Randomised controlled trial

Liraglutide, a glucagon-like peptide-1 agonist, prevented cardiovascular outcomes in patients with type 2 diabetes

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Commentary on: Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–22.

Context

Despite the treatments available for type 2 diabetes, about two-thirds of these patients die from associated heart disease or stroke.[1] Approval of the first glucagon-like peptide-1 agonist (GLP-1), exenatide, by the FDA in 2005 generated an expectation that the clinical outcomes in type 2 diabetes would be improved. However, we still do not have definitive evidence that exenatide does this, although a clinical trial to determine this, the Exenatide Study of Cardiovascular Even Lowering (EXSCEL) trial, is under way.[2] Subsequently, other GLP-1 agonists, including liraglutide, have also been approved and used for 10 years without clinical outcome data.[3] Recently, the results of Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER) have been published.

Methods

LEADER was a double-blinded, randomised, multinational, non-inferiority clinical trial comparing liraglutide and placebo in persons with type 2 diabetes and high cardiovascular risk (eg, prior myocardial infarction). The non-inferiority margin was chosen as 1.30 for the upper boundary of the 95% CI of the HR. Patients had to have an HbA1c of ≥7%, with or without other treatment for type 2 diabetes. Only patients who were able to adhere to the injection regimen (liraglutide or placebo subcutaneously) in a 2-week run in were randomised. The primary composite outcome was the first occurrence of death from cardiovascular disease, non-fatal myocardial infraction or non-fatal stroke.

Findings

After a median follow-up of 3.8 years, the primary outcome had occurred in fewer patients in the liraglutide group (608 of 4668, 13.0%) than in the placebo group (694 of 4672, 14.9%) (HR, 0.87; 95% CI 0.78 to 0.97; p<0.001 for non-inferiority; p=0.01 for superiority), and this was due to a reduction in cardiovascular deaths. Microvascular events were also significantly reduced by liraglutide. At baseline, the mean HbA1C was 8.7%, and at the end of the study, the difference was ~0.4%. During the study, more medications (antidiabetic, diuretics and lipid-lowering) were given to patients in the placebo group than in the liraglutide group. Weight loss was 2.3 kg with liraglutide. The main adverse effects of liraglutide were gastrointestinal, and there were 9.1% discontinuations in the liraglutide group (vs 7.3% in the placebo group). Pancreatic carcinoma occurred in 5 patients in the placebo group and 13 in the liraglutide group (p=0.06).

Commentary

The main reason that patients with type 2 are encouraged to take antidiabetic medications is to reduce clinical outcomes such as cardiovascular deaths, rather than surrogate outcomes such as HbA1c. Thus, clinical trials with clinical outcomes are extremely important and should be timely. Although it has taken 11 years since approval by the FDA for the use of liraglutide to the publication of LEADER, I welcome the finding that liraglutide does reduce cardiovascular deaths, but still there is a question why we had to wait so long for this vital information. Also, I note that there are some limitations and unanswered questions in LEADER. First, as LEADER only included patients who were adherent to subcutaneous injections, the results can only be applied to this cohort, and not to all patients with type 2 diabetes. Second, the level of β blocker use was higher at baseline with liraglutide, and the introduction of diuretics and antidiabetic medications (other than GLP-1 agonists) was higher in the placebo group than the liraglutide group during the study, and it is not known whether these differences contributed to the outcomes. Third, the reduction in HbA1c with liraglutide was modest, and other factors, for example, weight loss, may have contributed to the benefit observed with liraglutide. Probably the most important findings were that HbA1c levels remained high, and the reductions in cardiovascular deaths were modest with liraglutide. This suggests that there is room for further improvements in the treatment of type 2 diabetes.

Implications for practice

In addition to liraglutide, the GLP-1 agonist semaglutide has also recently been shown to reduce cardiovascular outcomes in patients with type 2 diabetes and high cardiovascular risk,[4] whereas lixisenatide did not reduce these outcomes in persons with type 2 diabetes and acute coronary syndromes.[5] Thus, liraglutide and semaglutide should presently be considered the leaders among the GLP-1 agonists to treat patients with type 2 diabetes and high cardiovascular risk. Unless cardiovascular outcomes are established, the other GLP-1 agonists (exenatide, albiglutide, dulaglutide) should be the second choice.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

References

1. **Khardori R**. Diabetes mellitus, type 2. http://emedicine.medscape.com/article/117853-overview (accessed 28 Sep 2016).
2. **Holman RR**, Bethel MA, George J, *et al*. Rationale and design of the Exenatide study of cardiovascular event lowering (EXSCEL) trial. *Am Heart J* 2016;**174**:103–10.
3. **Doggrell SA**. Are we waiting too long for the cardiovascular outcome trials with the glucagon-like peptide-1 receptor agonists? *Expert Opin Drug Safety* 2015;**14**:801–5.
4. **Marso SP**, Bain SC, Consoli A, *et al*. Semiglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016. Published Online First.
5. **Pfeffer MA**, Claggett B, Diaz R, *et al*. Lixisenatide in patients with type 2 diabetes and acute coronary syndromes. *N Engl J Med* 2015;**373**:2247–457.