











# Global Trials Focus

June-July 2023

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

-  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 

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

@ISNeducation 

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**ISN-ACT Clinical Trials Toolkit**

[www.theisn.org/isn-act-toolkit](http://www.theisn.org/isn-act-toolkit)

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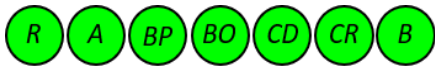
Contact us at [research@theisn.org](mailto:research@theisn.org)

ISN Academy: [Dialysis](#)

## A CONVINCING trial for Hemodiafiltration

### Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure

[Blankestijn et al., N Engl J Med. \(2023\).](#)



Reviewed by Michele Provenzano

**Summary:** In the pragmatic CONVINCING trial, 1360 adult participants who had been receiving high-flux hemodialysis for at least 3 months were randomized to either high-dose hemodiafiltration (n=683) or high-flux hemodialysis (n=677) for a median follow-up of 30 months. The average convection volume in the high-dose hemodiafiltration group was 25.3 liters per session. The primary outcome of death from any cause occurred less often with hemodiafiltration, occurring for 118 participants (17.3%) in the hemodiafiltration group and in 148 participants (21.9%) in the hemodialysis group (hazard ratio, 0.77; 95% confidence interval [CI], 0.65 to 0.93; P=0.005). Secondary outcomes, including death from cardiovascular causes, the composite outcome of fatal or nonfatal cardiovascular outcomes, and the risk of recurrent hospitalization were similar between groups. Death due to infection was reduced in the hemodiafiltration group.

**Comment:** Hemodialysis and hemodiafiltration are two currently used methods for patients with kidney failure requiring replacement therapy. Haemodialysis relies on the process of 'diffusion' to remove waste molecules. Hemodiafiltration is similar in that it uses the process of diffusion, but it also uses 'convection' which involves the removal of large volumes of fluid via ultrafiltration and replacement with substitution fluid. The mechanisms of benefit are not certain, but adding convection may result in increased removal of larger uremic toxins such as urea and  $\beta_2$  microglobulin, better hemodynamic stability, and reduced endothelial dysfunction. The CONVINCING trial supports a lower risk of death from any cause among patients treated with high-dose hemodiafiltration than those receiving conventional high-flux hemodialysis. While this pragmatic trial achieved high convection volumes of 25.3L/session (which has not been possible in previous studies), the generalizability of the results may be reduced by the relatively young population (mean age 62.5 years) and a very high percentage (>80%) of arteriovenous fistulas. Moreover, hemodiafiltration can be an expensive procedure, and treatment effectiveness with cost-utility need to be

balanced. Additional data on patient-reported outcomes and cost-effectiveness from the trial are expected and would be important when considering implementation of the intervention. The High-Volume Hemodiafiltration vs. High-Flux Hemodialysis Registry (H4RT) study which is presently underway in the UK will provide further insight into the debate of high dose hemodiafiltration versus high-flux hemodialysis ([link here](#)).

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ISN Academy: [Transplant](#)

## Prophylaxis or pre-emptive valganciclovir therapy in kidney transplant recipients: the ongoing debate?

### A randomized trial of valganciclovir prophylaxis versus preemptive therapy in kidney transplant recipients

[Reischig et al, JASN 34: 920-934, \(2023\).](#)



Reviewed by *Maria Chiara Pelle*

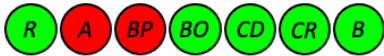
**Summary:** This open-label, single-center trial compared valganciclovir prophylaxis versus pre-emptive therapy in 140 kidney transplant recipients on triple immunosuppression (tacrolimus, mycophenolate mofetil and corticosteroids) at high risk of cytomegalovirus (CMV) as defined by donor (D) and recipient (R) CMV serologic combinations of D+R-, D+R+, or D-R+. Participants were randomized 1:1 to valganciclovir prophylaxis (900mg daily for 3 months, or 6 months if D+R-) or pre-emptive therapy (weekly CMV DNA PCR testing for 4 months after transplantation, then monthly for 12 months thereafter; on detection of CMV DNAemia >1000IU/ml, valganciclovir was started at 900mg BD until two consecutive negative PCR tests a week apart). At 12 months, there was no significant difference between the prophylaxis and pre-emptive groups in incidence of acute rejection (13%, 9/70 versus 23%, 16/70, P=0.112 [HR, 0.52, 95% CI, 0.23 to 1.19]). Three-month protocol biopsy performed in 134 participants showed less frequent subclinical rejection in participants in the prophylaxis group (13% versus 29%, P=0.027). CMV disease did not occur commonly in either group (4% vs 4%, P=0.974). In the pre-emptive group, there was a higher incidence of CMV DNAemia (75% versus 44%, P<0.001), with a higher proportion that had a high CMV load (>2000IU/ml) and a longer duration of CMV DNAemia (42 versus 25 days, P=0.002). Participants in the pre-emptive group had fewer episodes of neutropenia, but there was no difference in severe neutropenia needing granulocyte colony stimulating factors.

**Comment:** CMV infection is a common opportunistic infection in kidney transplant recipients which can cause 'direct effects' such as bone marrow suppression or tissue-invasive CMV disease, but also 'indirect effects' such as acute and chronic allograft rejection, increased susceptibility to other opportunistic infections and new-onset diabetes. It is postulated that CMV stimulates HLA expression on endothelial kidney cells and thus increases the risk of T-cell and antibody mediated rejection, which may eventually lead to chronic allograft dysfunction. Preventing direct CMV effects may prevent downstream indirect effects such as acute rejection, which is what this trial is aiming to assess by examining the efficacy of CMV prophylaxis vs pre-emptive therapy in reducing acute rejection as its primary outcome. In this trial, however, there were no significant differences of acute rejection within 12 months between valganciclovir prophylaxis and pre-emptive groups, but there was a lower risk of subclinical rejection at month 3 and a lower incidence of CMV DNAemia in the prophylaxis group. By using an 'indirect' measure as the primary outcome, this trial highlights the need to rigorously evaluate surrogate endpoints and ensure they are clinically meaningful. This study is further limited by its single-center and small sample size, reducing its generalizability. Longer follow-up studies, a better definition of the endpoints (both direct and indirect effects of CMV in the transplant population), and how the intervention may impact these endpoints is needed.

## Forewarned or forearmed: do automated medication-targeted alerts improve AKI outcomes?

### A randomized clinical trial assessing the effect of automated medication-targeted alerts on acute kidney injury outcomes

[Wilson et al, Nature Communications, 14, 2826, \(2023\).](#)



Reviewed by *Nikolay Bulanov*

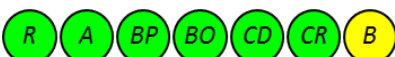
**Summary:** In this parallel-group, pragmatic, open-label trial, 5060 hospitalized adults with acute kidney injury (AKI) who received non-steroidal anti-inflammatory drugs (NSAIDs), renin-angiotensin-aldosterone system inhibitors (RAASi) and/or proton-pump inhibitors (PPIs) were randomized to the intervention, a “pop-up” electronic alert embedded within the electronic health record to prompt the healthcare provider to consider the discontinuation of the aforementioned potentially nephrotoxic medications, or usual care (n=2528). A medication of interest was discontinued within 24 hours of randomization in 61.1% participants of the alert group versus 55.9% participants of the usual care group (Relative Risk [RR] 1.08, 1.04 –1.14, P<0.001). However, there was no significant difference in the primary composite outcome of progression of AKI, dialysis, or death within 14 days, which occurred in 585 (23.1%) of participants in the alert group and 639 (25.3%) participants in the usual care group (RR 0.92, 0.83–1.01, P = 0.09). Of note, in the PPI subgroup, alerts were associated with a significant decrease in the relative risk of the composite outcome (RR 0.88, 0.79-0.98, P=0.02). The discontinuation of these three medications did not result in any significant worsening in the safety outcomes.

**Comment:** Current best practice guidelines suggest avoiding potentially nephrotoxic medications in patients with AKI, however the rate of their discontinuation in real-life practice is lower than expected. In this large RCT, automated medication-targeted electronic alerts increased discontinuation rates of common potentially nephrotoxic medications, but this did not improve outcome of progression of AKI, dialysis, or death. However, in a subgroup of patients receiving PPI, there was clinical improvement in the composite outcome. The results of the trial should be interpreted with caution because of the limited number of targeted medications and the open-label design meant that AKI alerts were 3randomized at the patient level, not facility level, thereby increasing risk of contamination between providers who received alerts. Like previous clinical decision support studies in this field which have shown mixed results, the current trial does not indicate broad-based benefits of electronic alerts to patients with AKI. Nevertheless, the effect of PPI discontinuation in an AKI setting should be reassessed in future studies.

## Not so MAGiCAL: magnesium supplementation may not decrease vascular calcification in CKD patients

### The Effect of Magnesium Supplementation on Vascular Calcification in CKD: A Randomized Clinical Trial (MAGiCAL-CKD)

[Bressendorf et al., JASN 34 : 886–894, \(2023\).](#)



Reviewed by *Anastasiia Zykova*

**Summary:** In this double-blinded trial, 148 adult participants with chronic kidney disease (CKD, median eGFR 25ml/min/1.73m<sup>2</sup>) were randomized to receive either oral slow-release magnesium hydroxide twice daily (Mablet 360 mg BD, equivalent to 30mmol of elemental magnesium per day), or placebo for 52 weeks. Despite a significant increase in plasma magnesium and high adherence to the study medication, magnesium supplementation did not result in a significant between-group difference in the coronary artery calcification (CAC) score at week 52 adjusted for baseline CAC score, age and diabetes (0.9%, 95% CI -10.2% to 13.4%, P=0.44). In fact, the CAC score increased by 33.3% (95% CI, 19.9% to 48.2%) in the intervention group and 31.2% (95% CI, 18.5% to 45.2%) in the placebo group over the study period. In addition, there was a higher incidence of major cardiovascular events including sudden cardiac death, stroke, and incident heart failure

in the intervention arm compared to placebo (6 vs 0), as well as gout (6 vs 1). Almost 50% of participants randomized to magnesium supplementation also had gastrointestinal-related adverse events, compared to 12% in the placebo group.

**Comment:** Animal CKD models have shown promising results regarding the use of magnesium to prevent vascular calcification, with a previous RCT in patients with CKD and cardiovascular risk factors showing that magnesium supplementation slowed progression of CAC ([link here](#)). It is hypothesized that magnesium supplementation reduces platelet aggregation and retards inflammation and oxidative stress. In this trial however, magnesium supplementation did not slow the progression of CAC after one year despite significant increase in plasma magnesium and high adherence (97% of participants taking more than 95% of the study drug). This trial is limited by the fact that it did not reach planned sample size (n=250) due to slow recruitment, and so the trial may have been underpowered to detect any difference in the CAC scores between the groups.

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*ISN Academy: [Chronic Kidney Disease](#)*

### Self-educational materials can decrease dietary salt intake in CKD patients

Evaluation of a simple low-cost intervention to empower people with chronic kidney disease to reduce their dietary salt intake: OxCKD1, a multi-center randomized controlled trial

[O'Callaghan et al., Kidney360, \(2023\).](#)



*Reviewed by Anastasiia Zykova*

**Summary:** In this trial, 193 adult participants with CKD (eGFR >20ml/min/1.73m<sup>2</sup>) were randomized to 1 month of the OxSalt care bundle intervention or one month of routine care, with extended follow up for a further 11 months where all participants resumed routine care. The intervention care bundle ([available here](#)) is guided by three principles that empowered participants to understand the health benefits of reducing salt intake, how to evaluate salt content in food, and how to prepare appetizing low salt food. The intervention involved a set of self-paced self-explanatory slides on a tablet which the participants viewed at their baseline visit, practical written information which was taken home, and a series of automated pre-programmed emails and text messages around the same themes over the one-month active phase. After one month of the intervention, the mean change in 24-hour sodium excretion from baseline was -32.4 (±49.7) mmol/day for the intervention group versus -6.28 (±46.2) mmol/day for the control group (P<0.001), equating to a salt reduction intake of -1.9 (±2.9) g/day and -0.4 (±2.7) g/day, respectively. The benefits of the intervention persisted beyond the one-month, with sodium excretion reduced from baseline at 11 months post intervention (-16.9 ± 49.1 mmol/day; P=0.03), while there was no change in the control group (0.1 ± 36.6 mmol/day; P=1.0). Additionally, there was a mild reduction in diastolic blood pressure at one month (71.9mmHg vs 74.3mmHg, p=0.04), but no significant change in systolic blood pressure, proteinuria or eGFR between the groups.

**Comment:** Salt reduction is important in patients with CKD as it has been shown to reduce blood pressure and albuminuria. However, there is paucity of evidence about how this can be practically translated at the patient level. This trial aimed at empowering people with CKD to reduce their salt intake and the OxSalt bundle was developed with input from the patients themselves. The aim was to develop a cheap and simple intervention that could be incorporated into regular routine. The significant reduction in dietary salt intake of 1.9g after 1 month, with effects still present after 11 months is promising. Further studies could assess the economic costs of the implementation of this bundle, and consider the impact of implementing an annual reminder.

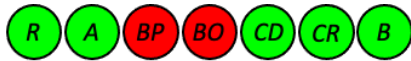
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*ISN Academy: [Dialysis](#)*

## Structured goal-setting feedback in addition to a wearable Fitbit increased step count in hemodialysis patients

### The Impact of a Wearable Activity Tracker and Structured Feedback Program on Physical Activity in Hemodialysis Patients: The Step4Life Pilot Randomized Controlled Trial

[Malhotra R, et al. Am J Kidney Dis. 82\(1\):75-83 \(2023\).](#)



*Reviewed by Megan Borkum*

**Summary:** In this single-center 12-week pilot trial, 55 maintenance hemodialysis (HD) participants were randomized 1:1 to a Fitbit wearable activity tracker with regular structured feedback intervention versus the wearable activity tracker alone. All participants were instructed to wear the activity tracker on their non-access arm throughout the day, other than during bathing. All participants received training for online applications and websites to monitor step count as well as physical activity education. Participants in the intervention arm also received weekly 15-20 minutes face-to-face goal-setting counselling sessions by a healthcare professional using personalized data on weekly steps achieved. The mean daily step count at baseline was similar between the groups (intervention arm: 3704 steps/day vs comparator arm: 3,808 steps/day). The intervention of structured feedback significantly increased daily step count from baseline to week 12 compared with the comparator group ( $920 \pm 580$  vs  $281 \pm 186$ ;  $P < 0.05$ ). The effect of the intervention was maintained in all subgroups evaluated; however, the effect was greatest in the first 4 weeks of the intervention, in younger participants ( $< 65$ ) and in those participants without heart disease or severe anemia.

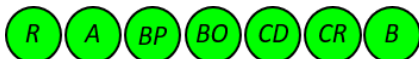
**Comment:** Patients on maintenance hemodialysis have lower levels of physical activity and this is strongly correlated with mortality. Increasing exercise tolerance and levels of physical activity may improve frailty and sarcopenia, and prevent functional decline, reduced life participation, health care costs and mortality. This trial suggests that the application of wearable technologies to obtain activity data, with additional sessions sequentially informing patients quantitatively about their levels of physical activity and their progress toward achieving their individual exercise goals, can meaningfully increase step count in patients receiving hemodialysis, by nearly 17%. Limitations of this study include that it was a single-center trial with small sample size and no long-term adherence or health outcome data. Future larger, longer-term studies are needed to evaluate if the impact of this intervention can be sustained and the effect of an increased step count on morbidity and mortality.

*ISN Academy: [Dialysis](#)*

## Low dialysate sodium concentrations (dNa 135mmol/L) are associated with reduced interdialytic weight gain in children and young adults on maintenance hemodialysis

### Low dialysate sodium in children and young adults on maintenance hemodialysis: a prospective, randomized, crossover study

[Caporale, O et al, Pediatric Nephrology, 38\(5\):1599-1607.](#)



*Reviewed by Rupesh Raina*

**Summary:** In this single-center, prospective, crossover trial, the impact of low dialysis fluid sodium concentration (dNa) on interdialytic weight gain (IDWG) and blood pressure (BP) was investigated among a cohort of 15 pediatric participants undergoing maintenance hemodialysis on antihypertensive medication. Participants were administered two distinct treatments in a randomized sequence: a 'standard' dNa of 138 mmol/L and a 'low' concentration of 135 mmol/L. Each phase lasted four weeks, preceded by a two-week washout period, where hemodialysis was conducted with the same dNa as the upcoming phase, but no data was collected during this time. Treatment with 'low' dNa resulted in a significantly decreased median IDWG as a percentage of dry body weight (IDWG%) compared to 'standard' dNa ( $2.12 \pm 1.39\%$  vs.  $2.77 \pm 1.53\%$ ,

P=0.008). This was an absolute IDWG of  $0.97 \pm 0.71$  kg with 'low' dNa and  $1.27 \pm 0.73$  kg for 'standard' dNa ( $p=0.009$ ). Pre-HD systolic and diastolic BP were no different between the two treatment groups. A first-hour refill index which is indicative of pre-hemodialysis volume overload in pediatric patients was found to be significantly lower during treatment with 'low' dNa ( $1.65 \pm 0.77$  ml/kg/hr/% vs  $2.27 \pm 1.06$  ml/kg/hr/%,  $P=0.018$ ). There was no difference in the incidence of adverse intradialytic events necessitating intervention between the groups, including for cramps, vomiting, or hypotension.

**Comment:** Adult populations have consistently shown a correlation between high dialysate sodium concentrations and increased blood pressure, interdialytic weight gain, and even mortality rates. However, these findings cannot be directly applied to the pediatric populations due to the distinct etiologic characteristics, comorbidities, and treatment needs of hypertensive children and young adults undergoing regular hemodialysis. While this was a single center study with small sample size and short-term design, it nonetheless provides valuable insights into a less-explored area of dialytic research highlighting the beneficial effect of a low dNa on IDWG without any difference in adverse events in the pediatric and young adult population. The strength of the study is further reinforced by its prospective, randomized, crossover design. Future longitudinal studies conducted across multiple centers would improve the generalizability of these findings, and the effect of lower dNa on BP may be better delineated.

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*Edited by Daniel O'Hara, Michele Provenzano, Neeru Agarwal and Anastasiia Zykova*