Welcome to the latest issue of Nephrology Research Review.

In this issue, a meta-analysis reports that NOACs have a better benefit-risk profile than VKAs in early-stage CKD, a phase 2 study shows that the acid binder veverimer improves metabolic acidosis in CKD patients, and a cohort study reports that a high-dose influenza vaccine does not appear to provide additional protection beyond a standard-dose vaccine in haemodialysis patients. A pilot study reports that fixed-dose ferric citrate coordination complex has an excellent safety profile in patients with advanced CKD and merits further study, and a phase 2 Japanese study reports positive renal effects for the mineralocorticoid receptor antagonist esaxerenone in patients with type 2 diabetes and microalbuminuria.

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
vlado.perkovic@researchreview.com.au

Benefits and harms of oral anticoagulant therapy in chronic kidney disease

Authors: Ha J et al.

Summary: This systematic review and meta-analysis compared the benefits and harms of VKAs and NOACs in adults with CKD stage 3–5. A search of MEDLINE, EMBASE, and Cochrane databases identified 45 trials involving 34,082 patients with CKD who received anticoagulation for atrial fibrillation (AF; 11 trials), venous thromboembolism (VTE; 11 trials), thromboprophylaxis (6 trials), prevention of dialysis-access thrombosis (8 trials), and cardiovascular disease other than AF (9 trials). All but the 8 trials involving patients with ESKD were in patients with early-stage CKD. In AF patients, NOACs reduced the risk of stroke or systemic embolism (risk ratio [RR], 0.79) and the risk of haemorrhagic stroke (RR, 0.48) compared with VKAs; the effects of NOACs on recurrent VTE or VTE-related death were less certain. In all trials combined, NOACs appeared to be associated with a reduction in major bleeding risk compared with VKAs.

Comment: Anticoagulation is widely used for many conditions, and many aspects of thrombosis are known to be abnormal in people with kidney disease. But there are few adequately powered studies that specifically define the risks and benefits of anticoagulation in kidney disease. This review pooled all of the available data and suggests that NOACs are superior to warfarin in early CKD. It also highlighted the paucity of data in advanced CKD, and the need for more trials in this area.


Abstract

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Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension

Authors: Wesson D et al.

Summary: This study evaluated the long-term safety and efficacy of the acid binder veverimer in patients with metabolic acidosis in CKD. 196 patients with CKD and metabolic acidosis who had completed a 12-week parent study in which they were randomised (4:3) to receive oral suspensions of veverimer 6 g/day or placebo then entered a 40-week extension at 29 sites in 7 countries (Bulgaria, Georgia, Hungary, Serbia, Slovenia, Ukraine, and the US). Fewer veverimer than placebo recipients discontinued treatment permanently during the study (3% vs 10%, respectively), and no veverimer recipients stopped treatment because of an adverse event. Serious adverse events occurred in 2% and 5% of patients in the veverimer and placebo groups, respectively, and renal system adverse events were reported in 8% and 15% of patients in the respective groups. More veverimer than placebo recipients had an increase in bicarbonate (≥4 mmol/L or normalisation) at week 52 (63% vs 38%; p=0.0015) and significantly higher bicarbonate concentrations were seen in veverimer recipients at all time-points.

Comment: A growing number of trials have suggested that correcting metabolic acidosis with sodium bicarbonate might protect kidney function in CKD. But it hasn’t been clear whether this is due to the acidosis correction, or perhaps the impact of additional sodium on volume or perfusion. This phase 2 study shows that an acid binder that does not include sodium improves acidosis, and intriguingly may also improve physical function. The effects on important kidney outcomes will be defined in the ongoing VALOR-CKD trial.

Reference: Lancet 2019;394(10196):396-406

Comparative effectiveness of high-dose versus standard-dose influenza vaccine among patients receiving maintenance haemodialysis

Authors: Butler A et al.

Summary: This cohort study compared the effectiveness of high-dose versus standard-dose influenza vaccine in patients receiving maintenance haemodialysis. Data for 507,552 adults undergoing maintenance haemodialysis between the 2010/11 and 2014/15 influenza seasons were retrieved from the US Renal Data System. Within 225,215 influenza patient-seasons among older haemodialysis patients (≥65 years), 97.4% received standard-dose and 2.6% received high-dose influenza vaccine. Risk estimates did not differ significantly between high-dose and standard-dose vaccines for mortality, hospitalisation due to influenza or pneumonia, and influenza-like illness. Findings were similar for younger adults.

Comment: This observational study does not suggest additional benefit with high-dose compared to standard-dose vaccine. While the limitations of the observational design need to be borne in mind, the study does not support the current use of the high-dose vaccine in haemodialysis patients.

Reference: Am J Kidney Dis 2019; published online Aug 1

Hospitalization risk among older adults with chronic kidney disease

Authors: Wong E et al.

Summary: This analysis of the ARIC study determined the relationship between all-cause hospitalisation risk and the current CKD staging system in older adults. 4766 ARIC participants were assessed for CKD according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, using creatinine-based eGFR and albumin-creatinine ratio (ACR). Incidence rates of all-cause hospitalisation associated with each CKD risk group were analysed. Participants experienced 5548 all-cause hospitalisations during the study period and 29% had CKD. Decreased eGFR, increased ACR, and KDIGO risk stages (based on a combination of these measures) were strong risk factors for all-cause hospitalisation. Hospitalisation rates per 1000 person-years according to KDIGO risk categories were 208–223 (“low risk”), 288–376 (“moderately increased risk”), 363–548 (“high risk”), and 499–1083 (“very high risk”). The increased risk associated with low eGFR and high ACR persisted in adjusted analyses.

Comment: There is growing recognition that CKD is a risk factor for increases in the risk of not only cardiovascular disease, but also a range of other conditions. This study adds further information, showing that hospitalisation from any cause is increased with reduced kidney function. It highlights the importance of further research to understand how we might improve outcomes for this important patient population.


A pilot randomized trial of ferric citrate coordination complex for the treatment of advanced CKD

Authors: Block G et al.

Summary: This pilot study investigated the effects of fixed-dose ferric citrate coordination complex on various biochemical parameters in patients with advanced CKD. 203 patients with eGFR ≤20 ml/min/1.73 m2 were randomised 2:1 to receive a fixed dose of ferric citrate coordination complex (two tablets per meal, 210mg ferric iron per tablet) or usual care for 9 months or until 3 months after starting dialysis. Ferric citrate coordination complex significantly increased haemoglobin, transferrin saturation, and serum ferritin levels, and significantly reduced serum phosphate and intact fibroblast growth factor 23 (all p<0.001). Compared with usual care, treatment with ferric citrate coordination complex resulted in fewer annualised hospital admissions, fewer days in hospital, and a lower incidence of the composite end-point of death, provision of dialysis, or transplantation.

Comment: There is growing evidence that ferric citrate-based phosphate binders improve both anaemia and phosphate control in people with CKD. This phase 2 trial confirmed these findings, but also suggests the possibility that it may also prevent kidney failure and related end-points. As the trial was underpowered for these outcomes, and there were potentially important imbalances in various factors between groups, the results need to be tested in a larger trial.

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Efficacy and safety of esaxerenone (CS-3150) for the treatment of type 2 diabetes with microalbuminuria

Authors: Ito S et al.

Summary: This phase 2 trial evaluated the efficacy and safety of the nonsteroidal mineralocorticoid receptor blocker esaxerenone in Japanese patients with type 2 diabetes mellitus and microalbuminuria. 365 hypertensive or normotensive patients with type 2 diabetes mellitus and microalbuminuria treated with a renin-angiotensin system inhibitor were randomised to receive 0.625, 1.25, 2.5, or 5 mg/day esaxerenone or placebo for 12 weeks. The primary end-point was the change in urinary albumin-to-creatinine ratio (ACR) from baseline to week 12. Esaxerenone 1.25, 2.5, and 5 mg/day significantly reduced urinary ACR by 38%, 50%, and 56%, respectively, compared with placebo (7%; all p<0.001). The urinary ACR remission rate was 21% in the 2.5- and 5-mg/day groups versus 3% in the placebo group (both p<0.05). Hyperkalaemia was the most common drug-related adverse event, and was dose proportional.

Comment: There are growing amounts of data suggesting a potential role for mineralocorticoid receptor antagonists for protecting kidney function in people with diabetes. This study adds to that, suggesting that esaxerenone produces substantial reductions in albuminuria among microalbuminuric participants. The effects on major renal outcomes remain to be demonstrated, and we look forward to the publication of the finerenone trials in the relatively near future.

Abstract

Socioeconomic status and risk of kidney dysfunction: the Atherosclerosis Risk in Communities study

Authors: Vart P et al.

Summary: This analysis of the ARIC study investigated the association between socioeconomic status and CKD. The cohort comprised 14,086 participants with eGFR ≥60 ml/min/1.73m² at baseline. A total of 432 participants developed ESKD and 3510 developed CKD during a median 23 years of follow-up. After adjustment for demographics and baseline eGFR, the hazard ratio (HR) for incident ESKD compared with the high-income group was 1.56 in the medium-income group and 1.30 in the low-income group (p-trend <0.001). After full adjustments, the HR for ESKD was 1.33 in the medium-income group and 1.50 in the low-income group (p-trend <0.001). The eGFR decline was 5% and 15% steeper in the medium- and low-income groups, respectively, than in the high-income group. The Atherosclerosis Risk in Communities study provides further evidence of the relationship between socioeconomic status and the risk of both kidney failure and more rapid loss of kidney function. It does not prove causation, but suggests particular attention should be paid to people from lower socioeconomic backgrounds, and that further exploration of potential mechanisms is important.

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Reference: Nephrol Dial Transplant 2019;34(8):1361-68
Abstract

The Primary-Secondary Care Partnership to Improve Outcomes in Chronic Kidney Disease (PSP-CKD) study

Authors: Major R et al.

Summary: This cluster randomised trial in UK primary care evaluated the impact of a nurse-led CKD management programme on the rate of renal function decline in patients with CKD stage 3–5. 46 primary care practices were randomised to the intervention or usual care. In the 23 intervention practices (n=11,651), a nurse practitioner worked to implement guideline-based patient-level CKD management interventions. The 23 control practices (n=11,706) continued usual CKD care. After 42 months, eGFR did not differ significantly between intervention and usual care groups, but the number of patients achieving BP targets was significantly better in the intervention group.

Comment: It is great to see more implementation research starting to appear in the renal literature. This study implemented a nurse practitioner-led model to achieve guideline-based CKD management but this was not shown to improve kidney function. It did improve several other process and care markers, and highlights just how difficult it is to demonstrate improved outcomes in this sort of environment.

Abstract

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