Renal trials, sex disparities in treatment, amputation and ADA nutrition guidelines

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CREDENCE

In the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, people with type 2 diabetes and albuminuric diabetic kidney disease treated with canagliflozin 100 mg versus placebo demonstrated a highly significant 30% relative risk reduction (RRR) in the primary composite endpoint of end-stage renal disease (ESRD), doubling of serum creatinine level or death from renal or cardiovascular causes (Perkovic et al, 2019).

Background: The three published cardiovascular outcome trials (CVOTs) with SGLT2 inhibitors (Zinman et al, 2015; Neal et al, 2017; Wiviott et al, 2019) suggested this class of drug may improve renal outcomes in people with chronic kidney disease (CKD) and type 2 diabetes, but this was not the primary endpoint. CREDENCE is the first of the studies designed specifically to evaluate impact on renal progression. EMPA-KIDNEY and Dapa-CKD studies, with empagliflozin and dapagliflozin respectively, are ongoing and will report in 1–2 years.

Identifying therapies to slow progression of diabetic kidney disease is clinically important, since up to 40% of people with type 2 diabetes will develop it, resulting in significant increases in early renal and cardiovascular mortality, morbidity, and poorer quality of life with increased infections, fatigue and depression. Renin–angiotensin blockade with ACE inhibitors or angiotensin receptor blockers (ARBs), and tight glycaemic and blood pressure control are known to slow progression of diabetic kidney disease, but excess risk persists.

Methodology and design: In this double-blind, randomised trial involving 4401 people with type 2 diabetes and albuminuric CKD, participants received canagliflozin 100 mg or placebo for a mean duration of 2.62 years before the study was stopped (see below). Participants had albuminuria (>300 mg/g to <5000 mg/g [(>33.9 mg/mmol to 565 mg/mmol)]), an eGFR of 30 to <90 mL/min/1.73 m^2, and were treated with ACEI or ARB. Mean baseline HbA_{1c} was 8.3% (67 mmol/mol), 60% had CKD stage 3, and around half had established cardiovascular disease (CVD) at entry to the study.

Primary outcome was a composite of:

- ESRD (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2);
- a doubling of serum creatinine level; or
- death from renal or CV causes.

There were seven pre-specified secondary outcomes, including a composite of CV death and hospitalisation for heart failure (HF), and individual components of the renal and CV composites.

The study was stopped early at the recommendation of the independent monitoring panel after a pre-planned interim analysis once 405 events were achieved, which demonstrated that the primary outcome had been met.

Results: A highly significant 30% RRR in the primary composite outcome (shown above) was observed, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio [HR], 0.70 [95% confidence interval (CI), 0.59–0.82; *P*=0.00001]).

The RRR for the renal-specific composite of ESRD, a doubling of the creatinine level, or death from renal causes was 34% (HR, 0.66 [95% CI, 0.53–0.81; *P*<0.001]), and the RRR of ESRD was 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; *P*=0.002) in those treated with canagliflozin versus placebo.

The canagliflozin group also had a lower risk of 3-point major adverse CV events (MACE; CV death, myocardial infarction, or stroke) (HR, 0.80 [95% CI, 0.67–0.95; *P*=0.01]) and hospitalisation for HF (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; *P*<0.001).

The slope of the decline in renal function was less steep in those treated with canagliflozin after a short-term reduction of eGFR (around 3–4 mL/min/1.73 m^2) in most patients in the first 3 weeks of treatment. Importantly, there were no significant differences in the rates of amputation or fracture in those treated with canagliflozin compared with placebo, unlike in the CANVAS programme (Neal et al, 2017). As anticipated, DKA occurred more frequently with canagliflozin treatment, but this was a rare side effect, with 2.2 cases/1000 patient-years versus 0.2 cases/1000 patient-years with placebo.

Presenting the results, Prof Perkovic stressed that the finding of no increased risk of amputation in those treated with canagliflozin versus placebo in CREDENCE was not due to there being too few events or that this was a lower-risk population for amputation than that in the CANVAS programme. Additional guidance on foot care was implemented during the course of the trial, but evaluation of results even before this did not demonstrate any increase in amputation in the canagliflozin-treated group.

Clinical trial teams were instructed to undertake foot inspection at each clinic visit, treatment was suspended in those developing foot lesions until these healed and people with previous amputation were not recruited during later stages of the trial.

Limitations of the study: As the trial was stopped early, this may have impacted on its power for some of the secondary outcomes, which were not significant (e.g. CV mortality rate). People with an eGFR <30 mL/min/1.73 m^2 were excluded from the study and, therefore, it is not known whether the findings can be generalised to this population.

For further discussion of the implications of this study, see editorial comment.

DELIGHT

In participants with type 2 diabetes and moderate to severe CKD, dapagliflozin, with or without saxagliptin for 24 weeks, reduced urine albumin excretion rate compared to placebo (Pollock et al, 2019).

In this double-blind, placebo-controlled trial, 448 individuals with eGFR 25–75 mL/min/1.73 m^2 and albuminuria (urine albumin–creatinine ratio [ACR] 30–3500 mg/g [3.39–395.5 mg/mmol]) already treated with an ACEI or ARB were randomised to dapagliflozin 10 mg daily, dapagliflozin 10 mg and saxagliptin 2.5 mg daily or placebo. At 24 weeks, dapagliflozin reduced ACR by a significant 21% and dapagliflozin–saxagliptin combination by a significant 38% compared to placebo; it was not clear from the paper whether the saxagliptin–dapagliflozin combination reduced albuminuria significantly compared to dapagliflozin alone. HbA_{1c} was reduced by 0.58% (6.3 mmol/mol) in the group treated with dapagliflozin and saxagliptin.

The Dapa-CKD study with dapagliflozin is ongoing, with a primary outcome of composite of ≥50% sustained decline in eGFR or reaching ESRD or CV death or renal death.

Sex disparity in CVD management

Women newly diagnosed with type 2 diabetes continue to receive less prevention and treatment of CVD than newly diagnosed men, according to a Diabetes UK-funded cohort study (Wright et al, 2019) of 79 000 people, published in *Circulation*. However, the increased risk of CVD events amongst women developing type 2 diabetes may not be as high as previously thought and may be similar to the increased risk in men. These UK-based data, from people newly diagnosed with type 2 diabetes in the UK Clinical Practice Research Datalink, demonstrated a CVD HR of 1.2 (95% CI, 1.12–1.28) in women newly diagnosed compared to those without type 2 diabetes. This compared with a HR of 1.12 (95% CI, 1.06–1.19) in men, which was not significantly different.

In the years following type 2 diabetes diagnosis, this case-controlled cohort study suggests women were more likely to have good glycaemic control, and more likely to be obese, hypertensive and have hyperlipidaemia, than newly diagnosed men. Women were less likely to receive optimal preventive treatment for CVD. They were 16% less likely to be prescribed statins and 26% less likely to be prescribed ACEI for prevention than men with type 2 diabetes. If they already had established CVD, women were 41% less likely to receive statins, 37% less likely to receive ACEIs and significantly less likely to be prescribed aspirin than men.

Although CVD remains the leading cause of death in people with type 2 diabetes and the risk remains greater than in the general population, changes in demographics and treatment options encouraged the investigators to assess whether ongoing primary and secondary prevention in those with type 2 diabetes had had any impact on CVD rates. It was previously demonstrated that CVD mortality rate was 27–50% greater in women with type 2 diabetes compared to men and potential reasons postulated included less aggressive management of risk factors. Within the cohort of people in this study, MACE occurred in 12.3% of those newly diagnosed with type 2 diabetes (11.6% of women and 12.8% of men [non-significant difference]) compared to 7.8% overall in those without type 2 diabetes (7.4% of women and 8.1% of men).

Only 17% of women in the study were aged <50 years, and therefore concerns regarding prescribing statins and ACEI to women of child-bearing age could not have had a significant impact on the under-prescribing seen in women.

The lower treatment levels in women despite greater risk factors suggests there remains scope to improve our care and ensure women with diabetes and CVD risk factors or established CVD are treated promptly.

Nearly 10-fold variation in diabetic major lower-limb amputation rates across CCGs

Although there has been no significant change in major (above-ankle) amputation rates in people living with diabetes across England (Public Health England, 2019), figures released in April 2019 demonstrate that CCGs across England had directly standardised rates of major amputation that varied from 2.5/10 000 population-years to more than 20/10 000 population-years in the period from 2015/16 to 2017/18. The rate across England has been stable at just over 8/10 000 population-years for several years, with a small increase in absolute numbers from 6957 (for 2012/13–2014/15) to 7545 (for 2015/16–2017/18). Minor diabetic lower-limb amputation rates had significantly increased to nearly 20 000, up from just over 17 000 in the previous reporting period, with a directly standardised rate of 21.4/10 000 population-years. Again, there was significant variation across CCGs, from 8/10 000 to more than 40/10 000 population-years.

Data from the April 2019 *Foot Care Profiles* confirm there were just under 150 000 hospital stays for diabetic foot disease in the latest period, with an average length of stay of 8 days, consuming more than 1.8 million bed-days and placing a significant burden on hospital services.

The bulletin reminds us that major amputation rates in people with diabetes can be used as a proxy for effectiveness of healthcare and diabetic foot care services, while minor amputations usually represent preventive action (attempts to remove damaged tissue to encourage healing). Directly standardised rates allow more accurate comparisons between populations, as there is a lower amputation rate in South Asians and Blacks, and rates increase with age.

ADA consensus: Nutrition therapy for adults with diabetes and pre-diabetes

The American Diabetes Association (ADA) has published *Nutrition therapy for adults with diabetes or pre-diabetes: A consensus report* (Evert et al, 2019), which provides practising clinicians with evidence-based guidance about individualising nutrition therapy to help people with diabetes and pre-diabetes to achieve weight management, and improve CV risk factors. The content includes responses to a series of key questions relevant to UK as well as US clinicians, and stresses the importance of medical nutrition therapy in diabetes management. It provides an update to the previous ADA nutrition position statement, published in 2014.

There is no single eating pattern or recommended change to diet likely to suit everyone, so the report highlights the importance of individualisation of recommendations and support. Some of the recommendations on frequency and level of dietetic support are unachievable at present in the UK, but there is a very useful summary of the evidence base for commonly recommended eating patterns and much practical information that is useful when counselling people with diabetes.

The consensus is published as part of a special nutrition article collection in *Diabetes Care* and a **podcast** on the consensus report is also available.

The next issue of the Journal will include articles on nutrition and diabetes.

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