More cardiovascular outcomes trials in people with diabetes: time to change the NICE guidelines

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There is a demand from regulators that new treatments for the management of hyperglycaemia in people with type 2 diabetes should not increase cardiovascular risk.1-3 For most new therapies this will include the performance of a dedicated randomised-controlled cardiovascular outcomes trial (CVOT). This can be conducted prior to licensing, like the SUSTAIN-6 trial with semaglutide,4 or post-licensing, like the LEADER trial with liraglutide.4 The results of CVOTs with albiglutide, a once-weekly GLP-1 receptor agonist, and liraglutide, a DPP-4 inhibitor, were presented at the recent meeting of the European Association for the Study of Diabetes (EASD) in Berlin.5,6 As there are now several completed trials with GLP-1 receptor agonists and DPP-4 inhibitors it is relevant to place the results of these studies in the context of the results of previous studies.

Harmony Outcomes

Albiglutide is a once-weekly GLP-1 receptor agonist composed of two copies of modified human GLP-1 fused to human albumin. It was available for clinical use in the US and Europe from 2014. In the summer of 2017 the manufacturer GlaxoSmithKline announced that albiglutide would be withdrawn from the worldwide market by 2018 for economic reasons that were not detailed, and marketing ceased in July 2018. A lack of potency compared to other GLP-1 receptor agonists,7 and the inconvenience to the patient of having to reconstitute the lyophilised powder with a diluent and wait 15–30 minutes before injection8 may have contributed to the low use of albiglutide in countries where other once-weekly GLP-1 receptor agonists were available.

Harmony Outcomes was a post-licensing CVOT comparing albiglutide and placebo in 9463 people with type 2 diabetes and established cardiovascular disease, including coronary vascular disease, cerebrovascular disease and peripheral arterial disease.9 Other inclusion criteria included age over 40 years, and HbA1c over 7.0% (53mmol/mol). At baseline 70% of participants had coronary heart disease, 47% had a previous myocardial infarction and 20% were recorded as having baseline heart failure by their local clinical investigator. Subjects were followed for a median of 1.6 years and the primary outcome was major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Subjects in the albiglutide arm had a statistically significant 22% reduction in MACE compared to the placebo group. This was despite one-quarter of the subjects discontinuing therapy during this short study. Of the components of the MACE outcome, myocardial infarction (fatal or non-fatal) was significantly reduced, with insignificant effects on stroke and cardiovascular death. The number of subjects needed to treat with albiglutide for 1.6 years to prevent one major adverse cardiovascular event was 50. In the placebo group there was as expected a greater use of sulphonylureas and insulin, including greater use of bolus insulin. Hypoglycaemia rates were lower with albiglutide, including less severe hypoglycaemia. Pancreatitis and pancreatic cancer were the same in the two groups, and there was no difference in retinopathy events.

The results of Harmony Outcomes, with a significant reduction in MACE, are similar to the results of LEADER with liraglutide and SUSTAIN-6 with semaglutide.3,4 It seems unlikely that the cardiovascular benefits seen in Harmony Outcomes were due to effects on conventional risk factors as the reductions in HbA1c, body weight and blood pressure that were observed were modest, suggesting some other mechanism of cardiovascular benefit. Albiglutide, liraglutide and semaglutide are all true GLP-1 analogues with an amino-acid structure similar to native GLP-1. The ELIXA trial with lixisenatide was neutral,9 and the EXSCEL trial with once-weekly exenatide showed non-inferiority but failed to demonstrate superiority.10 These are both GLP-1 receptor agonists based on the exenatid molecule, so have a structure that contains multiple different amino acids from native GLP-1. One explanation for the different results of these CVOTs is that the molecules may be interacting differently with GLP-1 receptors in the vascular tree. We have to be cautious, however, as EXSCEL was a study following a pragmatic trial design which meant that subjects were exposed to the trial drug for much shorter than was intended.11 ELIXA was performed in subjects with a recent acute coronary syndrome, and lixisenatide has been shown to be metabolically inferior to liraglutide in a well-conducted, double blind trial.12 It remains possible that there is a true class effect of GLP-1 receptor agonists in reducing cardiovascular outcomes when these are administered in suitable doses for a reasonable period of time. Dulaglutide is a once-weekly GLP-1 receptor analogue composed of two molecules of GLP-1 linked to a modified human IgG4 Fc fragment by a small peptide. The REWIND CVOT with dulaglutide includes a large number of patients without prior cardiovascular disease,13 and REWIND should be completed soon.

The positive results of Harmony Outcomes were clearly not anticipated by GlaxoSmithKline, who have to be congratulated for finishing the study after they had decided to stop marketing the product. GlaxoSmithKline have indicated that they will continue to explore opportunities to divest albiglutide to a company with the right expertise and resources to realise its full potential for patients.

CARMELINA

Previous CVOTs with DPP-4 inhibitors have shown no reductions in major adverse cardiovascular events.14-16 CARMELINA examined the effects of lixisenatide versus placebo in a large group of patients with type 2 diabetes, and the study cohort was enriched by targeting people
with chronic kidney disease (CKD). Of the 6991 study participants 57% had established cardiovascular disease, 74% had CKD and 33% had both established cardiovascular disease and CKD.6 Subjects were followed for a median of 2.2 years and the primary outcome was MACE, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.17

No difference was seen in MACE in subjects treated with linagliptin compared to placebo, and linagliptin was non-inferior but not superior to placebo. This is similar to the results of SAVOR TIMI with saxagliptin,13 EXAMINE with alogliptin,15 and TECOS with sitagliptin.16 No difference was seen in all-cause mortality with alogliptin, and this was higher than in previous trials with DPP-4 inhibitors reflecting the high mortality of patients with diabetes and CKD. The SAVOR-TIMI study with saxagliptin demonstrated an increase in adjudicated hospitalisation for heart failure,18 and in the EXAMINE trial with alogliptin there was a similar increase in hospitalisation for heart failure a subgroup.19 The results of CARMELINA sit alongside the results of the TECOS trial with sitagliptin in showing neutrality for heart failure outcomes.

The slight but significant reduction in the progression of albuminuria disease was seen with alogliptin in CARMELINA, and this should be considered as a weak surrogate outcome as there was no reduction in a composite of harder renal outcomes. Nevertheless, the subjects in CARMELINA were a high-risk group, with a lot of baseline renal disease, so linagliptin can continue to be used with safety in this group of patients based on the cardiovascular safety that has been demonstrated in CARMELINA.

Should guidelines change based on the results of CVOTs?

We now have the results of several CVOTs with DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists. The results of these studies have been incorporated into national and international guidelines on the management of type 2 diabetes. As an example, the recent guideline from the Scottish Intercollegiate Guidelines Network on the pharmacological management of glycaemic control in people with type 2 diabetes has included key recommendations that ‘in individuals with type 2 diabetes and established cardiovascular disease SGLT2 inhibitors with proven cardiovascular benefits (currently empagliflozin and canagliflozin) should be considered’ and ‘for individuals with type 2 diabetes and established cardiovascular disease GLP-1 receptor agonist therapies with proven cardiovascular benefits (currently liraglutide) should be considered.’20 Semaglutide and albiglutide can now be added to the list of GLP-1 receptor agonist therapies with proven cardiovascular benefits.

The recently published ADA/EASD consensus statement is even more specific and recommends that following metformin as foundation therapy patients with established atherosclerotic vascular disease should be treated with an SGLT2 inhibitor and/or a GLP-1 receptor agonist.21

Despite this wealth of accumulating evidence the NICE guidelines remain unchanged, with no acknowledgement that recent CVOTs have demonstrated that specific drugs have proven cardiovascular benefits in identifiable groups of patients, and no update is planned to start before 2020.22

Three years ago when the results of EMPA-REG OUTCOME became available I suggested that it was time to change the guidelines.23 Three years later it is an imperative that NICE updates guidelines on the management of type 2 diabetes. How many people with type 2 diabetes and established cardiovascular disease will have to suffer the consequences of a possibly fatal further cardiovascular event, which could have been prevented with easily-available modern therapies for type 2 diabetes, before NICE will act?24

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Declaration of interests

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References