Type 2 diabetes: liraglutide reduces cardiovascular risk in people at high risk of having a cardiovascular event

A randomised controlled trial has compared the GLP-1 mimetic liraglutide with placebo, as an add-on to standard care, in people with type 2 diabetes who had established cardiovascular disease or were at high risk of developing it. Liraglutide reduced the risk of cardiovascular events and death from any cause, over the average 3.5 years of the study. NICE guidance on type 2 diabetes recommends that GLP-1 mimetics are used as an alternative to insulin in people who meet certain criteria relating to body weight or for whom insulin therapy would have significant occupational implications.

Overview and current advice

It is well known that type 2 diabetes is associated with an increased risk of macrovascular disease (such as myocardial infarction) and microvascular disease (including nephropathy and retinopathy). The NICE guideline on type 2 diabetes has recommendations on patient education, dietary advice, blood pressure management, antiplatelet therapy, management of blood glucose and management of complications. Recommendations on the management of blood lipids in people with type 2 diabetes are given in the NICE guideline on lipid modification. All these components – not only blood glucose management – should be given due consideration in the care of people with type 2 diabetes.

Although all blood-glucose-lowering medicines are effective (at a population level) in reducing HbA1c levels, clinical outcome data – particularly data relating to cardiovascular (CV) outcomes – are few. Improvements in surrogate markers (including HbA1c levels) do not automatically confer benefits on mortality or morbidity. As discussed in the NICE key therapeutic topic on type 2 diabetes, the evidence that, compared with conventional control, tight glycaemic control per se reduces macrovascular or microvascular risks or risk of death from any cause is limited. Moreover, risks may become apparent only over time when medicines are used widely in a diverse population. Despite its effectiveness in reducing HbA1c levels, rosiglitazone (launched in 2000) was found to increase the risk of CV disease and its marketing authorisation was finally suspended in 2010 (see the Drug Safety Update article from October 2010).

The evidence for clinical benefits from blood-glucose-lowering medicines is summarised in the NICE key therapeutic topic on type 2 diabetes. Metformin, sulfonylureas and insulin have positive data for some CV outcomes from the UK Prospective Diabetes Study (UKPDS). Other blood glucose lowering medicines have not shown such CV benefits. For example, in the PROACTIVE study (Dormandy et al. 2005) of pioglitazone in people with type 2 diabetes and pre-existing major macrovascular disease,
pioglitazone did not reduce the primary end point – a composite of death from any cause or several specified CV outcomes, but did increase the incidence of oedema, weight gain and heart failure.

More recently, and partly in response to the experience with rosiglitazone, drug regulators have started to demand cardiovascular safety assessments of new blood-glucose-lowering medicines. Such studies for alogliptin, saxagliptin and sitagliptin found that, although they were non-inferior to control with regard to the study composite endpoints (death from CV causes or specified nonfatal CV outcomes), they did not reduce the risk of these endpoints. For more information, see the medicines evidence commentaries Type 2 diabetes: study finds no benefit from alogliptin on cardiovascular outcomes in people with a recent acute coronary syndrome (discussing the EXAMINE study [White et al 2013]¹), Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes (discussing the SAVOR–TIMI 53 study [Scirica et al 2013]²), and the TECOS study (Green et al. 2015)³.

A CV outcome study (EMPA-REG OUTCOME [Zinman et al. 2015]) of the sodium glucose cotransporter 2 (SGLT-2) inhibitor empagliflozin has recently been published⁴. This large randomised controlled trial (RCT) found that adding empagliflozin to standard care in people with type 2 diabetes and established cardiovascular disease reduced the risk of the composite end point of death from CV causes, non-fatal MI or non-fatal stroke. However, this was driven by a reduction in the risk of CV death, not the risk of MI or stroke. See the medicines evidence commentary Type 2 diabetes: study finds empagliflozin reduces adverse cardiovascular outcomes, which discusses this study in more detail. The MHRA has warned of the risks of diabetic ketoacidosis with all SGLT-2 inhibitors: see the Drug Safety Update Article published in April 2016.

The NICE guideline on type 2 diabetes recommends that, if triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, glucagon-like-peptide-1 (GLP-1) mimetics in combination with metformin and a sulfonylurea should be considered, but only in people who meet certain criteria relating to body weight or for whom insulin therapy would have significant occupational implications. GLP-1 therapy should be continued only if the person has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months). GLP-1 mimetics in combination with insulin should be offered only with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

**New evidence**

The effects on CV risk of liraglutide, a GLP-1 mimetic, have been assessed in a multicentre double blind RCT, the LEADER study (Marso et al, 2016)⁵. The study recruited 9340 people (64% men, mean age 64 years) with type 2 diabetes (mean duration 13 years), who were either aged 50 years or older and had one or more specified CV conditions (81% of participants) or were 60 years or older with one or more specified CV risk factors. Specified CV conditions were coronary heart disease (including prior myocardial infarction [MI] 31% and prior revascularisation 39%), cerebrovascular disease (16%), peripheral vascular disease, chronic kidney disease of stage 3 or greater (26%), or chronic heart failure of New York Heart Association (NYHA) class II or III (14%). CV risk factors were microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index <0.9. Major exclusion criteria included the use of dipeptidyl peptidase-4 (DPP-4) inhibitors, pramlintide (an amylin analogue not available in the UK), or rapid-acting insulin.

At baseline, 92% of people were taking antihypertensive medication, and in 83% of the total study population this included an ACE inhibitor and/or an angiotensin receptor blocker. Fewer people (72%) were taking a statin. The most commonly used blood-glucose-lowering medicine was metformin, taken by 76% of participants at baseline. Half the study population (51%) were taking a sulfonylurea and 45% of the population were using insulin. The mean HbA1c was 8.7% (72 mmol/mol), mean body
mass index (BMI) was 33 kg/m\(^2\) and mean blood pressure was 136/77 mmHg. Lipid levels were not reported.

After a 2-week placebo run-in phase to establish whether patients were able to adhere to the injection regimen, patients were randomly assigned, in a 1:1 ratio, to receive either 1.8 mg (or the maximum tolerated dose) of liraglutide or matching placebo once daily as a subcutaneous injection in addition to standard care. The median duration of exposure to liraglutide or placebo was 3.5 years (median follow up 3.8 years). The prespecified analysis at 36 months found a mean between-group difference in HbA1c of 0.40% (about 4 mmol/mol) At that time point, weight loss compared to baseline was a mean 2.3 kg (95% CI 2.0 kg to 2.5 kg) greater in the liraglutide group than in the control group, and systolic blood pressure was a mean 1.2 mmHg lower and diastolic blood pressure was a mean 0.6 mmHg higher.

The primary composite outcome in the time-to-event analysis was the first occurrence of death from CV causes, nonfatal (including silent) MI, or nonfatal stroke. This occurred in statistically significantly fewer people in the liraglutide group than the placebo group: 13.0% compared with 14.9% respectively, hazard ratio (HR) 0.87, 95% confidence interval [CI] 0.78 to 0.97, p=0.01. There was also a statistically significant reduction in the risk of death from any cause (8.2% compared with 9.6%, HR 0.85, 95% CI 0.74 to 0.97, p=0.02), death from CV causes (4.7% compared with 6.0%, HR 0.78, 95% CI 0.66 to 0.93, p=0.007). There was no statistically significant difference in the rates of nonfatal MI or nonfatal stroke. The risk of nephropathy (new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml per minute per 1.73 m\(^2\), the need for continuous renal-replacement therapy, or death from renal disease) was lower in the liraglutide group (1.5 events compared with 1.9 events per 100 patient years, HR 0.78, 95% CI 0.67 to 0.92, p=0.003), but there was no statistically significant difference in the risk of retinopathy.

There was no statistically significant between-group difference in the rate of adverse events overall, but more people in the liraglutide group than the placebo group discontinued treatment because of adverse effects (9.5% compared with 7.3%, p<0.001). The authors state that this appears to have been due mainly to gastrointestinal disorders in the liraglutide group.

Severe hypoglycaemia (requiring third party assistance) was less common in the liraglutide group than in the placebo group (2.4% compared with 3.3%, rate ratio 0.69, 95% CI 0.51 to 0.93, p=0.02). The authors note that, during the trial, fewer patients in the liraglutide group were treated with medicines associated with hypoglycaemia (insulin, sulfonylurea, and glinides) than in the placebo group. Conversely, acute gallstone disease was more common in the liraglutide group (3.1% compared with 1.9%, p<0.001). Rates of pancreatic adverse events were too low to draw meaningful conclusions.

**Commentary**

**Commentary provided by Ian Lewin, Honorary Consultant Endocrinologist, North Devon District Hospital**

It is perhaps surprising and also disappointing that simply lowering blood glucose in type 2 diabetes confers such little benefit in terms of cardiovascular risk reduction. It is clearly important to know that new treatments for type 2 diabetes do not increase cardiovascular risk, and it would also be a great advantage if they were known to reduce such risk. Data are now coming through which help to inform the debate on this subject. The published outcome studies for the DPP-4 inhibitors alogliptin, saxagliptin and sitagliptin have not shown a reduction in risk, nor did a meta-analysis of data from studies for vildagliptin\(^4\); the CAROLINA study of linagliptin is not expected to complete until 2019.

In a different class of treatments, empagliflozin appeared to reduce the risk of composite cardiovascular endpoints\(^4\). Can we assume cardiovascular outcomes are a class effect of SGLT-2
inhibitors, or do we need further trials? The CANVAS study of canagliflozin and the DECLARE-TIMI 58 study of dapagliflozin are expected to complete in 2017 and 2019 respectively. We now have the beginnings of a parallel discussion with GLP-1 agonists. The LEADER trial showed a reduction in cardiovascular endpoints in a high risk population with liraglutide whereas lixisenatide, in a people with recent acute coronary syndrome, did not.

The LEADER trial was well conducted but it will surely come under much careful scrutiny. Was practice consistent across all 410 contributing sites in the 32 countries? How comparable is a placebo injection when the active drug has characteristic side effects and the dose may be titrated to the limits of tolerance? Which glucose lowering drugs were used to escalate treatment in the placebo group? How matched are the 2 groups when there is a greater non-cardiovascular death rate in the placebo group? If the cardiovascular death rate was lower in the treatment group would you also expect a significant reduction in non-fatal cardiovascular events? Do we have enough data to decide whether both groups were balanced for cholesterol, lipid lowering and other cardiovascular risk reduction measures? The authors point out that 66 patients with high cardiovascular risk, within the age range and therapeutic framework defined by their study, would need to be treated with liraglutide at the upper dose for 3 years to prevent one event in their composite primary outcome. What are the implications of this treatment, in terms of cost effectiveness, for people of different ages, at lower risk, and already on effective preventive measures?

The LEADER trial adds interest and optimism to an important subject but, as yet, it does not provide robust evidence to depart from the current recommendations in the NICE guidance.

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References

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