Cardiovascular outcome trials of glucose-lowering drugs in type 2 diabetes: 10 frequently asked questions

A few cardiovascular outcome trials (CVOTs) of glucose-lowering drugs have recently reported their results (TECOS, EMPA-REG-OUTCOME, ELIXA, SAVOR-TIMI 53 and EXAMINE) and many more such trials are ongoing.

Dr Jyothis George (Clinical Lead for the EXSCEL trial and an academic diabetologist at the University of Oxford Diabetes Trials Unit) answers frequently asked questions on CVOTs.

Trials discussed in this article are listed in Box 1.

1. Why are all these cardiovascular outcome trials being carried out?

Patients with type 2 diabetes have at least twice the cardiovascular (CV) risk of their non-diabetic peers, and lose around half a decade in life expectancy. There is a clear need to develop therapeutic strategies to mitigate this increased CV risk.

The 2008 US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance on new diabetes therapies triggered much of the recent increase in CVOTs. This guidance requires manufacturers of new glucose-lowering drugs to institute a clinical trial programme demonstrating CV safety as a prerequisite for their approval.

Figure 1 shows the cumulative number of patients enrolled in CVOTs over time, and the clear impact of the 2008 FDA/EMA guidance, which was triggered by controversies around the CV safety of rosiglitazone.

The FDA guidance places the emphasis on the demonstration of CV safety. It does not require a demonstration of reduction in CV events – in other words, the trials do not necessarily need to be powered to demonstrate a reduction in the number of CV events (i.e. ‘superiority’). Therefore these trials are designed to test primarily for ‘non-inferiority’ – and, if this is achieved, most trial protocols employ a superiority test as a subsequent step. It is important for clinicians to understand that superiority and inferiority are essentially two sides of the same coin. Hazard ratios in the active group with 95% confidence interval margins <1 show ‘superiority’, but as long as the upper bound of this confidence interval is <1.3, the drug would be considered safe enough for clinical use. This latter scenario is often called ‘non-inferiority’ from a statistical perspective, but for clinicians and patients there is nothing ‘inferior’ about having a drug demonstrate its CV safety.

2. What do we know about glucose lowering and cardiovascular risk?

The UKPDS trial remains the only randomised controlled trial to compare intensive versus less stringent glucose lowering in a group of patients with recently diagnosed type 2 diabetes. A 16% relative risk reduction in myocardial infarction was observed in UKPDS, approaching statistical significance (p=0.052). This reduction persisted during post-trial follow up, with a 15% relative risk reduction that reached statistical significance (p=0.01), associated with a 13% relative risk reduction for all-cause mortality (p=0.007). Taking the main UKPDS study and the post-trial follow up together, the overall follow up was about 25 years.

The ACCORD, ADVANCE and VADT trials also compared intensive versus standard glucose-lowering strategies – albeit in populations with well-established diabetes. These trials did not show a significant reduction in CV events over approximately five years each of follow up. The ACCORD trial closed prematurely because of an unexpected increase in mortality in the intensive treatment group where HbA1c target was set at <6% (42mmol/mol), but no conclusive mechanistic explanation has been provided for this unexpected finding. A meta-analysis of data from these three trials, along with data from UKPDS, showed that more intensive glucose control reduced the risk of major CV events by 9% (HR 0.91, 95% CI 0.84–0.99), primarily arising from a 15% reduction in the risk of myocardial infarction (HR 0.85, 95% CI 0.76–0.94).

3. If glucose lowering can reduce cardiovascular risk, why is this not seen in recent cardiovascular outcome trials like TECOS, SAVOR, EXAMINE and ELIXA?

The EMPA-REG OUTCOME study has recently reported its results.
showing reduction in CV events in the treatment group, while TECOS, SAVOR, EXAMINE and ELIXA studies showed non-inferiority.

These recently reported CVOTs10–13 did not compare intensive versus less intensive glucose-lowering strategies, but were designed to assess CV safety. In these trials, an investigational glucose-lowering drug (or placebo) was added to patients’ usual diabetes care regimen. In addition to the trial drug, investigators were allowed to add other clinically appropriate glucose-lowering drugs to treat patients to clinically acceptable glycaemic targets. By aiming for glycaemic equipoise in this manner, these studies estimate the potential for their respective study medications to alter CV event rates – without the confounding effect of differential glucose control in the two groups. In other words, if the CV event rates are decreased (or increased, for that matter) in trials like these, it is specifically to do with the drug studied. These trials do not ask the question whether intensive glucose lowering should be a therapeutic strategy to decrease CV risk.

4. Differences in HbA1c levels between treatment and control arms in recent CVOTs are pretty modest. Why is this?

As we have discussed above (in question 3), recently reported CVOTs are not designed to compare intensive versus less intense control. Patients in these trials are permitted to receive additional glucose-lowering therapies to achieve glycaemic targets. The objective is to achieve glycaemic equipoise between the treatment and control groups to allow clear comparisons to be made on the occurrence of CV events in the two randomised groups.

Given this trial design, it is indeed interesting that there is any HbA1c difference at all between the treatment and placebo groups in these CVOTs. Despite the objective to achieve glycaemic equipoise, modest differences could arise and be due to a number of factors.

Firstly, many trial protocols recommend against adding in additional treatment in the first few weeks following randomisation – a precaution to minimise the risk of hypoglycaemia. This can lead to an early glycaemic differential between the treatment and placebo groups.

Secondly, while HbA1c improves in the active treatment group due to the glucose-lowering effects of the drug, patients in the placebo group will continue to remain in their previous glucose trajectories, unless the physician and/or patient actively intervenes. In this setting, treatment inertia on the part of patient, physician or health care systems to intensify glucose-lowering therapy in the control arm can also contribute to further glycaemic separation of the two cohorts. Some of this inertia could even be justifiable – for example when the adverse effects of alternative treatment options available preclude their addition to the therapeutic mix.

5. Why are these trials much shorter than previous trials such as UKPDS, ADVANCE or VADT?

Recent CVOTs have indeed had shorter durations of follow up than earlier trials. These trials are ‘event-driven’ – with the trial follow up stopping when a pre-specified number of CV events have occurred in the trial population. Within an event-driven design, the requisite number of CV events can be achieved more quickly by:

- Increasing the number of patients (i.e. the sample size) in the trial.
- Enriching the study population with patients at high CV risk.

Both these strategies have been employed by recent CVOTs, leading to the rapid accrual of CV events. TECOS and SAVOR-TIMI 53 had over 14,000 patients, while ELIXA and EXAMINE recruited patients with a history of recent acute coronary syndrome – and therefore at higher risk of sustaining a subsequent CV event.

In contrast to modern CVOTs, the ‘classic’ CVOTs (e.g. UKPDS) had a minimum duration of follow up. This ensures longer exposure to the intervention – and therefore a higher likelihood for the putative mechanistic processes to have a bearing on CV outcomes. Nevertheless, a ‘duration-driven’ design may not accrue sufficient events to make meaningful comparisons – and hence the intentional design of modern CVOTs to be ‘event-driven’.

One solution is to have a pre-specified minimum number of events and a minimum number of years of follow up but this could increase the cost of these trials substantially.

Given the markedly different baseline CV risk profiles between patients
with and without a cardiovascular history, the application of these findings will require clinical judgement.

6. Should I aim for less-stringent glucose control for my patients, now that TECOS, SAVOR, EXAMINE and ELIXA have not shown reductions in cardiovascular events? No.

These trials did not compare the effect of less stringent versus intensive glucose-lowering targets on CV events (as discussed earlier). Therefore, the results of these trials should not influence your glycaemic targets – even in patients with a prior history of cardiovascular disease.

These trials provide the reassurance that within the range of potential drugs that can be employed to reduce glucose, these drugs have been proven not to worsen CV risk. In other words, you (and your patients) can be reassured that controversies on CV safety, such as that which we saw with rosiglitazone, are unlikely to be repeated with drugs with clearly demonstrated CV safety in a CVOT.

Moreover, it shouldn’t be forgotten that the objective of glucose-lowering is not only to minimise the risk of developing CV events but also to prevent/delay the development of microvascular complications.

7. There are many cardiovascular outcome trials currently ongoing. Are some of them different from the recently reported trials? Most of the ongoing CV trials (reviewed elsewhere) are comparable to those recently reported in being event-driven trials, which compare CV events between a specific therapeutic agent or placebo.

A couple of trials have unique characteristics that set them apart from their peers:

- The CAROLINA trial (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes) has an active comparator (glimepiride, a sulphonylurea) instead of a placebo arm. This allows for a direct comparison to be made between a sulphonylurea and a DPP-4 inhibitor – certainly a clinically relevant question. However, if the trial does show differences between the two groups, it would be challenging to discern if linagliptin or glimipide drives such differences.

- The EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering) aims to enrol patients without a previous history of cardiovascular, cerebrovascular or peripheral arterial disease within the overall target of 14,000 participants. As there are likely to be fundamental biological differences between primary and secondary prevention of CV events, having such a population without prior CV risk burden could be clinically illuminating. Nevertheless, it remains to be established if meaningful differences can be observed in a relatively low-risk population during an event-driven follow-up design.

8. What have we learnt about pancreatitis or pancreatic cancer from these cardiovascular outcome trials? Concerns have been expressed about the safety of incretin-based therapies (DPP-4 inhibitors and GLP-1 analogues) – specifically, whether they increase the risk of pancreatitis and pancreatic cancer. Reassuringly, the occurrence of these has been relatively infrequent in the large CV outcome studies that have been published. While there were numerical imbalances, no statistically significant differences are discernable between treatment groups and their placebo comparators.

Reassurance can certainly be drawn from the infrequent occurrence of these events in studies with tens of thousands of patient-years of follow up and prospective ascertainment of safety. Additional clinical reassurance can be drawn from recent safety assessments published by regulators such as the FDA and EMA. Furthermore, a reassessment of the clinical and microscopy data that initially triggered these concerns identified multiple insufficiencies in the methodologies originally employed by Butler and co-investigators. While the nuances of immunohistochemistry are for specialists in that field to debate, practising diabetologists would note that one academic group could not replicate another group’s published findings.

It has to be emphasised that the lack of an association between incretin mimetics and pancreatic cancer observed in these CVOTs does not absolutely rule out a possible association. All that we can say, at the present time, is that no such association has been picked up in tens of thousands of patient-years of follow up. Therefore, any association, if there is one, has to be a relatively weak one.

9. What have we learned about heart failure from the recent cardiovascular outcome trials? First and foremost, these trials have highlighted that heart failure is indeed a common occurrence in people with type 2 diabetes. This is driven by a multitude of factors, including increased survival, especially following myocardial infarctions.

The SAVOR-TIMI trial had hospitalisation for heart failure as one of the many pre-specified secondary outcomes. There was an imbalance across the two arms, with the saxagliptin arm showing higher occurrence of hospitalisation for heart failure. From a clinical perspective, it is important to note that this was only one of the multiple end points tested, with no statistical correction for this multiple testing. Nevertheless, the FDA has deemed this signal strong enough to consider a change in the labels of saxagliptin and alogliptin (which also showed a similar numerical imbalance) to reflect this potential increase in heart failure risk.

The TECOS trial (studying sitagliptin) showed no imbalance between the treatment and placebo arms in hospitalisation for heart failure. This provides reassurance that even if the increased heart failure signal seen in earlier trials is true, it is not a ‘class effect’ associated with all DPP-4 drugs – especially as TECOS had a larger sample size and longer follow up.

A 35% reduction (95% CI 0.5 to 0.85) in hospitalisation for heart failure was observed in the EMPA-REG OUTCOME trial, further highlighting the need to consider the impact on heart failure while choosing glucose-lowering therapy.
10. Are these trials the best use of limited resources?
As multiple trials have now reported with ‘non-inferiority’ with only one reporting superiority, it is reasonable to ask if the resources expended on these trials are justified, especially as each of them are likely to be spending many multiples of the landmark UKPDS study (which reportedly cost £25 million). Quite legitimately, there are concerns that the investment made into these mega-trials will lead to increased cost of prescription medicines. The challenge, however, is in balancing safety and efficacy concerns while developing novel drugs.

It has to be recognised that the FDA and EMA made it mandatory for all new diabetes therapies to demonstrate their CV safety, which in effect requires companies to undertake CVOTs. Given the budgetary pressures involved, many of these studies are also designed to achieve earliest completion. These drivers are not necessarily fully aligned with a clinical desire to achieve longer-term follow up – perhaps an unintended consequence of the FDA and EMA 2008 guidance not specifically asking for evidence of superiority or a minimum duration of follow up of patients. The guidance does indeed ask for a minimum trial duration of two years but, because of the length of time it takes to recruit the trial cohort, the mean duration of follow up of patients in any trial would be shorter than the overall trial length. For example, although the EXAMINE trial ran from October 2009 to June 2013, the mean follow up was 1.5 years, in contrast to the 3.1 years EMPA-REG-OUTCOME study, which showed reductions in CV events.

There is some evidence to suggest that the high bar set by the FDA and EMA might be stopping new diabetes therapies with potential safety concerns from being launched first in the USA and Europe. For example, a dual peroxisome proliferator-activated receptor (PPAR) alpha/gamma agonist called saroglitazar has been approved in India since 2013, but is not available elsewhere. The author gratefully acknowledges Angelyn Bethel, Jonathan Levy, Andrew Farmer and Ruth Coleman for constructive feedback on this manuscript.

Declaration of interests
Dr George has had consulting, speaking, travel and/or research support from Amylin, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Takeda.

References
11. White WB, et al. Alogliptin after acute coronary syn-