

ISN Global Trials Focus

April 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.

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: [Hemodialysis](#)

Lower salt, but no sweeter: no effect of lowered dialysate sodium on left ventricular hypertrophy
Effect of Low-Sodium versus Conventional Sodium Dialysate on Left Ventricular Mass in Home and Self-Care Satellite Facility Hemodialysis Patients: A Randomized Clinical Trial
[Marshall et al. J Am Soc Nephrol. 2020 Mar 18. pii: ASN.2019090877](#)

Population	99 maintenance haemodialysis recipients	
Intervention vs Comparator	Dialysate sodium 135mmol/L vs. 140mmol/L	Time 12 months
Outcomes	There was no difference in the primary outcome of left ventricular mass index (LVMI) at 12 months (mean difference -3.94 g/m ² [95%CI -10.52 to 2.63]). Lower dialysate sodium reduced interdialytic weight gain (-0.6kg [95%CI -0.9 to -0.3]) and extracellular fluid (-0.6L [95%CI -1.5 to 0.3]). It also increased the incidence of intradialytic hypotension (OR 7.5 [95%CI 1.1 to 49.8]) at 6 months, although this difference was not significant at 12 months (OR 3.6 [95%CI 0.5 to 28.8]). There were no differences on quality of life, thirst or dietary sodium intake.	

There is no consensus as to the optimal dialysate sodium prescribing practice, although anecdotally there is a trend to towards lower dialysate sodium concentrations (i.e. 136-138mmol/L). The SOLID trial confirms the core of our understanding of the benefits (lower interdialytic weight gain and improved volume status) and risks (increased intradialytic hypotension) of lowering dialysate sodium. The lack of improvement in LVMI may dampen enthusiasm for this intervention; but given the complexity of cardiac pathophysiology in ESKD, lack of change in this surrogate outcome does not exclude benefit (or harm) with respect to clinical endpoints. Further studies are required to

determine whether a general policy of lower dialysate sodium is optimal or if emphasis should shift to some form of individualised prescribing.



ISN Academy: [Fluid and Electrolytes](#)

Keeping it simple with restriction: fluid restriction as good as diuretics and oral salt for SIAD

Efficacy of Furosemide, Oral Sodium Chloride, and Fluid Restriction for Treatment of Syndrome of Inappropriate Antidiuresis (SIAD): An Open-label Randomized Controlled Study (The EFFUSE-FLUID Trial)

Krisanapan et al. *AJKD*. 2020. <https://doi.org/10.1053/j.ajkd.2019.11.012>

Population	92 adult patients with serum Na \leq 130 mmol/L with SIAD (serum osmolality < 275 mOsm/kg, urine osmolality > 100 mOsm/kg, clinical euvolemia, and urine [Na ⁺] > 30 mmol/L)	
Intervention vs Comparator	Fluid restriction alone (FR), fluid restriction and furosemide 20-40mg daily (FR+FM), and fluid restriction, frusemide and NaCl tablet supplementation 3g daily (FR+FM+NaCl)	Time 28 days
Outcomes	The mean increase in serum [Na ⁺] in all three groups was 5 mmol/L at day 4. The day 7 change in serum [Na ⁺] was higher in the FR+FM+NaCl group but at day 28 there was no statistically significant difference in the three groups. The percentage of participants and time to reach [Na ⁺] \geq 130 mmol/L was not different in either treatments. Adherence to FR <1L/day was 79% and to <500ml/day was 43%. Ten patients died of which 9 had underlying malignancy as cause of SIAD with none related to study treatments. There was no significant difference in overly rapid correction of [Na ⁺] (13% in the FR+FM+NaCl group compared to 7% in FR+FM and 6% in FR; P = 0.7). AKI was numerically more common in the FR+FM+NaCl group at 32% compared to 17% and 10% respectively (P = 0.07).	

Fluid restriction alone compared to fluid restriction with frusemide or with frusemide and NaCl supplementation in SIAD has similar efficacy in sodium correction with potentially fewer adverse events (non-significantly lower AKI and overly rapid correction). A further study comparing urea or salt tablets with FR alone would be beneficial.



ISN Academy: [Hemodialysis](#)

Deciding HDF or HD: nothing to lose sleep over

Effect of Hemodiafiltration on Self-Reported Sleep Duration: Results from a Randomized Controlled Trial

Han et al. *Therapeutic Blood Purif* 2020; 49:168-77.

Population	173 adults on chronic haemodialysis (HD) (3-24 months prior to randomisation)	
Intervention vs Comparator	High volume online HDF (post-dilution target convection volume 22L per treatment) versus high flux HD	Time 6 months
Outcomes	There was no difference in self-reported sleep duration in the HDF versus HD groups at 3 or 6 months (6 month mean: 532 \pm 74 min versus 519 \pm 80 min). At 6 months, sleep duration was significant lower on the 1 st shift (6am to 10am) compared to 2 nd shift (10am to 2pm) (mean difference -65 min, p<0.001) and 3 rd shift (after 2pm) (mean difference -69 min, p<0.001). Sleep duration was highest on nights after HD/HDF and lowest on nights before the HD/HDF treatment but there was no difference between HDF or HD for sleep duration in relation to dialysis shift.	

Dialysis recipients tend to have poor sleep compared to the general population, with potential causes including pruritis and restless legs, the effects of fluid overload and acidosis on respiration, and disruption of circadian rhythm due to uremia. This small multicentre RCT in Brazil found no difference in self-reported sleep duration between HDF and HD, and average duration of self-reported sleep exceeded 8 hours per night. However, self-reported sleep duration was not corroborated with objective measurement (eg. actigraphy). Sleep duration was worse before dialysis treatment and before the 1st dialysis shift. The impact of dialysis timing on sleep quality and duration may warrant further investigation as a potentially modifiable means of improving sleep for those patients for whom it is a prominent issue.



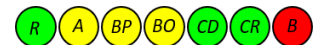
Telbivudine maybe superior to Entecavir for Hepatitis B control in patients with kidney disease receiving glucocorticoid therapy

Potential Effects of Telbivudine Versus Entecavir on Renal Function in Patients with Chronic Hepatitis B Virus Receiving Glucocorticoids Therapy

[Liu et al. Ther Apher Dial. 2020; DOI:10.1111/1744.9987.12839](#)

Population	60 adult patients with chronic hepatitis B and chronic kidney disease receiving glucocorticoid therapy in the management of their renal disease	
Intervention vs Comparator	Telbivudine (LdT) vs Entecavir (ETV)	Time 18 months
Outcomes	<p>No significant changes were observed in the eGFR of patients on ETV therapy compared to baseline, while in patients on LdT therapy, eGFR increased significantly (7.4 and 19.0mL/min/1.73m² at 12 and 18months, respectively; P<0.05 for both). Further analysis of those patients with impaired renal function in the LdT arm of the study revealed significant improvement in eGFR at 12 and 18 months (11.8 and 23.3mL/min/1.73m² respectively; P < 0.05 for both)</p> <p>Serum HBV DNA load decreased significantly at 3, 6, 12, 18 months, compared to the baseline value in both LdT and ETV cohorts (P < 0.05).</p> <p>None of the patients achieved HBeAg loss-seroconversion or HBsAg loss-seroconversion with ETV therapy whilst one patient experienced HBeAg and HBsAg loss seroconversion with LdT therapy.</p>	

This study demonstrated that long term therapy with LdT and ETV have similar efficacy in suppressing viral load, and LdT may confer a better renal protection than ETV in patients with chronic hepatitis B and kidney diseases on glucocorticoids. The heterogeneity of renal diseases and their indication for glucocorticoids limit the interpretation of the eGFR findings in this trial.



ISN Academy: [Anemia, Iron and Trace elements](#)

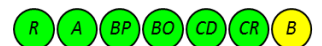
JR-131: bio-equivalent to Darbepoetin Alfa?

JR-131 a Biosimilar of Darbepoetin Alfa, for the Treatment of Haemodialysis Patients with Renal Anaemia: a Randomised, Double Blinded, Parallel-Group Phase 3 Study

[Nishi et al. Ther Apher Dial. 2020. Apr 24 \(2\): 126 – 135.](#)

Population	Haemodialysis patients with stable haemoglobin (Hb) on IV Darbepoetin	
Intervention vs Comparator	IV JR-131 (lower cost biosimilar of Darbepoetin alfa) vs. IV Darbepoetin alfa	Time 24 weeks
Outcomes	<p>The mean change and standard deviation in Hb level was -0.42 ± 0.73g/dL in the JR-131 group and -0.43 ± 0.77 g/dL in the Darbepoetin group. The between group difference was 0.01g/dL which is within the equivalent margin of -0.5 to 0.5g/dL. Similar results were noted in subgroup analysis. Hb levels at each time point remained steady in both treatment groups without any significant difference. There was no significant difference in the total administered dose of JR-131 and Darbepoetin and no difference in the incidence of treatment related adverse events between the two groups.</p>	

This study demonstrates therapeutic equivalence of JR-131 and Darbepoetin alfa with no significant difference in the mean change in Hb between the two groups, at least for a Japanese population.



ISN Academy: [Hypertension](#)

COBRA-BPS study strikes hypertension in rural South Asia

A Community-based intervention for Managing Hypertension in Rural South Asia

[Jafar et al. N Engl J Med. 2020;382:717-26.](#)

Population	2645 hypertensive adults aged >40 in 30 communities in rural Bangladesh, Pakistan and Sri Lanka	
Intervention vs Comparator	Multicomponent, community-based hypertension intervention vs usual care in cluster-randomised design. Total of 30 clusters each cluster consisting of 250-300 households; 15 clusters in each arm.	Time 24 months
Outcomes	<p>Mean SBP fell by 9mmHg (95%CI, 7.7 to 10.4) in the intervention group and 3.9mmHg (95% CI, 2.5 to 5.3) in the control group at 24 months. Controlled BP was achieved in 53.2% of participants in the</p>	

intervention group, as compared with 43.7% in the control group (RR 1.22; 95% CI, 1.10 to 1.35). Diastolic BP was better controlled, antihypertensive use was higher, medication compliance was higher and individuals reported better self-reported health status in the intervention arm vs standard care group. Cost scale-up per patient was \$10.70, \$10.50 and \$4.70 USD per annum in Bangladesh, Pakistan and Sri Lanka, respectively.

This RCT demonstrated a capacity to improve blood pressure control in three rural settings across three different Asian countries, within pre-existing health care infrastructure at relatively low additional cost. Its benefits extended across a broad range of cardiovascular outcomes and serves as a potential model for adaptation in other rural communities.

