Global Trials Focus

June - July 2025

The ISN-ACT (Advancing Clinical Trials) team presents the May-June 2024 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: Chronic Kidney Disease

Stronger Together: Finerenone & Empagliflozin Boost Kidney Outcomes in Diabetes

Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes

Agarwal R, et al., N Engl J Med. 2025 Jun 5.

R A BP BO CD CR B

Reviewed by Michele Provenzano

Summary: The CONFIDENCE trial was a double-blind, randomized study enrolling 800 participants with chronic kidney disease (CKD) (eGFR 30–90 ml/min/1.73 m²), albuminuria (urinary albumin-to-creatinine ratio [UACR] 100–5000 mg/g), and type 2 diabetes, all of whom were receiving renin–angiotensin system inhibitors. Participants were randomly assigned in a 1:1:1 ratio to receive finerenone (10 or 20 mg daily), empagliflozin (10 mg daily), or both therapies, with matching placebos to ensure blinding. The treatment lasted for 180 days, followed by a 30-day observation period. At baseline, median UACR values were comparable across groups: 574 mg/g in the combination group, 578 mg/g in the finerenone group, and 583 mg/g in the empagliflozin group. By day 180, combination therapy resulted in a 29% greater reduction in UACR compared to finerenone alone (least-squares mean ratio [LSMR] 0.71; 95% CI, 0.61–0.82; P<0.001) and a 32% greater reduction compared to empagliflozin alone (LSMR 0.68; 95% CI, 0.59–0.79; P<0.001), with similar safety profiles across the groups. After treatment discontinuation, UACR increased in all groups but remained below baseline levels in all groups, with LSMR at day 210 of 1.63 (95% CI, 1.49–1.78) for combination therapy, 1.45 (95% CI, 1.32–1.59) for finerenone, and 1.44 (95% CI, 1.32–1.58) for empagliflozin. Serious adverse events occurred in 7.1% (combination therapy), 6.1% (finerenone), and 6.4% (empagliflozin) of participants, with treatment discontinuation due to adverse events being rare (≤4.5%). A ≥30% decline in eGFR at 30 days was seen in 6.3% of the combination group, 3.8% with finerenone, and 1.1% with empagliflozin, mostly reversible upon discontinuation. Hyperkalemia was more common with finerenone (11.4%) than with combination therapy (9.3%) or empagliflozin (3.8%). Combination therapy also led to the greatest reduction in systolic blood pressure, with a mean decrease of 7.4mmHg within 30 days, compared to 5.3mmHg for finerenone and 2.6mmHg for empagliflozin.

Comment: The CONFIDENCE trial provides evidence on the effectiveness and safety of combining empagliflozin and finerenone simultaneously for patients with CKD and type 2 diabetes. While both medications are backed by strong evidence and included in international guidelines, data on initiating them at the same time were previously lacking. This trial fills that gap, showing that the combination is well tolerated, does not result in problems with hyperkalemia,and as expected does reduce albuminuria, an important marker that is associated with a decreased

risk of CKD progression. Notably, the more profound reduction on albuminuria appears within four weeks, with the combination, than either drug alone indicating a possible synergistic effect between the two drugs. From a safety standpoint, the simultaneous combination did not significantly increase adverse events such as acute kidney injury or hyperkalemia.
Additionally, it achieved a greater reduction in systolic blood pressure, which could improve blood pressure control in CKD patients. However, the study has limitations, including a relatively small sample size (800 patients), a short follow-up period of 180 days, and a 30-day post-treatment observation that restricts insights into long-term efficacy and safety. Furthermore, relying on UACR as a surrogate endpoint limits definitive conclusions about long-term clinical benefits. Although UACR reduction is an accepted intermediate endpoint, trials focused on clinical outcomes are necessary. In conclusion, the CONFIDENCE trial supports early co-initiation of empagliflozin and finerenone as a promising strategy for people with diabetes and CKD, based on their additive effects on reducing albuminuria. Nonetheless, further long-term research is needed to determine whether this dual therapy provides significant clinical benefits over each medication alone in lowering risks of kidney failure, cardiovascular events, and death.

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*ISN Academy: **Dialysis***

Testing whether less is more: A large-scale trial confirms the feasibility of comparing different anticoagulation strategies - including no anticoagulation - in dialysis patients with AF

Anticoagulation for Patients with Atrial Fibrillation Receiving Dialysis: A Pilot Randomized Controlled Trial
Harel Z et al. J Am Soc Nephrol. 2025 May 1;36(5):901-910.

Reviewed by Nikolina Basic-Jukic
Summary: The Strategies for the Management of Atrial Fibrillation in Patients Receiving Dialysis (SAFE-D) trial was a parallel-group, open-label, allocation-concealed, pilot trial conducted at 28 dialysis centers from December 2019 to June 2022. It enrolled 151 adult dialysis participants with nonvalvular atrial fibrillation (AF) who met the CHADS-65 criteria. They were randomized 1:1:1 to apixaban (n=51; 5mg BD), warfarin (n=52; target INR 2-3), or no oral anticoagulation (n=48). Participants were followed for 26 weeks, with primary outcomes assessing recruitment feasibility and adherence to allocated treatment (>80%). Secondary outcomes included the incidence of stroke and bleeding episodes. Despite the COVID-19 pandemic, recruitment was completed in 30 months, and 83% of participants completed follow-up in their allocated treatment arm. Notably, there was only one adjudicated stroke event occurring in the no oral anticoagulation group. Eight participants experienced a major bleeding event (four in the warfarin group, two in the apixaban group, and two in the no oral anticoagulation group). Fifteen participants died during the study (nine in the warfarin group, two in the apixaban group, and four in the no oral anticoagulation group).

Comment: The SAFE-D trial is the first to evaluate a therapeutic approach of no oral anticoagulation for patients on dialysis with AF. The trial successfully demonstrated the feasibility of recruiting participants and adhering to protocols while comparing three anticoagulation strategies in dialysis patients with AF. Results indicated that bleeding and mortality were significantly more common than thrombotic events, especially in those treated with warfarin. Although the SAFE-D trial was not powered to detect differences in clinical event rates among the treatment groups, its findings have important implications for the design of future large-scale trials. The low incidence of ischemic stroke, combined with a high rate of all-cause mortality in the dialysis population, may require an impractically large sample size to achieve sufficient statistical power. However, new trial designs that include multiple events of interest, such as stroke, bleeding, and cardiovascular death, could address this issue and foster more effective research in this area. Future trials should aim to include more female patients and extend follow-up periods, as some clinical outcomes may be underestimated.

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*ISN Academy: **Pediatric nephrology***

Comparing Health-Related Quality of Life for Kids on Different Forms of Peritoneal Dialysis

A comparison of health-related quality of life between continuous ambulatory peritoneal dialysis and automated peritoneal dialysis in children with stage 5 chronic kidney disease in Thailand: a randomized controlled trial
Thavorncharoensap M et al.. Pediatric Nephrology (2025) 40:2029–2041.

Reviewed by Ahad Qayyum

Summary: This multi-center randomized control trial compared the quality of life of pediatric patients with kidney failure using Chronic Ambulatory Peritoneal Dialysis (CAPD) versus those using Automated Peritoneal Dialysis (APD). Participants were randomized 1:1 to APD or CAPD, and health-related quality of life (HRQoL) was measured at baseline, 16 weeks, and 48 weeks using EQ-5D (3L, 5L) and PedsQL tools (parent proxy and child self-report). Although the APD group showed slightly greater improvement in some HRQoL domains (e.g., school and social domains), these changes were not statistically significant. As such, there was no conclusive evidence supporting superiority of APD over CAPD in pediatric HRQoL outcomes.

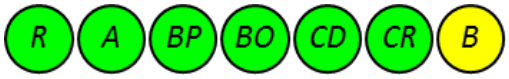
Comment: This is the first RCT to our knowledge assessing quality of life between APD and CAPD patients in the pediatric population. While the study addresses an important gap in pediatric nephrology, several methodological concerns limit its internal validity. The lack of blinding in both participants introduces risk of performance and detection bias, especially given the subjective nature of HRQoL measures. Although randomization and allocation concealment were appropriate, the sample size was below the planned target, reducing the study's statistical power to detect clinically meaningful differences. Despite these limitations, the trial was well-conducted overall and provides valuable data to inform clinical decisions and future research into pediatric dialysis modalities. That no differences were demonstrated also suggests that pediatric patients selecting either modality would do so based on values and preferences of the individual or family?

ISN Academy: Acute Kidney Injury

Reassessing AKI Management: The Need for Comprehensive Care Beyond Diagnostics?

Early, Individualized Recommendations for Hospitalized Patients With Acute Kidney Injury: A Randomized Clinical Trial

Aklilu AM et al. JAMA. 2024;332(24):2081–2090.



Reviewed by Rupesh Raina

Summary: This multicentre trial assessed whether early, real-time, tailored AKI recommendations from a Kidney Action Team (KAT)—comprising a physician and a pharmacist—could enhance outcomes among hospitalized adults with AKI. A total of 4,003 patients across 7 US hospitals were enrolled and randomized following an AKI diagnosis based on KDIGO criteria. Randomization to the intervention or usual care took place after the recommendations were prepared. The KAT produced personalized notes covering diagnostics, volume status, potassium, acid-base, and medications within one hour of AKI detection. The note was only sent to the clinicians of those patients assigned to the intervention group. The primary outcome (composite of AKI progression, dialysis, or mortality within 14 days) did not differ between the intervention (19.8%) and control (18.4%) groups (P = 0.28).
Among the 14,539 recommendations, 33.8% were implemented in the intervention arm vs. 24.3% in the control. While diagnostic and medication-related recommendations were more frequently adopted, therapeutic interventions (e.g., fluid management, potassium correction) saw minimal difference. No differences were found in secondary outcomes (e.g., need for dialysis, mortality, nephrology consults, or discharge to hospice).

Comment: This extensive pragmatic trial is the most comprehensive to date, assessing the usefulness of personalized electronic clinical decision recommendations in managing AKI. Despite showing improvements in process metrics (such as diagnostic testing and medication dose adjustments), the clinical outcomes did not significantly change. This raises longstanding concerns about the assumption that interventions focused solely on diagnostics can positively influence the course of AKI. These findings emphasize the limitations of recommendations that do not incorporate physical examinations and suggest the need for a more integrated and ongoing approach to AKI management. Such an approach may include team-based care strategies that go beyond alert-driven diagnostic interventions to improve patient outcomes more holistically.

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