American Diabetes Association 2017: a primary care overview of scientific sessions

Mark Kennedy
Honorary Clinical Associate Professor, University of Melbourne and Chair, PCDS Australia

The American Diabetes Association (ADA) 77th Annual Conference was held in San Diego in June 2017. The highlight of the scientific sessions was the release of the data from the CANVAS (Canagliflozin Cardiovascular Assessment Study) outcome study, which has since been published (Neal et al, 2017). These results are reviewed and interpreted in the broader context of the sodium–glucose cotransporter 2 (SGLT2) inhibitor class here.

As always, there were many other sessions of interest and relevance to primary care. A few of the more interesting ones are also briefly reviewed in this report.

CANVAS outcome study

The results of the CANVAS outcome study have been eagerly anticipated since the publication of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial data almost 2 years ago. The EMPA-REG data showed dramatic reductions in all-cause mortality and cardiovascular (CV) mortality in patients with type 2 diabetes at high CV risk who were treated with empagliflozin (Zinman et al, 2015).

The CANVAS outcome study combined the results of two outcome trials: CANVAS and CANVAS-R (the renal endpoints trial). Although they both had similar inclusion criteria, patient populations and interventions, the trial durations were different and there were differences in the significance levels of some findings in the different arms.

Cardiovascular benefits

The pooled data showed 14% lower rates in the primary major adverse cardiac events three-point outcome of CV death, non-fatal myocardial infarction and non-fatal stroke in the canagliflozin-treated patients compared to placebo in patients with type 2 diabetes who were known to have, or who were at high risk for, CV disease (Neal et al, 2017). Despite showing a trend towards a reduction in all-cause death, CV death, myocardial infarction and stroke, none of these showed statistical significance as individual outcomes. The canagliflozin-treated patients also had a 33% reduction in heart failure admissions and a 27% reduction in the progression of albuminuria compared to those in the placebo arm.

During the average follow-up of 295.9 weeks in CANVAS and 108.0 weeks in CANVAS-R, the rate of the primary CV outcome per 1000 patient-years was 26.9 in the canagliflozin group vs 31.5 in the placebo arm.

Amputations and fractures

Despite the CV benefits, the CANVAS outcomes study also raised significant safety concerns. There was a 97% increase in lower-limb amputations and a 26% increase in fracture rates. Individuals treated with canagliflozin had an increased risk for amputation of toes, feet or legs compared to placebo (6.3 vs 3.4 per 1000 patient-years, respectively; Neal et al, 2017). In the pooled data, those treated with canagliflozin had increased fractures, with rates of 15.4 vs 11.9 per 1000 patient-years in the canagliflozin and placebo groups, respectively (Neal et al, 2017). Interestingly, this increase was statistically significant in the longer CANVAS trial, but not in the CANVAS-R trial.

Class effects

Since the EMPA-REG study, there has been considerable debate about whether the CV safety outcomes were too good to be true. The CANVAS trials were, therefore, very important in helping to establish whether the substantial CV benefits would be replicated with other agents in the same class.

CANVAS – along with the recently-presented CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users

of SGLT-2 Inhibitors) retrospective database analysis (Kosiborod et al, 2017) – would suggest that the CV benefits, reductions in heart failure admissions and renal benefits seen with empagliflozin are probably a class effect, extending to canagliflozin and dapagliflozin. CANVAS also expands the group of patients likely to benefit from treatment with this class of drugs because the patients in this study included individuals at high risk for CV events rather than just those who had established CV disease. This would suggest that, as a class, SGLT2 inhibitors do provide cardio-protection, at least for high-risk patients.

The implications for clinical practice

I believe that we now have enough data from EMPA-REG OUTCOMES, CANVAS and, to a lesser extent, from CVD-REAL to consider SGLT2 inhibitors as a class of medication with additional benefits beyond glucose lowering for people with type 2 diabetes and high CV risk. For every 1000 patient-years of exposure in the CANVAS study, treatment with canagliflozin prevented 4.6 major adverse cardiac events at a cost of 2.9 amputations and 3.5 fractures. The increased amputations and fractures seen in CANVAS, however, certainly adversely impact the benefit-to-risk calculation for canagliflozin.

A history of amputation or peripheral artery disease at baseline did not help to identify those at higher risk for subsequent amputation, making it difficult to recommend canagliflozin be avoided just in specific higher-risk groups. The fact that these problems have not been identified with empagliflozin (Kohler et al, 2017) makes it hard to imagine a situation where an informed patient would choose canagliflozin as his or her preferred SGLT2 inhibitor. Until we see the CV safety study results for dapagliflozin (the DECLARE-TIMI 58 trial [Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events], which should be complete in late 2018 or early 2019) to establish the presence or absence of any associated amputation or fracture risk with that agent, it would seem that empagliflozin is the safest option for providing this CV benefit to high-risk patients without serious adverse risk.

SGLT2 inhibitors and CV outcomes: the CVD-REAL study

The results of another study looking at SGLT2 inhibitors and CV outcomes (Kosiborod et al, 2017) were also presented at the ADA conference. In this study, real-world data were collected from databases in the UK, US, Norway, Denmark, Sweden and Germany. CVD-REAL compared the risk of hospitalisation, heart failure and/or death in adults with type 2 diabetes who were new users of SGLT2 inhibitors with those new to other diabetes medications.

There were more than 150 000 patients in the SGLT2 group and a matching number in the control group of CVD-REAL. In the SGLT2 inhibitor group, 53% were using canagliflozin, 42% were using dapagliflozin and 5% were using empagliflozin.

The data collected did vary a little between databases. The follow-up period, however, equated to in excess of 190 000 person-years of treatment. Those using SGLT2 inhibitors had 39% lower rates of hospitalisation for heart failure, a 51% reduction in death and 46% lower rates of hospitalisation or death. There did not appear to be significant heterogeneity in these results between countries.

Implications of the results

Although this is not a randomised-controlled study, the results do provide additional support for SGLT2 inhibitors having a class effect when it comes to CV outcome benefits. Interestingly, a large proportion of the patients in this study were at much lower CV risk than the patients in the EMPA-REG OUTCOMES or CANVAS trials, providing some hope that these benefits may eventually extend to primary prevention as well as secondary reduction of CV events.

Metabolic abnormalities in adolescence linked to gestational diabetes

It is now well-known that increased diabetes risk can begin early in life through a combination of genetic, intrauterine and postnatal environmental exposure. The intrauterine environment seems to be particularly important to the early development of type 2 diabetes.

EPOCH (Exploring Perinatal Outcomes in

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Children) has been following 437 children in a historical prospective study for more than 15 years (Sauder et al, 2017). The authors reported that intrauterine exposure to gestational diabetes or obesity was associated with greater insulin resistance in adolescence than in those without such exposure. This finding adds further support to the hypothesis that fetal overnutrition results in metabolic abnormalities in childhood and adolescence.

The study is ongoing and it is possible that a clearer effect of diabetes exposure may emerge as the cohort grows into adulthood. In the meantime, as we know that early-onset type 2 diabetes is associated with accelerated development of complications and greater morbidity and mortality than later-onset type 2 diabetes (Constantino et al, 2013), it would seem appropriate for those managing children and adolescents who were subjected to such intrauterine exposure to keep in mind these risks and monitor individuals as appropriate.

Teens who lose excess weight reduce their risk of developing type 2 diabetes

A registry-based study by Bjerregaard et al (2017) examined the effect of weight loss in young adulthood in men who had been obese or overweight in childhood. The records of more than 60 000 men in Denmark who had weight measurements taken at 7 years and then again between 17 and 26 years of age were studied.

In this study, 5.4% of the men had been overweight in childhood and 8.2% in young adulthood. Those who were overweight as children had an increased risk of having type 2 diabetes at age 30, and those who were overweight in young adulthood had an almost three-fold higher risk of type 2 diabetes (hazard ratio, 2.96) when compared to those who were not overweight.

When the investigators looked at the 60% of boys who were overweight at age 7 years but who subsequently lost their excess weight in adolescence, they found that the risk of type 2 diabetes at age 30 was no higher than in those who had never been overweight. The risk of type 2 diabetes at age 30 was almost three times higher, however, for those who were overweight at both measurement times or for those who became overweight in young adulthood when compared to those who had managed to lose weight during adolescence.

The possibility of reversing metabolic consequences of childhood obesity

While this is a registry-based study rather than a prospective controlled trial, it does raise hope that it may be possible to reverse the adverse metabolic consequences of childhood obesity. The results also provide support for the notion that efforts to normalise weight in children who are overweight are useful and should be encouraged.

Treating major depression in type 2 diabetes with exercise or with cognitive behavioural therapy

The Program ACTIVE II randomised-controlled trial (de Groot et al, 2017) compared the use of cognitive behavioural therapy (CBT) and exercise in people with type 2 diabetes and major depression on blood glucose levels and on their depressive symptoms. The 140 subjects were randomised into one of four arms:

- CBT: 10 individual sessions.
- Exercise: 12 weeks if a community-based program and six classes run by a personal trainer.
- CBT and exercise.
- Usual care.

All interventions led to significantly increased rates of full remission of depression when compared to usual care. The likelihood of full remission was increased by 5.0 times in the CBT group, 6.8 times in the exercise group and 5.9 times in the CBT plus exercise group.

When considering a combined endpoint of full or partial remission of depression, only CBT or exercise showed significant benefit, with the rates of full or partial remission of depression being 12.4 higher with CBT and 5.8 higher with exercise. The CBT plus exercise arm did not have any significant benefit over usual care. The exercise arm also showed a reduction in HbA_{1c} of 7.7 mmol/mol (0.7%) when compared to usual care or CBT in those with a starting base-line

HbA_{1c} of greater than 53 mmol/mol (>7.0%). This study is ongoing and further follow-ups at 6 and 12 months are planned.

Although this is only a small study, the results provide hope that exercise has additional benefits for people with type 2 diabetes and depression, not just in optimising individuals' glycaemic levels but also on the remission of full or partial depression.

Nasal glucagon for hypoglycaemic episodes in type 1 diabetes

An abstract presented at the ADA conference showed that a glucagon nasal spray was effective and efficient in managing moderate or severe hypoglycaemic episodes in adults with type 1 diabetes. The spray was effective in more than 96% of participants using it for symptomatic hypoglycaemia, with blood glucose levels returning to normal within 30 minutes. The nasal glucagon was associated with similar side-effects to injected glucagon, such as nausea and vomiting, but was also associated with some transient headache and nasal irritation.

A possible alternative to injectable glucagon

This new delivery form for glucagon may be a useful alternative to injectable glucagon. If similar results are found when it is tested in children and adolescents, nasal glucagon may prove to be a popular alternative for those who would prefer to avoid giving or receiving an injection. It should be noted that these data are yet to be published in a peer-reviewed journal. ■

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