

# ISN Global Trials Focus

February 2020



The ISN-ACT (Advancing Clinical Trials) team presents this monthly showcase of randomized trials in nephrology from around the world. The trials selected are not necessarily those likely to have the highest impact. Our aim is to showcase the diversity of trials recently published and to review these in context, assessing their risk of bias in seven key areas. We hope that our efforts will drive improvement in trial quality and promote greater engagement in trial activity.

Join the debate on Twitter by following **@ISNeducation**:  
*Will these trials affect your practice? Are the results valid?  
How could the trials have been improved? What further studies are needed?*

If you would like to suggest any trials for inclusion in future editions, please send suggestions to [research@theisn.org](mailto:research@theisn.org)

**Key to risk of bias assessment**

Random sequence generation	High risk
Allocation concealment	Uncertain risk / not stated
Blinding of participants/personnel	Low risk
Blinding of outcome assessment	
Complete outcome data	
Complete outcome reporting	
No other sources of bias	

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ISN Academy: [Transplant](#)

## Reduced-dose tacrolimus appears to be safe in the short-term for standard immune risk de novo Korean kidney transplant recipients.

Clinical Study of Standard- vs Reduced-Dose Tacrolimus Combined With Generic Mycophenolate Mofetil in De Novo Kidney Transplantation: A Prospective Randomized Trial

[Bang et al. Transplant Proc. 2020;52\(1\):133-139](#)

Population	108 de novo live or deceased kidney transplant recipients (20-65 years old) with low-to-standard immune risk (ABO incompatible, donor-specific antibodies, donor cardiac death and multiple organ transplants excluded)
Intervention vs Comparator	Reduced-dose tacrolimus (trough 3-8; actual mean 6-7ng/mL) + standard-dose mycophenolate mofetil (MMF) (1.5-2 g/day) versus standard-dose tacrolimus (trough 5-15; actual mean 8-9ng/mL) + reduced-dose MMF (0.5-1 g/day). Basiliximab induction and corticosteroids in both groups. Time 6 months
Outcomes	There was no difference in the primary outcome of eGFR (MDRD) at 6 months (mean difference 2.88ml/min/1.73m <sup>2</sup> [95%CI -4.33 to 10.09; P=0.43]*), with the lower limit of the one sided 97.5% CI being -4.52ml/min/1.73m <sup>2</sup> (within the prespecified non-inferiority margin of -16ml/min/1.73m <sup>2</sup> ).

There were no differences in adverse events and no episodes of graft loss and only 2 episodes of biopsy-proven acute rejection in each group.

\* result derived from published mean and standard deviations

This small short-term study found reduced-dose tacrolimus with standard-dose MMF to be non-inferior to standard-dose tacrolimus with reduced-dose MMF in low-to-standard immune risk de novo Korean kidney transplant recipients, though whether this reduces long-term graft loss from calcineurin nephrotoxicity or late rejection remains unanswered.



ISN Academy: [Transplant](#)

## Different proton pump inhibitors demonstrate differential effects on cyclosporin levels and kidney function

**Esomeprazole vs pantoprazole effects on cyclosporine levels in kidney transplantation: A randomized clinical trial**

[El-Bohy et al. Ther Apher Dial. 2019 Dec 19. doi: 10.1111/1744-9987.13464](#)

Population	70 adult kidney transplant recipients on stable maintenance immunosuppression for a minimum of 3 years	
Intervention vs Comparator	Esomeprazole 40mg daily versus Pantoprazole 40mg daily	Time 6 months
Outcomes	At 6 months, mean trough cyclosporin levels were higher in the pantoprazole group compared to the esomeprazole group ( $150.6 \pm 60.9 \mu\text{g/L}$ versus $107.3 \pm 43.9 \mu\text{g/L}$ ; $p=0.007$ ) Serum creatinine levels decreased significantly in the esomeprazole group from baseline to 6 months ( $1.4 \pm 1.5 \text{ mg/dL}$ versus $1.1 \pm 0.4 \text{ mg/dL}$ ; $p=0.004$ ), while no difference in kidney function was observed in the pantoprazole group over time. No episodes of rejection occurred.	

This study suggests that choice of PPI may affect cyclosporin levels in kidney transplant recipients. However,  $C_0$  did not diverge until month 5 of the study. The authors postulate that difference in CYP450 enzyme and P-glycoprotein interactions might explain the difference, although why this would manifest only after 5 months is not clear. It is possible that, in this small study with a high rate of loss to follow up, these findings are due to chance. Nevertheless, it serves as a reminder to pay attention to calcineurin inhibitor levels when changing concurrent medications.



ISN Academy: [Hypertension](#)

## A web-based sodium restriction self-management program improved initial but not long-term dietary sodium consumption.

**A self-management approach for dietary sodium restriction in patients with CKD: a randomised controlled trial**

[Humalda et al. Am J Kidney Dis. 2020 Jan 16. pii: S0272-6386\(19\)31126-6](#)

Population	99 people with stage 1-4 CKD or a functioning kidney transplant	
Intervention vs Comparator	Web-based dietary sodium restriction self-management program vs Routine Care	Time 9 months (3 months intervention and further 6 months follow-up)
Outcomes	At 3 months sodium excretion was 24.8 (95%CI 0.1-49.6) mmol/day lower in the intervention group ( $p=0.049$ ). However, there was no difference between groups at the end of the maintenance period. There was no significant difference in systolic blood pressure between groups.	

Sodium intake decreased in the intervention group, but this difference was lost over the 6 months following the intervention period. The participants reported that objective data, such as 24-hr sodium results, were very useful and that they preferred a mix of face-to-face and web-based interactions rather than web-based alone.



ISN Academy: [Acid-Base Disorders, Chronic Kidney Disease](#)

## Sodium bicarbonate may help maintain muscle mass and kidney function in CKD with metabolic acidosis

**Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: A randomized controlled trial**

[Dubey et. al, Nephrol Dial Transplant 2020; 35:121-129. doi: 10.1093/ndt/gfy214](#)

Population	188 adult patients (age 18-65 years) with CKD stages 3 and 4 and bicarbonate levels <22 mEq/L	
Intervention vs Comparator	Oral sodium bicarbonate supplementation to maintain venous bicarbonate levels at 24-26 mEq/L <i>plus</i> standard care vs. standard care alone	Time 6 months
Outcomes	Intervention group lean body mass (LBM) at conclusion of the study was 36.8kg (95% CI 36.5-37.1), representing a 0.3kg increase from initial measurement vs. 36kg (95% CI 35.7-36.4) in the control group (p<0.002), representing a 0.2kg decrease. The mid-arm muscle circumference (MAMC) was 22.9cm (95% CI 22.8-23) in the intervention group vs. 28.2 (95% CI 27-29.4); p<0.001. 39 (41.5%) of patients in the control arm had a decline in eGFR >3ml/1.73m <sup>2</sup> vs. 19 (20.2%) in the intervention arm. There was a significantly higher number of adverse effects in the bicarbonate group (77.7% vs. 41.4%; p=0.01), most commonly increased requirement for diuretic use and worsening oedema.	

In this study at a single centre in India with a high proportion (52%) of participants with CKD of uncertain etiology (CKDu) sodium bicarbonate treatment resulted in significantly higher lean body mass and mid-arm muscle circumference after 6 months. While the clinical significance of these observed differences may be debated, this finding is in line with other previous studies. Moreover, the secondary outcome of change in renal function provides further evidence that sodium bicarbonate may preserve renal function. While not definitive, this study does provide useful additional information, particularly to clinicians practicing in areas with a high prevalence of CKDu.



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

### Sodium thiosulphate for vascular calcification in HD? It's complicated.

Sodium thiosulphate and progression of vascular calcification in end-stage renal disease patients: a double-blind, randomised, placebo-controlled study

[Djuric et al. Nephrol Dial Transplant. 2020;35\(1\):162-169](#)

Population	60 chronic hemodialysis patients >18 y.o with moderate to severe abdominal aortic calcification scores (AACS) as determined using the Agatston method	
Intervention vs Comparator	25g/1.73m <sup>2</sup> sodium thiosulphate (NaTS) in 100mL normal saline vs. 100mL normal saline IV in the last 15mins of every thrice-weekly dialysis session	Time 6 months
Outcomes	AACS increased in both groups with no statistically significant difference in absolute change in score between the two arms. Participants on NaTS had a reduced iliac artery calcification score (-137±641 vs 245±755; P=0.049), reductions in in pulse wave velocity as a measure of arterial stiffness (9.6±2.7vs 11.4±3.6; P<0.001), better preservation of normal left ventricular mass parameters, no new cardiac valvular calcification (0/26 vs 8/29) and lower carotid intima-media thickness (0.77±0.1 vs 0.83±0.17; P=0.033) compared with placebo.	

This randomised trial with a relatively short period of follow up failed to demonstrate any effect on abdominal aortic calcification when compared to a saline placebo, despite suggested benefits in other vascular territories. This highlights the complex pathogenesis of arterial calcification in CKD. NaTS was however, well tolerated and may facilitate further studies with longer follow up and larger cohorts of patients to better determine if it has vascular benefits.



ISN Academy: [Glomerular Diseases](#)

### Tacrolimus monotherapy, a safe and effective alternative to corticosteroids for initial therapy for adult minimal change disease

A randomized, controlled trial of tacrolimus and prednisolone monotherapy for adults with *de novo* minimal change disease.

[Medjeral-Thomas et al. Clin J Am Soc Nephrol. 2020;15\(2\):209-218](#)

Population	55 adult patients with nephrotic syndrome and biopsy confirmed <i>de novo</i> minimal change disease	
Intervention vs Comparator	Tacrolimus at 0.05mg/kg twice daily vs Prednisolone at 1mg/kg daily	Time 18 months after complete remission

**Outcomes** While the prespecified criteria for non-inferiority was not met for tacrolimus, there were no significant differences in the proportion of patients in remission between the treatment arms at 8 weeks (21/25 [84%] for prednisolone and 17/25 [68%] for tacrolimus cohorts; P=0.32), 16 weeks (23/25 [92%] and 19/25 [76%] respectively; P=0.25) or 26 weeks (23/25 [92%] and 22/25 [88%] respectively; P=0.99).  
 There was no significant difference in relapse rates among those that achieved complete remission (74% for prednisolone and 73% for tacrolimus cohorts; P=0.99)  
 There were no significant differences in adverse events recorded between the two cohorts (0.72 and 0.74 events per patient in the Prednisolone and Tacrolimus cohorts respectively; P=0.99)

This important study is the first multicentre randomised controlled trial to demonstrate that tacrolimus monotherapy for incident minimal change disease is safe and effective, although it did not prove that tacrolimus was non-inferior to corticosteroids. There was evidence in post hoc analyses that corticosteroids may induce complete remission more rapidly than tacrolimus, but further studies would be required to confirm this finding.



ISN Academy: [Peritoneal Dialysis](#)

### No evidence that allopurinol preserves renal function in hyperuricemic patients receiving PD Allopurinol Effects on Residual Renal Function in End-Stage Renal Disease Patients Undergoing Peritoneal Dialysis: Randomized Controlled Trial

[Moeinzadeh et al. J Res Pharm Pract. 2019; 8\(4\):189–195](#)

<b>Population</b>	80 adult peritoneal dialysis participants with hyperuricemia (uric acid $\geq 7\text{mg/dL}$ in men, and $\geq 6\text{ mg/dL}$ in women)	
<b>Intervention vs Comparator</b>	Allopurinol dosed to normalise serum uric acid vs. not receiving allopurinol	Time 6 months
<b>Outcomes</b>	Participants treated with allopurinol had significantly lower systolic and diastolic blood pressures (P=0.001), but there was no difference in the primary outcome of residual renal function assessed either by GFR (P=0.2) or Kt/V (P=0.384) at 6 months	

Although interesting effects on blood pressure were noted, this relatively small study with a short follow-up period did not show any evidence that allopurinol aids in preserving residual renal function in patients receiving peritoneal dialysis.



ISN Academy: [Nutrition and Hydration, Genetic Kidney Diseases](#)

### Pilot study paves the way for larger trial of high water intake for preventing progression of ADPKD High water vs. ad libitum water intake for autosomal dominant polycystic kidney disease: a randomized controlled feasibility trial

[El-Damanawi et al. QJM. 2020 Jan 20. pii: hcz326](#)

<b>Population</b>	42 adults with ADPKD and an eGFR $\geq 20\text{ml/min/1.73m}^2$	
<b>Intervention vs Comparator</b>	High water intake (target urine osmolality $\leq 270\text{mOsm/kg}$ ) vs. <i>ad libitum</i> water intake	Time 8 weeks
<b>Outcomes</b>	At 8 weeks, there was a significantly more participants in the high water intake group had a urine osmolality $\leq 270\text{mOsm/kg}$ (x/X [67%] vs. x/X [24%]; P=0.001) and urine volume was significantly greater (3155 [IQR 2270-4295] vs. 1920 [1670-2960] ml/day; P=0.02). Two cases of hyponatremia requiring alteration of fluid prescription occurred in the high water intake group and 7/42 (17%) of participants withdrew prematurely.	

The DRINK trial found clear differences in urine osmolality and urine volume (surrogates for vasopressin levels) with high water intake, suggesting it is feasible to conduct a larger trial of high water intake for preservation of renal function in those with ADPKD. The relatively high rate of drop out suggests that a subset of patients may find such therapy challenging to maintain. However, this limitation also applies to tolvaptan, the only agent currently shown to slow decline in renal function in ADPKD. A larger trial of this simple and inexpensive intervention would be a welcome step forward for those living with ADPKD.

