Review

Cardiovascular benefits of GLP-1 agonists in type 2 diabetes: a comparative review

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Abstract

Type 2 diabetes (T2D) carries risks of both cardiovascular (CV) (myocardial infarction, stroke, peripheral vascular disease) and microvascular (retinopathy/ nephropathy/ neuropathy) complications. Glucose-lowering is an effective strategy for preventing microvascular complications, but the extent to which it can reduce CV complications is less certain. Glucagon-like peptide-1 (GLP-1) agonists are potent glucose-lowering agents but also have potentially beneficial effects on other traditional (body weight, BP, LDL cholesterol) and non-traditional risk factors (low grade inflammation, endothelial dysfunction). The results of four large CV outcome trials (CVOTs) with GLP-1 agonists are now available. These have compared lixisenatide (ELIXA), liraglutide (LEADER), semaglutide (SUSTAIN-6), and long-acting exenatide (EXSCEL) with placebo and standard of care over 2-4 years; four others (including with dulaglutide and albiglutide) are ongoing. LEADER and SUSTAIN-6 have demonstrated reductions in rates of major adverse CV events (MACE) with active GLP-1 treatment but ELIXA and EXCSEL have not. In this review we discuss the mechanisms by which GLP-1 receptor agonists act on the CV system and the design and conduct of these trials. Contrary to the assertions that (a) all GLP-1 agonists reduce CV disease in T2D but to different extents, or (b) the magnitude of CV protection is predominantly related to glucose-lowering, we argue that CV benefit is specific to agents that provide longer acting agonism at the GLP-1 receptor. The mechanisms involve reduction in body weight and BP, and lowering of LDL-cholesterol and glucose, but pleiotropic effects – including suppression of low grade inflammation, vasodilation and natriuresis - are also likely relevant.

(250 words)

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Abbreviations

BP	blood pressure
CV	Cardiovascular
CVOT	Cardiovascular Outcome Trial
ELIXA	The Evaluation of Lixisenatide in Acute Coronary Syndrome
GLP-1	Glucagon Like Peptide 1
HR	Hazard ratio
LEADER	The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	Major Adverse Cardiovascular Events
SUSTAIN-6	Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
EXSCEL	Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes
REWIND	Researching Cardiovascular Events With a Weekly Incretin in Diabetes
T2D	Type 2 Diabetes

Introduction

People with Type 2 Diabetes Mellitus (T2D) have a much higher risk of premature CV (CV) disease compared with those without T2D and a poorer prognosis following an adverse CV event [1,2]. Contemporary data indicate that life expectancy is still reduced by 3-4 years and that CV disease is responsible for more than 80% of deaths in those aged 65 years and older [3,4]. The importance of the management of BP and other vascular risk factors in T2D has been recognised for over two decades, particularly since the publication of the UK Prospective Diabetes Study (UKPDS) in 1998 [5,6]. In the USA and other developed countries, CV morbidity attributable to T2D is falling, but is offset by a doubling in incidence and a tripling in prevalence of the condition (driven in part by greater longevity) [7].

Advances in the management of risk factors (dyslipidaemia and BP) and clinical care (acute metabolic care, revascularisation) have resulted in considerable success in reducing cardiovascular and other complications associated with T2D [7]. The impact of a glucose-lowering strategy using traditional agents (sulphonylureas, insulin) has been less clear [8,9]. However, more recently, the response of international regulatory systems to a meta-analysis suggesting adverse CV effects of the thiazolidinedione rosiglitazone [10] was a catalyst for change. Over the last eight years, pharmaceutical companies have been required to conduct large double-blind randomised placebo-controlled CV outcome trials (CVOTs) assessing the effects of newer agents, including glucagon-like peptide-1 (GLP-1) receptor agonists, on rates of Major Adverse Cardiovascular events (MACE) [defined as time to either CV death, non-fatal myocardial infarction or non-fatal stroke][11].

Glucose lowering with GLP-1 receptor agonists is associated with weight loss, systolic BP reduction, favourable changes in lipid profile and a low risk of hypoglycaemia [11]. Such properties make CV benefit with GLP-1 receptor agonists biologically plausible. Six GLP-1 receptor agonists for subcutaneous injection have been approved for the treatment of T2D (exenatide, liraglutide, lixisenatide, dulaglutide, albiglutide, and semaglutide) although the

number available fell to five in July 2018 when albiglutide was withdrawn by its manufacturer for commercial reasons [12]. A further agent, taspoglutide was halted in development in 2010 due to injection-site reactions [13].

The original formulation of (twice daily) exenatide became available in 2008 before the introduction of the requirement to conduct CVOTs. Four large CV outcomes trials (CVOTs), including a total of 33,457 participants, have now evaluated the efficacy and safety of other GLP-1 receptor agonists to date: The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) [14], The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) [15], Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) [16] and Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXSCEL) [17]. All have demonstrated safety ("non-inferiority") of the GLP-1 agonist under investigation with respect to placebo and standard of care (hereinafter referred to as "placebo"). However, two have also revealed reduction in rates of CV events ("superiority"): LEADER and SUSTAIN-6; the reasons for differences in results between these CVOTs are discussed below.

A further four GLP-1 CVOTs await publication:

(1) FREEDOM-CVO: ITCA 650 is a 3-6 monthly implant that delivers subcutaneous exenatide continuously with favourable metabolic effects [18]. In May 2016 a press statement was released declaring that the FREEDOM-CVO trial (NCT01455896) in more than 4000 participants with T2D had met its primary safety endpoint by demonstrating non-inferiority for CV safety [19]. However, this has not yet been followed by a full publication.

(2) PIONEER-6: This is a CVOT with oral semaglutide (NCT02692716) that randomized 3176 participants with T2D and is due to complete follow-up later in 2018. Like SUSTAIN-6

- which studied the injectable form of the drug – it was designed to confirm safety (non-inferiority) in comparison with placebo for its primary MACE outcome [20].

(3) REWIND: The forthcoming Researching Cardiovascular Events With a Weekly Incretin in Diabetes (NCT01394952) trial with dulaglutide is due to report later in 2018 [21] and is discussed in more detail below.

(4) HARMONY-Outcomes: Although albiglutide was withdrawn from the market in July 2018, the HARMONY CVOT (NCT02465515) which randomized 9575 participants to albiglutide or placebo was continued to completion and is due to report its findings in Autumn 2018 [22]. It was designed to confirm safety (non-inferiority, primary outcome) and superiority (secondary outcome) in comparison with placebo for its primary MACE outcome.

Mechanisms by which GLP-1 agonists may impact CV outcomes are depicted in Figure 1.

It has been suggested that all GLP-1 agonists reduce CV disease in T2D but to different extents [23], or alternatively that the magnitude of CV protection they provide is predominantly related to glucose-lowering [24, 25]. In this review, we attempt to understand the differences in the outcomes of the trials to date in the context of their design and conduct as well as the pharmacological properties of the individual agents assessed.

Key trial characteristics

Key characteristics of each of the four CV outcome trials published to date are shown in Table 1.

1) ELIXA randomized 6068 participants with T2D at high risk of CV disease, all within 180 days of an acute coronary event (i.e. a secondary care population), to lixisenatide up to 20 mcg once daily or placebo [14]. The primary endpoint was an expanded MACE outcome (i.e. time to hospitalization for unstable angina in addition to the standard three MACE components listed above). The trial was designed to test initially for non-inferiority vs placebo, and subsequently to test for superiority. It was event-driven with a final median follow-up of 2.1 years.

2) LEADER randomised 9340 participants with T2D to liraglutide up to 1·8 mg once daily or placebo [15]. They were either aged ≥ 50 years with "prior CVD" [defined as concomitant CVD, cerebrovascular disease, peripheral vascular disease, chronic heart failure (NYHA class II or III), chronic kidney disease (stage 3 or higher)] or ≥ 60 years with "no prior CVD" and at least one CV risk factor. The power calculation anticipated 660 primary MACE events but the final number was 1302 due to: (i) a higher proportion of participants being recruited into the "prior CVD" group than anticipated (81%); (ii) a minimum follow-up period per participant of 3.5 years being pre-specified per protocol; and (iii) continuation of the trial as planned under the auspices of the Data and Safety Monitoring Board. This provided much greater statistical power than originally anticipated. Final median follow up was 3.8 years.

3) SUSTAIN 6 [16] was similar in many respects to LEADER, including entry criteria, but smaller as it was designed to demonstrate safety (non-inferiority) of semaglutide over placebo rather than superiority, which was not pre-specified. 3297 people with T2D were randomized to semaglutide (0·5 mg or 1·0 mg once per week) or placebo with a power calculation based on 122 primary MACE events occurring during follow-up. Final median follow up was 2.1 years.

4) EXSCEL was the largest GLP-1 CVOT to date [17]. It compared extended-release

exenatide with placebo in 14,752 patients with T2DM aged ≥60 years; 73% (vs. an intended 70%) had prior CVD. The design specified an initial assessment of the primary outcome for non-inferiority followed by a hierarchical test for superiority. The trial was stopped as planned after a median of 3.2 years when 1744 participants had experienced a confirmed primary outcome.

Risk factor reduction

In all four CVOTs, as the main comparison was between GLP-1 agonist and placebo, the intention was to treat all participants randomised (including those taking placebo injections), actively to target with lifestyle advice, non-incretin glucose-lowering agents (including insulin), BP-lowering drugs and statins throughout the trial period. If this aim had been realised, there would therefore have been no differences between the active and placebo groups in terms of HbA1c, body weight, or BP as site staff were blinded to treatment allocation. However, because of the powerful glucose-lowering effects and weight-reducing properties of GLP-1 agonists in the active group, and the weight gain-inducing properties of other agents (particularly sulphonylureas and insulin) used to try and achieve targets in the comparator group, differences in risk factors between the randomised groups occurred in all four trials.

Summary data for these differences in risk factor control during follow up for the individual trials are given in Table 1. It can be seen that differences between groups were most marked for HbA1c and body weight in SUSTAIN-6 with semaglutide, but these were also seen in LEADER with liragutide and with long-acting exenatide in EXSCEL. These largely reflect the differential efficacy of these individual agents at their marketed doses.

Main results (CV outcomes)

In ELIXA, the primary expanded MACE outcome occurred in 406 patients (13.4%) with lixisenatide compared with 399 (13.2%) with placebo [HR 1.02 (95% CI 0.89–1.17)] i.e. non-inferiority ($p < 0.001$) was demonstrated with no indication of superiority ($p = 0.81$) [14]. In contrast, in LEADER the primary composite outcome (myocardial infarction, stroke, or CV death) occurred less frequently with liraglutide (13.0%) when compared with the placebo (14.9%) [HR 0.87 (95% CI 0.78–0.97)] demonstrating not only non-inferiority ($p < 0.001$) but also superiority ($p = 0.01$) [15]. Deaths from CV causes were also reduced (4.7% with liraglutide vs 6.0% with placebo) [HR 0.78 (95% CI 0.66–0.93) as was all cause mortality. The number need to treat to prevent a MACE event was 53 over 3.8 years. In SUSTAIN-6 the primary MACE outcome occurred in 108 patients (6.6%) on semaglutide compared with 146 patients (8.9%) on placebo [HR 0.74 (95% CI 0.58–0.95); $p < 0.001$] [16]. The number needed to treat to prevent one CV death, non-fatal MI or non-fatal stroke was 45 for 2 years. In EXSCEL [17]**,** the primary MACE end point occurred in 839 patients (11.4%) in the extended release exenatide group and in 905 patients (12.2%) in the group receiving placebo [HR 0.91 (95% CI 0.83–1.00); $p<0.001$] confirming non-inferiority. The test for superiority for MACE indicated only a strong trend ($p = 0.06$) although a significant reduction in all-cause mortality was noted [HR 0.86 (95% CI 0.77–0.97); $p=0.016$)].

Other results (microvascular outcomes)

(i) Nephropathy: In LEADER, the rate of the pre-specified renal secondary composite outcome (new-onset macroalbuminuria, doubling of serum creatinine, end-stage renal

disease, or death due to renal disease) was reduced with liraglutide vs placebo [15% vs 19%; HR 0.78 (95% CI 0.67 to 0.92); p=0.0003). This was driven by progression to new-onset macroalbuminuria [9.0% versus 12.1%; HR 0.74 (95% CI 0.60 to 0.91); p=0.004] [26]. In SUSTAIN-6, the rate of a similar renal composite outcome (also pre-specified as a secondary endpoint) was also reduced over a shorter time course by semaglutide vs placebo: [3.8% versus 6.1%; HR 0.64 (95% CI 0.46-0.88); p=0.005] [16]. In ELIXA, the investigators did not consider a modest difference in a pre-specified comparison of percentage change of urinary albumin-to-creatinine ratio from baseline between groups (lixisenatide 24% vs. placebo 34%, p = 0.004) to be clinically significant as there was little change in absolute values and the difference was attenuated after adjustment for HbA1c (p=0.07) [14]. In EXSCEL, no renal outcomes were pre-specified but the rate of new-onset macroalbuminuria was lower with exenatide than with placebo (2.2% vs 2.8%) [17]; this difference is nominally statistically significant if compared without correction for multiple testing.

(ii) Retinopathy: Retinal outcomes were pre-specified in LEADER and SUSTAIN-6, but not in the other trials [15,16]. These were collected on the basis of local screening methods in place at study sites, rather than systematic analysis of retinal photographs, before adjudication by a dedicated committee masked to treatment allocation. In LEADER, the rate of a pre-specified composite retinal outcome (requirement for photocoagulation, requirement for treatment with intravitreal agents, vitreous haemorrhage, or new-onset blindness) was numerically slightly higher with liraglutide than placebo [2.3% versus 2.0% events per 100 patient-years; HR 1.15 (95% CI, 0.87 to 1.52); p = 0.33]. In SUSTAIN-6 the rate of an identical composite retinal outcome (pre-specified as a secondary endpoint) was significantly higher with semaglutide vs placebo [3.0% versus 1.8%; HR 1.76 (95% CI 1.11 to 2.78); p = 0.02] [27]. Notwithstanding the limitations of the data, and the potential concerns they raise, onset of the effect soon after randomisation has been interpreted (including by international

regulatory bodies) as secondary to an initial, rapid improvement in glycaemic control [28]. An early worsening of retinopathy in response to glucose-lowering was first described in type 1 diabetes in the Diabetes Control and Complications Trial and subsequently in the Diabetes in Early Pregnancy study [29, 30], but was infrequently seen in type 2 diabetes prior to the advent of GLP-1 agonists. In ELIXA, retinal outcomes reported as adverse events were similar between groups [14]. In EXSCEL, these were pre-specified as adverse events of clinical interest: observed rates were similar between groups (2.9% with exenatide vs 3.2% with placebo) [17].

(iii) Composite microvascular outcomes: In LEADER, development of a pre-specified composite outcome consisting of the individual components of the above retinopathy and nephropathy outcomes was less likely with liraglutide than with placebo [HR 0.84 (95% CI, 0.73 to 0.97); p=0.02] [15]. As with the renal composite outcome, this was driven by reduced onset of new-onset macroalbuminuria. Composite microvascular outcomes were not pre-specified in any of the other GLP-1 CVOTs.

Why were CV events reduced in some trials but not others?:

Thus, while lixisenatide, liraglutide, semaglutide and exenatide are all agonists at the GLP-1 receptor, and their respective CVOTs all met boundaries of regulatory safety, only liraglutide and semaglutide reduced rates of CV outcomes i.e. were superior to placebo and standard of care. A number of possible explanations for these apparent differences can be considered.

(i) Differences in molecular structure: Exenatide is a synthetic form of the peptide exendin-4, a 39 amino acid peptide originally isolated from the salivary secretions of the Gila monster: a single alanine to glycine substitution conferring resistance to degradation by dipeptidyl-peptidase-4. The long-acting (once weekly) form used in the EXSCEL trial is the same molecule encapsulated in biodegradable polymer microspheres. Lixisenatide shares 38 amino

acids with exendin-4 plus an additional six lysine residues. These GLP-1 agonists have only 53% and 50% sequence homology respectively with native human GLP-1. In contrast, liraglutide and semaglutide as synthetic analogues of native GLP-1 have respectively 97% and 94% sequence homology. As native GLP-1 has a half-life of less than five minutes, a half-life suitable for therapeutic use is conferred by the addition of a C16 palmitic acid chain (liraglutide) or a C18 fatty di-acid side chain (semaglutide) to promote albumin binding, and a single (position 34, liraglutide) or dual (positions 8 and 34, semaglutide) amino acid substitution [31,32].

(ii) Differences in duration of action: The GLP-1 receptor agonists vary widely in half-life: twice daily exenatide 2.4 hours; lixisenatide 2.7-4.3 hours; liraglutide 11-15 hours; dulaglutide 5 days; and semaglutide 1 week; it is more difficult to define a pharmacokinetic half-life for long-acting exenatide but it reaches a pharmacodynamic steady state at 6-7 weeks. It is notable that those agents for which CV superiority has been demonstrated in CVOTs to date are those with longer half-lives and/or duration of action. This property allows them to be administered in a more effective dose range as lower peak-to-trough ratios at steady state are associated with less nausea, the main adverse effect of the class (thought to be due to acute impairment of gastric emptying). GLP-1 receptors are not widely found in the CV system (except in the sino-atrial node) [33]. However, agonism at the GLP-1 receptor may reduce the progression of atherosclerosis indirectly via anti-inflammatory effects, which may be associated with a longer duration of action [34, 35].

(iii) Differences in study population: The four CVOTs published to date have studied populations at different baseline CV risk: in ELIXA, all participants had experienced a prior CV event, in contrast with only 73% of those in EXSCEL. From a statistical perspective, a

higher risk population predicts a higher rate of events and therefore a smaller sample size should be required to detect a given effect size (c.f. n = 9340 in LEADER vs n = 14,752 in EXSCEL). However, from a biological perspective, a high risk population may have disease that is too advanced to be susceptible to therapy: thus, despite the short duration of action of lixisenatide, it is at least in theory possible that it might have reduced rates of CV events if it had been studied in a larger, lower risk population, over a longer period of follow-up.

(iv) Differences in HbA1c between groups: As discussed above, despite "treat to target" designs incorporating standard of care in both active and placebo arms, there were differences in HbA1c (and other risk factors) between groups in all four of the CVOTs (Table 1). It has been suggested that glycaemic exposure between study arms [36-39] is closely associated with CV outcome in these trials [24,25]: while this may not have been the main driver of differences in results among the trials, it may have played a role. For HbA1c, the difference was largest in SUSTAIN-6 in which semaglutide was associated with a 0.7% mean difference (7.7 mmol/mol) for the 0.5mg dose and a 1.0% mean difference (10.9 mmol/mol) for the 1 mg dose. The difference between arms was almost as marked three months after randomisation in LEADER with liraglutide at 1.0% (10.9 mmol/mol), but diminished during the trial to 0.4% as participants were treated to target with other agents over a longer follow up (4.4 mmol/mol). The difference in HbA1c between randomised groups was smaller in both ELIXA with lixisenatide (0.27%, 3.0 mmol/mol) and EXSCEL with exenatide (0.53%, 5.8 mmol/mol). This may in part have related to lower efficacy of these agents in the doses selected, and/or lower HbA1c concentrations at baseline: no upper boundary for HbA1c was specified in the inclusion criteria for LEADER or SUSTAIN-6.

(v) Differences in rates of hypoglycaemia between groups: Hypoglycaemia, particularly severe hypoglycaemia, is associated with adverse CV outcomes [40]. As addition of

traditional glucose-lowering medications with a propensity to cause hypoglycaemia (sulphonylureas and insulin) was permitted by protocol in both arms of all four CVOTs, some have suggested that larger reductions in rates of CV events in some trials could be attributed to higher rates of use of these concomitant medication with consequent excess hypoglycaemia in the comparator groups. However, although LEADER was the only trial to demonstrate a significant reduction in rates of severe hypoglycaemia (and rates of CV events) in the active GLP-1 agonist arm vs placebo, there was also a strong numerical trend towards a reduction in ELIXA (in which there was no reduction in CV event rates). Moreover, there was no significant difference in rates of hypoglycaemia between active and placebo arms in either SUSTAIN-6 or EXSCEL and in the former there was a marked reduction in CV event rates with semaglutide. Finally, in a sensitivity analysis in which participants experiencing severe hypoglycaemia were excluded, the primary outcome of LEADER was robust [41]. There is therefore little evidence to support differential rates of hypoglycaemia as a key predictor of the CV outcome results of these trials.

(vi) Differences in weight and other CV risk factors between groups: Although small mean reductions in body weight occurred in comparison to placebo with lixisenatide (-0.7 kg) in ELIXA and exenatide (-1.27 kg) in EXSCEL, much larger reductions were observed with liraglutide (–2.3 kg) in LEADER and semaglutide [-2.9 kg with 0.5 mg, -4.4kg with 1.0 mg) in SUSTAIN-6. Similarly, systolic BP was reduced by lixisenatide (0.8 mmHg) in ELIXA but - perhaps in part due to higher baseline levels (Table 1) - greater reductions were observed with liraglutide in LEADER (1.2mmHg), semaglutide in SUSTAIN-6 [1.3 mmHg with 0.5 mg and 2.6 mmHg with 1.0 mg), and exenatide in EXSCEL (1.6 mmHg). Thus, significant reductions in CV events occurred consistently with those treatments that induced the largest reductions in body weight and BP. While differences in risk factor control between trial arms were not intended in the design of these CVOTs, their occurrence is clinically

relevant, as they reflect the real-life pharmacological profile of each agent in doses used in the clinic.

(vii) Other differences in trial design: It has been suggested that a minimum duration of follow-up is required for a reduction in CV risk to be detected. Median duration of follow-up varied between the CVOTs from 2.1 years for ELIXA and SUSTAIN-6 to 3.8 and 3.2 years in LEADER and EXSCEL. That semaglutide was associated with a reduction in rates of CV events in SUSTAIN-6 goes against this suggestion; however, it could still be argued that longer duration of follow-up increases the chance of detecting a biological effect: for example, this might have allowed the trend observed towards reduction of CV disease with exenatide in EXSCEL to reach formal statistical significance.

(viii) A class effect?: It has been argued that the effect of GLP-1 receptor agonists to reduce rates of CV events can be seen across the class. In a recent meta-analysis by the EXSCEL study group of all four GLP-1 CVOTs published to date, treatment with a GLP-1 receptor agonist led to a 10% overall relative risk reduction versus placebo in three-point MACE [HR 0·90 [95% CI 0·82–0·99); p=0·033], as well as reductions in both CV and all-cause mortality [23]. While the result of the EXSCEL trial itself is certainly consistent with this position, there was considerable heterogeneity in the MACE component of this meta-analysis (I^2 = 50%), apparently driven by the ELIXA trial. In our view it is difficult to substantiate a claim that any "class effect" of GLP-1 agonists in relation to CV outcomes extends to lixisenatide.

In contrast, those agents that act on the GLP-1 receptor for most (or all) of the 24 hour period are associated with reductions (or strong trends towards reductions) in rates of CV events. As some of these effects may be mediated by reductions in body weight, BP, cholesterol and HbA1c, the extent to which there are differences in the control of traditional risk factors between the active and placebo arms of the four CVOTs may explain, at least in part, the

observed differences in outcomes. However, these do not appear to account for all of the variability. It is likely therefore that there are direct and beneficial actions of GLP-1 agonists on the CV system that may include suppression of low grade inflammation, vasodilation, natriuresis [34] - and possibly other as-yet-unknown anti-atherosclerotic mechanisms.

Forward to REWIND (and HARMONY Outcomes):

As discussed above, whether a GLP-1 receptor agonist can be demonstrated to reduce rates of CV events in a large outcome trial may depend on:

a) Trial design: sufficient statistical power (determined by the sample size and accuracy of the predicted event rate); adequate duration of follow-up.

b) Pharmacological profile of the agent: long duration of action; adequate dosing (cf. tolerability).

c) Trial conduct: reduction of traditional CV risk factors; greater reduction of HbA1c in the active vs placebo arm.

At the time of writing, the REWIND trial (see Table 2) comparing dulaglutide 1.5mg per week with placebo in 9901 people with T2D has completed recruitment, baseline data have been published [21] and results are awaited. It is of similar size to LEADER but includes a lower risk population. Whereas in LEADER the "no prior CV disease" group over 60 years of age were required to have strong CV risk factors such as microalbuminuria, left ventricular hypertrophy or impaired LV function, in REWIND the required risk factors include weaker risk markers such as concomitant medication with ACE inhibitors or statins. Due to this lower risk (and hence more generalizable) population, a much longer duration of follow-up

was planned (up to 8 years per participant) giving 90% power to detect a reduction in MACE of 18% i.e. somewhere between the reductions of 13% and 26% detected in LEADER and SUSTAIN-6. Despite these considerations, the power calculation was based on a predicted event rate slightly higher than the 1.8% (under)estimate used in designing LEADER and SUSTAIN-6 (see Table 1). Observed event rates will therefore need to be higher than predicted to detect an effect size similar to that detected in LEADER.

The half-life of dulaglutide (five days) is somewhere between liraglutide and semaglutide, indicating adequate duration of action. However, a recent 40 week head-to-head trial (SUSTAIN-7) indicated that the marketed doses of dulaglutide have about half the effect on weight of the corresponding doses of semaglutide and only 75% of the glucose-lowering efficacy [37]. It might therefore be predicted that smaller differences in HbA1c will be seen between the active and placebo arms of REWIND than occurred in LEADER and SUSTAIN, and that the weight differential between arms may also be smaller as seen in EXSCEL (see Table 1), decreasing the chances that a reduction in CV events can be demonstrated due to constraints of the study design.

The methods and baseline characteristics of the HARMONY-Outcomes CVOT with the (shortly-to-be discontinued) once-weekly GLP-1 agonist albiglutide was accepted for publication just as this article was submitted [42]. It was designed to test non-inferiority for MACE (safety) with a subsequent test for superiority. Only participants with prior CV disease were included i.e. a higher risk population than any of the other trials except ELIXA. It was pre-specified that participants would require to be followed up for between three and five years to accumulate 611 major CV adverse events. However, as the (blinded) event rate was much higher than anticipated there was a risk that the trial would be stopped without adequate exposure to ensure safety. The protocol was therefore amended to stipulate a median follow-up of at least 1.5 years. As weekly albiglutide is less-effective than daily liraglutide in terms

of HbA1c lowering over 32 weeks [43], differences in HbA1c between the active and placebo arms are likely to be smaller than were seen in LEADER. For the same reasons as speculated above in relation to REWIND, and given a limited time to impact atherosclerosis in participants with established CV disease, it might therefore be predicted that the trial has a better chance of demonstrating safety (non-inferiority) than it has of demonstrating a reduction in CV events (superiority).

The two other forthcoming trials (FREEDOM-CVO and PIONEER-6) were designed only to detect non-inferiority: given other results with GLP-1 agonists discussed above, it is likely that both will achieve this predominantly regulatory aim [for FREEDOM-CVO see the 2016 press release cited above (19)].

Summary

The advent of GLP-1 agonists ten years ago transformed the treatment of T2D, and has made a major impact on metabolic and CV complications. The regulatory requirement for large CVOTs has accelerated this process and allayed early fears on safety, originally focusing on pancreatitis, pancreatic carcinoma and medullary thyroid carcinoma. Taken together, the results of the four large trials published to date indicate that although differences exist between the GLP-1 receptor agonists in their structure, potency, and effect on CV risk, longer-acting agents given in adequate dose are particularly beneficial for the CV system. Their effects are mediated by a combination of body weight and BP reduction, lowering of LDL cholesterol and glucose, and other mechanisms including, suppression of low grade inflammation, vasodilation, and natriuresis. Although GLP-1 agonists are still principally used as “third line” agents in many countries (in part due to route of administration and acquisition cost), it is likely that they will increasingly be used at earlier stages of T2D,

facilitated by the emergence of oral formulations and better appreciation of the economic value to healthcare systems of reducing long–term complications.

(4574 words)

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Legends for Tables

Table 1: Design, baseline characteristics, main results and differences in risk factors between groups in the four GLP-1 agonist CV outcome trials published to date

Table 2: Design and baseline characteristics (where available) of the ongoing GLP-1 CV outcome trials

Legend for Figure

Mechanisms by which GLP-1 agonists may exert beneficial effects on the CV system

Table 1

Acronym	ELIXA	LEADER	SUSTAIN-6	EXSCEL
Registry	**NCT01147250**	**NCT01179048**	**NCT01720446**	**NCT01144338**
Intervention	Lixisenatide	Liraglutide	Semaglutide	Long-acting Exenatide
Route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Dose	Up to 20 mcg daily	Up to 1.8 mg daily	0.5 mg or 1.0 mg weekly	Up to 2 mg weekly
Comparator	Placebo and standard of care	Placebo and standard of care	Placebo and standard of care	Placebo and standard of care
Conducted	2010-2015	2010-2015	2013-2016	2010-2017
Randomized (n)	6068	9340	3297	14752
Mean age (years)	59.9	64.3	64.6	61.0
Mean BMI (kg/m^2)	30.1	32.5	32.8	32.7
Mean HbA_{1c} at inclusion (% units)	7.7	8.7	8.7	8.1
Mean duration of diabetes (years)	9.2	12.8	13.9	13.1
Systolic BP (mmHg)	130	138	136	136
Treatment (%)				
Insulin[1]	33	45	58	46
ACE/ ARB[1]	85	81	84	77
Statin[1]	93	73	73	74
Prior CVD[1] (%)	100	81	83	73
Heart failure (%)	22.5	17.	24	16
eGFR < 60 ml/min/1.73m^2 (%)	22	24	28.5	21.3
Primary outcome	MACE expanded[2]	MACE	MACE	MACE
Follow-up (years)	2.1	3.8	2.1	3.2
Target primary events in power calculation	844	660	122	1360
Predicted MACE event rate (% per year)	7	1.8	1.8	3.8
Primary events observed	805	1302	254	1744
Observed event rate (per year)	6.3%	3.7%	3.7%	3.7%
Non-inferiority for MACE demonstrated?[3]	Yes	Yes	Yes	Yes
Superiority for MACE demonstrated?[3]	No	Yes (13% reduction)	Yes[4] (26% reduction)	Borderline (9% reduction)[5]
CV death rate reduced ?	No	Yes	No	No
All cause mortality reduced?	No	Yes	No	Yes
Difference in HbA1c (% units)	0.27***	0.4*[6]	1.0***[7]	0.53***
Reduction in rate of severe hypoglycaemia if any (%)	Numerically fewer	25*	None	None
Mean reduction in weight (kg)	0.7***	2.3***	4.3***[7]	1.27***
Mean difference in systolic BP (mmHg)	0.8**	1.3 *	2.6 ***[7]	1.6**
Retinopathy reported	As adverse events	As secondary outcome	As secondary outcome	As adverse events of clinical interest

eGFR -= estimated glomerular filtration rate

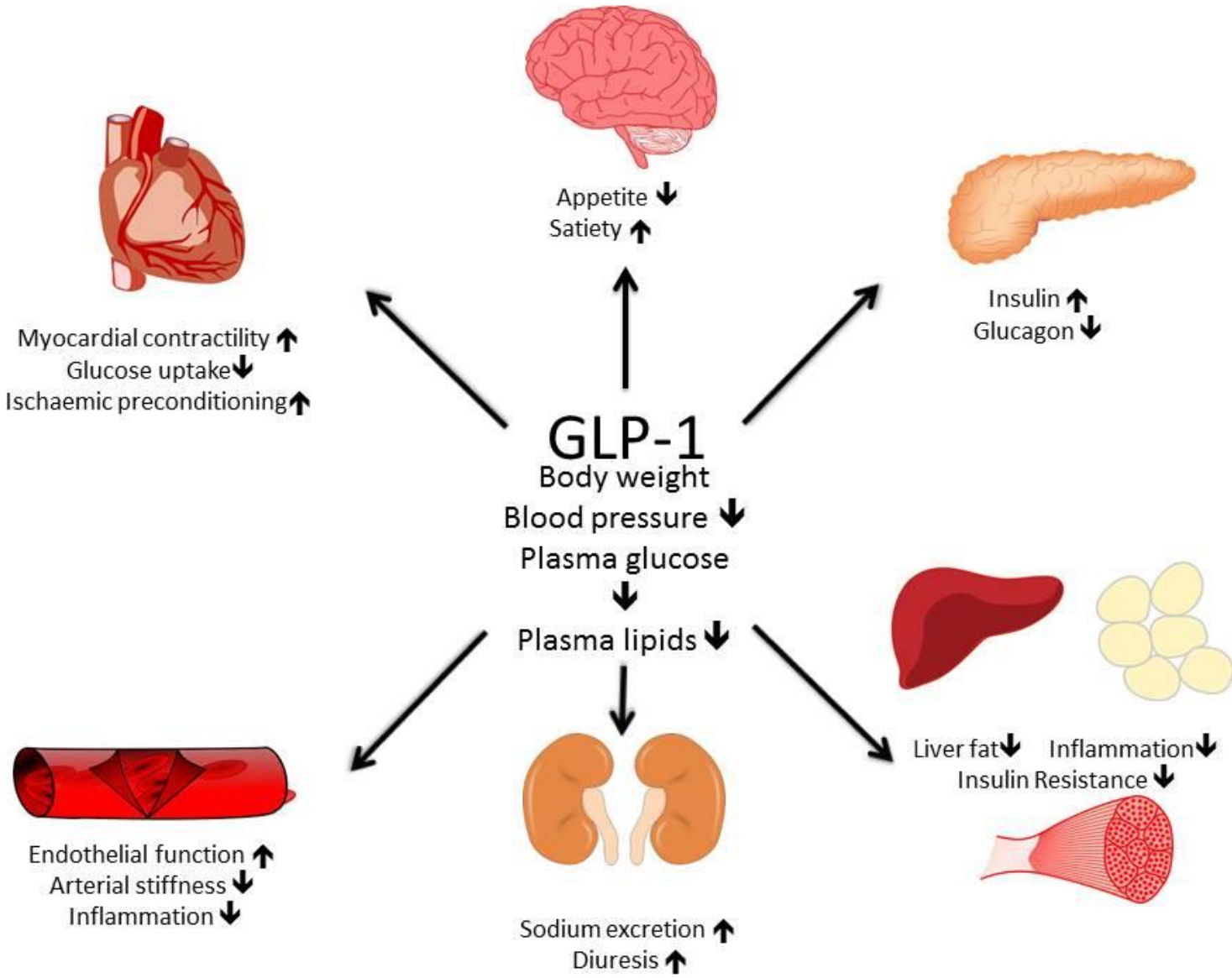
[1]at baseline; [2]including unstable angina; [3]compared with placebo and standard of care; [4]result could not be used for regulatory purposes as the comparison was not pre-specified; [5]p=0.06; [6]at 36 months; [7]only results for 1.0 mg dose are shown. *p<0.05; **p<0.01; ***p<0.001 vs placebo and standard of care

Table 2

Acronym	FREEDOM-CVO	PIONEER-6	REWIND	HARMONY
Registry	NCT01455896	NCT02692716	NCT01394952	NCT02465515
Intervention	Exenatide	Semaglutide	Dulaglutide	Albiglutide
Route	Implant	Oral	Subcutaneous	Subcutaneous
Dose	60mcg/day	3-7 mg/day[1]	1.5mg weekly	Up to 50 mg
Comparator	Placebo and standard of care	Placebo and standard of care	Placebo and standard of care	Placebo and standard of care
Conducted	2013-2017	2017-Present	2011 - present	2015 – present
Randomized (n)	4156	3176	9901	9463
Age for inclusion/ mean age (years)	Over 40 years	Over 50 years	66.2	64.1
Mean BMI (kg/m^2)	NK	NK	32.3	32.3
Mean HbA_{1c} at inclusion (%)	NK	NK	7.3	8.7
Mean duration of diabetes (years)	NK	NK	10.0	13.8
Treatment				
Insulin (%)[1]	NK	NK	24	59.3
ACE/ ARB[1] (%)	NK	NK	81.4	81.6
Statin[1](%)	NK	NK	66	84
Established CVD[1](%)	100	NK	31.4	100
Heart failure (%)	NK	NK	8.6	20.2
eGFR < 60 ml/min/1.73m^2	NK	NK	22.2	22.6
Primary outcome	MACE	MACE	MACE	MACE
Primary events in power calculation	NK	NK	1200	611
Predicted MACE event rate (per year)	NK	NK	2%	2-3%
Designed to detect non-inferiority?	Yes	Yes	Yes	Yes
Designed to detect superiority?	No	No	Yes	Yes
Expected to report	NK	NK	2019	2018

[1]approximate dose range

NK, not known


Appetite ↓
Satiety ↑
Myocardial contractility ↑
Glucose uptake ↓
Ischaemic preconditioning ↑
Insulin ↑
Glucagon ↓
GLP-1
Body weight
Blood pressure ↓
Plasma glucose
↓
Plasma lipids ↓
Liver fat ↓
Inflammation ↓
Insulin Resistance ↓
Endothelial function ↑
Arterial stiffness ↓
Inflammation ↓
Sodium excretion ↑
Diuresis ↑