The year of change continues

We predicted potential for significant changes in diabetes care delivery in the UK in 2015 as we implement the recommendations of five new NICE guidelines. In the previous edition, we highlighted the key implications for primary care of the diabetes in pregnancy guideline, while our "In the consultation room" feature took a hands-on approach to the diagnosis and management of gestational diabetes based on this guideline.

August 2015 saw the publication of the NICE guidelines on type 1 diabetes in adults and on types 1 and 2 diabetes in children and young people and in this issue we cover the important messages from these two publication for our day-to-day practice.

With the final version of the type 2 guideline delayed past September 2015, we plan to take a look at this in our next edition, as well as exploring the NICE guideline *Diabetic foot problems: prevention and management*, which was also published in August 2015.

First do no harm

Having type 2 diabetes doubles the risk of major cardiovascular complications in those with and without pre-existing cardiovascular disease (CVD; Bhatt et al, 2010). Mortality from CVD for those diagnosed when aged 50–55, at the time of publication of UKPDS, was 40–70 times higher than the risk of dying from microvascular disease (Turner et al, 1996), and 20 years later CVD remains the commonest cause of death in the people we look after with diabetes. Although there is evidence of slowly improving mortality rates from CVD among the general population, there may be a slower rate of reduction in coronary heart disease in those with type 2 diabetes (Ecclestone et al, 2015). Against this background, it is important that the drugs we use for glucose lowering do not increase the risk of cardiovascular-related mortality or morbidity and that they might offer benefit.

Readers of the Journal will be aware that following concerns about cardiovascular safety of rosiglitazone, in 2008 the US Food and Drug Administration mandated that all manufacturers of new diabetes drugs must undertake studies to rule out excess cardiovascular risk, looking at major adverse cardiovascular events (MACE), namely the composite of cardiovascular mortality, non-fatal myocardial infarction (MI) and non-fatal stroke. The first of these studies, the RECORD trial, looked at rosiglitazone and did not suggest an increase in MACE (Home et al, 2007). However, the study design and data integrity were criticised and the product was withdrawn in the UK in 2010.

In 2013, the cardiovascular outcome trials for two dipeptidyl peptidase-4 (DPP-4) inhibitors – alogliptin (EXAMINE; White et al, 2013) and saxagliptin (SAVOR-TIMI 53; Scirica et al, 2013) – were published, while the results of the cardiovascular safety studies of sitagliptin (TECOS; Green et al, 2015) and lixisenatide (ELIXA; Pfeffer, 2015) were published earlier this year. These all confirmed that there was no difference in MACE between each of the drugs and placebo, with no evidence of cardiovascular benefit. Saxagliptin was associated with an increased risk of hospitalisation for heart failure (Scirica et al, 2013); there was a trend with alogliptin in EXAMINE, but this did not reach statistical significance (White et al, 2013). The results of other safety studies on antidiabetes agents targeting the incretin pathway are awaited.

A further step forward

A further step forward in our understanding of the cardiovascular safety of the newer glucose-lowering drug classes was presented at the recent *51st Annual Meeting of the European Association for the Study of Diabetes*. The EMPA-REG OUTCOME study (Zinman et al, 2015) is the cardiovascular safety study for the sodium–glucose cotransporter 2 (SGLT 2) inhibitor empagliflozin. In all, 7020 participants were randomised to receive 10 mg or 25 mg of empagliflozin or placebo (added to good standard care including control of glucose, lipids and blood pressure) and followed for a median of 3.1 years. Data from the two empagliflozin groups were pooled in the planned analysis and compared with the placebo group. The primary end-point, as in the other studies,

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Trial expansions

ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome

EMPA-REG OUTCOME = BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care

RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

SAVOR–TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53

TECOS = the Trial Evaluating Cardiovascular Outcomes with Sitagliptin

UKPDS = UK Prospective Diabetes Study

Trial expansions

CANVAS = Canagliflozin Cardiovascular Assessment Study

DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58

Bhatt D, Eagle K, Ohman E et al (2010) Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* **304**: 1350–7

Ecclestone T, Yeates D, Goldacre M et al (2015) Fall in population-based mortality from coronary heart disease negated in people with diabetes mellitus: data from England. *Diabet Med* 21 Apr [Epub ahead of print]

Gaede P, Vedel P, Larsen N et al (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* **348**: 383–93

Gaede P, Lund-Andersen H, Parving HH et al (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* **358**: 580–91

Green J, Bethel M, Armstrong P et al (2015) Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **373**: 232–42

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Home PD, Pocock SJ, Beck-Nielsen H et al (2007) Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *N Engl J Med* **357**: 28–38

Neal B, Perkovic V, de Zeeuw D et al (2013) Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS) – a randomized placebo-controlled trial. *Am J Heart* **116**: 217–23

Pfeffer M (2015) The Evaluation of Lixisenatide in Acute Coronary Syndrome – the results of ELIXA. Presented at: *American Diabetes Association 75th Scientific Sessions*, June 5–9, Boston, MA, USA

Scirica B, Bhatt D, Braunwald E et al (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* **369**: 1317–26

Turner R, Cull C, Holman R (1996) The effect of improved metabolic control on complications of NIDDM: UKPDS 17. *Ann Intern Med*, **124**: 136–45

White WB, Cannon CP, Heller SR et al (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* **369**: 1327–35

Zinman B, Wanner C, Lachin J et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 17 Sep [Epub ahead of print]

was MACE, which occurred in 490 (10.5%) of the pooled empagliflozin-treated group and 282 (12.1%) of the placebo group, giving a hazard ratio of 0.86 (95.02% confidence interval, 0.74–0.99). There were no significant differences in the rates of MI or stroke between the treated versus placebo groups, but there was a significant 38% relative risk reduction in the cardiovascular death rate (3.7% versus 5.9%) in those treated with empagliflozin. There was also a significant 32% relative risk reduction for all-cause death in the empagliflozin group. The mortality rates between placebo and treatment groups separated very early – within the first 6 months – and the benefits were maintained throughout the study.

There is, as yet, no definitive explanation for the mechanism of the mortality reductions. Although there were small reductions in systolic and diastolic blood pressure, weight, waist circumference and HbA_{1c}, these changes would not be expected to account for this degree of mortality reduction. Several additional mechanisms have been postulated to contribute to the reduced mortality, including effects on arterial stiffness, cardiac function and cardiac oxygen demand, cardiorenal effects, and reduction in albuminuria and uric acid (Zinman et al, 2015). A 35% relative risk reduction in hospitalisation for heart failure in the empagliflozin-treated group was also noted. This, and the rapid separation of the mortality rates in the trial (similar to that seen in people treated with eplerenone for heart failure), suggests that beneficial effects on left-ventricular function may be involved.

Experts speculate that this could be a class effect. Unfortunately, we will have to wait until at least 2017 to find out. CANVAS (Neal et al, 2013) will not complete until at least April 2017, and DECLARE-TIMI 58 is expected to complete 2 years later. In the meantime, NICE is undertaking a multiple technology appraisal (MTA) of SGLT 2 inhibitors as monotherapy, with publication anticipated in 2016. Publication of these mortality data for empagliflozin, although unlikely to influence the NICE type 2 guideline, could possibly have an impact on the outcome of this MTA.

Implications for practice

So what are the implications for our management of people with type 2 diabetes? Unfortunately, as with all cardiovascular outcome studies, the study population is somewhat restricted (participants had a moderate duration of diabetes and only a small proportion was older than 75 years), and so the results may not be fully generalisable to our long-duration and elderly diabetes populations.

We should of course continue to address CVD risk with all people with type 2 diabetes, encouraging lifestyle changes including smoking cessation, Mediterranean diet, weight and waist circumference reduction as appropriate, and use of drug therapy to manage blood pressure and lipids. Tight glycaemic control (especially using metformin) – if achieved early and without causing hypoglycaemia – has been demonstrated to reduce rates of CVD risk and result in a legacy effect, even when control later deteriorates (Holman et al, 2008). The STENO-2 study (Gaede et al, 2003; 2008), although a small trial, demonstrated what is achievable with multiple interventions in the real world, and the follow-up results (Gaede et al, 2008) demonstrated a legacy effect of reduced cardiovascular mortality in those treated intensively during the randomised part of the study.

Looking to the future

Evaluation of the EMPA-REG OUTCOME results are ongoing, and the findings will almost certainly spark further studies of this agent. Hopefully, we will eventually unravel the mechanisms for these significant benefits in this high-risk population. In the meantime, it may be appropriate to offer this class of drug to people with diabetes who match the trial population, provided that it is safe and acceptable to them.

I believe that this was a well-constructed and well-executed study which provides hope that even after 10 years of type 2 diabetes, in those at very high risk of CVD, we can still intervene and have a significant impact on mortality, a hard end-point that is important to our patients. However, I also believe that this study, and the new guidelines discussed in this issue, should spur us on to try harder to motivate and inspire all of the people we see with diabetes to adhere to medication and make lifestyle changes, so that they too can reduce their risks of morbidity and mortality. ■