Nephrology Research Review™

Making Education Easy

Issue 71 - 2024

In this issue:

Abbreviations used in this issue:

CKD = chronic kidney disease; **DOAC** = direct-acting oral anticoagulant; **eGFR** = estimated glomerular filtration rate; **Ig** = immunoglobulin; **SGLT2** = sodium glucose co-transporter 2.

Welcome to the latest issue of Nephrology Research Review.

In this issue, the CONVERT investigators report the safety of the anticoagulant osocimab (an inhibitory factor XI antibody) in patients undergoing haemodialysis, an Australian study finds that SGLT2 inhibitors are underprescribed in primary care patients with CKD, and a systematic review determines that representation of patients with CKD in cardiovascular trials has unfortunately not improved over the past two decades. Also in this issue, a phase 2 trial reports promising results for stereotactic ablative body radiotherapy in patients with primary renal cell cancer.

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
david.mudge@researchreview.com.au

Anticoagulation with osocimab in patients with kidney failure undergoing hemodialysis

Authors: Weitz JI et al., for the CONVERT Investigators

Summary: This phase 2 trial investigated the safety of the anticoagulant agent osocimab in patients undergoing haemodialysis. 704 haemodialysis patients (64% male) were randomised 1:1:1 to receive lower-dose osocimab (105mg loading dose then 52.5mg monthly maintenance dose), higher-dose osocimab (210mg loading dose then 105mg monthly maintenance dose) or placebo for up to 18 months. The co-primary outcomes were clinically relevant bleeding and a composite of moderate, severe or serious adverse events. Clinically relevant bleeding occurred in 6.9% of patients taking lower-dose osocimab, 4.9% of those taking higher-dose osocimab, and 7.8% of those taking placebo. The composite adverse event end-point occurred in 51%, 47% and 43% of patients in the respective groups.

Comment: Anticoagulation in haemodialysis patients at risk for thromboembolic events has traditionally used warfarin but is limited by substantially high risks of bleeding. The newest class of novel anticoagulants, the specific clotting factor antibodies, may be about to change this due to their lowered bleeding risk compared to warfarin and even the DOACs such as apixaban. One example is osocimab, an inhibitory factor XI antibody which can be administered with haemodialysis. This Canadian phase 2 study examined the efficacy of two dosages of osocimab versus placebo over an 18-month period and rates of bleeding. The drug was almost as well tolerated as placebo with lower bleeding rates than are typically seen with the use of warfarin – although that was not a comparator in this study. A head-to head study versus warfarin and/or apixaban may be next and will be needed to confirm whether factor XI inhibition is indeed safer in haemodialysis patients.

Reference: Nat Med. 2024;30(2):435–42
Abstract

Estimating the population-level impacts of improved uptake of SGLT2 inhibitors in patients with chronic kidney disease

Authors: Neuen BL et al.

Summary: This Australian study estimated the population-level impact of improved uptake of SGLT2 inhibitors in Australian patients with CKD. Primary care data from 392 Australian general practices were analysed for the period 2020–2021. It was determined that up to 44.2% of adults with CKD would have met inclusion criteria for key SGLT2 inhibitor trials (7.5% for CREDENCE, 17.3% for DAPA-CKD, and 44.2% for EMPA-KIDNEY), but baseline use of SGLT2 inhibitors ranged from 4.1% in EMPA-KIDNEY eligible patients to 14.4% in CREDENCE eligible patients. When extrapolated to the Australian population, it was estimated that 230,246 patients with CKD would be eligible for treatment with an SGLT2 inhibitor. Optimal implementation (75% uptake) of SGLT2 inhibitors was predicted to reduce 3644 cardiorenal events and 1312 kidney failure events annually in Australia.

Comment: These Australian authors sought to examine the uptake of SGLT2 inhibitor use in a large primary care database which is representative of the local CKD population. Similar studies in the UK and US suggest an under-utilisation of this class of medication in eligible primary care patients based on the risk factors of CKD including reduced eGFR and significant albuminuria measured on at least two occasions. This analysis found that only around 10% of patients at risk were actually being treated, suggesting very significant under-prescribing in Australia. Interestingly, the rate was very similar to comparative studies on both sides of the Atlantic. The implication for Australia is that over 3000 excess cardiorenal events are not being prevented annually, which is a significant and costly public health concern. The reasons for under-prescribing of this class of drug need to be examined as a matter of priority.

Reference: Lancet Reg Health West Pac. 2024;43:100988
Abstract

Representation of patients with chronic kidney disease in clinical trials of cardiovascular disease medications

Authors: Colombijn JMT et al.

Summary: This systematic review quantified the under-representation of patients with CKD in cardiovascular drug trials. A search of ClinicalTrials.gov, MEDLINE, Embase, and Google Scholar identified 1194 randomised controlled trials (n=2,207,677) of antiplatelets, anticoagulants, antihypertensive drugs, glucose-lowering drugs, and cholesterol-lowering drugs that were suitable for inclusion. Analysis of the data showed that, since 2000, the percentage of cardiovascular drug trials excluding patients with CKD increased from 66% to 79%. In almost three-quarters of the trials (72%), more CKD patients were excluded than anticipated on safety grounds. Overall, 158 trials (13%) reported results for patients with CKD separately (e.g. in subgroup analyses). Only 23 trials (2%) reported results for patients with eGFR <30 ml/min/1.73m^2, 15 (1%) reported results for dialysis patients, and one (0.1%) reported results for kidney transplant recipients.

Comment: Amongst the nephrology community there has been an awareness of the exclusion of people with advanced CKD in many cardiovascular studies, despite such patients being among the highest risk group for death from cardiovascular disease. This Dutch systematic review examined changes in the inclusion of CKD patients in cardiovascular trials over the last 20 years or so and found that although there has been a slight increase over time, less than one-sixth of cardiovascular trials reported data on a CKD subgroup, and that patients particularly with advanced CKD are largely being excluded. The rate of exclusion is much higher than would be expected purely on safety grounds. Kidney researchers need to work harder with cardiovascular trialists to ensure the inclusion of this high-risk group in future trials to ensure CKD patients do not miss out on beneficial new treatment advances.

Reference: JAMA Netw Open 2024;7(3):e240427
Abstract

Earn CPD

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Dapagliflozin utilization in chronic kidney disease and its real-world effectiveness among patients with lower levels of albuminuria in the USA and Japan

Authors: Tangri N et al.

Summary: This study in the US and Japan investigated the real-world utilisation and effectiveness of SGLT2 inhibitors in patients with CKD with lower levels of albuminuria. Claims data were used to identify patients with CKD and urinary albumin-to-creatinine ratio (UACR) <200 mg/g who were eligible for dapagliflozin 10mg treatment. Analysis of the data showed that dapagliflozin initiators mostly had stage 3–4 CKD, and 53–81% of them were already taking a renin–angiotensin system (RAS) inhibitor. Their most common comorbidities were type 2 diabetes, hypertension and cardiovascular disease. Patients who were eligible for dapagliflozin but were untreated were older, had a higher eGFR, and had a lower comorbidity burden than initiators. After initiation of dapagliflozin, the differences in median eGFR slope between initiators and matched non-initiators were 1.07 ml/min/1.73m^2 per year in all patients with UACR <200 mg/g, and 1.28 ml/min/1.73m^2 per year in patients with UACR <200 mg/g without type 2 diabetes.

Comment: This large, observational study from the US and Japan was a 'real world' investigation of the effect of dapagliflozin in CKD patients with more modest levels of albuminuria both with and without diabetes and used propensity score matching to compare those initiated to those not initiated on dapagliflozin with estimated slope of decline in eGFR over time as the comparator. The majority of patients were also on RAS-blocking therapy, which enhanced the external validity. In the larger group with type 2 diabetes, there was a significant attenuation of the decline in kidney function by estimated GFR, and the benefit also extended to the non-diabetic group although there was less certainty regarding the benefit of dapagliflozin in this group due to smaller numbers.

Reference: Adv Ther. 2024;41(3):1151–67
Abstract

Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II)

Authors: Siva S et al., for the FASTRACK II Investigator Group

Summary: The FASTRACK II trial investigated the efficacy of stereotactic ablative body radiotherapy (SABR) in patients with primary renal cell cancer. At seven centres in Australia and one centre in the Netherlands, 70 patients (median age 77 years) with biopsy-confirmed primary renal cell cancer (single lesion) who were medically inoperable received either a single fraction SABR of 26 Gy (for tumours ≤4cm in diameter) or 42 Gy in three fractions (for tumours 4–10cm). 70% of patients had documented serial growth on initial surveillance imaging, and median tumour size was 4.6cm. All patients had T1–T2a and N0–N1 disease. Local control at 12 months from treatment commencement was 100%. Seven (10%) patients had grade 3 treatment-related adverse events (nausea and vomiting, abdominal, flank, or tumour pain, colonic obstruction, and diarrhoea), but no grade 4 adverse events were reported. No cancer- or treatment-related deaths occurred during follow up.

Comment: SABR is a major advance in the field of radiation oncology and is being studied for new indications as an alternative to surgery, particularly in people who may be at too high a perceived perioperative risk. This world-leading team from Melbourne report the first phase 2 trial of SABR as an alternative to nephrectomy in primary renal cell cancer who were medically inoperable and had tumours in the 4–10cm range, median 4.6cm (T1b disease). The treatment resulted in good tumour control and was well tolerated with significant side effects mostly in the range of <5%. As this technique becomes more widely available in Australia it seems likely to become a genuine alternative to surgery for selected patients with inoperable renal cell cancer.

Reference: Lancet Oncol. 2024;25(3):308–16
Abstract

Nephrology Research Review™

Independent commentary by Professor David Mudge MBBS, MD, FRACP, FASN.

David Mudge is the Director of Nephrology at Redland Hospital, as well as Professor of Medicine at the PA-Southside Clinical unit of the University of Queensland.

He is a clinical researcher in the UQ Centre for Kidney Disease Research, where his clinical research interests include the thrombotic microangiopathies, peritoneal dialysis guideline implementation, antiviral medications in CKD, and the use of medical honey to prevent infections in dialysis. He has authored more than 140 scientific papers and abstracts with over 4,500 citations and currently serves on the editorial board of several nephrology journals.

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Evaluation of novel candidate filtration markers from a global metabolomic discovery for glomerular filtration rate estimation

Authors: Fino NF et al.

Summary: This study analysed untargeted metabolomics data (seven studies; n=2851) to identify candidate filtration markers for a new multi-analyte eGFR determination assay using mass spectrometry that potentially offers better accuracy than current eGFR biomarkers. Overall, 17 metabolites were found that had strong associations with measured GFR (mGFR) and little dependence on demographic factors. From these, 12 new candidate filtration markers were identified that had maximal joint association with mGFR and minimal dependence on demographic variables across various clinical settings. These metabolites are excreted in urine and represent diverse metabolic pathways and tubular handling.

Comment: Measuring kidney function by eGFR remains a major limitation of clinical nephrology practice and an ongoing topic of debate. There remains a clinical need for a more accurate and precise measurement of true kidney function. This fascinating study utilised metabolomics data from seven diverse research studies which also included measured GFR as a comparator. From a starting point of almost 2000 metabolites, it was possible to identify 17 with a high correlation to measured GFR across a variety of patient populations, and these metabolites performed well independently of demographic factors such as age and race and also independently of measured creatinine. The authors plan to further investigate these novel filtration markers as a panel to estimate GFR which could provide greater accuracy for individual patients.

Reference: Kidney Int. 2024;105(3):582–92
Abstract

Comparative safety and effectiveness of warfarin or rivaroxaban versus apixaban in patients with advanced CKD and atrial fibrillation

Authors: Fu EL et al.

Summary: This nationwide US cohort study compared the safety and effectiveness of warfarin or rivaroxaban versus apixaban in patients with advanced CKD and atrial fibrillation. Two nationwide US claims databases were searched to identify patients with nonvalvular atrial fibrillation and CKD stage 4/5 who initiated warfarin versus apixaban (matched cohort, n=12,488) or rivaroxaban versus apixaban (matched cohort, n=5720). The primary outcomes were major bleeding and ischaemic stroke. Cox regression analysis showed that both warfarin and rivaroxaban were associated with a higher rate of major bleeding than apixaban (HR 1.85 [95% CI 1.59–2.15] and HR 1.69 [95% CI 1.33–2.15], respectively). Rates of all-cause mortality and ischaemic stroke did not differ significantly between warfarin and apixaban or between rivaroxaban and apixaban.

Comment: The use of warfarin in dialysis patients has long been known to be associated with higher rates of bleeding than in the general population due to the qualitative clotting defects seen in dialysis and possibly also the frequent use of heparins. This has led to a number of (mostly retrospective) studies using DOACs such as rivaroxaban and apixaban as an alternative to warfarin in patients with low GFR or on dialysis despite being relatively contraindicated in such patients with lower GFR, due to their renal clearance. This large retrospective analysis of 2 US claims databases of people with CKD stage 4/5 found a significantly lower risk of both GI bleeding and intracranial bleeding with apixaban as compared to either warfarin or rivaroxaban, consistent with other similar comparative studies of these agents. An adequately-powered randomised controlled trial of a dialysis-appropriate dose of apixaban will be required to reassure nephrologists that apixaban may be a better alternative to warfarin for dialysis patients, and hopefully such a study will be reported soon.

Reference: Am J Kidney Dis. 2024;83(3):293–305.e1
Abstract

Ofatumumab in rituximab-resistant and rituximab-intolerant patients with primary membranous nephropathy

Authors: Podestà MA et al.

Summary: This Italian case series investigated the efficacy of ofatumumab (a fully human second-generation anti-CD20 antibody) in rituximab-resistant and rituximab-intolerant patients with primary membranous nephropathy. Outcomes for 17 patients with membranous nephropathy who were either rituximab-intolerant (n=7) or rituximab-resistant (n=10) and received a single intravenous infusion of ofatumumab 50–300mg at a nephrology unit were reviewed. During a median 5 months of follow up, 100% of the rituximab-intolerant patients and 30% of the rituximab-resistant patients had complete or partial remission of nephrotic syndrome. Circulating B-cells were similarly depleted in all patients within 1 week. Ofatumumab significantly reduced 24-hour urinary protein and IgG excretion; these effects were greater in rituximab-intolerant than in rituximab-resistant patients. Measured GFR increased by a mean 13.4% at 24 months compared with baseline in all patients (p=0.036). Nine patients had infusion-related adverse events that recovered with temporary infusion interruption.

Comment: The anti-CD20 monoclonal antibody rituximab has been something of a revolution in the treatment of membranous glomerulonephritis in patients with anti-phospholipase A2 receptor (PLA2R) antibodies, with significantly better tolerability than the combination of oral steroids and cyclophosphamide used historically. However, it is limited in some patients by the development of treatment resistance or infusion reactions. These Italian authors report a retrospective case series of patients who had previously developed reactions or resistance to rituximab who were then offered the fully humanised anti-CD20 antibody ofatumumab as an alternative. Ofatumumab appears to be equally efficacious in terms of its B-cell depleting ability and its ability to reduce albuminuria and restore albumin and IgG levels in membranous glomerulonephritis and was generally well tolerated.

Reference: Am J Kidney Dis. 2024;83(3):340–9.e1
Abstract

Heterogeneous treatment effects of intensive glycemic control on kidney microvascular outcomes and mortality in ACCORD

Authors: Charu V et al.

Summary: This post hoc analysis of the ACCORD trial investigated whether the Kidney Failure Risk Equation (KFRE) is able to identify patients with type 2 diabetes who would benefit most from intensive glycaemic control. ACCORD participants were divided into quartiles on the basis of 5-year kidney failure risk according to the KFRE. Treatment effects were assessed within each quartile and compared with the average treatment effect in ACCORD. The two treatment effects evaluated were the 7-year restricted mean survival time (RMST) differences between intensive and standard glycaemic control arms in time-to-first development of severely elevated albuminuria or kidney failure, and 7-year RMST between-group differences for all-cause mortality. Patients with higher kidney failure risk at baseline derived the most benefit from intensive glycaemic control with regard to kidney microvascular outcomes (7-year RMST difference: 114.8 vs 48.4 days across the entire trial population), but they also had a shorter time to death (7-year RMST difference: –56.7 vs –23.6 days).

Comment: One of the issues related to extrapolating the results of randomised controlled trials to an individual patient is the concept of competing risks, particularly related to the differing risks of a particular outcome in a patient with a disease where multiple complications of that disease are simultaneously possible. This interesting post-hoc analysis of the ACCORD study sought to differentiate the risks and benefits of intensive glycaemic control in the context of a patient's individual kidney failure risk, which they calculated based on the KFRE and then correlated with kidney function decline and mortality. Although intensive glycaemic control reduced kidney-related microvascular events, it was also associated with an increased risk of hypoglycaemia and mortality, highlighting the need for individual risk assessments in extrapolating clinical trial results to individuals.

Reference: J Am Soc Nephrol. 2024;35(2):216–28
Abstract

Prognostic biomarkers in kidney transplantation

Authors: Raynaud M et al.

Summary: This systematic review and clinical appraisal evaluated the clinical benefit of prognostic biomarkers in kidney transplantation. A search of PubMed, Embase, Scopus, Web of Science, and Cochrane Library (2005–2022) identified 804 studies that assessed the association between biomarkers and kidney allograft outcome; median follow-up post-transplant was 4.8 years. Analysis of the studies revealed that 43% of them did not adjust their biomarker for key prognostic factors, and only 3.1% of them adjusted the biomarker for standard-of-care patient monitoring factors. Less than 5% of studies were externally validated. Only 8.8%, 1.1% and 4.6% of studies used data sharing, code sharing, and registration, respectively, and 20% of the studies reported the clinical relevance of the biomarker despite it having a nonsignificant association with the outcome measure.

Comment: Kidney biomarkers have been something of a hot topic in research for more than a decade, but in transplantation seem to be slow to make their way into clinical practice. This review systematically examined over 800 publications in the field of kidney transplant research published between 2005 and 2022. The majority were retrospective, single centre, and recruited less than 250 patients. There was little collaboration with other groups and data sharing, and less than 5% were externally validated. Almost half did not adjust for known prognostic factors. The conclusion of the authors is that the vast majority of such studies are flawed, and that poor design probably explains the limited uptake of new biomarkers in transplantation to clinical practice. This type of research may be improved with greater clinical oversight and collaboration within the transplant community.

Reference: J Am Soc Nephrol. 2024;35(2):177–88
Abstract

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