Title: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE trial)

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INTRODUCTION AND AIM

The CREDENCE trial was the first trial dedicated to investigating the renoprotective properties of canagliflozin (1). The primary outcome was a composite outcome of end-stage kidney disease (ESKD), doubling of serum creatinine, or renal/cardiovascular death. Secondary outcomes included renal and cardiovascular complications.

METHODS AND STUDY DESIGN

This was a multi-centre, double-blinded, placebo controlled trial. 4401 patients were enrolled and stratified randomisation based on eGFR was undertaken.

Inclusion criteria:

- >30 years
- T2DM (HbA1C 6.5%-12.0%)
- eGFR 30-60ml/min/1.73m^2
- Albuminuria (ACR 300–5000 mg/g)
- Maximal ACE inhibitor or angiotensin receptor blocker therapy.

Exclusion criteria:

- Known non-diabetic kidney disease, previous haemodialysis or renal transplant

The trial aimed for 844 events to achieve 90% power to detect a 20% difference in the primary outcome. Interim analysis at 405 events recommended early cessation given achievement of the pre-specified target of a p-value <0.01 in the primary outcome.

RESULTS AND CONCLUSIONS

The relative risk of the primary outcome in the intervention group was reduced by 30% ($p<0.00001$) with a number needed to treat of 22. A secondary composite outcome of ESKD, doubling of serum creatinine, or renal death was similarly reduced (Hazard Ratio 0.66; $P<0.001$). Cardiovascular outcomes were improved in the intervention group, consistent with previous data1. The safety profile in both groups was similar with no difference noted in amputation, contrary to the findings of the CANVAS study (2).

The authors concluded canagliflozin conferred clear renoprotective effects in those with albuminuric chronic kidney disease and T2DM.

STUDY CRITIQUE

Strengths include selection of patients at risk of progression to ESKD to ensure the study was adequately powered to assess renal outcomes. It was a multi-centre, international study allowing for generalisability of findings.

A limitation is early trial closure; generally, this causes over-stated benefits of interventions and can reduce adverse events recorded. Patient selection excluded those with eGFR <30mls/min, albumin creatinine ratio <300mg/g, or non-diabetic kidney disease, limiting broader applicability.

REFLECTION

CREDENCE is a landmark paper in nephrology; previously renin-angiotensin-aldosterone system blockade was the only pharmacotherapy proven to significantly impact progression of proteinuric diabetic kidney disease (3-4).

Studies with other SGLT-2 inhibitors are underway to investigate a potential class effect (5-6). These studies include lower eGFR and non-diabetic patients, possibly broadening applicability of these findings. It has recently been announced DAPA-CKD, a study of this type with dapagliflozen, is to close early given early positive outcomes (7).

CREDENCE is lauded as practice changing and has informed the practices of many in the field. Recently published American Diabetes Association guidelines also reflect this evidence (8).

It is estimated ~5% of the Irish population have T2DM, and it is expected to increase in the coming years (9). Given the prevalence of T2DM in Ireland, and the associated morbidity and mortality, all general internal medicine physicians should be aware of strategies for reducing the rate of T2DM complications.

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