

# ISN Trial-List

January 2019



Once a month, the ISN-ACT (Advancing Clinical Trials) team collects and publishes a list of important nephrology trials from the latest medical literature. Each trial is reviewed in context and their risk of bias in seven key areas assessed.

## Key to risk of bias assessment

- |    |                                    |                             |
|----|------------------------------------|-----------------------------|
| R  | Random sequence generation         | High risk                   |
| A  | Allocation concealment             | Uncertain risk / not stated |
| BP | Blinding of participants/personnel | Low risk                    |
| BO | Blinding of outcome assessment     |                             |
| CD | Complete outcome data              |                             |
| CR | Complete outcome reporting         |                             |
| B  | No other sources of bias           |                             |

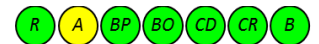
ISN Academy: [Transplant](#)

### C1 esterase inhibitor reduces the burden of delayed graft function in early phase trial

A phase I/II, double-blind, placebo-controlled study assessing safety and efficacy of C1 esterase inhibitor for prevention of delayed graft function in deceased donor kidney transplant recipients

[Jordan, et al. Am J Transplant. 2018;18\(12\):2955-2964](#)

Delayed graft function (DGF) is associated with worse graft function and lower patient and graft survival. Expansion of the donor pool to more marginal kidneys is likely to increase its frequency. DGF is believed to be a manifestation of ischemia-reperfusion injury and may be mediated by complement activation. Jordan, et al. randomized 70 deceased donor kidney transplant recipients at high risk of DGF to receive a C1 esterase inhibitor (via infusions intraoperatively and at 24 hours) or placebo. While there was no difference in the primary outcome of need for dialysis in the first week post-transplant (15/34 vs. 21/35,  $P=0.023$ ), there was a significant reduction in the number requiring dialysis between 2 and 4 weeks (0/34 vs. 5/35;  $P=0.23$ ). Interestingly, eGFR was higher at 12 months in the treatment arm ( $57.33\pm 15.77\text{ml/min}/1.73\text{m}^2$  vs. placebo  $44.90\pm 20.52\text{ml/min}/1.73\text{m}^2$ ;  $P=0.006$ ). This early phase, single center study cannot be considered proof of efficacy, but this novel approach appears promising and further research is awaited.



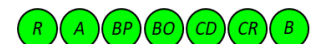
ISN Academy: [Hemodialysis](#)

### Spirolactone passes first hurdle on the way to larger studies in dialysis recipients

Safety and cardiovascular efficacy of spironolactone in dialysis-dependent ESRD (SPin-D): a randomized, placebo-controlled, multiple dosage trial

[Charytan, et al. Kidney Int. 2018 Nov 22. pii: S0085-2538\(18\)30641-0](#)

Mineralocorticoid antagonism is hypothesized to improve outcomes in patients with end-stage kidney disease by inhibiting the myocardial fibrosis that is a hallmark of uremic cardiomyopathy. However, there is concern that it may exacerbate hyperkalemia or hypotension. In this pilot study to assess safety, Charytan, et al. randomized 129 hemodialysis patients (1:1:1:2) to spironolactone 12.5mg, 25mg or 50mg daily, or placebo for 36 weeks. Overall, there were no significant differences in hyperkalemia (potassium  $>6.5\text{mmol/l}$ ) (0.49 vs. 0.50 events per patient-year;  $P=0.9$ ) or hypotension (0.11 vs. 0.0 events per patient year;  $P=0.1$ ). Although, there was evidence of increased risk of hyperkalemia at the 50mg dose (8/25 participants had hyperkalemia;  $P$  for trend=0.04). However, there were no differences in cardiac diastolic function. While necessarily small and underpowered, this study did not reveal any insuperable safety signals and paves the way for further studies.



ISN Academy: [Chronic Kidney Disease, Hypertension](#)

### ARB better tolerated than ACE inhibitor or combination

The Long-Term Impact of Renin-Angiotensin System (RAS) Inhibition on Cardiorenal Outcomes (LIRICO): A Randomized, Controlled Trial

[Saglimbene, et al. J Am Soc Nephrol. 2018 Nov 12. pii: ASN.2018040443](#)

While it is often assumed that ACE inhibitors are equivalent to angiotensin receptor blockers (ARB) there are few head-to-head comparisons. Saglimbene, et al. aimed to compare the two agents individually and in combination in

patients with macroalbuminuria ( $\geq 30\text{mg/g}$ ) and at least one cardiovascular risk factor. Owing to slow recruitment, the trial was stopped early, after randomizing 1287 participants (59% of their target) to ACE inhibitor, ARB or combination (using locally available agents within each class). Their final analysis included 1243 participants (with a median follow up of 2.7 years) and was unable to demonstrate any clear differences in the comparative rates of major cardiovascular events (ACE inhibitor vs. ARB: HR 1.05 [95%CI 0.63, 1.75]; ACE inhibitor vs. combination: HR 0.75 [95%CI 0.47, 1.21], ARB vs. combination: HR 0.71 [95%CI 0.44, 1.15]) or in all-cause mortality (ACE inhibitor vs. ARB: HR 0.76 [95%CI 0.39, 1.48]; ACE inhibitor vs. combination: HR 0.84 [95%CI 0.42, 1.67], ARB vs. combination: HR 1.11 [95%CI 0.59, 2.10]). ARB alone appeared to be the best tolerated of the three regimes, with only 6.3% discontinuing treatment (vs. 15.7% for ACE inhibitor and 18.3% for the combination;  $P<0.001$  for both comparisons). Although the trial was unable to answer its primary hypothesis, the results are consistent with the results of recent trials demonstrating a lack of benefit from combination ARB and ACE inhibitor therapy. They do suggest that ARB may be better tolerated. We look forward to the planned analysis combining this data with that of the related ONTARGET study.



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ISN Academy: [Glomerular Diseases](#)

### Low-dose steroids plus mycophenolate vs. standard-dose steroids: no change for minimal change

An open-label randomized controlled trial of low-dose corticosteroid plus enteric-coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults (MSN Study)

[Rémy, et al. Kidney Int. 2018;94\(6\):1217–1226](#)

Minimal Change Disease (MCD) is responsible for 10-25% nephrotic syndrome presentations in adults. Current first line treatment is high-dose glucocorticoid (1mg/kg/day), however there is incomplete data on treatment efficacy and no trials evaluating steroid-sparing regimens. The open-label MSN study randomized 116 adult participants with biopsy-proven MCD to receive either a steroid-sparing combination regimen (0.5mg/kg/day of prednisone and 720mg twice daily of mycophenolate sodium) or control treatment (1mg/kg/day of prednisone) for 24 weeks. In both groups, prednisone weaning began after 4 weeks if complete remission (CR) was achieved. The primary outcome of complete (CR) remission at 4 weeks was similar in the combination group (64.9%) and control group (57.9%) (RR 1.12 [95%CI 0.84, 1.50;  $P=0.44$ ]). The incidence of CR reached 80.4% and 79.6%, respectively, at 24 weeks and did not differ between the two groups ( $P=0.92$ ). There were also no differences in the frequency of adverse events (AEs) or serious AEs between the 2 groups ( $P=0.54$  and  $P=0.99$ , respectively) although the numbers in each group were small. This study did not identify any clear benefits from a steroid-sparing combination regimen compared to the conventional high-dose glucocorticoid therapy for MCD. However, formal proof of non-inferiority of this novel approach must await further trials.



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ISN Academy: [Hemodialysis, Mineral and Bone Disorders](#)

### No benefit from vitamin D analogue in hemodialysis patients with normal mineral parameters

Effect of Oral Alfacalcidol on Clinical Outcomes in Patients Without Secondary Hyperparathyroidism Receiving Maintenance Hemodialysis: The J-DAVID Randomized Clinical Trial

[Shoji et al. JAMA. 2018;320\(22\):2325-2334.](#)

Deranged phosphate, calcium and parathyroid hormone (PTH) homeostasis is usual in patients with end stage renal disease (ESRD), particularly those on hemodialysis, and is associated with a high risk of cardiovascular disease (CVD). Overt secondary hyperparathyroidism is treated with vitamin D receptor activators (VDRA) but the role of this therapy in those without hyperparathyroidism is not known. The J-DAVID open-label study randomized 976 participants without secondary hyperparathyroidism (serum calcium  $\leq 2.50\text{mmol/l}$ , phosphate  $\leq 1.94\text{mmol/l}$ , PTH  $\leq 18.9\text{pmol/l}$ ) on maintenance hemodialysis to receive either alfacalcidol or no VDRA over a 48-month period. The primary outcome was a composite of fatal and nonfatal cardiovascular events and coronary or lower limb revascularisation. The primary outcome occurred in 103 participants (21.1%) in the intervention group and 85 participants (17.9%) in the control group (absolute difference 3.25% [95%CI -1.75%, 8.24%;  $P=0.13$ ]). There was also no significant difference in the rate of all-cause death (18.2% vs. 16.8%;  $P=0.46$ ). Overall, this study suggests that there is unlikely to be a role for VDRA administration in hemodialysis patients with mineral parameters within the target range. It should be noted that approximately one third of participants in each group crossed-over to the alternate treatment arm during the study due owing to the need to maintain recommended levels of calcium, phosphate or PTH, a reminder that randomized controlled trials testing these recommendations are still required.

## Recombinant alkaline phosphatase does not improve sepsis-induced AKI

### Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial

[Pickkers et al. JAMA. 2018;320\(19\):1998-2009](#)

Acute kidney injury (AKI) in patients with sepsis is common and associated with increased mortality, and survivors are at risk of developing chronic kidney disease (CKD). Alkaline phosphatase (ALP) is an endogenous enzyme that exerts detoxifying effects through dephosphorylation of various compounds, including bacterial endotoxins and proinflammatory mediators. Two small trials have noted improvement in kidney function in patients with sepsis who received bovine ALP. The STOP-AKI trial was an international randomized, double-blind, placebo-controlled, adaptive phase 2A/2B trial conducted in critically ill adults with sepsis-associated AKI. Of the 301 participants, 133 were randomized to receive placebo or one of three doses (0.4, 0.8, or 1.6mg/kg) of a human recombinant ALP in the dose ranging phase, after which a further 168 participants were randomized to a dose of 1.6mg/kg or placebo in the efficacy phase. Participants received their allocated treatment as an infusion for three consecutive days. The primary endpoint of 7-day averaged creatinine clearance (estimated from daily 6-hour urine collections) between the groups was not significantly different in the efficacy phase: 55.1ml/min (IQR 15.0, 93.9) in the 1.6mg/kg ALP group vs 45.6ml/min (IQR 17.7, 112.4) in the placebo group (P=0.47). Kidney injury biomarkers, as well as other non-kidney secondary endpoints were not significantly influenced by the treatment. Among the exploratory endpoints, average creatinine clearance was higher over the 28-day follow up period in the 1.6mg/kg ALP group (P=0.04) and all-cause mortality was lower (n=16 [14.4%] vs. n=31 [26.7%]; P=0.02). All-cause mortality remained lower in the treatment group at day 90 (n=19 [17.1%] vs. n=34 [29.3%]; P=0.03). Although this trial failed to show an improvement in short term renal outcomes in patients with sepsis-related AKI, the results raise the possibility of overall benefit. Larger trials are needed to clarify this finding.



## No role for somatostatin analogue lanreotide in ADPKD

### Effect of Lanreotide on Kidney Function in Patients With Autosomal Dominant Polycystic Kidney Disease – The DIPAK 1 Randomized Clinical Trial

[Meijer et al. JAMA. 2018;320\(19\):2010-2019](#)

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic condition characterized by bilateral renal cyst formation, with a majority of affected patients progressing to end stage renal disease (ESRD). Although few therapies are currently available to slow the disease process, as the molecular mechanisms underlying ADPKD are elucidated, new therapeutic targets are being identified. Somatostatin, a peptide hormone, inhibits cyst formation and growth and has been shown to slow growth of kidney volume in small studies. The DIPAK 1 trial, an open-label, randomized study, was designed to test the efficacy and safety of lanreotide, a somatostatin analogue, in adult participants with ADPKD and stage 3 chronic kidney disease (eGFR of 30–60ml/min/1.73m<sup>2</sup>). Three hundred and nine participants were randomized to receive 120mg of subcutaneous lanreotide and standard care or standard care alone over a 120-week period. Aside from a slight, but statistically significant, decline in eGFR in the lanreotide group in the first 12 weeks of the study, there was no difference in eGFR between the treatment and control groups over the 2.5-year treatment period (mean difference in eGFR slope -0.08ml/min/1.73m<sup>2</sup> [95% CI -0.71, 0.56; P=0.81]). There was also no significant difference in the incidence of worsening kidney function (HR 0.87 [95%CI 0.49, 1.52; P=0.87]). The rate of change in height-adjusted total kidney volume (htTKV) was significantly lower in the lanreotide group (difference -1.33% per year [95%CI -2.41, -0.24; P=0.02]), however it was noted that after treatment cessation there was a rebound increase in the htTKV that was not observed in the control group. In addition, more adverse events were noted with lanreotide use, including injection site discomfort (32% vs 0.7%), loose stools (91% vs 6.6%), abdominal discomfort (79% vs 20%), and hepatic cyst infections (5.2% vs 0%). This study is consistent with a previous study of an alternate somatostatin analogue (octreotide). Collectively, they suggest that somatostatin analogues do not have a role in the management of ADPKD.

