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EXPERT OPINION

Are we waiting too long for the cardiovascular outcome trials with the glucagon-like peptide-1 receptor agonists?

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Several new medicines are in development for the treatment of type 2 diabetes, and cardiovascular outcome trials are the gold standard for these medicines. This editorial demonstrates that despite being available for over 10 years, there are no cardiovascular outcome studies for any of the glucagon-like peptide-1 receptor agonists, which demonstrate cardiovascular safety or benefit in subjects with high cardiovascular risk. The author argues that the FDA should be ensuring that clinical outcome studies for subjects with type 2 diabetes and high cardiovascular risk be undertaken in a timelier manner.

Keywords: cardiovascular outcomes, cardiovascular safety, clinical trials, glucagon-like peptide-1 receptor agonists, type 2 diabetes

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In the US, about 90% of the 24 million people who have diabetes have type 2 diabetes [1]. The initial treatment of type 2 diabetes is lifestyle changes, but when these fail, medicines are used. Metformin is the standard first drug treatment for type 2 diabetes, and is the only medicine that has been shown indisputably to decrease cardiovascular outcomes [2]. However, despite the use of medicines for type 2 diabetes, about two-thirds of the subjects die from heart disease or stroke, and diabetes remains the leading cause of blindness, end-stage kidney failure and lower limb amputations [1].

Several new medicines are in development for the treatment of type 2 diabetes. As cardiovascular disease is associated with diabetes, cardiovascular beneficial outcomes are the gold standard in trials for new medicines in the treatment of diabetes, rather than the surrogate end point of reductions in HbA1c. Cardiovascular outcomes are especially important in the development of medicines for diabetes, as any straight forward relationship between surrogate end point of lowering HbA1c levels and cardiovascular risk was challenged by the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [3]. The initial findings of ACCORD were that the intensive lowering of HbA1c to a mean value of 6.4%, by more frequent use of metformin, a sulfonylurea or a thiazolidinedione, was associated with an increased risk of mortality (any cause or cardiovascular), compared to standard therapy (HbA1c of 7.5%) [3]. Thus, from this result, it seemed that the lowering of HbA1c levels may not always be considered as a surrogate for the degree of cardiovascular benefit or safety. Although this has been disputed since, at the time (2008), this was a consideration, when FDA required that all new glucose-lowering therapies be required to show cardiovascular safety [4]. Subsequently, the thiazolidinedione, rosiglitazone, was shown to lower HbA1c but to increase cardiovascular risk [5,6]. With the addition of these findings with rosiglitazone, the European

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Table 1. GLP-1 Receptor agonists under clinical development.

GLP-1 R agonist, trade name, company	Short (S) or long (L) acting	FDA approval date [7]
Exenatide synthetic, Byetta, Amylin/Eli Lilly/AstraZeneca	Short, sc, twice a day	28th April 2005
Liraglutide, Victoza, Novo Nordisk	Short, sc, once a day	25th January 2010
Lixisenatide, intended Lyxumia, Sanofi	Short, sc, once a day	Not approved
Albiglutide, Tanzeum, GlaxoSmithKline	Long, sc, once a week	15th April 2014
Dulaglutide, Trulicity, Eli Liily	Long, sc, once a week	18th September 2014
Semaglutide, Novo Nordisk	Long, sc, once a week	Not approved
Taspoglutide, Ipsen/Roche	Long, sc, once a week	Development stopped

GLP-1: Glucagon-like peptide-1; sc: Subcutaneously.

Medicines Agency concurred in 2010 that all new glucose-lowering therapies should be required to show cardiovascular safety [7].

One of the new paradigms in the treatment of diabetes is glucagon-like peptide-1 (GLP-1) receptor agonists. GLP-1 is released in response to a meal and augments, glucose-mediated insulin secretion, suppresses glucagon secretion, inhibits gastric emptying and reduces appetite, and these effects are mimicked by the agonists. Exendin-4 is a 39-amino acid peptide, which acts as an agonist at the GLP-1 receptors, and is resistant to proteolytic breakdown [8]. Synthetic exendin-4 (exenatide) was the first GLP-1 receptor agonist introduced for use in type 2 diabetes, and was registered in 2005 [8]. Within 6 months of introduction, exenatide was being used by 1.5% of subjects with type 2 diabetes in a population of 206,345 subjects in the US [9]. Given that there are 25 million subjects with type 2 diabetes in the US, it is likely that at least 200,000 were taking exenatide at this time, despite the lack of a cardiovascular outcomes trial with this agent.

Subsequently, other short-acting GLP-1 receptor agonists (liraglutide, lixisenatide) are under development (**Table 1**) [10]. When the short-acting GLP-1 receptor agonists are administered once or twice a day (b.i.d.), they are not as effective at continuously reducing plasma glucose levels during fasting, as the longer-acting agents [10]. Also, the short-acting agents have been shown to delay gastric emptying and this may reduce insulin levels postprandially [10]. To prolong the beneficial effects of stimulating the GLP-1 receptor in subjects with type 2 diabetes, long-acting GLP-1 receptor agonists (e.g., albiglutide, dulaglutide) are also being developed (**Table 1**). These long-acting GLP-1 receptor agonists reduce glucose throughout the day, but with long-term use do not reduce gastric emptying [10]. At present, we do not know whether the short- or long-acting GLP-1 receptor agonists should be used or preferred as we have no comparative cardiovascular outcome studies between these agents.

Exenatide b.i.d. was first registered for use in type 2 diabetes by the FDA, as a short-acting preparation in 2005, and, as this was before the ruling of the FDA requiring cardiovascular outcome studies for glucose-lowering drugs, this was not a requirement of approval. However, when an extended release preparation of exenatide was approved in 2012, a cardiovascular outcome study was a condition of approval [11]. The FDA has also ruled that cardiovascular outcome studies need to be performed for liraglutide, albiglutide and dulaglutide. To date, no single prospective cardiovascular outcomes trial has been completed for any of these agents (**Table 2**).

Rather the short-term studies, often with low-risk cardiovascular subjects, have been combined, in various ways, to determine cardiovascular safety. Thus, for exenatide, there have been retrospective analysis of studies with exenatide b.i.d., but this had few cases of Major Adverse Cardiac Events (MACE) (cardiovascular mortality, stroke, myocardial infarction, acute coronary syndrome and revascularisation), which limited its ability to demonstrate either cardiovascular safety or benefit (**Table 2**). Similar meta-analysis studies have been completed for liraglutide and albiglutide, with the completed short-term trials, with subjects with low cardiovascular risk, and these studies have also had low number of cases, limiting their interpretation (**Table 2**).

A search of the clinical trials website [12] showed that there are ongoing cardiovascular outcome studies with both forms of exenatide, and liraglutide (**Table 2**). To date, no trials on cardiovascular outcomes alone have been reported in the press or in progress for either albiglutide or dulaglutide [12]. Although lixisenatide and semaglutide have been used in clinical trials, they have not been approved by the FDA, and are not being subjected to cardiovascular outcomes trials. Clinical trials of taspoglutide have been halted due to serious hypersensitivity reactions [13].

Meta-analysis studies combining trials with GLP-1 receptor agonists have shown no cardiovascular safety concerns (**Table 3**). However, the trials included are all of subjects with low cardiovascular risk, and hence the incidence of MACE is low (**Table 3**). Thus, we do not know whether these results apply to subjects with high cardiovascular risk.

Results from dedicated cardiovascular outcome trials are not available for either the short- or long-acting GLP receptor agonists. Thus, it is not known whether short or long-acting agonists should be used or preferred.

Given that it is 10 years since the registration of exenatide, and we still do not know for certain whether any of

Table 2. Cardiovascular outcome trials in subjects with type 2 diabetes.

GLP-R agonist, and FDA approval date	Cardiovascular outcomes studies
Exenatide synthetic, b.i.d.	(1) Retrospective analysis of short-term studies of exenatide b.i.d. versus a pooled comparator group in 3945 subjects, which excluded subjects with active cardiac disease in the last year. Primary outcome was MACE; and the incidence was 0.009 (15 cases) with exenatide and 0.011 (11 cases) with the comparator, which was not significantly different [15] (2) A 2-year cardiovascular outcomes study of exenatide 650 b.i.d. in 4000 subjects with a history of coronary, cerebrovascular or peripheral artery disease, with a primary outcome of time to first MACE started enrolling subjects in March 2013 and is due for completion in July 2018 [12]
Exenatide synthetic, LAR	(1) Combining the two trials (one for 24 weeks, other for 26 weeks) of exenatide LAR versus pioglitazone in a meta-analysis, demonstrated a significant reduction in MACE with exenatide LAR, with four cases of MACE (three acute myocardial infarction) with pioglitazone versus none with exenatide [16] (2) EXSCEL (Exenatide study of cardiovascular event lowering trial) started enrolling 14000 subjects in June 2010 to exenatide versus usual care, and is estimated to be completed in April 2018, and has MACE as both the primary efficacy and primary safety outcome, and is collecting up to 7.5 years [12]
Liraglutide	(1) Pooling of 15 studies with 4257 subjects been treated liraglutide, and 2381 subjects who had been exposed to comparators only produced 39 MACE, and there was no significant difference between the rates in the liraglutide group versus the comparator group [17] (2) Meta-analysis of trials showed no significant difference in MACE for liraglutide versus placebo (n = 8) or versus comparator (n = 10) [18] (3) LEADER (liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results – a long-term evaluation) is comparing liraglutide to placebo, as an addition to standard therapy, over 60 months. LEADER has enrolled 9340 subjects with type 2 diabetes and high cardiovascular risk, and the primary end point is the time from randomisation to a MACE. The estimated completion date for LEADER is October, 2015 [11]
Albiglutide	Meta-analysis of HARMONY trials showed no cardiovascular safety concerns with albiglutide, but the incidence of MACE was low (~ 1%/year) as HARMONY did not recruit high cardiovascular subjects [19]

b.i.d.: Twice a day.

Table 3. Completed cardiovascular outcome analysis of combinations of GLP-R agonists in subjects with type 2 diabetes.

Alone or combined: exenatide twice a day (b.i.d.), liraglutide, albiglutide, taspoglutide, lixisenatide, dulaglutide	A pair-wise and network meta-analysis of cardiovascular safety between individual or all GLP-1 receptor agonists and placebo or comparator drugs with 15883 subjects. There was no significant difference between GLP-1 receptor agonists and placebo (40 cases in 5826 subjects versus 18 in 2350) or comparator drugs (47 from 5425 vs 26 from 3494) on cardiovascular safety [20]
Alone or combined: exenatide b.i.d. and LAR, liraglutide, albiglutide and taspoglutide	Meta-analysis of 33 trials showed no significant difference between the combined GLP-1 receptor agonists and comparator drugs on MACE (75 vs 66 cases) [16]
Combined exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide and semaglutide	In 58 trials, there were 49 MACE events in the GLP-1 receptor agonist group and 42 events in the control group. Although, when 29 of the studies were combined there was a significant reduction in MACE with GLP-1 receptor agonists, compared to placebo (p = 0.047), this significance was lost when the short-term studies (< 26 weeks) were removed. Meta-analysis of trials for the combined preparations of exenatide versus placebo (n = 15) or versus comparator (n = 18) showed no significant difference in MACE [18]

GLP-1: Glucagon-like peptide-1.

GLP-1 receptor agonist have cardiovascular safety in subjects with type 2 diabetes and high cardiovascular risk, it seems to me that we are waiting too long for this important information. Although not considered in this editorial, this lack of cardiovascular outcome trials also applies to other groups of medicines being developed for the treatment of type 2 diabetes, for example, dipeptidyl peptidase 4 inhibitors, inhibitors of the sodium glucose co-transporter 2. It also remains controversial as to whether the sulphonylureas, which have been used for > 40 years in type 2 diabetes, have cardiovascular safety [14].

At present, it is not necessary to prove cardiovascular safety for drugs for type 2 diabetes prior to registration by the FDA. In my opinion, this should be reconsidered. It seems to me that the FDA should be ensuring that clinical outcome studies are undertaken in a timelier manner. One approach may be to require the initial Phase III studies to include subjects with type 2 diabetes and high cardiovascular risk, so that there are enough MACE to do meaningful meta-analysis, prior to any post-registration trials. Another possible way, to speed clinical outcomes studies, is to require Phase III clinical trials of GLP-1 receptor agonists against comparator drugs to continue until there are benefits, or not, on both surrogate and clinical end points.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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