

ISN Global Trials Focus

November 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

| | |
|------------------------------------|-----------------------------|
| Random sequence generation | High risk |
| Allocation concealment | Uncertain risk / not stated |
| Blinding of participants/personnel | Low risk |
| Blinding of outcome assessment | |
| Complete outcome data | |
| Complete outcome reporting | |
| No other sources of bias | |

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ISN Academy: [Hemodialysis](#)

Isometric handgrip exercises improve cephalic vein diameter in Malaysian patients with CKD stage 3 to 4

Effect of isometric handgrip exercise on the size of cephalic veins in patients with stage 3 and 4 chronic kidney disease: A randomized controlled trial.

[Kumar et al. J Vasc Access. 2019 Oct 4:1129729819879314](#)

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|-----------------------------------|--|--------------|
| Population | 36 adults with CKD stage 3 or 4 and distal forearm cephalic vein diameter <2.5mm | |
| Intervention vs Comparator | Daily handgrip exercises (monitored by weekly phone calls) vs no intervention | Time 8 weeks |
| Outcomes | Mean diameter of distal non-dominant forearm cephalic vein increased from week 0 to 8 in the hand exercise (mean difference [MD] 0.39 ± 0.06mm, p<0.05) but remained unchanged in the control group (MD 0.01 ± 0.02mm, p=0.653). Results were similar with tourniquet use. | |
| | Mean handgrip strength from week 4 to 8 improved in the hand exercise group (27.4 to 28.3kg, p=0.001) but remained unchanged in the control group (p=0.22). | |

This small short-term Malaysian study showed that isometric hand exercises increased cephalic vein diameter, which is an important factor in successful AV fistula creation. Whilst the end-of-study mean venous diameter did not reach the often-recommended threshold of 2.5mm, isometric handgrip exercise is an inexpensive strategy that may improve vein diameter, particularly relevant in the management of older incident haemodialysis patients with associated vascular disease. Whether it improves primary AV fistula patency rates and other patient-centred outcomes remain to be proven in larger long-term studies.



Still waiting for evidence to determine the effect of vitamin K on calcification in haemodialysis patients
The effect of vitamin K2 supplementation on vascular calcification in haemodialysis patients: a 1 year follow up randomized trial

[Oikonomaki et al. Int Urol Nephrol. 2019;51\(11\):2037–2044](#)

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|----------------------------|--|----------------|
| Population | 102 adult haemodialysis patients | |
| Intervention vs Comparator | Oral 200 µgr vitamin K2 vs. no treatment | Time 12 months |
| Outcomes | Uncarboxylated MGP (uc-MGP; the inactive form) concentrations were reduced by 47% from baseline in the vitamin K2 group after 1 year (P<0.01) but did not change in the control group. Agatston scores (measuring aortic calcification on abdominal CT) increased in both groups with no significant difference between control and treatment arms. Only 52/102 participants were available for the main analysis | |

Although vitamin K2 supplementation effectively lowered uncarboxylated matrix GLA protein (uc-MGP) suggesting greater availability of the active form, it had no effect on the rate of aortic calcification at 12 months. However this study was limited by a very high drop-out rate and the lack of intention-to-treat analysis. Adequately powered studies are required to address this important question.



Patiromer a promising potassium binder for those needing to stay on spironolactone

Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial

[Agarwal et al. Lancet. 2019;394\(10208\):1540-1550](#)

| | | |
|----------------------------|---|---------------|
| Population | 574 participants with CKD (GFR 25 to 45ml/min/1.73m ²) and uncontrolled resistant hypertension commencing spironolactone | |
| Intervention vs Comparator | Placebo vs. patiromer (8.4g once daily) | Time 12 weeks |
| Outcomes | By week 12, 98/148 (66%) participants in the placebo group compared to 126/147 (86%) in the patiromer group remained on spironolactone (Difference 20% [95%CI 10 to 29; P<0.0001]), with a significant difference in the rate of discontinuation due to hyperkalemia. There was no difference in systolic blood pressure (mean difference -1.0mmHg [95%CI -4.4 to 2.4; P=0.58]). Most common adverse event was gastrointestinal disorder in both groups and only few severe adverse events were reported. | |

Patiromer is an effective oral potassium binder allowing greater use of potassium sparing agents such as spironolactone in treating uncontrolled resistant hypertension. This approach has not yet been shown to result in lower blood pressures. Longer studies are needed.



Is ASK an answer? ASK1 inhibitor may slow progression of diabetic kidney disease

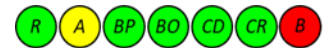
Effects of selonsertib in patients with diabetic kidney disease

[Chertow et al. J Am Soc Nephrol. 2019;30\(10\):1980-1990](#)

| | | |
|----------------------------|---|---------------|
| Population | 334 adults with diabetic kidney disease (CKD stage 3-4) | |
| Intervention vs Comparator | Selonsertib (at 2, 6 or 18mg) vs Placebo (1:1:1:1) | Time 48 weeks |
| Outcomes | No difference in the change in eGFR from baseline (p>0.4 for all pair-wise comparisons). However this was confounded by unexpected acute decreases in eGFR in the intervention group (believed to be due to inhibition of creatinine secretion). In an exploratory post-hoc analysis: between 4-48 weeks the rate of decline of eGFR in the 18mg group was lower than placebo (mean difference 3.1 ml/min/1.73m ² per year [95%CI 0.1 to 6.1; P=0.043]). | |

There was no difference in albuminuria nor in adverse events.

Apoptosis signal-regulating kinase 1 (ASK1) is involved in the progression of chronic kidney disease. This phase 2 study of a selective inhibitor of ASK1 has revealed the possibility of slowing disease progression independent of reduction in albuminuria. However it is early in the development process and further studies are anticipated.



ISN Academy: [Transplant](#)

Everolimus vs. cyclosporine for older recipients of older donor kidneys: many questions remain

Everolimus in de novo kidney transplant recipients participating in the Eurotransplant senior program: Results of a prospective randomized multicenter study (SENATOR)

[Brakemeier et al. PLoS One. 2019;14\(9\):e0222730](#)

| | |
|----------------------------|--|
| Population | 77 de-novo kidney transplant recipients aged over 65 receiving donor kidneys from donors aged over 65 and managed with early steroid withdrawal. |
| Intervention vs Comparator | Induction with basiliximab+cyclosporine (CsA)+ mycophenolate (MPA) (Corticosteroids ceased at week 2); randomized at week 7 to EVR (everolimus)+MPA+two further doses of basiliximab vs. continuing CsA+MPA. Time 6 months |
| Outcomes | Primary outcome of eGFR did not differ at 6 months (-0.72 ml/min [95%CI -5.93 to 4.5 ml/min; P=0.78]). Discontinuation of EVR+MPA due to side effects was common, 27.8%. No patients discontinued in the CsA+MPA regimen (P=0.005). |

This study was stopped early due to slow recruitment and so not powered to determine if EVR is superior to CsA in older recipients managed with early steroid withdrawal. To be randomized at 7 weeks, enrolled participants were required to have a creatinine <265umol/L, no acute rejection > Banff 1A, and no thrombocytopenia or leukopenia. That the majority of those enrolled were eventually excluded from randomization indicates the high risk of complications in this cohort. As seen in other studies, discontinuation of EVR was common due to adverse effects.



ISN Academy: [Hemodialysis](#)

Mid-cut off membranes do increase middle-weight molecule clearance

Comparison of the removal of uraemic toxins with medium cut-off and high-flux dialysers: a randomized clinical trial

[Belmouaz Nephrol Dial Transplant. 2019 Oct 3. pii: gfz189. doi: 10.1093/ndt/gfz189](#)

| | |
|----------------------------|--|
| Population | 40 maintenance hemodialysis recipients |
| Intervention vs Comparator | Cross-over design: 3 months of medium cut-off HD (MCO-HD) then 3 months of high flux HD (HF-HD) or vice versa. Time 6 months |
| Outcomes | Myoglobin reduction ratio was improved (36+/-8% vs. 57+/-13%; P<0.0001), along with greater clearance of other middle-weight molecules such as beta2-microglobulin, prolactin, FGF-23 and protein-bound toxins such as homocysteine. Albumin levels were significantly lower after MCO-HD (36.9+/-4.3 vs. 38.2+/-4.1; P=0.004), as were levels of 25-OH- and 1,25-OH-vitamin D. |

MCO-HD does improve clearance of middle-weight molecules compared to standard high flux membranes, however it remains to be seen whether this has clinically important effects on patient outcomes.

