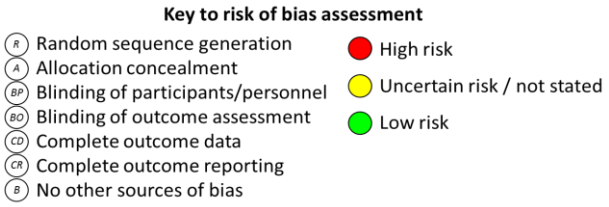
ISN Global Trials Focus

December 2019

The ISN-ACT (Advancing Clinical Trials) team presents a monthly showcase of randomized trials in nephrology from around the world. Featured trials are not just those with the highest impact, but also trials that highlight the **diversity of current research** in nephrology. Trials are reviewed in context and risk of bias assessed in seven key areas. We hope our efforts will stimulate improvement in trial quality and promote greater engagement in trial activity.

If you are interested in contributing, either by suggesting a trial or joining the team, please send a brief CV to research@theisn.org.

Join the conversation each month by following us *@ISNkidneycare*



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ISN Academy: Mineral and Bone Disorders, Hemodialysis

No change in vascular calcification scores with rivaroxaban or vitamin K in hemodialysis patients

Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study

De Vriese et al. J Am Soc Nephrol. 2019 Nov 8. pii: ASN.2019060579

Population	132 adult hemodialysis patients with non-valvular atrial fibrillation suitable for anticoagulation	
Intervention *vs* Comparator	Vitamin K antagonist (INR 2-3) vs. rivaroxaban (10mg daily) vs. rivaroxaban (10mg daily) + vitamin K2 (2000µg thrice weekly)	Time 18 months
Outcomes	After 18 months, there was no significant difference in changes in calcification at any of the measured sites (total coronary arteries Agatston score P=0.36, total coronary arteries volume score P=0.62, thoracic aorta Agatston score P=0.21, thoracic aorta volume score P=0.71). When recurrent episodes were considered, there was less life-threatening and major bleeding episodes with rivaroxaban than with VKA use (17/100 person-years vs. 36/100 person-years, P=0.04). Rates of death, stroke, and cardiovascular events were comparable.	

This well designed RCT found no evidence for a difference in progression of vascular calcification with rivaroxaban, with or without vitamin K supplementation, as compared to VKA in hemodialysis patients. Although the result is

disappointing, the study was not powered to examine clinical events and the apparent safety of rivaroxaban in this population may facilitate further studies.

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*ISN Academy: **Hemodialysis***

Dumbbell exercise improves AVF blood flow in hemodialysis recipients

Effect of dumbbell exercise on arteriovenous fistula in patients undergoing maintenance haemodialysis: a prospective randomized controlled trial

Mo et al. Blood Purif. 2019. Sep 19:1-9. DOI: 10.1159/000502332

Population	86 chronic haemodialysis recipients	
Intervention *vs* Comparator	Dumbbell exercise (weight) versus rubber ball exercise on non-dialysis days	**Time** 3 months
Outcomes	Draining vein blood flow (primary outcome) significantly improved with dumbbell exercise (mean difference 360 ml/min [95% CI 112-829]; P=0.001). There was no difference in arteriovenous fistula proximal artery or brachial artery flow, the diameter of the draining vein or adverse events.	

This single centre study compared a novel arm exercise using weights to the more usual squeeze ball technique as a means of improving fistula blood flow. Given the importance of adequate AVF blood flow, these positive results suggest this method deserves further attention.

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

No effect on muscle function or bone mineral density from sodium bicarbonate therapy in those with low-normal bicarbonate levels

Effects of sodium bicarbonate in CKD Stages 3 and 4: A randomized, placebo-controlled, multicentre clinical trial

Melamed et al. Am J Kidney Dis. 2019 Nov 5. pii: S0272-6386(19)30945-X

Population	149 adults with eGFR 15-59 mL/min/1.73m^2 and serum bicarbonate levels 20-26 mmol/L	
Intervention *vs* Comparator	Sodium bicarbonate (0.4 mmol/kg/day) vs placebo	**Time** 24 months
Outcomes	On follow up, serum bicarbonate levels were significantly higher in the intervention group compared to the placebo group (P<0.001). Serum potassium levels were decreased by an average of 0.1 mmol/L (P=0.047). There was no difference in renal function, bone mineral density, muscle function or quality-of-life between the two randomised groups. Muscle biopsies were performed in 12 participants (5 intervention, 7 placebo). There was no difference in markers of muscle insulin signalling, proteolysis and inflammation.	

With growing evidence in favour of alkali therapy of metabolic acidosis in CKD, Melamed et al. aimed to expand the study of alkali therapy into CKD patients with low-normal bicarbonate levels (mean baseline bicarbonate 24 mmol/L). No effects on muscle function or bone mineral density were identified after 24 months of therapy. However the mean difference in bicarbonate at end-of-study was only 0.8 mmol/L and the high rate of loss to follow up may have limited the ability to detect an effect of bicarbonate therapy on various clinical outcomes.

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*ISN Academy: **Peritoneal Dialysis***

Tidal PD may be a safer alternative to intermittent PD in acute-start APD

Low-Volume Tidal Peritoneal Dialysis Is a Preferable Mode in Patients Initiating Urgent-Start Automated Peritoneal Dialysis: A Randomized, Open-Label, Prospective Control Study

Xie et al. Ther Apher Dial. 2019 Oct;23(5):409-417

Population	47 ESKD patients initiating automated peritoneal dialysis (APD) immediately after Tenckhoff catheter insertion	
Intervention *vs* Comparator	Low volume tidal peritoneal dialysis (TPD) vs. intermittent peritoneal dialysis (IPD) as initial modality. All patients transitioned to CAPD after 2 weeks.	**Time** 14 days

Outcomes	Interim analysis led to early termination due to an excess of complications in the IPD group: omental wrapping requiring second surgery (6/22 in IPD vs. 0/27 in TPD; P<0.01), and drain pain (4/22 in IPD vs. 0/27 in TPD; P=0.02). Overall, 6/27 (22%) participants in the TPD group experienced at least one complication vs. 10/22 (45%) in the IPD group. There was no difference in technique or patient survival after 2 years long term follow up.

Urgent start PD for ESKD provides a useful alternative to hemodialysis in select patients and, if successful, may increase the uptake of PD – which may be a more economical modality in many regions. This small and single centre study is not able to provide conclusive evidence, but their success with tidal PD suggests it could be preferred to intermittent PD.

*ISN Academy: **Transplant***

Twice-Daily vs. Once-Daily Tacrolimus in Low Risk Filipino Transplant Recipients

Pilot study comparing the efficacy, safety, convertibility and tacrolimus trough levels of twice-daily tacrolimus (Profgraf) to Once-Daily tacrolimus (Advagraf) among standard-risk kidney transplant patients at the National Kidney and Transplant Institute

Danguilan et al. Transplant Proc. 2019;51(8):2615-2619

Population	42 recipients of living donor kidney transplant with standard immunologic risk who received either basiliximab or ATG on induction	
Intervention *vs* Comparator	Twice daily tacrolimus vs. Once daily tacrolimus	**Time** 6 months
Outcomes	Participants receiving once daily tacrolimus had lower trough levels (4.9ng/dl vs 6.9ng/dl; P=0.02) and required higher doses (mean increase of 8%). Other pharmacological parameters were similar (AUC, Cmax, Tmax). After 12 weeks, those on twice daily were converted to once-daily and all participants continued to be followed up. There were no differences in graft function at 6 months and no episodes of acute rejection.	

Once-daily tacrolimus appears safe and effective in this small cohort of Filippino transplant recipients. The authors note that conversion from twice-daily to once-daily tacrolimus typically requires a small increase in tacrolimus dose. This study has a number of limitations, most notably the lack of a proper randomization sequence and allocation concealment.

*ISN Academy: **Transplant***

Bleselumab, a novel CD-40 antibody, well tolerated in Phase 2 study in kidney transplantation

Efficacy and safety of bleselumab in kidney transplant recipients: A phase 2, randomized, open-label, noninferiority study

Harland et al. Am J Transplant. 2019 Sep 11. doi: 10.1111/ajt.15591

Population	138 adult standard risk kidney transplant recipients	
Intervention *vs* Comparator	Standard of care (tacrolimus [TAC], mycophenolate [MMF]) vs. Bleselumab + TAC vs. Bleselumab + MMF. Bleselumab 200mg was given on day 0, 7, 14, 28, 42, 56, 70 and 90, then monthly. All participants received basiliximab and corticosteroids.	Time 6 months
Outcomes	At 6 months, bleselumab + TAC was non-inferior to standard of care with respect to biopsy-proven acute rejection (BPAR) (4/44 vs. 3/48; difference in risk 2.8% [95%CI -8.1 to 13.8]). Bleselumab + MMF was inferior to standard of care (17/46 vs. 3/48; difference in risk 30.7% [95%CI 15.2 to 46.2]). In long-term follow up, the risk of BPAR did not differ between the bleselumab + TAC arm and standard of care, although was significantly higher in the bleselumab + MMF arm. There were no additional safety concerns.	

Bleselumab is a novel-antibody directed against CD40, part of the co-stimulatory signal required for T-cell activation. While the authors declare bleselumab+TAC to be non-inferior to standard of care for preventing acute rejection in kidney transplant recipients, the limitations of this study (including small size, lack of blinding and lack of intention-

to-treat analysis) mean that non-inferiority cannot be considered proven. Further studies will be required to define a role for this agent in kidney transplantation.

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

No demonstrable renal benefit to supplementation of vitamin D and fatty acids in an American adult diabetic population

Effect of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function in Patients With Type 2 Diabetes: A Randomised Clinical Trial

De Boer et al. JAMA. 2019;322(19):1899-1909

Population	1312 adults (men >50 years and women >55 years of age) with type 2 diabetes	
Intervention *vs* Comparator	2x2 factorial design- vitamin D_3 (2000 IU/d) and omega- 3 fatty acids (eicosapentaenoic acid 1g/d) vs. vitamin D_3 and placebo vs. placebo and omega- 3 fatty acids *vs* two placebos	**Time** 5 years
Outcomes	There was no difference in change in eGFR from baseline to 5 years in the vitamin D_3 group *vs* placebo (-12.5 [95% CI -13.4 to -11.2] mL/min/1.73m^2 *vs* -13.1 [95% CI, -14.2 to -11.9] mL/min/1.73m^2). Nor was there any difference between the fatty acid group *vs* placebo (-12.2 [95% CI -13.3 to -11.1] mL/min/1.73m^2 *vs* -13.1 [95% CI, -14.2 to -12.0] mL/min/1.73m^2). There was no interaction between study arms (P=0.42). Likewise, there was no significant difference between treatment assignment arms in all three secondary outcomes of composite time to 40% decrease in eGFR/kidney failure/death; time to 40% decrease in eGFR and change in uACR from baseline to 5 years.	

This study cohort failed to demonstrate benefit in the prescription of supplemental vitamin D_3 or fatty acids in preventing or improving renal outcomes in adult diabetics in Northern America.

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

Novel inhibitor slows vascular calcification in patients receiving hemodialysis

Slowing Progression of Cardiovascular Calcification with SNF472 in Patients on Hemodialysis: Results of a Randomized, Phase 2b Study

Raggi et al. Circulation. 2019 Nov 11. doi: 10.1161/CIRCULATIONAHA.119.044195

Population	Maintenance hemodialysis recipients with a coronary artery calcium (CAC) score of 100-3500	
Intervention *vs* Comparator	1:1:1 SNF472 300mg vs. SNF472 600mg vs. placebo; IV thrice weekly	**Time** 52 weeks
Outcomes	Mean change in log CAC volume in the combined SNF472 group was significantly lower than in the placebo group (11% [95%CI 7-15] vs. 20% [95%CI 14-26]; P=0.016). SNF472 also slowed progression of calcification score in the aortic valve, but not in the thoracic aorta. There were no differences in adverse events or discontinuation of allocated treatment.	

Raggi et al. have shown that this novel intravenous formulation of myo-inositol hexaphosphate - also known as phytate; a naturally occurring, but poorly bioavailable, inhibitor of hydroxyapatite formation - holds promise as an inhibitor of vascular calcification in hemodialysis patients. While a relatively high proportion of participants were lost to follow up, sensitivity analyses did not suggest that this affected the outcome. Given the heavy burden of cardiovascular disease in those with ESKD, future studies exploring the effect of SNF472 on clinical outcomes will be welcome.