# Global Trials Focus

**February - March 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-ACT Clinical Trials Toolkit**

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***ISN Academy: Dialysis***

## Remote monitoring for automated PD improves cardiovascular outcomes

**Remote monitoring of automated peritoneal dialysis reduces mortality, adverse events and hospitalizations: a cluster-randomized controlled trial**

Paniagua et al., 2025.

R A BP BO CD CR B

*Reviewed by Anastasiia Zykova*


**Summary:** A device integrated into the automated PD cycler facilitates remote monitoring (RM) of automated peritoneal dialysis (APD), enabling medical staff to track essential PD parameters. This multicentre, cluster-randomized, open-label trial included 403 patients in the RM-APD group and 398 patients in the conventional treatment group. The mean age of participants was 50.5 years (±15.4), with a predominance of males and diabetic nephropathy as the primary cause of end-stage kidney disease (ESKD). Hypertension and peripheral vascular disease were less common in the RM-APD group. The primary outcomes, analyzed using restricted mean survival time (RMST) analysis, were the time to the first occurrence of events in two composite endpoints: (1) all-cause mortality, first adverse event, or hospitalization for any reason, and (2) cardiovascular mortality, first adverse event, or hospitalization related to cardiovascular disease, fluid overload, or insufficient dialysis efficiency. The median follow-up duration was 9.5 months. A significant difference between the two groups was observed only in the second composite endpoint (ΔRMST: –0.86 months; P=0.02). Secondary outcomes, including all-cause mortality, hospitalization rates for any reason, cardiovascular deaths, and rates of adverse events and hospitalizations related to cardiovascular disease, fluid overload, or insufficient dialysis efficiency, were higher in the conventional treatment group. The dropout rate was also slightly greater in the conventional treatment group.

**Comment**: This is the first large, randomized trial assessing the impact of RM-APD on clinically significant outcomes. Notably, the groups showed minor imbalances, with a lower prevalence of hypertension and peripheral vascular disease in the RM-APD group, which may have influenced the results. Furthermore, due to the uneven global distribution of PD—where younger patients are more frequently prescribed this treatment in some countries—the generalizability of the findings may be limited. Nonetheless, these results highlight the potential of RM to improve patient safety and clinical outcomes by enabling early intervention and individualized care. Its impact on mortality, cardiovascular disease, and hospitalization may stem from peritonitis prevention, better volume management, or increased patient engagement and adherence. Further studies are needed to clarify these mechanisms. RMST analysis

further strengthens this study by providing an absolute measure of the survival benefit between the two groups (APD vs RM-APD) without being concerned about the proportional hazard assumption, which assumes constant risk ratios. This assumption is often violated in PD studies where early treatment effects, such as infections or catheter-related issues, may decrease over time, while the benefits of remote monitoring may increase. RMST provides a more robust and interpretable comparison by focusing on survival time differences. Further research is needed to assess the long-term benefits and implementation strategies of RM-APD, whilst also considering PD patient selection criteria (e.g. cognitive alertness, dexterity, age, home environment) for real-world impact.

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***ISN Academy: Dialysis***

## Pain coping skills training for patients receiving hemodialysis

**Pain Coping Skills Training for Patients Receiving Hemodialysis: The HOPE Consortium Randomized Clinical Trial**

Dember et al., 2025.


*Reviewed by Rupesh Raina*

**Summary:** This multicenter trial assessed the effectiveness of pain coping skills training (PCST), a cognitive behavioural intervention, in reducing pain interference among patients undergoing maintenance hemodialysis. Eligible participants (≥18 years) had been on hemodialysis for at least 90 days, were fluent in English or Spanish, and reported moderate to severe chronic pain. Exclusion criteria included substance use disorder, suicidal intent, severe cognitive impairment, expected dialysis modality change, or life expectancy <6 months. The intervention comprised 12 weekly virtual coach-led sessions followed by 12 weeks of daily interactive voice response sessions for reinforcement. Seven hundred fifty-three patients were screened, and 643 were randomized (319 to PCST, 324 to usual care). Baseline characteristics included a mean age of 60.3 years, 44.8% female participants, and a racial/ethnic composition of 47.9% Black, 32.7% White and 18.5% Hispanic or Latino, with diabetic nephropathy as the leading cause of kidney failure (37.2%) and 59.2% had diabetes. The primary outcome was pain-related interference with function and quality of life domains, measured via the Brief Pain Inventory (BPI) Interference subscale, with secondary outcomes including pain intensity, pain catastrophizing, quality of life, depression, anxiety, opioid use, falls, hospitalizations, and death. Results showed PCST significantly reduced pain interference at 12 weeks (between-group difference in BPI Interference score: -0.49; 95% CI, -0.85 to -0.12; P = 0.009), with effects persisting at 24 weeks but effects diminished by 36 weeks. More participants in the PSCT group also achieved a clinically meaningful reduction in BPI Interference score (>=1 point) compared to usual care at both 12 weeks (50.9% vs 36.6%, OR 1.79) and 24 weeks (55.0% vs 42.8%, OR 1.59), but not at 36 weeks (48.2% vs 42.4$, OR 1.26). Improvements in pain intensity, quality of life, anxiety, and depression followed a similar pattern, weakening over time. In conclusion, while PCST provided a modest and clinically meaningful reduction in pain interference and related outcomes, its benefits waned over time.

**Comment**: Chronic pain is a significant challenge for patients undergoing maintenance hemodialysis, impacting their quality of life and overall well-being. This trial demonstrated that PCST led to a modest but statistically significant reduction in pain interference at 12 and 24 weeks, though the effect diminished by 36 weeks. Additionally, PCST improved secondary outcomes such as pain intensity, quality of life, anxiety, and depression, suggesting broader benefits beyond pain interference. A key strength of the trial was its large, diverse sample and rigorous randomized design, ensuring broad applicability. Notable was the waning effects after intervention cessation, indicating the need for sustainable intervention strategies such as shorter duration PSCT or booster sessions, to maintain long-term benefits and enhance durability.

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***ISN Academy: Transplant***

## Reducing mycophenolate mofetil was faster and more effective than switching to everolimus in lowering BK Polyomavirus DNA load.

**Insights from the BKEVER Trial comparing everolimus versus mycophenolate mofetil for BK Polyomavirus infection in kidney transplant recipients**

Caillard et al., 2025.


*Reviewed by Nikolina Basic-Jukic*

**Summary:** The BKEVER trial was conducted from January 1, 2018, to June 30, 2020, and involved 130 patients who developed BK Polyvirus (BKPyV) DNAemia across 16 transplant centers in France. These patients were randomized in a 1:1 ratio into two groups. In the mycophenolate mofetil (MMF) group, the dose of MMF was reduced by 50%, along with a decrease in calcineurin inhibitor (CNI) levels (3-6ng/ml). In the everolimus (EVR) group, MMF was replaced with EVR, accompanied by a similar reduction in CNI levels. The target trough level for EVR was set between 3 to 8 ng/ml. The study's primary endpoint was the proportion of patients who achieved BKPyV clearance at six months. Secondary endpoints included the kinetics of BKPyV replication over time, the incidence of BKPyV-associated nephropathy, kidney graft function, rejection rates, and medication tolerability over two years. At six months, 55.7% of patients in the EVR group and 81.3% in the MMF group demonstrated BKPyV clearance. The odds ratio for clearance was 3.4 in the MMF group (95% CI, 1.5–7.7; P=0.003). The reduction in BKPyV DNA load was significantly more rapid in the MMF group. The median time to viral clearance was 121 days (range, 107–368 days) for the EVR group, compared to 63 days (range, 58–87 days) for the MMF group (P=0.0023). CNI and EVR trough levels remained within target ranges and CNI levels were comparable between groups throughout the study. Biopsy-proven BKPyV nephropathy occurred in 11 patients in the EVR group and six in the MMF group.

**Comment**: BKPyV remains a significant challenge in kidney transplantation due to the lack of a targeted antiviral treatment. While reducing immunosuppression is the primary strategy, the optimal approach remains uncertain. In this study, Caillard et al. examined BKPyV clearance six months after randomly assigning patients to reduced CNI doses with either lower-dose MMF or switching from MMF to EVR. Their findings contradict previous research, showing lower BKPyV DNAemia incidence with mTOR inhibitors. However, the MMF group achieved superior viral clearance in speed and effectiveness. Notably, EVR with moderately reduced CNI doses was ineffective for early BKPyV DNAemia, and the study suggests that switching to EVR is not a reasonable strategy compared to maintaining lower MMF with CNIs.
Additionally, BKPyV infection remains classified as "presumptive BK nephropathy," complicating treatment decisions. Excessive immunosuppression reduction risks acute rejection, while insufficient reduction may lead to graft loss. Given these challenges, novel preventive strategies—such as increased kidney biopsy use for earlier intervention and immunoglobulin therapy—should be explored while awaiting a targeted antiviral drug.

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

## Oral lactoferrin is a new frontier in treating pediatric chronic kidney disease anemia.

**Oral lactoferrin as a treatment of pediatrics' anemia resulted from chronic kidney diseases: a randomized controlled trial.**

Hegazy et al., 2025.


*Reviewed by Chiara Ruotolo*

**Summary:** This randomized parallel study included 60 pediatric patients with chronic kidney disease (CKD) stages 4–5 and compared the efficacy of oral lactoferrin and intravenous (IV) iron dextran for treating CKD-related anemia. Patients were randomly assigned oral bovine lactoferrin (n=30; 100 mg/day) or IV iron dextran (n=30; 50 mg, thrice weekly) for three months. Both groups also received erythropoietin therapy. After 3 months of treatment, both treatments were similarly effective in managing CKD-induced anemia, with no significant differences in key hematological parameters, including hemoglobin, red blood cell count, white blood cell, mean corpuscular hemoglobin (MCH), serum iron levels, red cell distribution width-standard deviation (RDW-SD), and mean corpuscular hemoglobin concentration (MCHC). However, the two compounds had distinct effects on intermediary factors. Further, significant differences were observed in growth differentiation factor-15 (GDF-15) (P=0.014), transferrin saturation (TSAT) (P= 0.004), interleukin-6 (IL-6) (P<0.001), and glomerular filtration rate (GFR) (P<0.001). Lactoferrin significantly improved nearly all parameters before and after treatment except WBC count, TSAT, and GFR, suggesting broader systemic effects. In contrast, IV iron dextran primarily influenced only five parameters (serum iron, GFR, IL-6, GDF-15, and RDW-SD), with no significant differences in the remaining six parameters.

**Comment**: Anemia is a common and significant complication in pediatric patients with CKD, negatively affecting the quality of life, growth, energy levels, and academic performance. Iron deficiency in CKD is multifactorial, driven by blood loss, impaired iron absorption, and inflammation, with elevated IL-6 increasing hepcidin expression and reducing iron bioavailability. Frequent iron supplementation can worsen this cycle, making IV iron necessary. GDF-15, a regulator of hepcidin and inflammation, may serve as a key biomarker for anemia management in CKD. This study provides valuable evidence that lactoferrin and IV iron dextran, when used adjunctively with ESA, have varying effects on different parameters associated with hematological health. While both maintain similar hematological outcomes, their distinct impacts on inflammatory and iron metabolism markers highlight the need for further mechanistic and long-term studies to determine their relative value in pediatric CKD-related anemia. Its strengths include a randomized, parallel, and controlled trial design, a well-matched study population, and clinically relevant findings applicable to pediatric CKD management. Despite promising results, the lack of established dosing guidelines remains a limitation. Further research should explore the function and role of GDF-15 in CKD anemia and its potential as a surrogate marker. Given lactoferrin's safety and adherence benefits, it represents a promising therapeutic option requiring further investigation to optimize its use in pediatric CKD patients.

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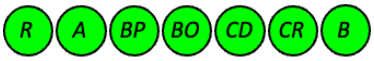
***ISN Academy: Dialysis***

## Predialytic oral protein supplementation in hemodialysis: impact on nutrition and quality of life

**The impact of predialytic oral protein-based supplements on nutritional status and quality of life in hemodialysis patients: a randomized clinical trial**

Elsayed et al., 2025.




*Reviewed by Ahad Qayyum*

**Summary:** This multi-center randomized control trial aimed to assess the effect oral protein supplementation (25 grams of protein powder; Fresubin) on the nutritional status and quality of life in chronic hemodialysis patients. A total of 100 patients were randomized into two groups: Group 1 received the oral protein supplement one hour before each dialysis session, while Group 2 followed their usual diet. Both groups had their clinical, nutritional, anthropometric, quality of life, dialysis adequacy and median subjective global assessment measurements done at baseline and the end of the 3-month study period. This study showed that the supplemented patients showed a significant increase in serum albumin ($p< 0.001$), improvements in three Kidney Disease Quality of Life-36 subscales, and a non-significant improvement in their median subjective global assessment score from baseline. However, supplemented patients had significantly higher blood pressure ($p= 0.037$), lower urea reduction ratio ($p= 0.020$), lower Kt/V ($p= 0.021$), higher serum calcium, lower total cholesterol and lower CRP ($p=0.047$). Adverse events, body mass index and anthropometric measures did not differ between the groups.

**Comment**: This trial provides valuable insights into the potential benefits of oral protein supplementation before hemodialysis sessions. The significant improvement in serum albumin and quality of life scores highlights the possible role of protein supplementation in addressing malnutrition, a common challenge in dialysis patients. While the study is well designed, it has a relatively small sample size with a short follow-up period, limiting the ability to draw long-term conclusions. More extensive pragmatic randomized studies with extended follow-up are needed to confirm these findings and determine pre-dialysis protein supplementation's safety, tolerability and sustainability as a routing strategy in hemodialysis care.

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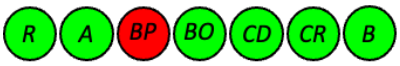
***ISN Academy: Dialysis***

## Assessing Apixaban for preventing recurrent thrombosis after thrombectomy in hemodialysis vascular access

**A randomized controlled trial evaluated the efficacy and safety of apixaban for prevention of recurrent thrombosis after thrombectomy of hemodialysis vascular access**

Ko et al., 2025.




*Reviewed by Nayef Habashi*

**Summary:** Thrombosis in vascular access sites is a common complication in hemodialysis patients, often leading to access failure, repeated interventions, and poor patient outcomes. Apixaban, a direct oral coagulation factor Xa inhibitor, has been used in other thrombotic conditions but has not been studied in hemodialysis vascular access patients. This trial, therefore, aimed to evaluate the efficacy and safety of apixaban in preventing recurrent thrombosis after thrombectomy in patients with hemodialysis vascular access. One hundred eighty-six participants were randomly assigned to receive either apixaban (2.5 mg twice daily for 3 months, n=93) or a placebo (n=93) within 48 hours after successful endovascular thrombectomy. Anti-platelet therapy was mandated for the first 14 days after thrombectomy in both groups and then continued as needed. At three months, the incidence of recurrent access thrombosis was significantly lower in the apixaban group compared to the placebo group (24% vs. 40.8%; HR 0.52 [95% CI 0.31-0.88]; P=0.01) with better primary patency failure rates (32.2% vs 49.5%, HR 0.57 [0.36-0.91]; P=0.02). The rate of major bleeding complications was similar between both groups (2.2% in apixaban vs. 4.3% in placebo). However, minor bleeding events were more frequent in the apixaban group (22.6% vs. 7.5%; P=0.01). These findings suggest that apixaban effectively reduces the recurrence of thrombosis after thrombectomy in hemodialysis patients. While more minor bleeding events were noted, they did not lead to severe clinical outcomes.

**Comment**: This trial addresses an essential issue in managing patients undergoing hemodialysis—recurrent thrombosis at the vascular access site. These complications can lead to frequent interventions, reduced dialysis efficiency and poorer patient outcomes. While apixaban is widely used in other thrombotic conditions, its use in the specific setting of hemodialysis vascular access remains relatively unexplored. Some patients may have contraindications to anticoagulants or a high bleeding risk, so careful selection of candidates is crucial. The study demonstrated that apixaban effectively reduced the recurrence of thrombosis after thrombectomy compared to placebo, with no significant increase in major bleeding events. These findings suggest that apixaban could be a helpful strategy for preventing thrombosis in this high-risk population. Future research should include larger, multicenter randomized controlled trials with extended follow-up to assess long-term safety, durability of benefit, and overall survival impact. Pragmatic trials comparing apixaban to standard anticoagulation (e.g., warfarin or low-dose heparin) in real-world settings could provide further insights into its relative efficacy and safety. Studies incorporating patient-reported outcomes, and cost-effectiveness analyses would also be valuable in determining apixaban's overall impact on dialysis care. Strengthening this evidence base would help guide anticoagulation strategies in hemodialysis patients and inform clinical practice.

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