ISN Trial-List
February 2018

Once a month, the ISN-ACT (Advancing Clinical Trials) team collects and publishes a list of important nephrology trials from the latest medical literature. Each trial is reviewed in context and their risk of bias in seven key areas assessed.

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

Acute Kidney Injury

ISN Academy: *Acute Kidney Injury*

Post-operative administration of mesenchymal stem cells fails to ameliorate post-cardiac surgery AKI

Allogeneic Mesenchymal Stem Cells for Treatment of AKI after Cardiac Surgery

Swaminathan, et al. J Am Soc Nephrol. 2018;29(1):260-267

Bone-marrow derived mesenchymal stem cells (MSC) are hypothesised to encourage repair after injury by localising to damaged tissue and secreting mediators that favour cell division and repair over apoptosis and fibrosis. Swaminathan, et al. aimed to determine if infusion of allogeneic MSC improved time to recovery of renal function in patients with AKI after cardiac surgery, a common complication associated with increased mortality and morbidity. In this randomized double-blind, placebo controlled trial of 156 patients with evidence of early AKI within 48hr of cardiac surgery (defined as >0.5mg/dl [44umol/l] rise in serum creatinine from baseline) were randomised to receive an intra-aortic infusion of MSC or placebo. The median time for creatinine to return to baseline levels was 15 days in the MSC group, versus 12 days in the placebo group (hazard ratio 0.81 (0.53, 1.24); p=0.32). Neither 30-day mortality, dialysis requirement nor adverse events differed significantly. Pre-specified subgroup analysis, including between those with baseline eGFR < or > 60ml/min/1.73m^2 did not show any differential effects. This disappointing result will undoubtedly dampen enthusiasm for MSC therapy in AKI. Despite promising pre-clinical results evidence of efficacy in a clinical setting remains elusive.

Hemodialysis, Hypertension

ISN Academy: *Hemodialysis,* *Hypertension*

A first step towards establishing the optimal blood pressure target in haemodialysis patients.

BP in Dialysis: Results of a Pilot Study

Miskulin, et al. J Am Soc Nephrol. 2018;29(1):307-316

Management of hypertension in hemodialysis patients is controversial. While pre-dialysis blood pressure (BP) is easily obtained, its U-shaped relationship with mortality differs from the linear relationship seen between mortality and home or ambulatory BP. Debate continues as to the optimal measurement to guide treatment. Moreover, no high-quality evidence exists to inform clinicians of the appropriate target BP in these patients. Miskulin, et al. present the results of a pilot study randomising 126 participants with a baseline SBP > 155mmHg to intensive (110-140mmHg) versus standard (155-165mmHg) targets for predialysis systolic BP. In this open-label study, treating clinicians were advised to optimise fluid balance prior to adding additional antihypertensives and angiotensin system blockade was recommended as the first-line pharmacotherapy. A clear separation between the two arms was rapidly achieved and was maintained for the 12 months of the study with the mean difference in SBP from 4-12 months being 12.9mmHg. While no significant differences in adverse events or LV mass were observed, a non-significant excess of vascular access events was noted (incidence rate ratio 3.09 (0.96, 8.78); p=0.06). Also, the authors observed that, while predialysis SBP measurements were available in at least 75% of participants at each timepoint, per-protocol ABPM and home BP measurements were available in only 22-58% or participants at any timepoint. Overall, this study suggests that a randomised study of differing predialysis BP targets is feasible and highlights that important questions surrounding the risks and benefits of different treatment targets remain.

Chronic Kidney Disease, Nutrition and Hydration

ISN Academy: Chronic Kidney Disease, Nutrition and Hydration

Weight-loss and exercise reduce proinflammatory markers in CKD

Metabolic Effects of Diet and Exercise in Patients with Moderate to Severe CKD: A Randomized Clinical Trial

Ikizler, et al. J Am Soc Nephrol. 2018;29(1):250-259

The adverse effects of obesity in patients with CKD may, at least in part, be driven by oxidative stress and a pro-inflammatory state. In a pilot study, Ikizler, et al. sought to test the hypothesis that caloric restriction and aerobic exercise lead to improved body composition and reduced levels of F_2-isoprostane and IL-6 (markers of oxidative stress and inflammation) in patients with CKD. They randomised 111 participants in a 2:2 factorial design to standard of care dietary counselling and usual activity, a specified calorie restricted diet of 10-15% of baseline caloric intake, an individualised aerobic exercise program or both diet and exercise combined. The median (interquartile range) BMI in each of the groups at baseline was 35.5 (30.6, 41.5), 32.8 (28.7, 37.1), 31.0 (28.0, 36.2) and 32.8 (30.4, 35.8) respectively. The cohort was 42% women with a mean age of 60±11 years and mean cystatin-C based eGFR of 41±18.6mg/ml/1.73m^2. After 4 months, both diet groups had a lower BMI compared with no intervention, although this was significant only in the diet and exercise group (diet alone -0.55 (-1.22, 0.12); diet and exercise -0.83 (-1.51, -0.14). The exercise only group did not demonstrate significant change in BMI (0.17 (-0.53, 0.87)). In contrast, both exercise, diet and their combination were associated with significantly reduced levels of F_2-isoprostane and IL-6 versus no intervention. There were no significant changes in peak oxygen uptake compared with no intervention in any of the intervention groups. These results corroborate the known physiological improvements that result from exercise and diet under experimental conditions. The challenge remains to translate these short-term gains into sustainable changes in weight and activity and to demonstrate reductions in clinical events.

R A BP BO CD CR B

Acid-Base Disorders, Chronic Kidney Disease

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

Novel acid binder increased serum bicarbonate but may be hard to swallow for patients

Randomized, Controlled Trial of TRC101 to Increase Serum Bicarbonate in Patients with CKD

Bushinsky, et al. Clin J Am Soc Nephrol. 2018;13(1):26-35

Metabolic acidosis is common in the later stages of CKD and is associated with more rapid progression of kidney disease and adverse effects on both bone and muscle. Current guidelines suggest correction of acidosis (based on moderate evidence of a decline in loss of renal function and improved nutritional parameters), although concern exists regarding the potential for sodium alkalis to promote hypertension and fluid retention. Bushinsky, et al. report the results of a double-blind, placebo-controlled trial of a novel sodium-free oral acid binder (TRC101) in a cohort of 135 patients with CKD and acidosis (mean eGFR 35±13 ml/min/1.73m^2, mean HCO_3 17.7±1.2 mmol/l). Participants received TRC101 (in one of four dosing regimens, up to 4.5g twice daily) or placebo for 14 days while residing in a study facility and receiving a controlled diet. At the end of this period, the mean increase (95% CI) in serum HCO_3 in the treatment groups ranged from 3.2 (2.2, 4.3) to 3.9 (2.9, 5.0)mmol/l compared with placebo. Gastrointestinal side effects, such as diarrhoea (affecting 20% of participants in the treatment arms), were the most common adverse events. While new therapies are often interesting, TRC101 must be considered in the context of existing low-cost sodium alkalis and dietary approaches to correcting metabolic acidosis. The relative merits of this new therapy cannot be known until larger studies with clinical endpoints and standard-of-care comparators become available.

R A BP BO CD CR B