Global Trials Focus

August 2021

The ISN-ACT (Advancing Clinical Trials) team presents this monthly round up of randomized trials in nephrology. Trials are selected not just for impact, but also to showcase the diversity of research produced by the global nephrology community. Each trial is reviewed in context and has a risk of bias assessment. We hope to drive improvement in trial quality and promote greater engagement in trial activity.

Key to risk of bias assessment

- (R) Random sequence generation
- (A) Allocation concealment
- (BP) Blinding of participants/personnel
- (BO) Blinding of outcome assessment
- (CD) Complete outcome data
- (CR) Complete outcome reporting
- (B) No other sources of bias

High risk
Uncertain risk / not stated
Low risk

Do you agree with our trial of the month? Tell us what you think!
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*ISN Academy: **Acute Kidney Injury***

Failure to engage slow recruitment hampers evaluation of post-AKI nephrologist care

Nephrologist Follow-Up versus Usual Care after an Acute Kidney Injury Hospitalization (FUSION). A Randomized Controlled Trial

Silver et al. CJASN 2021. 16:1005–1014

R A BP BO CD CR B

Reviewed by A. Gallagher

Summary: Seventy-one adults with an inpatient KDIGO acute kidney injury (AKI) stage two or above were randomised to receive early post-discharge nephrologist follow up with use of a care bundle (including advice for the management of CKD and cardiovascular risk factors, and 3-monthly blood tests for 12 months) or standard care. Of 269 eligible patients, only 26% consented to participate. There was no difference in the number of major adverse kidney events (a composite of death, maintenance dialysis, or incident/progressive CKD) at 1 year (44% of patients in the early nephrology follow-up group and 43% of the patients in the usual care group [RR, 1.02, 95% CI, 0.60 to 1.73]). 12% of patients died in the nephrology follow-up group and 8% in the usual care group (RR, 1.45; 95% CI, 0.35 to 6.02). Sixty-two percent of participants were rehospitalized in the one year follow up period, with 24% of participants rehospitalized with AKI. Patients in the intervention arm were more likely to have creatinine and urine albumin checked within 90 days of the original AKI, but this did not result in any difference in medication changes or other management outcomes. The trial was stopped early due to slow recruitment.

Comment: Prior to this trial, observational evidence had suggested a mortality benefit to early follow up with a nephrologist for those experiencing a severe AKI during an inpatient encounter. While this trial confirmed the high frequency of morbidity and mortality associated with AKI in hospitalised setting, authors were unable to demonstrate sufficient recruitment to justify proceeding with a larger study that would have provided the power to adequately test the hypothesis that routine nephrologist follow up improves outcomes. Common reasons reported for declining participation being hospitalization fatigue, reluctance to add doctors to the health care team, and long travel times. Future efforts to determine the effectiveness of post AKI interventions will need to consider more flexible programmes that better engage participants and thus prove more reliable for real-world application.

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*ISN Academy: **Haemodialysis***

Bioimpedance analysis in assessment of fluid status in chronic haemodialysis patients

Bioimpedance analysis is not superior to clinical assessment in determining hydration status: A prospective randomized-control trial in a Western dialysis population

Sommerer et al. Haemodial Int 2021. 25(3):380-390

R A BP BO CD CR B

Reviewed by M. Twinning and P. Franca Gois

Summary: In this prospective randomized controlled trial, bioimpedance analysis (BIA) was compared to clinical assessment of fluid status in chronic haemodialysis patients. Sixty-five patients were randomized to BIA

(interventional group) and 67 to clinical assessment (control group) for 16 ± 2 weeks with a further 12 weeks of follow up. Clinical assessment included evaluation of overhydration signs, blood pressure, antihypertensives, reported fluid intake and body weight increase. Participants in both BIA and the control group had inferior vena cava diameter measured by ultrasound. The primary endpoint was decline in N-terminal pro brain natriuretic peptide (NT-proBNP), as a surrogate marker for risk of cardiovascular events. Secondary endpoints included rates of overhydration, and adverse dialysis events such as cramps and intradialytic hypotension. The reduction in pre-dialytic NT-proBNP was 352 ± 8869 pg/mL in the BIA group and 442 ± 11,388 pg/ml in the clinical group (p = 0.961). Severe overhydration (>2L) was more frequent in the BIA group (46% vs 30.6%, p = 0.04). Adverse dialysis events occurred more often in the BIA group (69 events in BIA group compared to 46 events in control group p = 0.032). Cumulative hypovolaemic events were significantly higher in the BIA group (p = 0.002) as were muscle cramps (30.1 vs 9.7%, p =0.002). Four patients died from cardiac events in the clinical group and no deaths were reported in the BIA group. Three participants were hospitalized due to cardiac events in the BIA group.

Comment: Bioelectrical impedance is a non-invasive bedside tool to objectively assess fluid status. Patients assessed with BIA experienced a higher rate of adverse dialysis-related events compared to patients who had fluid assessment assessed by standard clinical assessments. The incidence of cardiac deaths and hospitalizations reported in this study suggests that reduction of NT-proBNP may not have performed well as a surrogate marker for cardiovascular events, notwithstanding the limitations of small sample size and short term follow up. Another shortcoming of the study was that BIA was both an intervention and outcome measure. This study suggests that BIA cannot not replace clinical assessment to estimate hydration status in haemodialysis patients, hence should not be used alone to determine ultrafiltration.

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*ISN Academy: **Haemodialysis***

Text messages targeting dietary behaviours are feasible and acceptable among people receiving hemodialysis

A Text Messaging Intervention for Dietary Behaviors for People receiving Maintenance Hemodialysis: A Feasibility Study of KIDNEYTEXT

Dawson et al. Am J Kidney Dis 2021. 78(1):85-95

R A BP BO CD CR B

Reviewed by M. Mawaad

Summary: KIDNEYTEXT was a six-month text message intervention in which 130 Australian haemodialysis patients were randomised to standard dietary care, or to receive 3 text messages per week providing advice, information, motivation and support to improve renal dietary behaviors. The primary outcome was feasibility as determined by recruitment and retention rates. 48% of eligible patients (130 of 272) consented to participate, and 88% (115 of 130) completed the study. Post-trial semi-structured interviews suggested that the intervention was well-received. There was no difference in adherence to dietary recommendations across treatment groups (OR, 1.21 [95% CI, 0.55-2.72]; P = 0.6). In exploratory secondary outcomes, there was a reduction in average phosphate levels of 0.19mmol/L (95% CI, −0.32 to −0.06) with the intervention, and improved odds of meeting guidelines for interdialytic weight gain (OR 6.23 [95% CI, 2.12-20.43]; P = 0.001).

Comment: Strategies to increase dietary adherence among people receiving haemodialysis are important to their biochemical stability and long-term health. The use of text messages is a promising strategy, particularly with the commonplace use of mobile phones, and may be especially helpful where access to renal dietitians is limited. Translation to other languages may improve the generalizability of the intervention, as language barriers resulted in exclusion of 40% of the screened patients. Further studies in other cohorts and in pre-dialysis patients would also be valuable.

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*ISN Academy: **Genetic Kidney Diseases***

A pilot trial shows safety of pioglitazone in patients with autosomal dominant polycystic kidney disease

A randomized phase 1b cross-over study of the safety of low-dose pioglitazone for treatment of autosomal dominant polycystic kidney disease

Blazer-Yost et al. Clin Kidney J 2021. 14(7)1738-46

R A BP BO CD CR B

Reviewed by N. Bulanov

Summary: Eighteen patients with autosomal dominant polycystic kidney disease (ADPKD), eGFR > 50 mL/min/1.73 m^2 and no history of diabetes were randomized to low-dose pioglitazone (15 mg once daily) or placebo. After one year and a two- to four-week washout period, the patients were transitioned to the opposite therapy. Fifteen patients completed both arms. The primary objective was to assess the safety of pioglitazone. Patients who

received pioglitazone had no signs of water retention (a known side-effect), and in fact there was a reduction in total body water as measured using bioimpedance analysis. There was no significant difference in the number of episodes of heart failure or edema, or in echocardiographic changes (change in end-diastolic volume or pericardial effusion). There was no difference in the percentage change in total kidney volume on MRI scanning after 12 months of treatment (mean difference between groups –3.5% (–8.4 to 1.4%), p = 0.015). There were no significant differences in liver cyst growth, kidney function, proteinuria, or blood pressure. Only 1 patient developed mild asymptomatic fasting hypoglycaemia with pioglitazone but was able to continue therapy. There were no concerning safety signals.

Comment: ADPKD is one the most common genetic kidney diseases, which results in end-stage kidney disease in a large proportion of patients. Preclinical studies showed that pioglitazone attenuated cyst growth in the rat model of PKD, at a lower dose than used for glycemic management. This Phase 1b trial suggests that the safety profile of low-dose pioglitazone was comparable to placebo in ADPKD patients without diabetes. Larger-scale studies will be needed to provide additional safety information and sufficient powering to detect an improvement in kidney volume growth. Testing of different dosing strategies may also be required.

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*ISN Academy: **Chronic Kidney Disease***

Residual proteinuria: the potential effect of epithelial sodium channels inhibitors

The Effect of Amiloride on Proteinuria in Patients with Proteinuric Kidney Disease

Shen et al., Am J Nephrol 2021;52:368-77

Reviewed by A. Zykova

Summary: Twenty patients with various proteinuric kidney diseases with >1g daily proteinuria (PU) despite maximum tolerated dose of RAAS inhibition were randomly assigned to receive either amiloride or triamterene for 8 weeks followed by cross-over to 8 weeks of the alternative therapy, with a four-week washout period between agents. The baseline level of 24-h proteinuria was 2.90±1.67 g and baseline eGFR (CKD-EPI) was 80.6±23.1 ml/min/1.73m2. Amiloride reduced proteinuria by 38.7% (p=0.002), with benefits seen in ten of the twelve patients who completed the study. Triamterene reduced proteinuria by 32.8% (p=0.02), with benefits seen in all patients. There was no difference in 24-h proteinuria between treatment arms before (p=0.85) or after (p=0.45) treatment. Three patients had significant hyperkalemia and withdrew from the study; it was not stated which agent they were receiving at the time. Four patients withdrew without reported adverse effects. Triamterene resulted in a 9mL/min/1.72m2 reversible reduction in eGFR.

Comment: Residual proteinuria is a well-recognised modifiable risk factor for progressive decline in kidney function. The search for additional anti-proteinuric agents continues. Amiloride, but not triamterene, has demonstrated effects in reduction of proteinuria in pre-clinical trials and in case studies. Given the encouraging results seen in this trial, both agents warrant further testing, including with placebo control.

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*ISN Academy: **Haemodialysis***

Intradialytic resistance training in the Haemodialysis population

Effectiveness of a resistance exercise program for lower limbs in chronic renal patients on hemodialysis: A randomized controlled trial

Exel et al. Hemodial Int 2021. Online ahead of print

Reviewed by M. Gittus

Summary: Exel et al. recruited 107 haemodialysis patients then randomised them to a lower limb stretching exercise group (STG) or resistance exercise group (REG). The interventions occurred for 30 minutes three times per week when they would usually be undergoing sedentary haemodialysis, over an eight-week period. The primary outcome was the comparison of functional capacity using the 6-minute walk test (6MWT). Participants in the REG demonstrated a 26-metre improvement in the distance walked (mean difference 95% CI = -45.40 to -7.14m). There was also an increase in lower limb muscle strength with the REG group of 1.99 kilograms of force (measured by knee flexion against a dynamometer; mean difference MD = −1.99, 95% CI = −2.77 to −1.21). There was no improvement in respiratory muscle strength.

Comment: This study adds to the existing literature on the effectiveness and optimal form of intradialytic exercise in haemodialysis patients. Resistance training improved functional capacity and lower limb muscle strength compared to stretching exercises. As is the case for most intradialytic exercise trials, there were low recruitment rates, with 46% of screened patients declining to participate. Dropout rates after study commencement were equivalent in the two groups. The study was undertaken at a single dialysis centre, so the generalisability of the

results is uncertain. Furthermore, the resources required to facilitate these interventions were not described and may limit implementation in other settings.

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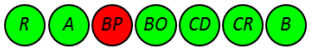
*ISN Academy: **Interventional Nephrology***

Paclitaxel-coated balloons may improve patency and intervention-free survival compared to conventional high-pressure balloons in AVF stenosis

Efficacy and Safety of Paclitaxel-Coated Balloon Angioplasty for Dysfunctional Arteriovenous Fistulas: A Multicenter Randomized Controlled Trial

Yin et al. Am J Kidney Dis 2021. 78(1):19-27.e1



Reviewed by R. El-Damanawi

Summary: In this multi-centre, open-label, blinded-endpoint, randomised controlled trial, 161 adults with arteriovenous fistula dysfunction were randomised 1:1 to percutaneous angioplasty using either paclitaxel drug-coated balloon (DCB, n=78) or conventional high-pressure balloon (HPB, n=83). The primary outcome was primary patency at 6 months, defined as target lesion intervention-free survival with peak systolic velocity ratio ≤2 (indicating no restenosis). Primary patency at 6 months was higher in the DCB group (65%) compared to controls (37%), with a between group difference of 28% (95% CI 13%-43%, p<0.001). Intervention-free survival was not different between groups at 6 months (p=0.2) but superior in the DCB group at 12 months (HR 0.57, 95% CI 0.34-0.93, p=0.04). Adverse event rates, along with technical, device and clinical success rates were not different between groups.

Comment: Robust vascular access is crucial to the delivery of maintenance haemodialysis and successful interventions that target stenosis and preserve patency are much needed. This study adds to existing evidence that DCB are safe and associated with improved patency and intervention-free access survival. Limitations of the study include significant procedural differences between groups in terms of balloon length, inflation pressure and duration, which may have impacted outcomes. Furthermore, the prevalence of forearm fistulas and single lesions in this Chinese population may limit the generalisability of the study.

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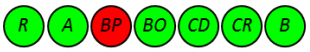
*ISN Academy: **Interventional Nephrology***

Do drug-coated balloons PAVE the way for sustained patency in dysfunctional AVFs?

A multicenter randomized controlled trial indicates that paclitaxel-coated balloons provide no benefit for arteriovenous fistulas

Karunanithy N, et al. Kidney Int. 2021;100(2):447-56



Reviewed by JK Ng

Summary: This multi-center study included 212 haemodialysis (HD) patients who underwent angioplasty for a dysfunctional arteriovenous fistula (AVF) with a stenotic segment amenable to treatment by a single balloon. Following a high-pressure balloon angioplasty, patients were randomized to insertion of a paclitaxel-coated balloon (Lutonix) (n=106) or a standard balloon (n=106). Primary endpoint was time to loss of target lesion primary patency (TLPP), which was defined as freedom from clinically driven reintervention, or thrombosis, of the treated segment. There was no observed difference in median time to loss of TLPP in the paclitaxel-coated balloon group (159 days) compared with the standard balloon group (215 days) (HR, 1.18; 95% CI, 0.78, 1.79; P = 0.44). There was also no significant between-group difference in access circuit patency or adverse events.

Comment: Restenosis of AVF over time is not uncommon after conventional balloon angioplasty. The Paclitaxel-assisted balloon Angioplasty of Venous stenosis in haemodialysis access (PAVE) trial aimed at studying the efficacy of paclitaxel-coated balloons in AVFs, with emphasis on a single diseased segment and with well-defined endpoints. In contrast to the positive results of other studies, including the study by Yin et al discussed above, this investigator-led trial cast uncertainty on the benefit of drug-coated balloon (DCB) on dysfunctional AVFs. One possible explanation is a difference in dose density of paclitaxel and inflation time between studies. Future studies should identify the subgroup of patients who are most prone to AVF restenosis to better clarify which patients may derive benefit from DCB.

Editors A. Gallagher, D. O'Hara and B. Smyth