Nephrology Research Review™

Making Education Easy

Issue 14 - 2013

In this issue:

Abbreviations used in this issue:

CKD = chronic kidney disease
ESRD = end-stage renal disease
GFR = glomerular filtration rate
HD = haemodialysis
HR = hazard ratio

Welcome to the latest issue of Nephrology Research Review.

Highlights this month include 2 analyses of the large cross-sectional CRIC study dataset. The first analysis demonstrated links between elevated NT-proBNP levels and cardiac abnormalities in patients with CKD, and the second showed retinopathy to be associated with cognitive impairment in CKD. The latter findings suggest that retinopathy may be a potential screening tool for CKD patients. We have also included a worrying report of anatomical brain disease in haemodialysis patients, and, at last, a positive haemodiafiltration trial.

We hope you find these and the other selected papers interesting and useful in your current practice.

Kind Regards,

Professor Neil Boudville

neil.boudville@researchreview.com.au

Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC])

Authors: Mishra RK et al

Summary: This study used data from the Chronic Renal Insufficiency Cohort to evaluate the association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and cardiac abnormalities in patients with CKD without clinical heart failure (n=3,232). Fully adjusted regression models showed that the highest quartile of NT-proBNP was associated with an increased risk of left ventricular (LV) hypertrophy, LV systolic dysfunction and diastolic dysfunction (odds ratio 2.7, 2.7 and 2.0, respectively). When evaluated on its own as a screening test, NT-proBNP was modestly predictive of LV hypertrophy and LV systolic dysfunction and poorly predictive of diastolic dysfunction. When added to a clinical model, NT-proBNP significantly reclassified patients' likelihood of having LV hypertrophy and LV systolic dysfunction but not diastolic dysfunction. In conclusion, NT-proBNP had strong associations with prevalent LV hypertrophy and LV systolic dysfunction in patients with CKD without heart failure.

Comment: Elevated BNP levels in the general population are associated with poor prognosis but the significance in CKD (where elevated levels are more common) is uncertain. This paper used the large cross-sectional CRIC study dataset (n=3,232) to examine the association between NT-proBNP and echo findings in CKD (eGFR 20–70 ml/min per 1.73m^2) patients without heart failure. They demonstrated a relationship between elevated NT-proBNP levels and LV hypertrophy on multivariate analysis. In addition, they demonstrated an association with LV systolic and diastolic dysfunction, less with the latter.

Reference: Am J Cardiol 2013;111(3):432–8
http://www.ajconline.org/article/S0002-9149(12)02300-4/abstract

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RESEARCH REVIEW™
the Australian perspective

Retinopathy and cognitive impairment in adults with CKD

Authors: Yaffe K et al

Summary: This analysis of Chronic Renal Insufficiency Cohort data examined the association between retinal microvascular abnormalities and cognitive impairment in patients with CKD. Retinopathy (graded using the Early Treatment Diabetic Retinopathy Study severity scale and diameters of retinal vessels) and neuropsychological status (measured using a battery of 6 cognitive tests) were assessed in 588 patients aged ≥52 years. The overall prevalence of retinopathy was 30.1% and the prevalence of cognitive impairment was 14.3%. Multivariable-adjusted regression models showed that patients with retinopathy had an increased likelihood of cognitive impairment on executive function (odds ratio 3.4), attention (odds ratio 3.0), and naming (odds ratio 2.1) compared with patients without retinopathy. Increased levels of retinopathy were associated with lower cognitive performance on executive function and attention. Microaneurysms were also associated with cognitive impairment. In conclusion, retinopathy is associated with cognitive impairment in patients with CKD.

Comment: There is a documented association between retinopathy and cognitive impairment in the general population but this has not been examined in CKD. The CRIC study once again use their large dataset to explore this question. Indeed they did demonstrate that retinopathy was significantly associated with cognitive impairment, even after adjusting for the usual influencing factors. These findings suggest that this may be a potential screening tool for CKD patients if its role is more precisely defined.

Reference: Am J Kidney Dis 2013;61(2):219–27
http://www.ajkd.org/article/S0272-6386(12)01321-2/abstract

Anatomic brain disease in hemodialysis patients

Authors: Drew D et al

Summary: This study used magnetic resonance imaging (MRI) to evaluate the prevalence of brain abnormalities in haemodialysis patients. MRI findings in 45 maintenance haemodialysis patients were compared with those in 67 controls without reported kidney disease (none of the patients in either group had a history of stroke). Anatomic brain disease was reported on a semiquantitative scale (0–9 for white matter disease and cerebral atrophy, and 0–3 for hippocampal size) and infarct prevalence. Compared with controls, haemodialysis patients had more severe white matter disease (1.6 vs 0.7; p<0.001) and cerebral atrophy (sulcal prominence, 2.3 vs 0.6; ventricular enlargement, 2.3 vs 0.9; hippocampal size, 1.3 vs 1.0; all p<0.001). Multivariable analyses showed that haemodialysis status was independently associated with worse white matter disease and atrophy grades. Haemodialysis patients also had a higher prevalence of small- and large-vessel infarcts than controls (p<0.001). In conclusion, haemodialysis patients have more white matter disease and cerebral atrophy than controls without known kidney disease, and a high prevalence of unrecognised infarcts.

Comment: This cross-sectional study performed MRI on 45 prevalent HD patients without a history of stroke and a group of controls based in the Boston area. Compared to controls the HD group had significantly greater white matter changes. In addition, there was more cerebral atrophy and dilated ventricles in the HD group. There was a high prevalence of infarcts found in the HD group despite none having a history of strokes.

Reference: Am J Kidney Dis 2013;61(2):271–8
http://www.ajkd.org/article/S0272-6386(12)01177-8/abstract

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High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients

Authors: Maduell F et al for the ESHOL Study Group

Summary: This study compared the impact of online haemodiafiltration (OL-HDF) and standard haemodialysis on mortality in patients with ESRD. 906 chronic haemodialysis patients were randomised in an open-label design to either continue haemodialysis (n=450) or to switch to high-efficiency postdilution OL-HDF (n=456). Compared with patients who continued with standard haemodialysis, those who switched to OL-HDF had a lower risk of all-cause mortality (HR, 0.70; p=0.01), cardiovascular mortality (HR, 0.67; p=0.06), and infection-related mortality (HR, 0.45; p=0.03) during follow-up (mean 1.9 years). It was calculated that switching 8 patients from haemodialysis to OL-HDF may prevent 1 annual death. The number of dialysis sessions complicated by hypotension was lower in the OL-HDF group, as were all-cause hospitalisations. In conclusion, high-efficiency postdilution OL-HDF reduces all-cause mortality compared with standard haemodialysis in patients with ESRD.

Comment: Despite the enthusiasm for haemodiafiltration and its potential to increase survival, this was not confirmed in 2 recent randomised trials, including one that I reviewed last month. In this Spanish trial, 906 prevalent HD patients were randomised to either 3 times a week HD or on-line haemodiafiltration (OL-HDF), and with a mean follow-up of 1.9 years. At least 18L per session of replacement volume was prescribed for patients on postdilution OL-HDF, with a median volume of replacement fluid ranging from 20.8 to 21.8L per session. 355 patients prematurely stopped participation in the trial for various reasons, the most common one being transplantation. There was a 30% (95% CI, 0.53–0.92) relative risk reduction in the 3-year all-cause mortality (absolute incidence of 18.6% in the OL-HDF group versus 27.1% in the HD group). Intriguingly, when the specific causes of death were examined there was only a significant difference in stroke and infection causes of death. In a posthoc analysis, the amount of convective volume per session was inversely related to mortality. This study had a larger fluid replacement volume than the other 2 recent negative trials which may help to explain the difference in the results. Finally a promisingly positive HDF trial but I believe further investigation is needed before making this the standard.

Reference: J Am Soc Nephrol 2013; published online Feb 14
http://jasn.asnjournals.org/content/early/2013/02/13/ASN.2012080875.full

Treatment of early immunoglobulin A nephropathy by angiotensin-converting enzyme inhibitor

Authors: Li P et al

Summary: This study investigated the efficacy of the ACE inhibitor ramipril in patients with early immunoglobulin A (IgA) nephropathy. 60 patients with IgA nephropathy, proteinuria (<0.5 g/day), normal blood pressure and normal renal function were randomised to receive ramipril 2.5 mg/day or no treatment for 5 years. At study end, no significant between group differences were observed for event-free survival, proteinuria-free survival, and hypertension-free survival. Estimated GFR was 108.1 and 105.7 ml/min per 1.73m^2 in the respective groups at 60 months (p=NS). None of the patients developed impaired renal function, and the rate of GFR decline was similar in each group. In conclusion, treatment with ramipril 2.5 mg/day for 5 years did not offer any benefits in patients with early IgA nephropathy.

Comment: There is ongoing uncertainty of the most effective way to treat IgA nephropathy. This group recruited 60 patients with biopsy-proven IgA nephropathy (with mild proteinuria, normal blood pressure and serum creatinine <120 µmol/L) and randomised them to ramipril 2.5mg a day or no treatment. Follow-up was for 5 years. The primary end-point was a composite of the development of hypertension, proteinuria >1 g/day and the development of 20% decline in eGFR. I am not sure that this is the most clinically relevant composite end-point. Regardless, there was no significant difference between groups at the end of the follow-up period. The ongoing clinical equipoise on the appropriate treatment for IgA nephropathy demands participation in further clinical trials.

Reference: Am J Med 2013;126(2):162–8
http://www.amjmed.com/article/S0002-9343(12)00596-7/abstract

Renin-angiotensin inhibition in diastolic heart failure and chronic kidney disease

Authors: Ahmed A et al

Summary: This study examined the role of renin-angiotensin inhibition in older patients with diastolic heart failure and CKD. 1340 patients aged ≥65 years who were hospitalised with diastolic heart failure (ejection fraction ≥45%) and CKD were included. Of these, 717 patients received a renin-angiotensin system (RAS) inhibitor (either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker) on discharge. 421 matched pairs of patients who were either receiving or not receiving an RAS inhibitor were then followed for over 8 years. During this time, all-cause mortality was lower in patients receiving vs not receiving RAS inhibitors (63% vs 69%; p=0.021) but there was no association between RAS inhibitors and heart failure hospitalisation. In conclusion, a discharge prescription for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with a significant reduction in all-cause mortality in older patients with diastolic heart failure and CKD.

Comment: This study examined just over 1,300 patients aged 65 years or older with diastolic heart failure (and an ejection fraction ≥45%) that were admitted to an Alabama hospital. Just over half the patients were discharged on RAS inhibitors, with these authors dividing these patients into below and at/above target doses. After 8 years of follow-up, and utilising specialised statistical methods to match controls to the CKD patients (to try and account for imbalances between the groups), they demonstrated an 11-month longer median survival (and an 18% relative risk reduction) in those prescribed an RAS inhibitor. In addition, those prescribed an RAS inhibitor had a significantly longer median time to hospitalisation.

Reference: Am J Med 2013;126(2):150–61
http://www.amjmed.com/article/S0002-9343(12)00631-6/abstract

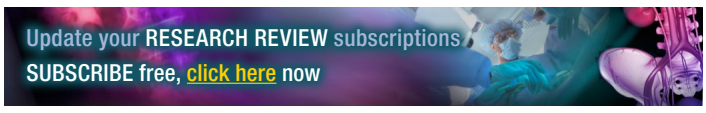
Risk of vascular access complications with frequent hemodialysis

Authors: Suri R et al

Summary: These 2 trials evaluated the risk of vascular access complications associated with frequent haemodialysis. In the Daily Trial, 245 patients were randomised to receive in-center daily haemodialysis (6 days per week) or conventional haemodialysis (3 days per week) for 12 months. In the Nocturnal Trial, 87 patients were randomised to receive home nocturnal haemodialysis (6 nights per week) or conventional haemodialysis for 12 months. The main outcome was time to first access event (repair, loss, or access-related hospitalisation). In the Daily Trial, the risk of a first access event was 76% higher with daily haemodialysis than with conventional haemodialysis (HR, 1.76; p=0.017); the risk was even higher in patients with an arteriovenous (AV) access at randomisation (HR, 1.90; p=0.02). Daily haemodialysis patients had more total AV access repairs than conventional haemodialysis patients (p=0.011) but loss of AV access did not differ between groups. Similar trends were observed in the Nocturnal Trial, but the results were not statistically significant. In conclusion, frequent haemodialysis increases the risk of vascular access complications.

Comment: This is a re-analysis of the FHN Daily and Nocturnal Trials aiming to examine the risk of increased vascular access complications with increased frequency dialysis. With daily dialysis, these authors demonstrated an increased hazard of vascular access events of 1.76 (95% CI 1.11–2.79). A similar magnitude increased hazard ratio was seen with nocturnal dialysis (1.81) but this did not reach statistical significance (though they did detect statistical significance in a subgroup analysis of only those with AVF/G). Similar findings were seen with respect to vascular access surgery. Contrary to some other recent studies, buttonhole technique was found to be protective of access complications. These findings do suggest that there may be a 'price' to pay for increased frequency dialysis.

Reference: J Am Soc Nephrol 2013;24(3):498–505
http://jasn.asnjournals.org/content/24/3/498



Fractional excretion of phosphorus modifies the association between fibroblast growth factor-23 and outcomes

Authors: Dominguez J et al

Summary: This study investigated the association between fibroblast growth factor-23 (FGF-23) and mortality in patients with CKD, stratified for urinary phosphorus excretion. Serum FGF-23 and 24-hour urine fractional excretion of phosphorus (FePi) were measured in 872 outpatients with stable cardiovascular disease and a mean eGFR of 71 ml/min per 1.73m^2. Patients were then followed for a mean 7.5 years. 337 deaths and 199 cardiovascular disease events occurred during follow-up. Urinary FePi significantly modified the association of FGF-23 with each outcome. In models adjusted for cardiovascular disease risk factors, kidney function, and PTH, patients who had above-median FGF-23 levels (≥42.3 relative units/ml) but below-median FePi (<15.7%) had the highest risks of both all-cause mortality and cardiovascular disease events (hazard ratios 1.98 and 1.92, respectively) compared with patients with low FGF-23 levels and low FePi.

Comment: FGF-23 continues to gain momentum as playing an important role (or being an important marker) in the high complication rate of adverse outcomes in CKD. This study utilises the dataset from another observational study to examine the relationship between serum FGF-23 and mortality, stratified for urinary phosphorus excretion. This group had relatively preserved kidney function with a mean eGFR of 71 ml/min per 1.73m^2 and a mean follow-up of 7.5 years. There was a significant association between FGF-23 and all-cause mortality and cardiovascular events (hazard ratio was 1.30 per doubling of FGF-23 for both) but no relationship was seen with urinary phosphate excretion. However, urinary phosphate excretion did significantly modify the relationship between FGF-23 and outcomes, such that those with the highest FGF-23 levels and lowest urinary phosphate excretion had the highest risk of poor outcomes.

Reference: J Am Soc Nephrol 2013;24(4):647–54
http://jasn.asnjournals.org/content/24/4/647

Neil is sub-Dean of the Faculty of Medicine at the University of Western Australia, Head of the Department of Renal Medicine at Sir Charles Gairdner Hospital and Medical Director of the WA Home Dialysis Program. His research interests are in living kidney donor outcomes, dialysis and CKD. However, his real interest is snow skiing, and he hopes to complete 10 marathons in 2013 or 2014.

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