ISN Trial-List

September 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: Anemia, Iron and Trace Elements, Dialysis, Mineral and Bone Disorder

Iron-based binder may lower FGF-23 levels

Ferric Citrate Decreases Fibroblast Growth Factor 23 and Improves Erythropoeitin Responsiveness in Hemodialysis Patients

Maruyama, et al. Am J Nephrol. 2018;47(6):406-414

Fibroblast growth factor 23 (FGF-23) is a bone-derived hormone that plays a key role in phosphate metabolism. Increased levels are associated with cardiovascular events and reduced survival. This open-label, multicenter study compared the impact of the phosphate binder, ferric citrate, to lanthanum carbonate on FGF-23 levels in 60 patients on hemodialysis. The binder dose was adjusted to achieve target serum phosphate. After 24 weeks, FGF-23 levels were significantly reduced in the ferric citrate group compared to the lanthanum group (mean change from baseline -6,160 vs -1,118 pg/mL; P=0.026). Use of intravenous iron and of erythropoietin stimulating agents (ESA) was also reduced in the ferric citrate group, with median weekly epoetin alpha doses falling from 6000units to 2875units in the ferric citrate group versus 6000units to 4500units in the lanthanum group (P=0.001). There were no significant between-group differences in haemoglobin, calcium, phosphate or PTH. Both treatments were well tolerated, with two participants in the ferric citrate arm having transient loose stools that did not require treatment cessation. Although small, this trial suggests that ferric citrate results in lower intravenous iron and ESA requirements. The significance of the reduction in FGF-23 is unclear, but does support further studies to determine if this translates into improved clinical outcomes.

ISN Academy: Hypertension

Mixed results for electronic medical record-based medication self-management program in hypertension

Effect of Electronic Health Record–Based Medication Support and Nurse-Led Medication Therapy Management on Hypertension and Medication Self-management: A Randomized Clinical Trial

Persell, et al. JAMA Intern Med. 2018;178(8):1069–1077

Better medication self-management may improve outcomes and reduce adverse effects in patients with hypertension. Persell, et al. tested the provision of electronic medical record (EMR)-generated tools (individualized medication plans and drug information sheets) designed to improve medication self-management, with or without nurse-led individualized medication education and review. Twelve primary care centers in a single metropolitan area were cluster-randomized to provide EMR tools, EMR tools plus nurse education or usual care to patients with hypertension and at least three regular medications (for any cause). Of the 920 enrolled participants, 794 completed 12 months of follow-up. Systolic BP was significantly higher in the EMR tools alone group (adjusted mean difference +3.6mmHg [95%CI 0.3, 6.9]; P=0.03 vs usual care) and lower in the EMR tools plus education group (adjusted mean difference -2.0mmHg [95%CI -5.2, 1.3]; P=NS vs usual care, P<0.001 vs EMR tools alone). Both interventions improved agreement between EMR medication lists and patient-reported medication lists. This study highlights the challenges of testing complex interventions: for example, recruitment was slower than expected (leading to an underpowered study) and the authors hypothesize that drug information alone may have discouraged adherence in a minority of participants by highlighting possible side-effects. Overall, further study of medication management improvement and adherence programs remains vitally important.

ISN Academy: Acid-Base Disorders, Chronic Kidney Disease

Bicarbonate therapy may preserve renal function and muscle mass

Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: a randomized controlled trial

Dubey, et al. Nephrol Dial Transplant. 2018 Jul 24. doi: 10.1093/ndt/gfy214

Oral sodium bicarbonate therapy for metabolic acidosis of chronic kidney disease (CKD) has been associated with a slower decline in renal function and may help to preserve muscle mass. Dubey, et al. investigated the effect of treating bicarbonate levels <22mmol/L in a cohort of patients with CKD stage 3-4 comprised predominantly of rural agricultural workers in India with unexplained CKD (believed to be similar to Mesoamerican nephropathy). They randomized 188 participants in an open-label study to oral sodium bicarbonate (targeting a serum bicarbonate of 24 to 26mmol/L) or no bicarbonate therapy for 6 months. At the study conclusion, the lean body mass had improved in the bicarbonate group (mean change 383 g [95% CI 21, 744]) but decreased in the control group (- 378 g [95% CI -686, -70]), resulting in a significant difference between mean lean body mass (36.8 kg [95%CI 36.5, 27.1] vs 36.0 kg [95%CI 35.7, 36.4]; P=0.002). In addition, eGFR improved in the bicarbonate group and declined in the control group, leading to a significant difference in mean eGFR (28.2 ml/min/1/73m^2 [95% 27.0, 29.4] vs 32.7 ml/min/1/73m^2 [31.5, 33.9]; P<0.001). Twice as many participants in the bicarbonate group commenced or increased diuretics (18 vs 35%) and edema and gastrointestinal discomfort were more common. Overall, this provocative study is limited by being open label, single centre and of short duration; however further studies, especially in underserved communities, will be important.

ISN Academy: Glomerular Diseases

Lower doses of mycophenolate may be effective in lupus nephritis

Low dose mycophenolate mofetil versus cyclophosphamide in the induction therapy of lupus nephritis in Nepalese population: a randomized control trial

Sedhain et al. BMC Nephrology. 2018;19:175

Mycophenolate and cyclophosphamide are both acceptable therapy for lupus nephritis with a similar incidence of adverse events. Sedhain, et al. hypothesised that a dose of mycophenolate lower than the 3g/day target dose used in previous trials might also be effective. They randomized 49 participants from a single centre in Nepal with a new diagnosis of biopsy-proven class III-V lupus nephritis to monthly IV cyclophosphamide (0.5-1.0g/m^2) or oral mycophenolate (1-1.5g/day in divided doses). Both groups received oral corticosteroids. At six months, a similar proportion of participants in each arm had reached the primary endpoint of reduction in proteinuria (to <3.5g/day if nephrotic, or by >50% if subnephrotic range) and stabilisation or improvement in creatinine (4/21 cyclophosphamide vs 6/21 mycophenolate; P=0.57), or the secondary endpoint of remission (14/21 vs 14/21). There were no significant between-group differences in eGFR or proteinuria at study end. Adverse events were non-significantly higher in the cyclophosphamide arm (56 vs 15), primarily driven by an excess of alopecia and nausea. This study suggests that a lower dose of mycophenolate may be comparable to cyclophosphamide in some patient populations. However, the limitations of this study (short follow up, lack of blinding, computerized randomization or allocation concealment, and the loss to follow up of 14% of randomized participants) need to be borne in mind. Larger studies with longer follow up will be required.

ISN Academy: Chronic Kidney Disease, Healthcare Policy

Electronic record based identification of CKD patients and associated treatment targets can boost adherence to recommended therapies

Impact of a Primary Care CKD Registry in a US Public Safety-Net Health Care Delivery System: A Pragmatic Randomized Trial

Tuot, et al. Am J Kidney Dis. 2018;72(2):168-177

Many patients with CKD do not achieve treatment targets or receive therapies recommended by evidence-based guidelines. Electronic medical record (EMR) based CKD case identification, facilitating structured team-based care, potentially represents an important way to improve guideline adherence and reduce morbidity and mortality. Tuot, et al. randomized primary care teams (consisting of several physicians, nurses and allied health practitioners) at two

large primary care clinics to receive access to an electronic system automatically flagging patients with CKD, their blood pressure, eGFR, albuminuria and the presence or absence of ACEi/ARB prescription; or to the standard electronic system which did not autonomously collate and highlight this information. The intervention teams also received quarterly feedback on achievement of guideline-based goals such as blood pressure <140/90mmHg and prescription of ACEi/ARB. They followed 746 patients treated by 79 physicians over a 12 month period. Those patients treated by intervention teams had a higher likelihood of being screened for albuminuria (OR 2.44 [95%CI 1.38, 4.29]) and for being prescribed an ACEi/ARB (OR 2.25 [95%CI 1.45, 3.49]). There were no differences in blood pressure between the two groups. This study suggests that the combination of EMR-based care packages for patients with CKD, involvement of non-physicians within a care team and the provision of feedback on guideline compliance may help to optimise care.

Patient self-management program reduces sodium intake in hemodialysis patients

Effectiveness of self-management support in maintenance haemodialysis patients with hypertension: A pilot cluster randomized controlled trial

Huang, et al. Nephrology. 2018;23(8):755-763

Hypertension is common in patients on hemodialysis and is a risk factor for cardiovascular events and mortality. Huang, et al. tested a program encouraging patient self-management aiming at improving blood pressure via home blood pressure monitoring and adherence to medications and fluid and salt restriction. They recruited 90 participants on hemodialysis from a single centre and divided them into two groups by dialysis day and randomly selected which group would receive the intervention – a series of individual and group education sessions using motivational interviewing techniques, including individualized goal-setting and provision of an automated sphygmomanometer. The intervention group had a greater decrease in systolic BP at 1 month (-5.9mmHg [95%CI -11.0, -1.1]; P=0.04), but this difference did not persist at 3 and 6 months. Significant reductions in salt intake (measured by salt-balance formula) were evident at 1 and 3 months, and were near significant at 6 months (-1.6 g/day [95% -3.4, 0.1]; P=0.08). There were no changes in self-reported medication adherence. This small study is limited by size and the lack of a robust randomization method. However, caring physicians were blinded and the improvement in salt intake was large and objectively measured. Similar programs may deserve study in larger and more diverse settings.