



Global Trials Focus

March 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

- Random sequence generation
- Allocation concealment
- Blinding of participants/personnel
- Blinding of outcome assessment
- Complete outcome data
- Complete outcome reporting
- 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](#)

Water we waiting for?: Oral hydration as effective as intravenous in preventing post-contrast AKI

Oral hydration compared to intravenous hydration in the prevention of post-contrast acute kidney injury in patients with chronic kidney disease stage IIIb: A phase III non-inferiority study (NICIR study)

[Sebastia et al. Eur J Radiol 2021; 136](#)



Reviewed by Gittus M

Summary: Sebastia et al. randomised 264 outpatients with an eGFR 30-44ml/min undergoing contrast CT to either oral hydration (500ml of water 2 hours before and 2000ml in the following 24hr after contrast-CT) or intravenous hydration (sodium bicarbonate 3ml/kg/h starting one hour before then 1ml/kg/h during the hour post contrast-CT). The rate of post-contrast Acute Kidney Injury (PC-AKI) - an increase in serum creatinine ≥ 0.3 mg/dl or ≥ 1.5 x individualised baseline at 48-72hrs – in the oral arm (4.4%; 95 %CI: 1.4–9.9 %) was similar to the intravenous arm (5.3%; 95 %CI: 2.0–11.1%) and fulfilled their criteria for non-inferiority. There were no significant differences in change eGFR (p=0.17) or creatinine (p=0.14) from baseline.

Comment This study adds to the current literature that oral hydration is as effective as intravenous

hydration in preventing post contrast AKI in stable outpatients with CKD. The primary limitation of this study is the per protocol analysis, which is presented without an accompanying intention-to-treat analysis and so leaves open the possibility of bias. Nevertheless, the finding that oral hydration is not inferior to intravenous hydration is consistent with existing literature and is clinically important, given the practical and financial benefits for oral hydration regimens.

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

High dose phosphate binders may improve calcification propensity in hemodialysis patients

The effect of phosphate binder therapy with sucroferric oxyhydroxide on calcification propensity in chronic haemodialysis patients: a randomized, controlled, crossover trial

[Thiem et al. Clinical Kidney Journal. 2021;14\(2\);631-638](#)



Reviewed by Flahault A

Summary: This single-centre crossover trial included 39 hemodialysis participants randomised to either low-dose (250 mg/day) sucroferric oxyhydroxide (SO) followed by high-dose (2000 mg/day) SO or vice versa, with washout phases before and after SO treatment. The primary endpoint was a per-protocol analysis of the change in calcification propensity measured by T50 test (calcioprotein particle formation time) between the washout phase and the high-dose SO treatment among patients with high adherence to intervention ($\geq 85\%$). High dose SO treatment induced a mean increase in T50 of 66 min (95% CI, 49-84 min) and plasma phosphate levels were lower after treatment with high dose SO (1.63 ± 0.43 mmol/l) compared to the washout period (2.28 ± 0.5 mmol/l, $p < 0.0001$). Results from the intention-to-treat analysis yielded similar results. No major adverse event occurred during the study.

Comment: This study evaluated the biological effects of high dose phosphate binders in hemodialysis patients, and found a significant effect on calcioprotein particle formation time (T50). Whether these results translate into favourable clinical outcomes, including cardiovascular risk, remains to be investigated, and the predictive value of a change in T50 for clinical outcomes is unclear. Further, the low number of individuals included, the exclusion of a high number of screened participants and the use of a per-protocol analysis for the primary outcome limits the conclusions from this study to proof of concept.

ISN Academy: [Interventional Nephrology](#)

An attractive alternative to flexible cystoscopy for stent removal post transplantation

Comparison of a magnetic retrieval device vs. flexible cystoscopy for removal of ureteral stents in renal transplant patients: A randomized controlled trial

[Kapoor et al. Can Urol Assoc J 2021;15\(2\):E97-102.](#)



Reviewed by Gallagher A

Summary: Forty one deceased donor renal transplant recipients were randomised to either a magnetic or conventional ureteric stent placement at the time of transplantation. The control arm underwent flexible cystoscopy six weeks post transplantation while the intervention group had a magnetic retrieval device used in place of this procedure. There was no significant difference in urinary index scores for discomfort between the two arms with the stent in situ [mean Ureteral Stent Symptom Questionnaire (USSQ) score of 21.48/56 (± 5.47) with magnetic stent and 22.47/56 (± 3.89) with the control $p = 0.515$] nor one week post removal [mean USSQ score 21.75/56 (± 4.06) for magnetic stent and 20.64/56 (± 4.06) for controls $p = 0.481$]. The cost saving of the intervention was \$304.02 CAD per case and removal time was significantly shorter with the magnetic stent. There was no difference in rates of urinary tract infections

(p=0.213).

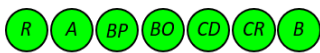
Comment: The use of magnetic ureteric stents for renal transplantation enabled the elimination of flexible cystoscopy, resulting in a shorter stent removal time, lower cost and no greater amount of discomfort or clinical complications for their participants. Commendably, the patient-centred outcome of comfort using the USSQ was the main outcome assessed here. While only a small exploratory trial, this method seems a promising addition to the renal transplantation process. Risk of late complications were not captured with only one week post stent removal follow up. Moreover a larger, higher powered study is needed to assess for any other potential associations with this device. The generalisability of this trial will be limited to centres able to access these devices and staffed with skilled proceduralists to use them. Additional consideration to patient selection is required for those with complex genitourinary anatomy which was not explicitly detailed in this trial.

ISN Academy: [Glomerular Diseases](#)

ADVOCATE trial makes a case for steroid-sparing treatment of ANCA-associated vasculitis

Avacopan for the Treatment of ANCA-Associated Vasculitis

[Jayne et al, NEJM 2021, 384: 599 – 608 DOI: 10.1056/NEJMoa2023386.](#)



Reviewed by Zykova A

Summary: 331 patients with ANCA-associated vasculitis (AAV) (mean BVAS =16, 81% with kidney involvement) were randomly assigned in a 1:1 ratio to receive oral avacopan (C5a receptor antagonist) or oral prednisone on tapering schedule. All the patients received induction treatment (rituximab in 65%, cyclophosphamide in 35%); steroids were used in the avacopan group as part of the induction phase but were weaned by week 4 of the study. Remission at week 26 was observed in 72.3% of patients receiving avacopan and in 70.1% receiving prednisone (difference in the incidence of remission, 3.4 percentage points; 95% CI, -6.0 to 12.8; P<0.001 for noninferiority; P=0.24 for superiority). Sustained remission at week 52 was observed in 65.7% receiving avacopan and in 54.9% receiving prednisone (difference in the incidence of remission, 12.5 percentage points; 95% CI, 2.6-22.3; P<0.001 for noninferiority; P=0.007 for superiority). The percentage of patients with serious adverse events was the same in both groups. As expected, the number of any adverse event potentially related to steroids was lower in avacopan group (66.3% vs. 80.5%).

Comment: AAV is characterized by life-threatening complications due to organ damage and toxic effects of immunosuppressive treatment, including a high cumulative dose of steroids. Different approaches to steroid-sparing regimens are under active discussion, and inhibition of alternative complement is among them. This study found that avacopan in addition to standard treatment was at least non-inferior with respect to remission than oral prednisone at week 26 and was superior at week 52. While further trials are needed to assess long-term safety and efficacy, this study supports the phase 2 CLEAR study results and opens a new era of expanding treatment options for patients with AAV.

ISN Academy: [Transplant](#)

Long term follow up of RCT supports viability of corticosteroid withdrawal in selected kidney transplant recipients.

Early Corticosteroids Cessation vs Long-term Corticosteroid Therapy in Kidney Transplant Recipients: Long-term Outcome of a Randomized Clinical Trial

[Woodle et al. JAMA Surg. 2021 Feb 3;e206929](#)



Summary: In this multi-centre randomised clinical trial, 385 low-to-moderate immune risk participants were randomised to withdraw (n=191) or continue (n=194) corticosteroid 7 days after renal transplant, while receiving tacrolimus and mycophenolate mofetil. The trial period lasted 5 years, which was reported separately, and then long-term follow up occurred for a median of 15.8 years via registry data linkage. The original 5 year trial demonstrated no difference in the composite primary end point of death, allograft loss censored for patient death, or moderate to severe short-term rejection, although the group with corticosteroid withdrawal had a higher rate of biopsy-confirmed rejection (17.8% versus 10.8%). This long-term follow-up study found no significant difference in the primary outcome of kidney allograft failure from any cause including death, requirement for long-term dialysis or repeat transplant (adjusted hazard ratio 0.83, 95% CI 0.62-1.10, p=0.19). The conclusions were similar in the subset of 223 participants who maintained their allocated treatment for the full 5 years of the trial period.

Comment: Early withdrawal in selected low-to-moderate immune risk renal transplant recipients appears to be safe compared to the traditional approach of continuing corticosteroids, out to as long as 15 years. The strengths of this study include the intention to treat analysis and low rate of loss to follow up. Further studies are needed to explore the benefits or risks of this approach on outcomes other than death and graft survival, for example to examine the differences in long-term incidence of cardiovascular disease, diabetes, infections and metabolic bone disease.