

# ISN Global Trials Focus

March 2020



The ISN-ACT (Advancing Clinical Trials) team presents a monthly showcase of randomized trials in nephrology from around the world. Featured trials are not just those with the highest impact, but also trials that highlight the diversity of current research in nephrology. Trials are reviewed in context and risk of bias assessed in seven key areas. We hope our efforts will stimulate improvement in trial quality and promote greater engagement in trial activity.

If you are interested in contributing, either by suggesting a trial or joining the team, please send a brief CV to [research@theisn.org](mailto:research@theisn.org).

Join the conversation each month by following us @ISNkidneycare

#### Key to risk of bias assessment

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

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ISN Academy: [Glomerular Diseases](#)

### Less could be more for ANCA-associated vasculitis. The PEXIVAS Trial

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

[Walsh et al. N Engl J Med 2020;382:622-31](#)

<b>Population:</b>	704 patients with severe ANCA-associated vasculitis and renal involvement
<b>Intervention vs Comparator</b>	2x2 factorial design with randomisation to either plasma exchange (PLEX) (7 sessions over 14 days of 60 ml/kg each) or no PLEX (control). Also randomised to either standard-dose oral glucocorticoid regimen or a reduced dose oral glucocorticoid regimen (50% of the standard dose from week 2 to week-18). Patients received cyclophosphamide or rituximab as induction therapy.
<b>Outcomes</b>	Death or ESKD occurred in 100 of 352 patients (28.4%) in the PLEX group and in 109 of 352 (31.0%) with control (HR with PLEX, 0.86; 95% confidence interval [CI], 0.65 to 1.13; P=0.27). Death or ESKD occurred in 92 of 330 patients (27.9%) in the reduced-dose group and in 83 of 325 (25.5%) in the standard-dose group (absolute risk difference, 2.3 percentage points; 90% CI, -3.4 to 8.0; 95% CI, -4.5 to 9.1). There were less serious infection in the reduced steroid group at one year (142 infection in reduced-dose group [27.2%] vs 180 in the standard dose group [33.0%] with an incidence rate ratio of 0.69;95% CI, 0.52 to 0.93)

In patients with severe ANCA-associated vasculitis and renal involvement plasma exchange did not reduce the incidence of death or ESKD. A reduced-dose regimen of glucocorticoids was non-inferior to a standard-dose regimen with respect to death or ESKD.

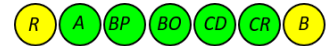


### EMLA cream for AVF intervention pain: can invasive analgesia be avoided?

Lidocaine-Propitocain Cream, a Eutectic Mixture of Local Anesthetics, Effectively Relieves Pain Associated with Vascular Access Intervention Therapy in Patients Undergoing Hemodialysis: A Placebo-Controlled, Double-Blind Crossover Study  
[Aihara et al. Therapeutic Apheresis and Dialysis 2020; 24\(1\):34-41](#)

Population	30 maintenance HD patients with mature AV fistulas undergoing routine fistuloplasty	
Intervention vs Comparator	Topical EMLA applied over area of stenosis vs placebo cream 60-120 mins prior to fistuloplasty. Crossover to alternate arm at next fistuloplasty in three months	Time one fistuloplasty on each treatment ≥3 months apart (cross-over study)
Outcomes	EMLA reduced pain on visual analogue scale (score -/100mm) compared to placebo (47.0 ± 21.1 vs. 68.6 ± 20.7mm; P<0.05) No adverse events occurred in either arm.	

Topical EMLA therapy appears a promising alternative to invasive analgesia in routine care of AVF for HD but will need to be compared against standard of care practices such as local anaesthetic and nerve blocks before its use can be advised more widely. Moreover, its role in the management of urgent access intervention is yet to be elucidated.



### Medium cut-off membranes: short cut to middle molecular clearance?

Comparison of the removal of uraemic toxins with medium cut-off and high-flux dialysers: a randomized clinical trial  
[Belmouaz et al. Nephrol Dial Transplant. 2020;35:328-335](#)

Population	40 maintenance HD patients	
Intervention vs Comparator	Medium cut-off (MCO-HD) vs standard high flux (HF-HD) hemodialysis (HD)	Time 3 months on each treatment (cross-over design)
Outcomes	Clearance of middle molecules was increased with MCO-HD vs. HF-HD, including higher reduction ratios of myoglobin (36±8 vs. 57±13%, P<0.0001), beta2-microglobulin (68±6 vs. 73±15%, P=0.04) and fibroblast growth factor 23 (20±21 vs. 41±22%, P=0.0002). Pre-dialysis levels of beta2-microglobulin (28.4±5.6 vs. 26.9±5.1) and albumin (38.2±4.1 vs. 36.9±4.3 g/L, P=0.004) were lower with MCO-HD. Levels of myoglobin were similar.	

This randomized cross-over study shows that MCO-HD does increase middle molecule clearance. The results of randomized studies of hemodiafiltration suggest that the benefits of increased middle molecule clearance may be modest. Whether MCO-HD leads to meaningful improvements in clinical outcomes will need to be tested in rigorous clinical trials.



### No pre-hydration prior to contrast enhanced CT appears safe in low risk patients with Stage 3 CKD

Effect of No Prehydration vs Sodium Bicarbonate Prehydration Prior to Contrast-Enhanced Computed Tomography in the Prevention of Postcontrast Acute Kidney Injury in Adults with Chronic Kidney Disease. The Kompas Randomized Clinical Trial.  
[Timal et al. JAMA Intern Med. 2020. Feb 17. DOI: 10.1001/jamainternmed.2019.7428](#)

Population	Stage 3 CKD patients undergoing elective, outpatient contrast-enhanced computed tomography	
Intervention vs Comparator	Pre-hydration with 250ml of 1.4% sodium bicarbonate administered over 1 hour vs. no pre-hydration	Time 2 months
Outcomes	The mean increase in serum creatinine at 2-5 days post contrast was 3.0% in the no pre-hydration group vs. 3.5% in the pre-hydration group (mean difference 0.5%; 95% CI -1.3 to 2.3; P <0.001 for non-inferiority).	

There was no significant difference in the number of post-contrast AKI 2-5 days post contrast or in the difference in serum creatinine 7-14 days post contrast between the 2 groups. No patients developed heart failure or required dialysis. There was significant difference in cost between the two groups due to the cost of hydration.

No pre-hydration made no difference to average creatinine values following contrast enhanced CT scan and reduced costs. The risk of contrast nephropathy in this cohort was low, as was the volume of administered fluid. It remains unclear whether hydration with crystalloid fluids improves the outcomes for patients at higher risk.



ISN Academy: [Chronic Kidney Disease, Glomerular Diseases](#)

## Oral prostacyclin analogue not effective in slowing the progression of chronic kidney disease

Effects of Sustained-Release Beraprost in Patients with Primary Glomerular Disease or Nephrosclerosis: CASSIOPEIR Study Results

[Nakamoto et al. Therapeutic Apheresis and Dialysis 2020; 24\(1\):42–55.](#)

Population	885 adults with progressive non-diabetic CKD and macroalbuminuria	
Intervention vs Comparator	Beraprost (oral prostacyclin analogue) 120 µg or 240 µg daily versus placebo (concurrent ACE inhibitor or angiotensin receptor blocker (ARB) in 70-77%)	Time 4 years
Outcomes	<p>There was no difference in the renal composite endpoint of doubling of serum creatinine or ESKD (dialysis, transplantation or serum creatinine ≥ 530 µmol/L) between placebo and beraprost 120 µg (HR 0.98, 95% CI 0.78 to 1.22) or 240 µg (HR 0.91, 95% CI 0.7 to 1.14).</p> <p>There were no between-group differences in blood pressure, albuminuria or adverse events.</p>	

This multicentre RCT in Asia of an oral prostacyclin analogue in advanced proteinuric non-diabetic CKD found no benefit compared to placebo regarding doubling of serum creatinine, ESKD, all-cause mortality or cardiovascular events.



ISN Academy: [Fluid and Electrolytes](#)

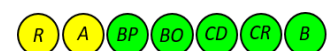
## Let the glucose out to get the sodium up: Could SGLT-2 inhibitors play a role in SIADH?

A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis (SIADH)

[Refardt et al. JASN 2020](#)

Population	88 hospitalised patients with SIADH-induced hyponatraemia (<130 mmol/L)	
Intervention vs Comparator	Empagliflozin 25mg daily vs placebo (in addition to 1L fluid restriction)	Time 4 days
Outcomes	<p>Patients treated with empagliflozin had a higher increase of median plasma sodium concentration compared with placebo (10 vs 7 mmol/L; P&lt;0.04). This treatment effect was more pronounced in patients with lower baseline plasma sodium and osmolality levels</p> <p>In the empagliflozin arm, four patients had a transient decrease in renal function and two had plasma sodium overcorrection (15 and 17 mmol/L within 24 hrs), leading to relaxing of their fluid restrictions.</p>	

This short term study found that empagliflozin resulted in a modest improvement in plasma sodium concentration compared to fluid restriction in patients with SIADH. Given the cost involved compared with fluid restriction alone and the risk of sodium overcorrection, further studies are needed before the true role of SGLT2 inhibitors in this common condition is properly understood.



ISN Academy: [Hypertension](#)

## Diuretics and salt restriction effectively lower blood pressure

Randomized Trial of Distal Diuretics versus Dietary Sodium Restriction for Hypertension in Chronic Kidney Disease

[Bové, D. et al. JASN. 2020 <https://doi.org/10.1681/ASN.2019090905>](#)

<b>Population</b>	26 patients with CKD stage 3 or 4 and hypertension	
<b>Intervention vs Comparator</b>	Combination Amiloride /Hydrochlorothiazide (5mg/50mg) daily vs. dietary sodium restriction to 60mmol/day.	<b>Time</b> 6 weeks (crossover design with 2 weeks on each treatment)
<b>Outcomes</b>	<p>Diuretics had a greater effect on reducing 24-hour SBP (<math>p &lt; 0.01</math>), albeit both had a significant effect. The mean difference in SBP was <math>-14\text{mmHg}</math>; 95% CI <math>-10</math> to <math>-18</math>; <math>p &lt; 0.001</math> for diuretics compared to a mean difference <math>-5\text{mmHg}</math>; 95% CI <math>-1</math> to <math>-9</math>; <math>p &lt; 0.05</math> for sodium restriction.</p> <p>There was no significant difference to albuminuria in either groups. Diuretics had a significantly greater effect on reducing extracellular water. Both reduced eGFR and creatinine clearance but this was greater in the diuretic group.</p>	

Distal diuretics were non-inferior to dietary sodium restriction in lowering systolic blood pressure and extracellular fluid volume in CKD stages 3 and 4. Future studies could focus on the effective implementation of these interventions over time and on their roles in various patient subgroups.

