# Global Kidney Trial Watch (ISN TrialWatch)

## August-September 2025

**The ISN-ACT (Advancing Clinical Trials) team presents the July-August 2025 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* 🟢

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*ISN Academy: Chronic Kidney Disease*

### Spironolactone did not ACHIEVE cardiovascular risk reduction in dialysis

**Spironolactone versus placebo in patients undergoing maintenance dialysis (ACHIEVE): an international, parallel-group, randomized controlled trial**

Walsh, et al., The Lancet, Aug 6, 2025.

R A BP BO CD CR B

*Reviewd by Megan Borkum*

**Summary:** The ACHIEVE trial randomized 2,538 hemodialysis and peritoneal dialysis patients who tolerated a 4-week spironolactone run-in (25 mg daily) to spironolactone versus placebo, with a median follow-up of 1.8 years. Approximately 63% of participants were male, 43% had diabetic kidney disease, and the mean age was 62 years. The primary composite outcome of cardiovascular death or hospitalization for heart failure occurred in 13.1% of patients in the spironolactone group and 14.5% in the placebo group, with no significant difference (HR 0.92, 95% CI 0.78–1.09; P = 0.35). Secondary outcomes, including all-cause mortality (12.1% vs 12.9%; HR 0.95, 95% CI 0.80–1.14) and all-cause hospitalization (63.3% vs 63.1%; HR 1.00, 95% CI 0.92–1.08), were likewise neutral. Subgroup analyses revealed no significant heterogeneity of treatment effect by sex, dialysis modality, duration on dialysis, presence of diabetes, or baseline cardiovascular disease. However, spironolactone was associated with higher rates of severe hyperkalemia (6.6% vs 4.5%; HR 1.54, 95% CI 1.07–2.22). There were no differences in sudden cardiac death or stroke between groups. The trial was terminated early for futility based on prespecified interim analyses, confirming that spironolactone does not confer cardiovascular protection in dialysis patients and increases the risk of clinically significant hyperkalemia.

**Comment:** The ACHIEVE trial showed that a daily 25 mg dose of spironolactone does not decrease cardiovascular events or mortality in patients on maintenance dialysis. This result remains true despite earlier biological plausibility and preliminary research suggesting possible benefits. The absence of a therapeutic effect was consistent across various patient groups, including differences in sex, dialysis method, diabetic status, and existing cardiovascular issues. Importantly, spironolactone use was linked to a notable rise in severe hyperkalemia, underscoring the inherent risks of mineralocorticoid receptor antagonist therapy in this group. Overall, these conclusive findings, in this well-done, large pragmatic RCT, do not support the routine use of spironolactone for lowering cardiovascular risk in dialysis patients. Continued research is essential to discover safer and more effective options for cardiovascular risk reduction in this high-risk population.

*ISN Academy: Dialysis*

## Less is More: Incremental Hemodialysis and Keto-Supplemented Diet Maintain Residual Kidney Function

### Stepwise Incremental Hemodialysis and Low-Protein Diet Supplemented with Keto-Analogues Preserve Residual Kidney Function: A Randomized Controlled Trial

Kittiskulnam, et al., Nutrients, 2025.


*Reviewd by Ahad Qayyum*

**Summary:** In this trial, 30 non-dialysis CKD stage 5 participants with an eGFR of 5-10 ml/min/1.73m2 and a daily urine output >=800ml were randomized to either once-weekly hemodialysis combined with a low protein diet (0.6g/kg/day) plus oral keto-analogues (0.12g/kg/day), or twice-weekly hemodialysis with a regular protein diet and no keto-analogues. The study was conducted over 12 months, with the primary outcome being change in residual renal function as measured by urinary urea clearance and urine volume. Baseline demographic, clinical characteristics, residual renal function and urine volume were comparable between the two groups. Over 12 months, both groups exhibited a decline in residual renal function and urine output after starting hemodialysis. However, from 6 month onward, the once-weekly hemodialysis group showed significantly higher urine urea clearance when compared to the twice-weekly hemodialysis group (3.2 ± 2.3 vs. 1.7 ±1.0 mL/min; P=0.03), with differences persisting through 12 months. Similarly, urine volume remained significantly higher in the once-weekly hemodialysis group from 3 months onwards (1921 ± 767 mL/day vs. 1305 ± 599 mL/day; P=0.02), a difference that persisted through 12 months. Serum albumin levels, skeletal muscle mass, anemia status, metabolic parameters, and quality of life scores were comparable between the groups.

**Comment:** With the global burden of kidney failure steadily increasing, thrice-weekly hemodialysis has remained the default standard of care. However, this often accelerates loss of residual renal function due to the abrupt shift from advanced CKD to intensive dialysis. Incremental hemodialysis has been proposed as a strategy to better preserve residual renal function as supported by observational data. This prospective RCT, evaluating once-weekly hemodialysis plus a low-protein diet with keto-analogue supplementation compared with twice-weekly hemodialysis with a normal protein diet, adds to the evidence that incremental hemodialysis is a feasible option for selected patients with substantial residual kidney function at initiation. Although both groups lost residual kidney function over 12 months, patients receiving once-weekly hemodialysis maintained a higher urine urea clearance and urine volume, with differences persisting through to one year. While these findings are encouraging, the study's very small sample size (n=30) and short follow up limit the strength and generalisability of its conclusion. These findings are hypothesis-generating and highlight the need for large multicentre randomised trials that are pragmatic or registry-embedded in design powered for clinically meaningful outcomes to confirm efficacy. A platform or umbrella style master protocol could efficiently test multiple incremental dialysis strategies and identify which patients derive the greatest benefit.

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*ISN Academy: Dialysis*

## Anrikefon: Relief at last for CKD-associated Pruritis in Dialysis Patients

### Efficacy and safety of anrikefon in patients with pruritus undergoing haemodialysis: multicentre, double blind, randomised placebo controlled phase 3 trial

Liu, et al., BMJ, 2025.


*Reviewd by Neeru Agarwal*

**Summary:** This multicentre, double-blind, placebo-controlled phase 3 trial evaluated anrikefon, a peripherally restricted kappa opioid receptor agonist, in 545 haemodialysis participants with moderate to severe CKD-associated

puritis. Participants were randomised 1:1 to receive intravenous anrikefon (0.3 µg/kg body weight) or placebo thrice-weekly during dialysis for 12 weeks, followed by an optional 40-week open-label extension. After 12 weeks, 37% of participants receiving anrikefon achieved at least a 4-point improvement on the weekly mean 24-hour Worst Itching Intensity Numerical Scale (WI-NRS) compared with 15% in the placebo group (P<0.001). Improvements in itch-related quality of life (5-D Itch and Skindex-10 scores) were also greater with anrikefon, with benefits sustained through the 40-week extension. The drug was well tolerated, with mild to moderate dizziness as the main adverse event.

**Comment:** CKD-associated pruritus is a common, distressing, and often under-treated complication of haemodialysis. In this phase 3 trial, anrikefon, a selective peripherally restricted kappa opioid receptor agonist, demonstrated clinically meaningful reductions in itch intensity and quality-of-life improvements compared with placebo, with sustained improvements during the extension phase. Nevertheless, this study has several limitations. The double-blind phase lasted only 12 weeks, while the longer extension was open-label, potentially biasing both efficacy and adverse event reporting. Moreover, the efficacy and safety in non-dialysis dependent CKD remains unknown. Importantly, difelikefalin, another peripherally restricted kappa opiod receptor agonist, has already shown efficacy in CKD-associated puritis in hemodialysis patients and has gained regulatory approval in several countries. Without head-to-head comparisons, it is unclear whether anrikefon offers meaningful advantages in efficacy, tolerability or cost. Thus, while anrikefon broadens the therapeutic pipeline, its ultimate role will depend on comparative effectiveness, long-term safety, and cost-effectiveness data from future pragmatic trials.

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*ISN Academy: **Chronic Kidney Disease***

## Zibotentan with Dapagliflozin for CKD: Outcomes in Patients With and Without Diabetes

### Effects of combined treatment with zibotentan and dapagliflozin compared to dapagliflozin alone in patients with diabetic and non-diabetic chronic kidney disease

Wasehuus, V et al., Diabetes Obes Metab. 2025.


*Reviewd by Chiara Ruotolo*

**Summary:** This post-hoc subgroup analysis of the phase 2b ZENITH-CKD trial investigated whether diabetes status modified the effects of zibotentan plus dapagliflozin versus placebo plus dapagliflozin on urinary albumin-to-creatinine ratio (UACR), systolic blood pressure (SBP), and markers of fluid retention. The analysis included 447 participants with CKD (261 with type 2 diabetes, 186 without), randomized to zibotentan 1.5 mg + dapagliflozin 10 mg, zibotentan 0.25 mg + dapagliflozin 10 mg, or placebo + dapagliflozin 10 mg. Zibotentan 1.5 mg reduced UACR similarly in diabetic and non-diabetic participants (–33.0%, 90% CI –42.2 to –22.5 vs –34.0%, 90% CI –45.0 to –20.8; P-interaction=0.921). With 0.25 mg zibotentan, UACR reductions were –17.9% (90% CI: –31.3 to –2.0) versus –37.7% (90% CI: –49.4 to –23.4) in diabetic and non-diabetic participants, respectively (P-interaction=0.096). SBP reductions were –6.9 mmHg and –3.7 mmHg in participants with diabetes, versus –2.6 mmHg and –3.8 mmHg in those without, at the 1.5mg and 0.25mg doses, respectively, with a significant diabetes interaction only for the 1.5mg dose (P-interaction=0.045). Changes in body weight and BNP did not differ significantly by diabetes status. Adverse events were more frequent with 1.5 mg zibotentan, with fluid-related events occurring predominantly in participants with diabetes.

**Comment:** This analysis addresses a clinically relevant question: whether combining a selective endothelin receptor antagonist with an SGLT2 inhibitor confers differential benefit or risk in CKD patients with and without type 2 diabetes. The findings suggest that zibotentan plus dapagliflozin provides comparable short-term antiproteinuric efficacy across subgroups, with safety concerns emerging primarily at the higher zibotentan dose. However, several limitations restrict clinical applicability. The analysis was post-hoc and not powered to detect interactions by diabetes status, making subgroup results exploratory. The short 12-week duration precludes conclusions on long-term kidney outcomes (e.g., eGFR decline, kidney failure) and sustained safety (e.g., heart failure, fluid overload). Treatment-arm discontinuations during the trial complicate randomization balance, and the absence of a zibotentan-only arm prevents assessment of its independent contribution. Moreover, while biomarkers such as BNP and bioimpedance were included, the clinical significance of small changes over 12 weeks remains uncertain. Strengths include the randomized, double-blind design and objective safety assessments. Overall, the results

warrant further investigation in larger, longer, prospectively powered trials to confirm kidney-protective effects, clarify dose–safety relationships, and define patient subgroups most likely to benefit. Ongoing studies, including ZENITH-HP and ZODIAC, are expected to provide more definitive data. For now, the combination therapy represents an intriguing option but should be regarded as hypothesis-generating evidence rather than a practice-changing intervention.

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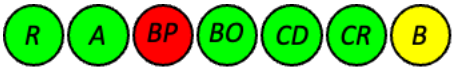
*ISN Academy: **Acute Kidney Injury***

## Albumin Overload: Postoperative 20% Albumin Infusion and Increased AKI Risk in Cardiac Surgery

**Postoperative 20% Albumin Infusion and Acute Kidney Injury in High-Risk Cardiac Surgery Patients: The ALBICS AKI Randomized Clinical Trial**

Shehabi et al., JAMA Surg. 2025.




*Reviewd by Rupesh Raina*

**Summary:** The ALBICS AKI trial was an investigator-initiated, pragmatic, multicenter, open-label, randomized trial of 611 high-risk cardiac surgery patients conducted in Australia and Italy from July 2019 to August 2024. Eligible patients had preoperative eGFR 15-60 mL/min/1.73 m2, or underwent combined cardiac or major aortic surgery, and did not have prolonged postoperative ICU stay (>6h), severe hypoalbuminemia (<20 g/L), dialysis dependence, or other contraindications. Participants were randomized within 6 hours after surgery to receive either 300 mL of 20% albumin infused over 15 hours (n=307) or usual care at the discretion of the clinicians, which included the use of balanced crystalloids and blood products as needed (n=304). The primary outcome was the incidence of acute kidney injury (AKI; KDIGO stage 1-3), which occurred in 48.9% of albumin recipients compared with 43.4% of usual care (unadjusted relative risk [RR], 1.13; 95% CI, 0.95-1.34; P=0.18; strata-adjusted RR 1.12; 95% CI, 1.04–1.21; P=0.003), with the effect more pronounced in participants with eGFR <60 mL/min/1.73 m2 (adjusted RR 1.14; 95% CI, 1.07–1.22; P<0.001). Blood transfusions were more common in the albumin group (37.8% vs 29.9%; P=0.04), while major adverse kidney events, mortality, or length of stay were similar. These findings indicate that post-operative hypertonic albumin increases AKI risk and does not support its routine use in high-risk cardiac surgery.

**Comment:** Discrepant with the hypothesis that hyperoncotic 20% albumin is nephroprotective by augmenting oncotic pressure and improving intravascular volume and renal perfusion, this large multicenter RCT demonstrated that postoperative albumin infusion increased the risk of AKI, particularly in patients with baseline eGFR <60 mL/min/1.73m², without affecting mortality, major advese renal events, or length of stay. The authors postulated several mechanisms for potential harm, including a direct deleterious intrarenal hemodynamic response to increased colloid oncotic pressure (consistent with prior RCTs of synthetic colloids versus crystalloids), an excessive colloid osmotic load that may induce tubular stress or injury, and an indirect effect via increased blood transfusion requirements, which were more frequent in the albumin group. Strengths of this study include its multicentre, pragmatic design and inclusion of a representative high-risk surgical population. Limitations include the open-label design, though the primary outcome was objective and data was collected by research staff separate from clinical management, minimising reporting bias. AKI was also defined based on creatinine without urine output, which may underestimate incidence, but the study's higher than anticipated AKI rate confirms the population was appropriately high-risk. Clinically, these findings suggest that the theoretical benefits of hyperoncotic albumin infusion in preventing AKI after high-risk cardiac surgery are outweighed by the potential for harm, highlighting the need for caution and challenging routine use in this setting.

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