Series: Cardiovascular outcome trials for diabetes drugs
Liraglutide and LEADER

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Abstract

LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) was an FDA-mandated cardiovascular outcome trial with liraglutide and was the first trial with a glucagon-like peptide-1 (GLP-1) receptor agonist to demonstrate a significant reduction in cardiovascular events. It compared liraglutide and placebo in 9,340 people with type 2 diabetes and either existing cardiovascular disease or age >60 years with at least one cardiovascular risk factor. LEADER demonstrated superiority for major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), and cardiovascular deaths were significantly reduced, as was all-cause mortality. Hospitalisation for heart failure, which was a secondary outcome, was not significantly reduced. Compared with the EMPA-REG OUTCOME trial, the curves for major adverse cardiovascular events in LEADER separated later, and the absence of a clear effect on hospitalisation for heart failure or on estimated glomerular filtration rate suggests that the mechanism of cardiovascular benefit for liraglutide was different from that for empagliflozin

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Introduction

Licensing requirements for new anti-diabetes drugs changed in the USA in 2008, and between 2008 and 2020 a dedicated randomised controlled cardiovascular outcome trial (CVOT) was usually required either before or after licensing.[1,2] This series describes and summarises the results of these CVOTs in the order in which they were published, describing the primary endpoint and important secondary outcomes from the principal publication, and directs attention to important subsequent publications of data from subgroups and post hoc analyses. LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) was the second published FDA-mandated CVOT using a glucagon-like peptide-1 (GLP-1) receptor agonist.[3] It came after three negative trials with dipeptidyl peptidase 4 (DPP-4) inhibitors[4–6] and a negative trial with the GLP-1 receptor agonist lixisenatide,[7] whereas the EMPA-REG OUTCOME trial with empagliflozin had demonstrated reductions in major adverse cardiovascular events (MACE), cardiovascular deaths, all-cause mortality and hospitalisation for heart failure.[8]

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Background

Liraglutide was approved in 2009 by the EMA for use in Europe and in 2010 by the FDA for use in the USA. It was the second GLP-1 receptor agonist to be approved by the FDA and EMA following twice-daily exenatide, which was approved before the new licensing requirements. The cardiovascular safety of liraglutide was assessed in a patient-level pooled analysis of 15 phase 2 and phase 3 clinical development studies.[9] Major adverse cardiovascular events (MACE) were identified by querying the study database using Medica Dictionary for Regulatory Activities (MeDRA) terms combined with serious adverse events recorded by study investigators. The incidence ratio for MACE associated with liraglutide was 0.73 (95% CI 0.38 to 1.41) versus all comparator drugs, satisfying the FDA safety criteria requirements pre-licensing.

LEADER

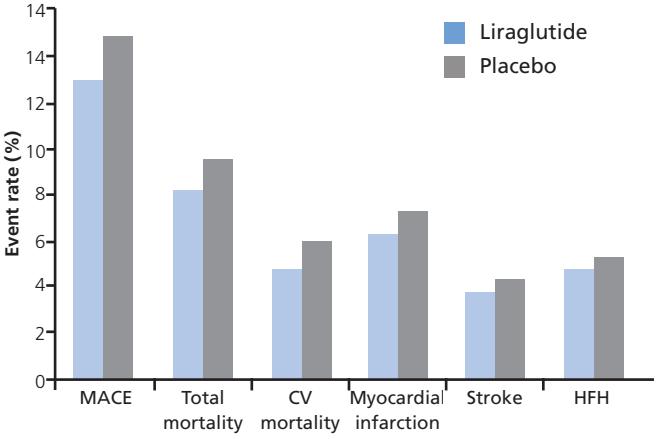
A paper describing the design and baseline characteristics of LEADER was published in 2013.[10] The principal LEADER results were presented in 2016 at the meeting of the American Diabetes Association and published simultaneously in the *New England Journal of Medicine*.[3] The design of the study and key baseline characteristics of LEADER are shown in Box 1.

In LEADER there was a significant reduction in MACE with liraglutide, demonstrating superiority (Figure 1, Box 2). In the liraglutide group there were statistically significant reductions in cardiovascular death and death from any cause. There were no significant differences in the rates of myocardial infarction, stroke or hospitalisation for heart failure. The rate of gastrointestinal events was increased with liraglutide and there was no increase in other adverse events. There were significantly fewer episodes of severe hypoglycaemia and confirmed hypoglycaemia in the liraglutide group compared with the placebo group. There were 13 patients with pancreatic cancer in the liraglutide group and 5 in the placebo group. Acute pancreatitis occurred in 18 patients in the liraglutide group and 23 in the placebo group.

Box 1 Key features of LEADER[3,10]

- LEADER compared liraglutide (1.8 mg or the maximum tolerated dose) versus placebo for a median follow-up of 3.8 years in 9,340 subjects
- Mean age of subjects was 64 years with a mean duration of diabetes of 13 years
- Mean baseline HbA_{1c} was 8.7% (72 mmol/mol)
- 81% of subjects had established atherosclerotic disease, 31% prior myocardial infarction, 39% prior revascularisation, 16% prior stroke or transient ischaemic attack and 14% investigator-reported heart failure, but this diagnosis was not well characterised
- 76% of subjects were on metformin, 51% sulfonylureas, 6% thiazolidinediones, 44% insulin

Figure 1. 3.8-year event rates (%) comparing liraglutide and placebo for major adverse cardiovascular events (MACE), total mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke and hospitalisation for heart failure (HFH)



Other results from LEADER

Further publications from LEADER are shown in Box 2. A detailed publication on pre-specified renal outcomes was published one year later in the *New England Journal of Medicine*.[11] The pre-specified secondary renal outcome was a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease or death due to renal disease, and it was significantly reduced with liraglutide. The result was driven by reductions in new onset of persistent macroalbuminuria, and there was no difference in persistent doubling of serum creatinine or the need for renal replacement therapy.

Discussion

LEADER was the first CVOT with a GLP-1 receptor agonist to demonstrate significant cardiovascular benefits with a reduction in MACE. The pattern of cardiovascular benefit differed from that seen in EMPA-REG OUTCOME.[8] In both trials there was a significant reduction in cardiovascular deaths and all-cause mortality, but in LEADER the benefit emerged later than in EMPA-REG OUTCOME and no reduction was observed in heart failure events. Similarly, the pattern of renal benefit differed from the detailed renal results of EMPA-REG OUTCOME,[12] with no effect on doubling of serum creatinine. The LEADER investigators suggested that the cardiovascular benefits in LEADER might be related to modified progression of atherosclerotic vascular disease.

Box 2 Results of the LEADER trial

Principal result

- Significant reduction in MACE, cardiovascular death, and death from any cause[3]

Other results from LEADER

- A pre-specified composite renal outcome was reduced in the liraglutide group, driven primarily by reductions in new onset of persistent macroalbuminuria[11]
- MACE and all-cause mortality were significantly reduced by liraglutide in patients with an estimated glomerular rate <60 mL/min/1.73 m^2 [13]
- Patients in the liraglutide group had lower HbA_{1c}, with an estimated reduction at 36 months of 0.4%, with a lower risk of hypoglycaemia, including severe hypoglycaemia, and less glycaemic deterioration[14,15]
- When both groups were combined, patients with severe hypoglycaemia had longer duration of diabetes, more use of baseline insulin, and were more likely to experience a MACE, with higher risk shortly after hypoglycaemia[15]
- Overall there were similar proportions of diabetes-related foot ulcers in the two groups, but there was a significant reduction in amputations with liraglutide versus placebo[16]
- Patients in the liraglutide group reported a modest but significant benefit in patient-reported health status using the European Quality of life Questionnaire (EQ-50) compared with placebo[17]
- There was a significantly increased risk of acute gall bladder or biliary disease with liraglutide versus placebo (141 events versus 88 events)[18]
- There were numerically fewer events of acute pancreatitis; amylase and lipase levels increased in the liraglutide group but did not predict the future risk of acute pancreatitis[19]

Key messages

- LEADER was the sixth published cardiovascular outcome trial of a new diabetes drug, the second with a GLP-1 receptor agonist, comparing liraglutide and placebo
- In LEADER, liraglutide significantly reduced major adverse cardiovascular events, cardiovascular death and all-cause mortality, with no effect on hospitalisation for heart failure
- Subsequent cardiovascular outcome trials with GLP-1 receptor agonists have demonstrated variable results
- The possible mechanisms of benefit of liraglutide and other GLP-1 receptor agonists are under investigation

Conflict of interest The author has received personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Lexicon, MSD, NAPP, Novo Nordisk and Sanofi, outside the submitted work.

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