Selected Summaries

Reducing risk of kidney failure in people with diabetes

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SUMMARY

This randomized, double-blind clinical trial was designed to investigate the effect of sodium-glucose cotransporter-2 (SGLT2) inhibitor, canagliflozin, on clinically important renal outcomes in people with type 2 diabetes mellitus (T2DM) and established chronic kidney disease (CKD).

The inclusion criteria were: age over 30 years, established T2DM, estimated glomerular filtration rate between 30 and 90 ml/min/1.73 m^2 and urinary albumin creatinine ratio (ACR) of 300–5000 mg/g. All individuals were required to be on standard of care treatment for diabetes and kidney disease, including maximally tolerated dose of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Those with other kidney diseases or NYHA class IV heart failure were excluded. After a 2-week placebo run-in, individuals were randomized in 1:1 ratio to receive placebo or oral canagliflozin 100 mg once a day.

The primary study end-points were: a composite of end-stage kidney disease, doubling of serum creatinine or renal or cardiovascular (CV) death. The secondary end-points were: CV death or hospitalization for heart failure, major CV events (CV death, myocardial infarction [MI] or stroke), hospitalization for heart failure, end-stage kidney disease (ESKD), doubling of serum creatinine or renal death, CV death, all-cause mortality and CV death, MI, stroke, hospitalization for heart failure or hospitalization for unstable angina.

For this event-driven study, it was estimated that 844 events will provide 90% power to detect a 20% relative risk reduction for the primary composite outcome. The study had a pre-specified interim analysis plan at 405 confirmed primary efficacy end-points and 2 years of exposure, with pre-specified stopping rules.

The trial was stopped early when after a planned interim analysis, the independent data and safety monitoring committee recommended terminating recruitment because it had already achieved the pre-specified efficacy criteria. By that time, a total of 4401 individuals had been randomized at 690 sites in 34 countries, 2199 to the placebo arm and 2202 to canagliflozin, 99.1% of whom had completed the study with a median follow-up of 2.62 years.

The relative risk of primary outcome was 30% lower in the canagliflozin group than in the placebo (hazard ratio 0.70; 95% confidence interval [CI] 0.59–0.82; p=0.00001). The renal end-point relative risk (composite of ESKD, doubling of serum creatinine or renal death) was lower by 34% (hazard ratio 0.66; 95% CI 0.53–0.81; p<0.001), and the relative risk of ESKD alone was lower by 32%. In line with previous studies of SGLT2 inhibitors, canagliflozin reduced the risk of CV death, MI or stroke by 20% and hospitalization for heart failure by 39%. Subgroup analyses showed the effect to be consistent.

In terms of important safety end-points, those on the study drug had a lower risk of developing hyperkalaemia but higher risk of genital mycotic infections and diabetic ketoacidosis. The overall rates of the latter were low (2.2 *v*. 0.2 per 1000 patient-years). There was no difference in the risk of amputation or fracture in the two groups.

The authors concluded that in individuals with T2DM and kidney disease, canagliflozin reduced the risk of kidney failure and CV events at a median follow-up of 2.6 years.

COMMENT

Even as CKD, primarily driven by the rampaging global epidemics of diabetes, hypertension and obesity continue its relentless march up the list of causes of death globally, the medical community has been frustrated by the failure of emergence of new treatments.

Globally, 30%–40% of an estimated 422 million people living with diabetes will develop CKD. The current management of these individuals includes good glycaemic and blood pressure control, cholesterol-lowering drugs and angiotensin pathway blockade. The latter was the last definitive approach proven to be of benefit, way back in the 1990s.

Over the past few years, three large clinical trials[1–3] have shown the CV benefits of SGLT2 inhibitors. Wanner *et al*.[4] showed that empagliflozin, another SGLT2 inhibitor, reduced the risk of renal events in those with T2DM compared to placebo. However, there were no data on the effect of these agents in patients with established kidney disease.

Through CREDENCE, we now have clear evidence of the renal and CV benefits of SGLT2 inhibition in individuals with T2DM who are at high risk of adverse renal outcomes. About 60% of CREDENCE participants had eGFR <60 ml/min/1.73 m^2

and 88% had high urinary ACR (>300 mg/g). In terms of numbers needed to treat (NNT), 22 patients will need to be treated with canagliflozin over 2.5 years to prevent one primary composite outcome, 28 to prevent one composite renal outcome, 40 to prevent one CV death, 43 to prevent one ESKD, MI or stroke and 46 to prevent one hospitalization for heart failure. In those with eGFR 30–45 ml/min/1.73 m^2, the NNT for primary outcome is impressively low—16.

A notable finding was the remarkable safety profile of this agent. In the previous CANVAS programme,[5] canagliflozin use was associated with increased risk of lower limb amputation. Knowledge of these findings led to introduction of an enhanced protocol of foot care in CREDENCE, but whether this was the only reason is hard to guess. Another notable point is that CREDENCE used only 100 mg dose whereas CANVAS also included those on 300 mg/day dose.

The trial was well designed and conducted; it truly included a high-risk population and managed to achieve a remarkable low (<1%) loss to follow-up. These findings have huge implications for clinical practice. Even though this is just one study, the magnitude and precision of effect and the consistency with previous trials of this class of agents lend high degree of confidence in the findings. Other trials are ongoing and will doubtless add to the evidence of the value of SGLT2 inhibition for the management of kidney disease in those with type 2 diabetes.

The unequivocal and impressive benefits of treatment with SGLT2 inhibitors will likely change the way we treat our patients. The American Diabetes Association has already updated its guidelines, suggesting that SGLT2 inhibitors be considered as first-line drugs for glycaemic control in those with T2DM and CKD who are already receiving metformin.

A question that remains unresolved is the mechanism of renal benefit of this drug. As the authors note, the between-group differences in blood glucose levels, weight and blood pressure were modest, suggesting a mechanism independent of the glycaemic effect. The most accepted hypothesis is the beneficial effect on intraglomerular pressure because of afferent arteriolar constriction secondary to increased sodium and glucose delivery to the distal renal tubule, which sends a signal to the juxtaglomerular apparatus as if this was as a result of glomerular hyperfiltration. Other suggested factors include reduction in sympathetic output, uric acid and increase in glucagon levels. Other intrarenal actions such as reduced inflammation and increased oxygenation are being investigated.

Even as we celebrate these results, we are mindful of the remaining questions; this trial excluded those without albuminuria and those with microalbuminuric disease. We know that urinary protein excretion may not rise in a substantial proportion of people with diabetes who go on to develop kidney disease. About 27% of participants discontinued the drug during the study period; more analyses will help provide clarity on this population. Another question is whether we will still see the benefit once the eGFR has fallen below 30 ml/min/1.73 m^2?

Finally, the theory that the mechanism of action of SGLT2 inhibitors is truly independent of glycaemic effect throws open the door for examining the effect of this drug in other non-diabetic kidney diseases.

For us in India, the use of SGLT2 inhibitors is likely to remain limited due to costs. The increased risk of genital mycotic infections needs to be noted and patients should be counselled appropriately.

Conflicts of interest. None declared

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