Inconclusive effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes

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Following the rosiglitazone controversy, where rosiglitazone was associated with an increase in myocardial infarctions in its phase 3 development programme, regulatory bodies including the Food and Drug Administration (FDA) and European Medicines Agency (EMA) mandate robust cardiovascular safety for new antidiabetes drugs. This includes recruiting patients at high cardiovascular risk to the phase 3 programme e.g. older patients, patients with chronic kidney disease and patients with established cardiovascular disease, and blindly adjudicating cardiovascular events in the programme. It also usually includes a dedicated, randomised-controlled cardiovascular outcomes trial (CVOT), which may be completed before or after licensing has been approved.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce glucose concentrations in people with type 2 diabetes mellitus through various mechanisms, with additional favourable effects on weight, blood pressure and the lipid profile. Three cardiovascular outcome trials with GLP-1 RAs have been completed and published (ELIXA with lixisenatide, LEADER with liraglutide, and SUSTAIN-6 with semaglutide). All three trials confirmed cardiovascular safety by demonstrating non-inferiority for MACE (major adverse coronary events, i.e. cardiovascular death, non-fatal myocardial infarction, non-fatal stroke). Two of these trials (LEADER and SUSTAIN-6) then demonstrated superiority with reductions in MACE. In addition, the top-line results of the FREEDOM-CVO trial with ITCA 650, an implanted subcutaneous system for the delivery of exenatide, have been reported as showing non-inferiority but not superiority.

The original twice-daily formulation of exenatide was licensed before these stringent requirements were enforced so no CVOT with twice-daily exenatide is planned. The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial was academically led by the Diabetes Trials Unit in Oxford and the Duke Clinical Research Institute and designed to satisfy the FDA criteria and further assess the effect of exenatide once-weekly on cardiovascular outcomes in patients with type 2 diabetes.

EXSCEL study design, subjects, and results
EXSCEL recruited 14 752 patients with diabetes from 687 sites in 35 countries. Three-quarters of the subjects had prior cardiovascular disease at randomisation, and the rest were deemed to be at various levels of cardiovascular risk. The investigators adopted a ‘pragmatic’ approach to the trial, so there were broad inclusion/exclusion criteria to give a representative patient population, there was no run-in phase, and study visits were every six months to minimise interference with usual care.

The primary composite outcome of major adverse cardiovascular events (MACE, i.e. cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) confirmed non-inferiority with a p-value of <0.001. Superiority was not demonstrated, and the p-value for differences in the MACE rate was 0.061. As superiority was not demonstrated, formal statistical analysis of other outcomes should not be performed. Nevertheless, in the oral presentation of the results at the EASD in Lisbon, but not in the formal New England Journal of Medicine publication, the investigators suggested a reduction in all-cause mortality with a ‘nominal’ p-value of 0.016. No benefits were claimed for cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospitalisation for acute coronary syndrome, or hospitalisation for heart failure.

Premature permanent discontinuation of trial regimen
One of the major limitations of the trial is the very high premature discontinuation of the trial regimen in both groups (up to 45%). As a consequence, patients were only on the trial regimen two-thirds of the time. There are at least two possible explanations for this high discontinuation rate. Firstly, the older more complex injection device for exenatide once-weekly was used in the study, and patients find this difficult to use in routine clinical practice. Secondly, the low frequency of contact with the patients because of the so-called pragmatic study design would undermine any possibility of local investigators and research nurses encouraging participants to continue with the allocated study treatment. We can only speculate what the results would have been if there had been a run-in phase, participants had been seen more frequently, and more patients had continued the study drug.

Comparisons of EXSCEL with other CVOTs
There were some differences between the EXSCEL trial and the previous GLP-1 RA outcome trials. The ELIXA trial recruited patients aged ≥30 years with an acute coronary syndrome within the previous 180 days, and demonstrated non-inferiority for MACE but not superiority over a median follow up of 2.1 years. The patients recruited to EXSCEL were more similar to LEADER and SUSTAIN with a mixture of patients with existing cardiovascular disease and patients with cardiovascular risk factors. The EXSCEL investigators comment that EXSCEL patients had a shorter median follow up than in LEADER, with a duration of exposure to the trial regimen that was less than in LEADER, and a higher discontinuation rate than in LEADER. Not openly acknowledged was that LEADER was a more conventional and more successful study design with a much higher participant retention rate!
The EXSCEL investigators also comment that effects on conventional cardiovascular risk factors were modest, and finally they acknowledge that GLP-1 RAs may not be bioequivalent, a suggestion that is supported by the head-to-head study comparing once-weekly exenatide to daily lixisenatide (DURATION-6), where lixisenatide was superior to exenatide at reducing HbA1c. They do not comment on the clear differences in molecular structure between exenatide and lixisenatide, which are exendin-4 based molecules, and lixisenatide and semaglutide which are true GLP-1 analogues, and whether that might explain the different results.

Implications for clinical practice
The results of the LEADER trial with daily lixisenatide demonstrated clear superiority in reducing cardiovascular events compared to placebo, and the intervention was well tolerated. In EXSCEL, the results were at best inconclusive, and the treatment was not well adhered to by the participants. With lixisenatide clearly demonstrating cardiovascular benefits and a reduction in all-cause mortality in the LEADER trial, it is likely that clinicians managing patients with type 2 diabetes will prefer it over exenatide or lixisenatide. Despite this, clinicians may still wish to consider the once-weekly injection in a selected group of patients where self-administration might be an issue requiring input from the community team for home visit. Semaglutide is not yet available for clinical use, and albiglutide has recently been withdrawn from the market for commercial reasons, so the current choice is between once-weekly exenatide, with inconclusive cardiovascular benefits, and dulaglutide, where the results of the REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial will not be available until 2018.

Conclusions
With the emergence of robust cardiovascular-outcomes data from clinical trials with new antidiabetic therapies, the differences among them are increasingly clear. Clinicians managing patients with type 2 diabetes mellitus should consider not only antidiabetic therapies which improve glycaemic control but also therapies which modify cardiovascular risk, as cardiovascular disease remains the major cause of death in this population. Liraglutide, with clear benefits in reducing MACE and all-cause mortality and better tolerability, may be the preferred choice of GLP-1 RA over other currently available options.

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References