Cardiovascular outcome trials in type 2 diabetes – 2015

Caroline Day and Clifford J Bailey

Caroline Day is Editor of *British Journal of Diabetes and Vascular Disease* and Visiting Senior Fellow at Aston University, Birmingham.

Clifford J Bailey is Professor of Clinical Science, Aston Medical School, Aston University, Birmingham.

In December 2008 the US Food and Drug Administration (FDA) required that new drug applications for glucose-lowering agents must include a meta-analysis of all cardiovascular (CV) events during phase 2 and 3 trials (FDA, 2008). The level of relative risk would then be used to determine the need, or otherwise, for post-marketing studies (*Table 1*). This action was spurred by controversy about rosiglitazone, which raised the possibility that an anti-diabetic drug might exacerbate CV risk in people with type 2 diabetes. Thus the so-called CV outcome (or safety) trials were born. Although these safety trials are a "must do" if the meta-analysis shows a signal for concern, sponsors have been prepared to undertake such trials to provide reassurance, even in the absence of a signal in phase 2 and 3 trials.

To obtain an adequate number of events for statistical reliability within a reasonable time, these CV outcome studies are undertaken mostly in people with type 2 diabetes who already have established CV disease (notwithstanding the association between type 2 diabetes and CV risk). The main objective of these event-driven trials is to investigate whether inclusion of the treatment precludes CV risk compared to standard care using other agents. The predefined metrics are usually powered to confirm non-inferiority but may also permit assessment of superiority to standard care. These trials can additionally provide data on other aspects of current concern.

Several CV safety trials are ongoing and some have already reported results (*Table 2*). The TECOS (sitagliptin) and ELIXA (lixisenatide) studies reported earlier this year and SAVOR-TIMI 53 (saxagliptin) and EXAMINE (alogliptin) reported last year, all demonstrated non-inferiority in their composite endpoint of CV events. A small increase in heart failure hospitalisation with saxagliptin remains unexplained. Other parameters of interest studied in these trials provided reassuring evidence of general safety at the doses used over the periods studied in these high-risk populations.

Three sodium–glucose cotransporter 2 (SGLT2) inhibitors have become available in the last 2 years. They lower blood glucose levels by competitively inhibiting the SGLT2 transporters in the kidney tubules, reducing the re-uptake of filtered glucose and eliminating excess glucose via the urine. The loss of calories in this way is typically accompanied by some weight loss, and the osmotic diuresis associated with the glucosuria appears to be at least one of the factors contributing to an accompanying reduction in blood pressure.

The EMPA-REG study randomised 7020 people with type 2 diabetes with established CV disease in a double-blind design with the SGLT2 inhibitor empagliflozin (10 mg or 25 mg daily) or placebo (Zinman et al, 2015). After a median 3.1 years, 772 events were recorded. The primary endpoint, which was a 3-point major adverse cardiovascular event (MACE; composite of CV death and non-fatal myocardial infarction and stroke) showed a 14% reduction ($P<0.04$) with the pooled empagliflozin treatments. Several key secondary endpoints also showed benefits of

Table 1. Relative risk of cardiovascular events in meta-analyses of phase 2 and 3 trials guide the FDA requirements for additional cardiovascular safety studies.

If the upper limit of the 95% CI is >1.8, the drug will not be approved and further safety trials are required.
If the upper limit of the 95% CI is 1.3–1.8, and if the overall risk–benefit profile supports approval, a post-marketing cardiovascular trial generally will be necessary to confirm an upper limit of the 95% CI <1.3.
If the point estimate is ≥1.5, FDA may require additional cardiovascular safety studies.
If the upper limit of the 95% CI is <1.3 and if the overall risk–benefit profile supports approval, a post-marketing cardiovascular trial is generally not necessary.

CI=confidence interval; FDA=Food and Drug Administration.

empagliflozin treatment, notably reductions in CV deaths (by 38%), overall mortality (by 32%) and hospitalisation for heart failure (by 35%). These are intriguingly positive results.

What caused the early decrease in CV events in EMPA-REG?

Evidence of a reduction in CV events in people treated with empagliflozin emerged by 3–6 months into the study. This does not appear to be explained by an effect on glycaemic control. EMPA-REG, like other CV safety studies, was designed for glycaemic equipoise. Thus, investigators could adjust other glucose-lowering therapies in all arms to achieve and maintain standard glycaemic control. Although this design could not compensate or disguise all of the glucose-lowering effect of the SGLT2 inhibitor, many studies of intensified glycaemic control have shown that lowering glucose levels does not benefit macrovascular complications within such a short time-frame. The accompanying reduction in weight with empagliflozin would also not be expected to yield CV dividends to this extent within such a short period. The accompanying reduction in blood pressure, however, is an attractive candidate for the early CV benefit.

Can the EMPA-REG study be extrapolated to the general type 2 population?

The success of EMPA-REG may not, of course, transfer to the same extent to the type 2 diabetes population as a whole. The majority of people with type 2 diabetes will not have had a CV event and will, in essence, be receiving treatment for primary (not secondary) prevention. If the CV benefits of empagliflozin are mainly accounted for by a sub-group of individuals with a particular CV presentation, such as established heart failure, then these patients would constitute a smaller proportion of a more typical type 2 diabetes population.

Can the EMPA-REG results be extrapolated to other SGLT2 inhibitors?

The MACE events meta-analyses from the phase 2 and 3 clinical trials programmes for dapagliflozin and canagliflozin, as reviewed before regulatory approval by the FDA advisory committee, revealed a small reduction in CV events for dapagliflozin and no overall difference

Trial expansions

CANVAS
Canagliflozin Cardiovascular Assessment Study

CARMELINA
Cardiovascular and Renal Macrovascular Outcome Study with Linagliptin in patients with Type 2 Diabetes Mellitus at High Vascular Risk

CAROLINA
Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes

DECLARE-TIMI 58
Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events

ELIXA
Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment with AVE0010 (Lixisenatide)

EMPA-REG=C-SCADE 8
Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

EXAMINE
Examination of Cardiovascular Outcomes: Alogliptin versus Standard of Care

EXSCEL
Exenatide Study of Cardiovascular Event Lowering

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

REWIND
Researching Cardiovascular Events with a Weekly Incretin in Diabetes

SAVOR-TIMI 53
Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

TECOS
Trial to Evaluate Cardiovascular Outcomes with Sitagliptin

Table 2. Post-marketing cardiovascular safety studies – completed (in blue) and in progress (in black).

Trial	Test agent	Start	End	Mean duration (years)	Participant number	Primary endpoint
EXAMINE	Alogliptin	2009	2014	1.5	5380	3-point MACE
SAVOR-TIMI 53	Saxagliptin	2010	2014	2.1	16 492	3-point MACE
TECOS	Sitagliptin	2008	2015	2.8	14 671	4-point MACE
ELIXA	Lixisenatide	2010	2015	~4	6075	4-point MACE
EMPA-REG	Empagliflozin	2010	2015	3.1	7020	3-point MACE
LEADER	Liraglutide	2010	2016	~5	9340	3-point MACE
CANVAS	Canagliflozin	2009	2017	~4	4407	3-point MACE
EXSCEL	Exenatide QW	2010	2018	~5.5	14 000	3-point MACE
CAROLINA	Linagliptin	2010	2018	~8	~6000	4-point MACE
CARMELINA	Linagliptin	2013	2018	~4	~8300	4-point MACE
DECLARE-TIMI 58	Dapagliflozin	2013	2019	~6	17 150	3-point MACE
REWIND	Dulaglutide	2011	2019	~6.5	~9600	3-point MACE
ACE	Acarbose	2009	?	~4	~700	3-point MACE

3-point major adverse cardiovascular event (MACE)=composite of cardiovascular death and non-fatal myocardial infarction and stroke; 4-point MACE=3-point MACE plus hospitalisation for additional cardiovascular problem; QW=once weekly.

for canagliflozin. Given the short time-frame and modest numbers of patients included in these analyses, it is not possible to predict the extent to which they may apply across the class. Although presented to the FDA, the empagliflozin phase 2 and 3 MACE meta-analysis data were not made publicly available to avoid compromising the ongoing EMPA-REG study (FDA, 2014). However, each drug in the class exerts similar glucosuric, glucose-lowering, weight-lowering and blood pressure-lowering effects.

The incidence of stroke was not reduced in EMPA-REG, and was increased during the initial weeks of canagliflozin treatment in a meta-analysis of the phase 2 and 3 clinical trials. Whether this could be related to an initial hypovolaemic effect remains to be seen, but this emphasises the importance of advising patients to ensure adequate fluid intake at the outset of SGLT2 inhibitor therapy. Although no increase in hypovolaemic or thromboembolic events was seen in EMPA-REG, the inability to reduce stroke despite a reduction in blood pressure remains a conundrum.

Non-CV events during the EMPA-REG study were also reassuringly low. The occurrence of mycotic genital infections (presumably due to glucosuria) reduce with time as glucosuria stabilises, and this did not produce serious problems. Also, there were no overall increases in urinary tract infections, acute kidney conditions, bone fractures or overall adverse events including hypoglycaemia.

Will EMPA-REG alter the algorithm for treating type 2 diabetes?

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines already include the SGLT2 inhibitor class as an option for second-line therapy, and they could be used as first line if metformin is not tolerated. The EMPA-REG results, we believe, will certainly increase awareness and interest in the use of empagliflozin and this new class of agents.

For the person with diabesity, EMPA-REG is particularly pertinent because it provides evidence that addressing hyperglycaemia and weight control alongside at least one other important CV risk factor, notably blood pressure, can benefit survival. Indeed EMPA-REG emphasises the value of glucose-lowering agents that address multiple features of type 2 diabetes.

Whether these CV safety trials are a worthwhile investment will continue to be debated, given the data generated in phase 2 and 3 trials and the ongoing study of real-world databases while the CV trials are proceeding. However, the EMPA-REG study, as well as the other reported trials, has provided welcome reassurance that appropriate attention to hyperglycaemia, weight and other more conventional CV risk factors can substantially improve the prognosis for diabesity. ■

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