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REVIEW ARTICLE

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Cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists: A comparison of study designs, populations and results

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Abstract

Despite treatment advances leading to improved outcomes over the past 2 decades, cardiovascular (CV) disease (CVD) remains the leading cause of morbidity and mortality in people with diabetes. People with type 2 diabetes (T2D) have a 2- to 4-fold increased risk of CVD and CV death. Individuals with T2D have not seen the same improvements in CV morbidity and mortality as those without T2D. Given this, it is important to understand the CV impact of drugs used to treat T2D. In patients with T2D, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown a reduction in HbA1c and body weight regardless of their differences in chemical structure and pharmacokinetic variables. Glycaemic efficacy, accompanied by the potential for weight reduction and a low risk of hypoglycaemia, has moved GLP-1RAs to the first treatment of choice following metformin monotherapy in the latest American Diabetes Association treatment guidelines. Additionally, all GLP-1RAs have shown CV safety and several have proven CV benefit. GLP-1RAs have been evaluated in cardiovascular outcomes trials (CVOTs) of varying sizes, designs and patient populations with differing reported effects on CV outcomes. The purpose of this article is to review the completed GLP-1RA CVOTs with special attention to how their design, size, patient populations and conduct may influence the interpretation of results.

KEYWORDS

cardiovascular disease GLP-1 type 2 diabetes

1 | INTRODUCTION

People with diabetes, especially those with type 2 diabetes (T2D), have an increased risk of developing cardiovascular (CV) disease (CVD), partly because of existing co-morbidities and risk factors such as hypertension, dyslipidaemia and an increased weight-to-hip ratio.[1] Compared with people without diabetes, the incidence of CVD is up to 3- to 4-fold higher in women with T2D, and up 2- to 3-fold higher in men with T2D.[2] In a retrospective study published in 2016, the reported prevalence of CVD was 21.6% in ~1.4 million people in the

United States with T2D.[3] Despite major therapeutic advances leading to improved outcomes over the past 2 decades, CVD remains the leading cause of morbidity and mortality in people with T2D.[4] In 2017, the economic burden of diagnosed diabetes in the United States was US$327 billion, including direct medical costs and reduced productivity, with CV complications accounting for 27% of the total costs for diabetes treatment.[5]

Concerns for CV risk development associated with T2D treatment led the Endocrinologic and Metabolic Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA) to recommend CV assessments in the premarketing and postmarketing periods.[6,7] In 2008, the FDA issued guidance suggesting that sponsors provide evidence that new therapies for T2D do not result in an unacceptable increase in CV risk; sponsors were also provided with strategies to consider during clinical trial planning and upon trial completion.[8] Key features of the FDA guidance for conducting cardiovascular outcomes trials (CVOTs) and statistical considerations are provided in Appendix S1.

2 | GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST CVOTS

As of this review, in order of the publication of primary results, the completed glucagon-like peptide-1 receptor agonist (GLP-1RA) CVOTs include: Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)[9]; Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER)[10]; Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6)[11]; EXenatide Study of Cardiovascular Event Lowering (EXSCEL)[12]; Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes [referred to as Harmony])[13]; Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)[14]; and Peptide Innovation for Early Diabetes Treatment (PIONEER 6).[15] An exenatide subcutaneous implant (ICTA 650) was evaluated in A Study to Evaluate Cardiovascular Outcomes in Patients with Type 2 Diabetes Treated with ITCA 650 (FREEDOM-CVO [NCT01455896]).[16] The FREEDOM-CVO trial was completed in March 2016,[16] however, at the time of publication, details regarding the study design, baseline characteristics of patients and primary results were not published.

Prior GLP-1RA CVOT comprehensive reports have primarily focused on the heterogeneity of primary results,[17] the generalizability of results to the overall T2D population,[18,19] potential pathophysiological mechanisms associated with the cardioprotective properties of GLP-1 RAs,[20,21] comparisons with sodium-glucose co-transporter-2 inhibitor CVOTs[22,23] and meta-analyses of completed trials.[24,25] The present review provides a thorough description of the individual GLP-1RA CVOTs included in this report with regard to inclusion and exclusion criteria and emphasis on study design. To our knowledge, this is the first report to expound upon the methodology of completed GLP-1RA CVOTs. The purpose of this review is to detail and contextualize central features of CVOTs across the GLP-1RA class.[9–15,26–32] Key inclusion and exclusion criteria and definitions of CVD for each trial are provided in Tables 1 and 2, respectively. A summary of baseline patient characteristics is provided in Table 3.

2.1 | ELIXA

ELIXA was the first CVOT to evaluate the effects of a GLP-1RA (lixisenatide once-daily subcutaneous injection) added to T2D therapy on CV outcomes.[32] The primary endpoint in the time-to-event analysis was a composite of the first occurrence of death from CV causes, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalization for unstable angina (major adverse CV events [MACE]-4).[9] ELIXA was the only GLP-1RA CVOT to use a four-point MACE as the primary outcome, all the other trials used a three-point MACE. ELIXA was designed as a CV safety study in a patient population with a recent history of acute coronary syndrome (ACS), defined as an ST-segment elevation MI (STEMI), non-STEMI or unstable angina.[9] All patients were required to have had an ACS event within 180 days before screening.[9] This is a unique inclusion criterion among the GLP-1RA CVOTs. Many of the other CVOTs excluded patients who had recent events (acute coronary or cerebrovascular events within 14-90 days prior to screening/randomization).

ELIXA was event-driven with a target of 844 positively adjudicated events for the primary CV endpoint out of an estimated patient population of 6000 (3000 patients in each of the lixisenatide and placebo arms), assuming an annual event rate of 10% for the first year and 7% for each subsequent year.[32] The study was designed to first test for non-inferiority, and if the prespecified criterion for non-inferiority was met, then for superiority. A step-down procedure was utilized to account for multiplicity between primary and secondary efficacy endpoints: if superiority to placebo was shown for the primary composite endpoint, prioritized secondary endpoints (i.e. time to first occurrence of CV death) would have been tested for superiority until an endpoint was found to be not statistically significant.[9] ELIXA was designed with 96% power to show non-inferiority to placebo with the 1.3 non-inferiority boundary (assuming a true HR of 1.0) and 90% power to show superiority (assuming a true HR of 0.80).[32] A Cox proportional hazards model with treatment and geographic region as covariates was used to estimate the HR between lixisenatide and placebo.[9] Two interim analyses were planned to assess non-inferiority with the 1.8 criterion for the primary composite endpoint.[9] To control the overall type 1 error at the one-sided alpha of 0.025, an alpha of 0.02 was spent at the first interim analysis and alpha of 0.005 at the second interim analysis, which were planned for assessment at 122 and 300 events, respectively.[9]

Upon initiation of end-of-study visits, the trial sponsor assumed that an appropriate amount of time had been allotted to allow for the observation of the prespecified number of adjudicated events. Although recruitment targets were met (6068 enrolled vs. 6000 target), the number of primary endpoint events was less than anticipated at 805 rather than 844, providing greater than 95% and greater

TABLE 1 Study design

Study	Follow-up period/planned number of events	Treatment arms	Primary outcome	Key inclusion/exclusion criteria
ELIXA, 2015[9,32] (NCT01147250)	Event-driven • 844 primary endpoint events • 37 months with ≥10 months of follow-up for the last randomized patient	• Lixisenatide 10-20 μg once-daily • Placebo once-daily	4-component MACE[a]	Inclusion • T2D • Acute coronary event ≤180 days prior to screening Exclusion • Age <30 years • Type 1 diabetes • History of metabolic acidosis • Use of non-study incretin agents • History of pancreatitis, pancreatectomy, gastric surgery, IBD, history of or genetic predisposition to MTC • Planned coronary revascularization procedure ≤90 days after screening or coronary-artery bypass graft surgery for the qualifying event • Percutaneous coronary intervention ≤15 days prior to screening • HbA1c <5.5% or >11.0% Renal Excluded if eGFR <30 mL/min/1.73m^2
LEADER, 2016[10,30] (NCT01179048)	• Event- and time-driven • 611 primary endpoint events • 42-60 months of follow-up	• Liraglutide 1.8 mg or maximum tolerated dose once-daily • Placebo once-daily	3-component MACE[a]	• Inclusion T2D • HbA1c ≥7.0% • Antidiabetes medication naïve or treated with ≥1 OAM or NPH insulin or basal insulin or premixed insulin, alone or with ≥1 OAM • Age ≥50 years, existing CVD defined as ≥1 of the following: prior MI; prior stroke or TIA; prior coronary, carotid, or peripheral arterial revascularization; >50% stenosis of coronary, carotid or lower extremity arteries; history of documented symptomatic CHD; chronic heart failure NYHA class II-III; asymptomatic cardiac ischaemia; chronic renal failure • Age ≥60 years, existing CV risk factors defined as ≥1 of the following: microalbuminuria or proteinuria; hypertension

(Continues)

TABLE 1 (Continued)

Study	Follow-up period/planned number of events	Treatment arms	Primary outcome	Key inclusion/exclusion criteria
				and left ventricular hypertrophy; left ventricular systolic or diastolic dysfunction; ankle-brachial index <0.9 Exclusion • Type 1 diabetes • Calcitonin ≥50 ng/L • GLP-1RA, DPP-4 inhibitor, pramlintide • Use of insulin other than those listed in the inclusion criteria ≤3 months prior to screening • Acute decompensation of glycaemic control • Acute coronary or cerebrovascular event in the previous 14 days • Planned coronary, carotid or peripheral arterial revascularization • Chronic heart failure NYHA class IV • End-stage liver disease • History of or awaiting solid organ transplant • Malignant neoplasm • Family or personal history of multiple endocrine neoplasia type 2 or familial MTC • Personal history of non-familial MTC Renal Excluded if receiving continuous renal replacement therapy
SUSTAIN-6, 2016[11] (NCT01720446)	• Event- and time-driven • 122 primary outcomes • Minimum of 104 weeks after last randomized subject	• Semaglutide 0.5 or 1.0 mg once-weekly • Placebo once-weekly	3-component MACE[a]	Inclusion • T2D • HbA1c ≥7.0% • Antidiabetes medication naïve or 1-2 OAMs or NPH insulin or basal insulin or premixed insulin, alone or with 1-2 OAM • Age ≥50 years, existing CVD defined as ≥1 of the following: prior MI; prior stroke or TIA; prior coronary, carotid or peripheral arterial revascularization; >50% stenosis of coronary, carotid or lower extremity arteries; history of documented symptomatic CHD; chronic heart failure

TABLE 1 (Continued)

Study	Follow-up period/planned number of events	Treatment arms	Primary outcome	Key inclusion/exclusion criteria
				NYHA class II-III; asymptomatic cardiac ischaemia; chronic renal impairment • Age ≥60 years, existing CV risk factors defined as ≥1 of the following: microalbuminuria or proteinuria; hypertension and left ventricular hypertrophy; left ventricular systolic or diastolic dysfunction; ankle-brachial index <0.9 Exclusion • Type 1 diabetes • GLP-1RA or pramlintide or insulin other than basal or premixed ≤90 days prior to screening • DPP-4 inhibitor use ≤30 days prior to screening • Acute decompensation of glycaemic control • History of pancreatitis • Acute coronary or cerebrovascular event in ≤90 days prior to randomization • Planned coronary, carotid or peripheral artery revascularization • Chronic heart failure NYHA class IV • End-stage liver disease • History of or awaiting solid organ transplant • Malignant neoplasm diagnosis in prior 5 years • Family or personal history of MEN2 or familial MTC • Personal history of non-familial MTC • Calcitonin ≥50 ng/L at screening Renal Long-term dialysis
EXSCEL, 2017[12,29] (NCT01144338)	• Event-driven • 1360 primary outcomes	• Exenatide extended release 2 mg once-weekly • Placebo once-weekly	3-component MACE[a]	Inclusion • T2D • HbA1c 6.5%-10.0% • 0-3 OAMs or insulin therapy (basal and prandial) with up to 2 OAMs • Age ≥18 years and any level of CV risk, such that ~30% will not have had a prior CV event and ~70% will have had a prior CV event

(Continues)

TABLE 1 (Continued)

Study	Follow-up period/planned number of events	Treatment arms	Primary outcome	Key inclusion/exclusion criteria
				• CV events were defined as history of major clinical manifestation of coronary artery disease (history of MI, coronary revascularization or coronary angiography showing at least one stenosis ≥50% in a major epicardial artery or branch vessel); ischaemic cerebrovascular disease (history of ischaemic stroke or history of carotid artery disease as documented by ≥50% stenosis [with or without symptoms of neuro deficit]); or atherosclerotic PAD (amputation because of vascular disease, symptoms of intermittent claudication confirmed by ankle- or toe-brachial pressure index <0.9, or history of percutaneous revascularization) Exclusion • Type 1 diabetes or history of ketoacidosis • ≥2 severe hypoglycaemia events within 12 months of enrolment • Prior GLP-1RA use • Planned or anticipated revascularization procedure • Medical history indicates life expectancy <2 years • History of gastroparesis • Personal or family history of MEN2 or MTC or calcitonin ≥40 ng/L • History of pancreatitis Renal Excluded if ESKD or eGFR <30 mL/min/1.73m^2
Harmony, 2018[13,28] (NCT02465515)	• Event-driven • 611 primary outcomes • Minimum median follow-up of 1.5 years	• Albiglutide 30-50 mg once-weekly • Placebo once-weekly	3-component MACE[a]	Inclusion • T2D • HbA1c >7.0% • Age ≥40 years, existing CVD defined as ≥1 of the following: coronary artery disease (spontaneous MI or documented coronary artery disease [≥50% stenosis in 1 or more major epicardial coronary arteries or history of percutaneous coronary revascularization]);

TABLE 1 (Continued)

Study	Follow-up period/planned number of events	Treatment arms	Primary outcome	Key inclusion/exclusion criteria
				cerebrovascular disease (history of ischaemic stroke, carotid arterial disease with ≥50% stenosis [with or without symptoms of neuro deficit], or carotid vascular procedure); or PAD (intermittent claudication and ankle-brachial index <0.9, or prior non-traumatic amputation or peripheral vascular procedure because of arterial ischaemia) Exclusion • GLP-1RA use at screening • Severe gastroparesis ≤6 months prior to screening • Prior pancreatitis or substantial pancreatitis risk factors • Personal or family history of MEN2 or MTC Renal Excluded if eGFR <30 mL/min/1.73m^2
REWIND, 2019[14,27] (NCT01394952)	• Event-driven • 1200 primary outcomes • 8 years max.	• Dulaglutide 1.5 mg once-weekly • Placebo once-weekly	3-component MACE[a]	Inclusion • T2D • HbA1c ≤9.5% • BMI ≥23 kg/m^2 • Stable dose of 0–2 OAMs ± basal insulin for ≥3 months prior to screening • Age ≥50 and established clinical vascular disease defined as ≥1 of the following: prior MI; prior stroke; prior coronary, carotid, or peripheral revascularization; hospitalization for unstable angina, myocardial ischaemia, or percutaneous coronary intervention • Age ≥55 and subclinical vascular disease defined as ≥1 of the following: documented myocardial ischaemia; >50% coronary, carotid, or lower extremity artery stenosis; ankle-brachial index <0.9; eGFR persistently <60 mL/min/1.73 m^2; hypertension with left ventricular hypertrophy; or persistent albuminuria

(Continues)

TABLE 1 (Continued)

Study	Follow-up period/planned number of events	Treatment arms	Primary outcome	Key inclusion/exclusion criteria
				• Age ≥60 years and ≥2 of the following risk factors: tobacco use; use of lipid modifying therapy or documented untreated LDL cholesterol ≥130 mg/dL ≤6 months of screening; HDL cholesterol <40 mg/dL for men and <50 mg/dL for women or triglycerides ≥200 mg/dL ≤6 months of screening; use of ≥1 blood pressure drug or untreated systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥95 mmHg; or waist-to-hip ratio >1.0 (men) and >0.8 (women) • Run-in drug adherence of 100% Exclusion • Uncontrolled diabetes • Severe hypoglycaemia in 12 months prior to randomization • Acute coronary or cerebrovascular event in 2 months prior to randomization • Revascularization plans of coronary, carotid or peripheral artery • Gastric bypass or emptying abnormality • Prior pancreatitis • Liver disease or ALT of ≥3x normal • Personal or family history of/or C-cell hyperplasia or MTC or MEN 2A or 2B or calcitonin value of ≥20 pg/mL • Unwilling to stop GLP-1RA, DPP-4 inhibitor or weight loss drug • History of or awaiting organ transplant • Cancer in the previous 5 years • Life expectancy <1 year Renal Excluded if eGFR <15 mL/min/1.73m^2 or on dialysis
PIONEER 6[15,26] (NCT02692716)	• Event-driven • 122 primary endpoint events	• Oral semaglutide 14 mg (target dose) once-daily • Placebo once-daily	3-component MACE[a]	Inclusion • T2D • Age ≥50 years and established CVD defined as ≥1 of the following: prior MI; prior stroke or TIA;

TABLE 1 (Continued)

Study	Follow-up period/planned number of events	Treatment arms	Primary outcome	Key inclusion/exclusion criteria
				prior coronary, carotid or peripheral arterial revascularization; >50% stenosis of coronary, carotid or lower extremity arteries; history of documented symptomatic CHD; asymptomatic cardiac ischaemia; chronic heart failure NYHA class II-III; or moderate renal impairment • Age ≥60 years and ≥1 CV risk factors defined as the following: microalbuminuria or proteinuria; hypertension and left ventricular hypertrophy; left ventricular systolic or diastolic dysfunction; ankle-brachial index <0.9 Exclusion • GLP-1RA, DPP-4 inhibitor or pramlintide use ≤90 days prior to screening • Personal or family history of MEN 2 or MTC • History of pancreatitis • History of major gastric surgical procedures that may affect study drug absorption • NYHA class IV heart failure • Planned coronary, carotid or peripheral artery revascularization • MI, stroke or hospitalization for unstable angina or TIA within 60 days prior to screening • History or presence of malignant neoplasms ≤5 years of screening • History of diabetic ketoacidosis • Current treatment for proliferative retinopathy or maculopathy Renal • Long-term or intermittent haemodialysis or peritoneal dialysis or severe renal impairment (eGFR <30 mL/min/1.73m^2)

Note: All treatment arms included standard of care therapy based on country-specific guidelines.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL, high density lipid; IBD, irritable bowel disease; LDL, low density lioprotein; MACE, major adverse cardiac events; MEN2, multiple endocrine neoplasia type 2; MI, myocardial infarction; MTC, medullary thyroid cancer; NYHA, New York Heart Association; OAM, oral antidiabetes medication; PAD, peripheral arterial disease; TIA, transient ischaemic attack.

[a]Three-component included non-fatal myocardial infarction, non-fatal stroke or cardiovascular death; four-component also included hospitalization for unstable angina.

TABLE 2 Definitions of established cardiovascular disease

Trial	Definition
ELIXA[9]	Acute coronary syndrome defined as ST-segment elevation MI (STEMI), non-STEMI or unstable angina.
LEADER[10]	≥1 of the following criteria: • Prior MI • Prior stroke or TIA • Prior coronary, carotid or peripheral arterial revascularization • >50% stenosis of coronary, carotid or lower extremity arteries • History of symptomatic CHD documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes • Asymptomatic cardiac ischaemia documented by positive nuclear imaging test, exercise test or dobutamine stress echo • Chronic heart failure NYHA class II-III • Chronic renal failure (eGFR <60 mL/min per 1.73m^2)
SUSTAIN-6[11]	≥1 of the following criteria: • Prior MI • Prior stroke or TIA • Prior coronary, carotid or peripheral arterial revascularization • >50% stenosis of coronary, carotid or lower extremity arteries • History of symptomatic CHD documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes • Asymptomatic cardiac ischaemia documented by positive nuclear imaging test, exercise test, stress echo or any cardiac imaging • Chronic heart failure NYHA class II-III • Chronic renal impairment (eGFR <60 mL/min/1.73m^2)

EXSCEL[12]	≥1 of the following criteria:
	• History of a major clinical manifestation of CAD, i.e. MI, surgical or percutaneous (balloon and/or stent) coronary revascularization procedure or coronary angiography showing ≥50% stenosis in a major epicardial artery or branch vessel
	• Ischaemic cerebrovascular disease, including:
	  ○ History of ischaemic stroke. Strokes not known to be haemorrhagic will be allowed as part of this criterion
	  ○ History of CAD as documented by ≥50% stenosis documented by carotid ultrasound, MRI or angiography, with or without symptoms of neuro deficit
	• Atherosclerotic PAD, as documented by objective evidence such as amputation because of vascular disease, current symptoms of intermittent claudication confirmed by an ankle-brachial pressure index or toe brachial pressure index less than 0.9, or history of surgical or percutaneous revascularization procedure

Harmony[13]	≥1 of the following criteria:
	• CAD with either of the following:
	  ○ Documented history of spontaneous MI, at least 30 days before screening
	  ○ Documented CAD ≥50% stenosis in 1 or more major epicardial coronary arteries, determined by invasive angiography, or a history of surgical or percutaneous (balloon and/or stent) coronary revascularization procedure (at least 30 days before screening for percutaneous procedures and at least 5 years before screening for CABG)
	• Cerebrovascular disease—any of the following:
	  ○ Documented history of ischaemic stroke, at least 90 days before study entry
	  ○ Carotid arterial disease with ≥50% stenosis documented by carotid ultrasound, magnetic resonance imaging or angiography, with or without symptoms of neuro deficit
	  ○ Carotid vascular procedure (e.g. stenting or surgical revascularization), at least 30 days before screening
	• PAD with either of the following:
	  ○ Intermittent claudication and ankle-brachial index <0.9 in at least 1 ankle
	  ○ Prior non-traumatic amputation or peripheral vascular procedure (e.g. stenting or surgical revascularization) because of peripheral arterial ischaemia

REWIND[14,33]	≥1 of the following criteria: • Prior MI • Myocardial ischaemia by a stress test or with cardiac imaging • Prior ischaemic stroke • Coronary, carotid or peripheral revascularization • Unstable angina • Hospitalization for unstable angina with ECG changes, myocardial ischaemia on imaging, or need for percutaneous coronary intervention
PIONEER 6[15]	≥1 of the following criteria: • Prior MI • Prior stroke or TIA • Prior coronary, carotid or peripheral arterial revascularization • >50% stenosis of coronary, carotid or lower extremity arteries

TABLE 2 (Continued)

Trial	Definition
	• History of symptomatic CHD documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes • Asymptomatic cardiac ischaemia documented by positive nuclear imaging test, exercise test, stress echo or any cardiac imaging • Chronic heart failure NYHA class II-III • Moderate renal impairment (30-59 mL/min per 1.73m^2)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CABG, coronary artery bypass graphing; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL, high density lipid; IBD, irritable bowel disease; LDL, low density lipoprotein; LV, left ventricular; MACE, major adverse cardiac events; MEN2, multiple endocrine neoplasia type 2; MI, myocardial infarction; MRI, magnetic resonance imaging; MTC, medullary thyroid cancer; NYHA, New York Heart Association; OAM, oral antidiabetes medication; PAD, peripheral arterial disease; TIA, transient ischaemic attack.

than 88% power to detect non-inferiority and superiority to placebo, respectively.[9] The inclusion criteria yielded a patient population with a prior ACS event and a primary endpoint event incidence of 6.4 and 6.3 events/100 patient years for the lixisenatide and placebo treatment arms, respectively.[9] Lixisenatide treatment was non-inferior but not superior to placebo (HR 1.02, 95% CI [0.89, 1.17]; $P < .001$ and $P = .81$, respectively).[9]

2.2 | LEADER

Unlike ELIXA, which exclusively enrolled patients with a recent ACS event, LEADER was designed to assess the effect of liraglutide (1.8 mg once-daily subcutaneous injection) versus placebo on the incidence of CV events in patients from two distinct high-risk groups: established CVD or one or more CV risk factors.[30] Patients who had a recent acute coronary or cerebrovascular event were included if the event was not within 14 days before screening and randomization. The established CVD subpopulation was defined as patients aged 50 years or older with one or more of the following CV co-existing conditions: prior MI, stroke or transient ischaemic attack, prior coronary, carotid or peripheral arterial revascularization, greater than 50% stenosis of coronary, carotid or lower extremity arteries, a history of coronary heart disease, asymptomatic cardiac ischaemia, chronic heart failure New York Heart Association class II-III, and chronic renal failure of stage 3 or higher.[30] Criteria for the CV risk factor subpopulation included patients who were aged 60 years or older with one or more of the following characteristics: microalbuminuria or proteinuria, hypertension and left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, and an ankle-brachial index of less than 0.9.[30] The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, non-fatal MI or non-fatal stroke (MACE-3)[10]; this design was distinct from ELIXA, which also included hospitalization for unstable angina in its MACE composite.[9] The use of MACE-4 in ELIXA was primarily to increase the number of CV events that could be observed, which in turn increased the power to detect a difference between the lixisenatide and placebo treatment arms. After ELIXA, the FDA shifted their expectations to use MACE-3 for prospectively designed CVOTs. From LEADER onwards, GLP-1RA CVOTs were designed to analyse the time-to-event for MACE-3.[10–15,26–31]

LEADER was both event- and time-driven.[10] The trial was designed to compare CV events in patients treated with liraglutide or placebo for a minimum of 3.5 years and a maximum of 5 years.[10] Sample size calculations were estimated from the assumption of a primary outcome event rate of 1.8% in each of the liraglutide and placebo arms, a uniform enrolment over 1.5 years and a maximum follow-up of 5 years, 1.3 as the upper limit of the two-sided 95% CI for non-inferiority to placebo, a total drop-out rate of less than 10%, a one-sided alpha of 0.025, and 90% power to reject the null hypothesis.[10] These assumptions led to an estimated need of 8754 patients for randomization to observe 611 primary outcomes.[10] An annual event rate of 1.8% was noted as conservative relative to the 2.3% observed in other large CVOTs (Action to Control CV Risk in Type 2 Diabetes [ACCORD] and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE]) that enrolled patients with a history of diabetes and a high risk of CV outcomes (32%-35% prevalence of a prior CV event or risk factors).[10] Randomization was stratified according to the estimated glomerular filtration rate (eGFR) at screening (<30 or ≥30 mL/min/1.73m^2).[10]

Unlike ELIXA, which included both treatment and geographic region as a covariate, the primary outcome in the time-to-event analysis for LEADER was based on a Cox proportional hazards model with treatment as a covariate.[10] LEADER was designed to first test for non-inferiority and then superiority, whereby non-inferiority and superiority were established if the upper bound of a two-sided 95% CI was less than 1.3 and less than 1.0, respectively, requiring no adjustment for significance because of the closed-testing procedure.[10] No interim analyses were performed.

LEADER exceeded its recruitment target (9340 enrolled vs. 8754 target) and reported greater than 2-fold (1302 events) its projected observation of 611 primary outcomes, the latter of which was probably a result of the predominance of established CVD in the recruited population.[10] The difference in design and outcomes may reflect the conservative assumption for a primary event rate of 1.8% from LEADER's design. The primary event rate was 3.4 and 3.9 events/100 patient-years for the liraglutide and placebo treatment arms, respectively.[10] Furthermore, the majority of randomly assigned patients met

TABLE 3 Baseline characteristics

Study (median follow-up)	Arms	Age, years	Female	BMI, kg/m^2	HbA1c, %	eGFR, mL/min/1.73m^2	Duration of diabetes, years	Prior MI	Prior stroke	CV risk factors	Established CVD
ELIXA (2.1 years)[9]	LIXI (N = 3034)	59.9 ± 9.7	923 (30)	30.1 ± 5.6	7.7 ± 1.3	76.7 ± 21.3	9.2 ± 8.2	672 (22)[a]	143 (5)	ND	3034 (100)
	PL (N = 3034)	60.6 ± 9.6	938 (31)	30.2 ± 5.8	7.6 ± 1.3	75.2 ± 21.4	9.4 ± 8.3	672 (22)[a]	188 (6)	ND	3034 (100)
LEADER (3.8 years)[10]	LIRA (N = 4668)	64.2 ± 7.2	1657 (35)	32.5 ± 6.3	8.7 ± 1.6	ND	12.8 ± 8.0	1464 (31)	730 (16)[b]	837 (18)	3831 (82)
	PL (N = 4672)	64.4 ± 7.2	1680 (36)	32.5 ± 6.3	8.7 ± 1.5	ND	12.9 ± 8.1	1400 (30)	777 (17)[b]	905 (19)	3767 (81)
SUSTAIN-6 (2.1 years [mean])[11]	SEMA 0.5 mg (N = 826)	64.6 ± 7.3	331 (40)	32.7 ± 6.3	8.7 ± 1.4	ND	14.3 ± 8.2	266 (32)	117 (14)[c]	295 (18)	1353 (82)
	SEMA 1.0 mg (N = 822)	64.7 ± 7.1	304 (37)	32.9 ± 6.2	8.7 ± 1.5	ND	14.1 ± 8.2	264 (32)	113 (14)[c]		
	PL 0.5 mg (N = 824)	64.8 ± 7.6	342 (42)	32.9 ± 6.4	8.7 ± 1.5	ND	14.0 ± 8.5	267 (32)	123 (15)[c]	267 (16)	1382 (84)
	PL 1.0 mg (N = 825)	64.4 ± 7.5	318 (39)	32.7 ± 6.0	8.7 ± 1.5	ND	13.2 ± 7.4	275 (33)	138 (17)[c]		
EXSCEL (3.2 years)[12]	EXE (N = 7356)	62.0 (56.0, 68.0)	2794 (38)	31.8 (28.2, 36.2)	8.0 (7.3, 8.9)	76.6 (61.3, 92.0)	12.0 (7.0, 17.0)	ND	ND	1962 (27)[d]	5394 (73)
	PL (N = 7396)	62.0 (56.0, 68.0)	2809 (38)	31.7 (28.2, 36.1)	8.0 (7.3, 8.9)	76.0 (61.0, 92.0)	12.0 (7.0, 18.0)	ND	ND	2008 (27)[d]	5388 (73)
Harmony (1.6 years)[13]	ALB (N = 4731)	64.1 ± 8.7	1427 (30)	32.3 ± 5.9	8.76 ± 1.5	79.1 ± 25.6	14.1 ± 8.6	2223 (47)	827 (17)	0 (0)	4731 (100)
	PL (N = 4732)	64.2 ± 8.7	1467 (31)	32.3 ± 5.9	8.72 ± 1.5	78.9 ± 25.4	14.2 ± 8.9	2236 (47)	854 (18)	0 (0)	4732 (100)
REWIND (5.4 years)[14,27]	DU 1.5 mg (N = 4949)	66.2 ± 6.5	2306 (47)	32.3 ± 5.7	7.3 ± 1.1	75.3 (61.6, 91.8)	10.5 ± 7.3	ND	ND	3093 (62)	1560 (32)
	PL (N = 4952)	66.2 ± 6.5	2283 (46)	32.3 ± 5.8	7.4 ± 1.1	74.7 (61.2, 90.6)	10.6 ± 7.2	ND	ND	3128 (63)	1554 (31)
PIONEER 6 (1.3 years)[15]	SEMA 14 mg[e] (N = 1591)	66 ± 7	507 (32)	32.3 ± 6.6	8.2 ± 1.6	74 ± 21	14.7 ± 8.5	561 (35)[b]	242 (15)	241 (15)	1350 (85)
	PL (N = 1592)	66 ± 7	500 (31)	32.3 ± 6.4	8.2 ± 1.6	74 ± 21	15.1 ± 8.5	589 (37)[b]	263 (17)	247 (16)	1345 (84)

Abbreviations: ACS, acute coronary syndrome; ALB, albiglutide; BMI, body mass index; CV, cardiovascular; DU, dulaglutide; eGFR, estimated glomerular filtration rate; EXE, exenatide; LIRA, liraglutide; LIXI, lixisenatide; MI, myocardial infarction; ND, no data (values not determined or explicitly provided); PL, placebo; SEMA, semaglutide.

[a]Prior MI before index ACS.

[b]Includes stroke or transient ischaemic attack.

[c]Sum of haemorrhagic/ischaemic stroke.

[d]Patients could have any level of CV risk as long as other inclusion criteria were met.

[e]Oral semaglutide once-daily 14 mg was target dose. Data are mean ± SD, n (%) or median (interquartile range), unless otherwise indicated.

LEADER's criteria for established CVD (7598 [81.3%]).[10] Hierarchical testing showed the non-inferiority and superiority of liraglutide to placebo (HR 0.87, 95% CI [0.78, 0.97]; $P < .001$ and $P = .01$, respectively) for MACE-3, a first for the GLP-1RA class of medications.[10]

2.3 | SUSTAIN-6

SUSTAIN-6 was the first published CVOT for a once-weekly GLP-1RA (semaglutide, 0.5 and 1.0 mg subcutaneous injection) and was designed to assess the non-inferiority of semaglutide to placebo on CV safety.[11] Like LEADER, SUSTAIN-6 enrolled patients with established CVD or more than one CV risk factor.[11] The inclusion and exclusion criteria for SUSTAIN-6, including definitions for prior CVD and CV risk factors (subclinical vascular disease), were also highly comparable with those for LEADER (Tables 1 and 2).[11] Lastly, SUSTAIN-6 was also both time- and event-driven.

Nevertheless, several components of the design of SUSTAIN-6 were distinct from LEADER. SUSTAIN-6 included four treatment arms: one for each dose of semaglutide (0.5 and 1.0 mg) and two placebo arms.[11] For each study drug, treatment arms were pooled for statistical analysis of the primary endpoint (MACE-3) and three additional CV-related secondary endpoints.[11] SUSTAIN-6 did not include patients if they had an acute coronary or cerebrovascular event within 90 days before randomization, versus 14 days for LEADER. SUSTAIN-6 was planned for a minimum duration of 104 weeks after randomization of the last patient.[11] Sample size calculations were contingent upon showing that the upper bound of a two-sided 95% CI of the HR for semaglutide versus placebo would be less than 1.8 for time to first occurrence of MACE.[11] Assuming an equal MACE risk between the semaglutide and placebo populations, a minimum of 122 events were needed for at least 90% power to determine whether the upper bound of a two-sided CI was less than 1.8 at a significance level of .05.[11] SUSTAIN-6 was the first GLP-1RA CVOT to implement the preapproval safety margin of 1.8 for non-inferiority. The annual MACE-3 rate was assumed to be 2.0%, with a mean time in trial of 2.1 years, a true HR of 1.0, and lost to follow-up rate of a maximum of 10%, leading to an estimate of 3260 patients required to obtain 122 primary CV events.[11] SUSTAIN-6 was designed to randomize patients stratified according to CVD status, insulin treatment and eGFR (≤30 or >30 mL/min/1.73m^2), and to analyse the primary endpoint with a stratified Cox proportional hazards model with pooled treatment as a fixed factor, assuming different hazards according to different levels in the stratification variable.[11] The primary hypothesis was non-inferiority for the primary outcome; superiority testing in SUSTAIN-6 was not prespecified or adjusted for multiplicity.[11] No interim analyses were performed.

SUSTAIN-6 randomized 3297 patients either to semaglutide or placebo, similar to the projected sample size of 3260 patients required to obtain 122 primary events.[11] Like LEADER, the total number of primary composite outcomes in SUSTAIN-6 was greater than 2-fold higher (254 events) than the number projected in sample size calculations, which was probably caused by the predominance of established CVD in the recruited population. The projected MACE-3 rate was 2.0%, and similar to LEADER, the in-trial incidence rate was higher for the semaglutide and placebo treatment arms (3.2 and 4.4 events/100 patient-years, respectively).[11] It is noteworthy that many aspects of the LEADER and SUSTAIN-6 trials overlapped, which may be reflected in the consistency of the randomized patient populations with established CVD (LEADER, 81.3%; SUSTAIN-6, 83.0%).[10,11] Seventeen per cent of SUSTAIN-6 patients had CV risk factors. SUSTAIN-6, however, was powered to exclude a preapproval safety margin of 1.8,[11] as opposed to the margin of 1.3 tested in LEADER.[10] Semaglutide met the criteria for non-inferiority to placebo (HR 0.74, 95% CI [0.58, 0.95]; $P < .001$).[11] Although SUSTAIN-6 did not prespecify or power for superiority testing, it was examined in a post hoc analysis.[11] The accrual of more events than anticipated and the effect of semaglutide treatment resulted in $P = .02$ for superiority to placebo.[11] The primary objective of SUSTAIN-6 was non-inferiority with a margin of 1.8, as indicated by the number of primary endpoint events (122) planned for the end of the study. The FDA and other regulatory bodies do not give the same consideration to non-prespecified and post hoc findings of superiority as is given to prespecified findings of superiority.

2.4 | EXSCEL

EXSCEL was an event-driven trial designed to test for both non-inferiority and superiority as co-primary objectives for the efficacy of exenatide (2 mg once-weekly subcutaneous injection) to placebo for the primary composite CV outcome (MACE-3).[29] EXSCEL was unique to all other GLP-1RA CVOTs in that it was pragmatic in design, and did not include the strict ancillary CV risk reduction optimization included in other trials.[29] Patients with any level of CV risk were enrolled if all other inclusion criteria were met.[12] EXSCEL was also unique to LEADER and SUSTAIN-6 in that it was designed so that ~70% of enrolled patients had established CVD, whereas LEADER and SUSTAIN-6 did not approximate the proportion of patients with established CVD in their study design.[12] EXCEL also differed in its definition of CV disease, which included coronary artery disease (CAD; history of MI, coronary revascularization or coronary angiography showing ≥1 stenosis of ≥50% in a major epicardial artery or branch vessel); ischaemic cerebrovascular disease (history of ischaemic stroke or history of carotid artery disease as documented by ≥50% stenosis [with or without symptoms of neuro deficit]); or atherosclerotic peripheral artery disease (PAD; documented by objective evidence such as amputation because of vascular disease, symptoms of intermittent claudication confirmed by an ankle-brachial pressure index or toe-brachial pressure index of <0.9, or a history of percutaneous revascularization).[12]

Sample size calculations were performed consistent with the superiority hypothesis.[12] EXSCEL was designed to have 85% power to detect a risk of a primary composite outcome event that was 15% lower with exenatide compared with placebo, at a two-sided alpha of 0.05.[12] To test the above hypothesis, 1360 composite CV events

were required from a projected patient population of 14 000.[29] It was assumed that the annual composite primary CV endpoint event rate would be 3.8%, the lost-to-follow up rate would be 1%, treatment discontinuation would be 5% and the accrual period would span 5-6 years.[29] The planned number of events was anticipated to provide in excess of 90% power to assess the trial's primary safety objective of non-inferiority. The non-inferiority margin specified in EXSCEL (upper bound of 95% CI <1.3) was consistent with the previously published ELIXA and LEADER CVOTs.

The HR for the first occurrence of a CV event in the primary composite endpoint comparing exenatide with placebo was estimated using a Cox proportional hazards model stratified by baseline CV risk group and treatment group as a covariate.[12] Tests for non-inferiority and superiority were conducted hierarchically, first testing for non-inferiority then superiority for the primary composite endpoint.[12] A superiority test for the secondary outcome of all-cause death was conducted only if non-inferiority and superiority were significant for the primary composite endpoint.[12] Two formal interim efficacy analyses were planned to test for superiority ($P < .0001$ and $P < .001$) after 453 and 906 events, corresponding to one- and two-thirds of the targeted 1360 primary CV events.[12] This design was to ensure a significance level of .0499 for the final analysis.[12]

A total of 14 752 patients were randomized and 10 782 had established CVD (73.1%), with 3970 (26.9%) having CV risk factors, mirroring projections of a patient pool of 14 000, with 70% having established CVD.[12] There were 1744 primary composite outcome events observed, exceeding the minimum of 1360 needed to test EXSCEL's superiority and non-inferiority hypotheses.[12] The incidence rate for MACE-3 was 3.7 and 4.0 events/100 patient-years for exenatide and placebo, respectively, exceeding the 2.2% assumed for testing EXSCEL's primary outcomes.[12] Primary composite outcome events occurred in 839 and 905 patients treated with exenatide or placebo, respectively; exenatide showed non-inferiority to placebo with respect to safety, but not superiority to placebo with respect to efficacy (HR 0.91, 95% CI [0.83, 1.00]; $P < .001$ and $P = .06$, respectively).[12] Among other factors, EXSCEL's pragmatic design, shorter follow-up, duration of treatment regimen exposure and lower baseline HbA1c compared with LEADER may have contributed to its lack of observed CV efficacy.[12] Compared with other GLP-1RA CVOTs, EXSCEL had low treatment regimen compliance (exenatide, 76.0%; placebo, 75.0%), defined as the duration of time that patients received the trial regimen relative to the duration of time that they were expected to receive the regimen during the trial.[12]

2.5 | Harmony

The study of albiglutide (30-50 mg once-weekly subcutaneous injection) on CV outcomes was the second GLP-1RA CVOT designed to exclusively enrol patients with prior CVD.[13] Eligible patients were aged 40 years or older with an HbA1c of less than 7.0% (<53 mmol/mol) and established CVD defined as CAD, cerebrovascular disease or PAD.[13] CAD was defined as a documented history of spontaneous MI, a documented 50% or higher stenosis in one or more major epicardial coronary arteries, or a history of coronary revascularization.[13] Cerebrovascular disease was defined as a documented history of ischaemic stroke, carotid arterial disease with 50% or higher stenosis, or a carotid vascular procedure.[13] PAD was defined as intermittent claudication and an ankle-brachial index of less than 0.9 in at least one ankle or a prior non-traumatic amputation or peripheral vascular procedure caused by peripheral arterial ischaemia.[13] Definitions of CAD, cerebrovascular disease and PAD were similar to EXSCEL.

Harmony was an event-driven trial also requiring a minimum follow-up of 1.5 years, and was designed to first test for the non-inferiority of albiglutide to placebo by a margin of 1.3 with respect to its effect on adjudicated MACE, followed by superiority testing if the prespecified criterion was met.[13] It was determined that 611 events were needed for 90% power to rule out a non-inferiority margin of 1.3 for the HR with a type I error of 0.05, assuming a true HR of 1.0.[13] A total of 9400 patients were planned for enrolment and followed until 611 events occurred.[13] Assuming the number of patients lost to follow-up would be 1% or less, the mean follow-up would be 3.2 and 2.2 years for an observed rate of MACE of 2% and 3%, respectively.[13]

The primary endpoint was time to first occurrence of MACE-3, with the HR and *P*-value for the primary endpoint calculated using a Cox proportional hazards regression model with treatment group as the only covariate.[13] Harmony implemented a closed testing procedure to test for superiority subsequent to confirming non-inferiority; no adjustments for multiplicity were made for prespecified secondary or other endpoints.[13]

A total of 9463 patients with established CVD were randomly assigned out of the 10 793 screened, close to the target patient population of 9400.[13] Of all the trials, Harmony had the greatest proportion of patients (47%) with a history of prior MI.[13] The primary composite outcome occurred in 766 patients, exceeding the projection of 611 needed for non-inferiority testing: 338 of 4731 patients (7%) treated with albiglutide and 428 of 4732 patients (9%) treated with placebo (HR 0.78, 95% CI [0.68, 0.90]), showing that albiglutide was both non-inferior ($P < .0001$) and superior ($P = .0006$) to placebo.[13] The median follow-up was 1.6 years and the incidence rate was 4.6 and 5.9 events/100 patient-years in the albiglutide and placebo treatment arms, respectively.[13] Harmony had the second shortest follow-up time of all the trials, which can be attributed to its event-driven design and also the fact that nearly 50% of patients had a prior MI, enabling accrual of the necessary events in a shorter amount of time compared with most trials.

2.6 | REWIND

REWIND was an event-driven trial designed to evaluate whether dulaglutide (1.5 mg once-weekly subcutaneous injection) safely reduces the incidence of CV outcomes compared with placebo.[14] REWIND was designed to study patients aged 50 years or older with established CVD, patients aged 55 years or older with subclinical

vascular disease (defined below), or patients aged 60 years or older with multiple CV risk factors.[27] REWIND was more representative of the population of patients with T2D diabetes than other GLP-1RA CVOTs.[27] Patients were required to have an HbA1c of 9.5% or less (≤81 mmol/mol) on stable doses of up to two oral glucose-lowering medications with or without basal insulin.[27] Additionally, patients were required to have a BMI of 23 kg/m^2 or higher.[27] Patients were included if they were aged 50 years or older and had a previous MI, ischaemic stroke, revascularization of the coronary, carotid or peripheral arteries, hospitalization for unstable angina, image-proven myocardial ischaemia, or a need for percutaneous coronary intervention.[27] Patients aged 55 years or older, and aged 60 years or older, were included with either subclinical vascular disease or two or more risk factors for CV outcomes, respectively.[27] Subclinical vascular disease was defined as a history of myocardial ischaemia by a stress test or cardiac imaging, greater than 50% vascular stenosis upon imaging of the coronary, carotid or lower extremity arteries, an ankle-brachial index of less than 0.9, an eGFR of less than 60 mL/min/1.73m^2, and a history of hypertension with documented LV hypertrophy, microalbuminuria or macroalbuminuria.[27] Risk factors for CV outcomes included current tobacco use, documented low-density lipoprotein cholesterol of 3.4 mmol/L or higher, or high-density lipoprotein cholesterol of less than 1.0 mmol/L and less than 1.3 mmol/L for men and women, respectively, or triglycerides of 2.3 mmol/L or higher within 6 months prior to randomization, a waist-to-hip ratio of greater than 1.0 for men and greater than 0.8 for women, and the use of blood pressure medication to treat hypertension or untreated systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 95 mmHg or higher.[27]

Sample size calculations were performed to provide the statistical power to detect the superiority of dulaglutide over placebo (with 90% power).[27] The following assumptions were used: (a) a two-sided significance level of 0.05; (b) 90% power for the primary endpoint; (c) uniform patient accrual over 3 years; (d) an annual placebo group event rate of 2.0% for the primary endpoint; (e) minimum and maximum durations of follow-up of 5.6 and 8 years, respectively; (f) an HR of 0.82 between dulaglutide and placebo for the primary endpoint; and (g) an annual dropout rate of 0.15%.[27] A total sample size of 9600 patients was estimated to result in a total of 1200 patients with one or more primary outcome over the maximum follow-up.[27]

The effect of dulaglutide on the time to the first occurrence of the primary outcome (MACE-3) was analysed using Cox proportional hazards regression models with the only independent variable being treatment allocation.[27] If the null hypothesis of no effect was rejected for the primary outcome (superiority hypothesis), a graphical testing approach was used to analyse all secondary outcomes to control for the overall type 1 error.[27] This approach would distribute the alpha level across secondary outcomes grouped in prespecified tiers, maximizing the opportunity to detect an effect while minimizing the likelihood of type 1 error.[27] However, in the event the superiority test for the primary outcome failed, a test of non-inferiority with a 1.3 margin would be performed.[14] Non-inferiority of dulaglutide versus placebo was to be declared if the upper limit of the adjusted 95% CI of dulaglutide versus placebo was greater than 1 and less than 1.3.[14] Interim analyses were planned for when ~61% (730 events) out of the anticipated 1200 primary endpoints had accrued.[27]

A total 9901 of 10 917 eligible patients were randomized to dulaglutide and placebo treatment arms (4949 and 4952, respectively), which was above the target of 9600 patients.[14] At baseline, only 3114 (31.5%) had established CVD, whereas 6787 (68.5%) had CV risk factors.[14] It is notable that among all of the GLP-1RA CVOTs completed prior to REWIND, the trial with the lowest population with established CVD was EXSCEL with 73.1%. The annual incidence rate of the primary composite outcome for placebo was assumed to be 2% during the trial design; the actual incidence rate was 2.4 and 2.7 events/100 patient-years for the dulaglutide and placebo treatment arms, respectively.[14] Despite the low proportion of patients with established CVD, REWIND reduced the relative risk of MACE-3 by 12% (HR 0.88, 95% CI [0.79, 0.99]; P = .026) over a median follow-up of 5.4 years, with the primary outcome occurring in 594 (12.0%) and 663 (13.4%) patients in the dulaglutide and placebo arms, respectively.[14]

2.7 | PIONEER 6

PIONEER 6 was an event-driven trial designed to rule out an excess in CV risk for the oral formulation of semaglutide (a maximum dose of 14 mg once-daily) in patients with established CVD or CV risk factors.[15] The injectable formulation of semaglutide was evaluated in SUSTAIN-6; however, regulatory agencies required both the injectable and oral formulations to show CV safety. Criteria for CVD or CV risk factors were stratified by age and baseline characteristics.[15] The criteria for CVD or CV risk factors for PIONEER 6 closely mirrored those of the LEADER and SUSTAIN-6 CVOTs.[15] Unlike LEADER, PIONEER 6 and SUSTAIN-6 were not designed to explicitly enrol more than 200 patients with end-stage renal disease; rather, PIONEER 6 excluded patients with severe renal impairment corresponding to an eGFR of less than 30 mL/min/1.73m^2.[15]

Like SUSTAIN-6, PIONEER 6 was designed to exclude an 80% excess in CV risk for oral semaglutide compared with placebo, with an upper limit of the two-sided 95% CI not exceeding an HR of 1.8.[15] Sample size calculations were informed by the assumptions of LEADER and SUSTAIN-6, which included a rate of 3% per 100 patient years for first MACE, uniform trial recruitment during 7 months, a lost-to-follow-up rate of 1% per year, and the last subject visit occurring 19 months after randomization of the first subject.[15] The sample size was made to ensure 90% power for testing the non-inferiority of oral semaglutide to placebo on the primary endpoint.[15] For 122 first MACE to occur in 19 months, 3176 patients needed to undergo randomization.[26] To ensure a sufficient number of events, PIONEER 6 limited the proportion of patients with CV risk factors to ~20% (650 patients).[26]

A stratified Cox proportional hazards model was used for the primary analysis of time from randomization to first MACE, with treatment as a fixed factor and stratification based on evidence of CVD at screening.[15] A hierarchical testing strategy was employed to first test

for non-inferiority then, if confirmed, to test for superiority, preserving the type 1 error in the strong sense at 5% (two-sided).[15] No interim analyses were planned for the trial.

A total of 3183 patients were randomly assigned to either the placebo or oral semaglutide treatment arms, close to the projected sample size of 3176.[15] Less than 650 patients (488 [15.3%]) had CV risk factors only at baseline, and 2695 (84.7%) had established CVD or chronic kidney disease[15] similar to that of LEADER and SUSTAIN-6. The incidence rate of the primary outcome was 2.9 and 3.7 events/100 patient-years in the oral semaglutide and placebo arms, respectively, comparable with the assumed incidence rate of 3% in sample size calculations.[15] The total number of primary MACE was 137, surpassing the need of 122 to test the primary safety hypothesis of non-inferiority to placebo.[15] Over a median time-in-trial of 15.9 months, PIONEER 6 met its primary objective of non-inferiority to rule out an 80% excess CV risk with oral semaglutide (HR 0.79, 95% CI [0.57, 1.11]; $P < .001$) but did not show superiority ($P = .17$).[15]

3 | CONCLUSIONS

GLP-1RAs have shown efficacy in HbA1c, body weight reduction, and have established CV safety; some have even shown a CV benefit (liraglutide, albiglutide and dulaglutide). The 2020 American Diabetes Association standards of medical care in diabetes note that there are four FDA-approved GLP-1RAs (liraglutide, albiglutide, semaglutide and dulaglutide) that report statistically significant reductions in CV events.[34] As part of the recommended patient-centred approach to choosing pharmacotherapies in T2D, CV co-morbidities should be considered.[35] Among patients with T2D and established CVD or at high risk, GLP-1RAs with a label indication are now recommended as part of the glucose-lowering regimen independent of HbA1c and in consideration of patient-specific factors.[35] In 2017, liraglutide became the first GLP-1RA in the United States with a label indication to reduce the risk of MACE in adults with T2D who have established CVD,[36] followed by injectable semaglutide in 2020.[37] In 2020, dulaglutide became the first agent in the United States with a label indication to reduce the risk of MACE in adults with T2D who have established CVD or multiple CV risk factors.[33] Meta-analysis results included here and those reported by others for GLP-1RA CVOTs suggest that MACE reduction with GLP-1RA treatment may be greater in patients with established CVD compared with those without established CVD; yet heterogeneity of the effect of GLP-1RAs on MACE has not been shown between patients with and without prior CVD.[24,38] Furthermore, dulaglutide reduced the risk of MACE in a trial where nearly twice as many patients had only CV risk factors than those with prior CVD.

The lack of consistency in trial design and outcomes has complicated comparisons between the CVOTs of GLP-1RAs. Individual GLP-1RA CVOTs have not yielded uniform outcomes, even among those with some similar design attributes. For example, definitions of established CVD in LEADER, SUSTAIN-6 and PIONEER 6 were comparable, and in contrast to the other GLP-1RA CVOTs. The baseline characteristics in these trials reflect similar proportions of patients with established CVD. Of these three trials, only LEADER prespecified a test for and showed superiority to placebo in reducing the incidence of MACE.[10] Based upon the primary outcomes, the results of SUSTAIN-6 and PIONEER 6 are both suggestive of a CV benefit; however, SUSTAIN-6 did not prespecify superiority testing and superiority was not achieved in PIONEER 6.[11,15] A post hoc analysis of the pooled data for SUSTAIN-6 and PIONEER 6 showed superiority for semaglutide over placebo for reduction in the incidence of MACE,[39] however, only injectable semaglutide was approved in the United States for the new label indication. As noted above, regulatory bodies do not give the same consideration to non-prespecified and post hoc findings of superiority as is given to prespecified findings of superiority. These caveats may reflect the trials' primary intent of ruling out excess CV risk compared with placebo, as a larger CVOT is currently enrolling patients with T2D to test for a benefit of oral semaglutide on CVD (SOUL; NCT03914326).

Two trials exclusively studied patients with CVD, ELIXA and Harmony, with the latter exhibiting a CV benefit.[9,13] The CV inclusion criteria for ELIXA were narrow, requiring all patients to have had an ACS event (STEMI, non-ST-elevation myocardial infarction [NSTEMI] or unstable angina) within 180 days before screening,[9] thus these very high risk patients may have limited their modification risk potential and stifled CV benefit potential with lixisenatide treatment. The time-to-event analysis in ELIXA was the first occurrence of MACE-4.[9] By contrast, Harmony's criteria for established CVD were much broader and tested the effect of albiglutide on the first occurrence of MACE-3.[13] Of the trials that did not limit randomization to patients with established CVD (LEADER, SUSTAIN-6, EXSCEL, REWIND and PIONEER 6), EXSCEL was the only trial not to define inclusion criteria for CV risk factors and it had the lowest age criteria for inclusion (≥18 years).[29]

Regarding statistical considerations, EXSCEL and REWIND were unique to all other GLP-1RA CVOTs. In EXSCEL, non-inferiority and superiority testing were co-primary objectives. EXSCEL was well powered to test for superiority and designed to make adjustments to the two-sided alpha significance level to account for two planned interim analyses. Hierarchical testing was prespecified for the primary composite outcome as well as for some secondary outcomes. REWIND was the only trial with superiority testing as the sole primary objective. Testing for non-inferiority in REWIND was to be performed in the event dulaglutide failed to show superiority to placebo. Testing of superiority and non-inferiority could be performed in any order as REWIND used the same population (all randomized patients) for both tests.

REWIND was designed to test the ability of dulaglutide to reduce the incidence of MACE-3 in patients who were comparatively more reflective of the general population of people with T2D in the United States as defined in prior reports.[14,18] In order to evaluate the generalizability of GLP-1RAs in the CVOTs, Boye et al.[18] published an article in 2019 including patients enrolled or eligible for inclusion in four CVOTs (LEADER, SUSTAIN-6, EXSCEL and REWIND) and found that none of the enrolled populations in any of these trials perfectly matched the reference population in key baseline characteristics. The EXSCEL population most closely matched in terms of both mean age (62.7 vs. 60.5 years) and

those with an eGFR of less than 60 mL/min/1.72m^2 (18.6% vs. 17.3%), while REWIND most closely matched in regard to HbA1c, sex distribution and proportion with a prior MI.[18] The study also estimated the proportions of individuals in the reference population that may have been enrolled in each GLP-1RA CVOT, based upon meeting the trial inclusion and exclusion criteria.[18] Based on inclusion and exclusion criteria, 42.6% of the reference population were eligible for enrolment in REWIND, 15.9% in EXSCEL, 13.0% in SUSTAIN-6 and 12.9% in LEADER.[18] The design of REWIND led to a mean baseline HbA1c of 7.3% (56 mmol/mol) and only 31.5% of patients had established CVD.[14]

Despite the lack of uniformity in trial design, the beneficial effects of some GLP-1RAs on CV outcomes have been achieved without a significant increase in the risk of severe hypoglycaemia, pancreatic adverse effects or thyroid cancer.[25] The results of completed GLP-1RA CVOTs have helped to inform decisions regarding treatment recommendations for patients with T2D and established CVD. Studies on the effectiveness and safety of GLP-1RAs in real-world settings are necessary to fully understand the CV impact of these agents. As more effectiveness and safety studies are reported for GLP-1RAs, better insight regarding the sustained CV benefits of these agents will be gained.

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CONFLICT OF INTEREST

KMP and KM do not declare any interests. CMH is a former employee of Eli Lilly and Company. CMA, OJV, JMM and MK are employees of Eli Lilly and own stock in the company.

AUTHOR CONTRIBUTIONS

All the named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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REFERENCES

1. American Heart Association. Cardiovascular Disease and Diabetes. https://www.heart.org/en/health-topics/diabetes/why-diabetes-matters/cardiovascular-disease–diabetes. Accessed August 16, 2019.
2. Juutilainen A, Kortelainen S, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. *Diabetes Care*. 2004;27(12):2898-2904.
3. Iglay K, Hannachi H, Joseph Howie P, et al. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. *Curr Med Res Opin*. 2016;32(7):1243-1252.
4. American Diabetes Association. *Statistics about Diabetes*. http://www.diabetes.org/diabetes-basics/statistics/. Accessed August 28, 2019.
5. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41(5):917-928.
6. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
7. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-2471.
8. US Food and Drug Administration. *Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*; 2008.
9. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373(23):2247-2257.
10. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322.
11. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
12. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly Exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377(13):1228-1239.
13. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519-1529.
14. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130.
15. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841-851.
16. A study to evaluate cardiovascular outcomes in patients with type 2 diabetes treated with ITCA 650. https://clinicaltrials.gov/ct2/show/results/NCT01455896. Accessed July 7, 2020.
17. Caruso I, Cignarelli A, Giorgino F. Heterogeneity and similarities in GLP-1 receptor agonist cardiovascular outcomes trials. *Trends Endocrinol Metab*. 2019;30(9):578-589.
18. Boye KS, Riddle MC, Gerstein HC, et al. Generalizability of glucagon-like peptide-1 receptor agonist cardiovascular outcome trials to the overall type 2 diabetes population in the United States. *Diabetes Obes Metab*. 2019;21(6):1299-1304.
19. Sciannameo V, Berchialla P, Orsi E, et al. Enrolment criteria for diabetes cardiovascular outcome trials do not inform on generalizability to clinical practice: the case of glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab*. 2020;22(5):817-827.
20. Bajaj HS, Al-Jabri B, Verma S. Glucagon-like peptide-1 receptor agonists and cardiovascular protection in type 2 diabetes: a pathophysiology-based review of clinical implications. *Curr Opin Cardiol*. 2018;33(6):665-675.
21. Li Y, Rosenblit PD. Glucagon-like Peptide-1 receptor agonists and cardiovascular risk reduction in type 2 diabetes mellitus: is it a class effect? *Curr Cardiol Rep*. 2018;20(11):113.
22. Giorgino F, Caruso I, Moellmann J, Lehrke M. Differential indication for SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with established atherosclerotic heart disease or at risk for congestive heart failure. *Metabolism*. 2020;104:154045.
23. North EJ, Newman JD. Review of cardiovascular outcomes trials of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Curr Opin Cardiol*. 2019;34(6):687-692.
24. Giugliano D, Maiorino MI, Bellastella G, Longo M, Chiodini P, Esposito K. GLP-1 receptor agonists for prevention of cardiorenal outcomes in type 2 diabetes: an updated meta-analysis including the REWIND and PIONEER 6 trials. *Diabetes Obes Metab*. 2019;21(11):2576-2580.

25. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7:776-785.
26. Bain SC, Mosenzon O, Arechavaleta R, et al. Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: rationale, design and patient baseline characteristics for the PIONEER 6 trial. *Diabetes Obes Metab*. 2019;21(3):499-508.
27. Gerstein HC, Colhoun HM, Dagenais GR, et al. Design and baseline characteristics of participants in the researching cardiovascular events with a weekly incretin in diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. *Diabetes Obes Metab*. 2018;20(1):42-49.
28. Green JB, Hernandez AF, D'Agostino RB, et al. Harmony outcomes: a randomized, double-blind, placebo-controlled trial of the effect of albiglutide on major cardiovascular events in patients with type 2 diabetes mellitus-rationale, design, and baseline characteristics. *Am Heart J*. 2018;203:30-38.
29. Holman RR, Bethel MA, George J, et al. Rationale and design of the exenatide study of cardiovascular event lowering (EXSCEL) trial. *Am Heart J*. 2016;174:103-110.
30. Marso SP, Poulter NR, Nissen SE, et al. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J*. 2013;166(5):823-830.
31. Mentz RJ, Bethel MA, Gustavson S, et al. Baseline characteristics of patients enrolled in the exenatide study of cardiovascular event lowering (EXSCEL). *Am Heart J*. 2017;187:1-9.
32. Bentley-Lewis R, Aguilar D, Riddle MC, et al. Rationale, design, and baseline characteristics in evaluation of lixisenatide in acute coronary syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo. *Am Heart J*. 2015;169(5):631-638.
33. Trulicity US Prescribing Information. 2020. http://pi.lilly.com/us/trulicity-uspi.pdf. Accessed February 6, 2020.
34. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S111-S134.
35. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S98-S110.
36. Victoza Prescribing Information. 2019. https://www.novo-pi.com/victoza.pdf. Accessed March 31, 2020.
37. Ozempic Prescribing Information. 2020. https://www.novo-pi.com/ozempic.pdf. Accessed March 31, 2020.
38. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation*. 2019;139(17):2022-2031.
39. Husain M, Bain SC, Jeppesen OK, et al. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. *Diabetes Obes Metab*. 2020;22(3):442-451.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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