ISN Trial-List

October 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

ISN Academy: Chronic Kidney Disease

Febuxostat does not slow decline in renal function in Japanese RCT

Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial

Am J Kidney Dis. 2018 Aug 31. pii: S0272-6386(18)30834-5

Hyperuricemia is associated with progression of chronic kidney disease (CKD) in observational studies but data from randomized control trials is currently inconclusive. The FEATHER trial assessed whether febuxostat, an inhibitor of xanthine oxidase, was superior to placebo in limiting the rate of decline in eGFR in Japanese patients with Stage 3 CKD (mean eGFR 45ml/min/1.73m^2) with asymptomatic hyperuricemia (>7.0mg/dl [0.42mmol/l]). This multicenter, double-blind, placebo-controlled trial randomized 442 participants to receive either febuxostat (40mg daily) or placebo. Over the 2-year follow-up period, there was no significant difference in eGFR slope between the febuxostat and placebo groups (mean difference 0.70ml/min/1.73m^2 per year (in favour of febuxostat) [95%CI -0.21, 1.62]; P=0.1) or in eGFR at study end (mean difference 0.5ml/min/1.73m^2 (in favour of febuxostat) [95%CI -0.5, 1.6], P=0.3). Subgroup analysis of the eGFR slope suggested a possible benefit in those without proteinuria (mean difference 1.79ml/min/1.73m^2 per year [95%CI 0.55, 3.03]; P=0.005) and in those with a baseline serum creatinine below the group median (mean difference 1.76ml/min/1.73m^2 per year [95%CI 0.44, 3.07]; P=0.009). There was no significant difference in blood pressure or adverse events over the study period. The low rate of CKD progression in this study cohort and the homogenous study population may limit the generalizability of the results. Previous meta-analyses have suggested that uric acid lowering may slow the rate of decline in CKD and so this this important trial adds to a growing – but still inconsistent – body of evidence. A number of studies of uric acid lowering in CKD are ongoing and further results are eagerly awaited.

ISN Academy: Transplant

Are two jabs better than one for transplant recipients?

Immunogenicity and safety of double versus standard dose of the seasonal influenza vaccine in solid-organ transplant recipients: A randomized controlled trial

Mombelli, et al. Vaccine. 2018;36(41):6163-6169

Infectious disease is a common complication of renal transplantation and yet common vaccines may be less effective owing to immunosuppression. An increased dose of antigen is a promising way of boosting response, and efficacy has been demonstrated with a 60ug dose (vs. standard 15ug dose) of influenza vaccine. As the high-dose (60ug) influenza vaccines are only available in North America, Mombelli, et al. compared immunogenicity of double-dose (30ug) vs standard-dose (15ug) influenza vaccine in 79 transplant recipients (63 kidney, 16 liver) from a single centre. Participants were randomized in an open-label fashion to either one (standard-dose) or two simultaneous doses (double-dose) of the 15ug trivalent vaccine. The proportion of vaccine responders (i.e. a 4-fold increase in titre) was not different at 2 weeks in the double-dose group (40% vs. 26%; P=0.174). Both groups demonstrated a significant increase in titre from baseline (for all three strains) that was sustained at 24 weeks, with a trend towards greater increases being observed in the double-dose group. This was associated with greater seroprotection to all strains (i.e. titre > 40) at 4 weeks (88% vs. 69%, P=0.048) but this difference did not persist at 24 weeks (70% vs. 70%). These results are encouraging, but it would appear the study lacked the power to draw a definitive conclusion. In the absence of wider availability of the 60ug dose, larger studies of the double dosing strategy should be considered.

ISN Academy: Hemodialysis, Interventional Nephrology

Small study raises question mark over drug-coated balloon angioplasty in AVF

Drug-Coated Versus Plain Balloon Angioplasty In Arteriovenous Fistulas: A Randomized, Controlled Study With 1-Year Follow-Up (The Drecorest Ii-Study)

Björkman, et al. Scand J Surg. 2018 Sep 5:1457496918798206

Restenosis following angioplasty of arteriovenous fistulas (AVF) is common and results in significant morbidity and cost. Drug-coated angioplasty balloons appear beneficial in observational studies and previous small randomized trials have shown improvements in AVF patency. In this context, Björkman, et al. randomized 39 dialysis recipients with AVF stenosis (excluding anastomotic or central venous stenosis) to drug-coated or standard balloon angioplasty. The majority of AVF were less than one year old. Three participants did not undergo the intervention for technical reasons and two were lost to follow up. At 12-months, fistula occlusion or need for target lesion revascularisation was higher in the drug-eluting balloon group (16/18) than the balloon angioplasty group (4/18) at 1 year (Relative risk 7.09, 95%CI 0.10–6.73; P=0.001). This study has a number of important limitations. Slow recruitment led to termination of the study prior to reaching the target of 140 participants. In addition, there were a number of non-significant, but potentially important baseline differences in lesion length, AVF age and co-morbidity burden which may have favoured simple balloon angiography. Overall, no firm conclusions are possible. Nevertheless, the authors caution that their data raise the possibility that drug-eluting balloons may be harmful, at least in 'young' AVF (less than 1 year old).

ISN Academy: Global Nephrology, Hypertension

Calcium channel blockers may have an edge over thiazides and ACE inhibitors in essential hypertension in Ethiopia

Comparative effectiveness of antihypertensive drugs prescribed in Ethiopian healthcare practice: A pilot prospective, randomized, open label study

Mengesha, et al. PLoS One. 2018;13(9):e0203166

Ethiopia, a country of over 100 million inhabitants, is experiencing a rise in hypertension and associated cardiovascular disease. Patients with African ancestry may be less responsive to beta-blockers and angiotensin converting enzyme inhibitors. To determine if this should affect prescribing in Ethiopia, Mengesha, et al. randomized 141 participants with newly diagnosed essential hypertension (BP ≥ 140/90) to nifedipine 20mg daily, hydrochlorothiazide 12.5mg daily or enalapril 5mg twice daily in an open-label study of the comparative effectiveness of these agents on blood pressure lowering. Dose up-titration, followed by the addition of a second agent was permitted at subsequent follow up visits. After adjusting for age and baseline systolic BP, there was a significant difference in mean reduction in systolic BP among the three drug groups (37mmHg [95%CI 34-40], 32mmHg [95%CI 29-35], 30mmHg [95%CI 27-34]; P=0.009) at 3 months. The mean difference in systolic BP reduction was significantly greater with nifedipine in head-to-head comparison with both hydrochlorothiazide and enalapril (P=0.036 and P<0.003, respectively). There were no significant differences in the need for second agents. Overall however there was no difference in the proportion of participants with controlled BP (95%, 95%, 89%; P=0.46) at 3 months. This pragmatic study suggests that nifedipine may be the preferred antihypertensive in an Ethiopian population – although all agents achieved high rates of BP control. Larger and longer-term studies with clinical endpoints and a cost-effectiveness analysis should be considered.

ISN Academy: Acute Kidney Injury, Peritoneal Dialysis

More evidence in favour of rising tide of peritoneal dialysis in the ICU

Acute Kidney Injury in Critically Ill Patients: A Prospective Randomized Study of Tidal Peritoneal Dialysis Versus Continuous Renal Replacement Therapy

Al-Hwiesh, et al. Ther Apher Dial 2018;22(4):371–379

Continuous veno-venous hemodiafiltration (CVVHDF) is the dominant modality for managing acute kidney injury (AKI) in the intensive care unit (ICU). However use of peritoneal dialysis (PD) is growing, especially in low- and middle-income countries. Few studies are available comparing hemodialysis to PD in the setting of AKI. Al-Hwiesh, et al. randomized 125 ICU participants with AKI requiring renal replacement therapy to CVVHDF or tidal PD. There was no statistically significant differences in baseline demographics or time from ICU admission to start of RRT. The

primary endpoint of 28-day survival (30.2% vs 53.2%, p=0.0028), as well as secondary outcomes including recovery of kidney function (60.3% vs 35.5%, p=0.0056), median time to resolution of AKI (5 days vs. 8 days, p=0.0044) and median duration of ICU stay (9 days vs. 19 days, p=0.0031) were all significantly better in those treated with tidal PD. In addition, infectious complications were seen more often in participants receiving CVVHDF (17.7% vs. 9.5%, p = 0.0036). This striking result suggests that tidal PD can be an effective and safe form of RRT in the ICU setting. However, given the potential for institution-specific factors affecting the outcomes of complex interventions, any conclusion regarding the comparative efficacy of acute PD versus CVVHD must await further multicenter studies.

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

Higher dialysate magnesium lowers serum calcification propensity

The Effect of Increasing Dialysate Magnesium on Serum Calcification Propensity in Subjects with End Stage Kidney Disease: A Randomized, Controlled Clinical Trial

Bressendorff, et al. Clin J Am Soc Nephrol. 2018;13(9):1373-1380

Hemodialysis (HD) patients have a 20-fold higher risk of cardiovascular mortality compared with the general population. A key driver of this may be deranged mineral and bone metabolism and accelerated arterial calcification. Serum calcification propensity (T_{50}) is a novel functional test that reflects the tendency toward ectopic calcification and is associated with long-term cardiovascular morbidity. *In vitro* studies suggest magnesium increases T_{50}, indicating a lower calcification propensity. Bressendorff, et al. conducted a double-blind trial randomizing 59 participants on maintenance HD to receive either 1.0 mEq/l or 2.0 mEq/l (0.5mmol/l or 1mmol/l) dialysate magnesium for 28 days. The intervention resulted in a significant increase in serum magnesium (0.88 mg/dl [95%CI 0.66, 1.10] (0.36mmol/l [0.27, 0.45]); P=0.001) with a parallel increase in the T_{50} (73 min [95%CI 30, 116]; P<0.001). There were no significant changes in serum calcium, phosphate, PTH or bicarbonate and no participants were withdrawn for excessively high magnesium levels (author defined as >4.4mg/dl [1.8mmol/l]). They recorded a numerically larger number of adverse events in the magnesium group (14 vs. 6), although these were not clearly related to elevated serum magnesium. Increasing dialysate magnesium is a simple and inexpensive treatment, however the significance of increasing T_{50} and its effect on clinical outcomes remain to be elucidated. Larger studies are warranted to further explore the potential for dialysate magnesium to improve outcomes for patients on HD.