Sparsentan could address unmet need in IgA nephropathy: interim analysis from the PROTECT Trial

Hydrochlorothiazide and prevention of kidney-stone recurrence


Summary: The PROTECT Trial is a phase 3 double-blind trial that compares sparsentan, a dual endothelin (ETₐ) receptor and angiotensin (AT₁) receptor blocker, to an active control, irbesartan, in adults with biopsy-proven IgA nephropathy (IgAN), eGFR ≥30mL/min/1.73m² and proteinuria ≥1.0g/day despite maximized renin-angiotensin system blockade for at least 12 weeks. In this prespecified interim analysis, across 404 participants randomized to sparsentan 400mg daily (n=202) or irbesartan 300mg daily (n=202), sparsentan-treated participants had significantly reduced proteinuria (urine protein creatinine ratio) at 36 weeks compared to baseline (-49.8%), while irbesartan-treated participants showed a smaller reduction (-15.1%). This resulted in a relative reduction in proteinuria between the groups of 41% (geometric least squares mean ratio [sparsentan/irbesartan] = 0.59; 95% confidence interval [CI] 0.51 to 0.69; p<0.0001). In terms of safety, treatment emergent adverse events were comparable between the two groups, although peripheral oedema (14% vs 9%), hypotension (14% vs 6%) and dizziness (13% vs 5%) were more common among sparsentan-treated participants. There was no increase in the risk of heart failure events, which have been seen with other endothelin receptor antagonists, noting that participants with New York Heart Association Class II-IV failure were excluded.

Comment: IgAN is the most common primary glomerular disease and an important cause of kidney failure worldwide. Recent years have seen growing interest in identifying effective therapeutic approaches to manage this disease. Systemic steroids were shown to reduce the risk of kidney function decline in the TESTING trial although concerns remain on systemic side effects. The two SGLT2 inhibitor trials, DAPA-CKD and EMPA-Kidney, included subgroups with IgAN and found that SGLT2i’s reduced kidney disease progression overall. Now the PROTECT trial has produced promising results for sparsentan. Earlier studies have suggested that endothelin-1 contributes to podocyte dysfunction and fibrosis through activating ETₐ receptors, which can be antagonized with sparsentan. The interim results of this industry-sponsored trial have shown that short-term treatment with sparsentan produced greater reduction in proteinuria than irbesartan alone, with a comparable safety profile. The trial is ongoing, and participants will continue to be followed for a total of 114 weeks, with an open label extension period for an additional 156 weeks, thereby allowing testing of the effects of sparsentan on the progression of chronic kidney disease and providing further safety information. The open label period will also allow the addition of SGLT2i, which may yield helpful information about the effect of combination therapy. In the meantime, sparsentan has received accelerated approval by the US Food and Drug Administration for reduction of proteinuria in adults with IgAN at high risk of disease progression.
Team-based coaching in a virtual learning collaborative with automated outcome surveillance effectively reduced contrast-associated AKI in the IMPROVE-AKI trial

Team-based coaching intervention to improve contrast-associated acute kidney injury: a cluster-randomized trial


Reviewed by Rupesh Raina

Summary: The IMPROVE AKI trial employed a factorial 2x2 cluster-randomized design over 18 months to evaluate prevention strategies for reducing postprocedural, contrast-associated acute kidney injury (AKI) due to diagnostic coronary angiography or percutaneous coronary interventions, both overall and for those with CKD (eGFR <60mL/min/1.73m²), not on dialysis. The study involved four methods of implementing an AKI Prevention Toolkit based upon KDIGO guidelines, which promotes standardized test order sets, guideline-directed intravenous/oral volume expansion, and reduced contrast volume. The treatment arms were (1) a Virtual Learning Collaborative (Collaborative model) involving monthly 60-minute group training calls with a Quality Improvement and Collaborative improvement specialist, and Automated Surveillance Reporting (Surveillance) providing site-level AKI performance over time, (2) Virtual Learning Collaborative without Surveillance, (3) Technical Assistance (Assistance Model) consisting of monthly 60-minute calls from an AKI improvement specialist to each site, with Surveillance; and (4) Technical Assistance without Surveillance. The study involved 20 Veterans Affairs medical centers (VAMCs) and 4,517 procedures, of which 1,314 involved participants with established CKD. There were 510 AKI events within 7 days of procedures, including 235 events among those with CKD. Across participants with or without CKD, AKI was prevalent among 13% in the Collaborative arm without Surveillance and 8% with Surveillance, while it was observed among 13% of participants in the Assistance arm without Surveillance and 11% with Surveillance. The combined Collaborative arms, as compared with the Assistance arms, were independently associated with a 28% reduction in the adjusted odds ratio of AKI, which was statistically significant following a Bonferroni correction (0.72; 0.58– 0.88; p=0.002). Surveillance was not associated with a statistically significant improvement in AKI rates. Among the subgroup of participants with CKD, there was no significant reduction in events within either the Collaborative or the Surveillance interventions. The Collaborative with Surveillance intervention had a 46% decrease in the odds of AKI and an absolute risk reduction of 5%, aligning with this study’s hypothesis as the best prevention protocol.

Comment: The authors suggest the results support the proposition that applying evidence-based AKI prevention guidelines was most effective in a Collaborative model with a Surveillance dashboard framework, resulting in a reduction in AKI events. There are some limitations to feasibility identified by the authors, including one Assistance with Surveillance VAMC site dropping out, variable monthly call attendance (41-81%), and missing postprocedural serum creatinine values for over half of the VAMC cohort. Comparison to a control group with no intervention would also be illustrative of the added value of this approach, particularly as the Collaborative and Assistance models appear somewhat similar in nature, but this wasn’t tested. Compared to the Contrast-Reducing Injury Sustained by Kidneys (Contrast RISK) trial, this study did achieve a notably greater reduction in AKI risk. Future implementation research should address the sustainability of these models post-training and their potential for scalability.

It’s a ‘no’ for nicotinamide as an add-on to phosphate binders in hemodialysis patients with hyperphosphataemia

Modified-release nicotinamide for the treatment of hyperphosphatemia in hemodialysis patients: 52-week efficacy and safety results of the phase 3 randomized controlled NOPHOS trial


Reviewed by Megan Borkum

Summary: In a previously reported initial phase of the NOPHOS study, investigators assigned 539 adult maintenance hemodialysis (HD) participants with serum phosphate levels ≥4.5 mg/dL and <8.7mg/dL, despite 1-2 phosphate binders, to receive nicotinamide modified release (NAMR; 250-1500mg/d) and 183 participants to receive placebo (3:1 randomization). The initial NAMR dose was 500mg/d for 2 weeks and could then be adjusted at further visits for efficacy. Some participants with secondary hyperparathyroidism also received active vitamin D analogues and calcimimetics. After 12 weeks, serum phosphate concentration was significantly lower (by 0.51 mg/dL) in the NAMR
versus placebo group (5.36 vs 5.88mg/dL, p<0.0001). In the current extension phase, at 24-weeks follow-up, serum phosphate remained significantly lower in the NAMR group compared with the placebo group (5.40 vs 5.79mg/dL, p<0.001) with a mean difference of −0.39mg/dL. However, a sustained treatment effect up to week 52 was not achieved in the intention to treat NAMR population versus placebo (5.66 vs. 5.75mg/dL, p=0.44) with a mean difference of 0.08mg/dL. In this continuation phase, co-medication could be adjusted; fewer participants receiving NAMR required rescue therapy for hyperphosphatemia (9.5% vs 16.4%). There was an increased occurrence of adverse events in the NAMR group consistent with previous studies, including diarrhea (44.4% vs 27.9%), thrombocytopenia (5.2% vs 1.1%), anemia (11.1% vs 7.1%) and pruritis (13.7% vs 6.6%). However, new safety signals were identified including Herpes Zoster infections which occurred exclusively in the NAMR group (29 vs 0 events). Serious adverse events and mortality were comparable between the 2 groups.

Comment: Nicotinamide (NA), a drug previously used to regulate lipid metabolism, has been experimentally found to lower serum phosphorus. NA is a known inhibitor of type-2b sodium-dependent phosphate cotransporters (NaPi-2b) which mediate phosphate reabsorption in the small intestine. This trial did not, however, provide evidence for the long-term safety and efficacy of NAMR added on to phosphate binders for HD patients with hyperphosphatemia. Several factors may have contributed to these negative findings including a high non-compliance rate in the study (confirmed by serum NA metabolite levels) as well as the inclusion of patients with severe secondary hyperparathyroidism which could mitigate the sustained phosphate-lowering effects of NAMR.

**Mycophenolate mofetil reduces the risk of IgA nephropathy progression**

Effectiveness of mycophenolate mofetil among patients with progressive IgA nephropathy a randomized clinical trial

**Hou FF et al. JAMA Network Open, (2023).**

Reviewed by Nikolay Bulanov

**Summary:** In this single-center, open-label, blinded end-point trial, 170 adult participants with IgA nephropathy (IgAN) and proteinuria greater than 1.0 g/d, and either reduced eGFR (>30 to <60 mL/min/1.73m²) or persistent hypertension, were randomized to receive either supportive care (SC; losartan with or without another antihypertensive agent), or SC with the addition of mycophenolate mofetil (SC+MMF). Mycophenolate was dosed at 1.5g daily for 12 months then 0.75-1.0g for at least 6 months. All participants underwent a 12-week run-in period, during which they were treated with SC to achieve a blood pressure of <130/80mmHg. During the 3-year trial phase, the primary composite end-point of doubling of serum creatinine, kidney failure with or without kidney replacement therapy, or death due to kidney or cardiovascular disease occurred significantly less frequently in the MMF+SC group (7.1%) than in the SC group (21.2%; adjusted HR, 0.23; 95%CI, 0.09 to 0.63). The secondary end-point of kidney disease progression also occurred less frequently in the MMF+SC group (8.2%) than in the SC group (27.1%; adjusted HR 0.23; 95%CI 0.10 to 0.57). During post-trial follow-up at a median length of 60 months, annual loss of eGFR accelerated after discontinuation of MMF from 2.9 to 6.1mL/min/1.73m². Gastrointestinal symptoms as well as infections were more common in the MMF group.

**Comment:** While the role of immunosuppressive therapy in IgAN has remained controversial for many years, recent evidence with glucocorticoid use in the TESTING trial has supported its potential benefits in terms of kidney function preservation over time. The present trial suggests a significant advantage of MMF at a lower than usual dose in the treatment of IgAN patients at high risk of disease progression. The trial has several limitations, including open-label single-center design, non-inclusion of patients with proteinuria levels above 3.5g/day, and predominance of patients of Chinese origin with consequently reduced generalizability. Nevertheless, the results indicate a potentially potent benefit of MMF as an alternative to corticosteroids in the treatment of progressing IgAN refractory to SC, that should be studied in further trials.
**Role of continuous positive airway pressure in patients with obstructive sleep apnea and diabetic kidney disease**

Continuous positive airway pressure effect on albuminuria progression in patients with obstructive sleep apnea and diabetic kidney disease: a randomized clinical trial

Zamarrón et al. Am J Respir Crit Care Medicine.

Reviewed by Maria Chiara Pelle

**Summary:** The DIANA study evaluated the long-term effects of continuous positive airway pressure (CPAP) compared with usual care for reducing urinary albumin-to-creatinine ratio (UACR) in participants with obstructive sleep apnea (OSA) and diabetic kidney disease (DKD, defined as either eGFR <30 to <60 mL/min/1.73m² or urine albumin ≥30mg/24 hour). A total of 185 participants were randomized to receive CPAP and usual care (n=93) or usual care alone (n=92), of whom a total of 125 participants (68%) were sufficiently adherent to the program over 52 weeks. For the primary outcome of the change in UACR from baseline during treatment, no difference was observed on intention-to-treat analysis, but among the 125 adherent participants, CPAP treatment was associated with a greater reduction in UACR (mean difference -10.6%, 95% CI, -19.06 to -2.06%, p=0.015). CPAP was also associated with improvements in HbA1c, sleepiness and quality of life.

**Comment:** OSA is associated with impairment of glycemic control, related at least in part to elevated sympathetic nervous activity, endothelial dysfunction, and renal RAS activity. Current evidence suggests that suppression of apnea–hypopneas by CPAP might improve glycemic control in subjects with diabetes and OSA. This trial evaluated the role of CPAP on complications of diabetes such as DKD, demonstrating improvements in albuminuria, metabolic parameters and quality of life. There was greater improvement in albuminuria among patients with more severe OSA, worse renal function or more recent DKD diagnosis, and above all with better adherence in CPAP treatment (at least 4 hours per night). Limitations of the DIANA study includes difficulties maintaining CPAP adherence, which reflects a similar challenge in real-world care, and the White European predominance, which limits generalizability. Further studies would be needed to confirm these important findings.

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**Usage of vitamin D in a high dose didn’t show non-skeletal benefits in kidney transplant recipients, but reduced fracture frequency compared with low-dose**

Nonskeletal and skeletal effects of high doses versus low doses of vitamin D3 in renal transplant recipients:

Results of the VITALE (VITamin D supplementation in renAL transplant recipients) study, a randomized clinical trial


Reviewed by Anastasiiya Zykova

**Summary:** This prospective double-blind trial recruited 536 non-diabetic kidney transplant recipients with vitamin D deficiency (mean baseline 25-hydroxy vitamin D level 19-20ng/ml), to receive high or low dose vitamin D, i.e. 100 000 IU or 12 000IU, every 2 weeks for 2 months and then monthly for 22 months. All participants were transplanted 12 to 48 months prior to randomization; almost 60% of the participants in each group were on corticosteroid treatment. In the intention-to-treat cohort, the frequency of the first event of the composite primary end-point (de novo diabetes mellitus or major cardiovascular event or de novo cancer or death) was similar between the two groups at 24 months (15% vs 16%, hazard ratio [HR] 0.94 [95% CI 0.6 to 1.48], p=0.78). The incidence of symptomatic fracture was lower in the high-dose group (1% vs 4%, odds ratio [OR] 0.24 [0.07 to 0.86], p=0.03) and, as expected, this group had more rapid increase in vitamin D serum concentration and reduction in PTH. Protocol deviations were recorded for ~ 60% of participants in both groups, predominately due to non-compliance. According to per-protocol analysis, the rate of a first event of the composite end-point was markedly lower in the high-dose group (HR 0.37 [0.15 to 0.9], p=0.03), relating predominantly to fewer major cardiovascular events, while the rate of symptomatic fracture was the same between the groups (OR 0.18 [0.02 to 1.58], p=0.12). Generally, the treatment was well-tolerated, except for higher rates of hypercalciuria in the high dose group.

**Comment:** Recipients of kidney transplants are at greater risk of metabolic disorders due to immunosuppressive agents and CKD, and evidence from the general population suggests that higher dose vitamin D supplementation may have benefits for cardiovascular, diabetes and cancer risk. The VITALE trial supports the idea that the target level of vitamin D should be more than 30 ng/ml in these patients, due to reductions in the risk of fracture and improved...
vitamin D and PTH dynamics. The present study did not, however, demonstrate improvement in non-skeletal outcomes on intention-to-treat analysis, although it is unclear whether this relates to lack of efficacy, dose selection, non-compliance, or the relatively young age of participants reducing the likelihood of events within the 2-year follow-up period. The per protocol analyses should be interpreted with some caution given potential bias due to non-random participant drop-out. The dose-dependent hypercalciuria also raises some concerns about long-term safety.

Edited by Daniel O’Hara, Michele Provenzano, Neeru Agarwal and Anastasiia Zykova