# Global Trials Focus

**February 2021**

**The ISN-ACT (Advancing Clinical Trials) team presents this monthly round up of randomized trials in nephrology. Trials are selected not just for impact, but also to showcase the diversity of research produced by the global nephrology community. Each trial is reviewed in context and has a risk of bias assessment. We hope to drive improvement in trial quality and promote greater engagement in trial activity.**

**Key to risk of bias assessment**

- (R) Random sequence generation
- (A) Allocation concealment
- (BP) Blinding of participants/personnel
- (BO) Blinding of outcome assessment
- (CD) Complete outcome data
- (CR) Complete outcome reporting
- (B) No other sources of bias

*High risk*
*Uncertain risk / not stated*
*Low risk*

*Do you agree with our trial of the month? Tell us what you think!*
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## Contents



*ISN Academy: **Glomerular Diseases***

### Short sharp steroid regimen sufficient for SSNS

**Results of the PROPINE randomized controlled study suggest tapering of prednisone treatment for relapses of steroid sensitive nephrotic syndrome is not necessary in children**

Gargiulo et al. Kidney Int. 2021 Feb;99(2):475-483.

(R) (A) (BP) (BO) (CD) (CR) (B)

*Reviewed by Smyth B*


**Summary:** Gargiulo et al. recruited 78 children with a relapse of steroid sensitive nephrotic syndrome (SSNS). All children were treated with corticosteroids to induce remission, after which they were randomised to receive prednisone 40mg/m$^2$ on alternate days for 36 days (short course) or to receive the same cumulative dose in a tapered regimen lasting 72 days (long course). At 6 months, 16/38 (42%) and 23/40 (58%) participants in the short and long arms, respectively, had relapsed. This difference was not significant (P=0.26) and fulfilled the prespecified non-inferiority criteria. No differences in side effects, blood pressure, or body weight were identified.


**Comment:** Unfortunately, relapse of SSNS is common, resulting in repeated exposure to corticosteroids, with profound effects- shorter stature, reduced bone mass and increased weight – which may have lifelong

implications. This study fills an important gap in the literature by providing guidance as to the necessary duration of steroid treatment for relapse and the answer – less is more - will be welcome.

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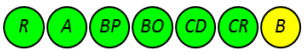
*ISN Academy: **Haemodialysis***

## Clot left unbusted: indeterminate result of rt-PA use as catheter lock

**Substitution of citrate with tissue plasminogen activator (rt-PA) for catheter lock does not improve patency of tunnelled haemodialysis catheters in a randomised trial.**

Richtrova et al. BMC Nephrology(2021)22:41




*Reviewed by Gallagher A*

**Summary** Eighteen incident haemodialysis patients dialysing via tunnelled central venous catheters (tCVC) were randomised to either mid-weekly recombinant tissue plasminogen activator (rt-PA), lock and continuation of trisodium citrate 4% locks with the first and third sessions, or usual care with thrice weekly citrate locks. Due to under recruitment, the authors were unable to analyse their primary endpoint of number of catheter-related blood stream infections (CR BSI) at 6 months post tCVC insertion. There was no significant difference between treatment arms in regards to catheter patency (4 non-functions and 55 malfunctions in the rt-PA arm and 2 non-functions and 46 malfunctions in the citrate arm; p=0.47 and p=0.24, respectively). Mean blood flow achieved did not differ significantly between the groups: 326±1,8 and 326±1,9ml/min (p=0.95) in the rt-PA and citrate groups, respectively.

**Comment:** tCVC patency continues to garner importance as mounting numbers of elderly, vasculopathic patients become dependent on them as their definitive dialysis access. Costliness of rt-PA use is also an important consideration, thus evidence-based used of this agent is required. This single centre study was unable to determine the utility of scheduled rt-PA use in preventing CR BSI due to its lack of power attributable to under recruitment and an unexpectedly low event rate. This may relate to selection bias generated by their exclusion criteria. Regardless, we are left wanting an answer to this important management issue.

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*ISN Academy: **Transplant***

## A step towards personalised immunotherapy dosing using flow cytometry?

**Steering Transplant Immunosuppression by Measuring Virus-Specific T Cell Levels: The Randomized, Controlled IVIST Trial**

Ahlenstiel-Grunow et al, JASN 2021, 32 (2) 502-516; DOI: https://doi.org/10.1681/ASN.2020050645


*Reviewed by Chou A*

**Summary:** Sixty four paediatric kidney transplant recipients were randomised to standard care vs. additional steering of immunosuppressant therapy by measurement of virus-specific T-cell levels (via cytokine flow cytometry). There was no difference in eGFR at 2 years post-transplantation (adjusted mean difference: 1.7; 95% CI, −10.2 to 13.6; *P*=0.77). Everolimus trough and cyclosporine trough levels were lower in the intervention group (Everolimus: 3.5 vs. 4.5 μg/L, *P*<0.001; CysA 67.4 vs. 64.1 μg /L, p<0.001). Less patients in the intervention group received glucocorticoids 2 years after transplant (20% vs. 47%, p=0.04) and there were similar numbers of donor specific antibodies and adverse events.

**Comment:** The IVIST trial suggests that additional virus-specific T-cell level monitoring to steer post-transplant immunosuppression dosing can personalise therapy and decrease immunosuppression exposure without increasing risk of rejection in children. The low numbers had implications on imbalance with baseline demographics, such as difference in eGFR at randomisation (higher in control group). Further studies in an adult population, who may have a higher risk of pre-formed DSAs or immune sensitisation, would be insightful.

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## Systemic anticoagulation using low dose warfarin may increase the longevity of tunnelled central venous haemodialysis catheters

**Randomized clinical trial of low dose warfarin therapy for improving the longevity of permanent arteriovenous catheters**

Saroukhani et al. Annals of Vascular Surgery (2021), http://doi.org/10.1016/j.avsg.2021.11.032

R A BP BO CD CR B

*Reviewed by El-Damanawi R*

**Summary:** Eighty six adult haemodialysis patients undergoing a second tunnelled central venous catheter access insertion were randomly allocated to low dose warfarin (N=43, target INR 1.5-2.0) or a control group (N=43, no treatment). The primary efficacy outcome was a combination of the incidence of catheter thrombosis and the length of time between catheter insertion and subsequent thrombosis. The secondary safety outcome was the incidence of warfarin-related haemorrhage. The results demonstrated that low dose warfarin was associated with greater catheter longevity over a follow period of 12 months (intervention group 8.30±1.75 months versus control group 3.90±1.12 months). Four patients in the interventional group had a post procedure haematomas that resolved with temporary cessation of the drug. No serious warfarin-related haemorrhages occurred.

**Comment:** Several RCTs have explored the role of systemic anticoagulation in the prevention of thrombosis-induced catheter dysfunction. Overall, the evidence is mixed, and current guidelines do not recommend its routine use. Although the current single-centre study did provide evidence for the efficacy of low dose warfarin it has several limitations. Firstly, the authors do not use the standardised definition for catheter dysfunction and there is lack of clarity on how other causes were investigated and ruled out making it difficult to confidently attribute thrombosis as the cause. Furthermore, the incidence rate of catheter failure for each group and the average time after insertion that these occurred is not reported which is a vital outcome for access patency studies. Finally, only the mean dose of warfarin used and not the average INR is reported making it a challenge to deduce whether a clinically meaningful separation in INR was achieved between the groups thereby supporting the biological plausibility of the study findings.

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## Sotagliflozin decreases the risk of cardiovascular events in patients with diabetes and chronic kidney disease

**Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease**

Bhatt DL et al. N Engl J Med 2021; 384:129-139

R A BP BO CD CR B

*Reviewed by Bulanov N*

**Summary:** 10584 patients with type 2 diabetes mellitus (glycated hemoglobin of ≥7%), chronic kidney disease (estimated GFR 25 to 60 ml/min/1.73 $m^2$), and age-stratified cardiovascular risk factors were to receive sotagliflozin or placebo. There were no statistically significant differences in the baseline characteristics of the two groups. The median eGFR was 44.5 (37.0; 51.4) ml/min/1.73 $m^2$. The revised primary end point was total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. The rate of primary end-point events was significantly lower in the sotagliflozin group than in the placebo group: 5.6 vs. 7.5 events per 100 patient-years, respectively (HR 0.74; 95%CI, 0.63 – 0.88; P<0.001). The rate of deaths from cardiovascular causes per 100 patient-years was similar in the sotagliflozin and the placebo groups (HR 0.90; 95% CI, 0.73 to 1.12; P = 0.35). Adverse events were significantly more common in patients treated with sotagliflozin than in those who received placebo.

**Comment:** In this large multinational trial, Bhatt et al showed that SGLT-2 inhibitor sotagliflozin decreased the rates of cardiovascular events (CVE) in patients with diabetes mellitus and chronic kidney disease, which both are significant risk factors for CVE. In addition, the trial didn't require the patients to have high albumin-to-creatinine ratio to be included (median urinary albumin-to-creatinine ratio 74mg/g [17; 481]) thus broadening the generalisability of these finding for those with early or less severe CKD. However, the premature cessation of the

trial and the change of primary outcomes could potentially bias the results in favour of sotagliflozin. Further studies with longer follow up and potentially narrower spectrum end points will help to assess the role of SGLT-2 inhibitors in CVE prevention.

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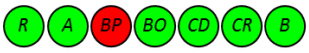
*ISN Academy: **Fluid and Electrolytes***

## Correcting hyponatraemia- rapid intermittent bolus or slow continuous infusion?

**Substitution Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients with Symptomatic Hyponatraemia-SALSA trial**

Baek et al. JAMA Intern Med. 2021;181(1):81-92


*Reviewed by Yeung W*

**Summary:** A prospective, investigator-initiated, multi-centre, open-label, randomized clinical trial. 178 participants were randomised to rapid intermittent correction (n=87) or slow continuous correction (n=91) with hypertonic saline in patients with symptomatic hyponatraemia (serum Na <125mmol/L). There was no difference in the primary outcome of incidence of overcorrection (rise in sNA >12mmol/L within first 24hr or >18mmol/L within 48hr). No significant differences between the groups were observed in symptoms at 24 and 48 hours after treatment initiation or rate of correction. The rapid intermittent group showed lower incidence of relowering treatment (absolute risk difference, −15.8% [95%CI, −30.3%to −1.3%]; P = 0.04).

**Comment:** This is the first RCT comparing two methods of administering hypertonic saline for hyponatraemia; a common clinical problem. Both appear to be safe and effective, with no difference in risk of overcorrection. Rapid intermittent correction may have the slight advantage of lower incidence of therapeutic relowering treatment, although the preferred treatment will likely remain centre-dependent.

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*ISN Academy: **Hypertension***

## Hypertension management from a social distance

**Home and Online Management and Evaluation of Blood Pressure Monitoring (HOME BP) using a digital intervention in poorly controlled hypertension: randomised controlled trial**

McManus et al. BMJ 2021;372:m4858


*Reviewed by De Souza L*

**Summary:** 622 patients were recruited from general practice with poorly controlled hypertension (mean BP >140/90 but <180/110 and taking ≤ 3 antihypertensive medications). 305 were randomised to digital intervention for management of their blood pressure. Compared with usual care, at 12 months the intervention was associated with a reduction of −3.4 mmHg in systolic blood pressure (95% confidence interval −6.1 to −0.8) and −0.5 mmHg in diastolic blood pressure (−1.9 to 0.9). The effect was greatest on younger patients (<67 years) with fewer comorbidities. Adverse effects were similar between groups. Patients with chronic kidney disease stage IV-V, postural hypotension (>20mmHg systolic drop) or hypertension not previously managed by their general practitioner were excluded.

**Comment** Home blood pressure monitoring is a useful aid in decision making, particularly in this era of telehealth. This study method utilised email-based communication to facilitate accurate and timely review of persistent hypertension. Hence ready access to the internet was a major selective factor. Reduced face to face interaction with health care professionals is potentially convenient, but loss of opportunistic general health checks may be detrimental – especially as the optional lifestyle online modules in the program were taken up by less than one third of participants. It would be useful to see longer term outcomes of these study groups to justify short term costs (particularly equipment) for long term benefits such as reduction in cardiovascular and renal disease.

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