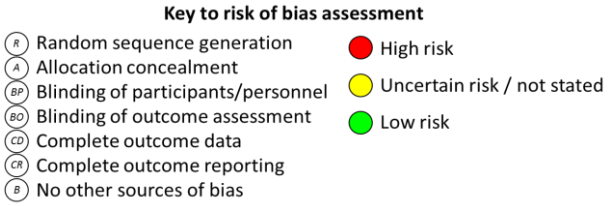
ISN Global Trials Focus

June 2020

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



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*ISN Academy: **Anemia, Iron and Trace elements***

Is higher better? A comparison of haemoglobin targets using darbepoetin alfa in non-diabetic stage 4 and 5 CKD

Darbepoetin Alfa in Patients with Advanced CKD without Diabetes: Randomized, Controlled Trial

Hayashi et al. Clin J Am Soc Nephrol. 2020; 15(5):608-615.

Population	491 Japanese adults with non-diabetic CKD (eGFR 8-20 ml/min/1.73m2) and hemoglobin (Hb) <100g/l
Intervention *vs* Comparator	Darbepoetin alfa targeting a higher Hb (110-130 g/l) vs lower Hb (90-110 g/l) **Time** 74 weeks
Outcomes	• The primary composite kidney end point (starting maintenance dialysis, kidney transplantation, eGFR ≤6ml/min/1.73m2, and 50% reduction in eGFR) was not different between the high and low Hb groups (HR 0.78, 95% CI 0.60 to 1.03) though the risk of a 50% reduction in eGFR was lower in the high compared to low Hb group (HR 0.53, 95% CI 0.33 to 0.85). • There were no differences in the secondary composite cardiovascular endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, hospitalisation for heart failure, hospitalisation for angina, or amputation of lower extremities) (HR 1.07, 95% CI 0.55 to 2.10), all-cause death (HR 1.28, 95% CI 0.56 to 2.90), thrombovascular events (including stroke and myocardial infarction) or malignancy.

This Japanese study in advanced CKD participants without diabetes had theorised that the cardiovascular risk in an Asian population was lower than in Western populations and the potential benefits of a higher Hb target was therefore attractive to prevent CKD progression. They were however unable to show a benefit with higher Hb targets. Separation of the two arms in terms of Hb may not have been sufficient to prove a benefit although the median haemoglobin values in the high and low Hb groups were approximately 114 g/L vs 101 g/L, respectively. Ultimately, further studies of erythropoietin-stimulating agents with pre-dialysis CKD are required to support a higher Hb target for reducing the progression of CKD.

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*ISN Academy: **Acute Kidney Injury***

Nicorandil for prevention of contrast-induced nephropathy

Efficacy of nicorandil on the prevention of contrast-induced nephropathy in patients with coronary heart disease undergoing percutaneous coronary intervention

Zhang X, et al. Coron Artery Dis. 2020 May;31(3):284-288

Population	300 Chinese participants with coronary artery disease undergoing percutaneous coronary intervention	
Intervention *vs* Comparator	Oral nicorandil TDS (starting D1 to D3) plus intravenous fluids vs. conventional therapy (intravenous fluids only)	Time 14 days
Outcomes	• 3.3% (5/150) participants in the nicorandil group, and 10.7% (16/150) in the conventional therapy group had a 25% or ≥ 44.2 umol/L rise in serum creatinine (OR 0.18, 95% CI 0.04 to 0.79). • No significant difference in any of the secondary endpoints.	

Although interesting, larger trials with placebo-matched controls done in a more generalised population would be needed before nicorandil use became common practice.

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*ISN Academy: **Interventional Nephrology***

Ligation of the dorsal branch of the cephalic vein does not improve AV fistula patency

Does ligation of the dorsal branch of the cephalic vein affect the patency of a distal forearm arteriovenous fistula (AVF)? A randomised study.

Zhang H, et al. BMC Nephrology (2020) 21:155

Population	115 patients undergoing surgical establishment of a radiocephalic AVF	
Intervention *vs* Comparator	Dorsal ligation of the dorsal branch of the cephalic vein vs no ligation	**Time** 12 months
Outcomes	• The patency rate did not differ significantly between the two groups. The combined primary patency rates from both groups were 87.6, 82, and 74.5% at 3, 9, or 12 months after the procedure.	

A radiocephalic AVF is the most commonly used vascular access for patients receiving haemodialysis based on its high patency rate and lower incidence of complications. It has been suggested that ligation of the dorsal branch of the cephalic vein may reduce haemodynamic abnormalities and the risk of stenosis in the AVF. This study tested this interesting hypothesis and found that there was no effect on the patency of the AVF within 1-year follow up.

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*ISN Academy: **Chronic Kidney Disease***

Active review of kidney care KPIs improves identification and monitoring of CKD in primary care

Translating CKD Research into Primary Care Practice: a Group-Randomised Study

Litvin et al. J Gen Intern Med 35(5):1435-43

Population	21 primary care practices caring for 107,094 people with group randomisation of 11 practices to intervention and 10 to control arms	
Intervention *vs* Comparator	Quality measure reports, feedback regarding performance, education and strategic advice to improve performance vs quality measure reports only	**Time** 1.5 years
Outcomes	Primary outcome was adherence to 11 CKD quality measures. Greater annual screening for albuminuria in people with diabetes or hypertension absolute change 22% in the intervention group vs -2.6% in the control group p<0.0001) and annual monitoring of people with CKD (absolute change 21% in the intervention group vs -2.0% in the control group, p<0.0001).	

This interesting study demonstrates the power of accountability in the form of constructive advice and education when added to simple provision of performance data. It would be interesting to know whether this effect falls over time through longer duration of follow up.

R A BP BO CD CR B

The resurrection of renal denervation: does a small effect justify the endeavour?

Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial

Böhm et al. Lancet. https://doi.org/10.1016/S0140-6736(20)30554-7

Population	331 participants with unmedicated hypertension.	
Intervention *vs* Comparator	Catheter-based renal denervation involving radiofrequency ablation of the renal arteries and branch vessels vs a sham-control procedure	**Time** 3 months
Outcomes	• Renal denervation resulted in a significant reduction in 24 hour (treatment difference -3.9mmHg, 95% Bayesian Credible Interval [BCI] -6.2 to -1.6) and office measured systolic blood pressure (treatment difference -6.5, 95% BCI -9.6 to -3.5) compared to a sham-control. • No major procedural or device-related safety events were observed in the first 3 months, although data will continue to be monitored for 3 years	

In this well-designed study, catheter-based renal denervation was associated with a significant reduction in 24 hour and office systolic blood pressure compared to a sham procedure. Given that previous renal denervation studies have been limited by the variability of anti-hypertensive regimens, the current study chose to randomise unmedicated hypertensive patients. The procedure appeared safe in the short term with an absence of major adverse events at 3 months. Notably, the blood pressure lowering effect achieved in the study was small and whether this would lead to a clinically meaningful reduction in hypertension-driven vascular events and medication burden for patients remains unclear. Despite the use of a standardised denervation method across centres along with single operators, the success of the procedure in achieving full renal nerve blockage remains a challenge to measure. Enduring effects of the procedure will need to be confirmed after the full three year follow up.