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COMMENTARY

Lessons from a cardiovascular outcome trial with liraglutide in type 2 diabetes

Cardiovascular disease (CVD) is the leading cause of death and one of the common diabetes-related complications in patients with type 2 diabetes[1]. After the US Food and Drug Administration issued guidelines for assessing the CVD risk of all new glucose-lowering agents for type 2 diabetes in 2008[2], randomized controlled CV outcome trials with new antidiabetic drugs, such as the dipeptidyl peptidase-4 inhibitors (saxagliptin, alogliptin and sitagliptin) and the glucagon-like peptide-1 receptor agonist (GLP-1 RA), lixisenatide, showed CV safety in high CV risk patient populations with type 2 diabtes[3].

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed that liraglutide, a GLP-1 RA, is not only safe, but also helps reduce CV risk and the incidence of death from CV causes[4]. The LEADER trial began in 2010, and followed 9,340 high CV risk adults with type 2 diabetes who were randomized to either a subcutaneous injection of liraglutide once daily or placebo along with standard treatment. The hypothesis of the LEADER trial was that liraglutide would be non-inferior to a placebo on the three-point major adverse cardiac events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). Over a median follow-up period of 3.8 years, three-point major adverse cardiac events were 13% lower in the liraglutide group, and liraglutide was significantly superior for improving outcomes compared with those in the placebo group. CV mortality decreased by 22%, and death from any cause decreased by 15% in the liraglutide group. The rates of non-fatal myocardial infarction and non-fatal stroke tended to be lower in the liraglutide group[4].

A few months before the LEADER trial results were released, those of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial were reported, in which empagliflozin, an inhibitor of sodium-glucose cotransporter 2, lowered the composite outcome of CV mortality, non-fatal myocardial infarction or non-fatal stroke in patients with type 2 diabetes at high risk of CVD[5]. Although direct comparisons cannot be made between the trials, the features of cardiovascular benefits of liraglutide observed in the LEADER trial differed from those of empagliflozin in the EMPA-REG OUTCOME trial. The cardiovascular benefits of empagliflozin were seen earlier at 3 months, compared with 12–18 months in the LEADER trial[4,5]. Empagliflozin markedly reduced the hospitalization for heart failure, which was not significantly reduced in the LEADER trial. The favorable, but not statistically significant effect on non-fatal stroke in the LEADER trial (hazard ratio 0.89) contrasted with a numerical increasing trend in non-fatal stroke (not significant, hazard ratio 1.24) in the EMPA-REG OUTCOME trial. These results suggest that the benefits of empagliflozin observed in the EMPA-REG OUTCOME trial could be related to hemodynamic changes and possible switching of metabolism to fatty acid utilization, whereas the observed benefits in the LEADER trial might have been linked to the modified progression of atherosclerosis[4,5].

The liraglutide group showed a greater reduction in bodyweight (−2.3 kg) and systolic blood pressure (−1.2 mmHg) than the placebo group in the LEADER trial. Fewer nephropathic events and less hypoglycemia were observed in the liraglutide group, possibly because fewer patients used sulfonylureas or insulin. The beneficial CV effects of liraglutide can have been mediated by these favorable factors, and possibly augmented by a direct advantageous effect on cardiovascular tissues, such as myocardium or endothelium. It was also suggested that liraglutide acts as a direct calorie restrictor by reducing appetite, and as calorie restriction mimetic by modifying the adenosine monophosphate-activated protein kinase action[6].

Some questions from the LEADER study need to be addressed. The percentage of patients with established CVD was high in the LEADER trial (81.3% had CVD), and it is unknown whether the results can be extrapolated to other patient groups, such as those without CVD. Does a lower dose of liraglutide also have cardiovascular benefit? What were the principal mechanisms by which cardiovascular events were reduced? Did hypoglycemia affect cardiovascular outcomes? What accounts for the nephroprotective effect of liraglutide? Why was the retinopathy outcome not impacted favorably within the nephropathy outcome time frame? Can these liraglutide results be extended to other drugs in the same class? Answers to these questions will require further analysis of the LEADER data and further studies. The results are valid for the particular groups enrolled in the study up to now, and it is unclear whether they are translatable to the general patients with type 2 diabetes.

Comparing results from CV outcome trials is difficult, because the definition of CV risk or CVD is different in each trial, and accompanying diseases and disease severity of the enrolled participants vary. In addition, event rates, baseline patient characteristics, trial duration and routine

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Table 1 | Cardiovascular outcome trials with glucagon-like peptide-1 receptor agonists

	ELIXA	LEADER	SUSTAIN-6
Trial characteristic			
Drug	Lixisenatide	Liraglutide	Semaglutide
Comparator	Placebo	Placebo	Placebo
No. patients	6,068	9,340	3,297
Median follow up (years)	2.1	3.8	2.1
Primary composite outcome	Death from CV causes, non-fatal MI, non-fatal stroke, hospitalization for unstable angina	Death from CV causes, non-fatal MI (including silent), non-fatal stroke	Death from CV causes, non-fatal MI (including silent), non-fatal stroke
Patients characteristics			
Age, years (mean ± SD)	60.3 ± 9.6	64.3 ± 7.2	64.6 ± 7.4
Diabetes duration, years (mean ± SD)	9.3 ± 8.2	12.8 ± 8.1	13.9 ± 8.1
Baseline HbA1c (mean ± SD)	7.6 ± 1.3	8.7 ± 1.5	8.7 ± 1.5
Baseline BMI (mean ± SD)	30.2 ± 5.7	32.5 ± 6.3	32.8 ± 6.2
% with CV disease	100	81.3	83.0
No. events/100 person-years in placebo arm (%)	6.3	3.9	4.44
CV outcome			
Primary composite outcome, HR (95% CI)	1.02 (0.89–1.17)	0.87 (0.78–0.97)*	0.74 (0.58–0.95)*
Expanded composite outcome†, HR (95% CI)	1.00 (0.90–1.11)	0.88 (0.81–0.96)*	0.74 (0.62–0.89)*
CV death, HR (95% CI)	0.98 (0.78–1.22)	0.78 (0.66–0.93)*	0.98 (0.65–1.48)
Any death, HR (95% CI)	0.94 (0.78–1.13)	0.85 (0.74–0.97)*	1.05 (0.74–1.50)
Non-fatal MI (95% CI)	1.03 (0.87–1.22)‡	0.88 (0.75–1.03)	0.74 (0.51–1.08)
Non-fatal stroke (95% CI)	1.12 (0.79–1.58)§	0.89 (0.72–1.05)	0.61 (0.38–0.99)*
HHF, HR (95% CI)	0.96 (0.75–1.23)	0.87 (0.73–1.05)	0.82 (0.47–1.44)
NNT primary end-point (3 years)	N/A	53	45
Microvascular outcome			
Retinopathy		1.15 (0.87–1.52)	1.76 (1.11–2.78)*
Nephropathy		0.78 (0.67–0.92)*	0.64 (0.46–0.88)*
Metabolic effects			
HbA1c change (%)	−0.27 (−0.31 to −0.22)*	−0.4 (−0.45 to −0.34)*	−1.05 (−1.19 to −0.91)*¶
Bodyweight change (kg)	−0.7 (−0.9 to −0.5)*	−2.3 (−2.5 to −2.0)*	−4.35 (−4.94 to −3.75)*¶
Systolic blood pressure (mmHg)	−0.8 (−1.3 to −0.3)*	−1.2 (−1.9 to −0.5)*	−2.59 (−4.09 to −1.08)*¶

*$P < 0.05$. †The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure. ‡Fatal or non-fatal myocardial infarction (MI). §Fatal or non-fatal stroke. ¶For semaglutide 1.0 mg. CI, confidence interval; CV, cardiovascular; HbA1c, glycated hemoglobin; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat.

care background can be dissimilar between studies. Three CV outcome trials using GLP-1 RAs have been published, including the Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus After Acute Coronary Syndrome During Treatment With Lixisenatide (ELIXA)[7], LEADER[4], and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6)[8] (Table 1). The ELIXA study showed CV safety, but reported no significant CV benefit of the GLP-1RA, lixisenatide[7]. Patients in the ELIXA study were a less broad-based high cardiovascular risk group (acute coronary event in the past 180 days) than those in the LEADER trial, and the trial was of shorter duration. Lixisenatide is short-acting (4–6 h); thus, patients are not covered by the drug for the majority of the day. The SUSTAIN-6 trial showed that treatment with once-weekly semaglutide for 2 years significantly reduces cardiovascular risk[8], which can support a class effect, at least with long-acting GLP-1RAs, and the results of ongoing trials with GLP-1RAs, such as the Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL, exenatide once weekly)[9] and Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND, dulaglutide) are also awaited.

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DISCLOSURE

The authors declare no conflict of interest.

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