ISN Global Trials Focus

September 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	High risk
(A) Allocation concealment	Uncertain risk / not stated
(BP) Blinding of participants/personnel	Low risk
(BO) Blinding of outcome assessment	
(CD) Complete outcome data	
(CR) Complete outcome reporting	
(B) No other sources of bias	

Contents

ISN Academy: Interventional Nephrology, Hemodialysis

Brachial plexus block superior to conscious sedation during endovascular treatment of fistulas

Comparison of Sedoanalgesia Versus Ultrasound-Guided Supraclavicular Brachial Plexus Block for the Prevention of the Pain During Endovascular Treatment of Dysfunctional Hemodialysis Fistulas

Gedikoglu, et al. Cardiovasc Intervent Radiol. 2019 Jul 24.

Population	68 patients undergoing endovascular treatment of dysfunctional hemodialysis fistulas
Intervention *vs* Comparator	Ultrasound-guided supraclavicular brachial plexus block vs. conscious sedation (midazolam and fentanyl) plus local anesthetic at the puncture site
Outcomes	Median visual analogue scale was lower in the plexus block arm (0 [IQR 0-4] vs. 6 [2-10]; P<0.001) and patient and operator satisfaction was also higher with plexus block (97 vs. 3% and 100 vs. 6%, respectively) Hypoxia requiring supplemental oxygen occurred more often in the conscious sedation arm (15 vs. 0%)

This pragmatic, although small, study suggests that – with the appropriate skill and training – ultrasound-guided supraclavicular brachial plexus block may be more effective and possibly safer than conscious sedation during endovascular treatment of haemodialysis fistulas.

Roxadustat holds its own in China, although long-term studies are still needed

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

Chen, et al. N Engl J Med. 2019 Jul 24

Population	305 dialysis recipients receiving erythropoetin therapy	
Intervention *vs* Comparator	Roxadustat vs. Epoetin alpha (2:1 randomization) three times per week and dosed to target Hb 100-120g/l	**Time** 26 weeks
Outcomes	Roxadustat was noninferior to epoetin alpha, with the difference in Hb rise of 2±12g/l (95%CI −0.2 to 5). Hepcidin was lower in the roxadustat arm (-30.2 ng/ml [95%CI −64.8 to −13.6] vs. 2.3 ng/ml [95% CI −51.6 to 6.2]) with no difference in the need for rescue iron or red cell transfusion (3 vs. 1). Adverse events were more common with roxadustat (47 vs 38%), including higher rates of hyperkalemia and upper respiratory tract infection, but blood pressure was lower.	

Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

Chen, et al. N Engl J Med. 2019 Jul 24

Population	154 participants with CKD 3-5 (not on dialysis) and anemia (Hb<100g/l)	
Intervention *vs* Comparator	Roxadustat (3 times/week) vs placebo	**Time** 8 weeks
Outcomes	The mean rise in Hb in the roxadustat arm was 19±12 g/l vs. -4±8 g/l in the placebo group (mean difference 22g/l [95%CI 19 to 26]; P<0.001). Hb rose by at least 10g/l in 84% of the roxadustat group vs. 0% in placebo. Although there was no overall difference in adverse events, hyperkalemia and metabolic acidosis were more common in the roxadustat arm. There was no difference in upper respiratory tract infections.	

Together, these two studies confirm the short term efficacy of thrice weekly roxadustat for anemia of chronic kidney disease in Chinese dialysis and non-dialysis populations. Large comparative efficacy studies are now required to help clinicians choose among the growing options for anemia treatment.

Everolimus lowers incidence of CMV compared with mycophenolate in ECD Kidney transplants but this may be at the cost of more graft loss and acute rejection

Prospective randomized study comparing everolimus and mycophenolate sodium in de novo kidney transplant recipients from expanded criteria deceased donor

Ferreira, et al. Transpl Int. 2019 Jul 6.

Population	171 adult de-novo extended criteria deceased donor (ECD) kidney transplant recipients not treated with CMV prophylaxis	
Intervention *vs* Comparator	Everolimus (EVR) vs. mycophenolate (MPS), both groups received anti-thymocyte globulin induction, corticosteroids and delayed initiation tacrolimus	**Time** 12 months
Outcomes	The risk of CMV infection and disease was lower in the EVR group compared with MPS (13.6% vs 71.6%, p=0.001). The study was halted early as the incidence of rejection (16% vs. 5%, P=0.02), graft loss (11% vs. 1%, P=0.008) and death (10% vs. 1%, P=0.013) was higher in the EVR group.	

According to the authors, limited access to CMV prophylaxis provided the rationale for this interesting study. While everolimus was superior to mycophenolate in lowering the incidence of CMV infection in ECD donor kidney transplants, it may not be a viable alternative owing to a higher incidence of acute rejection, graft loss and death. This data should assist the authors in advocating for greater access to CMV prophylaxis for their patients.

ISN Academy: Anemia, Iron and Trace elements, Dialysis

Iron based phosphate binders lower ESA dose requirements

Randomised clinical trial of ferric citrate hydrate on anaemia management in haemodialysis patients with hyperphosphataemia: ASTRIO study

Yokoyama, et al. Sci Rep. 2019; 9: 8877

Population	93 Japanese hemodialysis patients receiving both phosphate binder(s) and an erythropoiesis-stimulating agent (ESA)	
Intervention *vs* Comparator	Swap to ferric citrate hydrate (FC) vs. continue usual phosphate binder (control); phosphate level controlled within target range (1.13 to 1.94mmol/l)	**Time** 24 weeks
Outcomes	FC reduced the mean ESA dose from baseline to end of treatment. The mean (SD) change in ESA dose was -1212 (3610) IU/week in the FC group vs +1195 (6663) IU/week in the control group (P=0.03). Hemoglobin, phosphate, PTH and intact-FGF23 did not differ between groups. The number of adverse events did not differ, although there were a higher number of cases of diarrhea (7 vs. 1) and withdrawals (8 vs. 1) from the FC group.	

Ferric citrate hydrate was superior to non-iron based phosphate binders in reducing ESA dosage in hemodialysis patients while maintaining control of hyperphosphatemia. However, there was a 25% drop-out rate from the treatment group, suggesting that tolerability may limit its utility in some patients.

ISN Academy: Hemodialysis

Is there a role for intra-dialytic exercise in those doing twice-weekly hemodialysis?

The effect of intradialytic exercise twice a week on the physical capacity, inflammation, and nutritional status of dialysis patients: A randomised controlled trial

Suhardjono, et al. Hemodial Int. 2019 May 17. doi: 10.1111/hdi.12764

Population	120 adult patients performing twice weekly hemodialysis	
Intervention *vs* Comparator	Aerobic exercise vs. combined aerobic and resistance exercise vs. control group. Intradialytic aerobic exercise consisted of cycling, and resistance exercise of ankle weightlifting.	**Time** 12 weeks
Outcomes	Compared to control, lower extremity strength was significantly better in both aerobic and combination exercise groups. KDQOL-SF Physical Component Score (PCS) was also improved in both the aerobic and combined exercise groups but did not change in the control group (median change 4.7, 3.2 and 0, respectively)	

Intra-dialytic exercise (aerobic or combination) may provide some benefits, although the long-term feasibility and effects remain unclear. However, it is useful to see that gains in some aspects of physical function may be achievable with twice weekly sessions.

ISN Academy: Chronic Kidney Disease, Diabetes

Esaxerenone – a novel mineralocorticoid receptor antagonist - reduces albuminuria in Type 2 DM

Effect and Safety of Esaxerenone (CS-3150) for the treatment of Type 2 Diabetes with Microalbuminuria

Ito, et al. Clin J Am Soc Nephrol. 2019;14(8):1161-1172

Population	Type 2 diabetics with microalbuminuria (urine albumin to creatinine ratio of 45-300mg/g creatinine) and eGFR ≥ 30 ml/min.1.73m2 on RAS blockade	
Intervention *vs* Comparator	Esaxerenone (0.625mg vs. 1.25mg vs. 2.5mg vs. 5mg/day) vs placebo	**Time** 12 weeks
Outcomes	Esaxerenone treatment at 1.25, 2.5 and 5mg daily significantly reduced urinary ACR compared with placebo (38%, 50%, 56% vs. 7%; all P <0.001). Systolic blood pressure was lower than placebo by 8-10mmHg in the 2.5mg and 5mg/day groups.	

	Adverse events and discontinuation were similar in the placebo and the lower dose esaxerenone groups (0.625mg, 1.25mg and 2.5mg/day) although were marginally higher in the 5mg/day group. The most common adverse event was hyperkalaemia which was dose related.

This phase 2 study suggests that esaxerenone in addition to a RAS inhibitor further reduces albuminuria however carries a risk of hyperkalaemia at higher doses. Results from phase 3 studies are awaited.

ISN Academy: ***Transplant***

No increased risk of wound-healing complications with immediate start everolimus post-transplant

A 3-month, multicenter, randomized, open-label study to evaluate the impact on wound healing of the early [vs. delayed] introduction of everolimus in de novo kidney transplant recipients, with a follow-up evaluation at 12 month after transplant (NEVERWOUND study).

Manzia et al. Transplantation. 2019 Jun 26. doi: 10.1097/TP.0000000000002851

Population	394 living and deceased-donor renal transplants from 22 centres	
Intervention *vs* Comparator	Everolimus started within 48h of graft perfusion vs. starting everolimus 28 ± 4 days after an initial period of mycophenolate	**Time** 3 months
Outcomes	The 3-month rate of survival free of wound-healing complication (a composite of fluid collection >5cm, prolonged lymphatic drainage, wound dehiscence, wound infection, and incisional hernia) was 0.68 (95% CI 0.62-0.75) in the early start group and 0.62 (95% CI 0.55-0.68) (log-rank test: p=0.56) in the delayed start group. There were no differences in graft outcomes, including rejection, nor in other adverse events.	

This useful study provides reassurance that use of everolimus in the immediate post-transplant period does not lead to an increase in wound complications.

ISN Academy: ***Hypertension, Obstetrics & Pregnancy***

Nifedipine may be superior for the acute management of severe hypertension in pregnancy

Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial

Easterling et al. Lancet. 2019 Aug 1. pii: S0140-6736(19)31282-6

Population	Pregnant women in 2 hospitals, beyond 28 weeks of gestation, with severe gestational hypertension (SBP >160mmhg, or DBP >110mmHg).
Intervention *vs* Comparator	Delayed release nifedipine (10mg dose every 1 hour until response or maximum dose of 30mg) vs. labetalol (200mg dose every 1 hour until response or maximum dose of 600mg) vs. methyldopa (single dose of 1000mg).
Outcomes	The primary outcome of blood pressure control (SBP 120–150 mmHg and DBP 70–100 mmHg within 6h) was most common in the nifedipine group (249 [84%] women), this difference was significant with respect to the methyldopa group (230 [76%] women; P=0.03), but not the labetalol group (228 [77%] women; P=0.05). There was no difference beween the labetalol and methyldopa groups (P=0.80), although rescue medication was required more often in the methyldopa group. While tachycardia and headache were more common in the nifedipine group, than in the labetalol or methyldopa group (15%, 10% and 6%; and 31%, 14% and 17%, respectively). There were no important differences in serious adverse events.

This practical study shows that oral nifedipine (delayed-release) likely to be more effective in the short term control of severe hypertension in pregnancy than oral labetalol or methyldopa.

Cefepime monotherapy an effective strategy to manage CAPD peritonitis

Intraperitoneal Cefepime Monotherapy Versus Combination Therapy of Cefazolin Plus Ceftazidime for Empirical Treatment of CAPD-Associated Peritonitis: A Multicenter, Open-Label, Noninferiority, Randomized, Controlled Trial.
Kitrungphaiboon et al. Am J Kidney Dis. 2019 Jul 19. doi: 10.1053/j.ajkd.2019.05.011.

Population	Adult incident peritoneal dialysis patients with CAPD peritonitis
Intervention *vs* Comparator	Cefepime monotherapy vs. cefazolin plus ceftazidime (continuous IP dosing used in both arms)
Time	28 days
Outcomes	Resolution of peritonitis on day 10 was equivalent: 82.6% and 81% in the cefepime monotherapy and cefazolin plus ceftazidime groups, respectively (90%CI -9.1% to 12.1%, p=0.04 for a 1-sided 95% confidence non-inferiority at a margin of -10%) There were no differences in the rate of complete cure (at 28 days) or need for catheter removal.

Cefepime monotherapy is a reasonable alternative to cefazolin plus ceftazidime combination therapy. This finding may simplify treatment of peritonitis at some centers.