Cardiovascular outcomes trials for glucose-lowering therapies: What do the results mean for practice?

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we discuss the outcome of the cardiovascular safety trial of empagliflozin, and what the results mean for clinical practice in the UK.

Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes.

Zinman, B, Wanner C, Lachin JM et al (2015) *N Eng J Med* 17 Sept [Epub ahead of print]

N Engl J Med

Empagliflozin cardiovascular safety outcomes

1 Empagliflozin is a sodium–glucose cotransporter 2 (SGLT2) inhibitor and following guidance from the US Food and Drug Administration, a trial was conducted to investigate the cardiovascular morbidity and mortality effect of the drug among people with T2D at high-cardiovascular risk.

2 From 590 sites in 42 countries, 7020 people were randomly assigned to receive either 10 mg or 25 mg empagliflozin once-daily or placebo (1:1:1 ratio) added to standard care. The primary composite outcome was death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke (i.e. 3-point major adverse cardiovascular event [MACE]). A secondary composite outcome was the primary outcome plus hospitalisation for unstable angina (i.e. 4-point MACE). The trial continued until an adjudicated primary outcome event had occurred in at least 691 participants.

3 The median observation time for the cohort was 3.1 years.

4 The primary composite outcome occurred in 10.5% (490/4687) of the pooled empagliflozin group and 12.1% (282/2333) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95% confidence interval [CI], 0.74–0.99; P=0.04 for superiority).

5 There was a significantly lower rate of death from cardiovascular causes in the empagliflozin group (38% relative risk reduction), and a significantly lower rate of hospitalisation for heart failure (35% relative risk reduction) and all-cause mortality (32% relative risk reduction) in the empagliflozin group.

6 There were no significant between-group differences in the rates of myocardial infarction or stroke, or in the secondary outcome.

7 There was an increase in the rate of genital infection in the empagliflozin group, which is a known adverse effect when using SGLT2 inhibitors.

8 Those at high risk of cardiovascular events who received empagliflozin alongside standard care had a lower rate of the primary composite outcome and of death from any cause than the placebo group.

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The EMPA-REG OUTCOME study, the first of the cardiovascular (CV) outcome trials for sodium–glucose cotransporter 2 (SGLT2) inhibitors, has created somewhat of a buzz among specialists in the field of diabetes, and rightfully so. Since 2008, due to issues surrounding safety of rosiglitazone, the US Food and Drug Administration (FDA) requires manufacturers to run trials to seek to definitively exclude unacceptable CV risk of diabetes medications. Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists have so far met primary objectives in showing non-inferiority to placebo when considering cardiovascular outcomes. Since the results from EMPA-REG were published in September showing superiority in 3-point major adverse cardiovascular event, CV death, relative risk of hospitalisation from heart failure and all-cause mortality, the dust has settled leaving many questions for what this actually means for modern diabetes practice.

The SGLT2 inhibitors are medicines licensed for glucose lowering, and with the observed lower risk of CV events in the pooled empagliflozin group, the first question is: is this likely to be related to glucose lowering, weight lowering or blood pressure lowering or, what

is seeming to be more likely, could it be related to the diuresis effect with the small benefits of all three reductions? Also due to the high-risk population studied, does this evidence only relate to this high-risk group, or will it be extrapolated to presume benefits in the larger population? I am sure there will be a large number of sub-analyses to try and unpick the data to show which patients would benefit the most depending on their underlying CV risk.

Another question is whether the observed results are a predictor of how the other SGLT2 inhibitors will fair? Everyone has their opinion, but with three SGLT2 inhibitors, all with NICE technology appraisals and all at a similar price, one must surely prescribe based on evidence of benefits in the population studied. The spanner in the works is the lack of any head-to-head studies for the benefit of SGLT2 inhibitors on HbA_{1c}; therefore, comparable data will be hard to interpret due to confounders. With estimated completion dates for CANVAS (Canagliflozin Cardiovascular Assessment Study) and DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) being 2017 and 2019 respectively, we will have a while to wait to cement any CV benefits of the SGLT2 inhibitor class among high-CV risk individuals. In addition, DECLARE-TIMI 58 will also look at the CV outcomes in both primary and secondary prevention cohort arms.

We are on the cusp of a new NICE guideline for the management of type 2 diabetes; as a final thought, what will be the level of disconnect between the most up-to-date evidence and NICE guidance? Time will tell. ■

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There is no doubt that the EMPA-REG OUTCOME study has resurrected our belief in the importance of randomised controlled trials (RCTs) to give us the best guidance for managing our patients. Recently we have been concerned in regard to NICE guidelines, and health policy in general, so we are grateful for clinical guidance and clarity from a large RCT. Put simply, the EMPA-REG OUTCOME study showed that the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin reduces the rate of heart failure hospitalisations by 35% and reduces the risk of death from any cause by 32% compared to placebo, in people with type 2 diabetes and high cardiovascular disease (CVD) risk. The number needed to treat (NNT) is the number of people who need to be treated to prevent one negative outcome. The NNT in the study was large (approximately 40 individuals over 3 years for the death outcome) but this number is comparable to the statin and angiotensin-converting-enzyme inhibitor cardiovascular benefit trials. Sub-group analyses of these trials have shown general universal benefit tendency.

How did this happen? The question is important as several trials such as the VADT (Veterans Affairs Diabetes Trial) and the rosiglitazone sub-analyses have shown a detrimental effect of either aggressive glycaemic control or a specific agent on CVD outcomes. We have to remember that the benefits of empagliflozin observed in the EMPA-REG study were additional to the background treatment in both groups of statin treatment, renin–angiotensin system (RAS) inhibitors and aspirin. There was an approximately four-fold increase in the reported cases of genital infections in the pooled empagliflozin group compared to placebo.

After nearly 4 years, the HbA_{1c} was 2.6 mmol/mol (0.24%) lower in the empagliflozin group compared to placebo. The systolic blood pressure (BP), weight and waist circumference were also lower as presented at the European Association for the Study of Diabetes conference in Stockholm, Sweden, this year (Inzucchi, 2015). This has not been reported in the paper by Zinman et al. It is likely that the benefits are multi-factorial and based on small but distinct and interactive benefits due to a small improvement in glycaemic control, BP, diuresis and lipid profile. Marc Evans, an editor in this journal, alluded to the idea that SGLT2 inhibitors may promote the reabsorption of alternate "fuels" for the heart (ketone bodies) that could be of benefit in the high-risk cardiovascular patient. Following the now published results of the EMPA-REG study, we can conclude that this SGLT2 inhibitor is safe and beneficial in a specific group of individuals at high-CVD risk. I remain intrigued as to whether other SGLT2 inhibitors will show a similar benefit. ■

Inzucchi S (2015) Session: Results of the EMPA-REG OUTCOME™ Study. Presented at *51st European Association for the Study of Diabetes*. Stockholm, Sweden, 15–18 September

For more commentary on the EMPA-REG OUTCOME study see

Day C and Bailey CJ (2015) Cardiovascular outcome trials in type 2 diabetes – 2015. *Diabesity in Practice* [in press]

Day C (2015) Meeting report: 51st Annual Meeting of the European Association for the Study of Diabetes. *Diabetes and Primary Care* [in press]

due to publish in December 2015. View in print or online at **www.diabetesonthenet.com/journals.**