Global Trials Focus

June – July 2024

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

FLOWing Benefits of Semaglutide in People with Type 2 Diabetes and CKD

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Perkovic et al, NEJM, 2024, July 11;391(2):109-121.

R A BP BO CD CR B

Reviewed by Michele Provenzano

Summary: The FLOW study evaluated the efficacy and safety of using semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), for preventing kidney failure, loss of kidney function, and death from kidney or cardiovascular (CV) causes in patients with type 2 diabetes and chronic kidney disease (CKD). A total of 3533 participants (mean age 66.6 years, 30% female, mean eGFR 47ml/min/1.73m^2, median urine albumin-to-creatinine ratio [uACR] 567.6mg/g) on stable maximal therapy with renin-angiotensin system inhibitors (RASi), were randomized (1:1) to either weekly subcutaneous semaglutide (n=1767; starting at 0.25mg weekly and uptitrating every 4 weeks to maximum dose of 1mg weekly) or placebo (n=1766) for a mean follow-up of 3.4 years. Sodium-glucose co-transport 2 inhibitors (SGLT2i) and mineralocorticoid receptor antagonists (MRAs) were allowed, and randomization was based on using SGLT2i at baseline. The primary endpoint was a composite of major kidney events, including the onset of kidney failure (persistent eGFR <15ml/min1.73m2 or initiation of dialysis or kidney transplantation), a persistent >=50% reduction in eGFR, or death from kidney or cardiovascular (CV) causes. Secondary endpoints included the annual rate of change in eGFR (total eGFR slope), major CV events, and death from any cause. The risk of primary events was 24% lower in the semaglutide group compared to the placebo group (331 vs 410 events; hazard ratio [HR], 0.76; 95% confidence interval [CI] 0.66-0.88; P=0.0003). Results for all secondary endpoints favoured the semaglutide group compared to placebo, which showed a slower mean annual decline in eGFR (by 1.16 ml/min/1.73m^2; P <0.001), an 18% lower risk of major CV events (HR, 0.82; 95% CI, 0.68-0.98; P=0.029), and a 20% lower risk of death from any cause (HR, 0.80; 95% CI, 0.67-0.95, P=0.01). Other efficacy results included a greater reduction in uACR by 38% at 104 weeks, a lower loss of kidney function as calculated based on cystatin C-eGFR (3.39 ml/min/1.73m^2), and greater mean weight loss (4.1kg) in the semaglutide group. Serious adverse events were fewer in the semaglutide group than in the placebo group (49.6% vs 53.8%), although treatment discontinuation was more common (13.2% vs 11.9%), mainly driven by gastrointestinal side effects (4.5 vs 1.1%)

Comment: Patients with type 2 diabetes and CKD are at high risk for CV events and death. The FLOW study of a large, diverse population of people with diabetes and CKD shows that administering 1.0 mg weekly semaglutide

reduces the risk of major kidney events by 24%, CV outcomes, and death while slowing the decline of eGFR. Current guidelines recommend RASi, SGLT2i, and MRAs for kidney protection; semaglutide could be an additional option. Given the timing of the study, FLOW was not designed to evaluate semglutide with other new agents, including SGLT2i and non-steroidal MRAs. Despite the large sample size, there were relatively few patients to allow meanginful evaluation of semaglutide in the context of SGTL2i. However, no differences were found between patients taking SGLT2i and those not. Future studies should evaluate timing and combination therapies but also further evaluate semaglutide for side effects, such as gastrointestinal issues and increased hypoglycemia risk in combination with SGLT2i. The mechanisms by which semaglutide is nephroprotective are under study and are postulated to be multifactorial (direct actions on the kidney in addition to their indirect actions that improve conventional risk factors for diabetic kidney disease).

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*ISN Academy: **Dialysis***

Depression Management with Sertraline in Maintenance Hemodialysis Patients

The Efficacy and Safety of Sertraline in Maintenance Hemodialysis Patients With Depression: A Randomized Controlled Study

Zhang et al, J Affect Disord, 2024 May, 1:353:60-66

Reviewed by Marimar Contreras Nieves

Summary: This study evaluated the efficacy and safety of sertraline in 125 maintenance hemodialysis patients with depression, defined as Hamilton Depression Rating Scale (HAMD) scores of 8 or higher. Participants were randomized (1:1) to the treatment group (sertraline, initial dose 25-50 mg daily and up-titrated to response) or the control group (no antidepressants). Parameters compared after 12 weeks included HAMD, Medication Adherence Report Scale-5 (MARS-5), Mini Nutritional Assessment short-form (MNA-SF), and Kidney Disease Quality of Life-36 (KDQOL-36) scores, along with clinical and laboratory indicators and drug-related adverse reactions. At baseline, the groups had no significant demographic or clinical differences. After 12 weeks, HAMD scores in the treatment group decreased from baseline (96.8% effective rate, z=-6.8, p<0.001) and were lower than those in the control group (z=-6.2, p<0.001). The KDQOL-36, MARS-5, and MNA-SF scores in the treatment group significantly improved from pre-treatment levels and were superior to those in the control group. Albumin and hemoglobin levels in the treatment group significantly increased, while C-reactive protein significantly decreased. Twelve patients in the treatment group experienced mild nausea, and one experienced somnambulism, but most could continue treatment with dose adjustments.

Comment: Depression is a common, often overlooked, mental health disorder in maintenance hemodialysis patients, seriously affecting their quality of life and contributing to higher cardiovascular risk and mortality. There are few evidence-based pharmacologic and non-pharmacologic treatments for depression in people on hemodialysis. This study adds to current evidence for sertraline use in such patients, showing an effective and safe reduction of depressive symptoms and improving quality of life, treatment adherence, nutritional status, chronic inflammation, and anemia. However, this is a small, single-centre study with a short follow-up period. Larger, multicenter trials are needed to confirm these findings.

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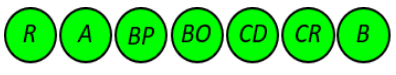
*ISN Academy: **Hypertension***

A New Intervention for TARGETing Resistant Hypertension

Effect of Alcohol-Mediated Renal Denervation on Blood Pressure in the Presence of Antihypertensive Medications: Primary Results From the TARGET BP I Randomized Clinical Trial

Kandzari et al, Circulation, 2024 Jun 11;149(24):1875-1884



Reviewed by Megan Borkum

Summary: The TARGET BP I study evaluated the efficacy and safety of a new renal denervation (RDN) method using dehydrated alcohol. It enrolled 301 adults with uncontrolled or treatment-resistant hypertension (office systolic BP

150-180 mmHg, office diastolic BP ≧90 mmHg, and mean 24-hour ambulatory systolic BP 135-170 mmHg, despite 2-5 antihypertensive medications, including diuretics). Participants were randomly assigned 1:1 to receive either RDN or a sham procedure. The primary endpoint was the mean 24-hour ambulatory systolic BP change at 3 months, adjusted for baseline. Secondary endpoints included mean differences in office and ambulatory BP between the groups at various times. Blood and urine tests were conducted to assess adherence to BP medication. The average age of the cohort was 56.1 years, with approximately 74% being men, and most were prescribed 3 or more antihypertensives at baseline. Compared to the sham controls, RDN led to a significant reduction in 24-hour ambulatory systolic BP at 3 months, with mean reductions of –10 mmHg for RDN versus –6.8 mmHg for the sham procedure, resulting in a treatment difference of –3.2 mmHg (95% CI, –6.3 to 0; P = 0.0487). At 3 months, the mean change in office systolic BP was –12.7 mmHg for the RDN group and –9.7 mmHg for the sham group, yielding a non-statstically siginifcant treatment difference of –3 mmHg (95% CI, –7 to 1; P = 0.173). During the study, there were no significant differences in ambulatory or office diastolic BP, medication changes or patient adherence. At 6 months, adverse safety events were rare, with one case of accessory renal artery dissection in the RDN group (0.7%).

Comment: This is the largest trial to date assessing alcohol-based RDN among patients with resistant hypertension. Alcohol-based RDN was associated with a reduction in 24-hour ambulatory systolic BP at 3 months, thus meeting the trial's primary endpoint. However, there were no significant differences between the two groups in terms of systolic or diastolic office BP at 3 months, as those receiving the sham procedure also experienced a substantial drop in office BP. Investigators speculate that similar to previous renal denervation trials, all participants adhered more consistently to their BP medications during the trial, which could account for the improvement. Nevertheless, this method appeared safe, but a longer-term evaluation is ongoing to assess sustained BP reduction in the RDN group and potential loss of BP control in the sham group. Larger, more varied populations should also be studied.

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

Is Clinical Decision Support Helpful to "NUDGE" Primary Care Practitioners in Determining the Best Way to Control Arterial Hypertension in CKD?

Clinical Decision Support for Hypertension Management in Chronic Kidney Disease: A Randomized Clinical Trial

Samal et al., JAMA Intern Med. 2024 May 1;184(5):484-492

Reviewed by Anastasiia Zykova

Summary: This trial randomised 174 primary care practitioners (PCPs) to a computerised clinical decision support system (CDSS) that delievered tailored, evidence-based recommendations for CKD patients with uncontrolled hypertension or the usual care group. Inclusion criteria for the study were patients with stage 3-4 CKD and uncontrolled hypertension, defined as having a systolic blood pressure (SBP) >140 mmHg at baseline with at least 1 outpatient visit documenting a SBP >140mmHg within two years preceding the trial. The CDSS consisted of a set of 5 best practice advisories built into the software. When patients meet certain criteria, such as a low dose of ACE inhibitor on their medication list, a special alert was sent to the PCP with an explanation and advice to correct drug dosage, check an additional metabolic panel, and consider referral to a nephrologist. Another nudging element to this intervention was the need for a justification from the PCP in case of unprescribed recommendations. At 180 days, the change in mean SBP, the primary endpoint, was greater in the intervention group than in the usual care group (-14.6 mmHg vs -11.7 mmHg; P=0.005). However, the overall percentage of patients achieving BP control, defined as <140/90 mmHg, at 180 days was the same in both groups. In addition, there was a higher rate of new antihypertensive prescriptions *de novo* and dosage corrections in the intervention group as per the CDSS recommendations compared with the usual care group. Notably, at 180 days eGFR was ordered in only 68% of patients and UACR in 11% of patients.

Comment: Awareness of CKD is increasing worldwide, but outcomes are not meeting targets, and prognosis remains poor. According to the well-known GBD study, CKD will be the fifth leading cause of death worldwide by 2040. Meanwhile, most patients are still cared for by primary care practitioners, who sometimes may be challenged with CKD care protocols. Trials of computerised CDS systems have shown mixed results, so it is still difficult to conclude how such a possibly costly implementation can change clinically relevant outcomes such as eGFR slope or major adverse cardiovascular events. Although the primary endpoint was met in this trial, the mean change in SBP was not

clinically significant, and the percentage of patients achieving adequate control (<140/80 mmHg) was similar. Another interesting point is that, despite all the efforts, we have not yet achieved the desirable frequency of eGFR and UACR measurements, so the question of "Do we have enough building blocks for a choice architecture?" is still open.

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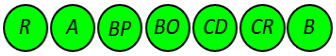
*ISN Academy: **Acute Kidney Injury***

From Fertilizer to Lifesaver: Inorganic Nitrate Improves Kidney and Cardiovascular Outcomes After Coronary Angiography

Inorganic Nitrate Benefits Contrast-Induced Nephropathy after Coronary Angiography for Acute Coronary Syndromes: The NITRATE-CIN Trial

Jones et al, Eur Heart J, 2024 May, 13;45(18)1647-1658



Reviewed by Kate Brotherton and Pedro Franca Gois

Summary: The NITRATE-CIN trial evaluated the efficacy of oral inorganic nitrates in preventing contrast-induced nephropathy (CIN). A total of 640 participants who were undergoing coronary angiography for non-ST-elevation acute coronary syndrome and considered at risk of CIN, including having established CKD (eGFR >20ml/min/1.73m^2), were randomized. The intervention group (n=319) received daily potassium nitrate capsules (12mmol) for 5 days before angiography, and the placebo group (n=321) received potassium chloride capsules per the same regime. The mean age of participants was 71 years, with 73% male and 75% Caucasian; 46% had diabetes, and 56% had CKD. Inorganic nitrates significantly reduced the incidence of CIN compared to placebo (9.1% vs 30.5%, p<0.001). This difference persisted after adjustment for baseline creatinine concentration and diabetes status (OR 0.21; 95% CI 0.13 to 0.34). Overall, 20% experienced CIN, and stage 1 AKI was the most common (91.9%), with a rate of 8.3% in the intervention group compared to 28% in the placebo group. The intervention was also well tolerated, with improved 3-month kidney function (eGFR change between groups 5.17; 95% CI 2.94-7.39, P<0.001), reduced 1-year major adverse cardiovascular events (9.1% vs 18.1%, P=0.001) and reduced 1-year major adverse kidney events, defined as all-cause mortality, new-onset kidney replacement therapy or persistent worsening kidney dysfunction (10.7% vs 28.4%, OR 0.30; 95% CI 0.20-0.46, P<0.001), compared to placebo.

Comment: The NITRATE-CIN trial demonstrated compelling results for the efficacy of inorganic nitrates in reducing the burden of CIN. The choice of inorganic nitrate as the intervention was based on its ability to reduce oxidative stress, a key factor in the pathophysiology of CIN, and is supported by previous research conducted by this group. It is uncertain whether the trial intervention directly prevented major cardiac and kidney outcomes at 3 months and 1 year as other patient-related factors during follow-up, such as proteinuria, hospitalizations or recurrent AKIs, were not assessed. Nevertheless, the intervention's simplicity, cost-effectiveness, and minimal side-effect profile provide a foundation for translation into clinical practice. It may also encourage future studies to explore long-term outcomes and broader applications of inorganic nitrates in non-coronary contrast studies.

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*ISN Academy: **Transplant***

Effect of Spironolactone on Kidney Function in Kidney Transplant Recipients

Effect of Spironolactone on Kidney Function in Kidney Transplant Receipients (the SPIREN trial): A Randomized Placebo-Controlled Clinical Trial

Mortensen et al, Clin J Am Soc Nephrol, 2024 Jun 1;19(6)755-766

Reviewed by Rupesh Raina

Summary: This trial, known as the SPIREN trial, was conducted to evaluate the effect of spironolactone on kidney function in kidney transplant recipients. Of the 950 patients assessed, 180 eligible patients were randomized in a 1:1 ratio to receive either spironolactone (initial dose 25mg daily, up titrated if tolerated) or placebo. The trial spanned 3 years, with the primary outcome being the change in measured glomerular filtration rate (GFR). The kidney allograft biopses were assesed in 60 patinets with 48 follow-ups. Secondary outcomes included 24-hour

proteinuria, kidney allograft fibrosis, and cardiovascular events. Key findings of the trial indicated that the spironolactone group experienced a significant initial decrease in measured GFR by 7.6 ml/min (95% CI, -10.9 to -4.3) compared to the placebo group. This reduction was independent of the time since transplantation and blood pressure, showing no long-term effect on the kidney function curve throughout the intervention. Although there was a transient reduction in 24-hour proteinuria in the spironolactone group after one year, this effect was not sustained in subsequent years. Additionally, there was no significant impact on the progression of interstitial fibrosis in kidney allograft biopsies between the 2 groups. The change in fibrosis from baseline to 2 years did not differ significantly, with the spironolactone group showing a change of -0.52 (95% CI, -5.22 to 4.18) compared to -3.08 (95% CI, -8.44 to 2.28) in the placebo group (P = 0.47). For cardiovascular outcomes, no significant differences were observed between the groups, with both experiencing similar rates of adverse events.

Comment: Calcineurin inhibitor (CNI) nephrotoxicity in kidney transplant recipients, characterized by arteriolar hyalinosis, interstitial fibrosis, and tubular atrophy, leads to kidney inflammation and ischemia. While mineralocorticoid antagonists (MRAs) like spironolactone are effective in heart failure and chronic kidney disease, their benefits in kidney transplant patients are not as well-documented. Results from the SPIREN trial found that spironolactone was safe for kidney transplant patients; however, it did not improve long-term kidney function, proteinuria, or interstitial fibrosis over the 3 years. The authors note several limitations, mainly that a follow-up time longer than 3 years may be necessary to detect a minor positive effect of spironolactone in patients with stable kidney function. Despite equal kidney function, the spironolactone group was noted to have older kidney allografts at inclusion and baseline biopsies, indicating more chronic lesions, potentially rendering them less susceptible to the beneficial effect of spironolactone. In addition, the assessment of fibrosis may be underpowered due to the smaller sample size, despity using a quantitive stereology method. This study holds validity as researchers attained the inclusion of a multicenter, national cohort and the use of kidney biopsies in many participants. Therefore, spironolactone may not be beneficial for enhancing kidney transplant outcomes under standard therapy conditions. However, these findings open up potential future research directions, offering hope for ongoing progress to another agents like eplerenone and finerenone.

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