

ISN Trial-List

March 2019



Once a month, the ISN-ACT (Advancing Clinical Trials) team collects and publishes a list of important nephrology trials from the latest medical literature. Each trial is reviewed in context and their risk of bias in seven key areas assessed.

Key to risk of bias assessment

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|----|------------------------------------|-----------------------------|
| R | Random sequence generation | High risk |
| A | Allocation concealment | Uncertain risk / not stated |
| BP | Blinding of participants/personnel | Low risk |
| BO | Blinding of outcome assessment | |
| CD | Complete outcome data | |
| CR | Complete outcome reporting | |
| B | No other sources of bias | |

ISN Academy: [Fluid and Electrolytes](#), [Hemodialysis](#)

Right on time: scheduling fluid intake may help hemodialysis patients combat thirst

Fluid Distribution Timetable on Adherence to Fluid Restriction of Patients with End-Stage Renal Disease undergoing Hemodialysis: Single-Blind, Randomized-Controlled Pilot Study

[Mina, et al. J Adv Nurs. 2019 Jan 31. doi: 10.1111/jan.13964](#)

Thirst is a common problem in hemodialysis patients and contributes to elevated interdialytic weight gain (IDWG) and the need for more aggressive ultrafiltration, both of which are associated with worse clinical outcomes. Mina, et al. sought to determine if a fluid distribution timetable - a personalized schedule of regular small amounts of fluid over the course of the day - could help patients manage their thirst and IDWG. They performed a single-blind, randomized controlled pilot study enrolling 24 participants on hemodialysis from a single clinic. Participants were randomized to receive a personalized fluid distribution timetable or standard care and were followed weekly for four weeks. While no significant differences in IDWG were observed, there was a significant decrease in thirst score at four weeks in the treatment group (12.6 vs 16.3; $P=0.003$). This pilot study has numerous limitations. In small studies, important baseline differences may not reach statistical significance and yet bias the results and the treatment group was seven years younger on average and may have had greater fluid overload at baseline. However, this study does suggest that this simple technique deserves further evaluation.



ISN Academy: [Anemia, Iron and Trace Elements](#), [Chronic Kidney Disease](#)

HIF stabilizer, enarodustat, could have a role in anemia of CKD

A Placebo-Controlled, Randomised Trial of Enarodustat in Patients with Chronic Kidney Disease Followed by Long-Term Trial

[Akizawa, et al. Am J Nephrol 2019;49:165-174](#)

Hypoxia-inducible factor prolyl hydroxylase inhibitors offer an alternative to erythropoietin stimulating agents (ESAs) and multiple novel agents in this class are currently under investigation. To test the efficacy and safety of enarodustat in patients with non-dialysis chronic kidney disease, Akizawa, et al. randomized 201 participants (94 ESA naïve and 107 on maintenance ESA) into four equal groups who received 2, 4 or 6mg of enarodustat or placebo daily for 6 weeks. In the treatment naïve group, enarodustat resulted in a dose-dependent increase in the rate of rise of hemoglobin ($P<0.0001$) at 6 weeks. In the participants who converted from maintenance ESA, stable hemoglobin levels were achieved in 54.2% of those in the placebo arm, 80.8% in the enarodustat 2 mg arm, 70.4% in the 4 mg arm, and 50.0% in the 6 mg arm. These differences were not statistically significant. All participants then entered a 24 week open-label period where all received enarodustat adjusted to target a hemoglobin 100-120g/l. At the end of this period, 71.4% and 78.9% of participants (in the ESA naïve and maintenance ESA groups, respectively) had hemoglobin levels in the target range. There were no significant differences in adverse events. This study suggests that enarodustat is safe and effective in the short term. Longer term studies against an active comparator may be warranted.



Denosumab vs alendronate: Mixed effects of antiresorptives in patients receiving dialysis

Effects of denosumab and alendronate on bone health and vascular function in hemodialysis patients: A randomized, controlled trial

[Iseri, et al. J Bone Miner Res. 2019 Jan 28. doi: 10.1002/jbmr.3676](#)

While antiresorptive agents such as bisphosphonates and denosumab have a well-established role in the management of primary osteoporosis, their role and safety profile in advanced CKD is poorly defined. This open-label study enrolled 46 hemodialysis patients with confirmed osteoporosis and without prior antiresorptive treatment. Participants were randomized to denosumab (6 monthly) or alendronate (every 4 weeks). Both groups received prophylactic calcium and calcitriol supplementation for 2 weeks following their injection. At 12 months, there was a similar improvement in lumbar spine bone mineral density (BMD) in the denosumab arm (+5.6% ± 4.3%) and alendronate arm (+5.4% ± 10.5%). In contrast, neither treatment resulted in significant changes in BMD at the distal radius or femoral neck. Significant reductions in markers of bone turnover were noted in both arms. Interestingly, there were no significant changes seen in either group on tests of vascular function and calcification (including coronary artery calcification and brachial-ankle pulse wave velocity and flow mediated dilatation). Although there was no significant difference in the absolute number of SAEs between the groups (p=0.5036), there were more episodes of early hypocalcemia with denosumab (p=0.0431) and early hypercalcemia with alendronate (p=0.0402). This study raises important questions about the benefits of antiresorptive therapy in patients receiving hemodialysis. It is not clear that an isolated improvement in lumbar spine BMD is of sufficient benefit to justify treatment. However, further studies with larger sample sizes, a placebo comparator and patient centred outcomes would help to clarify this issue.



Zoledronate does not increase adynamic bone disease post-transplant but has mixed effects on other measures of bone health

A Randomized Trial of Zoledronic Acid to Prevent Bone Loss in the First Year after Kidney Transplantation

[Marques, et al. J Am Soc Nephrol. 2019;30\(2\):355-65](#)

Bisphosphonates are thought to prevent bone loss after kidney transplantation based on improvements in bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry (DEXA). However, their effects on bone histomorphometry and BMD as measured by high-resolution peripheral quantitative computed tomography (HR-pQCT) are unclear. Moreover, concern remains regarding the risk of adynamic bone disease. Marques, et al. randomized 34 adults undergoing living donor renal transplantation (receiving tacrolimus-based immunosuppression and with an eGFR >30ml/min/1.73m² within the first week of transplant) to zoledronate 5mg versus no treatment and followed them for 12 months. All participants received cholecalciferol 50,000 IU monthly. Overall, transplantation itself was followed by an increase in BMD at the lumbar spine and total hip on DEXA, but also by a decrease in trabecular (but not cortical) BMD at the tibia and radius on HR-pQCT. On bone biopsy, transplantation was followed by a reduction in bone turnover and bone volume at 12 months (P<0.001 for turnover, P=0.01 for volume). The primary outcome of adynamic bone disease on bone biopsy at 12 months was similar in the zoledronate group compared to no treatment (43% versus 61%, P=0.48). Zoledronate was associated with improvement in BMD (by DEXA) compared to no treatment at the lumbar spine ([% change] 5.6% vs 1.1%; P=0.04) and femoral neck (5.8% vs. 2.5%; P=0.03) but no difference for total hip BMD. In addition, there were no differences in change in HR-pQCT or bone biopsy parameters between those assigned to zoledronate or no treatment. These results suggest that kidney transplantation decreases bone turnover and is associated with loss of trabecular bone in the peripheral, but not central, skeleton. Zoledronate may attenuate bone loss in the central skeleton (as measured by DEXA) but showed no benefit in addition to cholecalciferol in all other outcomes including bone histomorphometry. No firm conclusions can be drawn from this small, single centre study, however it may help in the design of future studies powered to determine the optimal screening tools and treatments for this complex disease state.

