Randomised controlled trial

Semaglutide is non-inferior to placebo for cardiovascular outcomes in patients with type 2 diabetes

10.1136/ebmed-2016-110652

Denise Campbell-Scherer

Department of Family Medicine and Alberta Diabetes Institute, University of Alberta, Edmonton, Alberta, Canada

Correspondence to: Dr Denise Campbell-Scherer, Alberta Diabetes Institute, Clinical Research Unit, 2-004 Li Ka Shing Ctr, 87 Ave and 112st, Edmonton, Alberta T6G 2E1, Canada; denise.campbell-scherer@ualberta.ca

Commentary on: Marso SP, Bain SC, Consoli A, *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *NEJM* 2016;375:1834–44.

Context

Semaglutide is a glucagon-like peptide 1 (GLP-1) analogue under development for the treatment of type 2 diabetes. It is molecularly related to liraglutide but has a longer half-life, requiring once weekly dosing. US Food and Drug Administration (FDA) regulatory guidance requires evidence that new therapies for type 2 diabetes are not associated with an unacceptable increase in cardiovascular risk.[1 2] This is defined as evidence that compared with placebo the risk ratio estimate has an upper 95% CI of 1.3; the initial preapproval phase may target the 1.8 margin; however, if 1.3 is not achieved then a postmarketing randomised safety trial is required.[1 2]

Methods

This was an industry-sponsored, non-inferiority randomised controlled trial in 3297 patients from 230 sites randomised (1:1:1:1), stratified (cardiovascular disease status, insulin treatment, and glomerular filtration rate at screening), to receive semaglutide (either 0.5 or 1.0 mg subcutaneously, weekly) or placebo. In all treatment arms, there was emphasis on adherence to best practice for blood pressure, lipid control, glycaemic control and control of other cardiovascular risk factors. Participants had type 2 diabetes and were at least 50 years of age with established cardiovascular disease, chronic heart failure, or chronic kidney disease (stage 3 or higher), or at least 60 years of age with at least one cardiac risk factor. Exclusions were appropriate. The primary outcome measure was a major adverse cardiac event (MACE) composite of death, non-fatal myocardial infarction (MI) and non-fatal stroke. Analysis was by intention-to–treat (ITT), with a post hoc per protocol analysis to test for increase in type 1 error. The non-inferiority margin was a HR of 1.8 in accordance with the FDA guidance.[1] Safety analyses to assess nephropathy and retinopathy were performed on all participants who had received at least one dose of their allocated medication. Testing for superiority was not prespecified in this study.

Findings

Randomisation, equal treatment with cardiovascular risk factor modifying medications and follow-up were excellent. Patients in the placebo arm received more supplemental glucose lowering medications; adherence to recommended cardiovascular risk lowering medications was very good in both groups. Semaglutide was non-inferior to placebo for the primary MACE outcome measure (HR 0.74; 95% CI 0.58 to 0.95), with most of the effect from differences in non-fatal stroke (HR 0.61; 95% CI 0.38 to 0.99), less from non-fatal MI (HR 0.74; 95% CI 0.51 to 1.08) and death from cardiovascular causes (HR 0.98; 95% CI 0.65 to 1.48). Hospitalisations due to heart failure had too few events to provide a clear estimate of risk (HR 1.11; 95% CI 0.77 to 1.61). Discontinuations of medication rates were similar in both arms, and per protocol estimates were similar to the ITT estimate. In the safety analyses, semaglutide had less new or worsening nephropathy, but there was an increase in retinopathy complications in the semaglutide arm (3%), compared to the placebo arm (1.8%) (HR 1.76; 95% CI 1.11 to 2.78). These included vitreous haemorrhage, blindness and the need for retinal photocoagulation or intravitreal agents. Gastrointestinal side effects were the most common side effects leading to discontinuation of semaglutide. There were no differences in pancreatitis, gallbladder disorders or neoplasms between the groups.

Commentary

GLP-1 receptor agonists are an exciting class of medications providing new therapeutic options in type 2 diabetes. With a more favourable impact on body weight and weekly dosing regimen, they are a potentially attractive addition to lifestyle interventions and biguanides. In this well-done phase III cardiovascular safety study, there was a higher than expected event rate in this high-risk population resulting in a robust estimate of non-inferiority of semaglutide over placebo for the primary MACE outcome measure; the trial was not designed for testing superiority, a distinction which is being missed in the literature.[3] The overall number of events was low for assessing important secondary outcomes such as heart failure and cardiovascular death.[2 4] This population was at high cardiovascular risk, and the authors caution that generalisability of these results to other populations with longer treatment times is unknown. In contrast, the LEADER study of liraglutide in 9340 high-risk patients compared to placebo had 1302 events and was able to demonstrate a reduction in the primary MACE outcome (HR 0.87; 95% CI 0.78 to 0.97) with prespecified superiority testing and improvement in cardiovascular death in the liraglutide group (HR 0.78; 95% CI 0.66 to 0.93); but there was no superiority for non-fatal MI or non-fatal stroke.[5] There are several large ongoing randomised controlled trials of assorted GLP-1 analogues that will examine long-term cardiovascular outcomes in patients with established cardiovascular disease.[3] There are compelling arguments that superiority trials should be conducted to examine efficacy in reducing cardiovascular risk.[2] More work will need to be performed to assess the higher risk of diabetic retinopathy complications seen in this trial.

Implications for practice

Ultimately, the most important thing is to provide patients and healthcare providers with robust estimates of efficacy and harms in terms of patient-important outcomes. Research to date suggests that liraglutide improves major adverse cardiovascular events and cardiovascular death. Further research is required to provide this information with confidence for semaglutide.

Competing interests DC-S has received support from the Canadian Obesity Network for an unrestricted educational grant for primary care obesity training supported by Novo Nordisk.

Provenance and peer review Commissioned; internally peer reviewed.

Linked

► http://dx.doi.org/10.1136/ebmed-2017-110685

Evid Based Med: first published as 10.1136/ebmed-2016-110652 on 7 March 2017. Downloaded from http://ebm.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

References

1. **Food and Drug Administration.** Guidance for industry—Diabetes mellitus evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM071627.pdf (accessed 13 Feb 2017)
2. **Menon V**, Lincoff AM. Cardiovascular safety evaluation in the development of new drugs for diabetes mellitus. *Circulation* 2014;**129**:2705–13.
3. **Singh AK**, Singh R. SAVOR-TIMI to SUSTAIN-6: a critical comparison of cardiovascular outcome trials of antidiabetic drugs. *Exp Rev Clin Pharmaco* 2017. doi:10.1080/17512433.2017.1287562 [Epub ahead of print 6 Feb 2017]
4. **Geiger MJ**, Mehta C, Turner JR, *et al*. Clinical development approaches and statistical methodologies to prospectively assess the cardiovascular risk of new antidiabetic therapies for type 2 diabetes. *Ther Innov Regul Sci* 2015;**49**:50–64.
5. **Marso SP**, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *NEJM* 2016;**375**:311–22.

Evid Based Med: first published as 10.1136/ebmed-2016-110652 on 7 March 2017. Downloaded from http://ebm.bmj.com/ on April 9, 2024 by guest. Protected by copyright.