











Global Trials Focus

January 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!

@ISNeducation 

Want to run your own trial?
ISN-ACT Clinical Trials Toolkit
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Would you like to write your own reviews?
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Contact us at research@theisn.org

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ISN Academy: [Chronic Kidney Disease](#)

Daily, weekly, or monthly cholecalciferol dosing regimens are similarly effective in children with CKD

Determining the optimal cholecalciferol dosing regimen in children with CKD: a randomized controlled trial

[Iyengar et al. Nephrol Dial Transplant. 2020 Dec 24;gfaa369](#)



Reviewed by Smyth B

About the study: Ninety children (ages 1-18) with CKD stage 2-4 and 25OH vitamin D levels <30ng/ml were randomised to three equal groups to receive daily (3,000IU), weekly (25,000IU) or monthly (100,000IU) cholecalciferol doses for three months. The three-month course could be repeated until the target 25OH vitamin D level was achieved.

Results: By 9 months, 70/90 (78%) of children reached a level of 25OHD \geq 30ng/ml, with no significant differences between groups. At the end of the first three month course, the number of children reaching the target was 22/30 (73%), 19/27 (70%), and 21/26 (81%) in the daily, weekly, and monthly groups, respectively (with 7 lost to follow up). Five (6%) of children developed asymptomatic hypercalcemia.

Comment: Chronic kidney disease in childhood, including mineral and bone disorders, can have important effects on health, growth and development. Practical dosing regimens may permit children to achieve adequate vitamin D replacement in line with local resources and patient preference. Intermittent dosing may also facilitate administration by community health care workers or simplify treatment for children in rural or remote areas. Even considering the limitations of this study, it still suggests that daily, weekly, or monthly cholecalciferol dosing regimens are generally comparable in effectiveness and safety, providing more options for children with low vitamin D and CKD.

ISN Academy: [Fluid and Electrolytes](#)

Self-measurement of urine chloride in CKD patients has a modest but unsustained effect on improving dietary sodium restriction

Reducing salt intake by urine chloride self-measurement in non-compliant patients with chronic kidney disease followed in nephrology clinics: a randomized trial.

[Panuccio et al. Nephrol Dial Transplant. 2020 Dec 8:gfaa262. doi: 10.1093/ndt/gfaa262](#)



Reviewed by Ng JK

About the study: This multicentre trial examined the efficacy of self-measurement of urinary chloride, a surrogate marker of sodium intake, to improve adherence to a low sodium diet. 138 patients with chronic kidney disease (CKD) and hypertension were randomized to using chloride-reactive strip (n=69) or standard care (n=69). Both groups received dietary counselling on reducing sodium intake. The primary outcomes were 24-hour urinary sodium (UNa) and ambulatory blood pressure monitoring (ABPM) at 3 and 6 months.

Results At 3 months, UNa was 35mmol/24 h (95% CI 10.8–58.8mmol/24 h; P = 0.005) lower in the active arm than the control arm. At 6 months, however, the between-arms difference in UNa decreased and was no longer significant (23mmol/24 h [95% CI 5.6–50.7]; P =0.11). Adherence to the low salt diet (defined as UNa <100mmol/24 h) only marginally increased from 28% to 30% from baseline to 6 month in active arm. In addition, there was no significant difference in estimated glomerular filtrate rate, proteinuria and ABPM readings between each arm.

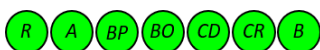
Comment: The use of chloride-reactive strips enables simple self-monitoring of a surrogate measure of UNa, and thereby provides feedback to patients on sodium excretion which may potentially improve adherence to low salt diet and foster self-management in chronic disease. However, the present study showed that this method only led to a modest and unsustained effect on dietary sodium compliance. Moreover, there was no effect on the clinically important outcome of blood pressure reduction. Further studies that focus on the development of strategies of sustained dietary sodium reduction in CKD patients are needed.

ISN Academy: [Diabetes](#)

Esaxerenone reduces microalbuminuria in diabetic kidney disease

Esaxerenone (CS-3150) in Patients with Type 2 Diabetes and Microalbuminuria (ESAX-DN): Phase 3 Randomized Controlled Clinical Trial

[Ito et al. CJASN. Dec 2020, 15 \(12\) 1715 – 1727.](#)



Reviewed by Kim D

About the study: 455 patients across 135 sites with type 2 diabetes mellitus, hypertension,

Results: Remission of albuminuria was higher at the end of treatment in the esaxerenone group vs. placebo (22% vs. 4%; difference 18% [95% CI 12-25%] p < 0.001). Reduction in uACR (> 30%) was also seen more with esaxerenone compared to placebo (69% vs. 20%), and fewer

<p>microalbuminuria (urine albumin:creatinine ratio [uACR] 45 to < 300mg/g) and eGFR > 30ml/min/1.73m², already established on RAS inhibitor therapy were randomised to esaxerenone or placebo for 52 weeks.</p>	<p>developed macroalbuminuria (1% vs. 7%). The change in eGFR from baseline was higher in the esaxerenone group (-11% vs. -1%) at the end of treatment, however recovered to a level similar to the placebo group 4 weeks following treatment cessation. 19 patients (8%) in the placebo arm and 43 (19%) in the esaxerenone arm discontinued treatment due to adverse events, of which 1 patient and 10 patients respectively stopped due to hyperkalaemia.</p>
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Comment: Following on the heels of the FIDELIO study ([GTF November 2020](#)), ESAX-DN adds to the rising interest in the benefits of mineralocorticoid blockade in diabetic kidney disease in addition to the effects of usual RAS inhibitor therapies. It shows moderate reduction in microalbuminuria however at the expense of lower eGFR whilst on therapy and, as expected, treatment limiting hyperkalaemia. Further data such as effects on macroalbuminuria, renal outcomes including, rate of eGFR decline, progression to renal failure and cardiac events over a longer follow-up period is required before esaxerenone is likely to be considered for regular clinical use in diabetic kidney disease.

Low fixed dose of darbepoetin may minimize blood transfusions and reduce cumulative dose exposure in non-dialysis CKD patients with anaemia

A randomized trial of strategies using Darbepoetin Alfa to avoid transfusions in CKD.

[Toto et al. JASN 32: JAN 2021](#)



Reviewed by *Omoso B*

<p>About this study: 756 non dialysis CKD stage 3-5, aged ≥18yrs who had two hemoglobin (Hb) concentrations ≤10.0 g/dl at least 2 weeks apart, and were iron replete were randomized to two darbepoetin treatment groups; fixed dose [FD] (received 0.45 mg/kg of darbepoetin every 4 weeks) versus titration dose [TD] (administered according to a Hb-based, titration-dose algorithm every 4 weeks), for 2 years.</p> <p>The primary end point was receipt of one or more blood transfusions (at investigator discretion).</p>	<p>Results: There was no difference in the proportion of participants transfused (24.1% and 24.4% for the FD and TD group, respectively; risk ratio (FD/TD): 1.00 ; 95% CI, 0.78 to 1.29), with similar time to first transfusion (Hazard Ratio, FD/TD was 1.01; 95% CI, 0.76 to 1.35). The median Hb was significantly higher in the TD group (9.9 g/dl) compared with the FD group (9.4 g/dl), as was the median cumulative dose of darbepoetin (53.6mg [IQR 31.1, 89.9] and 30.9mg [21.8, 40.0]; difference between treatment groups -22.1mg [95% CI, -26.1 to -18.1]). The incidence of adverse events were similar in both groups.</p>
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Comment: Results from this multicentre randomised controlled double-blind, parallel-group, phase-3 trial suggest a fixed dose of darbepoetin may be used as an alternative to a dose-titration approach that achieves the same transfusion requirements. This may not only serve as a way to simplify treatment regimens but also minimize cost, with less cumulative dosing in non-dialysis CKD patients. Data on variance in cardiovascular outcomes would require longer follow up.

Regulating graft inflammation with IL-6 blockade

Interleukin-6 Blockade with Tocilizumab Increases Tregs and Reduces T Effector Cytokines in Renal Graft Inflammation: A Randomized Controlled Trial.

[Chandran et al, Am J Transplant 2020, ISSN 0085-2538, https://doi.org/10.1016/j.kint.2020.10.014.](#)





Reviewed by Chung E

<p>About the study: Thirty three kidney transplant recipients with stable eGFR ≥ 30 ml/min/1.73 m² and graft inflammation (Banff i or ti scores of 1-2 with t0; ie. 10-50% interstitial mononuclear inflammation without tubulitis) on surveillance biopsy within the first year of transplantation, were randomised to the anti-IL-6 receptor monoclonal antibody tocilizumab 8mg/kg IV every 4 weeks for 6 doses or standard care. The primary outcome was a decrease in Banff ti score by 1 point at 6 months.</p>	<p>Results: At 6 months, a higher proportion of participants in the tocilizumab group had a decline in the ti-score (10/16 vs 3/14, p=0.03) compared to the control group (median change in ti-score from baseline -1 vs 0, p-value not reported). Peripheral blood regulatory T cell proportions were significantly higher (6.7\pm3.8% vs 3.7\pm1.8%, p=0.02), along with evidence of fewer CD4+ T cells producing IFNγ (p=0.02), IL-17 (p=0.001), and granzyme B (p=0.0006), and lower CD8+ T cells producing IFNγ (p=0.02) at 6 months in the tocilizumab group compared to control (quantitative results for effector T cell populations not reported).</p> <p>The eGFR was unchanged in both groups at 6 and 12 months. No participants died or experienced graft loss, acute T cell-mediated rejection, antibody mediated-rejection, or developed de novo DSAs. There were no between-group differences in infections or BK viraemia.</p>
<p>Comment This study found that tocilizumab increased the likelihood of reducing biopsy evidence of graft inflammation in kidney transplant recipients, potentially via increasing regulatory T cells and reducing effector T cell populations. While the short study duration and small sample size prevented the detection of changes in clinical outcomes such as acute rejection, graft function and infections, the observed changes suggest that further studies may be warranted.</p>	

ISN Academy: [Haemodialysis](#)

Patient backchat encouraged when it comes to phosphate

A bundled phosphate control intervention (4Ds) for adults with end-stage kidney disease receiving haemodialysis: A cluster randomized controlled trial protocol.

[Milazi et al. J Advanced Nursing 2020. 74.10 \(2018\): 2431–2441.](#)



Reviewed by Chou A

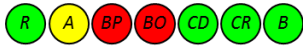
<p>About the study: Eighty three haemodialysis patients with hyperphosphataemia (>1.6mmol/L) were randomized to a bundled self-management intervention vs. standard care over 12 weeks in order to evaluate its effect on phosphate control and adherence to treatment. The intervention emphasised teaching patients to understand phosphate control in the form of the 4Ds: diet, drinks, drugs and dialysis. It utilised a ‘teach-back’ approach where the participant was encouraged to express the taught concepts in their own words.</p>	<p>Results: Mean serum phosphate levels were similarly decreased in both control and treatment groups by 3 months (control mean 1.79 mmol/L vs. intervention 1.75mmol/L, p=0.07). However, 46% (n= 21) of the intervention group achieved target serum phosphate (<1.6mmol/L) vs. 33% (n=12) of the control group; p=0.26. In addition, self-reported knowledge of phosphate in ESKD in the intervention group significantly improved by 3 months compared with control (F [1, 80.50] = 17.84 ,p<0.001) as was self –reported adherence diet (p<0.001) and drugs (p<0.03)</p>
<p>Comment: This pragmatic clustered randomized controlled trial used a ‘teach back’ bundled self-management intervention aiming to ensure the participant can ‘teach’ this information back to the educator. Self-reported adherence and knowledge of phosphate control was better in the intervention group, however, this difference was not necessarily reflected in serum phosphate levels at study</p>	

completion. Due to the nature of the trial, whereby blinding of participants is not possible, there may be a bias affecting the results of self-reported treatment adherence. Nonetheless, patients in the intervention arm reported higher self-efficacy and confidence levels compared to standard care arm that may confer benefits over time.

Does pre-operative exercise alter post-operative AVF outcomes?

Effect of preoperative exercise on vascular caliber and maturation of arteriovenous fistula: the physicalfav trial, a randomized controlled study.

Sauco et al. *J Nephrol.* 2021, Jan 2. doi: [10.1007/s40620-020-00907-w](https://doi.org/10.1007/s40620-020-00907-w).



Reviewed by Shah N

About the study: 138 participants across 4 sites in Spain were randomised to an 8-week preoperative isometric exercise program or no preoperative program with the hopes of evaluating the effect on primary AVF failure.

Results: After the 8-week exercise program, there was no significant difference in rate of primary AVF failure between the control and exercise arms (4/53 vs. 8/61, $P=0.373$). Although there were significant improvements in some physical characteristics (venous & arterial calibre, $p<0.001$; peak systolic velocity, $p<0.008$; maximum grip, $p<0.001$), this did not translate to an improvement in the primary (primary AVF failure) or any of the secondary clinical outcomes (need for intervention, $p=0.469$; thrombosis, $p=0.307$; re-anastomosis, $p=0.862$; angioplasty, $p=0.910$; or new AVF surgery, $p=0.364$)

Comment: Although a fascinating proposal, following on from previous studies showing increases in vascular diameter, this trial failed to show any significant improvement in the primary endpoint of primary AVF failure with pre-operative exercise. It will be interesting to see if the other 3 pending trials examining this question return with similar results.