Recent cardiovascular safety trials with anti-diabetic drugs: time to change the guidelines!

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The Food and Drug Administration in the US and the European Medicines Agency require evidence that new anti-diabetic drugs do not increase cardiovascular events, i.e. that they are safe from a cardiovascular perspective. To do this pharmaceutical companies have to collect blindly adjudicated information on cardiovascular outcomes during the Phase 3 development programme for the drug, and demonstrate that the new therapy is not associated with an unacceptable increase in cardiovascular events. Patients at high cardiovascular risk are recruited to the Phase 3 development programme so that there will be sufficient events to adjudicate, and the outcomes of interest are largely atherosclerotic events: myocardial infarction, stroke, cardiovascular death and unstable angina. Other cardiovascular outcomes, such as hospitalisation for heart failure, may be included as secondary outcomes. Certain statistical criteria have to be met, and often the licensing authorities will require the performance of a large, randomised, controlled cardiovascular safety trial, either to add data to cohort data from the Phase 3 studies before a licence is granted, or to confirm the results from the Phase 3 studies after licensing.

Three eagerly awaited large, randomised, controlled cardiovascular safety trials with new anti-diabetic drugs have recently been completed.1–3 The results of these studies are of wide interest to the diabetes and cardiology clinical scientific communities, and the results have been presented at diabetes and cardiology scientific meetings. These have studied drugs in each of the new classes of anti-diabetic drugs: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor; lixisenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist; and empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor. There are important differences in design of these trials, and this editorial briefly describes each study design, the results, and possible implications of the results for the management of people with type 2 diabetes.

TECOS

Previous cardiovascular safety studies with saxagliptin in diabetic patients with high cardiovascular risk or existing cardiovascular disease4 and alogliptin in diabetic patients following acute coronary syndromes5 had demonstrated cardiovascular safety for these drugs, with no increase in major adverse coronary events (non-inferiority), but neither had they demonstrated any benefit (superiority).6 Unexpectedly, an increase in hospitalisation for heart failure was seen in saxagliptin compared to placebo,7 and a similar increase in hospitalisation for heart failure was seen in one subgroup in EXAMINE.8 Both studies were relatively short, and in SAVOR patients received saxagliptin or placebo for a median of 2.1 years, and in EXAMINE alogliptin or placebo for a median of only 18 months.

TECOS was a longer study comparing sitagliptin and placebo in 14 671 patients with type 2 diabetes and existing cardiovascular disease for a median of 3.0 years. Sitagliptin was non-inferior to placebo and did not increase the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for unstable angina, and on a secondary analysis sitagliptin was not superior to placebo. Close scrutiny of hospitalisation for heart failure data did not show any hint of an increase with sitagliptin compared to placebo.

Collectively, the results of the three studies are reassuring with regard to atherosclerotic events. DPP-4 inhibitors have only minor effects on weight, lipids or blood pressure so the lack of any cardiovascular benefit is not surprising. It is not clear why saxagliptin and alogliptin increased hospitalisation for heart failure, while sitagliptin did not. DPP-4 inhibitors also have effects in inhibiting the degradation of multiple other peptides, including BNP, substance P, and NPY.9 It is possible that saxagliptin and alogliptin are having adverse effects on one of these peptides, which are not shared with sitagliptin, and further research is required in this area. There are no plans for a cardiovascular safety trial with vildagliptin.10 There are two large cardiovascular safety studies with linagliptin, comparing linagliptin with a sulphonylurea and with placebo, and these will be examined closely for heart failure outcomes.

ELIXA

Lixisenatide is a short-acting GLP-1 receptor agonist, and like exenatide it is a synthetic version of exendin-4. As a class, GLP-1 receptor agonists have multiple favourable effects on cardiovascular risk factors and risk makers, including reductions in glycaemia, weight, and systolic blood pressure. Lixisenatide has been promoted as a once-daily injection, and has its main effect on postprandial blood glucose, with little effect on fasting blood glucose.

ELIXA was a large, randomised, controlled trial comparing lixisenatide with placebo in 6068 patients with type 2 diabetes who had suffered an acute coronary syndrome within the previous 180 days.2 There was no significant difference in the primary endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for unstable angina. Again, non-inferiority was confirmed, so the safety criteria established by the FDA and the EASD were met, but there was no suggestion of superiority. There were no effects on hospitalisation for heart failure, which was a secondary outcome.
ELIXA is the first of the cardiovascular safety studies with a GLP-1 receptor agonist to report, and studies are ongoing with lixisenatide, exenatide once-weekly, dulaglutide, albiglutide, and semaglutide. There are bigger differences among the different drugs in the GLP-1 receptor agonist class than exist between DPP-4 inhibitors, so some of these studies may give different results. As mentioned, lixisenatide is relatively short acting, so longer-acting drugs might give different results. Lixisenatide targets postprandial blood glucose, and while there is a large literature indicating the importance of postprandial glucose as a risk factor for cardiovascular events in non-diabetic subjects, studies in people with type 2 diabetes have been less conclusive. Indeed, a previous study targeting postprandial blood glucose with lispro insulin in people with type 2 diabetes following acute coronary syndrome showed no difference compared to targeting fasting and pre-meal blood glucose. One interpretation of the ELIXA results is that targeting postprandial blood glucose is not of any benefit in patients following acute coronary syndromes.

EMPAGLIFLOZIN

There are now three SGLT2 inhibitors available for clinical use in Europe: dapagliflozin, canagliflozin and empagliflozin.

EMPAGLIFLOZIN was a large cardiovascular safety study in 7020 people with type 2 diabetes and existing cardiovascular disease. It compared empagliflozin 10mg, empagliflozin 25mg, and placebo in addition to usual standards of care, and nearly half of the participants were on insulin. The first patient was enrolled in 2010 and the study was completed in 2015. Nearly half of the patients had a prior myocardial infarction, a quarter had a previous coronary artery bypass graft, a quarter had a history of stroke, and a fifth had peripheral arterial disease. One quarter had baseline eGFR between 30 and 60ml/min/1.73m², and 10% had heart failure, so this was a very high-risk group of subjects.

The results were remarkable, as empagliflozin was superior to placebo in reducing major adverse coronary events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) and reduced total mortality by 32%. The effects were the same for both doses of empagliflozin. Hospitalisation for heart failure was also significantly reduced by a third. With regard to side effects and safety, there was the expected increase in genital infections in patients treated with empagliflozin, and there was a slight increase in urosepsis, but there was no increase in hypoglycaemia, fractures or ketoacidosis.

Several mechanisms for the benefit can be postulated, including reductions in blood pressure, weight loss and diuresis, and it seems likely that all of these mechanisms contribute to the benefit rather than it being a single factor. It will not be possible to say if this benefit is unique to empagliflozin, or if this is a class effect shared with other SGLT2 inhibitors, until the cardiovascular safety trials with the other SGLT2 inhibitors are completed.

Discussion

The impressive reduction in total mortality that was seen with empagliflozin in the EMPA-REG OUTCOME trial will lead to a change in the management of this challenging group of patients, who have existing cardiovascular disease and may be uncontrolled on insulin therapy, and initially the increased use of empagliflozin should be focused on this group. As there are currently no data to support a similar benefit with dapagliflozin or canagliflozin it is likely that empagliflozin will quickly become the most prescribed drug in this class.

Three studies have now demonstrated no cardiovascular benefits with DPP-4 inhibitors, and although these drugs are well tolerated they are weight neutral. From a patient perspective empagliflozin was also well tolerated and reduced weight. The prescribing of DPP-4 inhibitors may well decline in favour of empagliflozin.

Writers of guidelines will need to consider revision of guidelines based on the results of these studies, and in time empagliflozin could become the favoured second-line therapy after metformin. In particular, the current draft guideline from NICE for the management of type 2 diabetes, which includes mention of SGLT2 inhibitors as a footnote, will need extensive further revision as reductions in mortality are a strong driver to improved cost-effectiveness, as well as a desirable outcome for clinicians and people with diabetes.

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Declaration of interests

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References