CREDENCE and the management of diabetic kidney disease

**Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy**

Recent trials have suggested that the sodium-glucose co-transporter-2 inhibitors (SGLT2i) are renoprotective, however these trials included few patients with established diabetic kidney disease (DKD). The CREDENCE study (Perkovic, et al.) enrolled 4401 participants with type 2 diabetes, macroalbuminuria and an eGFR between 30 and <90ml/min/1.73m², and randomized them to receive 100mg canagliflozin or placebo daily. Participants were required to be on a stable dose of RAS blockade. After a median follow up of 2.6 years, planned interim analysis resulted in termination of the trial. The risk of the primary composite outcome (end-stage kidney disease [ESKD], sustained doubling of serum creatinine, or death from renal or cardiovascular causes) was 30% lower in the canagliflozin group (HR 0.70 [95%CI 0.59, 0.82; P<0.001]). This included a significant difference in the occurrence of ESKD of 116 vs. 165 events (HR 0.68 [95%CI 0.54, 0.86; P=0.002]). Rates of diabetic ketoacidosis were low overall, but higher in the canagliflozin group (11 vs. 1 events). Rates of fracture or amputation did not differ between groups. This study represents an exciting advance in the management of DKD and is likely to establish SGLT2 inhibition as an important facet of the management of DKD.

**SONAR study highlights potential of endothelin receptor antagonism in diabetic kidney disease**

Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial

Endothelin receptor (ET) antagonists have shown promise in previous studies for their ability to reduce albuminuria in diabetic kidney disease (DKD). Heerspink, et al. enrolled 5117 participants with DKD (eGFR 25-75ml/min/1.73m²) and macroalbuminuria in a 6-week enrichment phase during which all participants received 0.75mg atrasentan. At the end of enrichment, 2648 these participants were deemed to be responders – defined by a reduction in urine albumin-creatinine ratio (UACR) without evidence of fluid retention (≥3kg weight gain and BNP ≥300pg/mL) or excessive creatinine rise (>0.5mg/dl and 20% above baseline) – and were randomized to continue atrasentan or commence placebo. In addition, 1020 non-responders without evidence of fluid retention or excessive creatinine rise were also randomized to atrasentan or placebo. After a median follow up of 2.2 years in the responder group, the composite primary outcome (doubling of serum creatinine, end-stage kidney disease or death from kidney failure) occurred in 79 (6.0%) of 1325 patients in the atrasentan group compared vs. 105 (7.9%) of 1323 patients in the placebo group (HR 0.65 [95%CI 0.49, 0.88]; P=0.0047). Among the non-responders, fewer primary outcomes were observed in the atrasentan group (73 [14-3%] vs. 87 [17.0%]). While this difference was not significant (HR 0.75 [95% CI 0.55, 1.03]; P=0.079), it was consistent with the effect seen in the responders (P_{interaction}=0.41). Adverse events were more common with atrasentan than placebo, including an increased occurrence of fluid retention (36.6% vs. 32.3%; P=0.022) and anemia (18.5% vs. 10.3%; P<0.001). Even considering trial limitations, including a 10% rate of loss to follow up and 19% treatment discontinuation (both balanced equally between arms), this interesting study shows that atrasentan slows progression of DKD And suggests a potential role of ET antagonists, although none are currently on the market for this indication.

**Key to risk of bias assessment**

- Random sequence generation: High risk
- Allocation concealment: Uncertain risk / not stated
- Blinding of participants/personnel: Low risk
- Blinding of outcome assessment: No other sources of bias

**ISN Academy: Chronic Kidney Disease, Diabetes**
Direct renin inhibition with imarikiren reduces albuminuria in diabetic nephropathy
Efficacy and Safety of Imarikiren in Patients with Type 2 Diabetes and Microalbuminuria: A Randomized, Controlled Trial
Diabetic nephropathy is a leading cause of end-stage kidney disease and new therapies are urgently needed. Ito, et al. randomized 415 participants with type 2 diabetes, microalbuminuria and an eGFR of at least 45ml/min/1.73m2 to 5, 20, 40 or 80mg of imarikiren (a novel direct renin inhibitor); placebo or candesartan 8mg daily. Like candesartan, compared to placebo, the reduction in urine albumin:creatinine ratio (UACR) at 12 weeks was significantly greater for all doses of imarikiren (varying from -16% with 5mg daily to -39% with 80mg daily; all P<0.001). Imarikiren was well tolerated. While a positive early-phase study, caution is warranted in light of previous trials (using aliskiren) which have not shown a benefit from direct renin inhibition on progression of diabetic nephropathy when used on top of RAS blockade.

Ciprofloxacin prophylaxis does not reduce BK viremia after renal transplantation
Ciprofloxacin for BK viremia prophylaxis in kidney transplant recipients: Results of a prospective, double-blind, randomized, placebo-controlled trial
BK virus continues to present a vexing problem for renal transplant recipients. Fluoroquinolone antibiotics have been proposed as possible prophylactic agents., Patel, et al. randomized 200 renal transplant recipients in a 2:1 ratio to receive 500mg of ciprofloxacin per day or placebo for the first 3 post-transplant months. BK viremia was more common during the first 6 months in the ciprofloxacin arm (19% vs 8% of participants; P=0.03) and, although not statistically significant, rates of BK viremia and BK nephropathy were numerically higher by 12 months. Moreover, those randomized to ciprofloxacin experienced more fluoroquinolone-resistant infections (83% vs 50%). These results are in line with those of a previous meta-analysis and suggest that ciprofloxacin does not have a role in the prevention of BK virus.

Equivocal result for eculizumab in the prevention of AMR in sensitized kidney transplant recipients
Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: A randomized trial
High-titres of pre-formed HLA-incompatible donor-specific antibodies markedly increase the risk of antibody mediated rejection (AMR) in patients undergoing renal transplantation. Eculizumab prevents terminal complement activation, an important step in the pathophysiology of AMR. This phase 2, multi-centre study randomized 102 participants who had required pre-transplant desensitisation to receive induction therapy with or without eculizumab. Eculizumab was given 1 hour prior to reperfusion and on day 1, then weekly for one month and biweekly until week 9 (total of 9 doses). The primary endpoint of treatment failure (a composite of biopsy-proven AMR (Banff grade II or III), graft loss, patient death, or loss to follow-up) at 9 weeks, was not different between the two groups (5 vs. 7 events; P=0.76) or at 12 months (10 vs. 9 events; P=0.80). There were no significant safety concerns. In a post hoc analysis when Banff grade I AMR was included, the treatment failure rate was found to be lower in the eculizumab group than in the SOC group (11.8% and 29.4%, respectively; nominal P=0.048). Given the limitations of this study, including its open-label design, and small sample size, this post-hoc finding would need to be confirmed in a well-designed RCT.

Novel acid binding resin raises serum bicarbonate in short term study
Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial
Treatment of metabolic acidosis may slow progression of chronic kidney disease and has been associated with preservation of bone and muscle mass. Wesson, et al. randomized 217 participants (in a 4:3 ratio) with an eGFR of...
20-40ml/min/1.73m² and bicarbonate concentration of 12-20mmol/l to veverimer (a novel binder of hydrochloric acid) or placebo. At 12 weeks, more participants in the veverimer group than the placebo group achieved a normal serum bicarbonate or 4mmol/l rise from baseline (59% vs 22%; P<0.0001). Adverse events (predominantly gastrointestinal) were more common in the veverimer group (13% vs 5%). While this study suggests veverimer is effective at raising serum bicarbonate, long term studies with an active comparator or patient-centered outcomes are necessary.

Hydroxychloroquine shows promise in IgA nephropathy
Effects of Hydroxychloroquine on Proteinuria in IgA Nephropathy: A Randomized Controlled Trial
Proteinuria remains one of the strongest predictors of loss of renal function in IgA nephropathy. Hydroxychloroquine (HCQ) has shown promise in earlier non-randomized analyses as an immunomodulatory agent that may reduce proteinuria and preserve renal function. In this trial, 60 participants with biopsy diagnosed IgA nephropathy and urine protein excretion of 0.75-3.5g/d despite 3 months of maximal RAAS blockade and blood pressure control, received HCQ at a renally adjusted dose or placebo for a total of 6 months. The primary outcome of percentage change in proteinuria at 6 months vs baseline at significantly different between the HQC group vs placebo (-48.4% [IQR -64.2%, -30.5%] vs 10% [IQR -38.7%, 30.6%]; P<0.001). This resulted in a 1g/day difference in median proteinuria between groups at 6 months (median 0.9g/d [IQR 0.6, 1.0] vs. 1.9g/d [IQR 0.9, 2.6]; P=0.002). No serious adverse events occurred in either arms of the study. While only an early phase trial, it has provided proof of concept and further evaluation in a larger trial is expected.

End of the road for high cutoff dialysis in myeloma?
High cutoff versus high-flux haemodialysis for myeloma cast nephropathy in patients receiving bortezomib-based chemotherapy (EuLITE): a phase 2 randomised controlled trial
High cutoff haemodialysis showed promise in early non-randomized studies, but has not been proven effective in a randomized study. In the EuLITE study, 90 participants with biopsy-proven cast nephropathy and need for dialysis were randomized to high cutoff (HCO) or standard high flux (HF) hemodialysis (HD) in combination with best evidence bortezomib-based chemotherapy. The frequency of the primary outcome of independence from dialysis at 90 days did not differ between groups: 24/43 vs. 24/47 in the HCO-HD and HF-HD groups, respectively (relative risk 1.09 [95%CI 0.74, 1.61; P=0.81]). In addition, those on HCO-HD had an increased risk of lung infections over the first 90 days (RR 4.64 [95%CI 1.42, 15.20; P=0.0008]), a reduced disease response to treatment at 12 months (RR 0.62 [95%CI 0.41, 0.92; P=0.022]) and exhibited a trend towards increased mortality at 2 years (16 vs. 9 participants; P=0.058). This important study, the second RCT to find no clear benefit from HCO-HD, does not support further application of this form of dialysis to myeloma management.

No benefit from spironolactone in patients on hemodialysis
A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients
Mineralocorticoid antagonism is hypothesized to modify key aspects of the cardiomyopathy associated with chronic dialysis, but safety concerns remain. Hammer, et al. randomized 97 participants receiving hemodialysis to spironolactone 50mg daily or placebo. At 40 weeks, there was no significant difference in change in left ventricular mass index (mean difference -2.3g/m² [-6.9, 2.4]; P=0.34) or ambulatory blood pressure. While moderate hyperkalemia (6.0-6.5mmol/l) was more common with spironolactone than placebo (155 vs. 80 events), there was no difference in episodes of severe hyperkalemia (>6.5mmol/l; 14 vs. 24 events). This study suggests that spironolactone does result in increased incidence of hyperkalemia in patients receiving hemodialysis and did not find evidence to suggest it has beneficial effects. Loss to follow up and the short duration of this study tempers these conclusions and, as prior studies have suggested a reduction in LVM, further RCTs in this area are expected.
Beating the blues on hemodialysis: Sertaline may have an edge over CBT
Comparative Efficacy of Therapies for Treatment of Depression for Patients Undergoing Maintenance Hemodialysis
A third of patients on hemodialysis describe depressive symptoms though there is limited evidence for the efficacy of antidepressants in this population. Mehrotra, et al. compared antidepressant therapy to cognitive behavioural therapy (CBT) in adults on hemodialysis for > 3 months with major depression or dysthymia. In phase 1 of the study, 184 participants were randomised to motivational interviewing or untrained discussion of treatment options, with no difference in the proportion accepting treatment for depression (66% vs 64%, p=0.77). In phase 2, 120 participants accepting treatment were randomised to individual CBT (n=60, 10 x 60 min sessions over 12 weeks during hemodialysis) or sertraline (n=60, 25mg/day titrated slowly up to 200mg/day if tolerated). By week 12, the primary outcome of change in Quick Inventory of Depressive Symptoms–Clinician Rated (QIDS-C) score (scale 0 to 27) was lower in the sertraline group compared to the CBT group (mean difference -1.84 [95%CI -3.54, -0.13]; P=0.035). There was no significant difference between sertraline and CBT in participants achieving a 50% reduction in QIDS-C score (risk ratio [RR] 1.18, 95% CI 0.75 to 1.87) or QIDS-C score <5 (RR 1.36, 95% CI 0.81 to 2.28). This study suggests that sertraline may provide a modest benefit in comparison to CBT in the treatment of depression in patients receiving hemodialysis.

Darbepoetin and erythropoietin appear similarly effective in Indian dialysis recipients
Efficacy, tolerability and safety of darbepoetin alfa injection for the treatment of anemia associated with chronic kidney disease (CKD) undergoing dialysis: a randomized, phase-III trial
Erythropoiesis-stimulating agents (ESA) are widely used for the treatment of anemia associated with CKD but there are few trials to compare the efficacy and safety of different ESAs outside of North American and European contexts. Sinha, et al. randomised 126 adults in India receiving hemodialysis or peritoneal dialysis with hemoglobin <120 g/L to erythropoetin alfa (EPO) (50 IU/kg thrice weekly) or darbepoetin alfa (DA) (0.45 µg/kg subcutaneous weekly), with prespecified dose adjustment to achieve target hemoglobin. Iron was replaced as per each individual centre’s protocol. At 36 weeks, the primary outcome of change in hemoglobin from baseline was significant in both the EPO group (mean difference [MD] +18.5 g/L [95%CI 13.7, 23.3]) and DA group (MD +18.4 g/L [95%CI 13.6, 23.2]) with no significant between-group difference. While providing some evidence that EPO and DA have similar efficacy in Indian dialysis recipients, this study was limited by its open-label design and a lack of reporting of confounding factors such as transfusion requirements and iron treatments.

Intestinal phosphate transport inhibition offers novel method of managing hyperphosphatemia
Efficacy and Safety of Tenapanor in Patients with Hyperphosphatemia Receiving Maintenance Hemodialysis: A Randomized Phase 3 Trial
Treatment of hyperphosphatemia in chronic hemodialysis patients with enteric phosphate binders results in a significant pill burden. Tenapanor is a minimally absorbed inhibitor of gastrointestinal sodium/hydrogen exchange 3 (NHE3) that limits dietary phosphate absorption. Initially a randomized dose-ranging study in which 219 participants were randomized to 3, 10 or 30mg tenapanor twice daily over 8 weeks; at the request of the regulator, it was converted into a phase 3 study, by adding a 4-week extension after re-randomization of participants to placebo or to continuing tenapanor. At the end of the 8-week period, serum phosphate was lower in all three groups by approximately 1mg/dl [0.32mmol/l]. Among the 164 participants re-randomized, the difference in serum phosphate between the pooled tenapanor group and placebo group was significant (mean difference -0.72mg/dl [95%CI -1.19,-0.25] [-0.23mmol/l [95%CI -0.38, -0.08]), P=0.003). Loose bowel motions were more frequent in the treatment arm. The relative merits of tenapanor compared to standard treatment and its impact on clinically meaningful outcomes such as cardiovascular events will need to be determined in further studies.