



Perspective

Advances in reducing cardiovascular risk in the management of patients with type 2 diabetes mellitus

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Abstract

Treatment intended to lower cardiovascular (CV) risk in patients with diabetes has always been a primary goal of diabetes treatment. Due to the subdued effects of reducing hemoglobin A1c (HbA1c) on macrovascular complications, controlling other CV risk factors such as hypertension and hyperlipidemia instead of hyperglycemia has been the mainstay treatment to improve CV outcome in patients with type 2 diabetes mellitus (T2DM) until recent years. This review is intended to summarize and compare the results from the available cardiovascular outcome trials (CVOTs) for the two classes of glucose lowering drug: sodium-glucose co-transporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1 RA). The results including the EMPA-REG, CANVAS program and DECLARE-TIMI 58 trials for SGLT2i, and the ELIXA, LEADER, SUSTAIN-6, EXSCEL and HARMONY trials for GLP-1 RA were summarized. The potential mechanisms of these CV beneficial effects and the optimal CV risk reduction treatment in patients with T2DM based on patient risk stratification and evidence from these CVOTs in real-world setting were discussed.

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Due to population growth, aging of populations, and urbanization with associated lifestyle change, the prevalence of diabetes mellitus (DM) has been substantially increasing worldwide over the last decade.^{1–3} It was estimated that the number of adult people with diabetes will rise to 642 million by 2040.³ Along

with the increase in the prevalence, there comes inevitably the increased economic cost.⁴ The estimated economic burden associated with diagnosed diabetes in the United States from both direct health care expenditures and indirect expenditures from lost productivity was \$327 billion in 2017.⁵ In addition, after adjusting for age and gender, annual per capita healthcare expenditure is 2.3 times higher for people with diabetes compared with those without diabetes.⁵ Cardiovascular disease (CVD) is the most prevalent cause of mortality and morbidity in diabetic population.⁶ CVD death rate in the United States is 1.7 times higher among patients with DM than those without.⁷ Thus, treatment intended

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to lower cardiovascular (CV) risk in patients with diabetes has always been a primary goal of diabetes management.

Studies have shown a strong association between hemoglobin A1c (HbA1c) and CV mortality. The risk of CV mortality increases 1.15-fold for every 1% increase in the HbA1c.^{8,9} However, the treatment reducing HbA1c has been shown to effectively reduce risk of only microvascular complications but not macrovascular complications. Many large-scale studies in diabetes history, including the United Kingdom Prospective Diabetes Study (UKPDS) and the Action in Diabetes and Vascular Disease (ADVANCE) trial, have all failed to show any significant decrease in CV risk. Furthermore, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study even showed that intensive glucose lowering had increased rates of all-cause mortality.^{10,11} Therefore, controlling other CV risk factors such as hypertension and hyperlipidemia instead of hyperglycemia has been the mainstay treatment to improve CV outcome in patients with type 2 diabetes mellitus (T2DM).

There have been accumulated data showing questionable CV safety of glucose lowering drugs. Metformin is the recommended first-line treatment for patients with T2DM due to its positive CV effects derived from the landmark UKPDS study,¹² in which metformin treatment in patients with overweight and T2DM showed a significant 36% decrease in all-cause mortality when compared with other conventional treatment at that time in 1998. However, recent meta-analysis has questioned its effectiveness in reducing CV risk,¹³ especially when it was in combination with sulfonylurea.¹⁴ A meta-analysis summarized the outcome from all the published randomized controlled trials of glucose lowering drugs in 95,000 patients with or at risk for T2DM up to Feb 20, 2015. The results showed that the treatment with glucose lowering drugs resulted in a 14% relative increase in the risk of heart failure overall. There was significant heterogeneity in the magnitude of this effect, with the highest risk for peroxisome proliferators-activated receptors (PPAR) agonists, intermediate risk with dipeptidyl peptidase 4 (DPP-4) inhibitors, and a neutral risk with insulin glargine, target-based intensive glycemic control, and intensive weight-loss strategies.¹⁵

Given the high level of uncertainty around CV safety of glucose lowering drugs, the U.S. Food and Drug Administration (FDA) issued a guideline in 2008¹⁶ that required clinical trials showing a two-sided 95% confidence interval upper boundary of 1.8 risk

ratio for major adverse CV events (MACE) versus the control group, with subsequent outcome trials having an upper boundary of 1.3. These regulatory requirements have prompted many CV outcome trials (CVOTs) with the newer agents. All the CVOTs were designed as randomized, double-blind, and placebo-controlled in patients with T2DM with established CVD or at high risk for CV events who were receiving standard care. The primary endpoint was time to first event included in the composite 3-point MACE (3p-MACE): death from CV cause, non-fatal myocardial infarction (MI), and non-fatal stroke. The secondary endpoint was time to first event of a composite of primary outcome plus other major CV events, such as hospitalization for unstable angina, hospitalization for heart failure, coronary revascularization procedure, transient ischemic attack, renal outcome, etc. Some of these trials have surprisingly showed significant CV risk reduction, which opens a new era in diabetes management. This review is to summarize and compare the results from the currently available CVOTs for the two classes of glucose lowering drug: sodium-glucose co-transporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1 RA).

SGLT2i

SGLT2i treats hyperglycemia in patients with T2DM by reducing renal glucose reabsorption and increasing urinary glucose excretion.^{17,18} SGLT2i also causes natriuresis and is associated with an antihypertensive effect and weight loss. An increased risk of genitourinary infection is the most common side effect.

Four SGLT2i agents, canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance) and ertugliflozin (Steglatro), have been approved for the treatment of T2DM in the United States. Dapagliflozin has been approved in China. As for the four drugs listed above, three CVOTs have been completed and one is in process.

The EMPA-REG outcome trial (The Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients—Removing Excess Glucose, NCT01131676, 7/2010-4/2015)^{19,20}

This study was designed to assess the CV safety of empagliflozin in patients with T2DM and established CVD.

A total of 7020 patients with a median age of 63 years were randomized to receive either empagliflozin

(10 mg or 25 mg) or a placebo in addition to standard care. Among those, 57% of patients had a long-standing diabetes history of more than 10 years. The average HbA1c was 8.0%. More than 99% of those patients had established CV disease. The medium follow-up duration was 3.1 years.

The treatment of empagliflozin resulted in a 14% relative risk reduction for the primary composite 3p-MACE outcome (significant for both noninferiority and superiority), which was primarily driven by a 38% relative risk reduction in CV death. The risk reduction in non-fatal MI and stroke was not statistically significant. In addition, there was a 32% relative risk reduction in all-cause mortality and a 35% relative risk reduction in the incidence of hospitalization for heart failure. Furthermore, empagliflozin was shown to be renal protective. The effects on these endpoints occurred as early as the first 6–12 weeks of treatment.

As for CV risk factors, the treatment of empagliflozin showed small reductions in HbA1c (−0.24% in 10 mg group, −0.36% in 25 mg group at week 206), weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as small increases in both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol without changing LDL/HDL ratio.

The trial was a breakthrough study, as it was the first to demonstrate that a glucose lowering drug could reduce CV events in addition to its glucose-lowering effect in such a short period of time.

The CANVAS program (Canagliflozin Cardiovascular Assessment Study)^{21–23}

The CANVAS program integrated analysis of CANVAS (NCT01032629, 12/2009–2/2017) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus, NCT01989754, 1/2014–2/2017). These are studies to evaluate the CVOT safety of canagliflozin.

A total of 10,142 participants with a median age of 63.3 years with T2DM and high CV risk were randomized to receive either canagliflozin (100 mg vs. 300 mg in CANVAS, 100–300 mg dose titration in CANVAS-R) or a placebo in addition to standard care and were followed up for a mean of 188.2 weeks (295.9 weeks in CANVAS and 108.0 weeks in CANVAS-R). The mean duration of diabetes was 13.5 years, and the mean HbA1c was 8.2%. Of those patients, 65.6% had a history of CVD.

The treatment of canagliflozin reduced primary endpoints 3p-MACE by 14% (significant for both noninferiority and superiority), although individual effects on the 3p-MACE did not reach significance. There was also a 33% reduction in hospitalization for heart failure but no significant differences in all-cause mortality. In addition, canagliflozin was confirmed to be renal protective. As for CV risks, the treatment of canagliflozin achieved a small reduction in HbA1c (−0.58%), weight (−1.60 kg), SBP and DBP, along with small increases in both HDL and LDL cholesterol. Unlike the EMPA-REG trial, the CANVAS program showed a higher risk of fractures (1.54% vs. 1.19%) and amputation (mainly at the level of toe and metatarsal, 0.63% vs. 0.34%) in patients treated with canagliflozin than in those given the placebo.²⁴

The DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events, NCT01730534, 4/2013–7/2017)^{25–27}

This study was designed to assess the CV safety of dapagliflozin in patients with T2DM. DECLARE–TIMI 58 is the largest CVOT study with SGLT2i in patients with T2DM. Unlike the EMPA-REG trial, it has enrolled large populations of both patients with established CV disease and patients without established CV disease but with multiple risk factors for CV disease.

A total of 17,160 patients with T2DM and a history of either established atherosclerotic cardiovascular disease (ASCVD) ($n = 6,974$, 40.6%) or multiple risk factors for ASCVD ($n = 10,186$, 59.4%) were randomized to dapagliflozin (10 mg/day) or placebo groups. Patients had a mean age of 63.9 years, and a mean HbA1c of 8.3%. The median duration of T2DM was 11.0 years. Patients were followed for a median of 4.2 years.

The treatment of dapagliflozin met the prespecified criterion for noninferiority with respect to MACE but not superiority. The treatment did not result in a lower rate of MACE or any difference in CV death or death from any cause. However, it reduced the rate of CV death or hospitalization for heart failure (hazard ratio, 0.83). Dapagliflozin treatment also reduced a composite of renal events by 24%. As for CV risks, the treatment of dapagliflozin achieved a lower HbA1c (−0.42%), weight (−1.8 kg), SBP and DBP. Patients treated with dapagliflozin developed more diabetic ketoacidosis (DKA, 0.3% vs. 0.1%) than those treated with placebo.

*The VERTIS CV Study (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease, NCT01986881, 11/2013-9/2019)*²⁸

This is a study to evaluate the CV outcome of ertugliflozin in treating patients with T2DM. It will enroll approximately 8000 patients with T2DM and established vascular disease.

In summary (see Table 1), all SGLT2is have demonstrated their safety in treatment for patients with T2DM. The EMPA-REG and CANVAS/CANVAS-R studies showed beneficial effects on the primary 3p-MACE in patients with T2DM, while DECLARE-TIMI 58 study only showed a neutral result. As shown in Table 1, the recent meta-analysis²⁹ derived from all these three CVOTs did show an overall mild reduction of death from all cause (15%) and CV death (16%), as well as a reduction of risk of MACEs (11%), and the risk of MI (11%), regardless of the significant heterogeneity in the patient population among those studies. Similar results were observed in other

population-based cohort studies such as CVD-REAL^{30,31} and EASEL,³² which better reflected patient population from the real world setting. Therefore, the beneficial effects on reducing MACE and death in patients with T2DM from SGLT2i could be accepted as a class effect.³³ Nevertheless, it is worth noting that those beneficial effects might be more consistent in patients with established CVD. The meta-analysis²⁹ from CVOTs showed that the benefit effect of SGLT2i on the 3p-MACE was entirely restricted to a 14% of reduction in patients with established CVD but not found in patients without CVD with only multiple risk factors.

Importantly, all these three CVOT studies with SGLT2i showed a unanimous reduction in hospitalization related to heart failure, as that was observed in many other population-based cohort studies.^{30–32} This effect existed and did not differ in both patients with established CVD and patients with multiple risk factors, and regardless of their baseline heart failure status.²⁹ Furthermore, a robust renoprotection effect with SGLT2i treatment was confirmed in all CVOTs reviewed here in patients with either established CVD

Table 1
Summary of the results of three completed CVOTs with SGLT2i.

Item	EMPA-REG (n = 7020)	CANVAS (n = 10,142)	DECLARE-TIMI 58 (n = 17,160)	Meta-analysis (n = 34,332)
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	All three
Patient mean age, years old	63	63	64	64
HbA1c, %	8.0	8.2	8.3	8.2
Mean DM duration, years	57% of patients >10	13.5	11.0	>10
Patients with established CVD	More than 99%	65.6%	40.6%	60.2%
Mean follow-up duration, years	3.1	3.6	4.2	3.8
Primary outcome ^a	14% ↓	14% ↓	Significant for non-inferiority but not for superiority	11% ↓
Death from all cause	32% ↓	NS	NS	15% ↓
Death from CV cause	38% ↓	NS	NS	16% ↓
MI	NS	NS	NS	11% ↓
Stroke	NS	NS	NS	NS
Hospitalization for heart failure	35% ↓	33% ↓	27% ↓	31% ↓
Renal composite outcome ^b	Reduction in acute renal failure rate (6.6% vs. 5.2%); reduction in acute renal injury rate (1.6% vs. 1.0%)	40% ↓	24% ↓	45% ↓
Side effects (except genital infection)	Increased hematocrit	Osmotic diuresis; volume depletion; amputation; fracture	DKA	DKA

CVOT: cardiovascular outcome trial; SGLT2i: sodium-glucose co-transporter 2 inhibitor; HbA1c: hemoglobin A1c; DM: diabetes mellitus; CVD: cardiovascular disease; CV: cardiovascular; NS: not significant; MI: myocardial infarction; DKA: diabetic ketoacidosis; ↓: reduction.

^a Primary outcome: a composite of 3-point major adverse cardiovascular events (3p-MACE) except DECLARE-TIMI 58 study (a composite of 3p-MACE plus a composite of cardiovascular death or hospitalization for heart failure).

^b Renal composite outcome: a 40% or more reduction in estimated glomerular filtration rate, new end-stage renal disease or death from renal or cardiovascular causes.

or only multiple risk factors. The effects presented across all baseline estimated glomerular filtration rate (eGFR) and were greatest in those with preserved renal function at baseline.²⁹

Overall SGLT2i treatment was well tolerated. Genital infection was common but DKA was rare. There was significant heterogeneity among the trials for amputation and fracture. It is unclear at this time whether this heterogeneity was due to patient characteristics or drug specificity.

GLP-1 RA

GLP-1 RA is a class of parenteral glucose-lowering drug that activates the receptor for the endogenous incretin glucagon-like peptide-1 (GLP-1).³⁴ These drugs lower glucose levels by inhibiting the secretion of glucagon, promoting the release of insulin in response to hyperglycemia, slowing gastric emptying, and augmenting satiety. It is effective in reducing both the fasting and the postprandial blood glucose levels in patients with T2DM. Several drugs in this class have been approved by the FDA, which include short-acting drugs such as exenatide (Byetta, twice daily; Bydureon once weekly), liraglutide (Victoza, daily), and lixisenatide (daily), as well as long-acting weekly albiglutide (Tanzeum), dulaglutide (Trulicity), and semaglutide (Ozempic). With respect to glycemic control, long-acting agonists are more effective in reducing HbA1c than short-acting agonists.³⁵ Exenatide (twice daily) and liraglutide are the two agents approved in China. Gastrointestinal symptoms are known side effects. Six CVOTs were designed and five of those were completed.

*The ELIXA study (Evaluation of Lixisenatide in Acute Coronary Syndrome, NCT01147250, 6/2010-2/2015)*³⁶

It was designed to evaluate the CV safety for lixisenatide. It was the first safety study carried out on GLP-1 RA.

A total of 6068 patients with T2DM and an average age of 60.2 years who had a myocardial infarction or been hospitalized for unstable angina within the previous 180 days were randomized into lixisenatide or placebo. The mean follow-up duration was 25 months. The average duration of diabetes was 9.3 years and the baseline average HbA1c was 7.7%.

Lixisenatide showed non-inferiority to placebo with the primary endpoints. The numbers of deaths from CV causes, non-fatal MI, non-fatal stroke, and

hospitalization for unstable angina were all similar in both groups. The same occurred with hospitalization for heart failure, coronary revascularization, and death from all causes. The study did not show superiority of lixisenatide when compared with placebo.

As for CV risk factors, lixisenatide showed a relatively small reduction in HbA1c (−0.27%), weight (−0.7 kg), SBP (−0.8 mmHg) and a very small increase in heart rate (+0.4 beats per minute) when compared with the placebo group. There were favorable results on renal protection.

Thus, lixisenatide showed a safe but neutral CV profile in patients with T2DM with a recent acute coronary syndrome.

*The LEADER trial (The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results, NCT01179048, 8/2010-12/2015)*³⁷

It was designed to evaluate the CV safety outcome for liraglutide. A total of 9340 patients with T2DM and an average age of 64.3 years and with a high CV risk were randomized into a liraglutide group and a placebo group. The median follow-up was 3.8 years. Of those, 81.3% of the patients had established CVD. The mean duration of diabetes was 12.8 years and the baseline average HbA1c was 8.7%.

The patients treated with liraglutide had a statistically significant 13% lower risk of primary MACE endpoints when compared with the placebo group (significant for both non-inferiority and superiority), which was mainly driven by the reduction (22%) from risk of deaths from CV cause, but not the risk of non-fatal MI and non-fatal stroke. The treatment of liraglutide also reduced the risk of deaths from all-cause by 15%. The treatment was also shown to be renal protective.

As for CV risk factors, the liraglutide group showed a small but significant reduction in HbA1c (−0.4%), weight (−2.3 kg), SBP (−1.2 mmHg) and an increase in DBP (+0.6 mmHg), and heart rate (+3 beats per minute).

This is the first CVOT of GLP-1 RA showing positive CV risk reduction in patients with T2DM.

*The SUSTAIN-6 Trial (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With T2DM, NCT01720446, 2/2013-3/2016)*³⁸

This was designed to evaluate the CV safety of semaglutide. A total of 3297 patients with an average age of 64.6 years were randomized into a semaglutide

group and a placebo group for a follow-up of 2.1 years. 83.0% of the patients had established CVD. The overall mean duration of diabetes history was 13.9 years, and the mean HbA1c was 8.7%.

Semaglutide-treated patients had a significant 26% lower risk of the primary outcome when compared with placebo-treated patients (significant for both non-inferiority and superiority). This lower risk was principally driven by a significant 39% decrease in the rate of non-fatal stroke and a significant 26% decrease in non-fatal MI, but not the risk of CV death. Unlike liraglutide, semaglutide also showed a significant 39% risk reduction in non-fatal stroke.

As for the CV risk factors, the treatment with semaglutide showed a reduction in HbA1c (−1.1% in 0.5 mg dose group and −1.4% in 1 mg dose group), weight (−2.9 kg in 0.5 mg dose group and −4.3 kg in 1.0 mg dose group), SBP (−1.3 mmHg in 0.5 mg group and −2.6 mmHg in 1 mg group), but an increase in heart rate (2 beats per minute in 0.5 mg group and 2.5 beats per minute in 1 mg group) when compared with the placebo group.

The SUSTAIN-6 study showed a higher risk of diabetic retinopathy in the semaglutide group than the placebo group (hazard ratio, 1.76), which was first seen very early in the trial. The worsening of retinopathy was related to the presence of pre-existing retinopathy at the baseline, poor baseline metabolic control, and greater reductions in HbA1c in the first 16 weeks of the trial.

*The EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering Trial: A Trial to Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly in Patients With Type 2 Diabetes Mellitus, NCT01144338, 6/2010-4/2017)*³⁹

It was the largest CVOT conducted for GLP-1 RAs to demonstrate the CV safety of extended-release exenatide. A total of 14,752 patients with T2DM and a wide variety of CV situations were followed up for 3.2 years. The average age was 62.0 years. Of those, 73.1% had previous CVD. The average diabetes duration was 12.0 years and the baseline HbA1c was 8.0%.

The treatment of weekly exenatide did not increase the incidence of the first episode of MACE compared to placebo (significant for noninferiority, but not significant for superiority). The rates of the first fatal or non-fatal MI, fatal or non-fatal stroke, and other secondary outcomes did not differ significantly between the two groups. A 14% reduction in death from any cause was seen but could not be accepted as formally significant in a hierarchical statistical analysis due to

the lack of significant impact on the primary composite endpoint.

As for the CV risk factors, the weekly exenatide group showed a reduction in HbA1c (−0.7%), weight (−1.27 kg), SBP (−1.57 mmHg), LDL cholesterol and triglycerides and an increase in DBP (0.25 mmHg) and heart rate (2.51 beats per minute).

Thus, once-weekly administration of extended-release exenatide in patients with T2DM appeared safe but not superior in reducing CV events, when compared with placebo.

HARMONY (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus, NCT02465515, 7/2015-6/2018)^{40–42}

A total of 9463 patients with T2DM and established CVD were randomized into either receiving albiglutide or placebo for 1.6 years. The average patient age was 64.1 years. The average diabetes duration was 14.1 years. The baseline HbA1c was 8.7%.

The patients treated with albiglutide had a significant 22% lower risk of the primary outcome when compared with placebo-treated patients (significant for both non-inferiority and superiority). There was no significant reduction in death from all cause or from CV cause. The treatment with albiglutide reduced fatal and non-fatal MI events by 25%.

As for the CV risk factors, albiglutide treatment showed a small reduction in HbA1c (−0.63% at 8 months, −0.52% at 16 months), weight (−0.66 kg at 8 months, −0.83 kg at 16 months), SBP (−0.65 mm Hg at 8 months, −0.67 mm Hg at 16 months) and a slight increase in heart rate (1.3 beats per minute at 8 months; 1.4 beats per minute at 16 months).

Other than injection site reaction, there was no significant side effects observed in the treatment group. GlaxoSmithKline has discontinued the manufacturing and sale of albiglutide in the United States in 2018.

*REWIND (The Effect of Dulaglutide on Major Cardiovascular Events in Patients With Type 2 Diabetes: Researching Cardiovascular Events With a Weekly Incretin in Diabetes, NCT01394952, 7/2011-7/2018)*⁴⁰

This trial has enrolled 9622 patients with T2DM and HbA1c <9.5% who are either older than 50 years with established clinical vascular disease or older than 55 years with subclinical vascular disease or at

least 60 years old and with at least two or more CV risk factors.

In summary, the five completed CVOTs for GLP-1 RAs have demonstrated their CV safety as shown in Table 2. Three of these CVOTs have showed significant CV events reduction with liraglutide, semaglutide and albiglutide but not with lixisenatide and exenatide. A meta-analysis published in early 2018⁴³ summarized all the data from the four trials including ELIXA, LEADER, SUSTAIN-6, and EXSCCEL. The results showed that treatment with GLP-1 RAs was associated with a 10% risk reduction in 3p-MACE, a 12% reduction in CV mortality and 13% reduction in all-cause mortality. The reduction in CV events was modest, but statistically significant. The HARMONY, recently published, was not included in the meta-analysis, but the beneficial effects on CV event reduction were consistent. Similar results were repeatedly observed in a systematic review of 189 randomised controlled trials (RCT) ($n = 155,145$)⁴⁴ that assessed the impact of incretin therapies on all-cause mortality in patients with T2DM. All these have demonstrated the safety and CV benefit of GLP-1 RAs in treating patients with T2DM and a high CV risk.

It must be noted that CV benefits observed with different GLP-1 RAs are largely variable, with more prominent benefit with semaglutide, albiglutide than liraglutide. The exact reason for this discrepancy is not clear. It might be related to differences in patient characteristics, or the duration of follow-up, and could also be related to pharmacokinetic and pharmacodynamic properties of the individual drug. Lixisenatide and exenatide have very short half-lives (2–3 hours) compared with liraglutide (13 hours), semaglutide (1 week) and albiglutide (1 week). Lixisenatide and exenatide are both of reptilian origin, which is different from the liraglutide and semaglutide that are of human origin.⁴⁵

GLP-1 RAs also showed neutral effects on MI, stroke, hospitalization for heart failure or unstable angina, which has demonstrated its safety in patients with T2DM. It is interesting that the same consistent CV safety was not seen with the other incretin-based glucose lowering drug, dipeptidyl peptidase IV (DPP-IV) inhibitor. Although CVOTs with alogliptin (EXAMINE trial⁴⁶), saxagliptin (SAVOR-TIMI 53 trial⁴⁷), and sitagliptin (TECOS trial⁴⁸) all have demonstrated their non-inferiority in treating patients with T2DM, saxagliptin treatment was associated with a small but statistically significant increase in the risk of hospitalization for heart failure (3.5% vs. 2.8%).⁴⁹ Similar trend was observed in the EXAMINE trial with alogliptin

although the difference was not statistically significant.⁵⁰ All these data led the FDA in 2016 to mandate label warnings for saxagliptin and alogliptin regarding the increased risk of heart failure.

Although not all the CVOT studies with GLP-1 RA investigated the renal outcome, LEADER trial and SUSTAIN-6 have demonstrated their moderate renal protective effects with liraglutide and semaglutide, and similarly favorable effects with albuminuria were seen with lixisenatide.

Overall GLP-1 RA was well tolerated with no increased risk of hypoglycemia, pancreatitis, pancreatic cancer or thyroid cancer.

Mechanisms of beneficial CV outcome

The additional HbA1c reduction achieved in these CVOTs was small (mostly <0.7% except in SUSTAIN-6) when compared with placebo, yet the reduction in CV events was significant in rather short period of time with SGLT2i and GLP-1 RA. Reduction in hyperglycemia usually takes a long time to induce benefit in primary CV outcome as demonstrated in UKPDS post-trial follow-ups⁵¹ (a 15% reduction in myocardial infarction and a 13% reduction in death from any cause emerged over 10 years of follow-up) and the Veterans Affairs Diabetes Trial (VADT) extended study⁵² (a 17% reduction in major CV events after an average 9.8 years of follow up). Therefore, it is unlikely that their glucose lowering effects are the main contributor to the benefit observed in those CVOTs. The exact mechanisms underlying these beneficial effects are unknown; however, several hypotheses may be considered for each class of drug.

As for SGLT2i, a hemodynamic hypothesis was suggested, which likely has played a large role in this process. SGLT2i can effectively reduce blood pressure and intravascular volume through osmotic diuresis to lower the cardiac workload.^{53,54} SGLT2i not only decreases blood pressure but also improves a disrupted circadian rhythm of blood pressure.⁵⁵ Furthermore, the SGLT2i reduces central sympathetic overactivity, which suppresses the renin-angiotensin system and augments circulating natriuretic peptide levels.⁵⁶ In addition, a “thrifty substrate” hypothesis was proposed by Ferrannini et al⁵⁷ to explain the benefit in heart failure outcomes. A switch in myocardial substrate metabolism away from fat and glucose oxidation and toward an “energy-efficient super fuel like ketone bodies” is associated with increased energy release, increased cardiac efficiency and function, and a reduction in myocardial oxygen consumption.

Table 2
Summary of the results of five completed CVOTs with GLP-1 RA.

Item	ELIXA (<i>n</i> = 6068)	LEADER (<i>n</i> = 9340)	SUSTAIN-6 (<i>n</i> = 3297)	EXSCEL (<i>n</i> = 14,752)	HARMONY (<i>n</i> = 9463)	Meta-analysis (<i>n</i> = 33,457)
Drug	lixisenatide	liraglutide	semaglutide	exenatide ER	albiglutide	lixisenatide, liraglutide, semaglutide, exenatide ER
Patient mean age, years	60.2	64.3	64.6	62.0	64.1	NR
HbA1c, %	7.7	8.7	8.7	8.0	8.7	NR
DM duration, years	9.3	12.8	13.9	12.0	14.1	NR
Patients with established CVD, %	100 ^a	81.3	83.0	73.1	100	NR
Follow-up duration, years	2.1	3.8	2.1	3.2	1.6	NR
Primary outcome ^b	Significant for non-inferiority but not for superiority	13% ↓	26% ↓	Significant for non-inferiority but not for superiority	22% ↓	10% ↓
Death from all cause	NS	15% ↓	NS	NS	NS	12% ↓
Death from CV cause	NS	22% ↓	NS	NS	NS	13% ↓
MI	NS	NS	26% ↓	NS	25% ↓	NS
Stroke	NS	NS	39% ↓	NS	NS	NS
Hospitalization for heart failure	NS	NS	NS	NS	NS	NS
Renal outcome	A modest favorable effect in albuminuria at 108 weeks observed	22% reduction in nephropathy	36% reduction in nephropathy	Not specified	No change in rate of renal impairment	Not specified
Serious side effects	NS	Injection site reaction; acute gall stone disease	Diabetic retinopathy	NS	Injection site reaction	NS (for severe hypoglycemia, pancreatitis, pancreatic cancer)

CVOT: cardiovascular outcome trial; GLP-1 RA: glucagon-like peptide-1 receptor agonist; ER: extended release; NR: not reported; HbA1c: hemoglobin A1c; DM: diabetes mellitus; CVD: cardiovascular disease; CV: cardiovascular; NS: not significant; MI: myocardial infarction; ↓: reduction.

^a All patients enrolled with a MI or been hospitalized for unstable angina within the previous 180 days.

^b Primary end point: a composite of the first occurrence of any 3-point major adverse CV event except ELIXA (plus hospitalization for unstable angina).

As for GLP-1 RA, the observed benefits are perhaps related to the modified progression of atherosclerotic vascular disease.^{45,58,59} Many studies have shown a direct relation between insulin resistance and atherosclerosis⁶⁰ and insulin resistance being an important risk factor for CVD.^{61,62} Improvements in insulin resistance and postprandial hyperlipidemia were considered to be possible factors. Its anti-inflammatory effects either directly from GLP-1 RA or indirectly from other confounded parallel decreases in weight loss, glucose and free fatty acids could be contributing factors as well. A direct effect on ischemic myocardium was also demonstrated in multiple clinical studies^{63–65} and genome-association study.⁶⁶

Translating CVOT results into clinical practice

It is very exciting to see that two glucose lowering drugs, SGLT2i and GLP-1 RA, are able to significantly reduce MACE in patients with T2DM, as demonstrated in CVOTs. Although these CVOTs provide the highest level of evidence, it is worth noting that the selected patients in this type of study limit the generalizability of these studies. These studies generally enroll patients with more advanced atherosclerotic CV risk or established CVD to accrue sufficient events in a timely manner as an efficient study design. However, the studied population is not representative of patients in real-world ambulatory diabetes care. Comparing data from the National Health and Nutrition Examination Survey (NHANES) and published patient eligibility criteria for the four SGLT2i CVOTs listed in this article, only 40.8% would have met the eligibility criteria for at least one of the CVOT trials, and just 1% would have met the criteria for all the four trials.⁶⁷ The DECLARE-TIMI 58 trial²⁶ was by far the most generalizable, but even this trial would only have included more than 10% of the population. Similarly, it was estimated that less than 23% of patients from NHANES would be eligible for each of the above CVOTs for GLP-1 RA except EXSCEL as EXSCEL had the most inclusive eligibility criteria and 47.2% of the US T2DM population would have been qualified.⁶⁸ Thus, it is important to recognize the differences in eligibility criteria when considering the applicability of these results to real-world patient care.

Considering the different mechanisms of the two drugs, it is theoretically possible that combination of SGLT2i and GLP-1 RA could be more potent in reducing CV risks. Early data indicate that these types of agents can be used together safely for the

management of diabetes.⁶⁹ However, data supporting combination therapy with the aim of further reducing CV events are lacking.

Conclusion

Data from CVOTs with both SGLT2i and GLP-1 RA have demonstrated their CV safety and significant CV benefits in patients with T2DM who are with established CVD or at high risk of CV disease. As recommended by American Diabetes Association,⁷⁰ the glucose lowering drugs with proven CV benefits should be firstly considered in patients with T2DM and established CVD after lifestyle management and metformin.

SGLT2i has shown mild but significant risk reduction in MACE, which has been mainly restricted to patient population with established CVD, not to those with only multiple risk factors. Furthermore, SGLT2i has shown a moderate benefit in reducing hospitalization for heart failure, and a robust benefit in reducing renal complications in all patients with T2DM, regardless of their CVD status. On the other hand, GLP-1 RA also has shown mild to moderate risk reduction in MACE in all patients with T2DM but only has neutral effects on hospitalization for heart failure. Its renal protection was mild and not as robust as SGLT2i. Therefore, both SGLT2i and GLP-1 RA should be highly considered in patients with T2DM for MACE risk reduction, though SGLT2i should be restricted in patents with established CVD only. However, for patients with high risk for heart failure and renal complications, SGLT2i should be favored over other glucose lowering medications.

Conflicts of interest

None.

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