart failure admissions, the main effects of this medication appear to be hemodynamic and myocardial rather than atherosclerotic. Moreover, it is notable that the heart failure and mortality outcome curves presented in EMPA-REG OUTCOME and the heart failure curve of the CANVAS program began to diverge within 3 months of treatment, making improved glycemic control a dubious explanation for its CV benefits.^{29,37} The main proposed theories are summarized in Figure 1 and include positive impacts of weight loss,³⁸ as well as decreased preload due to natriuresis and osmotic diuresis along with a neutral effect on the sympathetic nervous system,³⁹ decreased afterload by virtue of a decrease in systolic BP and arterial stiffness,^{39,40} and improvement in myocardial energetics. It is postulated that the enhancement of myocardial energetics is

Table 3 | Selected phase 3 trials of glucagon-like peptide agonists measuring cardiovascular outcomes

Trial	Drug	Study status	Sample size	Intervention	Primary outcome measured	Baseline HbA _{1c}	Baseline CV status	Baseline renal status	Hazard ratio (95% CI) and <i>P</i> value for primary composite endpoint
ELIXA ⁴⁷	Lixisenatide	Completed	6068	Lixisenatide versus placebo	CV death, MI, UA, or stroke	5.5%–11.0%	ACS within 180 days of screening	Not specified	1.02 (0.89–1.17) <i>P</i> = 0.81
LEADER ²²	Liraglutide	Completed	9340	Liraglutide versus placebo	CV death, MI, or stroke	≥ 7.0%	High-risk CVD events if aged ≥ 60 years, pre-existing CVD, renal failure, or heart failure if aged ≥ 50 years	Not specified	0.87 (0.78–0.97) <i>P</i> = 0.01
SUSTAIN-6 ²³	Semaglutide	Completed	3299	Semaglutide 0.5 mg versus 1.0 mg versus placebo	CV death, MI, or stroke	≥ 7.0%	Clinical evidence of CVD if aged ≥ 50 years, subclinical evidence of CVD if aged ≥ 60 years	Not specified	0.74 (0.58–0.95) <i>P</i> = 0.02 for superiority
EXSCEL ²⁵	Exenatide	Completed.	14,000	Exenatide once weekly versus placebo	CV death, MI, or stroke	6.5%–10.0%	Not specified	Excluded if GFR < 30 ml/min	Primary noninferiority endpoint; full results pending
REWIND ^a	Dulaglutide	Ongoing, estimated end date 07.2018	9622	Dulaglutide versus placebo	CV death, MI, or stroke	≤ 9.5%	Clinical evidence of CVD if aged ≥ 50 years, subclinical evidence of CVD if aged ≥ 55 years, CVD risk if aged ≥ 60 years	“Chronic renal failure” as exclusion criteria	
ITCA650 ^b	Exenatide in DUROS	Completed, results pending.	4000	ITCA650 versus placebo	CV death, MI, UA, or stroke	≥ 6.5%	History of CAD, stroke, or PAD	Not specified	

ACS, acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; PAD, peripheral artery disease; UA, unstable angina.

^aEli Lilly and Company. Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND). <https://clinicaltrials.gov/ct2/show/NCT01394952>.

^bIntarcia Therapeutics. A Study to Evaluate Cardiovascular Outcomes in Patients with Type 2 Diabetes Treated with ITCA650. <https://clinicaltrials.gov/ct2/show/NCT01455896>.

Figure 1 | Mechanisms postulated for cardiovascular and renal effects of sodium-glucose cotransporter 2 inhibitors. LV, left ventricular.

a result of the reduction in oxygen consumption, with lower preload and afterload coupled with a shift in myocardial fuel utilization away from free fatty acids and toward ketone bodies, a more efficient fuel.⁴¹ In addition, an increase in hematocrit has been reported with SGLT2is, which could generate hypotheses about favorable hematological effects and CV benefit.⁴²

An additional interesting observation made by analyzing the Kaplan-Meier curves published in EMPA-REG OUTCOME is the fact that the CV mortality graph also shows a progressive late separation between the empagliflozin-treated and placebo-treated groups, suggesting a mechanism of CV protection supplementary to the first, early separation, this time possibly representing a more substantial impact of fat loss, glucose control, and increased insulin sensitivity.³⁷

It remains unclear whether the beneficial CV outcome found with empagliflozin will be replicated in trials with other approved SGLT2is. As mentioned, the CANVAS program has reached its primary composite outcome and has also shown important reductions in rates of heart failure admissions. However, when the individual components such as CV death were analyzed, point estimates suggested benefits, although not reaching statistical significance. It appears that baseline risk for heart failure exacerbation will likely be a determinant of the CV benefit of SGLT2 inhibition. The 3-point MACE, which is a reflection of atherosclerotic events, appears to be less impacted by SGLT2 inhibition. Several ongoing studies, such as Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) and the ertugliflozin trial, will attempt to address this question (Table 1).

The second class of diabetes medications shown to be beneficial to the CV system is the GLP-1 RAs. Glucagon-like

peptide (GLP) and gastric inhibitory peptide (GIP) are incretin hormones, secreted from the intestine in response to an oral glucose load. Their main action is stimulation of glucose-dependent insulin secretion from pancreatic beta cells through activation of intracellular cyclic adenosine monophosphate. Although the hyperglycemic state of diabetes attenuates GIP receptor expression and responsiveness, preventing the application of GIP as a potential therapy for T2DM, the secretory function of GLP-1 was restored after administration of pharmacological levels in diabetes, and so this hormone has become the fundamental target in the development of incretin-based glucose-lowering therapies.^{43,44}

GLP-1 has numerous beneficial effects beyond stimulating insulin secretion. It is also responsible for promoting beta cell proliferation and inhibition of apoptosis, and it decreases post-prandial glucagon release, slows gastric emptying, and controls appetite centrally. The native form of GLP-1 is not applicable as a therapy for T2DM, given its short half-life due to prompt inactivation by the protease dipeptidylpeptidase-4 (DPP-4) and clearance by the kidneys. For this reason, injectable forms of GLP-1 RAs that are resistant to DPP-4 degradation have been developed and have been successful in enhancing the incretin effect.⁴³ The currently FDA-approved GLP-1 RAs are exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide. Semaglutide's approval is under review by the FDA and the European Medicines Agency.

As expected, clinical trials, pooled analyses, and meta-analyses of the above-mentioned FDA-approved GLP-1 RAs have shown efficacy in glucose control with a low risk of hypoglycemia and weight gain, as well as a good safety profile.^{43,45} In consonance with the trend since 2008,

numerous CVOTs have been initiated to test the CV safety of GLP-1 RAs systematically (Table 3). The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial,⁴⁶ published in 2015, was the first CVOT involving a GLP-1 RA. Patients with T2DM and a recent acute coronary syndrome were randomized to receive lixisenatide or placebo along with standard care. The trial reached its non-inferiority primary outcome of MACE (consisting of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina) with an HR of 1.02 (95% CI 0.89–1.17) against placebo as designed, but it was not found to be superior. Overall, this trial established the CV safety of lixisenatide with no sign of increased heart failure exacerbations or hospitalizations.

In June and September of 2016, 2 additional CVOTs involving the GLP-1 RAs liraglutide and semaglutide were published, this time with superiority against a placebo in reducing CV events. The LEADER trial randomized high-CV risk patients to receive liraglutide or placebo, and defined as the primary outcome the time to first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. After a median follow-up of 3.8 years, a significant reduction in 3-point MACE was found (HR 0.87; 95% CI 0.78–0.97; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority).²² There was a 14% reduction in rates of fatal or nonfatal MI ($P = 0.046$), a 22% reduction in CV death ($P = 0.007$), and a 15% reduction in overall mortality ($P = 0.02$) (Table 4). The SUSTAIN-6 trial had a similar design, with high-risk patients with T2DM randomized to receive the long-acting GLP-1 RA semaglutide 0.5 mg or 1.0 mg once weekly or a placebo. At a median follow-up of 2.1 years, there was a 26% reduction in 3-point MACE for semaglutide against the placebo (HR 0.74; 95% CI 0.58–0.95; $P < 0.001$) that was largely driven by a 39% reduction in nonfatal stroke occurrence ($P = 0.04$) (Table 5).²³ A significant reduction in rates of revascularization procedures was also found. The conclusion of superiority in this trial is controversial, because it was designed as a noninferiority study in which superiority was not pre-specified as the primary outcome.

In contrast to the EMPA-REG OUTCOME trial in which CV mortality accounted for most of the reduction in CV outcomes—with no difference found in rates of MI or stroke, and an early separation from placebo observed in the Kaplan-

Table 5 | Cardiovascular outcomes found in the SUSTAIN-6 trial²³

Cardiovascular outcomes	Hazard ratio (95% CI)	P value
Primary composite MACE	0.74 (0.58–0.95)	< 0.001/0.02 ^a
Cardiovascular death	0.98 (0.65–1.48)	0.92
Fatal or nonfatal MI	0.74 (0.51–1.08)	0.12
Fatal or nonfatal stroke	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina	0.82 (0.47–1.44)	0.49
Hospitalization for heart failure	1.11 (0.77–1.61)	0.57

CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction.

^aSuperiority test.

Data from Marso SP, Bain SC, Conso A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *New Engl J Med*. 2016;375:1834–1844.

Meier curves—in the LEADER and SUSTAIN-6 trials, decreases in the rates of MI and nonfatal MI or nonfatal stroke were observed, respectively. The Kaplan-Meier curves for the primary outcome for LEADER and SUSTAIN-6 showed clear separation only after about 1 year from randomization, implying that distinct mechanisms are responsible for the CV protection, with the potential to impact atherogenesis rather than produce myocardial effects. A possible explanation for such a difference may lie in the hypothesis that GLP-1 RA decreases inflammation and, more importantly, possibly influences specific reperfusion injury pathways that ultimately lead to cell death, as will be detailed subsequently.

Although a decrease in atherogenesis is one plausible hypothesis, the exact mechanism of cardioprotection from GLP-1 RA remains largely unknown. Figure 2 summarizes the main theories and includes the influence of GLP-1 RA on traditional CV risk factors through improvement in lipid profile, reduction in BP and weight, and improved glucose control. Several studies have shown that GLP-1 RA induces major reductions in postprandial hyperlipidemia, a meaningful component of diabetic dyslipidemia that is known to be atherogenic.^{47–49} Additionally, several preclinical and clinical studies have shown evidence of direct and indirect effects (through lower body weight and better glucose control) of GLP-1 RA on reducing inflammation, which could contribute to its beneficial CV actions.^{50–52} Interestingly, studies in humans also seem to suggest a direct effect of GLP-1 RA in the heart, specifically in ischemic conditions. Two placebo-controlled studies with exenatide infusion at different intervals and durations in patients presenting with ST segment elevation MI (STEMI) showed evidence of a decrease in infarct size in the treatment group compared with placebo.^{53,54} In contrast, the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial and the Effect of Liraglutide on Left Ventricular Function in Chronic Heart Failure Patients With and Without Type 2 Diabetes (LIVE) study, 2 prospective, randomized trials of liraglutide in patients with heart failure, failed to show improvement in left ventricular function, suggesting that the CV benefits found with GLP-1 RA are most likely not related to improvement in heart failure.

Table 4 | Cardiovascular outcomes found in the LEADER trial²²

Cardiovascular outcome	Hazard ratio (95% CI)	P value
Primary composite MACE	0.87 (0.78–0.97)	0.01
Cardiovascular death	0.78 (0.66–0.93)	0.007
Fatal or nonfatal MI	0.86 (0.73–1.00)	0.046
Fatal or nonfatal stroke	0.86 (0.71–1.06)	0.16
Hospitalization for unstable angina	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	0.87 (0.73–1.05)	0.14

CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction. Data from Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *New Engl J Med*. 2016;375:311–322.

Figure 2 | Mechanisms postulated for cardiovascular and renal effects of glucagon-like peptide-1 receptor agonists. GLP-1, glucagon-like peptide-1.

Clinical strategies for the treatment of coronary artery disease

Another provocative theory for cardioprotection with GLP-1 RA involves the concept of ischemic conditioning. The damage to the myocardium during infarction is a result of ischemia followed by reperfusion injury (IR injury), which is a complex event that begins with an epicardial coronary occlusion. After chemical or mechanical reperfusion, a cascade takes place leading to a flow of activated platelets and leukocytes and microvascular obstruction by distally embolized debris, which ultimately leads to additional injury induced by reperfusion.^{55,56} Reperfusion injury is known to be associated with myocardial stunning, late remodeling, and arrhythmia. Although recent advances in PCI have led to great improvements in patient outcomes following MI, revascularization does not undertake IR injury and thus does not address its known deleterious effects. Studies in preclinical models of MI have generated the hypothesis that GLP-1 RA might be able to protect the myocardium from IR injury, possibly by interfering with ischemic conditioning pathways including the reperfusion injury salvage kinase (RISK) and survivor-activating factor enhancement (SAFE) pathways. The RISK and SAFE pathways are composed of numerous molecular steps that converge to a final point that opens the mitochondrial K-ATP channel and prevents opening of the mitochondrial permeability transition pore during reperfusion, avoiding loss of membrane potential and ultimately cell death.^{57,58} Experimental animal studies and small clinical trials have reported reduction in MI size when the GLP-1 receptor is activated prior to reperfusion.^{59,60} Challenges remain in

translating the results of preclinical and small clinical studies to large-scale trials with the potential to modify clinical practice; nevertheless, important steps are being taken in determining optimum timing for intervention and target population.

Despite compelling evidence of cardioprotection from the LEADER and SUSTAIN-6 trials in patients with T2DM, further studies are currently in progress to elucidate additional clinical applications of GLP-1 RA and to better grasp its means of CV protection. The Combination Therapy in Myocardial Infarction (COMBAT-MI) trial (NCT02404376) will test the combination of ischemic conditioning and exenatide in patients with STEMI, while the GLP-1 Loading During Elective Percutaneous Coronary Intervention (GOLD-PCI) study (NCT02127996) will investigate the benefits of GLP-1 infusion during elective PCI.

In conclusion, despite recent advances in the field of cardiology with established guideline-directed therapies for the treatment of heart failure, arrhythmias, and coronary artery disease, patients with diabetic kidney disease have an exceedingly high residual risk of CV morbidity and mortality. While exclusion of patients with CKD from important trials persists as a notable barrier to therapeutic advancement, recent developments have revived optimism. Diabetes management has evolved and now pursues therapies with the potential to promote benefits that go beyond glucose control. Newer agents such as empagliflozin, canagliflozin, liraglutide, and semaglutide have shown remarkable results in their respective CVOTs and have raised expectations regarding other CVOTs and mechanistic studies yet to be published.

DISCLOSURE

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