ISN Global Trials Focus

August 2019

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

Key to risk of bias assessment

- (R) Random sequence generation
- (A) Allocation concealment
- (BP) Blinding of participants/personnel
- (BO) Blinding of outcome assessment
- (CD) Complete outcome data
- (CR) Complete outcome reporting
- (B) No other sources of bias

High risk / Uncertain risk / not stated / Low risk

Contents

ISN Academy: Glomerular Diseases

Rituximab superior to cyclosporine in membranous nephropathy

Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy (MENTOR trial)

Fervenza, et al. N Engl J Med. 2019 Jul 4;381(1):36-46

Population	130 adults with primary membranous nephropathy and proteinuria ≥ 5g / 24 hours, CrCl ≥40ml/min/1.73m^2 and on ACEi/ARB for ≥ 3 months	
Intervention *vs* Comparator	Rituximab (Two doses of 1g administered 14 days apart and repeated at 6 months if only partial response) vs. oral cyclosporine 6-12 months (target trough levels 125-175ng/ml)	**Duration** 24 months
Outcomes	The primary outcome of complete or partial remission at 24 months was more common with rituximab vs. cyclosporine (39/65 [60%] vs. 13/65 [20%]; risk difference 40% [95%CI 25-55]; P<0.001 for superiority) Adverse events were similar between both groups	

In this important study, rituximab proved superior to cyclosporine in primary membranous nephropathy. While cost-effectiveness was not assessed, the simplicity of the rituximab regimen is appealing and the effect size was large. Rituximab may soon be considered standard of care.

R A BP BO CD CR B

*ISN Academy: **Hypertension***

Amlodipine combination antihypertensive regimens best choice for first-line treatment in sub-Saharan Africans

Comparison of Dual Therapies for Lowering Blood Pressure in Black Africans

Ojji, et al. N Eng J Med. 2019;380:2429-39

Population	720 participants with uncontrolled hypertension	
Intervention *vs* Comparator	1:1:1 randomization to Amlodipine/Hydrochlorothiazide (10/25mg daily) vs. Amlodipine/Perindopril (10/8mg daily) vs. Perindopril/Hydrochlorothiazide (8/25mg daily)	**Duration** 6 months
Outcomes	All agents lowered BP (Mean decrease in ABPM: Amlo/HCT -17.1mmHg; Amlo/Perindo -18.1mmHg; Perindo/HCT -14.2mmHg) BP lowering effect was greater with Amlo/HCT or Amlo/Perindo vs. Perindo/HCT (-3.14mmHg [95%CI -5.90 to -0.38; P=0.03] or -3.00mmHg [-5.8 to -0.20; P=0.04], respectively)	

Amlodipine with either HCT or perindopril is more effective than perindopril/HCT as a first line agent in sub-Saharan Africans with hypertension. The publication of this practical study in a high profile journal also represents a important acknoledgement of the need to improve the profile of cardiovascular research in low-middle income countries.

R A BP BO CD CR B

*ISN Academy: **Mineral and Bone Disorders***

Dual action approach to phosphate control in CKD provides meagre results

Effects of Nicotinamide and Lanthanum Carbonate on Serum Phosphate and Fibroblast Growth Factor-23 in CKD: The COMBINE Trial

Ix, et al. J Am Soc Nephrol. 2019;30(6):1096

Population	205 normophosphatemic CKD patients with eGFR 20-45ml/min/1.73m^2	
Intervention *vs* Comparator	Lantanum 0.5-1g TDS plus nicotinamide 750mg daily-BD vs. Lanthanum and placebo vs. Nicotinamide and placebo vs. double placebo	**Duration** 12 months
Outcomes	No differences in serum phosphate or FGF-23 Adverse effects limited tolerance (eg. 42% discontinued in the lanthanum-nicotinamide arm vs. 14% in the double placebo arm)	

Despite the promising hypothesis, combination treatment with these agents did not appear to work in practice. The larger question of whether lowering phosphate and FGF-23 results in improves clinical outcomes remains untested.

R A BP BO CD CR B

*ISN Academy: **Diabetes**, **Chronic Kidney Disease***

Oral GLP-1RA effective in patients with T2DM and CKD 3

Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial

Mosenzon, et al. Lancet Diabetes Endocrinol 2019;7:515

Population	Adults with T2DM and eGFR 30 to 59ml/min/1.73m2	
Intervention *vs* Comparator	Oral semaglutide 14mg daily vs. placebo	**Duration** 26 weeks
Outcomes	Semaglutide lowered HbA1c (mean difference [MD] -0.8% [-1.0 to -0.6]; P<0.0001) and body weight (MD -2.5kg [-3.2 to -1.8]; P<0.0001) Blood pressure was lower in the semaglutide group (MD -7 mmHg [-9 to -4]; P<0.0001) and physical quality of life improved (MD in SF-36 PCS 1.98 [0.57 to 3.39]; P=0·0058)	

	Adverse effects (mostly gastrointestinal) and discontinuation were more common (15% vs. 5%)

Semaglutide improves glycemic control, weight and blood pressure in people with T2DM and CKD 3. The improvement in physical quality of life, while promising, may not represent a clinically meaningful difference. Whether this agent provides the same cardiovascular benefits as injectable GLP-1RA is not known.

R A BP BO CD CR B

*ISN Academy: **Transplant***

Growing evidence against treating asymptomatic bacteriuria after transplant

Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial

Sabe, et al. Open Forum Infect Dis. 2019;6(6):ofz243

Population	Adult renal transplant recipients in first year post-transplant	
Intervention *vs* Comparator	Antibiotic (as per sensitivities) vs. no antibiotics for asymptomatic bacteriuria	**Duration** 12 months
Outcomes	The risk of acute graft pyelonephritis did not differ between groups (treatment 12.2% [5/41] vs. no treatment 8.7% [4/46]; RR 1.40 [0.40 to 4.87]; P=NS). Results in a per-protocol analysis were similar (RR 2.07 [0.50 to 8.58]; P=NS). Antibiotic resistance was significantly more common in the treatment group. Other adverse events did not differ.	

No treatment of asymptomatic bacteriuria in the acute post-transplant setting was non-inferior to antibiotic treatment and was associated with lower rates of multi-resistant organisms. While the confidence intervals in this small study were wide and do not exclude harm, this study adds to a limited body of evidence suggesting that antibiotics may not be necessary in this common situation.

R A BP BO CD CR B

*ISN Academy: **Hemodialysis***

Lower dose alteplase sufficient to unblock occluded hemodialysis catheters

Efficacy of Alteplase 1 mg Versus 2 mg Dose in Restoring Hemodialysis Catheter Function (Alte-dose 2): A Randomized Double-Blind Controlled Study

El-Masri, et al. Nephrology. 2019 Jul 3. doi: 10.1111/nep.13631

Population	252 catheter occlusion events in 48 HD patients. Each catheter occlusion was randomized, with adjustment for correlation between multiple occlusion events in the same participant	
Intervention *vs* Comparator	1mg/ml vs. 2mg/ml of alteplase (instilled for 30 min)	**Duration** Not reported
Outcomes	Rate of clot resolution at catheter site was 84.9% in 1mg group and 85.7% in 2mg group (P=0.5) Time to recurrence of occlusion was similar between groups (192 days for 2mg and 120 days for 1mg; P=0.27)	

Although small, this practical study suggests that lower dose alteplase 1mg is non-inferior to 2mg for the treatment of occluded haemodialysis catheters and so could be a cost-saving measure.

R A BP BO CD CR B

*ISN Academy: **Chronic Kidney Disease**, **Acid-Base Disorders***

All about that base: fruit and vegetable rich diet slows decline in renal function

Fruit and vegetable treatment of chronic kidney disease-related metabolic acidosis reduces cardiovascular risk better than sodium bicarbonate

Goraya N et al. Am J Nephrol 2019;49:438-448

Population	108 non-diabetic participants with stage 3-4 CKD, macroalbuminuria and mild metabolic acidosis	
Intervention *vs* Comparator	Fruit and vegetable (F+V) diet vs. oral $NaHCO_3$ 0.3mEq/kg/day vs. control (1:1:1)	**Duration** 5 years
Outcomes	Change in eGFR was significantly less with $NaHCO_3$ and F+V diets (mean change -12.3ml/min/1.73m^2 [95%CI -12.9 to -11.7] and -10.0ml/min/1.73m^2 [95%CI -10.6 to -9.4], respectively) than in the	

	control group (-18.8ml/min/1.73m^2 [95%CI -19.5 to -18.2]), P<0.01. The HCO_3 and F+V groups did not differ. Systolic BP was lower with F+V than control and HCO_3, as was LDL-cholesterol and BMI, and vitamin K1 levels at 5 years were higher, in keeping with improved cardiovascular risk profile.

Both bicarbonate supplementation and a diet rich in fruit and vegetables appear to slow decline in eGFR. While small and single centre, this study adds to growing evidence suggesting that treating acidosis is renoprotective. As an apple a day keeps the doctor away, a plate of fruit and vegetables might also fend off the nephrologist.

*ISN Academy: **Transplant***

Kidney transplant education to marginalized groups improves treatment options knowledge base and capacity for informed consent

Direct delivery of kidney transplant education to black and low-income patients receiving dialysis: a randomised control trial
Waterman, et al. Am J Kidney Dis. 2019 Jun 18. pii: S0272-6386(19)30733-4

Population	561 adult, black and white low-income participants	
Intervention *vs* Comparator	Patient-guided transplant education modules (with text, video and paper resources) plus educator support (4 phone calls) vs. patient guided module alone vs. usual education practices (1:1:1)	**Duration** 8 months
Outcomes	Patient-guided education improved participant knowledge of living and deceased donor transplant improved with and without educator support (mean difference with control 1.4 and 0.8 points [P=0.02 and P=0.01], respectively) Informed decision making, change in attitudes in favour of transplantation and initiation of steps towards transplantation also increased in both treatment arms vs control Both intervention groups felt better able to make informed decisions about transplantation work up. There was no added benefit to educator-guided interventions compared to patient-guided intervention	

The impact of the improved knowledge base achieved in this trial has yet to be correlated to transplantation rates in this cohort however the authors have shown that targeted education programmes can potentially improve understanding and preparedness of marginalized patient groups.

*ISN Academy: **Glomerular Diseases***

Mycophenolate may not be as effective as oral cyclophosphamide in relapsing ANCA vasculitis

Mycophenolate Mofetil Versus Cyclophosphamide for the Induction of Remission in Nonlife-Threatening Relapses of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: Randomized, Controlled Trial
Tuin, et al. Clin J Am Soc Nephrol. 2019 Jul 5;14(7):1021-1028

Population	84 patients with 1st or 2nd non-life threatening relapse of ANCA vasculitis	
Intervention *vs* Comparator	Cyclophosphamide (1.5-2mg/kg/day) versus mycophenolate mofetil (1g BD) for 6 months [both groups received tapering doses of corticosteroids; then azathioprine maintenance]	**Duration** 4 years
Outcomes	At 6 months, stable remission was achieved in (27/41) 66% in the mycophenolate group vs. 35/43 (81%) treated in oral cyclophosphamide arm (P=0.11). Disease-free survival at two and four years was 43% and 32% in the mycophenolate arm and 61% and 39% in oral cyclophosphamide arm, respectively (log rank test P=0.10 and P=0.17, respectively).	

We cannot be confident that mycophenolate is as effective as oral cyclophosphamide in inducing remission in relapsing ANCA vasculitis. However in those with non-organ threatening disease or contraindications to other therapies it may still maintain a role.

Intradialytic protein supplementation and exercise does not improve physical function or quality of life

Results from the randomized controlled IHOPE trial suggest no effects of oral protein supplementation and exercise training on physical function in hemodialysis patients

Jeong et al. Kidney Int. 2019 Apr 2. pii: S0085-2538(19)30389-8

Population	138 hemodialysis recipients	
Intervention *vs* Comparator	Intradialytic oral protein supplementation + exercise (cycling) vs. Intradialytic oral protein supplementation alone vs. control	**Duration** 12 months
Outcomes	At 12 months, there were no significant differences in the primary outcome of shuttle walk test (physical activity). Quality of life and measures of strength did not significantly change, nor was there a significant impact on the pulse wave velocity, blood pressure, serum albumin, IL-6 or CRP.	

While limited by a high drop out rate in the protein+exercise group, this study found no evidence that oral protein supplementation and aerobic exercise improve physical function, risk of cardiovascular disease or quality of life in hemodialysis patients.