











Global Trials Focus

December 2020

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
www.theisn.org/isn-act-toolkit

Would you like to write your own reviews?
Join the GTF team.

Contact us at research@theisn.org

Edited by Gallagher A, O'Hara DV and Smyth B

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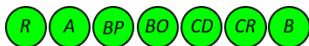
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ISN Academy: [Chronic Kidney Disease](#)

Phosphate binders appear to have little effect on vascular end-points in normophosphataemic CKD patients

A Randomized Trial on the Effect of Phosphate Reduction on Vascular End Points in CKD (IMPROVE-CKD)

Toussaint et al. JASN Nov 2020, 31 (11) 2653-2666; DOI: <https://doi.org/10.1681/ASN.2020040411>



Reviewed by Yeung W

About the study: a multi-centre, double-blind trial to assess the effects of non-calcium-based phosphate binders on intermediate cardiovascular markers in patients with stage 3b to 4 CKD. 278 participants were randomised to 500mg lanthanum carbonate or matched placebo thrice daily for 96 weeks. The primary outcome was carotid-femoral pulse wave velocity (PWV). Secondary outcomes included abdominal aortic calcification (measured by CT) and serum and urine markers of bone and mineral metabolism.

Results: At baseline, mean eGFR was 26.6 ml/min 1.73m², mean serum phosphate was 1.25 mmol/L, mean PWV was 10.8 m/s and 81.3% had abdominal aortic calcification. At 96 weeks, pulse wave velocity did not differ significantly between groups, nor did abdominal aortic calcification, serum phosphate, parathyroid hormone, FGF23, or 24-hour urinary phosphate.

Comment: Hyperphosphataemia has been strongly associated with increased arterial stiffness and calcification, increased risk of adverse cardiovascular events and mortality in CKD patients in epidemiological studies. Little is known with certainty about the benefits of phosphate binders in the CKD population beyond lowering serum phosphate. Although the investigators did not reach their target recruitment number of 488 participants due to slow recruitment and loss of funding, findings from this trial suggest that lanthanum has limited effect on the intermediate markers of cardiovascular risk in non-dialysis CKD patients with normophosphataemia.

Corticosteroids and cyclophosphamide may be superior to tacrolimus and rituximab in the treatment of primary membranous nephropathy at the cost of increased adverse events

The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy

[Fernández-Juárez et al, Kidney Int 2020, S0085-2538\(20\)31251-5. doi.org/10.1016/j.kint.2020.10.014](#)



Reviewed by Chung E

About the study: 86 adults with biopsy-proven primary membranous nephropathy, nephrotic-range proteinuria >4g/24h (not decreasing >50% in the last 6 months despite at least 2 months of ACE inhibitor or angiotensin receptor blocker therapy), hypoalbuminaemia (≤ 35 g/L) and an eGFR ≥ 45 ml/min/1.73m² (baseline 79.8 ± 23.5) were randomised to Corticosteroids/Cyclophosphamide (alternating months of corticosteroids [methylprednisolone 1g IV daily for 3 doses then methylprednisolone 0.5 mg/kg/day oral for 27 days] and cyclophosphamide [oral cyclophosphamide 1-2 mg/kg/day for 30 days] for 6 months) or Tacrolimus/Rituximab (oral tacrolimus 0.05 mg/kg/day aiming trough levels 5-7 ng/ml for 6 months then tapered by 9 months, and rituximab 1g IV as a single dose at month 6).

Results: At 2 years, treatment with Corticosteroids/Cyclophosphamide was associated with a higher rate of remission (complete or partial) compared to Tacrolimus/Rituximab (risk ratio [RR] 1.44, 95% confidence interval [CI] 1.07 to 1.93), which was driven by a higher rate of complete remission (RR 2.36, 95% CI 1.34 to 4.16).

Relapses occurred in 2.7% of the Corticosteroid/Cyclophosphamide group post-remission compared to 12% of the Tacrolimus/Rituximab group (p-value not reported). Corticosteroid/Cyclophosphamide was associated with more adverse events, especially leukopenia (30% vs 5%, p=0.003) and Cushing syndrome (16% vs 0%, p=0.01) compared to Tacrolimus/Rituximab but there were no differences in infection or cancer.

Comment: STARMEN found that Corticosteroid/Cyclophosphamide may be more effective than Tacrolimus/Rituximab in inducing remission of primary membranous nephropathy over 2 years but caused more adverse events. It is notable that the Tacrolimus/Rituximab group had a higher median PLA2R antibody level that did not reach statistical significance (113 vs. 59; P=0.1), which may have contributed to the worse outcomes in that group. Nevertheless, the groups were otherwise balanced, and it is safe to say that this study ensures that a modified Ponticelli regime remains the key reference point in the therapeutic landscape of membranous nephropathy.

Pumping iron in the elderly dialysis cohort: impacts on iron metabolism and inflammatory profiles

Effects of resistance training on hepcidin levels and iron bioavailability in older individuals with end-stage renal disease: A randomised controlled trial

Moura et al. *Experimental Gerontology* 2020;139 111017. <https://doi.org/10.1016/j.exger.2020.111017>



Reviewed by Chou A



About the study: 202 haemodialysis patients aged ≥ 60 years old were randomised to completing 24 weeks of resistance training (RT) 3 times per week vs. no exercise intervention.

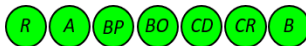
Results: There was a significant increase in iron ($+222\mu\text{g/L}$ versus $-10\mu\text{g/L}$) and decrease in hepcidin (-7.9ng/mL versus $+0.2\text{ng/mL}$) in the RT group compared to pre-training and control groups ($p<0.001$) with no significant differences in Hb and ferritin. There was a decrease in TNF-alpha and IL-6 in the RT group ($p<0.001$).

Comment: This unblinded study demonstrates that resistance training may improve iron bioavailability and decrease inflammatory markers in the haemodialysis population. The clinical implications of the study are unclear given that there were no significant differences in haemoglobin and ferritin levels, and blood and iron transfusion requirements were not explored. There was a relatively high drop-out rate of 22%, highlighting the challenges of implementing lifestyle interventions in this demographic. Also of note, patients with significant comorbidities such as decompensated heart failure or severe diabetes were excluded, limiting the generalisability to the dialysis population with high comorbidity burden.

Perioperative fosfomycin reduces urinary tract infections in acute transplant recipients

Perioperative fosfomycin disodium prophylaxis against urinary tract infection in renal transplant recipients: a randomized clinical trial

Rosado-Canto et al. *Nephrol Dial Transplant*. 2020 Nov 1;35(11):1996-2003.



Reviewed by O'Hara DV



About the study: 82 acute transplant recipients received either 4g fosfomycin disodium intravenous prophylaxis or placebo 3 hours before placement and removal of their urinary catheter, and before removal of their ureteral stent. All participants received trimethoprim/sulfamethoxazole prophylaxis 160/800mg daily once their eGFR was $> 30\text{mL/min/1.73m}^2$, and a single dose of 1g intravenous cephalothin at the time of renal transplantation. Participants were monitored for 7 weeks after renal transplantation including repeated urine culture testing.

Results: There were fewer symptomatic urinary tract infection (UTI) events with fosfomycin (7.3% versus 36.6%, $p=0.001$), and there was no difference in the incidence of asymptomatic bacteriuria between the groups. The mean number of symptomatic UTIs or asymptomatic bacteriuria events was lower in the fosfomycin group (0.29 versus 0.60, $p=0.04$). There was no significant difference in adverse events.

Comment: Fosfomycin effectively reduced the risk of symptomatic urinary tract infections in acute transplant recipients when given at the time of urological procedures. Advantages of fosfomycin include its limited interaction with immunosuppression, lack of dosage adjustment for renal function when given in single doses, and broad spectrum of antimicrobial activity. In the interests of antimicrobial stewardship, local antibiotic resistance patterns should be considered when determining prophylaxis protocols.

Ultrafiltration profiling and outcomes among hemodialysis patients

Effect of ultrafiltration profiling on outcomes among maintenance hemodialysis patients: a pilot randomized crossover trial

Flythe et al. *J Nephrol* (2020). <https://doi.org/10.1007/s40620-020-00862-6>



Reviewed by Pinter J

About the study: In this four-phase, single-blind, crossover trial, 34 adult hemodialysis patients with ultrafiltration (UF) rates > 10 mL/kg/h were assigned in random order to receive hemodialysis with UF profiling (constantly declining UF rate) vs. conventional UF. Each 3-week 9-treatment period was followed by a 1-week 3-treatment washout period. Participants crossed into each study arm twice (2 phases/arm); 18 treatments per treatment type. The primary outcomes were intradialytic hypotension, pre- to post-dialysis troponin T change, and change from baseline in left ventricular global longitudinal strain. Other outcomes included intradialytic symptoms and blood volume measured-plasma refill (post-dialysis volume status measure).

Results: Hemodialysis with UF profiling did not reduce the rate of hypotension (absolute rate: 14.3% (164 of 1149 treatments); OR (95% CI) 1.2 (0.8, 1.7)), occurrence of pre- to post-dialysis troponin T rise (OR (95% CI) 0.5 (0.2, 1.3)), or the degree of dialysis-associated left ventricular strain (OR (95% CI) 0.8 (0.1, 4.4)) compared to hemodialysis with conventional UF. Ultrafiltration profiling did result in lower odds of post-dialysis plasma refill (OR (95% CI) 0.2 (0.1, 0.9)) and intradialytic light-headedness (OR (95% CI) 0.2 (0.1, 0.9)) compared to conventional UF.

Comment: UF profiling is understudied and has potential to improve outcomes in the morbid hemodialysis population. Overall, the trial was well conducted and reported, but is limited by its pilot status. The hemodialysis patients studied were prevalent patients, mostly men and of Black and Hispanic ethnicity, in whom average treatment times were 220 minutes which differs from many standard European and Australasian regimens. This limits comparability across other populations and incident hemodialysis patients. Further clinical trials may be warranted before definitively determining that UF profiling is not effective.

Leflunomide may be an alternative to cyclophosphamide for primary membranous nephropathy

Efficacy of leflunomide combined with prednisone for the treatment of PLA2R-associated primary membranous nephropathy

Guo et al. *Renal Failure*. 2020;42(1):122-130. <https://doi.org/10.1080/0886022X.2020.1713806>



Reviewed by Omotoso B

About the study: 60 adult patients with nephrotic syndrome, biopsy proven primary membranous nephropathy, and positive anti-PLA2R antibody were randomised to either prednisolone (1mg/kg daily for 8 weeks then reduced by 10% every two weeks if the urine protein excretion was decreasing, until the dose reached 20mg, when it was reduced by 5mg every 4 weeks until it reached 10mg) and leflunomide (20mg/day) or a control group who

Results: After 24 weeks, there was no significant difference in clinical efficacy between the two groups ($p > 0.05$). The leflunomide/prednisone group had 7 complete and 13 partial remissions, and the control group had 9 complete and 14 partial remissions. The levels of 24-h urinary protein and serum albumin in the experimental and control groups improved significantly after 24 weeks of treatment ($p < 0.05$). The levels of triglyceride and cholesterol decreased significantly ($p < 0.05$), while serum creatinine, blood

received prednisolone (with the same dosing as the experimental arm) and cyclophosphamide (0.3-0.4g/m² every 2 weeks). The study endpoints were remission (complete and partial), change in 24 h urinary protein, kidney function markers, serum albumin levels, cholesterol and anti PLA2R antibody titres after 24 weeks follow up.

urea nitrogen levels or eGFR did not change ($p > 0.05$). There were fewer adverse reactions in the experimental group than in the control group ($p < 0.05$), with patients in the cyclophosphamide group having higher rates of vomiting, alopecia, abnormal liver function and thrombocytopenia.

Comment: This single centre trial in a solely Chinese cohort found that leflunomide combined with prednisolone may be an alternative treatment for patients with PLA2R associated primary membranous nephropathy with a safer side-effect profile. However, it did not show superiority to the cyclophosphamide regimen, and is limited by its small sample size and short follow up. Renal function endpoints such as ESRD or a 50% decrease in the glomerular filtration rate were also not assessed in this study. It is important to note that the control arm in this study used a unique dosing schedule not recommended in guidelines that limits its generalisability. Further larger trials with longer follow up will be required to validate these findings.
