











Global Trials Focus

September 2020

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

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ISN Academy: [Interventional Nephrology](#)

Drug-coated balloons improve patency of following fistuloplasty

Drug-coated balloons for dysfunctional dialysis arteriovenous fistulas

[Lookstein et al. N Engl J Med 2020; 383:733-742](#)



About the study: 330 patients with stenotic or re-stenotic unstenated lesions in their native upper extremity arteriovenous fistulas were randomised to either standard balloon angioplasty, or balloon angioplasty with a balloon coated in the anti-proliferative agent paclitaxel. The primary outcome was freedom from the need for repeat intervention, or access circuit thrombosis, within 6 months.

Results The use of paclitaxel-coated balloon was associated with higher rates of freedom from re-intervention or thrombosis (82.2% vs. 59.5%; difference in risk, 22.8 percentage points, 95% confidence interval [CI] 12.8-32.8; P<0.001). The percentage of participants undergoing clinically driven target-lesion revascularisation was 16.4% in the drug-coated balloon group and 38.5% in the standard balloon group, and there was no significant difference in the risk of access-circuit thrombosis between the treatment groups (2.0% versus 3.4%, risk difference -1.4%; 95% CI -5.1 to 2.3). There was no statistically significant difference in the risk of serious adverse effects within 30 days.

Comment In previous studies, approximately 50% of stenotic arteriovenous fistulas required re-intervention within 6 months. This multicentre trial shows substantial reductions in reintervention rates. There is a small risk of bias in reintervention rates as the drug-coated balloon has a different appearance than a standard balloon and therefore was unblinded to interventionists, however the trial was blinded to participants and to the external adjudicators.

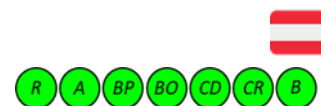
ISN Academy: [Kidney Transplant](#)

No clear benefit from mannitol during kidney transplantation

Mannitol and renal graft injury in patients undergoing deceased donor renal transplantation

– a randomized controlled clinical trial

[Reiterer et al. BMC Nephrol 2020;21:307](#)



About the study 34 patients undergoing deceased donor renal transplantation in a single centre were randomly assigned to receive either 20% mannitol (n=17) or 0.9% NaCl placebo solution (n=17) before, during, and after graft reperfusion.

Results Among 16 serum biomarkers which are potentially involved in ischemic kidney injury and inflammation, only 4 showed significant changes in concentration (VCAM1, Endostatin, KIM1, GH; P=0.007; P=0.013; P=0.004; P=0.033; respectively) that were attributed to mannitol at 24-hour after graft reperfusion. There was no difference in urine output, GFR or creatinine.

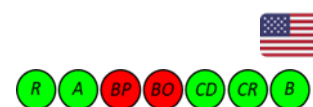
Comment Mannitol has been advocated for use in the peri-transplant period for its anti-inflammatory properties that may potentially attenuate ischemia-reperfusion injury. However, the present study showed positive changes in 4 of 16 tested biomarkers and no differences in clinical parameters, leaving the mannitol hypothesis on an uncertain footing.

ISN Academy: [Glomerular Diseases](#)

Belimumab underwhelming in early phase of relapsing lupus nephritis

CALIBRATE: A Phase 2 Randomized Trial of Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis

[Atisha-Fregoso. Arthritis Rheumatol 2020 Aug 4](#)



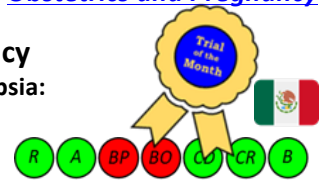
About the study: A multi-centre randomised open-label clinical trial in 43 participants with recurrent or refractory lupus nephritis, who had previously received mycophenolate or cyclophosphamide. All participants received methylprednisone 100mg, rituximab 1g and cyclophosphamide (CYC) 750mg at Weeks 0 and 2. They were randomised at Week 4 to either rituximab/CYC or rituximab/CYC/belimumab. Primary endpoint was safety of belimumab.

Results: The addition of belimumab was not associated with increased adverse events, but there was no significant difference in efficacy between the 2 groups. At Week 48, complete or partial renal response occurred in 11/21 (52%) in those receiving belimumab, versus 9/22 (41%) in those that did not (P=0.452). B cell depletion occurred to a greater extent in the belimumab group, with a greater decrease in total and autoreactive naïve B cells.

Comment: B cells are thought to play a critical role in the pathogenesis of SLE, but previous randomised controlled trials of rituximab (anti-CD20 biological therapy) have been equivocal. The hypothesis here was that concurrent treatment with belimumab (a monoclonal antibody against B-cell activating factor) may help prevent re-emergence of autoreactive B cells following B cell depletion. This Phase II trial of belimumab did not demonstrate any safety concerns, but neither was there any sign of greater efficacy. Nevertheless, the study was small and larger trials are needed to assess the efficacy of combination therapy with rituximab and belimumab.

Diltiazem may be superior to nifedipine for post-partum hypertension in pregnancy
Efficacy of diltiazem for the control of blood pressure in puerperal patients with severe preeclampsia: a randomized, single-blind, controlled trial

[Arias-Hernández et al. Int J Hypertens 2020 Article ID: 5347918](#)



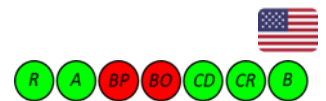
About the study 42 women less than 24 hours post-delivery with severe preeclampsia (BP \geq 160/110mmHg) were randomised to oral diltiazem 60mg or nifedipine 10mg 8-hourly. Participants were blinded to treatment. The primary outcome measures were blood pressure parameters performed via radial artery catheters over a 48-hour period.

Results At six hours the blood pressure in the diltiazem group was significantly lower (113.4/78.5mmHg vs 147.9/90.6mmHg; $P < 0.001$). This trend was maintained throughout the period of observation. There were no hypertensive episodes in the diltiazem group and 15 (71.4%) in the nifedipine group. The average intensive care admission was 2.47 days for the diltiazem arm and 4.57 days in the nifedipine arm ($P < 0.001$)

Comment This study showed efficacy and reduced lability in blood pressure control with diltiazem for women with pregnancy-induced hypertension in the early postpartum period. The inclusion criteria diagnosed pre-eclampsia by blood pressure alone, which may create a heterogeneous study population of pregnancy-induced hypertension and true pre-eclampsia; notably, no patients had abnormal liver function tests or creatinine, and proteinuria was not discussed. Treatment in this group resulted in lower adverse events (hypo/hypertension) and shorter intensive care stays, supporting its use in the acute phase. Additional studies to determine if this result is replicable seem warranted.

Automated decision support in primary care falls short, but lack of power leaves question unanswered

Electronic decision support for management of CKD in primary care: a pragmatic randomized trial
[Peralta et al. Am J Kidney Dis 2020 Online ahead of print](#)



About the study: 80 primary care providers caring for 524 adults with eGFR 30-59mL/min/1.73m² were randomised to one of three management strategies: (1) usual care (2) to use an electronic decision support system to assist their management of blood pressure, potassium, proteinuria, cardiovascular risk factors and patient education, or (3) to use the electronic support system with the addition of pharmacist patient counseling. CKD screening was performed with a triple-marker test of serum creatinine, serum cystatin C, and the urine albumin:creatinine ratio. The primary outcome was change in blood pressure over 12 months.

Results There was no significant difference in systolic blood pressure between groups (-2.1 ± 1.5 mmHg with usual care, -2.8 ± 1.8 mmHg with the electronic support system, and -1.1 ± 1.1 with the addition of pharmacist counselling; $P = 0.7$). There was limited uptake of the intervention; among patients randomised to care involving the electronic support system (with or without pharmacist counselling), only 53% of patients completed laboratory measurements in the study period, and 41% completed laboratory measurements and follow-up to allow use of the support tool. For eligible cases where a clinic appointment did occur, the support system was opened in 74% of cases. There were no differences in total use or new use of ACE inhibitors/ARBs or statins by study arm. Documentation of CKD diagnosis was 16% with usual care, 26% with the decision support tool, and 32% with the support tool and pharmacist counselling ($P = 0.09$).

Comment The study was underpowered to detect a difference with the intervention, with an original plan for 14000 participants. It utilised interesting strategies for improving CKD care including integration of the decision support system into the electronic medical record, and automated prompts to use the system based upon patient laboratory results. Further trials with more extensive follow-up would be needed to demonstrate the efficacy of the decision support system.

Thai study adds to evidence in favour of higher ferritin targets in HD

Effect of maintenance intravenous iron treatment on erythropoietin dose in chronic hemodialysis patients: a multicenter randomized controlled trial

[Susantitaphong et al. Can J Kidney Health Dis 2020; 7: 2054358120933397](#)



<p>About the study: 200 adult chronic haemodialysis patients with serum ferritin of 200-400ng/mL, transferrin saturation less than 30%, and hemoglobin 80-120g/L were randomised to either maintain their ferritin in this range (low ferritin group) or to target a higher range of 600 to 700ng/L (high ferritin group). The high ferritin group received 100mg iron per week for 6 weeks then both groups followed a protocol of iron supplementation to target their respective ferritin ranges, for a total duration of 6 months. The outcomes included mean iron and erythropoietin doses. The target hemoglobin was 100-120g/L.</p>	<p>Results The mean IV iron delivered was 108.3 ± 28.2 mg/month in the low ferritin group and 192.3 ± 36.2 mg/month in the high ferritin group. The mean serum ferritin at six months was 367 ± 225 ng/mL in the low ferritin group and 620 ± 265 ng/mL in the high ferritin group. The erythropoietin resistance index (the erythropoietin dose divided by the haemoglobin level) was significantly reduced in the high ferritin group after receiving the 6 weeks of iron loading (mean difference: -113 ± 189 vs 41 ± 207 unit/week/g/dL; P < 0.001) and at 3-months of follow-up (mean differences: -89 ± 234 vs -10 ± 218 unit/week/ g/dL; P = .02) but the difference did not reach statistical significance at 6 months (-62 ± 276 vs -108 ± 271 unit/week/g/dL; P = .09). The mean difference in erythropoietin dose was not provided. There was no difference in mortality; other adverse effects were not reported.</p>
<p>Comment Targeting a ferritin range of 600-700ng/L reduces the requirements for erythropoietin, and is in keeping with the KDIGO recommendation of transferrin saturation > 30% and ferritin > 500g/L. The results of this study are broadly in keeping with those of the PIVOTAL trial, showing efficacy of a higher ferritin target. That study also showed a lower rate of cardiovascular events in the high ferritin group (which the present study was not powered to assess). Susantitaphong et al. have provided useful evidence generalising the high ferritin target approach to the South East Asian context.</p>	