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Review

Glucagon-Like Peptide-1 Receptor Agonists in Adult Patients With Type 2 Diabetes: Review of Cardiovascular Outcome Trials

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Key Messages

- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are drugs used to treat type 2 diabetes (T2D) that also reduce body weight and blood pressure.
- Cardiovascular (CV) outcome trials with GLP-1RAs have all demonstrated CV safety; some also significantly reduce the risk for CV events.
- GLP-1RAs with CV benefits should be prioritized in adults with T2D at high CV risk to reduce CV events and lower blood glucose.

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ABSTRACT

People with type 2 diabetes are at heightened risk for developing cardiovascular (CV) events. CV disease is the leading cause of premature death among adults with type 2 diabetes. Unfortunately, historically, some antidiabetes agents were implicated in worsening CV function, despite improving glycemic and metabolic control. Accordingly, over a decade ago, health regulatory bodies modified approval requirements for novel antidiabetes pharmacotherapies, requiring prospective evaluation of CV safety through cardiovascular outcome trials (CVOTs). To meet regulatory requirements, CVOTs were primarily designed around establishing CV safety by demonstrating noninferiority to placebo in addition to standard of care, without significant differences in blood glucose. If appropriately designed and powered, however, these CVOTs could also determine superiority, and hence CV protection. Although many of these CVOTs were initiated several years ago, the recent reporting of the results for these CVOTs has been pivotal and practice-changing. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are one such class of antidiabetes therapies, wherein multiple GLP-1RA CVOTs, but interestingly, not all, have demonstrated CV benefits. In this review, we provide a comprehensive summary of all the reported CVOTs completed with GLP-1RAs to date. Although it remains unclear why some GLP-1RAs are associated with reducing CV events, whereas others have been consistent with CV safety alone, we highlight and provide an overview of some key differences between the various GLP-1RAs and their respective CVOTs and possible implications of study design differences. We also speculate on potential mechanisms of action for glucagon-like peptide-1 receptor signalling in the CV system.

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RÉSUMÉ

Les personnes atteintes de diabète de type 2 courent un risque accru de développer des événements cardiovasculaires (CV). Les maladies CV sont la principale cause de décès prématuré chez les adultes atteints de diabète de type 2. Malheureusement, dans le passé, certaines molécules antidiabétiques ont été impliquées dans la détérioration de la fonction CV, malgré l'amélioration du contrôle glycémique et métabolique. En conséquence, il y a plus d'une décennie, les organismes de réglementation de la santé ont modifié les exigences d'approbation des nouvelles pharmacothérapies antidiabétiques, exigeant une évaluation

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prospective de l'innocuité CV au moyen d'essais sur les conséquences cardiovasculaires (ECCV). Pour répondre aux exigences réglementaires, les ECCV ont été principalement conçus pour établir l'innocuité CV en démontrant la non-infériorité par rapport au placebo sans différences significatives de la glycémie, chez des patients recevant les normes standard de soins. Cependant, s'ils sont conçus et conduits de façon appropriée, ces ECCV pourraient également démontrer leur supériorité, en favorisant une protection CV. Bien que de nombreux ECCV aient été lancés il y a plusieurs années, le récent rapport sur les conclusions de ces ECCV a été déterminant et a participé aux changements dans la pratique clinique. Les agonistes du récepteur au glucagon-like peptide 1 (GLP-1RA) constituent l'une de ces classes de thérapies antidiabétiques pour lesquels plusieurs ECCV, mais pas toutes, ont démontré des avantages CV. Dans cette revue de littérature, nous présentons un résumé exhaustif de tous les ECCV qui ont été complétés sur les GLP-1RA à ce jour. Bien qu'on ne sache pas encore très bien pourquoi certains GLP-1RA sont associés à une réduction des événements CV, alors que d'autres ont seulement montré une innocuité CV, nous clarifions et donnons un aperçu de certaines différences clés entre les divers GLP-1RA et leurs ECCV respectifs, et de possibles implications de ces différences dans la conception des études. Nous spéculons également sur les mécanismes d'action potentiels de la signalisation du récepteur au glucagon-like peptide 1 dans le système CV.

Introduction

Cardiovascular disease (CVD) is the leading cause of premature death in adults with type 2 diabetes (T2D) (1). Given the recognized importance for any increased risk that could contribute to cardiovascular (CV) dysfunction in T2D, regulatory bodies have been prudent in providing enhanced guidance around approval for new pharmacotherapies for T2D. They specify that novel antidiabetes pharmacotherapies seeking regulatory approval should demonstrate no excess risk compared with placebo for CV events, including CV mortality, stroke and myocardial infraction (MI) (2,3), at pre- or postmarketing regulatory stages. The introduction of these regulatory approval changes in 2008 expanded the scope and cost of research necessary for drug approval, notably via the initiation of several long-term cardiovascular outcome trials (CVOTs), primarily involving 3 novel antihyperglycemic drug classes, including dipeptidyl peptidase-4 (DPP4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs). Some of these CVOTs were designed and planned nearly a decade ago, and several have recently been completed and reported, whereas others still remain ongoing. This review will focus primarily on the results of the currently completed and reported CVOTs for GLP-1RAs.

GLP-1 is an incretin hormone mainly synthesized and secreted by specialized enteroendocrine L cells in the gastrointestinal tract in response to nutrient intake. GLP-1 signals through the cognate GLP-1 receptor (GLP-1R), stimulating insulin secretion by pancreatic beta cells in a glucose-dependent manner, whereas GLP-1 inhibits glucagon secretion by the alpha cells. This coordinated action allows for the potent reduction of blood glucose, predominately in the postprandial state (4,5). Acute peripheral and central GLP-1 administration is also associated with inhibition of food intake, which translates into body weight loss after chronic administration. Although the mechanisms for GLP-1-associated weight loss are incompletely understood, the GLP-1R is located in key locations of the brain that control food intake and reward (5). GLP-$1^{7-36amide}$ is rapidly cleaved and inactivated by the ubiquitous enzyme DPP4. Hence, the development of GLP-1RAs for the treatment of T2D is centred around using recombinant human GLP-1 (or a nonmamalian GLP-1 known as Exendin-4) modified to prevent proteolysis by DPP4, and/or enhance binding to plasma proteins to increase plasma half-life (5–7). Presently, GLP-1RAs are approved around the world, including in Canada, for treating T2D because GLP-1RAs exert robust glycemic control in T2D, reducing glycated hemoglobin (A1C) (approximately 1% to 1.5%) without a significant risk of hypoglycemia. Importantly, GLP-1RAs also modestly reduce blood pressure (approximately −2 to −6 mmHg) in subjects with hypertension (5) and lower body weight in those with obesity, with and without T2D. The GLP-1RA, liraglutide at doses of 3 mg (Saxenda), is also approved for treating obesity in patients without T2D. Generally, GLP-1RAs are well tolerated, with the main side effects being transient nausea, vomiting and diarrhea (5), occurring within 10% to 20% of people, effects which usually subside within 1 to 2 months. Administration of GLP-1RAs is also commonly associated with an increase in heart rate of 2 to 4 beats/min (8–11). In this review, we summarize the main CV outcomes from the CVOTs completed to date with GLP-1RAs. We discuss the differences between the various CVOT study designs and speculate on potential mechanisms of action in the CV system for GLP-1R signalling.

GLP-1RAs

Since the first Food and Drug Administration (FDA) approval of a GLP-1RA (exenatide [Byetta]) in 2005, numerous other GLP-1RAs have been developed, approved and/or are under development for the treatment of T2D (Table 1). These pharmacotherapies have been designed through modification of either native human GLP-1 (liraglutide, semaglutide, dulaglutide and albiglutide) or nonmammalian GLP-1 peptides, known as exendin-4 (exenatide and lixisenatide) (12). Based on their peptide structures and susceptibility to enzymatic digestion in the gastrointestinal tract, the majority of approved GLP-1RAs require subcutaneous administration, either daily (lixisenatide and liraglutide) or once weekly (semaglutide, Exenatide IN DUROS, dulaglutide and albiglutide) (Table 1). To overcome the limited permeability of the gastrointestinal tract, low gastric pH and proteolysis, and to obviate the need for subcutaneous injections, an oral formulation of semaglutide was developed and received FDA approval in September 2019. Oral semaglutide is coformulated with an absorption enhancer known as N-(8-[2-hydroxybenzoyl]amino) caprylic acid (SNAC; Eligen Technology, Emisphere Technologies), which increases the local pH at the site of absorption, thereby preventing the proteolysis of semaglutide (13). Several pharmacokinetic studies with oral semaglutide in healthy subjects and those with T2D have demonstrated that it is principally absorbed in the stomach, stimulates insulin secretion, is safe and well tolerated and does not significantly interact with the absorption of other oral medications (14).

In addition to oral semaglutide, several alternative administration options for GLP-1RAs are in various stages of research and clinical development. An initial press release from Intarcia Therapeutics, Inc in May 2016 announced that continuously delivered exenatide by a subcutaneous implanted mini-osmotic pump demonstrated CV safety in the FREEDOM CVO trial (NCT01455896) (https://www.intarcia.com/media/press-releases/2016-may-6-cardiovascular-safety.html); however, formal reporting of this trial has yet to be completed. Several preclinical and clinical studies have

suggested that unimolecular peptides that are able to target multiple gastrointestinal hormone receptors, such as glucagon, glucose-dependent insulinotropic peptide (GIP) and GLP-1 receptors simultaneously, may enhance glycemic and metabolic effect(s) compared with selective GLP-1RAs alone (15). Notably, tirzepatide (Eli Lilly & Co), a once-weekly GLP-1/GIP dual-agonist, is entering the phase 3 clinical trial stage, with the clinical development program known as SURPASS trials (15).

CVOTs With GLP-1RAs

Herein, we summarize the characteristics and primary CV endpoints of 7 randomized, double-blinded, placebo-controlled trials evaluating the CV safety of GLP-1RAs, in addition to standard of care (Tables 2 and 3, and Figure 1).

CVOTs with exendin-4-based GLP-1RAs

The *Evaluation of LIXisenatide in Acute coronary syndrome* (ELIXA) trial, with administration of once daily lixisenatide (20 μg), exclusively enrolled patients with T2D with established coronary artery disease. Entry criteria for the ELIXA trial specified that all patients had to have experienced an acute coronary syndrome (ACS) event within the previous 180 days (10) prior to enrolment. In the ELIXA trial, the baseline characteristics included an average A1C of approximately 7.7%, an average age of approximately 60 years and an average duration of T2D of approximately 9.3 years. The follow-up period in the ELIXA trial was relatively short (2.1 years) (Table 2) (10). In the ELIXA trial, lixisenatide administration was demonstrated to have CV safety compared with placebo in this high-risk T2D population, with a hazard ratio (HR) of 1.02 (95% confidence interval [CI], 0.89 to 1.17) for the primary outcome of expanded 4-point major adverse cardiovascular events (MACE) (CV death, MI, stroke and hospitalization for unstable angina), an HR of 0.96 (95% CI, 0.75 to 1.23) for the risk of hospitalization for heart failure and an HR of 0.94 (95% CI, 0.78 to 1.13) for the rate of all-cause mortality (Table 2 and Figure 1) (10). With respect to microvascular endpoints, no statistically significant differences in the risk for retinopathy were observed (10).

The *EXenatide Study of Cardiovascular Event Lowering* (EXSCEL) trial enrolled the largest number of adult patients with T2D (N=14,752) among the GLP-1RA CVOTs completed to date. The entry criteria for EXSCEL included an A1C between 6.5% and 10%, in addition to a wide range of CV risks and history of CVD (73.1% of the population had prior CVD) (16). At the time of randomization, EXSCEL participants were on average 62 years of age, had T2D for approximately 12.0 years and had an A1C of approximately 8.0%. In EXSCEL, administration of once-weekly exenatide (2 mg) in addition to usual care was noninferior to placebo for the primary composite of MACE (HR, 0.91; 95% CI, 0.68 to 1.00) over a median follow-up period of 3.2 years (16). Although exenatide once weekly did not significantly reduce the risk for MACE, a significant reduction in all-cause mortality was observed with exenatide compared with placebo (HR, 0.86; 95% CI, 0.77 to 0.97; p=0.016). There were no significant differences between the exenatide and placebo-treated groups for the risk of nonfatal MI or stroke, CV death and hospitalization for heart failure or ACS, and effects on MACE were similar between all the prespecified study groups (16). The rate of new-onset macroalbuminuria was lower with exenatide than with placebo (2.2% vs 2.8%, respectively), and no differences in the risk for retinopathy were observed (16). This study had a high rate of discontinuation, with the average treatment duration being only 75% to 76% of the prespecified duration. This was similar between treatment and placebo groups and was attributed to patients objecting to the injections, the pragmatic nature of the study design, visits ocurring every 6 months and limited study reports (16). As a result, the total treatment time, and hence event numbers and statistical power, were reduced for this study.

CVOTs with human-GLP-1-based GLP-1RAs

The *Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome* (LEADER) trial and the *Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes* (SUSTAIN-6) (and the ELIXA trial, previously described) have been extensively reviewed elsewhere (17,18); as such, the characteristics and major findings of these trials are only briefly summarized.

In the LEADER trial with once daily liraglutide (1.8 mg), the average age of the study population was 64 years. Patients had an A1C of 8.7% (Table 2), an average duration of T2D of 12.8 years and most (81%) had established CVD (Tables 2 and 3) at enrolment (9). The follow-up period in the LEADER trial was longer compared to the ELIXA and EXSCEL trials, with an average follow-up period of 3.8 years (9). In the LEADER trial, the relative risk for the primary outcome of first occurrence to 3-point MACE was significantly lower for liraglutide compared with placebo (HR, 0.87; 95% CI, 0.78 to 0.97; p<0.001 for noninferiority; p=0.01 for superiority) (9). Analysis of the individual components of MACE revealed that reduction in the risk for MACE was driven primarily by a significant reduction in CV death (HR, 0.78; 95% CI, 0.66 to 0.93; p=0.007), whereas vascular events, such as nonfatal MI (HR, 0.88; p=0.11) and stroke (HR, 0.89; p=0.3) were not significant. Of note, there were no significant differences in the rate of hospitalization for heart failure (HR, 0.87; 95% CI, 0.73 to 1.05; p=0.14) between the 2 treatment groups (Figure 1), and the risk for MACE did not differ by heart failure status at baseline in post hoc analysis (19,20). The risk of diabetic retinopathy (DR) was not significantly higher in the liraglutide-treated group (Figure 1) (9).

In SUSTAIN-6, a CVOT evaluating once weekly semaglutide administration (0.5 mg or 1.0 mg) during premarketing regulatory stages, the baseline characteristics of the study population were similar to that of the LEADER trial, given similar inclusion and exclusion criteria (approximately 83% had established CVD, the average age of the patients was approximately 65 years and the average A1C was approximately 8.7%) (Tables 2 and 3). Compared with placebo, once-weekly semaglutide significantly reduced the risk for the primary outcome of 3-point MACE by 26% (HR, 0.74; 95% CI, 0.58 to 0.95; p<0.001 for noninferiority; p=0.02 for superiority), effects which were notably driven by a significant reduction in the risk for stroke (HR, 0.61; 95% CI, 0.38 to 0.99; p=0.04). SUSTAIN-6 was a smaller trial (compared with LEADER, ELIXA and EXSCEL trials) because it was a premarketing trial, enrolling 3,297 participants, and had a relatively short follow-up period, approximately 2.1 years (11). Notably, effects on body weight loss were robust with semaglutide in SUSTAIN-6 (approximately 6% to 14% body weight loss) (Table 2) (11). With respect to microvascular outcomes, semaglutide significantly increased rates of DR (Figure 1) (11), but decreased rates of new or persistent nephropathy (21). A long-term dedicated retinopathy trial known as FOCUS (NCT03811561) is investigating the effects of semaglutide on DR prospectively.

For the HARMONY-Outcomes trial, a CVOT evaluating the once-weekly GLP-1RA albiglutide (a GLP-1RA that is not presently marketed) the entry criteria for the 9,463 trial participants with T2D included having established atherosclerotic CVD and age >40 years with an A1C >7.0% (22). The HARMONY-Outcomes trial was an event-driven CVOT designed to adjudicate a minimum of 611 MACE (22). In terms of characteristics at trial enrolment, the average age of the trial participants was approximately 64.1 years, with an average diabetes duration of approximately 14.1 years and

Table 1
Characteristics and pharmacology of glucagon-like peptide-1 receptor agonists

GLP-1RA characteristics	ELIXA	EXSCEL	LEADER	SUSTAIN-6	HARMONY-Outcomes	REWIND	PIONEER 6
Drug	lixisenatide	exenatide	liraglutide	subcutaneous semaglutide	albiglutide	dulaglutide	oral semaglutide
Brand name	Adlyxine	Bydureon	Victoza	Ozempic	Tanzeum	Trulicity	Rybelsus
Company	Sanofi	AstraZeneca	Novo Nordisk	Novo Nordisk	GlaxoSmithKline	Eli Lilly	Novo Nordisk
Year of HC approval	2017	2016	2010	2018	2016 (not marketed)	2015	Seeking approval
Structure based (% hGLP-1 sequence homology)	Exendin-4 (50)	Exendin-4 (53)	hGLP-1 (97)	hGLP-1 (94)	hGLP-1 (97)	hGLP-1 (97)	hGLP-1 (94)
Half-life	2.7–4.3 h	6–7 days	11–15 h	7 days	5 days	5 days	7 days
Administration	Daily s.c.	Weekly s.c.	Daily s.c.	Weekly s.c.	Weekly s.c.	Weekly s.c.	Daily Oral
Dose	<20 μg	<2 mg	1.2–1.8 mg	0.5 or 1 mg	30 or 50 mg	1.5 mg	3, 7 or 14 mg

ELIXA, Evaluation of LIXisenatide in Acute coronary syndrome; *EXSCEL*, EXenatide Study of Cardiovascular Event Lowering; *hGLP-1*, human glucagon-like peptide-1; *HC*, Health Canada; *LEADER*, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome; *N/A*, not applicable; *PIONEER 6*, Peptide Innovation for Early Diabetes Treatment; *REWIND*, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; *s.c.*, subcutaneous; *SUSTAIN-6*, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

an A1C of approximately 8.7% (Table 2) (22). Compared with placebo, albiglutide (30 to 50 mg once weekly) was associated with a small reduction in A1C; however, notably, unlike the other CVOTs, in the HARMONY-Outcomes trial there were no statistically significant differences in body weight or systolic blood pressure between the 2 treatment arms (Table 2) (22). In patients with T2D with established CVD followed for >1.6 years, once-weekly albiglutide significantly reduced the relative risk for the primary outcome MACE by 22% (HR, 0.78; 95% CI, 0.68 to 0.90; p<0.001 for noninferiority; p=0.0006 for superiority) (22). This reduction in CV events with albiglutide was primarily driven by a 25% reduction in nonfatal MI (HR, 0.75; p=0.003). The risk for stroke (HR, 0.86; p=0.3) and CV death (HR, 0.93; p=0.58) were not significantly different between the placebo- or the albiglutide-treated groups. The composite of CV death and hospitalization for heart failure (HR, 0.85; 95% CI, 0.70 to 1.04) and the risk of renal impairment

Table 2
Baseline characteristics and major results of GLP-1RA cardiovascular outcome trials

Trial parameter	ELIXA	EXSCEL	LEADER	SUSTAIN-6	HARMONY-Outcomes	REWIND	PIONEER-6
Drug	lixisenatide	exenatide	liraglutide	subcutaneous semaglutide	albiglutide	dulaglutide	oral semaglutide
Registry	NCT1147250	NCT01144338	NCT01179048	NCT01720446	NCT02465515	NCT01394952	NCT02692716
n	6,068	14,752*	9,340	3,297	9,463	9,901	3,176†
Median F/U, years	2.1	3.2	3.8	2.1	1.6	5.4*	1.3†
Prior CVD, %	100*	73	81	83	100*	31.4†	84.7
Prior MI, %	NR	NR	30.7	32.5	47.0*	16.2†	36.0
History of HF, %	22.5	16.2	17.8	23.6*	20.3	8.6†	12.2
Mean age, years	59.3†	61	64.3	64.6	64.1	66.2	66*
BMI, kg/m^2	30.1†	32.7	32.5	32.8*	32.3	32.3	32.3
Women, %	30.7	38.0	35.7	39.3	30.6†	46.3*	31.6
DM duration, years	9.2†	13.1	12.8	13.9	14.2	10.5	14.9*
Baseline A1C, %	7.7	8.1	8.7	8.7	8.8*	7.3†	8.2
Baseline eGFR, %	76	76	75	75	79*	77	74†
eGFR <60, %	22	21.3†	24	28.5*	23.5	22.2	26.9
Medication excluded	GLP-1RA, DPP4i	GLP-1RA >3 OAD	GLP-1RA, DPP4i, pramlintide	GLP-1RA, DPP4i, pramlintide	GLP-1RA	GLP-1RA, DPP4i, >2 OAD	GLP-1RA, DPP4i
Insulin use, %	39	46	45	58	59	24†	61*
SGLT-2i use, %	N/A†	1.0†	N/A†	<1.0†	7.0	6.3	9.6*
Annual placebo MACE‡ rates, %	6.3*	3.7	3.7	4.4	5.9	2.7†	3.7
Primary MACE‡ event observed	805	1,744*	1,302	254	766	1,257	137†
Difference in A1C vs placebo, %	0.3†	0.5	0.4	1.0 for 1 mg*	1.0*	0.6	0.7
Mean reduction in body weight vs placebo, kg	0.7	1.3	2.3	4.3 for 1 mg*	0.0†	1.5	3.4
Mean reduction in systolic blood pressure vs placebo, mmHg	0.8	1.6	1.2	2.6 for 1 mg	0.0†	1.7	3.0*
Noninferiority for MACE‡?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Superiority for MACE‡?	No	No	Yes (13%)	Not prespecified (26%)	Yes (22%)	Yes (12%)	Not prespecified (21%)
CV death reduced?	No	No	Yes	No	No	No	No†
All-cause mortality reduced?	No	Yes	Yes	No	No	No	No†

A1C, glycated hemoglobin; *BMI*, body mass index; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DM*, diabetes mellitus; *DPP4i*, dipeptidyl-peptidase-4 inhibitor; *eGFR*, estimated glomerular filtration rate; *ELIXA*, Evaluation of LIXisenatide in Acute coronary syndrome; *EXSCEL*, EXenatide Study of Cardiovascular Event Lowering; *F/U*, follow-up; *GLP-1RA*, glucagon-like peptide-1 receptor agonist; *HF*, heart failure; *LEADER*, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome; *MACE*, major adverse cardiovascular event; *MI*, myocardial infarction; *N/A*, not applicable; *NR*, not reported; *OAD*, oral antidiabetic drugs; *PIONEER 6*, Peptide Innovation for Early Diabetes Treatment; *REWIND*, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; *SGLT-2i*, sodium-glucose cotransporter-2 inhibitor; *SUSTAIN-6*, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

* Highest value.
† Lowest value.
‡ Four-point MACE for the ELIXA trial and 3-point MACE for the EXSCEL, LEADER, SUSTAIN-6, HARMONY-Outcomes, REWIND and PIONEER 6 trials.

Table 3
Definition of established cardiovascular disease in the glucagon-like peptide-1 receptor agonist cardiovascular outcome trials

Parameter	EXSCEL	LEADER	SUSTAIN-6	HARMONY-Outcomes	REWIND	PIONEER 6
Prior MI or CVA	✓	✓	✓	✓	✓	✓
Prior TIA	X	✓	✓	X	X	✓
Revascularization (coronary, carotid or peripheral)	✓	✓	✓	✓	✓	✓
Hospitalization for unstable angina	X	✓	✓	X	✓	✓
Ischemia (by stress test or imaging)	X	✓	✓	X	✓ (imaging only)	✓
50% stenosis(coronary, carotid, or peripheral)	✓	✓	✓	✓	X	✓
CHF (NYHA class II or III)	X	✓	✓	X	X	✓
Moderate CKD (eGFR <60 mL/min/1.73 m^2)	X 21.3% with CKD	✓ 8.9% with CKD stage >3	✓ 10.7% with CKD stage >3	X 23.5% with CKD	X 22.2% with CKD	✓ 26.9% with CKD

✓, parameter included in the definition of established cardiovascular disease in the trial; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *CVA,* cerebrovascular accident; *eGFR,* estimated glomerular filtration rate; *ELIXA,* Evaluation of LIXisenatide in Acute coronary syndrome; *EXSCEL,* EXenatide Study of Cardiovascular Event Lowering; *LEADER,* Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome; *MI,* myocardial infarction; *NYHA,* New York Heart Association; *PIONEER 6,* Peptide Innovation for Early Diabetes Treatment; *REWIND,* Researching Cardiovascular Events With a Weekly Incretin in Diabetes; *SUSTAIN-6,* Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; *TIA,* transient ischemic attack; *X,* parameter not included in the definition of established cardiovascular disease in the trial.

(HR, 0.87; 95% CI, 0.75 to 1.02) were not significantly different between the treatment groups (22). Of note, albiglutide received regulatory approval in Canada; however, it was not fully marketed, and has been removed from the market by GlaxoSmithKline in Europe, the United States and Canada.

The *Researching Cardiovascular Events With a Weekly Incretin in Diabetes* (REWIND) trial evaluated the CV safety of once-weekly administration of dulaglutide (1.5 mg) compared with placebo (23). Of the 9,901 REWIND trial participants, the trial entry criteria stipulated that all participants had to be ≥50 years of age with T2D and an A1C <9.5%. Significantly different from the other GLP-1RA CVOTs, in the REWIND trial, only 31% of trial participants had established CVD at randomization (Table 2) (23). History of CVD was defined as history of MI, ischemic stroke, unstable angina with electrocardiogram changes, myocardial ischemia on imaging or stress test or revascularization (Table 3) (23). At baseline, the mean diabetes duration of the trial participants was approximately 10 years, and the mean A1C was approximately 7.3%, which is noticeably lower than the other GLP-1RA CVOTs completed to date. The median follow-up period for the REWIND trial was 5.4 years, the longest to date (23). Overall, the REWIND trial participant population was the most representative of the typical middle-aged patient with T2D seen in general community practice (Tables 2 and 3) (24).

Compared with placebo, once-weekly dulaglutide administration was associated with a significantly lower risk for the primary outcome MACE by 22% compared with placebo (HR, 0.88; 95% CI, 0.79 to 0.99; p=0.026) (25). Among the secondary CV outcomes, only the risk for nonfatal stroke was significantly reduced (HR, 0.76; 95% CI, 0.61 to 0.95), whereas nonfatal MI, hospitalization for unstable angina, heart failure, CV death and all-cause mortality did not reach statistical significance (25). Importantly, exploratory sensitivity analysis indicated that the primary MACE results were similar between most of the prespecified subgroups, including men vs women, A1C, diabetes duration, body mass index and, importantly, history vs no history of CVD (25). Of note, the risk for retinopathy was not significantly increased in the dulaglutide-treated group compared with placebo (HR, 1.24; 95% CI, 0.92 to 1.68) (Table 2 and Figure 1) (24).

The *Peptide Innovation for Early Diabetes Treatment 6* (PIONEER 6) trial evaluated the CV safety of once-daily oral semaglutide (3, 7, 14 mg) in 3,183 individuals with T2D at high risk for CV events (26). In the PIONEER 6 trial, at baseline, approximately 85% of trial participants had established CVD or moderate chronic kidney disease (CKD) (26), the average age was 66 years, A1C was approximately 8.2% and the duration of diabetes was approximately 14.8 years (27). By entry criteria definition, the study population in the PIONEER 6 trial was similar to the LEADER and SUSTAIN-6 trials (Tables 2 and 3).

The PIONEER 6 trial was planned and completed during premarketing regulatory stages for oral semaglutide, it was designed as a noninferiority trial to determine CV safety, not superiority. Hence it is important to point out that the PIONEER 6 trial adjudicated fewer MACE events (137 events) and had a shorter duration (15.9 months) than other GLP-1RA CVOTs (26). In the PIONEER 6 trial, once daily oral semaglutide was noninferior to placebo for the risk of the primary outcome, 3-point MACE (HR, 0.79; 95% CI, 0.57 to 1.11; p<0.001 for noninferiority; p=0.17 for superiority) (27). In key secondary CV endpoints, oral semaglutide administration was associated with a 51% reduction in the relative risk for CV death (HR, 0.49; 95% CI, 0.27 to 0.92), a 49% reduction in the risk of all-cause mortality (HR, 0.51; 95% CI, 0.31 to 0.84) and a 26% reduction in the risk for nonfatal stroke (HR, 0.74; 95% CI, 0.35 to 1.57) (27). The risk for the expanded MACE composite (MACE + hospitalization for unstable angina or heart failure) was not statistically significant between the oral semaglutide group compared with the placebo group (HR, 0.82; 95% CI, 0.61 to 1.10). There were no imbalances reported between the treatment groups for the risk of DR (Table 2 and Figure 1) (27).

Post hoc and meta-analysis

Two recent meta-analyses, which combined and analyzed the results of 4 or 5 GLP-1RA CVOTs (ELIXA, SUSTAIN-6, EXSCEL, LEADER trials and/or HARMONY-Outcomes trial), comprising data from 42,920 participants, reported that GLP-1RAs significantly reduce MACE in T2D by 10% to 12% (28,29). This estimate is similar to the MACE benefit reported for SGLT-2 inhibitors in comparable study populations (28). This estimated effect for GLP-1RAs on MACE was limited to patients with T2D and established atherosclerotic CVD (HR, 0.86; 95% CI, 0.80 to 0.93; p=0.002), whereas as no significant effects were observed in primary prevention participants in these short-term follow-up studies (2 to 4 years). These meta-analyses (28,29) did not include the REWIND trial participants, wherein approximately 70% of the study population did not have established atherosclerotic CVD. With the

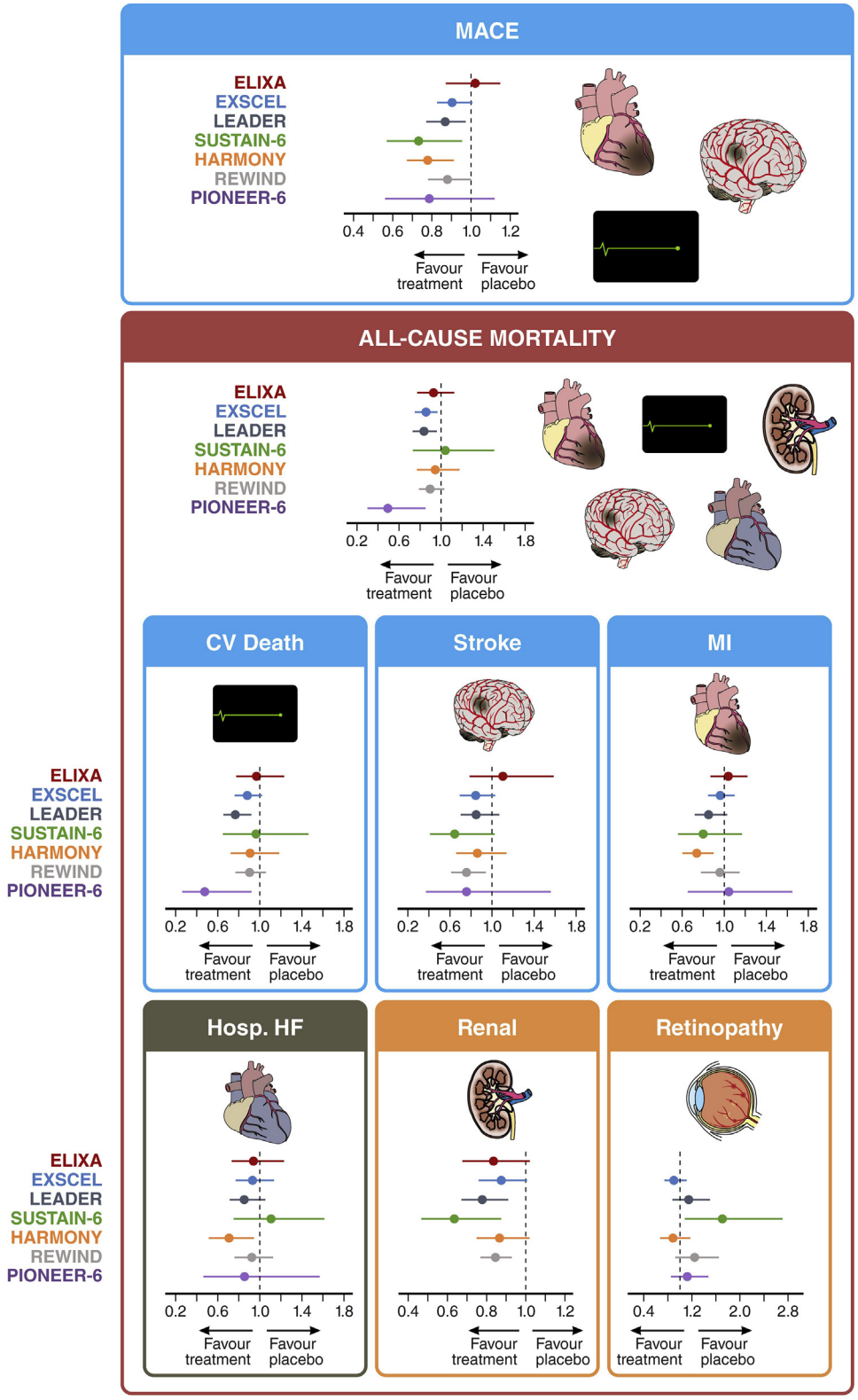

Figure 1. GLP-1RA CVOTs: Summary of endpoints in type 2 diabetes. Summary of the key outcomes from the 7 CVOTs for GLP-1RAs published to date including the ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY-Outcomes, REWIND and PIONEER-6 trials. Forest plots represent the hazard ratios and 95% confidence intervals for each of the following parameters: 1) primary outcome, 3-point MACE, defined as CV death, nonfatal MI and nonfatal stroke (or 4-point MACE which also included hospitalization for unstable angina for the ELIXA trial only); 2) all-cause mortality; 3) CV death; 4) fatal and nonfatal stroke; 5) fatal and nonfatal MI; 6) hospitalization for heart failure and 7) renal impairment predefined renal composite for SUSTAIN-6, LEADER, and REWIND trials, and secondary safety outcomes for the ELIXA, EXSCEL, and HARMONY-Outcomes trials (typically composed of time to new-onset macroalbuminuria, a sustained decline in estimated glomerular filtration rate of ≥30% from baseline, doubling of serum creatinine, end-stage renal disease, chronic renal replacement therapy and/or renal death) and diabetic retinopathy. *CV,* cardiovascular; *CVOT,* cardiovascular outcome trial; *ELIXA,* Evaluation of LIXisenatide in Acute coronary syndrome; *EXSCEL,* EXenatide Study of Cardiovascular Event Lowering; *GLP-1RA,* glucagon-like peptide-1 receptor agonist; *Hosp. HF,* hospitalization for heart failure; *LEADER,* Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome; *MACE,* major adverse cardiovascular event; *MI,* fatal and nonfatal myocardial infarction; *PIONEER 6,* Peptide Innovation for Early Diabetes Treatment; *Renal,* renal impairment; *Retinopathy,* diabetic retinopathy; *REWIND,* Researching Cardiovascular Events With a Weekly Incretin in Diabetes; *Stroke,* fatal and nonfatal stroke; *SUSTAIN-6,* Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; *TIA,* transient ischemic attack.

exclusion of the post-ACS trial ELIXA, there was no significant heterogeneity among the GLP-1RA trials for the effects estimate on MACE (28). Moreover, GLP-1RAs significantly reduced the risk of each individual outcome of MACE: 9% for MI, 14% for stroke and 12% for CV death (28). Effects on MACE were similar between all the subgroup populations and were independent of renal function (9,11,27,30–32).

In addition to reducing primary CV endpoints, secondary microvascular outcomes in CVOTs (9,11,31,32) and post hoc analyses of these trials have demonstrated that liraglutide, lixisenatide, semaglutide and dulaglutide also significantly reduce the risk for nephropathy. Unlike SGLT-2 inhibitors, dedicated renal outcome trials in patients with advanced CKD at high risk for developing end-stage kidney disease or renal death have not yet been completed with GLP-1RAs. Nevertheless, consistency around reducing composite renal endpoints (typically composed of time to new-onset macroalbuminuria, a sustained decline in estimated glomerular filtration rate [eGFR] of $\geq$30% from baseline or chronic renal replacement therapy) has been observed in several GLP-1RA CVOTs. The renal benefits associated with GLP-1RAs are mainly driven by a reduction in macroalbuminuria and urine-albumin ratios, as opposed to a reduction in hard renal endpoints (end-stage kidney disease, doubling of serum creatinine or renal death). However, most patients in the GLP-1RA CVOTs are at low renal risk wherein the rate for the development of end-stage kidney disease in the placebo group is low. The mechanisms for GLP-1RAs in lowering albuminuria are not completely understood, but may be partly related to effects on A1C, blood pressure and body weight loss (28,30,33); it is noteworthy that the GLP-1R was detected in vascular smooth muscle cells in a nonhuman primate kidney (34). In an exploratory sensitivity analysis of renal outcomes in the REWIND trial, administration of dulaglutide was also associated with a preservation in eGFR (31). Long-term use of dulaglutide significantly reduced the incidence of a sustained eGFR decline >40% and >50%, through mechanisms that are not fully understood, but may be partly related to blood pressure lowering based on results in the REWIND trial (31). Importantly, the renal benefits (predominantly driven by a reduction in macroalbuminuria) observed with GLP-1RAs liraglutide, semaglutide and dulaglutide were preserved in people with severe renal impairment (eGFR <30 mL/min/1.73 m^2) (9,11,30).

Limitations and Challenges

Due to innate differences in trial designs, study populations and heterogeneity among the GLP-1RA drug class, we remind and caution the reader that no direct comparisons can be made between the results of GLP-1RA CVOTs discussed. To further emphasize this point, next, we highlight and provide further details for the reader on some of the key differences among the GLP-1RA CVOTs discussed.

GLP-1RA pharmacokinetics

It is important to emphasize that the GLP-1R drug class has considerable heterogeneity compared with other antidiabetes therapies. The main differences in this drug class relate to the peptide backbone primary amino acid sequence of the various GLP-1RAs. Whereas some are based on human GLP-1, others are based on a nonmammalian GLP-1 known as exendin-4 (Table 1). Also, the mass and tertiary structure of the GLP-1RAs differ substantively, with drugs such as dulaglutide and albiglutide having tandem, dual copies of modified human GLP-1 covalently linked to large immunoglobulin and/or albumin moieties respectively. These differences alone significantly impact the effective concentration 50, the half-life, the mode of elimination (and consequently the duration of action and dose required), the degree of immunogenicity, the drug distribution, the penetration into various tissues (such as the brain) and potentially treatment persistence. It is unknown whether these primary amino acid sequence and secondary structural differences among the GLP-1RA are responsible for the heterogeneity on CV endpoints observed with the various GLP-1RAs in the CVOTs discussed.

Entry criteria: Baseline characteristics

When interpreting the results of these CVOTs, it is also important to be mindful that the entry criteria, and hence study populations, of these CVOTs differed. One baseline characteristic we wish to highlight is the differences in A1C. For example, in the LEADER and SUSTAIN-6 trials, the entry criteria specified that trial participants required an A1C >7%, and there was no upper A1C limit. Whereas in the REWIND trial, the A1C at the time of randomization had to be >9%. In contrast, there were no A1C entry criteria specified for the PIONEER 6 trial. Differences in A1C at enrolment are a significant contributor to the heterogeneity of the various CVOT study populations. The CV benefits of GLP-1RAs are widely thought to be through nonglycemic mechanisms; however, these A1C differences reflect significant heterogeneity in the study populations. It is noteworthy that A1C severity has been associated with the severity of coronary artery disease in T2D study populations (35).

Another noteworthy difference was the percentage of male trial participants. In most of the GLP-1RA CVOTs, the study populations were primarily composed of men (on average between 62% and 71%), whereas in the REWIND trial, 46% of participants were female. The effects of GLP-1R signalling are not thought to differ based on sex; however, this possibility cannot be ruled out.

A recent meta-analysis by Boye et al (24), compared the characteristics of the study populations in EXSCEL, LEADER, REWIND and SUSTAIN-6 trials, relative to a representative population of patients living with T2D in the United States. The authors concluded that the REWIND study population was the most generalizable to the United States adult population with T2D compared to any of the other GLP-1RA CVOTs (24). EXSCEL was the most representative in terms of age and renal function, whereas REWIND matched more closely to the general population in terms of A1C, sex and proportion of prior MI (24).

The goal of these CVOTs was to achieve glycemic equipoise between treatment arms. As such, investigators were encouraged to titrate glycemic, as well as lipid and blood pressure targets to current standards of care. Although most studies did not have significant differences in the use of adjunct antihyperglycemic (notably insulin), antihypertensive or lipid-lowering therapies between the treatment arms, there is protocol heterogeneity between the trials in terms of adjunctive use of antidiabetes therapies. For example, the use of DDP4 inhibitors was permitted in the ELIXA, EXSCEL and HARMONY-Outcomes trials only, but was excluded in the LEADER, SUSTAIN-6, REWIND and PIONEER 6 trials. Similarly, the proportion of trial participants prescribed an SGLT-2 inhibitor, a class known to reduce CV events, was relatively high in the PIONEER 6 (9.6%), HARMONY-Outcomes (7%) and REWIND (6.3%) trials, with imbalances in the placebo groups (27), but SGLT-2 inhibitors were not prescribed or were used in only <1% of the population in the ELIXA, LEADER, SUSTAIN-6 and EXSCEL trials (Table 2).

Entry criteria: CVD definition

Another difference between the GLP-1RA CVOTs is the definitions used to determine established CVD at baseline in the

trial participants, as summarized in Table 3. From a broad perspective, in terms of percentage of trial participants with CVD at baseline, EXSCEL, LEADER, SUSTAIN-6 and PIONEER 6 trials exhibited the most similarity, ranging from 73% to 84.6% of the study population having prior CVD and/or CKD at randomization (9,11,16,27). Whereas in the REWIND trial, only 31% of the trial participants enrolled had established CVD (32), as defined by the investigators at randomization. Nevertheless, significant heterogeneity exists among these CVOTs with respect to the definition criteria used to determine presence or absence of CVD. For example, in SUSTAIN-6 (83% with CVD), in LEADER (81% with CVD) and in PIONEER 6 (85% with CVD), patients with vascular (coronary, carotid or perivascular) stenosis >50%, moderate renal impairment or New York Heart Association class II or III congestive heart failure were classified with having prior CVD (Tables 2 and 3). In contrast, the trial participants meeting those criteria were not included in the group of patients categorized as having CVD in the REWIND trial (31% with CVD). Interestingly, the percentage of patients with CVD at baseline would have been lower in SUSTAIN-6, LEADER and PIONEER 6 trials, if the REWIND trial CVD definition criteria were used. In comparison, in the ELIXA trial, all trial participants had to have documented ACS within the previous 180 days of enrolment (10). Accordingly, by study design, the ELIXA study population differs considerably from that of other GLP-1RA CVOTs. In the HARMONY-Outcomes trial, all trial participants had to have established CVD at enrolment. This was defined as either central (coronary or cerebroventricular) or peripheral arterial diseases (36), whereas prior hospitalization for unstable angina, ischemia (by stress test or imaging), New York Heart Association class II or III congestive heart failure and moderate CKD were not part of the criteria used to define history of CVD (Table 3), as was done in other GLP-1RA CVOTs.

Differences in trial design, size and duration

Trial design, duration and size determine the statistical power of a CVOT, primarily based on the accrual of the total number of MACE (37). These key characteristics differed significantly among the GLP-1RA CVOTs completed to date. The average follow-up time for the REWIND trial was longer than all the other GLP-1RA CVOTs (5.4 years), and was prespecified, likely because a significant number of trial participants without CVD were expected to be enrolled in the REWIND trial. In addition, both SUSTAIN-6 (target 122 MACE) and the LEADER trials (target 660 MACE) had a minimum trial duration specified after randomization of the last patient (median, 2.1 and 3.8 years, respectively) (9,11). In contrast, the premarketing PIONEER 6 trial was an event-driven (122 MACE) trial, which did not prespecify a minimal trial duration (26). Accordingly, the shorter duration and event-driven nature of the PIONEER 6 trial limited the number of MACE adjudicated; hence, it was not powered to determine superiority for oral semaglutide compared with placebo. Of note, the HARMONY-Outcomes trial was also an event-driven trial (designed for 611 MACE) and was the shortest GLP-1RA CVOT reported to date (median follow up, 1.6 years). Despite the short duration and follow up period, in the HARMONY-Outcomes trial, albiglutide administration was associated with a significant reduction in the risk for MACE, without significant changes in body weight or blood pressure (36).

Mechanism of Action of GLP-1RA on the CV System

The mechanism(s) of action underlying the cardioprotective and renal benefits for GLP-1RAs observed in the CVOTs are incompletely understood. Insight into potential mechanisms are being addressed through further analyses of CVOTs, in addition to preclinical and clinical studies which have been described in detail elsewhere (5,38). GLP-1RA therapies exert important pharmacodynamic effects on several CV risk factors (body weight, blood pressure and low-density lipoprotein cholesterol/triglycerides). Although some of these effects have been proposed to explain some of the benefits observed in GLP-1RA CVOTs (17), further exploratory subgroup analyses have not found significant associations between any of these variables and the CV benefits of GLP-1RAs (39,40). This was evident in the recent HARMONY-Outcomes trial, wherein albiglutide was associated with a significant reduction in MACE without significant changes in body weight or blood pressure-lowering compared with placebo (22). Moreover, subgroup analysis of the LEADER trial revealed that the effects of liraglutide on MACE was independent of LDL lowering (41). Although small differences in body weight and blood pressure are observed in the GLP-1RA CVOTs compared with placebo, it is widely accepted that the cardioprotective effects of GLP-1RAs occur through nonglycemic mechanisms by activating GLP-1R signalling outside of the pancreas, such as in the brain and peripheral vasculature.

Precise tissue and cellular localization of the GLP-1R may provide a further biological basis and advance our mechanistic understanding of how GLP-1RAs reduce the risk for CV events in patients with T2D. The *GLP1R* messenger RNA transcript is expressed in all 4 chambers of the human heart, but the identity and location of these cell types in the heart is not clear (42). Possible GLP-1R-expressing cells include a specialized subset of cardiomyocytes, such as pacemaker cells (34,43), but this does not account for the detectable levels of the GLP-1R in samples taken from across the human heart (42). There is also a possibility that GLP-1R-expressing cells outside of the heart coordinate the cardioprotective effects of GLP-1RAs. Indeed, the GLP-1R is expressed in neurons in the gut and brain, which may beneficially modulate the neuronal regulation of the heart (5). Notably, administration of GLP-1RAs is associated with a small yet consistent effect on increasing heart rate, possibly through GLP-1R signalling in the sinoatrial node (34,43). These chronotropic effects associated with GLP-1RA administration are not thought to be cardioprotective; however, at the same time, a significant increase in arrhythmia-related adverse events has not been reported in GLP-1RA CVOTs.

There is increasing interest in the potential role(s) for GLP-1R signalling in the regulation of immune cell populations and inflammation. Presently, the only immune cell population that has been shown to robustly express the GLP-1R is intraepithelial lymphocytes in the intestine (44). In humans, chronic treatment with exenatide for 12 weeks was associated with a reduction in inflammatory markers, including circulating cytokines (45). It is not clear if GLP-1RAs directly signal to GLP-1R-expressing leukocytes that are involved in CV pathophysiology or have effects on immune cell populations and inflammation indirectly. Modulation of inflammatory processes, such as atherosclerotic plaque formation and stability, is a potential candidate mechanism underlying the cardioprotective effects of GLP-1RAs, which warrants further investigations (46).

GLP-1RAs are commonly associated with a modest reduction in systolic blood pressure (Table 2), effects which are present even when GLP-1RAs are coadministered with other antihypertensive therapies (diuretics, angiotensin-converting enzyme inhibitors, etc.). The magnitude of the blood pressure-lowering effect varies between −2 and −6 mmHg, and occurs within 3 weeks of administration in adults with hypertension and T2D. Although the blood pressure-lowering effects of GLP-1RAs are also poorly understood, they may be related to acute effects on natriuresis and/or the renin-angiotensin system (47–49). Effects on endothelial cells and/or vascular smooth muscle cells in blood vessels,

either peripherally or in the coronary vasculature, is another potential target mechanism for GLP-1RA CV benefits (37).

Implications of GLP-1RA CVOTs

Since the completion of the STENO-2 trial in 2003 (50), diabetes care guidelines have increasingly emphasized the need for multifactorial management of risk factors to reduce CV events in T2D. The Diabetes Canada clinical practice guidelines recommend following ABCDESSS for diabetes clinical care, which includes targeting glucose (**A**1C <7%), **B**lood pressure control (<130/80 mmHg), **C**holesterol (low-density lipoprotein Cholesterol <2.0 mmol/L), **D**rugs for CVD risk reduction (angiotensin-converting enzyme and/or angiotensin II receptor antagonist, statin and aspirin, including SGLT-2 inhibitor/GLP-1RA with CV benefit), **E**xercise goals and healthy eating, **S**creening for complications, **S**moking cessation and **S**elf-management (stress management and other barriers) (51). Currently, use of SGLT-2 inhibitors (empagliflozin and canagliflozin) and GLP-1RAs (liraglutide and semaglutide) are prioritized by Diabetes Canada and several other major international diabetes and cardiology organizations as a second-line treatment after metformin in patients with T2D and high CV risk (51–53). More recently, joint consensus guidelines from the American Diabetes Association and European Association for the Study of Diabetes (52) have further recommended that for patients with T2D with atherosclerotic CVD, a GLP-1RA or an SGLT-2 inhibitor (if eGFR is adequate) with proven CV benefit be considered preferentially. However, for patients with T2D with heart failure and/or CKD, an SGLT-2 inhibitor (with evidence in reducing heart failure and/or CKD) is preferred if renal function is adequate. If an SGLT-2 inhibitor is not tolerated or is contraindicated or if eGFR is inadequate, then a GLP-1RA (with proven CVD benefit) is preferable (54). Finally, in September 2019, the European Society of Cardiology put forth guidelines advocating for first-line treatment with an SGLT-2i or a GLP-1RA in those with T2D with atherosclerotic CVD or at high/very high CV risk (target organ damage or multiple risk factors) in advance of metformin.

Conclusions

All recently completed and reported CVOTs with GLP-1RAs have consistently demonstrated CV safety, with some, but not all, significantly reducing the risk for CV events in adults with T2D at high CV risk. Based on significant heterogeneities in study design and innate differences among the GLP-1RAs evaluated in the CVOTs, it is inappropriate to directly compare the results of the different GLP-1RA CVOTs. The mechanisms that are responsible for the cardioprotective effects of GLP-1RAs also remain speculative, and incompletely understood. The results of GLP-1RA CVOTs, however, are pivotal and robust, and reinforce the need to include GLP-1RAs (with demonstrated CV benefit) in our diabetes clinical practice. Future trials might benefit from focusing on populations more typical of those seen in routine care, with longer follow-up periods, and a greater consistency in the definition of CV outcomes. Moreover, prioritization of GLP-1RAs as primary CV preventive agents in advance of metformin, in drug naive T2D patients with atherosclerotic CVD or at high CV risk, is already reaching guidelines for diabetes clinical care. Future use of GLP-1RAs in other diabetes subtype populations, such as CKD and nonalcoholic steatohepatitis, will be determined as new evidence emerges and is interpreted.

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Author Contributions

E.M.V, B.A.M. and J.A.L. equally contributed to the preparation of this manuscript and its content.

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