ISN INTERNATIONAL SOCIETY OF NEPHROLOGY | RESEARCH ACT | CLINICAL TRIALS

Global Trials Focus

April - May 2025

The ISN-ACT (Advancing Clinical Trials) team presents this bi-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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ISN Academy: CKD

DAPA-Tolvaptan: First trial of SGLT2 inhibition in ADPKD with background tolvaptan therapy

Open-Label, Randomized, Controlled, Crossover Trial on the Effect of Dapagliflozin in Patients With ADPKD Receiving Tolvaptan

Uchiyama et al., KI Reports 2025.

R A BP BO CD CR B

Reviewed by Michele Provenzano

Summary: In this open-label, crossover trial, 27 autosomal dominant polycystic kidney disease (ADPKD) participants on stable high-dose tolvaptan (>60mg/day, >3 months, with eGFR >25 ml/min/1.73 m2) were randomized to receive dapagliflozin 10mg daily or usual care for 6-months, then crossed to the alternate arm for another 6 months, without a washout period. Participants with diabetes were excluded. The primary endpoint was the eGFR slope from months 1 to 6, based on creatinine levels (eGFRcr), cystatin C levels (eGFRcys), and combined estimates (eGFRcr-cys). Participants had a mean age of 49.7 years; 52% were male, and 15% had a family history of ADPKD. Significant attenuations in the eGFRcr-cys and eGFRcys slopes were observed during the dapagliflozin treatment period compared to the period without dapagliflozin (2.57 ± 7.88 vs. −5.65 ± 9.57 ml/min/1.73 m^2/year, P = 0.002; 3.91 ± 11.40 vs. −8.43 ± 13.44 ml/min/1.73 m2/year, P = 0.003, respectively). The eGFRcr slope showed a moderate improvement during dapagliflozin treatment, though this did not reach statistical significance (1.03 ± 10.78 vs. −3.66 ± 8.88 ml/min per 1.73 m2 per year, P = 0.06). An initial dip in eGFR was observed in the first month of dapagliflozin use, followed by a slight increase during the period without dapagliflozin. During dapagliflozin treatment, total kidney volume (TKV) growth was significantly attenuated compared to the period without dapagliflozin (−0.44 ± 4.91 vs. 5.04% ± 8.09%, P = 0.01). Additionally, body weight gain was smaller (P = 0.01), plasma vasopressin levels were higher (P = 0.002), and systolic blood pressure was lower (P = 0.04) during the dapagliflozin treatment period compared with the period without dapagliflozin.

Comment: SGLT2 inhibitors (SGLT2i) are now widely used for chronic kidney diseases of varying etiologies, demonstrating proven benefits for patients with and without diabetes, and across various levels of albuminuria and stages of kidney disease. However, most SGLT2i trials have excluded patients with ADPKD, making this trial a unique contribution to the field. A major concern is that SGLT2i may increase vasopressin levels, which could potentially stimulate cyst growth; however, the concurrent use of tolvaptan, a vasopressin V2 receptor antagonist, might mitigate this effect and enhance overall kidney protection. This open-label crossover trial assessed the combination of dapagliflozin and tolvaptan in patients with ADPKD. The trial demonstrated the additive benefits of dapagliflozin, including a slower decline in kidney function and reduced kidney volume growth, without significant safety concerns. In addition to kidney-specific effects, dapagliflozin improved other parameters, such as decreased body weight, lower

systolic blood pressure, and increased hemoglobin levels. These effects may work synergistically to slow disease progression and enhance patient outcomes including delaying time to dialysis and reducing symptom burden such as pain related to kidney size. This study has several limitations. As a small, short-duration pilot trial with an open-label, crossover design and no washout period, the risk of carryover effects and potential bias from lack of blinding cannot be excluded. However, key outcomes (eGFR and TKV) were objectively assessed by third-party reviewers. Imbalances in TKV between treatment periods could have influenced results, although this was minimized by the crossover design and consistent Mayo imaging classification across the groups. The lack of PRO-PKD scores limited stratification by disease progression risk, as genetic testing is not routinely performed in Japanese clinical practice. Nonetheless, these promising findings support the need for larger, longer-term parallel-group RCTs to confirm dapagliflozin's role as an adjunct therapy and potentially expand treatment options for patients with ADPKD.

ISN Academy: **CKD**

Intensive vs. Standard Blood Pressure Control in Advanced CKD: Still no clear winner

Intensive Home Blood Pressure Lowering in Patients With Advanced CKD

Ku et al., Am J Kidney Dis. 2025.

Reviewed by Anastasiia Zykova

Summary: The optimal blood pressure (BP) target in advanced chronic kidney disease (CKD) remains uncertain. In this non-blinded trial, adults with hypertension (defined as either use of antihypertensive medications or a screening clinic systolic BP (SBP) >140mmHg if untreated) and an eGFR≤30 mL/min/1.73m2 were randomised 2:1 to an intensive home SBP target of <120 mmHg (n=66) or a less intensive target of 130-140 mmHg (n=42). Antihypertensive treatment was titrated over the first 4 months to achieve the home SBP target. The median age of participants was 56 years; 43.5% were women, nearly one-third had diabetes, and 13% had a history of stroke. The primary outcome assessed the difference in clinic SBP between months 4 and 12. Secondary outcomes included hyperkalemia (serum potassium ≥6 mEq/L), a composite of self-reported falls or syncope, and the need for dialysis or kidney transplantation. At 12 months, the mean clinic SBP was significantly lower in the intensive group than the less intensive group (124.7 mmHg vs. 138.2 mmHg). The mean difference in clinic SBP, averaged over months 4-12, was 11.7mmHg (95% CL, 7.5-16; P <0.001) lower in the intensive SBP group compared to the less intensive SBP group. Similar differences were observed in home SBP measurements. There were no significant differences observed between groups (intensive vs less intensive groups) in the incidence of hyperkalemia (1 vs 2 episodes; P=0.3), falls or syncope (9 vs 7 episodes; P=0.7), or the initiation of dialysis or kidney transplantation (3 vs 0 participants; P=0.30) within the first 12 months. Cardiovascular-related and all-cause hospitalizations were less frequent in the intensive group, while the incidence of acute kidney injury (AKI) requiring hospitalization was similar between the groups.

Comment: This pilot trial contributes to the ongoing discussion regarding optimal blood pressure management in advanced CKD, highlighting not only the question of SBP targets, but also the feasibility of achieving them in clinical practice. This trial despite its explorative nature included a broad range of patients, including kidney transplant recipients and patients with diabetes and/or heart failure. While the intensive treatment group showed a numerically higher (though statistically non-significant) incidence of dialysis or transplantation, the absolute event rates remained low. Importantly, the frequency of AKI was also similar between both groups, suggesting that intensive hypertension control may still be a safe approach in this high-risk population. However, a notable 15% drop-out rate due to treatment non-adherence or reluctance to escalate therapy highlights the practical challenges of implementing strict blood pressure targets. Ultimately, larger, long-term randomized trials are needed to establish optimal BP goals in advanced CKD, with careful monitoring of safety outcomes such as AKI, hyperkalemia, and progression to kidney failure. In the meantime, these findings underscore the importance of individualized treatment strategies, balancing potential benefits against patient tolerance and real-world applicability.

ISN Academy: **Dialysis**

A novel cell-impermeable endoprosthesis has a patency advantage in AVF stenosis

Six-month safety and efficacy outcomes from the randomized-controlled arm of the WRAPSODY Arteriovenous Access Efficacy (WAVE) trial

Razavi et al., Kidney Int. 2025.

Reviewed by Nikolina Basic-Jukic

Summary: The WRAPSODY Arteriovenous Access Efficacy (WAVE) trial was a multicentre, prospective study conducted across the USA, Brazil, and the UK. It evaluated the safety and efficacy of a novel cell-impermeable endoprosthesis (CIE) compared with percutaneous transluminal angioplasty (PTA) in treating stenosis of the peripheral venous outflow circuit in arteriovenous fistulas (AVFs). From February 2021 to August 2023, a total of 246 participants were randomized; 245 patients were ultimately treated (122 patients with CIE and 123 with PTA). The primary efficacy endpoint was target lesion primary patency (TLPP) at 6 months, defined as freedom from clinically driven target lesion revascularization or thrombosis, and freedom from safety events through 30 days post-index procedure that affected the access circuit and resulted in reintervention, hospitalization, or death. Access circuit primary patency (ACPP) was assessed as a secondary endpoint. At six months, TLPP was significantly higher in the CIE cohort compared to the PTA group (89.6% vs. 62.3%; P < 0.0001) with an absolute difference of 27.3% (95% CI: 16.8%, 37.8%). Safety outcomes within 30-days of the procedure were comparable between groups, with no statistically significant difference (96.6% for CIE vs. 95.0% for PTA; P=0.54 for superiority), and non-inferiority was confirmed (P<0.0001). For the secondary endpoint, ACPP was significantly better in the CIE cohort. (72.2%) than in the PTA group (57.0%), corresponding to a 15.2% difference (95% CI: 2.9%, 27.4%; P=0.016). Additionally, the CIE arm, showed a significantly lower rate of clinically driven target lesion revascularization compared to PTA (10.4% vs. 37.7%; P < 0.0001).

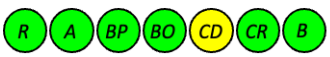
Comment: Stenosis of the AVF outflow circuit remains a major barrier to long-term dialysis access survival. While PTA is the current standard of care, its patency outcomes are suboptimal, often requiring frequent reinterventions due to re-stenosis. The WAVE trial evaluated a novel CIE designed to act as a physical barrier against neointimal hyperplasia – a key driver of AVF restenosis. By preventing cellular infiltration, the CIE aims to preserve vessel lumen integrity while supporting laminar flow. The results from this trial support CIE as a potentially practice-changing alternative to PTA, demonstrating superior short-term patency without compromising safety, and significantly reducing the need for re-intervention – thereby potentially lessening procedural burden on patients and healthcare systems alike. Although full blinding was not feasible due to procedural differences, randomisation concealment and the use of objective endpoints like TLPP strengthen the validity of the findings. Nevertheless, longer-term outcomes including 12-month patency, access survival and cost-effectiveness, remain to be evaluated. If its benefits are sustained in longer-term follow up, the CIE could play a pivotal role in transforming dialysis access maintenance strategies.

ISN Academy: **Dialysis**

SOLFA trial: hemodialysis without heparin? The ATA advantage

SOLFA study: a multicenter, open-label, prospective, randomized study to investigate the clotting propensity of asymmetric cellulose triacetate membrane compared to synthetic membranes in online HDF

Puerta et al., J Nephrol. 2025.



Reviewed by Rupesh Raina

Summary: The SOLFA study was a multicentre, open-label, prospective crossover trial conducted at four centres in Spain comparing the thrombogenicity of asymmetric cellulose triacetate (ATA) membranes with conventional high-flux synthetic membranes during hemodialysis. The study enrolled 32 patients on maintenance hemodialysis, of whom 25 completed both study phases. Each patient underwent two treatment phases using either ATA or synthetic membranes in random order. In each phase, the heparin dose was progressively reduced over six sessions until reaching a heparin-free dialysis in the last session. Patients then crossed over to the alternate membrane type, with the same heparin tapering protocol for the next six sessions. The primary outcome was the number of sessions completed with reduced or no heparin, while secondary outcomes included visual coagulation scores, dialysis efficacy, and micro-computed tomography (micro-CT) analysis of dialyzers. The mean participant age was 70.1 years; 60% were male. The mean dialysis vintage was 2 years. Most (68%) participants dialysed via a native arteriovenous fistula, and the predominant dialysis modality was online hemodiafiltration (84%). The study found that 60% of dialysis sessions with ATA membranes were completed without heparin, compared to 24% with synthetic membranes (P=0.025).

Additionally, 46% of ATA sessions completed the full heparin tapering protocol, versus only 7% in the synthetic group (P=0.01). Micro-CT analysis confirmed a significantly higher percentage of open fibres with ATA membranes during low-heparin sessions. Dialysis efficiency was not compromised, and post-dialysis myoglobin levels were significantly lower with ATA.

Comment: Anticoagulation-related complications remain a persistent challenge in dialysis, making strategies that safely reduce or eliminate the need for systemic heparin of great clinical relevance, particularly for patients at high bleeding risk. The SOLFA crossover study provides strong evidence that ATA membranes offer improved thrombogenic performance compared to conventional synthetic membranes, especially under conditions of reduced or absent heparin use. However, this study is limited by small sample size and open-label design, which may introduce bias in subjective measures like visual clotting scores. Nevertheless, the objective micro-CT data strengthens the reliability of the findings. In summary, this provides compelling evidence that ATA membranes may offer a safer alternative for patients with contraindications to systemic anticoagulation. Further large-scale, blinded studies are warranted to validate these results and to assess the long-term clinical outcomes and cost-effectiveness of ATA-based hemodialysis.

ISN Academy: **Glomerular diseases**

Mizoribine as induction therapy in Lupus Nephritis: a non-inferior oral alternative to IV cyclophosphamide?

Mizoribine or Cyclophosphamide for Lupus Nephritis A Randomized Clinical Trial

Dong et al., JAMA Netw Open. 2025.

R A BP BO CD CR B

Reviewed by Anastasiia Zykova

Summary: In this open-label, multicenter trial, 250 patients with proliferative LN (Class III+/-V, IV+/-V, or V) were randomized to oral mizoribine (50 mg three times daily for 52 weeks) or intravenous cyclophosphamide (CYC; six doses at 0.5–1.0 g/m² body surface area every 4 weeks, then additional pulses at weeks 32 and 44). All patients received methylprednisone pulse therapy (0.5g/day) for 3 days followed by oral steroids (0.8–1.0 mg/kg/day, max 60 mg/day) with subsequent tapering. The cohort was predominantly female (87.7%), with a mean age of 34.6 years. Participants had severe proteinuria (approximately 5 g/day), hypoalbuminemia (mean serum albumin approximately 27g/L), and mostly (62.1%) demonstrated preserved kidney function (eGFR ≥90 mL/min/1.73m2). At 52 weeks, total remission rates (comprising of complete remission plus partial remission rates) were 66.1% for mizoribine vs. 76.8% for CYC (relative risk [RR] 0.861, 95% CI 0.729–1.016), meeting the prespecified non-inferiority margin of 0.726. Both groups showed comparable improvements in proteinuria, serum albumin, and kidney function. Adverse events were similar, with upper respiratory infections being the most common. These findings support mizoribine as a non-inferior, oral induction option in LN.

Comment: The search for a safe and effective induction agent for lupus nephritis remains a significant challenge in nephrology. While cyclophosphamide remains a cornerstone treatment, its intravenous administration and toxicity profile limit its use. Mizoribine, an oral purine synthesis inhibitor structurally related to mycophenolate mofetil, offers a promising alterative by suppressing both T and B cell proliferation. In this study, although the absolute difference in remission rates between mizoribine and cyclophosphamide appear clinically meaningful, the trial met its pre-defined non-inferiority margin. The trial demonstrated non-inferiority at 52 weeks, with a modestly lower total remission rate for mirzoribine compared to cyclophosphamide (62.6% vs 74.1%) emerging from 32 weeks. However, this study is limited by its open-label design, ethnically homogenous population, and relatively short duration of follow-up. Nevertheless, mizoribine may have a role in the induction treatment of carefully selected LN patients, particularly where oral administration, convenience, and tolerability are key considerations. Further studies are needed to optimize dosing regimens and evaluate long-term outcomes, including relapse rates and renal survival, in a broader cohort.

ISN Academy: **Glomerular Diseases**

REGENCY results: Obinutuzumab shows promise in lupus nephritis, but questions remain

Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

Furie et al., N Engl J Med. 2025.

Reviewed by Anastasiia Zykova

Summary: Obintuzumab, a humanized anti-CD20 monoclonal antibody, is part of a therapeutic class that includes agents like rituximab, which have been used off-label in lupus nephritis (LN). In the phase 3 REGENCY trial, 271 adults with biopsy-confirmed active proliferative LN (Class III or IV, with or without concomitant Class V) were randomised to receive either obintuzumab or placebo, in addition to standard immunosuppressive treatment comprising of mycophenolate mofetil with prednisone. The cohort was predominantly female, with a mean age of 33 years. Baseline characteristics (obintuzumab vs placebo) were balanced (median eGFR 107 vs 109 mL/min/1.73m2, and urine protein:creatinine ratio (UPCR) 2.13 vs. 2.76mg/mg). The primary outcome was a complete renal response (CRR) at week 76, which was defined as a UPCR <0.5mg/mg, eGFR ≥85% of baseline, and no intercurrent events (e.g., rescue therapy, treatment failure, death, or withdrawal). CRR was achieved in 46.4% of the obinutuzumab group vs. 33.1% with placebo (adjusted difference, 13.4%; 95% confidence interval [CI], 2.0-24.8; P=0.02). More patients on obinutuzumab also maintained CRR with prednisone ≤7.5 mg/day (42.7% vs. 30.9%). Immunological markers (C3, C4, anti-dsDNA) improved more with obinutuzumab. Serious adverse events including infections (COVID-19, urinary tract infections, and pneumonia), and neutropenia were higher among patients who received obintuzumab than placebo. There were four deaths: three in the obinutuzumab group (two from COVID-19 pneumonia, one from nephrotic syndrome) and one in the placebo group (from COVID-19).

Comment: Obinutuzumab induces more profound B-cell depletion than rituximab, owing to its enhanced antibody-dependent cellular cytotoxicity. While the REGENCY trial met its primary endpoint, the clinical improvement – an absolute 13.4% increase in CRR - this was modest, particularly in light of obinutuzumab's potent mechanism of action. This suggests that deeper B-cell suppression alone may not fully address the complex pathophysiology of lupus nephritis. The safety profile, including a higher rate of serious infections and COVID-19-related mortality, reflects the known risks of B-cell depletion and was likely amplified by the timing of the trial during the COVID-19 pandemic. These results, while encouraging, highlight the need for longer-term follow-up to assess durability of response and relapse rates. Notably, patients with isolated Class V disease were excluded, limiting generalizability to that subgroup. If subsequent research confirms efficacy and establishes an acceptable safety profile, obinutuzumab could emerge as a valuable therapeutic alternative.

Edited by Neeru Agarwal, Megan Borkum, Michele Provenzano, Mohamed Elrgal and Anastasiia Zykova