LEADER and the new ‘cardiovascular’ glucose-lowering agents

Rachel Livingstone, James G Boyle, and John R Petrie

Nearly two decades ago the UK Prospective Diabetes Study (UKPDS) refocused type 2 diabetes management towards cardiovascular as well as microvascular prevention. This was largely based on blood pressure lowering data, but also on reduction in myocardial infarction in a subgroup of obese patients randomised to metformin. Although the latter evidence does not meet the rigour of today’s standards, it led to a major shift in prescribing and resulted in the current primacy of metformin in international glucose-lowering guidelines.

The search for agents other than metformin that may reduce cardiovascular complications in type 2 diabetes suffered at least one false start. The ‘insulin-sensitising’ PPARγ agonist thiazolidinediones (or ‘glitazones’) were strong candidates on theoretical grounds and a large cardiovascular outcome trial (CVOT) was initiated with pioglitazone (PROACTIVE). When the results became available in 2005, pioglitazone showed evidence of superiority over placebo in reducing fatal and non-fatal myocardial infarction and stroke. However, this was a secondary endpoint by design, and was offset by an excess of heart failure events. A prolonged period of uncertainty ensued, compounded by a concern regarding the cardiovascular safety of its sister compound rosiglitazone (never fully substantiated). Pioglitazone – now off patent – is currently enjoying a renaissance as an option for second-line therapy in NICE guidelines, although rosiglitazone remains unavailable. In the final analysis, experience with the thiazolidinediones provided a lesson to the diabetes community that lowering of blood glucose is not a sufficient property for a novel therapeutic agent: a much higher standard of evidence is required.

New glucose-lowering agents

The next classes of glucose-lowering agents to be introduced both targeted the incretin pathway: oral dipeptidyl peptidase-4 (DPP-4) inhibitors and injectable glucagon-like peptide-1 (GLP-1) agonists. Earlier agents from these classes were approved before the international authorities, led by the US Food and Drug Administration (FDA) in 2008, began to exert a much higher level of regulatory scrutiny as a response to the rosiglitazone experience. As outlined by Professor Miles Fisher in an editorial in this journal last year, pharmaceutical companies are now mandated to conduct large CVOTs (similar in design to PROACTIVE) as an essential component of the pathway by which a new agent is brought to market. As a result the number of people with type 2 diabetes participating in clinical trials has increased by an order of magnitude with tens of thousands currently participating in pharmaceutical company sponsored clinical research.

Due to the timing of their market approval, UK diabetologists gained experience of the twice-daily GLP-1 agonist exenatide and the once-daily GLP-1 analogue liraglutide prior to the implementation of new regulatory guidance and the initiation of their respective CVOTs. As these agents lower weight and BP as well as blood glucose, it was more biologically plausible to hypothesise that they would be associated with cardiovascular benefit than it was with their DPP-4 inhibitor counterparts. Large CVOTs with DPP-4 inhibitors (alogliptin [EXAMINE], saxagliptin [SAVOR-TIMI-3] and sitagliptin [TECOS]) nevertheless had to be performed – the latter commissioned before the new guidance (see Petrie for references). These provided reassuring evidence of safety but no evidence of any cardiovascular benefit. Until the release of the results of the EMPA-REG trial at the European Association for the Study of Diabetes (EASD) meeting in Stockholm in September 2015, there was a growing tide of scepticism within the diabetes community regarding the benefits of using scarce research funding to perform large-scale CVOT trials. This point of view gained traction with the publication in late 2015 of ELIXA, a CVOT with the short-acting GLP-1 agonist lixisenatide; again this showed evidence of safety but not of benefit.

EMPA-REG breakthrough

The situation was unexpectedly changed by EMPA-REG, a CVOT with the SGLT2 inhibitor empagliflozin. An early and dramatic reduction in outcomes including major adverse cardiovascular events, cardiovascular death and all-cause mortality was demonstrated in comparison with placebo. This was the first positive CVOT in type 2 diabetes in more than 10 years: initial evidence that the FDA’s new and more rigorous approach to regulation was bearing fruits. Given these exciting results with an SGLT2 inhibitor, and the above-mentioned results of the ELIXA GLP-1 agonist trial (i.e. safety but not benefit), expectations from the Liraglutide Effect and Action in Diabetes Evaluation of cardiovascular outcome Results (LEADER) trial were somewhat muted by the time of trial close-out early this year.

LEADER trial results

LEADER was an international, multicentre, phase 3B, randomised, double-blind, placebo-controlled CVOT comparing the safety and efficacy of the GLP-1 agonist liraglutide versus placebo (1:1) in over 9340 people with type 2 diabetes mellitus and high cardiovascular risk. More than 80% of participants had a history of previous cardiovascular disease. As in all the recent CVOTs mandated by the FDA, the primary endpoint was a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The results, presented recently at the American Diabetes Association Scientific Sessions (New Orleans,
June 2016), demonstrated a reduction in rates of major cardiovascular events in patients randomised to liraglutide versus placebo (13.0% versus 14.9% respectively; p<0.001 for non-inferiority, p=0.01 for superiority). Death from cardiovascular causes occurred in fewer patients in the liraglutide group than placebo (4.7% versus 6.0% respectively; p=0.007), and death from any cause was also lower in the liraglutide group (8.2% versus 9.6%; p=0.02). Rates of non-fatal myocardial infarction and non-fatal stroke were numerically lower in the liraglutide group compared to placebo, even though these differences did not reach statistical significance. For the primary outcome, the number of patients needed to treat to prevent one event was 66 over three years. The trial was well conducted with high rates of ascertainment of outcomes and very few participants lost to follow up. So, after waiting almost 20 years since UKPDS, not just one but two positive CVOTs had turned up almost at the same time.

Before and during the LEADER trial, a number of potential safety concerns regarding GLP-1 agonist therapy were quite vociferously raised within the diabetes community. In particular, these concerned medullary thyroid cancer, pancreatitis and pancreatic cancer. These issues were therefore monitored closely during the trial by an independent Data Monitoring Committee in order to protect participants. In the final analysis, although serum amylase and lipase levels were higher in the liraglutide group compared with placebo, acute pancreatitis occurred in fewer patients in the liraglutide group compared to placebo (18 versus 23). Pancreatic malignancy, reported by two different methods within the trial, occurred as an adverse event in 13 cases in the liraglutide group versus five in the placebo group; however, it was also the mode of death in four additional cases in the placebo group, i.e. a total of nine cases with placebo and 13 with liraglutide. No patients allocated to liraglutide developed medullary thyroid cancer during the trial but there was one case in the placebo group. Overall, the only adverse effect showing a clinically and statistically significant excess with liraglutide was gall stone disease: 145 cases in the liraglutide group versus 90 in the placebo group (severe disease in 40 versus 31 patients, respectively). This was not unexpected given that liraglutide is associated with significant weight loss.

**Possible mechanisms of CV event reduction**

The mechanisms by which liraglutide reduced cardiovascular events in LEADER are an important topic of current scientific investigation. Weight loss was 2.3kg greater than placebo with liraglutide (95% CI 2.5–2.0kg), while systolic BP was 1.2mmHg lower (95% CI 95% 1.9–0.5mmHg). However, diastolic BP was 0.6mmHg higher (95% CI 0.2–1.0mmHg) and heart rate was 0.0 beats per minute higher (95% CI 2.5–3.4 beats per minute). There were fewer nephropathy events with liraglutide, driven by fewer new cases of persistent macroalbuminuria (HR 0.74; 95% CI 0.60–0.91). Overall rates of adverse events were similar in the liraglutide and placebo groups, although rates of hypoglycaemia (including severe hypoglycaemia) were significantly lower with liraglutide (HR 0.80; 95% CI 0.74–0.88), probably because many fewer patients required use of sulphonylureas or conversion to insulin. The beneficial effects of liraglutide may have been mediated by small positive effects in all of these domains, possibly augmented by a direct beneficial effect on cardiovascular tissues, whether myocardial or endothelial. However, a ‘direct’ effect of this type cannot solely have been mediated by GLP-1 receptors as these are not widely expressed in human cardiac and vascular tissues.

**Differences between EMPA-REG and LEADER**

There are some important differences between EMPA-REG and LEADER. The cardiovascular benefits with empagliflozin were seen earlier in the trial when compared to LEADER (separation of the Kaplan-Meier survival curves at three months in the former and 12–18 months in the latter). Hospitalisation for heart failure was not significantly reduced in LEADER as it was in EMPA-REG, although these outcomes were numerically fewer. Only in EMPA-REG were the endpoints doubling of serum creatinine and initiation of renal replacement therapy significantly reduced. The main results paper of LEADER includes a forest plot which has been interpreted to show possible heterogeneity in terms of efficacy by geographic region; this specific analysis has not to our knowledge been provided for EMPA-REG. It should be remembered that subgroup analyses should be treated with caution and seen merely as hypothesis-generating; also that some of the apparent differences between the trials may have been due to differences in the population recruited (i.e. inclusion criteria).

**Future CV outcome trials**

In the coming months, there will be considerable further analysis of the data from LEADER and EMPA-REG. What were the exact mechanisms by which cardiovascular risk was reduced? Can the positive effects be extrapolated to younger patients or those with a lower baseline cardiovascular risk? Is a lower dose of liraglutide (1.2mg) also associated with cardiovascular benefit? Was hypoglycaemia associated with adverse cardiovascular outcomes? Again, even these very large CVOTs cannot definitively answer questions beyond those that their protocols were designed to address.

Acknowledging the remaining uncertainties, we can conclude that the results of recent type 2 diabetes CVOTs have helped to restore confidence in their value as a method of investigation and use of resource. In fact, these trials provide further hope that life expectancy in type 2 diabetes can be brought closer to that of the general population. At the time of writing, the FDA had narrowly voted that the evidence provided by EMPA-REG supported a label change towards a cardiovascular indication. This may be forthcoming in Europe in due course. The most controversial point discussed by the FDA was that empagliflozin is the only drug in the SGLT2 class so far to have demonstrated cardiovascular benefit; this point will be addressed when ongoing trials with canagliflozin (CANVAS) and dapagliflozin (DECLARE-TIMI) report their results in 2017 and 2019 respectively. In relation to GLP-1 agonists, such regulatory discussions will shortly commence. In this regard, a recent early
announced positive results from the SUSTAIN-6 CVOT with the once-weekly injectable GLP-1 agonist semaglutide is supportive of a class effect, at least with longer-acting agents,15 full results will be presented at the EASD meeting in September 2016. CVOTs with the weekly forms of the GLP-1 agonists exenatide (EXSCEL) and dulaglutide (REWIND) will both report in 2018.9

Summary

‘Paradigm shift’ is an over-used phrase in medicine and science, but is arguably appropriate to describe the extent to which the therapeutics of type 2 diabetes will have changed in the 12 months between the EASD meetings in 2015 and 2016. From having two glucose-lowering agents with limited evidence of cardiovascular benefit (metformin and pioglitazone), we are set to have a further three (empagliflozin, lixisenatide and semaglutide) in the armamentarium, each backed by robust evidence from well-designed, large CVOTs. For this we have to thank the bold changes made to the regulatory environment by the FDA in response to the rosiglitazone affair in 2008. Once licensing and labelling issues are resolved, cost-effectiveness will be an important factor driving the positioning of SGLT2 inhibitors and GLP-1 agonists, the new ‘cardiovascular’ glucose-lowering agents, within revised guidelines (particularly in the UK). Fortunately, it will be possible to estimate some of their benefits more directly than in the past, i.e. from actual trial outcomes rather than by extrapolation from changes in HbA1c.

Rachel Livingstone,1 BSc, MBChB
James G Boyle,1 MBChB, MD, MSc
John R Petrie,1 BSc, MBChB, PhD

1Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

Declaration of interests

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References