











Global Trials Focus

May 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

-  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 

Want to run your own trial?
ISN-ACT Clinical Trials Toolkit
www.theisn.org/isn-act-toolkit

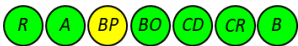
Would you like to write your own reviews?
Join the GTF team.
Contact us at research@theisn.org

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

HIF-stabiliser fails non-inferiority test vs darbepoetin

Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD

Chertow et al., *N Engl J Med* 2021;384:1589-600. DOI: [10.1056/NEJMoa2035938](https://doi.org/10.1056/NEJMoa2035938)



Reviewed by Zykova A



Summary: This pooled analysis of two phase 3, open-label noninferiority trials examined the efficacy and cardiovascular safety of vadadustat compared with darbepoetin alfa in patients with non-dialysis dependent chronic kidney disease, combining trials in 1751 treatment-naive patients and 1725 previously treated with erythropoietin-stimulating agents (ESA). Overall, the hazard ratio for major cardiac adverse event (MACE) was 1.17 (95% CI, 1.01 to 1.36), which did not meet the prespecified noninferiority margin of 1.25. With regard to the components of MACE, death from any cause occurred in 319 patients (18.3%) in the vadadustat group and in 307 (17.7%) in the darbepoetin alfa group; nonfatal myocardial infarction in 67 (3.9%) and 48 (2.8%), respectively; and nonfatal stroke in 34 (2.0%) and 28 (1.6%), respectively. The changes in hemoglobin were similar in both trials and between study arms.

Comment: Treatment of anemia with ESAs reduces the need for blood transfusion but increases the risk of cardiovascular events when hemoglobin levels in the near-normal range are targeted. Vadadustat is an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor, which stabilizes HIF and stimulates endogenous erythropoietin production. Previous studies have shown them to be similarly efficacious to ESA in the treatment of anaemia. This study provides long-awaited cardiovascular data and, while HIF-stabilisers are attractive given their oral administration, lower production costs, high stability and low immunogenicity, this result raises important questions about their safety compared to the current standard of care in those with CKD not yet on dialysis.

Vadadustat for anemia in dialysis requiring CKD patients, an “INNO2VATive” alternative to erythropoietin stimulating agents.

Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis.

[Eckardt et al. N Engl J Med 2021;384:1601-12](#)



Reviewed by Twining M and Franca Gois P

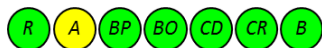
Summary: The INNO2VATE trials were two phase 3 randomized, open-label, non-inferiority trials comparing vadadustat versus darbepoetin alfa for safety and efficacy in the treatment of anemia in dialysis-dependent chronic kidney disease (DD-CKD) patients. The two trials were of incident and prevalent DD-CKD and accrued 3923 participants. The primary safety end point was first occurrence of major adverse cardiovascular events (MACE) and pooled results found a first MACE occurred in 355 patients (18.2%) in the vadadustat group and in 377 patients (19.3%) in the darbepoetin alfa group (HR, 0.96;95% CI, 0.83 to 1.11). Rates of any serious adverse events were similar between the vadadustat (n = 973, 55.0%) and darbepoetin alfa groups (n = 1032, 58.3%). The primary efficacy end point of mean change in hemoglobin from baseline found vadadustat noninferior at weeks 24 to 36 (least-squares mean (\pm SE) change in haemoglobin from baseline 1.26 ± 0.11 g/dL in the vadadustat group vs. 1.58 ± 0.11 g/dL in the darbepoetin group) and weeks 40-52 (vadadustat 1.42 ± 0.13 g/dL and darbepoetin alfa 1.50 ± 0.14 g/dL).

Comment: Vadadustat was non-inferior compared to darbepoetin alfa for the specified safety outcomes and efficacy in achieving target changes in mean haemoglobin concentration. The reassuring safety outcome in this study is at odds with the parallel trial in non-dialysis CKD patients (see above) but is consistent with meta-analysis of previous studies. Given darbepoetin alfa was the sole erythropoietin stimulating agent (ESA) used in the study, generalisability regarding non-inferiority of comparator ESAs remains less certain. A key strength of this study was the inclusion of peritoneal dialysis patients, where an orally administered agent is particularly desirable.

Pentoxifylline may prevent gentamicin induced nephrotoxicity

A randomized double-blinded placebo-controlled clinical trial on protective effects of pentoxifylline on gentamicin nephrotoxicity in infectious patients

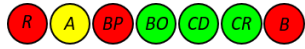
[Mousavinasab et al. Clinical and Experimental Nephrology <https://doi.org/10.1007/s10157-021-02032-9>](#)



Reviewed by Kim D

Summary: This multicentre randomised double-blind placebo-controlled trial was conducted between August 2019 to September 2020. 60 haemodynamically stable patients requiring systemic gentamicin for a minimum of 7 days were randomised in a 1:1 ratio to receive oral pentoxifylline (PTX) 400mg three times daily or placebo. Nephrotoxicity was defined by an increase in serum creatinine by > 0.5 mg/dL or a 50% increase compared to baseline. Acute tubular necrosis (ATN) was determined by a urinary sodium excretion fraction of $> 2\%$. The risk of gentamicin induced nephrotoxicity was 19.6 times higher in the placebo arm (95% CI = 3.08-114.32; $p = 0.001$), with 15 cases by day 7 (mean onset 6.36 ± 1.34 days) compared to none in the PTX group. Moreover, 56.7% in the placebo group and 10% in the PTX group had ATN by day 7 of treatment ($p = 0.001$). There was no significant difference in hypokalaemia or hypomagnesaemia between the 2 groups.

Comment: The incidence of aminoglycoside induced nephrotoxicity ranges from 7-50%, which can limit its clinical use for fear of this significant complication. This is the first clinical trial to address the role of PTX, a phosphodiesterase inhibitor which may have anti-inflammatory effects, in preventing gentamicin nephrotoxicity. Despite significant results, there are limitations of this study including small sample size and a short follow up period of only 7 days. While more data is required prior to any change in practice, this study suggests that larger studies attempting to replicate these results are warranted.

Treatment adherence transformed with tele-nursing?**Do the patient education program and nurse-led telephone follow-up improve treatment adherence in hemodialysis patients? A randomized controlled trial**Arad et al. *BMC Nephrology* (2021) 22:119 <https://doi.org/10.1186/s12882-021-02319-9>Reviewed by *Gittus M*

Summary: In this single centre trial, 66 participants were recruited from dialysis unit. Blinding of the participants and study personnel was not possible due to trial design. 33 participants in the intervention group received a patient education program (booklet with topics on diet, medication use and fluid restriction) and telemedicine follow-up (nurse-led scheduled phone calls and text message support). 33 participants in the control group received routine care consisting of regular dialysis treatment and staff answering questions during/after treatment. Blinded data analysis was conducted by one researcher. Four components of dialysis treatment (diet, medication use, fluid restrictions and HD attendance) adherence were assessed at four-time points of measurement (before intervention, immediately afterwards, 1-month post-intervention and 3 months post-intervention). There was no statistically difference between the two groups pre-intervention using the independent-sample t-test ($P=0.436$). Following the intervention there was a statistically significant difference using repeated measures ANOVA in the mean score of overall treatment adherence at the four-time points (intervention group $P<0.0005$; control group $P=0.076$).

Comment: Poor haemodialysis adherence has serious implications for patient morbidity and mortality; healthcare service utilisation and healthcare costs. This study adds to the growing evidence-base for telemedicine which has increased in popularity globally during the COVID pandemic. In contrast to the majority of similar patient education strategies, it combines this approach with a patient education booklet. I would agree with the authors that the main limitations are related to the small sample size and short follow-up period. As the study was performed at a single centre, this could reduce the generalizability of the results. Furthermore, convenience sampling and randomisation method (which relied on participants picking a one of two cards) could introduce serious potential bias. Computer generated randomisation is considered more reliable and simple randomisation schedules can be freely obtained online. See [ISN-ACT Clinical Trials Toolkit/Randomization](#).

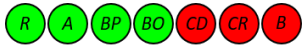
ISN Academy: [Glomerular Diseases](#)**Low-dose prednisolone is non-inferior to conventional-dose regimen for nephrotic syndrome relapses in children****Low-dose versus conventional-dose prednisolone for nephrotic syndrome relapses: a randomized controlled non-inferiority trial**Sheikh et al. *Pediatr Nephrol.* 2021 Apr 16. doi: 10.1007/s00467-021-05048-1. Online ahead of print.Reviewed by *Bulanov N*

Summary In this non-inferiority trial, 60 children aged 1-12 years with relapse of steroid-sensitive nephrotic syndrome were randomized to receive prednisolone 1 mg/kg/day (low dose) or 2 mg/kg/day (standard dose) for two weeks. Twenty-nine children (97%) in the low-dose group and 27 children (90%) in the standard-dose group achieved remission. The primary outcome – time to achieve remission – was comparable in the low-dose group (9.03 ± 2.2 days) and in the standard-dose group (8.63 ± 2.2 days), with a mean difference of 0.4 days (95% CI – 0.79 to 1.59 days; p-value of 0.49). Non-inferiority of low-dose regimen was established at the prespecified margin of 2 days. Median time to subsequent relapse was 86 (IQR 74.8, 97.2) days in the low-dose group and 150 (IQR 59.0, 240.9) days in the standard dose group, however the difference was not statistically significant (log rank $p = 0.39$). The proportion of patients with relapses, the frequency of relapses, and cumulative corticosteroid dose during follow-up period were similar in both groups.

Comment The study by Sheikh et al addressed an under-researched problem of the optimal corticosteroid regimen for the treatment of steroid-sensitive nephrotic syndrome relapses in children. The results of the trial support the use of steroid-sparing regimen for the treatment of this group of patients. However, the study has several limitations, including a relatively small number of participants, lack of power to show the significant differences in the secondary outcomes.

Paediatric acute kidney injury in intensive care

Trial of Furosemide to Prevent Acute Kidney Injury in Critically Ill Children: A Double-Blind, Randomized, Controlled Trial

Abraham et al. *Indian J of Pediatrics*. <https://doi.org/10.1007/s12098-021-03727-3>

Reviewed by De Souza L

Summary: In this single centre study, 75 children aged 1 month to 12 years of age with acute kidney injury (AKI) defined by the p-RIFLE criteria (paediatric-Risk, Injury, Failure, Loss, End stage kidney disease) and no known renal impairment were recruited from the paediatric intensive care unit (PICU). 38 patients were randomised to receive a frusemide infusion, titrated (to maximum 0.4mg/kg/hr) to target urine output 1-2ml/kg/hr for a minimum 24hr period vs placebo of 5% Dextrose infusion. Both arms received maintenance fluids concurrently. This trial was stopped on ground of futility before reaching the target of 110 children. No significant difference was noted in progression of AKI from 'risk' category to injury' or 'failure' (4/38 in the furosemide group vs. 8/37 in the placebo group, HR 0.49, 95% CI 0.16 to 1.48; $p = 0.22$), nor in secondary outcomes including need for renal replacement therapy (RRT), length of stay in hospital or 28 day mortality. Complications were similar between groups.

Comment: Careful fluid management in PICU is key to preventing progression of AKI and its sequelae. This pilot double-blind trial showed results similar to prior adult studies of the same nature, in that effect on urine output production was varied but no benefits were observed in terms of renal function and AKI recovery. There were several limitations to this trial, most significantly its early cessation. It was not clear what criteria were specified to determine futility, indeed results at the end of the study appeared to be favouring the furosemide infusion (with an effect estimate of a 50% relative risk reduction). Ideally, decisions regarding trial cessation should be made on the basis of prespecified criteria to ensure that issues relating to study power and risk of type 1 error are clearly understood in advance. Additionally, in contrast to previous AKI studies, serum and urine levels of novel biomarker neutrophil gelatinase associated lipocalin (NAGL) were not found to be elevated in either group, but the significance of these findings in this underpowered study is unclear.