Review: Cardiovascular safety of liraglutide for the treatment of Type 2 diabetes

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Abstract

Introduction: Liraglutide is a GLP-1 RA that is an option for treatment of T2DM. Typical of all new glucose-lowering agents, its CV safety profile is of great interest.

Areas covered: This article outlines the efficacy of the GLP-1 RA liraglutide from RCTs, moving through the pivotal phase 3 LEAD trials, and subsequent meta-analyses to assess CV safety. This review describes evolution of regulatory requirements to obtain safety information through dedicated CVOTs.

Expert opinion: Since the FDA mandated that CV outcomes for new diabetes therapies should be assessed via a dedicated CVOT, opinion of their utility in T2DM evolved from cynicism through to enthusiasm. In LEADER, liraglutide became the second modern glucose-lowering agent to demonstrate significant CV benefit. CVOTs are now providing important answers, highlighting the CV benefits of modern glucose-lowering agents, but also raising several questions, notably whether the effects seen with liraglutide and empagliflozin are class-effects or are unique to these molecules. Furthermore it is unknown if these results in patients with high CV risk are applicable to all patients with T2DM, and should be

incorporated into new treatment guidelines. In our view it's prudent to suggest that CVOT findings cannot currently be extrapolated to the whole T2DM population.

Article highlights

- Liraglutide efficacy versus a wide range of comparator diabetes therapies was shown by the Phase 3 LEAD studies. A subsequent meta-analysis then showed there to be no increase in major adverse cardiovascular events caused by liraglutide.

- In 2008 the FDA and subsequently the EMA mandated that new therapies for diabetes should be assessed via CVOTs, leading to mixed results and interpretations.

- In the LEADER trial, liraglutide significantly reduced the risk of the primary composite CV outcome, and lowered the risk of death from CV causes and death from any cause, compared with placebo, both in addition to standard of care.

- LEADER, as with other completed CVOTs, has raised fundamental questions concerning interpretation of the results, such as are effects seen class-effects or unique to individual molecules? Furthermore do CVOT results apply to all patients with T2DM and should therefore lead to changes in the treatment guidelines?

- Current CVOT findings cannot be extrapolated to the whole T2DM population, although some national guidelines have already made recommendations based on evidence from CVOTs.

1. Introduction

The global prevalence of diabetes is approximately 8.8%, equating to around 415 million people with this chronic condition [1]. Type 2 diabetes mellitus (T2DM) accounts for at least 95% of cases and, driven by rising rates of obesity, the prevalence of T2DM is set to increase. If inadequately controlled, T2DM increases the risk of large vessel disease (myocardial infarction [MI], stroke and amputation) and small vessel complications (visual loss, renal disease and neuropathy).

In addition to lifestyle modification (diet and exercise), there are now several different classes of glucose-lowering pharmacotherapy - eight in Europe and ten in the United States. Despite this, achievement of adequate glycemic control remains a challenge owing to the progressive decline of pancreatic beta-cell function. This necessitates treatment intensification, with step-wise addition of therapy classes, ultimately leading to the use of insulin [2]. Many diabetes treatment guidelines recommend a patient-centered approach with the aim of achieving individualized hemoglobin A1c (HbA1c) targets while avoiding adverse effects, especially hypoglycemia and weight gain [3, 4].

2. Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is a hormone that increases insulin secretion and decreases glucagon production from pancreatic islets in a glucose-dependent manner; 'glucose dependent' means that these effects are only seen when glucose levels are elevated. GLP-1 receptor agonist drugs (GLP-1 RAs) produce the equivalent of a pharmacologic level of GLP-1. These drugs reduce hyperglycemia and weight by increasing insulin secretion and

decreasing glucagon secretion while they also delay gastric emptying and increase satiety. Currently, all of the GLP-1 RA agents are administered as a subcutaneous (SC) injection [5].

Although the rates of adverse effects differ between GLP-1 RAs, the most common side-effects within the class are gastrointestinal (nausea, vomiting, and diarrhea) along with injection-site reactions. There are currently six GLP-1 RAs available for use in Europe: in order of license approval, these are exenatide (as Byetta™) given twice daily, liraglutide administered once daily, exenatide (as Bydureon™) once weekly, lixisenatide once daily and most recently albiglutide and dulaglutide, both once weekly.

The GLP-1 RAs are attractive options for the treatment of T2DM because they effectively lower HbA1c and weight while having a low risk of hypoglycemia.

3. Liraglutide

Liraglutide is a GLP-1 analogue that has 97 % amino acid sequence homology to endogenous human GLP-1 (7–37) [6, 7, 8]. It has been designed by a single amino acid substitution of lysine with arginine at position 34 and the attachment of a C16 fatty acid chain to lysine at position 26. These changes allow liraglutide to self-associate, delaying absorption from the SC injection site, while providing protection from degradation by the ubiquitous dipeptidyl peptase-4 (DPP-4) enzyme and other endopeptidases. This allows liraglutide to have a much longer half-life than endogenous GLP-1 (around 13 hours versus 1–2 minutes) [7, 8].

Liraglutide activates the GLP-1 receptor, which in the pancreatic beta-cells, is a membrane bound cell-surface receptor coupled to adenyl cyclase by a stimulatory G-protein [8]. Activation of the receptor creates an increase in intracellular cyclic monophosphate and, as a consequence, a dose-dependent insulin release in patients with hyperglycemia. In concert

with this effect, liraglutide acts in a glucose-dependent manner to decrease inappropriately high glucagon secretion (typically present in T2DM), thereby reducing hepatic glucose production. [7, 8, 9]. In addition to these direct gluco-regulatory effects, liraglutide increases satiety, probably by a central nervous mechanism, and delays gastric emptying, albeit it to a lesser extent than is seen with shorter-acting GLP-1 RAs (such as lixisenatide). The consequent reduction in hunger and lower energy intake lead to a fall in bodyweight and contribute to the beneficial effects of liraglutide in patients with T2DM [10, 11].

The Liraglutide Effect and Action in Diabetes (LEAD™) trial program was a pre-registration series of studies of liraglutide in patients with T2DM. It consisted of six randomized, controlled, parallel-group trials investigating the drug across the spectrum of T2DM: as monotherapy [12], in combination with a sulfonylurea (SU) [13], in combination with metformin [14], as a triple combination with a thiazolidinedione and metformin [15], as a triple combination with an SU and metformin versus insulin glargine [16] and as a combination with metformin and/or SU in a head-to-head comparison with exenatide [17]. Another head-to-head trial, performed after the LEAD program, investigated liraglutide versus sitagliptin, both in combination with metformin [18]. These studies were designed to cover the continuum of T2DM with a primary efficacy endpoint of change in HbA1c: other glycemic endpoints included attainment of HbA1c targets; changes in fasting plasma glucose; and plasma glucose profiles. Body weight and surrogate cardiovascular endpoints such as blood pressure and lipid profiles were also measured. Safety endpoints included hypoglycemia, pancreatitis, liraglutide antibodies and hematological and biochemical tests such calcitonin (due to the elevated risk of C-cell malignancy reported in rodent animal models [19]).

Overall the LEAD program showed that liraglutide lowered HbA1c to the same degree or a greater extent than other antidiabetic drugs. It also induced weight loss and improved β-cell function, blood pressure and some cardiovascular risk markers. Liraglutide was well tolerated with the most frequently reported adverse effect being transient nausea. A thorough corrected QT study also showed that steady-state concentrations of liraglutide did not produce prolongation of the corrected QT interval on ECG, a known risk factor for cardiovascular (CV) events [20]. In further support of the LEAD program, a number of retrospective and observational studies have also shown that liraglutide reduces major cardiovascular disease (CVD) risk factors in real-world settings [21, 22].

4. Cardiovascular outcome trials

CVD is the leading cause of mortality and adverse outcomes in patients with T2DM. More than 60% of patients die from CVD while an even greater proportion suffer serious CV-associated co-morbidities [23]. T2DM imparts a two-to-fourfold increase in the risk of coronary heart disease and life expectancy is reduced by 6-7 years for those aged 40 years and over [23, 24]. Despite this consistent correlation with negative outcomes, it has been difficult to establish that tight glycemic control reduces CV events [25, 26, 27, 28]. Indeed, the CV safety of glucose-lowering drugs was not routinely investigated until the 2008 United States (US) Food and Drug Administration (FDA) [29] declaration that all new therapies for diabetes should undergo a rigorous assessment of safety through large-scale cardiovascular outcome trials (CVOTs). This advice was subsequently reinforced by the European Medicines Agency (EMA) [30].

The FDA recommendations followed on from a meta-analysis which suggested that the thiazolidinedione rosiglitazone increased the risk of MI and heart failure (HF) in patients with

T2DM [31, 32]. Despite a subsequent trial [33, 34] showing only an excess risk for HF without any definitive results on MI, rosiglitazone's license was withdrawn in Europe and severely restricted in the US. The requirements for CVOTs that were produced in the 2008 FDA guideline included the following [29, 35]:

- A prospective independent adjudication of CV events in Phase 2 and 3 studies, so as to allow for a meta-analysis of CV events in all placebo-controlled, add-on (drug vs. placebo, plus standard therapy) and active-controlled trials.

- If the meta-analysis of Phase 2 and 3 trials demonstrates an upper bound of the 95% confidence interval for the risk of major adverse cardiac events (MACE) of below 1.8 but above 1.3, compared with placebo, then a single, large, CVOT should be conducted on high-risk populations, including those with advanced disease, elderly and those with renal impairment, and lasting for at least two years.

- CV events were to include CV mortality, MI and stroke, and possibly hospitalization for acute coronary syndromes, urgent revascularization and other end-points

- In order to exclude unacceptable CV risk, a two-sided 95 % confidence interval (CI) upper boundary of 1.8 risk ratio (pre-approval) and/or 1.3 risk ratio (post-approval) for MACE versus control group was required.

Because the results of previous trials evaluating glucose-lowering therapies could not exclude a CV benefit from tight glycemic control, the CVOTs which have followed on from the FDA regulation have focused on maintaining 'glycemic equipoise'. This means that investigators should attempt to produce equivalent lowering of HbA1c in both the active and placebo cohorts, so that the CV effect of the drug itself can be examined. This is achieved by allowing add-on of additional glucose-lowering therapies in the placebo arm [36]. There was also a

presumption that other CV risk factors, such as blood pressure and low-density lipoprotein cholesterol would be appropriately managed - so-called 'standard of care'.

Following on from these statutory requirements, the CV safety of liraglutide has been assessed by both meta-analyses of CV events in Phase 2 and 3 studies and a post-approval CVOT, known as LEADER (Liraglutide effect and action in diabetes: Evaluation of Cardiovascular Outcome Results)

5. Liraglutide Phase 2/3 cardiovascular meta-analysis

The objective of this analysis was to identify and report rates of MACE among patients randomized to liraglutide versus comparator using data from the liraglutide T2DM clinical development program [37]. All patient-level CV safety data from the completed Phase 2 and 3 randomized trials of liraglutide, plus open-label extensions were pooled. Since an assessment of MACE had not been pre-specified, a systematic approach was adopted to identify CV events **(Table 1)**.

Table 1: Systematic approach for identifying CV events

	Systematic approach for identifying CV events
1	Possible events were identified through queries of the study database using a classification system for adverse event and safety assessment: • Three standardized MedDRA searches – *broad*, *narrow*, and *custom* – were performed using the categories of 'myocardial infarction', 'central nervous system hemorrhage and cerebrovascular accidents', and 'cardiovascular death.' • For MI and stroke, the *broad* query resulted in 28 and 125 terms; *narrow* included 10 and 95; and *custom* included six and 30 respectively. It is of note that all of these data had been requested by the FDA prior to their final regulatory review of liraglutide in 2009 [37]
2	All MACE identified in the MedDRA query were classified as serious or non-serious adverse events, according to the view of site investigators
3	All candidate serious MACE were adjudicated *post hoc* by two investigators who were blinded to treatment. MI and stroke were pre-specified as 'definite', 'probable', 'unlikely', 'definitely not', or 'unknown'

MedDRA - Medical Dictionary for Regulatory Activities - terms)[38]

Table 2: characteristics of patients included in the meta-analysis

Number of studies included	15
Number of subjects	6,638 (4,257 exposed to liraglutide)
Age of subjects (years)	55±11
Baseline HbA$_{1c}$ (%)	8.4±1.0
Males: Females (%)	53:47
Duration of diabetes (years)	7±6
Total drug exposure (years)	2,882 (liraglutide) / 1,486 (comparators)
Patients with CVD (%)	25%
Patients on: monotherapy (%)	32.6%
combination therapy (%)	60.6%

Characteristics of patients included in this meta-analysis are shown in Table 2. Using the MedDRA broad, narrow, and custom criteria respectively, 114, 59, and 38 patients with MACE were initially identified. The overall incidence rate of adjudicated MACE associated with the broad MedDRA query was 0.9%. For each MedDRA search, the incidence ratio for adjudicated MACE associated with liraglutide was <1.0 and the upper 95% CI was <1.8; these both fell within the cardiovascular safety limits predefined by the US FDA for diabetes therapies under current investigation [29].

There were clearly issues that limited any definitive conclusions from this study and these were acknowledged by the authors. Low statistical power, enrolment of low-risk CV patients, and lack of pre-specified CV endpoints with independent adjudication in the drug development program were listed. In addition, there was heterogeneity in the use of comparator therapies, ranging from placebo to active comparators consisting of various oral and injectable anti-diabetic drugs. Although MACE were independently adjudicated by

blinded clinicians, it was also acknowledged that CV events may not have been identified by MedDRA search strategies.

In 2015, a further meta-analysis was performed, this time as part of the regulatory submission for liraglutide as a weight management (WM) agent, where it is recommended at a dose of 3.0 mg OD (versus the highest dose of 1.8mg OD for the treatment of T2DM) [40, 41]. The primary analysis included all available individuals from five randomized, controlled Phase 2 and 3 liraglutide WM trials (including data from an additional 120-day safety follow-up period). It examined the time from first date of drug administration to first occurrence of MACE for total liraglutide arms versus the total comparator arms. MACE were defined as CV death, non-fatal MI and non-fatal stroke (so-called 3-point MACE). MACE were prospectively adjudicated for three of the five WM trials with post-hoc adjudication conducted for the other two. Individuals who did not experience an event during the treatment period or within 30 days after last dose were censored at last treatment date plus 30 days. A further secondary analysis examined the time to first MACE for total liraglutide versus total comparator in the T2DM pool, which by then included additional studies. Data for this supportive analysis were provided from twenty-one randomized, controlled Phase 2 and 3 trials from the clinical development programs in T2DM where liraglutide was used in at least one treatment arm at doses of up to 1.8 mg OD.

Data from a total of 5,908 individuals across the liraglutide WM trials (liraglutide n=3,872; comparator n=2,036) and 8,259 individuals across T2DM trials (liraglutide n=5511; comparator n=2,748) were included in the analyses. In the primary analysis across WM trials the overall number of adjudicated MACE was low for both liraglutide and comparator, but numerically lower with liraglutide (total liraglutide: 10 events, frequency 0.2%, 0.2 events/ 100 patient-years of exposure [PYE]; liraglutide 3.0 mg: 7 events, 0.2%, 0.2 events/100 PYE) than with comparator (total comparator: 10 events, 0.5%, 0.4 events/100 PYE; placebo: 10

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events, 0.5%, 0.4 events/100 PYE). The hazard ratio (HR) for total liraglutide vs. total comparator (primary analysis) was 0.40 (95% confidence interval [CI]: 0.16; 1.01). In the secondary analysis of T2DM trials, higher event rates were observed compared with the analysis of WM trials, but as in the earlier meta-analysis, these were numerically lower in the liraglutide-treated cohort; total liraglutide: 26 events, 0.5%, 0.6 events/100 PYE vs. total comparator: 23 events, 0.8%, 1.3 events/100 PYE. HR was 0.64 (95% CI: 0.35; 1.15).

The conclusions from this second meta-analysis was that there was no indication of an increased risk of MACE with liraglutide at doses of up to 3.0 mg once-daily for WM in individuals with overweight/obesity with or without T2DM. Furthermore, there was no indication of an increased risk of MACE in individuals with T2DM with liraglutide up to doses of 1.8 mg OD.

6. Liraglutide cardiovascular outcome trial

The large, post-approval CVOT for liraglutide, known as LEADER, was simultaneously presented and published in June 2016 [42]. A total of 9,340 patients with T2DM were randomized, with 4,668 patients assigned to receive liraglutide and 4,672 in the placebo arm. A total of 96.8% of the subjects completed a final visit, died, or had a primary outcome and the vital status of trial participants was known in 99.7% of cases, indicating an extremely well-conducted study. The median time of exposure to liraglutide was 3.5 years and the mean percentage of time that patients received the trial regimen was 84% for liraglutide and 83% for placebo. The median daily dose of liraglutide was 1.78 mg and this included periods during which subjects did not receive study medication. The demographic and clinical characteristics of the patients were similar in the two groups with the majority (81.3%) having established cardiovascular disease, and the remainder being above 60 years of age

with at least one additional risk factor for CVD. At baseline, the mean duration of diabetes was 12.8 years, and the mean HbA1c was 8.7%.

The primary outcome was the 3-point MACE, composed of CV death, non-fatal MI and non-fatal stroke and this occurred in fewer patients in the liraglutide group (608 of 4,668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR 0.87; 95% CI 0.78; 0.97; $p < 0.001$ for non-inferiority; $p = 0.01$ for superiority). Death from CV causes occurred less frequently in liraglutide patients (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (HR 0.78; 95% CI 0.66; 0.93; $p = 0.007$). Death from any cause was also reduced in the liraglutide group (381 patients [8.2%]) compared with placebo (447 [9.6%]) (HR 0.85; 95% CI 0.74; 0.97; $p = 0.02$). The frequencies of non-fatal MI and non-fatal stroke were lower in the liraglutide group than in the placebo group, but these differences were not significant. Several sensitivity analyses were performed and these showed a similar magnitude of difference between the trial arms.

In subgroup analyses, significant interactions were observed for an eGFR of 60 ml or more per minute per 1.73 m^2 versus an eGFR of less than 60 ml per minute per 1.73 m^2, with a benefit favoring the lower eGFR, and for the presence versus absence of established CVD at baseline, with benefit for those with CV disease at baseline. The pre-specified analysis of HbA1c at 36 months showed a mean difference of −0.40% (95% CI −0.45; −0.34) between the liraglutide group and the placebo group. The placebo group had significantly more additional hypoglycemic medication added in during the course of the study; notably there were more frequent treatment intensifications with both insulin and sulfonylureas (SUs).

Concerning CV risk factors, there were significant differences between the liraglutide group and the placebo group in the change from baseline to 36 months in the following variables: weight loss was 2.3 kg (95% CI, 2.5; 2.0) more in the liraglutide group, systolic blood

pressure was 1.2 mm Hg (95% CI, 1.9; 0.5) lower in the liraglutide group, and heart rate was 3.0 beats per minute (95% CI, 2.5; 3.4) higher in the liraglutide group.

To summarize, in the LEADER trial, subjects in the liraglutide group had a lower risk of the primary composite outcome — first occurrence of CV death, nonfatal MI, or nonfatal stroke in the time-to-event analysis — and lower risks of death from CV causes and death from any cause than did those in the placebo group. The number that would need to be treated to prevent one primary outcome event in 3 years was 66. There had previously been concern about the risk of hospitalization for heart failure with the DPP-4 inhibitors, another incretin class of anti-diabetic medication [43]. In LEADER, there were fewer hospitalizations for heart failure among patients in the liraglutide group than among those on placebo, although this did not reach statistical significance.

The CV benefits were observed on a background of generally acceptable levels of CV risk-factor management (blood pressure, lipids and antiplatelet therapy) at baseline and during the trial. There were fewer add-on therapies for diabetes medications, lipid-lowering medications, platelet-lowering therapies and blood pressure-lowering therapies, and diuretics in patients in the liraglutide group than in those in the placebo group. Subgroup analyses suggested a greater benefit of liraglutide in patients with an eGFR of less than 60 ml per minute per 1.73 m^2 and in patients with a history of CV disease.

The pattern of CV benefit seen in LEADER was different to that seen with the sodium–glucose co-transporter 2 inhibitor empagliflozin in the EMPA-REG OUTCOME study [44]. The time to benefit emerged earlier and the heterogeneity of the direction and magnitude of the effects on components of the (same) 3-point MACE in that trial contrasts with the consistency of the effect in LEADER. Although these differences may reflect patient

populations or chance, the authors suggested that the benefits in EMPA-REG OUTCOME may be explained by hemodynamic changes, whereas with liraglutide, the observed benefits may indicate modification of progression of atherosclerotic vascular disease [42][44].

The authors of the primary LEADER results publication noted that in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, the GLP-1–receptor agonist lixisenatide did not show any CV benefit in patients with T2DM and a recent acute coronary syndrome [45]. The reasons behind the different results obtained with these two GLP-1RAs (lixisenatide and liraglutide) are unclear, but may be explained by differences in trial design (such as the short duration), or inherent properties resulting from their different molecular structures (exendin based versus human GLP-1 based) and durability of action. There are also several trials investigating CV outcomes in high-risk cohorts with T2DM where a similar difference in HbA1c to the one seen in LEADER had no impact on CV events or death. These include studies of basal analogue insulin [46] thiazolidinediones [31, 47] and three DPP-4 inhibitors [48, 49, 50] (Table 3). The LEADER trial had greater statistical power than most previous studies and included patients with a much higher baseline HbA1c.

One possible reason for the positive outcome compared with other studies relates to hypoglycemia. Many patients in each group were treated with SUs or insulin at baseline, but fewer patients in the liraglutide group had insulin added during the trial. There was a 31% lower rate of severe hypoglycemia and a 20% lower rate of confirmed hypoglycemia (plasma glucose level <3.1 mmol/l) in the liraglutide group compared with the placebo group. Such a reduction in hypoglycemia for the active agent has not been observed in other CVOTs.

Of course the trial has limitations, as were acknowledged by the authors. For example, patients were followed for only 3.5 to 5.0 years and so the safety and efficacy data are restricted to that time period. Also, the trial recruited a population of patients who were at high risk for CV events and who had a high baseline HbA1c (of 8.7%), and so the outcomes may not be seen in T2DM patients at lower risk. Additionally, patients were treated with liraglutide 1.8 mg, and although it may be possible to extrapolate the CV safety finding to patients receiving the lower dose of 1.2 mg, given the precise mechanisms for the CV benefits are presently unknown, this may merit additional investigation.

Table 3: comparison of intervention, inclusion criteria and primary CV result from published CVOTs

Trial	Intervention*	N	Inclusion criteria†	P
ELIXA [45]	Lixisenatide	6,068	ACS within 180 days	(p (p
ORIGIN [46]	Insulin glargine	12,537	CV risk factors	
PROactive [47]	Pioglitazone	5,238	Established CVD	
RECORD [33]	Rosiglitazone	4,447	CV risk factors	
SAVOR-TIMI-53 [48]	Saxagliptin	16,492	Established CVD and/or multiple risk factors	(p < (p
EXAMINE [49]	Alogliptin	5,380	ACS within 15-90 days	(p <
TECOS [50]	Sitagliptin	14,671	Age >50 + established CVD	(p <
EMPA-REG [44]	Empagliflozin	7,028	History of CVD	(p (p
LEADER [42]	Liraglutide	9,340	Age >50 + CVD or chronic renal failure, or age >60 + CV risk factors	(p < (p

ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; *Versus placebo; †All CVOTs included patients who were required where patients could instead have pre-diabetes (impaired fasting glucose or impaired glucose tolerance); [a]CV death, Non-fatal MI, Non-fatal stroke from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; [c]a composite of any of these events, a revascularization procedure (c for heart failure; [d]all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endo or leg arteries, or amputation above the ankle; [e]cardiovascular hospitalization or cardiovascular death; [f]CV death, Non-fatal MI or Non-fatal stroke

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7. Conclusions

Liraglutide is now the second agent, and first in the GLP-1 RA class, to demonstrate a significant reduction in CV events in the setting of a modern CVOT. This reduction in the primary outcome of a 3-point MACE was largely driven by a significant fall in CV deaths, although the other two components (non-fatal MI and non-fatal stroke) showed a signal for benefit. The study outcome is also consistent with meta-analyses of Phase 2 and 3 clinical trial data, which included WM studies where the dose of liraglutide used is higher than that recommended for the management of T2DM. The time course for the reduction in CV endpoints is consistent with an effect on the atherogenic process although other effects including lower rates of hypoglycemia and differential additional of other hypoglycemic agents cannot be excluded.

8. Expert opinion

In 2008 the FDA mandated that all new glucose-lowering therapies should be shown not to increase the risk of cardiovascular (CV) events in patients with T2DM. The first four CVOTs conducted as a result of this direction (SAVOR TIMI 53, EXAMINE, TECOS and ELIXA) were positive, in that they showed no evidence of increased CV risk, which was the aim of the exercise. They did not reach the glycemic equipoise which was part of the trial protocol, but differences in HbA1c between the treatment arms were modest in each study (between 0.2 and 0.4%). However, they also showed no evidence of CV benefit and so were widely regarded as neutral or negative, especially by clinicians who were unfamiliar with the study designs. Indeed, some questioned the utility of the drugs being tested since they appeared to have little impact on glycemic control (versus 'placebo') and did not reduce the large vessel complications of T2DM.

It is of note that for the three gliptins (saxagliptin, alogliptin and sitagliptin) which now have published CVOT data, meta-analyses (Phase 2 and 3 data) each suggested a favorable effect on CV outcomes (albeit without statistical significance).These CV benefits were not seen with the definitive CVOTs. This led some experts to further query the design of CVOTs, suggesting that only safety could be demonstrated. This was particularly the case for lixisenatide, a short-acting GLP-1 receptor agonist where patients in the ELIXA trial had all experienced a recent acute coronary syndrome and were only followed for a median of 25 months. If lixisenatide has a beneficial CV effect, the likelihood of showing it in this setting was always going to be remote.

There were other downsides. The SAVOR-TIMI 53 trial showed that more patients in the saxagliptin group were hospitalized for heart failure and a similar trend was seen for alogliptin in the EXAMINE CVOT. This led to doubts about the major adverse CV events (MACE) end-points being used in the studies – could the exclusion of heart failure be justified – and subsequently an FDA safety warning for both drugs regarding heart failure risk.

So, 7 years after the FDA's CV safety mandate, there was a great deal of cynicism regarding CVOTs in T2DM. It appeared that putative benefits of new drugs could not be demonstrated with the existing trial formats, all of which were extremely expensive and time-consuming. It was also uncertain if every new drug in a class would need assessment if several others had already been shown to be safe.

It was on this background that the EMPA-REG OUTCOME study reported in 2015, completely turning the field on its head. In this study, a total of 7,020 patients were randomly

assigned to receive the sodium-glucose transporter 2 (SGLT-2) inhibitor empagliflozin or placebo for approximately 3 years. Empagliflozin significantly reduced the risk of the primary outcome (hazard ratio 0.86, 95% CI 0.74; 0.99), demonstrating not just non-inferiority (p < 0.001), but also superiority (p = 0.04) compared with placebo.

The result was largely driven by the significantly lower rate of death from cardiovascular causes in the empagliflozin group (38% relative risk reduction [RRR]) but beyond the primary endpoint and components, hospitalization for heart failure (35% RRR), and death from any cause (32% RRR) were also significantly reduced. It was of great interest that all of these beneficial effects were seen after only a few months of trial observation.

Liraglutide became the second glucose-lowering agent to demonstrate significant CV benefit following the publication of the LEADER study in 2016.The positive results from EMPA-REG OUTCOME and LEADER, highlight the CV benefits of modern glucose-lowering agents, but they also raise several interesting questions. Are the effects seen with liraglutide and empagliflozin likely to be class-effects or be unique to these molecules? The answer to this question remains to be seen but will be definitively answered by on-going trials (for example, the CANVAS and DECLARE studies for the other two currently licensed SGLT-2 inhibitors, canagliflozin and dapagliflozin). In the ELIXA trial lixisenatide was not seen to confer any CV benefit compared with placebo, but recent results with the GLP-1RA semaglutide have made a class-effect appear more likely [50]. Semaglutide is a GLP-1 receptor agonist with marked similarities to liraglutide but which has a longer half-life allowing for once-weekly administration. In the SUSTAIN 6 trial of 3,297 patients with T2DM and very similar CV co-morbidities to those enrolled in the LEADER study, the 3-point MACE occurred in 6.6% of patients in the semaglutide group and in 8.9% of patients in

the placebo group (HR 0.74; 95% CI 0.58; 0.95; p < 0.001 for non-inferiority). A post-hoc analysis confirmed superiority with a p-value of 0.02. Interestingly, the primary end-point was driven by a significant reduction in non-fatal stroke and a non-significant reduction in non-fatal MI, with similar rates of death from CV causes in the two groups. This differs from LEADER and may simply be the play-of-chance or be related to the duration of observation. It should be noted that the SUSTAIN 6 study was much smaller and shorter than LEADER since it was a pre-license study, with consequently less robust criteria for non-inferiority (a CI margin of 1.8 versus that for LEADER – 1.3). Of interest, in SUSTAIN 6, diabetic retinopathy complications occurred in 50 patients (3.0%) in the semaglutide group and 29 (1.8%) in the placebo group (HR 1.76; 95% CI, 1.11; 2.78; p = 0.02). Although retinopathy event numbers were low, direct causation of this effect by semaglutide cannot be ruled out; however, the generalizability across the GLP-1 class is unclear. Though no such treatment effect was observed with liraglutide in LEADER, there was also no benefit observed in regards to retinopathy [42].

What seems certain is that the mechanisms underlying the positive outcomes seen in EMPA-REG OUTCOME and LEADER are different. The CV benefit seen with empagliflozin emerged very quickly, possibly implying a hemodynamic effect and being consistent with the dramatic fall in hospitalization due to heart failure. The effect of liraglutide was much more gradual which may point to a slowing of the atherogenic process [52]. There was also a signal for increased stroke seen with empagliflozin whereas all components of the primary end-point in LEADER moved in the same beneficial direction, again emphasizing the potential differences between the drug effects. Whether the co-administration of a GLP-1 receptor agonist and a SGLT-2 inhibitor would produce complimentary CV benefits is unknown although a positive impact on HbA1c and weight has recently been demonstrated [53].

It is also unclear as to what contribution the use of alternate glucose-lowering therapies in the placebo arm of LEADER may have made to the primary end-point reduction. The baseline HbA1c in LEADER was 8.7% at which point over 40% of patients were taking insulin and 50% were prescribed sulfonylureas (SUs). The standard-of-care target during study was an HbA1c <7.0% and since other incretin drugs were not permitted (and SGLT-2 inhibitors had not been licensed), significantly more insulin and SU were prescribed for the placebo group. There remains the possibility that these agents increase CV risk and so some of the beneficial effect of liraglutide could be due to lower use of insulin and SUs. Their use could also account for the higher rates of hypoglycemia seen in the placebo group and this could, in turn, lead to an increased CV event rate. To an extent, this is an academic argument since if one accepts that an HbA1c of 8.7% is unacceptable for patients with T2DM at high CV risk, then reducing it with liraglutide rather than conventional drug classes appears to be a rational choice.

A final question is whether these results apply to all patients with T2DM and hence should lead to changes in the treatment guidelines. The inclusion criteria for LEADER had both high and low CV risk categories. 'High risk' was defined as age > 50 years and a history of a previous CV event while 'low risk' patients were older (> 60 years) with a risk factor for CV disease, such as microalbuminuria. The study investigators anticipated that a majority of trial subjects would be in the 'low risk' category but it emerged that 81.3% were high risk at baseline. This is a very similar proportion to that seen in SUSTAIN 6 (83%) while all patients in the EMPA-REG OUTCOME study had established CV disease. In the subgroup analysis of LEADER, the benefit from liraglutide was only seen in the 'high risk' cohort (and there was a similar heterogeneity for low eGFR (which in patients with T2DM is essentially a marker of high CV risk). So, currently the CVOT findings cannot be extrapolated to the

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whole T2DM population, although some national guidelines (e.g. Canada [54]) have already recommended that established CV disease should lead to earlier consideration of those agents shown to provide CV risk reduction.

9. Acknowledgements

10. Disclosures

10. References

1. Diabetes Atlas 7th edition. Brussels, Belgium: International Diabetes Federation, 2015. Available at: http://www.idf.org/diabetesatlas

2. Type 2 diabetes in adults: management. London, UK: National Institute of Health and Care Excellence, 2015. NG28 https://www.nice.org.uk/guidance/ng28

3. Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1577–96

4. Garber A, Abrahamson M, Barzilay J, et al. AACE comprehensive diabetes management algorithm 2013. Endocrine Pract 2013;19: 327–36

5. Seino Y & Yabe D. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: incretin actions beyond the pancreas. J Diabetes Investig 2013;4:108–130.

6. Perry CM. Liraglutide: a review of its use in the management of type 2 diabetes mellitus. Drugs 2011;71:2347–73

7. Croom KF, McCormack PL. Liraglutide: a review of its use in type 2 diabetes mellitus. Drugs. 2009;69:1985–2004

8. Novo Nordisk A/S. Victoza liraglutide (rDNA origin) injection: US prescribing information. 2013. http://www.novo-pi.com/victoza.pdf

9. Armstrong M, Hull D, Guo K, et al. Effect of liraglutide on adipose insulin resistance and hepatic de-novo lipogenesis in non-alcoholic steatohepatitis: substudy of a phase 2, randomised placebo-controlled trial. The Lancet 2014 383: S21.

10. Flint A, Kapitza C, Zdravkovic M. The once-daily human GLP-1 analogue liraglutide impacts appetite and energy intake in patients with type 2 diabetes after short-term treatment. Diabetes Obes Metab 2013;15:958–62

11. Horowitz M, Flint A, Jones KL, et al. Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes. Diabetes Res Clin Pract 2012;97:258–66

12. Garber A, Henry R, Ratner R et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): randomized, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473–81

13. Marre M, Shaw J, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diabet Med 2009;26:268–78

14. Nauck M, Frid A, Hermansen K, et al., Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin in type 2 diabetes Care 2009;32: 84–90

15. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met + TZD). Diabetes Care. 2009;32: 1224–30

16. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial Diabetologia 2009;52:2046–55

17. Buse J, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6) Lancet 2009;374:39–47

18. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type

2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomized, parallel-group, open-label trial Lancet 2010;375:1447–56

19. Knudsen LB, Madsen L, Jacobsen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent, but not human, thyroid C-cells causing calcitonin release and proliferation. Endocrinology 151.4 (2010): 1473-1486.

20. Chatterjee DJ, Khutooryansky N, Zdravkovic M, et al. Absence of QTc prolongation in a thorough QT study with subcutaneous liraglutide, a once-daily GLP-1 analog for treatment of type 2 diabetes. J Clin Pharmacol. 2009;49:1353–62

21. Russo GT, Labate AM, Giandalia A, et al. Twelve-month treatment with Liraglutide ameliorates Visceral Adiposity Index and common cardiovascular risk factors in type 2 diabetes outpatients. J Endocrinol Invest. 2015;38:81–9.

22. Gautier JF, Martinez L, Penfornis A, et al. Effectiveness and persistence with liraglutide among patients with type 2 diabetes in routine clinical practice—EVIDENCE: A prospective, 2-year follow-up, observational, post-marketing study. Adv Ther. 2015;32:838 –53.

23. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and

Prevention 201.1 (2011) https://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

24. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, et al. Diabetes mellitus, fasting glucose, and risk of cause specific death. N Engl J Med. 2011;364:829–41

25. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus — mechanisms, management, and clinical considerations. Circulation. 2016;133:2459–502

26. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J. 2015;36:2288–96

27. Scheen AJ, Charbonnel B. Effects of glucose-lowering agents on vascular outcomes in type 2 diabetes: a critical reappraisal. Diabetes Metab. 2014;40:176–85

28. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet. 2014;383:2008–17

29. Guidance for industry diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. US Department of Health and Human Services,

Washington, DC: FDA/Center for Drug Evaluation, 2008. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

*This document outlines FDA recommendations for the design and conduct of cardiovascular outcome trials in type 2 diabetes.

30. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. European Medicines Agency, London, UK, 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf

31. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457–71

*This meta-analysis lead to the FDA guidance produced in 2008 and the withdrawal of rosiglitazone from the European market in 2010.

32. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010;170:1191–201

33. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. Lancet. 2009;373:2125–35

34. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013;166:240–9

35. Hirshberg B, Raz I. Impact of the US Food and Drug Administration cardiovascular assessment requirements on the development of novel antidiabetes drugs. Diabetes Care. 2011;34(Suppl 2):S101–6

36. Hirshberg B, Katz A. Insights from cardiovascular outcome trials with novel antidiabetes agents: what have we learned? An industry perspective. Curr Diab Rep. 2015;15:87

37. Marso SP, Lindsey JB, Stolker JM, et al. Cardiovascular safety of liraglutide assessed in a patient-level pooled analysis of phase 2: 3 liraglutide clinical development studies. Diab Vasc Dis Res. 2011;8:237-40

38. Medical dictionary for regulatory activities maintenance and support services organization (MedDRA MSSO) Available at: http://www.meddramsso.com/

39. Liraglutide (injection) for the treatment of patients with type 2 diabetes briefing document. United States Food and Drug Administration, Washington USA, 2009 NDA 22-341. Available at:

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/En docrinologicandMetabolicDrugsAdvisoryCommittee/UCM148659.pdf

40. FDA Briefing Document NDA 206321 Liraglutide injection, 3mg. Endocrinologic and Metabolic Drugs Advisory Committee Meeting, FDA, Washington, USA, 2014. Available at:

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/En docrinologicandMetabolicDrugsAdvisoryCommittee/UCM413317.pdf

41. Bain SC, Caterson ID, Gross JL, et al. Cardiovascular safety of liraglutide: meta-analysis of major adverse cardiovascular events across weight management and T2D development programmes. Diabetologia 2015;58(Suppl 1):S573 abstract 1193

42. Marso SP, Daniels GH, Brown-Frandsen K et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22

**The seminal study on the cardiovascular safety of liraglutide.

43. McGuire DK, Van de Werf F, Armstrong PW, et al. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus. JAMA Cardiol 2016;2:126–35

44. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and

mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28

**A landmark study – the first of the modern cardiovascular outcome trials to show superiority of the agent being assessed (empagliflozin)

45. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–57

46. The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–28

47. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet 2005;366:1279–89

48. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–26

49. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35

50. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–42

51. Marso SP, Bain SC, Consoli A et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–44
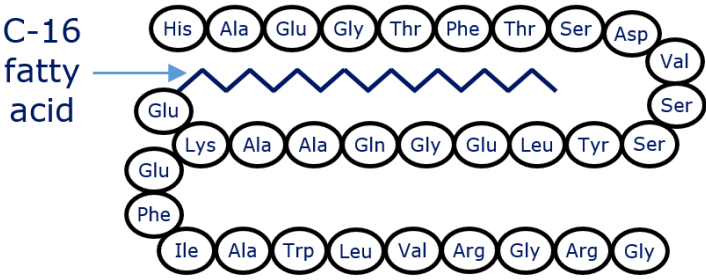
**The second cardiovascular outcome trial demonstrating superiority for a GLP-1 receptor agonist.

52. Hirano T and Mori Y. Anti-atherogenic and anti-inflammatory properties of glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and dipeptidyl peptidase-4 inhibitors in experimental animals. J Diabetes Investig 2016; 7 (Suppl 1):80–6

53. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomized controlled trial. Lancet Diabetes Endocrinol. 2016;4:1004–16

54. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update. Can J Diabetes. 2016 Dec;40(6):484-486

Drug summary box

Drug name	Liraglutide
Phase	IV
Indication	Treatment of adults with type 2 diabetes mellitus to achieve glycemic control
Mechanism of action	Glucagon-like peptide-1 receptor agonist
Route of administration	Subcutaneous
Chemical structure	$C_{172}H_{265}N_{43}O_{51}$
Pivotal trial(s)	[12, 13, 14, 15, 16, 17, 18, 42]