Nephrology Research Review™

Making Education Easy

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Abbreviations used in this issue:

CKD = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **ESKD** = end-stage kidney disease; **Ig** = immunoglobulin; **OR** = odds ratio; **SGLT2** = sodium glucose co-transporter 2; **uACR** = urinary albumin-creatinine ratio.

Welcome to the latest issue of Nephrology Research Review.

In this issue, the DUPLEX study finds little difference in disease progression despite proteinuria-reducing efficacy of sparsentan compared to irbesartan in patients with primary focal segmental glomerulosclerosis, the phase 2 ENVISION trial reports promising findings for sibeprenlimab in IgA nephropathy, and an Australian study uses sophisticated modelling to predict a likely increase in the burden of kidney disease with a warmer climate and an ageing population.

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

Kind Regards,

Professor David Mudge
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Sparsentan versus irbesartan in focal segmental glomerulosclerosis

Authors: Rheault MN et al., for the DUPRO Steering Committee and DUPLEX Investigators

Summary: The phase 3 DUPLEX trial compared the long-term efficacy and safety of sparsentan and irbesartan in patients with focal segmental glomerulosclerosis (FSGS). 371 patients aged 8–75 years were randomised to receive sparsentan or irbesartan (active control) for 108 weeks. At 36 weeks, 42.0% of patients in the sparsentan group and 26.0% in the irbesartan group had partial remission of proteinuria (p=0.009); this response was sustained through 108 weeks. However, the eGFR slope did not differ significantly between groups during the study. The mean change in eGFR from baseline to study end (week 112) was −10.4 ml/min/1.73m^2 with sparsentan and −12.1 ml/min/1.73m^2 with irbesartan. Sparsentan and irbesartan had similar safety profiles.

Comment: This trial compared the drug sparsentan, a novel dual endothelin and angiotensin receptor antagonist, to angiotensin receptor blockade alone in the form of irbesartan in primary FSGS. The primary end-point was the slope of eGFR decline over 2 years, with a secondary efficacy end-point of partial remission of proteinuria at 36 weeks of follow-up. Previous studies with sparsentan in FSGS showed an additional proteinuria benefit compared to angiotensin blockade alone, and endothelin inhibition in the kidney has been shown to reduce proteinuria, but potentially also to antagonise the profibrotic effects of endothelin. Although a greater proportion of sparsentan-treated patients achieved the partial remission of proteinuria end-point, the decline in kidney function in the two groups was similar at 108 weeks. The authors point out that this may have been related to the problem of the initial eGFR decline seen with initiation of both agents, which is difficult to separate from their proteinuria-reducing benefits. Side effects were similar, although there was a small increase in the incidence of hypotension in the sparsentan group.

Reference: N Engl J Med. 2023;389:2436–45
Abstract

A phase 2 trial of sibeprenlimab in patients with IgA nephropathy

Authors: Mathur M et al., for the ENVISION Trial Investigators Group

Summary: The phase 2 ENVISION trial investigated the efficacy and safety of sibeprenlimab in patients with IgA nephropathy. 155 adults with biopsy-confirmed IgA nephropathy who were at high risk for disease progression despite receiving standard-care treatment were randomised 1:1:1:1 to receive intravenous sibeprenlimab 2, 4, or 8 mg/kg or placebo once a month for 12 months. At study end, the geometric mean ratio reduction in 24-h urinary protein-creatinine ratio from baseline was 47.2%, 58.8%, 62.0%, and 20.0% with sibeprenlimab 2mg, 4mg, 8mg and placebo, respectively. Adverse events were reported in 78.6% of patients in the pooled sibeprenlimab group and 71.1% of patients in the placebo group.

Comment: IgA nephropathy has been a fertile area of research recently, as the pathogenesis of the disease has become clearer. The pathogenic role of a proliferation-inducing ligand (APRIL), that leads to overproduction of galactose-deficient IgA1, led to the development of the first monoclonal antibody (sibeprenlimab) to be trialled in the disease. This phase 2 study showed a significant benefit on proteinuria reduction with sibeprenlimab given monthly for a 12-month period. It is likely that this type of treatment may be combined with other less-specific treatments such as corticosteroids and angiotensin receptor blockade in the future depending on the stage of IgA disease identified at diagnosis, allowing for greater individualisation of therapy for a disease frequently diagnosed at varying stages in its course.

Reference: N Engl J Med. 2024;390:20–31
Abstract

Projection of high temperature-related burden of kidney disease in Australia under different climate change, population and adaptation scenarios

Authors: Liu J et al.

Summary: This population-based modelling study estimated the future burden of kidney disease in Australia under various climatic, population and adaptation scenarios. During the baseline period (2003–2018), high temperature was estimated to contribute to 2.7% of the observed burden of kidney disease in Australia. The projected future burden of kidney disease showed a gradually increasing trend when assuming no human adaptation, and was most strongly influenced by population change. High temperature related burden of kidney disease was projected to increase by 18.4–67.4% from baseline under a constant population, and by 100.2–291.2% when accounting for changes in population size and age structure.

Comment: The potential future impacts of climate change on human health are becoming an area of research interest and this paper from *Lancet Regional Health* examines the likely increase in the burden of kidney disease related to warmer climate and an ageing population in Australia. The authors used sophisticated modelling incorporating several different climate models to predict their impact on the incidence of kidney disease, based on previous data from 2003–2018 which estimated a fairly conservative 2.7% contribution of high temperature to the overall burden of kidney disease during that time period. The analysis took into account the various different climatic regions of Australia, as well as different models of population growth and ageing. This type of study may prove important for policymakers planning for the future costs of kidney disease in Australia.

Reference: Lancet Reg Health 2024;41:100916
Abstract

Earn CPD

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Impact of finerenone-induced albuminuria reduction on chronic kidney disease outcomes in type 2 diabetes

Authors: Agarwal R et al.

Summary: This mediation analysis study pooled data from two phase 3 trials to determine whether finerenone-induced changes in urine albumin-to-creatinine ratio (uACR) mediate its benefits on cardiovascular and kidney outcomes. Overall, data for 12,512 patients with CKD and type 2 diabetes who were treated with finerenone or placebo in the two double-blind trials were analysed. At baseline, median uACR was 514 mg/g. A total of 3338 (53.2%) patients receiving finerenone and 1684 (27.0%) receiving placebo had a ≥30% reduction in uACR. This level of reduction in uACR was found to mediate 84% of the treatment effect of finerenone on kidney outcomes and 37% of its treatment effect on cardiovascular outcomes.

Comment: Mediation analysis is a statistical technique that investigates the mechanism by which an exposure causes an outcome, which may include both direct and indirect effects. In the present study, the authors utilised data from the previously published studies of finerenone (a nonsteroidal mineralocorticoid receptor antagonist) to estimate the benefits of the reduction in uACR seen with the use of finerenone in patients with type 2 diabetes on the progression of CKD and cardiovascular events. Using this technique, the authors were able to establish that reduction of albuminuria of 30% or more by finerenone was responsible for 84% of the benefit of the kidney-related outcomes (including kidney failure, sustained decrease in kidney function or kidney disease death) but a more modest 37% of the cardiovascular end-points of death from cardiovascular causes, nonfatal myocardial infarction or stroke, or hospitalisation for heart failure. In real-world practice, demonstrating such a drop in uACR with finerenone treatment will reassure treating clinicians that they will be protecting patients from kidney and cardiovascular events.

Reference: Ann Intern Med. 2023;176(12):1606–16
Abstract

Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease

Authors: Tuttle KR et al.

Summary: This phase 2 study investigated the efficacy and safety of the aldosterone synthase inhibitor BI 690517 in patients with CKD. 586 patients with eGFR 30 to <90 ml/min/1.73m^2, uACR 200 to <5000 mg/g, and serum potassium ≤4.8 mmol/L who were taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were included. Patients were randomised to 8 weeks of empagliflozin or placebo initially, followed by a second randomisation (1:1:1:1) to additional BI 690517 (3mg, 10mg, or 20mg) or placebo once daily for 14 weeks. The primary end-point was the change in uACR from the second randomisation to the end of treatment, and was –3% with placebo, –22% with BI 690517 3mg, –39% with BI 690517 10mg, and –37% with BI 690517 20mg monotherapy. BI 690517 produced similar reductions in uACR when added to empagliflozin. Hyperkalaemia occurred in 10%, 15% and 18% of patients taking BI 690517 3mg, 10mg, and 20mg, respectively, with or without empagliflozin. Most (86%) cases of hyperkalaemia did not require intervention.

Comment: Combining blockade of the renin-angiotensin system (RAS) with aldosterone antagonists (such as spironolactone) is often problematic due to the occurrence of hyperkalaemia. Aldosterone synthase inhibitors are a novel class of agents which may be more safely combined with RAS blockers in the future. This paper reports the results of a phase 2 study of a Boehringer Ingelheim product in combination with RAS blockers for diabetic kidney disease with proteinuria, with some patients also being on empagliflozin. There was a dose-dependent increase in hyperkalaemia across the three different medication doses tested, but 86% of such events did not require specific therapy. The proteinuria reduction was significant and additional to the benefits of RAS blockade and SGLT2 inhibition.

Reference: Lancet 2024;403(10424):379–90
Abstract

Earn CPD

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Relationship between bone marrow iron load and liver iron concentration in dialysis-associated haemosiderosis

Authors: Rostoker G et al.

Summary: This French study investigated the relationship between bone marrow iron load and liver iron concentration in haemodialysis patients with haemosiderosis. 152 haemodialysis patients (38.8% female) had their liver iron concentrations and vertebral T2* levels (a surrogate marker of bone marrow iron) on MRI analysed retrospectively; almost half (47.4%) had iron overload according to quantitative MRI. Those with mild or moderate/severe liver iron overload also had higher bone marrow iron than those with normal liver iron concentration ($p<0.0001$).

Comment: Iron overload is a potential concern in haemodialysis patients, who are almost universally on significant doses of intravenous iron. The blood parameters for measuring iron in the body are limited (particularly by inflammatory states) and may not reflect total body iron stores. MRI has recently been used to assess both liver and bone marrow iron stores, with some studies suggesting a high prevalence of iron overload in dialysis patients prior to the advent of erythropoiesis-stimulating agents (ESA), although a paradoxically low level of iron in the bone marrow. These French investigators sought to establish the link between bone marrow and liver-stored iron in haemodialysis patients in the ESA era by using quantitative MRI in a retrospective cross-sectional study. They found that iron overload in the livers of haemodialysis patients was common and more pronounced than in peritoneal dialysis patients, but also that liver iron stores were more closely correlated with bone marrow iron levels, similar to a recently reported small autopsy study.

Reference: EBioMedicine 2024;99:104929
Abstract

Fixed low dose versus concentration-controlled initial tacrolimus dosing with reduced target levels in the course after kidney transplantation

Authors: Stumpf J et al., for the German S&L Study

Summary: This open-label German study evaluated a "Slow & Low" tacrolimus regimen after renal transplantation. 432 renal allograft recipients were randomised to receive basiliximab induction, mycophenolate and steroids and either standard prolonged-release tacrolimus (trough levels: 7–9 ng/ml; Standard Care arm), or an initial 7-day fixed dose of prolonged-release tacrolimus 5 mg/day followed by lower tacrolimus trough levels (5–7 ng/ml; Slow & Low arm). The primary end-point was the combined incidence rate of biopsy-proven acute rejections, graft failure, or death at 6 months; the non-inferiority margin was set at 12.5%. The overall rate of the primary end-point at 6 months was 22.1% in the Standard Care arm and 20.7% in the Slow & Low arm, demonstrating non-inferiority. Safety parameters did not differ between groups.

Comment: Tacrolimus has greater potency than its predecessor ciclosporin in the prevention of acute rejection in kidney transplantation. Early therapeutic drug monitoring (TDM) of tacrolimus in the acute post-transplant period can be problematic due to early levels sometimes being very high or low before reaching steady state. The importance of achieving an early therapeutic level in terms of preventing acute allograft rejection is not well known. This randomised controlled trial utilised fixed low-dose tacrolimus for the first week followed by a lower trough target thereafter ("Slow & Low") versus standard of care with TDM aiming for standard therapeutic levels. 432 patients were randomised in a non-inferiority design and the rates of biopsy-proven acute rejection were similar in both groups and also similar to other contemporary acute rejection data.

Reference: EClinicalMedicine 2023;67:102381
Abstract

Cost-effectiveness of school urinary screening for early detection of IgA nephropathy in Japan

Authors: Honda K et al.

Summary: This study evaluated the cost effectiveness of a school urinary screening programme for the early detection of IgA nephropathy in Japan. A computer-simulated Markov model was used to analyse the cost-effectiveness of the programme from a health care payer's perspective, using a hypothetical cohort of 1,000,000 children aged 6 years who were followed up through to the end of high school. The cost effectiveness of school urinary screening for IgA nephropathy was compared with no screening. In the base-case analysis, the incremental cost-effectiveness ratio was calculated to be $US39,127 per quality-adjusted life-year, which was considered cost effective according to a pre-set threshold. 60.3 per 1,000,000 patients in the no-screening strategy and 31.7 per 1,000,000 patients in the screening strategy had ESKD. The cost-effectiveness of the programme improved as the number of screenings decreased and the number of patients with ESKD due to IgA nephropathy increased.

Comment: Some Asian countries such as Japan have a much higher prevalence of IgA nephropathy than countries such as Australia, and this study examined the potential benefit of screening Japanese schoolchildren for the disease in order to prevent significant morbidity later, given the known benefit of early intervention and treatment in preventing or delaying the onset of ESKD. In Japan, a screening programme for kidney disease in children has been running for 50 years, allowing computerised modelling of cost effectiveness across different rates of disease prevalence and varying screening costs. The authors found that screening was cost-effective at around $US39,000, which is below the usually accepted benchmark of $US50,000, but cost-effectiveness declined with disease incidence in the model, which is relevant to other countries with a lower incidence of IgA nephropathy.

Reference: JAMA Netw Open 2024;7(2):e2356412
Abstract

A pragmatic, open-label, randomized controlled trial of Plasma-Lyte-148 versus standard intravenous fluids in children receiving kidney transplants (PLUTO)

Authors: Hayes WN et al.

Summary: The PLUTO trial compared the preoperative use of Plasma-Lyte 148 versus standard intravenous fluids on post-transplant electrolyte and acid-base abnormalities in 137 paediatric kidney transplant recipients. Fewer children in the Plasma-Lyte group than in the standard fluids group experienced acute hyponatraemia (primary outcome), but the difference was not significant (53% vs 58%; odds ratio [OR] 0.77, 95% CI 0.34–1.75). Children in the Plasma-Lyte group were more likely to experience hypernatraemia (OR 3.5, 95% CI 1.1–10.8), but were less likely to need changes to fluid prescriptions (rate ratio 0.52, 95% CI 0.40–0.67), and were less likely to experience hyperchloraemia (OR 0.17, 95% CI 0.07–0.4), acidosis (OR 0.09, 95% CI 0.04–0.22) and hypomagnesaemia (OR 0.21, 95% CI 0.08–0.50).

Comment: The landmark Better Evidence for Selecting Transplant Fluids (BEST-Fluids) study used Plasma-Lyte to reduce the incidence of delayed graft function in adult deceased-donor kidney transplant recipients in an Australian and NZ setting, and following on from that study, these authors compared Plasma-Lyte to normal saline in a paediatric kidney transplant cohort with an open-label trial design. Hyponatraemia is more of a concern in the paediatric cohort and was the end-point in this trial. The authors found that Plasma-Lyte did not reduce hyponatraemia occurrence but did lead to fewer prescription changes in the postoperative period compared to the use of normal or half-normal (0.45%) saline.

Reference: Kidney Int. 2024;105(2):364–75
Abstract

Unveiling a new era with liquid chromatography coupled with mass spectrometry to enhance parathyroid hormone measurement in patients with chronic kidney disease

Authors: Cavalier E et al.

Summary: This Belgian study recalibrated five parathyroid hormone (PTH) immunoassays using a recently developed liquid chromatography-tandem mass spectrometry (LC-MS/MS) method as the reference. The PTH immunoassays were recalibrated using a large panel of plasma samples with PTH concentrations determined by the LC-MS/MS method that was calibrated against the WHO 95/646 international standard. The recalibration successfully reduced inter-assay variability of PTH measurements across the different assays, thus demonstrating the feasibility for standardising PTH measurement results and using common reference ranges for PTH assays.

Comment: Secondary hyperparathyroidism (SHPT) management is one of the cornerstones of the treatment of CKD mineral and bone disorder, but is hampered by the variability across different laboratory assays for PTH. It is thus difficult to compare data related to SHPT across health systems and sometimes even within a single centre which uses different laboratories. These Belgian researchers sought to standardise PTH measurement by recalibrating assays against a WHO international standard LC-MS/MS method which has been recently developed and found they were able to harmonise five immunoassays against the LC-MS/MS method and provide a consistent reference range. A similar process is needed in Australia.

Reference: Kidney Int. 2024;105(2):338–46
Abstract

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Independent commentary by Professor David Mudge

Professor David Mudge is a Consultant Nephrologist at Princess Alexandra Hospital and visiting nephrologist at Redland Hospital, as well as a clinical researcher with the University of Queensland Centre for Kidney Disease Research. His clinical research interests include the thrombotic microangiopathies, iron supplementation in chronic kidney disease, antiviral medicals in CKD, and the use of honey to prevent infections in dialysis patients. He has published over 170 peer-reviewed papers and abstracts, with over 4000 citations. He has previously served on the Steering Committee of the KHA-CARI Guidelines, Kidney Health Australia's Medical and Scientific Advisory Committee, and the International Society of Nephrology's Young Nephrologists Committee.