Welcome to the latest issue of Nephrology Research Review.

In this issue, UK researchers report that a standard 8-week course of prednisolone is sufficient for children with a first episode of nephrotic syndrome, the CREDENCE trial reports that the oral SGLT2 inhibitor canagliflozin has beneficial renal effects in patients with type 2 diabetes and CKD, and an intriguing Chinese study suggests that hydroxychloroquine may have a place in the management of IgA nephropathy. We also report that fecal immunochemical testing is an accurate screening test for colorectal cancer in CKD patients, and oral magnesium oxide may inhibit coronary artery calcification in patients with advanced CKD.

We hope you find these and the other selected studies interesting and look forward to any feedback you may have.

Kind Regards,

Professor Vlado Perkovic
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Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome

Authors: Webb N et al., on behalf of the PREDNOS Collaborative Group

Summary: The PREDNOS trial evaluated whether extending prednisolone treatment from 8 to 16 weeks reduces disease relapse in children with idiopathic steroid-sensitive nephrotic syndrome. 237 children aged 1–14 years with a first episode of steroid-sensitive nephrotic syndrome were randomised to receive an extended 16-week course of prednisolone (total dose 3150 mg/m^2) or a standard 8-week course (total dose 2240 mg/m^2).

No significant between-group differences were found in relapse incidence, time to first relapse, or requirement for alternative immunosuppressive treatment. Extended course treatment was associated with an improvement in quality of life and cost savings.

Comment: It is great seeing more trials addressing key unanswered questions in glomerulonephritis. Extending steroid duration from 8 to 16 weeks did not reduce relapses, steroid dependence or other immunosuppressive therapy in childhood idiopathic nephrotic syndrome, but curiously appeared to be associated with better behaviour on one measure, and better quality of life. Confirmation of these benefits would appear important before offering them to patients.


Abstract

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Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

Authors: Perkovic V et al., for the CREDENCE Trial Investigators

Summary: The CREDENCE trial evaluated the renal effects of the oral SGLT2 inhibitor canagliflozin in patients with type 2 diabetes and albuminuric CKD. 4401 patients who were already receiving optimised RAAS blockade were randomised to receive canagliflozin 100mg or placebo long-term. The primary outcome was a composite of ESKD, a doubling of serum creatinine levels, or death from renal or cardiovascular causes. During a median follow-up of 2.62 years, the relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group (p=0.00001), and the relative risk of ESKD alone was 32% lower (p=0.002). The canagliflozin group also had a 20% lower risk of cardiovascular death, myocardial infarction, or stroke (p=0.01), and a 39% lower risk of hospitalisation for heart failure (p<0.001).

Comment: I have a clear interest here, so will not recapitulate the results, but would hope that all nephrologists and endocrinologists will discuss SGLT2 inhibitors with appropriate patients. Whether renal protection is achieved in non-diabetic kidney disease is now a key question, and will hopefully be answered in coming years.


Abstract

Effects of hydroxychloroquine on proteinuria in IgA nephropathy

Authors: Liu L et al.

Summary: This Chinese study evaluated the efficacy and safety of hydroxychloroquine in patients with IgA nephropathy who were already receiving optimised RAAS inhibition. 60 patients were randomised in a double-blind design to receive daily oral hydroxychloroquine or placebo for 6 months. Percentage change in proteinuria differed significantly between groups at 6 months (−48.4% with hydroxychloroquine vs +10.0% with placebo; p<0.001), and median proteinuria levels were significantly lower in the hydroxychloroquine group (0.9 vs 1.9 g/day; p=0.002). No serious adverse events were reported in either group.

Comment: This intriguing study suggests a possibly important effect of hydroxychloroquine on the kidney in IgA nephropathy. As well as confirming the results, effects on GFR decline and hard renal end-points will be important to assess. But hopefully we are moving to an era where we have multiple treatment options for people with this condition.


Abstract

One-time fecal immunochemical screening for advanced colorectal neoplasia in patients with CKD (DETECT Study)

Authors: Wong G et al.

Summary: The DETECT study evaluated the use of fecal immunochemical testing (FIT) for detecting colorectal cancer in patients with CKD. 1706 patients aged 35–74 years with CKD from 11 sites in Australia, NZ, Canada, and Spain underwent FIT screening and were followed up for 2 years. 369 patients (21.6%) had a positive result on FIT, and 323 of them underwent a colonoscopy. The detection rate of advanced colorectal neoplasia using FIT was 6.0%. Sensitivity, specificity, and positive and negative predictive values of FIT for advanced colorectal neoplasia were 0.90, 0.83, 0.30, and 0.99, respectively. Five patients (1.5%) who underwent colonoscopy had major colonoscopy-related complications, including bowel perforation and major bleeding.

Comment: Great to see this important Australian contribution to our understanding of the balance of benefits and risks associated with bowel cancer screening in CKD patients. The high complication rate associated with colonoscopy is perhaps the most important finding and has implications beyond cancer screening strategies.


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Abstract
A randomized trial of magnesium oxide and oral carbon adsorbent for coronary artery calcification in predialysis CKD

Authors: Sakaguchi Y et al.

Summary: This open-label Japanese study assessed the effects of magnesium oxide and the oral carbon adsorbent AST-120 on CAC progression in CKD. 125 predialysis patients with stage 3–4 CKD who had risk factors for CAC were randomised (using a two-by-two factorial design) to an MgO group or a control group, and to an AST-120 group or a control group. The percentage change in CAC score (primary outcome) was significantly lower in MgO versus control groups (11.3% vs 39.5%), and the proportion of patients with an annualised change in CAC score >15% was also significantly lower with MgO (23.9% vs 62.0%). However, MgO did not suppress the progression of thoracic aorta calcification. Dropout rates were higher in MgO versus control groups (27% vs 17%), primarily due to diarrhoea. AST-120 did not significantly affect CAC scores compared with controls.

Comment: It is fascinating to think that oral magnesium oxide may inhibit the coronary calcification that is so prevalent in advanced CKD, although the lack of effect on aortic calcification highlights the uncertainty about the clinical implications. A larger trial powered for patient-level outcomes would appear important.


Effects of nicotinamide and lanthanum carbonate on serum phosphate and fibroblast growth factor-23 in CKD

Authors: Ix J et al.

Summary: The COMBINE trial investigated the effects of the phosphate binder lanthanum carbonate and the active intestinal phosphate transport inhibitor nicotinamide on serum phosphate and FGF23 levels in patients with stage 3b–4 CKD. 205 patients with eGFR 20–45 ml/min/1.73m² were randomised to receive nicotinamide 750mg twice daily + lanthanum carbonate 1000mg three times daily, nicotinamide + placebo, lanthanum carbonate + placebo, or double placebo for 12 months. Mean rates of change in serum phosphate levels increased slightly over 12 months in all groups and did not differ significantly between groups. Percent changes in FGF23 also increased over 12 months in all groups (except the lanthanum carbonate + placebo group), and did not differ significantly across arms. Adherence was affected by gastrointestinal symptoms.

Comment: It is disappointing that neither lanthanum nor nicotinamide was able to lower phosphate or FGF23 in people with significant CKD. This study highlights the importance of these sorts of trials in helping us to understand the clinical effects of strategies that increase the pill burden on our patients.


Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease

Authors: Schlackow I et al., on behalf of the SHARP Collaborative Group

Summary: This study analysed data from the Study of Heart and Renal Protection (SHARP) to evaluate the effect of statins and ezetimibe on quality-adjusted life years (QALYs) and health care costs in patients with non-dialysis CKD in the US and the UK. Statin regimens with or without ezetimibe 10mg were investigated, and treatment effects on cardiovascular risk were estimated per 1-mmol/L reduction in low-density lipoprotein cholesterol. Net costs below $100,000/QALY (US) or £20,000/QALY (UK) were considered cost-effective. In the US, atorvastatin 40mg increased life expectancy by 0.23–0.31 QALYs in non-dialysis patients with stages 3b–5 CKD, at a net cost of $US20,300 to $US78,200/QALY. Adding ezetimibe 10mg increased life expectancy by an additional 0.05–0.07 QALYs, at a net cost of $US43,600 to $US91,500/QALY. Cost-effectiveness findings in the UK were similar.

Comment: SHARP remains a landmark trial demonstrating important benefits that should be offered to all patients with CKD not requiring dialysis, and arguably those receiving dialysis too. This analysis shows that this approach is reasonable from a cost-effectiveness perspective as well as a clinical one, for both statins and ezetimibe.


Duration of dual antiplatelet therapy in patients with CKD and drug-eluting stents

Authors: Mavrakanas T et al.

Summary: This meta-analysis compared outcomes after short and long-term dual antiplatelet therapy (DAPT) in CKD patients with a drug-eluting stent. A search of Medline identified 5 randomised controlled trials (n=1902) that were suitable for inclusion. The primary outcome was a composite of all-cause mortality, myocardial infarction, stroke, or stent thrombosis. Short-term DAPT (<6 months) was associated with a similar incidence of the primary outcome compared with 12-month DAPT in patients with CKD, and 12-month DAPT was associated with a similar incidence of the primary outcome compared with extended DAPT (>30 months). The number of major bleeding events did not differ significantly between short-term or 12-month DAPT, or between 12-month and extended DAPT.

Comment: Antithrombotic strategies are the least well studied cardioprotective options to date in CKD, so studies like this are important for highlighting important areas for ongoing study. It supports short duration DAPT in CKD patients overall, which may reduce the risk of bleeding outcomes in these people.


Early glomerular hyperfiltration and long-term kidney outcomes in type 1 diabetes

Authors: Molitch M et al., for the DCCT/EDIC Research Group

Summary: This analysis of data from the DCCT/EDIC trials evaluated the impact of glomerular hyperfiltration on the development of diabetic kidney disease in type 1 diabetes. Of 446 participants, 106 (24%) had glomerular hyperfiltration (i-iothalamate clearance [iGFR] >140 ml/min/1.73m²) at baseline. During a median follow-up of 28 years, the cumulative incidence of eGFR <60 ml/min/1.73m² was similar in patients with or without hyperfiltration at baseline (11.0% and 12.8%, respectively). A Cox proportional hazards model adjusted for confounding factors showed that hyperfiltration was not significantly associated with subsequent risk of developing eGFR <60 ml/min/1.73m².

Comment: The perceived importance of hyperfiltration as an early marker of kidney abnormalities in type 1 diabetes has almost become biblical, but is challenged by this study. The long-term follow-up and direct measurement of iGFR strengthen the reliability of the results. Is it that we can’t measure hyperfiltration well, or that it is less important than we had believed?

Effect of everolimus on renal function in patients with tuberous sclerosis complex

Authors: Bisler J et al.

Summary: This analysis of data from the phase 3 EXIST-1 and EXIST-2 studies evaluated the long-term renal effects of everolimus in patients with tuberous sclerosis complex. Everolimus was administered at a dosage of 4.5 mg/m² per day, adjusted to achieve target trough levels of 5–15 ng/ml (EXIST-1) or a dosage of 10 mg/day (EXIST-2). 111 patients from EXIST-1 and 112 patients from EXIST-2 were included in the analysis. Mean ages at everolimus initiation were 10.5 and 33.2 years, respectively, and 3.6% and 37.5% of patients in the respective studies had undergone prior renal intervention. Mean baseline eGFR was 115 ml/min/1.73m² in EXIST-1 and 88 ml/min/1.73m² in EXIST-2. Overall, mean eGFR remained stable over time in both studies, with a decline in renal function mostly confined to patients with severely compromised renal function prior to treatment. Patients with prior renal intervention had low eGFR throughout the study. The incidence of proteinuria (mostly grade 1–2) increased after initiating everolimus.

Comment: Obtaining reliable randomised data in rare conditions like tuberous sclerosis is very difficult and may never be achieved. The overall stability of kidney function in this single-arm study is somewhat reassuring but difficult to interpret in the absence of a control arm. Nonetheless, this may be the best that we can do.


Abstract

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PBS eligibility criteria

1. ≥18 years of age and

2. CKD stage 2 or 3 (eGFR 89 to 30 mL/min/1.73m²) at initiation of treatment and

3. Evidence of rapid progression determined by:
   – eGFR decline of ≥5 mL/min/1.73m² in one year or
   – eGFR decline of ≥2.5 mL/min/1.73m² per year over a period of 5 years

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