Global Trials Focus

May 2023

The ISN-ACT (Advancing Clinical Trials) team presents this 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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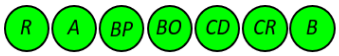
ISN Academy: ***Diabetes***

Ertugliflozin shows promising results in elderly patients: secondary analysis of the VERTIS CV trial

Cardiorenal outcomes, kidney function, and other safety outcomes with ertugliflozin in older adults with type 2 diabetes (VERTIS CV): secondary analyses from a randomised, double-blind trial

Pratley et al., Lancet Healthy Longev. 2023. Apr;4(4):e143-e154.



Reviewed by Anastasiia Zykova

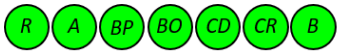
Summary: VERTIS CV was a double-blind multicenter trial recruiting 8246 patients aged ≥ 40 years with type 2 diabetes (HbA1c 7.0–10.5%), atherosclerotic cardiovascular disease, and eGFR ≥30mL/min/1.73m², to receive once-daily ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo. The primary results, published previously (Cannon et al., 2020), showed non-inferiority of the agent for major adverse cardiovascular events (MACE), while a separate analysis demonstrated superiority for prevention of a composite kidney failure outcome (Cherney et al, 2020). The present work is a secondary analysis of the VERTIS CV trial considering the participants' age. Half the trial participants were ≥65 years of age, while 11% were aged ≥75 years. Older-aged participants tended to have longer duration of diabetes, but lower plasma glucose, HbA1c, mean eGFR and BMI. The subgroup analysis with respect to the age (<65 years, ≥65 to <75years, or ≥75 years) showed no significant differences between groups in terms of MACE, cardiovascular death, hospitalization for heart failure, or the kidney composite outcomes. At week 260, the final eGFR was significantly higher and urine albumin-to-creatinine ratio was lower with ertugliflozin versus placebo across all subgroups. The rate of genital mycotic infections was higher with ertugliflozin, but with a similar magnitude of difference from placebo within each age group. The rates of urinary tract infection increased with age, with numerically higher rates with ertugliflozin, but there was no significant difference in the risk of serious urinary tract infections across treatment or age groups. The frequency of hypovolaemia, hypoglycaemia and fractures was also similar between treatment and age groups.

Comment: The treatment of older individuals with type 2 diabetes is often complicated by comorbidities, concern about a greater risk of side effects, and a lack of randomized controlled trial (RCT) data confirming efficacy in older persons. This dedicated efficacy and safety data for ertugliflozin in older persons is encouraging, as are the results from the recently published subgroup analysis of older persons receiving canagliflozin in the CREDENCE trial (Yi et al 2023), which demonstrated that the prevention of kidney adverse outcomes did not differ by age category. As discussed by the VERTIS CV authors, the study did not include assessment of frailty status, which just like the difference between the sexes, may alter the risk-benefit profile. Although the age analysis was concordant with other data and the results were consistent across studied cohorts, patient age and age categorization do not necessarily reflect comorbidity, so individualized treatment decisions still need to consider this. As new therapies continue to be developed, further efforts to study outcomes are needed to promote safe and effective care in elderly populations with CKD.

Pilot study suggests that medical cannabis may be a safe and feasible option for chronic pain in patients undergoing haemodialysis

Medical cannabis for pain management in patients undergoing chronic hemodialysis: randomized, double-blind, cross-over, feasibility study

Bassat OKB, et al. Clin Kidney J 2022. 16(4):701-10.



Reviewed by Neeru Agarwal

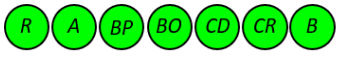
Summary: In this double-blind, placebo-controlled crossover study, 15 participants with chronic pain (pain level ≥ 5/10 reported by visual analogue scale [VAS] and maximum equivalent morphine dose £40mg/day) on maintenance hemodialysis were randomized to one of three study arms: whole-plant extract (WPE), purified cannabinoid or placebo. The sublingual oil-based WPE or purified cannabinoid each contained trans-delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:6 ratio. Each treatment period comprised of 2-weeks titration, followed by 6-weeks stable dose, and then a 2-week washout period before crossing over to a different treatment arm. A total of five participants discontinued the study due to adverse events before commencement of the second treatment period (WPE arm=2; purified cannabinoid arm=1; placebo arm=1; washout period=1). Of these, three participants discontinued due to the principal investigators' decision, with one considered to be related to study drug (purified cannabinoid arm: significant hypotension), and the others unrelated to the study drug, including one who subsequently died due to sepsis (WPE arm). Out of the 18 serious adverse events (SAEs), one was considered as related to the study drug (WPE arm: drug overdose that led to hallucinations and tachycardia). There was a relatively high number of adverse events (AEs) across all treatment arms (19-24 events per group) with somnolence and dizziness reported as the most common. Liver enzymes remained stable in all treatment arms, noting that liver enzyme derangement can be seen with recreational cannabis use. There was no difference in VAS score from baseline to end of treatment along the entire treatment period compared to placebo (WPE arm vs placebo, p=0.31; purified cannabinoid vs placebo, p = 0.54).

Comment: Pain management in patients with kidney failure is challenging, complicated by altered pharmacokinetics, multifactorial pain syndromes, and potential treatment side effects, particularly with the use of opioids. Cannabinoids may have a role in the management of pain and may improve other symptoms such as loss of appetite and nausea, however very little is known about their effects on the symptoms experienced by those with kidney failure. This trial found that short-term, supervised, and carefully titrated treatment with medical cannabis was generally well-tolerated and may be a safe option for patients on maintenance haemodialysis with chronic pain. WPE and purified cannabinoids demonstrated similar safety profiles. Limitations of this study include that it was a single center, small RCT, with gender imbalance, and because it was a feasibility and safety study, it was underpowered to assess efficacy. The legal restrictions on cannabinoid use internationally may also limit the applicability of these findings. Larger studies with longer follow-up periods and in different kidney failure populations are needed to assess the long-term safety and efficacy of medical cannabis.

Personalized medicine for better blood pressure control

Heterogeneity in blood pressure response to 4 antihypertensive drugs

Sundström et al. JAMA 2023. 329(14):1160-9.



Reviewed by Megan Borkum

Summary: This randomized, double-blind, repeated crossover trial tested the hypothesis that by targeting specific anti-hypertensive drugs to specific individuals, their blood pressure-lowering effects could be maximized. A total of 280 outpatients with grade 1 hypertension (54.3% men; mean age 64 years; mean duration of hypertension 3 years) were recruited. The trial excluded participants who had any of a range of comorbidities, including diabetes and cardiovascular disease. After a 2-week washout period, with no background anti-hypertensive agent use, participants were randomly assigned to a series of 6 treatment periods. Each participant had at least 1 treatment period with 16mg candesartan, 20mg lisinopril, 10mg amlodipine and 25mg hydrochlorothiazide. Each treatment lasted 7-9 weeks, with half doses for weeks 1 and 2. There was a 1-week washout period with a placebo between each treatment period. Participants had 24-hour ambulatory blood pressure monitoring during the last 24 hours of the run-in period and each treatment period. On average, lisinopril was found to be the most efficacious blood pressure-lowering medication, however the most efficacious agent varied between participants, such that by selecting the most efficacious treatment

for each individual, systolic blood pressure improved by 3.1mmgHg greater on average compared to selecting lisinopril as a fixed choice for everyone. Similarly, selecting the most efficacious therapy resulted in a 4.4mmHg better reduction compared to a fixed choice of any of the four agents overall. There was no evidence of large differences between candesartan and lisinopril, or amlodipine and hydrochlorothiazide, showing that within these pairs the choice of therapy was generally not of consequence. However, for all other comparisons tested, the choice was important, particularly personalizing the choice between candesartan vs amlodipine (p <0.001) and lisinopril vs amlodipine (p<0.001).

Comment: This trial found significant heterogeneity in blood pressure response to anti-hypertensive therapy. Additional multi-center studies are needed to confirm these findings. As with many other chronic illnesses, to truly personalize therapy, discovering a mechanism that can be used to identify individual phenotypes that will benefit most from specific treatments is key. Limitations of this trial include that this was a single-center study in a specific population group, which limits generalizability, and equivalently potent doses of agents were not used. Personalized dual therapy combinations were also not tested.

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

Venglustat does not improve cyst progression in adult polycystic kidney disease and may worsen renal function decline

Venglustat, a novel glucosylceramide synthase inhibitor, in patients at risk of rapidly progressing ADPKD: primary results of a double-blind, placebo-controlled, phase 2/3 randomized clinical trial

Gansevoort RT et al. Am J Kidney Dis 2023. 81(5):517-527.e1.

R A BP BO CD CR B

Reviewed by Rupesh Raina

Summary: This two-stage trial tested the role of oral venglustat for patients with autosomal dominant polycystic kidney disease (ADPKD) with high likelihood of disease progression, with Mayo Clinic imaging classification class 1C, 1D, or 1E and eGFR 30-<90mL/min/1.73m^2. Venglustat inhibits glucosylceramide synthase, which can otherwise contribute to the accumulation of glycosphingolipids implicated in ADPKD pathogenesis through effects on cellular membranes and cell signaling. Venglustat has been shown in preclinical studies to prevent the development of renal cysts and preserve renal function. In stage 1 of the clinical trial, participants were randomized to 8mg venglustat, or 15mg venglustat or placebo, while stage 2 recruited further patients to the 15mg dose (the highest dose identified as well-tolerated and safe in stage 1) or placebo. Overall, 78 participants received 8mg for a mean duration of 80 weeks, while 175 patients received placebo and 170 participants received 15mg venglustat for a mean duration of 47 weeks. The study was stopped early at the prespecified interim futility analysis due to lack of efficacy. There was no significant difference in the annualized rate of change in total kidney volume (TKV), with a 6-8% annual increase in size across groups, resulting in termination of the trial. There was a greater annual decline in eGFR with venglustat than with placebo (p<0.001), at −4.82ml/min/1.73m^2 with the 8mg dose (95% CI −5.82 to −3.83) and −4.89mL/min/1.73m^2 with the 15mg dose (95% CI −5.80 to −3.99) compared with −2.40mL/min/1.73m^2 with placebo (95% CI, −3.30 to −1.49). There were higher rates of serious adverse effects with venglustat compared with placebo (13.1% vs 7.0%).

Comment: The search for additional disease modifying therapies for ADPKD continues. Unfortunately, despite promising preclinical trials, venglustat does not appear to prevent disease progression, and may in fact cause harm. The eGFR analysis may be underpowered due to early termination of the trial. The authors propose that a venglustat-mediated rise in ceramide, a lipotoxic mediator, may contribute to renal vascular dysfunction and eGFR decline. Further studies of these mechanisms may be warranted to better understand the role of glucosylceramide synthase inhibition.

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

Febuxostat slows CKD decline in a small cohort of Chinese patients with asymptomatic hyperuricemia

Effects of febuxostat on delaying chronic kidney disease progression: a randomized trial in China

Yang H, et al. Int Urol Nephrol 2023. 55(5):1343-1352.

R A BP BO CD CR B

Reviewed by Nikolay Bulanov

Summary: In this multicenter open-label trial 100 patients with CKD stages 3 and 4 and asymptomatic hyperuricemia (serum uric acid ≥6.5mg/dL) were randomized to receive either febuxostat titrated to achieve serum uric acid level of <6mg/dL (maximum daily dose of 80mg) or routine medical care without urate-lowering therapy. Patients with acute

kidney injury, nephrotic syndrome, malignancies, or uncontrolled hypertension were not included. A total of 47 patients in the febuxostat group and 45 patients in the control group completed the 12-month study period. The primary outcome of eGFR decline ≥30% from baseline was observed in seven (14.9%) patients in the febuxostat group and 13 (28.9%) patients in the control group, without a statistically significant difference (p=0.104). The alternative primary outcome of eGFR decline ≥50% from baseline was significantly more common in the control group (22.2%) than in the febuxostat group (2.1%, p=0.003), noting a small number of events (11 vs 1 events). The change in eGFR after 12 months from baseline in the febuxostat group was +0.50mL/min/1.73m^2, which was significantly higher than that in the control group −4.46 mL/min/1.73m^2 (p=0.006). The proportion of patients who required commencement of dialysis over 12 months was similar in both groups. No severe adverse events were reported during the study.

Comment: Hyperuricemia is an established risk factor for CKD progression, however, the role of urate-lowering therapy (ULT) in patients with asymptomatic hyperuricemia is still debated. Previously, several larger RCTs with a longer follow-up period, including FEATHER, PERL, and CKD-FIX, failed to show significant effects of urate-lowering medications on eGFR decline. These studies did not include a significant proportion of Chinese participants, and it is possible that effects differ by race. The present study suggests a renoprotective effect of febuxostat in Chinese participants with stage 3-4 CKD, although there were conflicting trends between the categorical and continuous eGFR outcomes, perhaps owing to a small sample size, and to the low likelihood of a major decline in function within only 12 months. Other limitations include the open-label design, and significant differences in baseline serum urate levels between the groups. The role of ULT in CKD management will probably be defined in larger trials, as well as meta-analyses summarizing the findings of several major trials.

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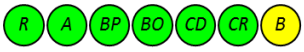
*ISN Academy: **Dialysis***

Warm or cold compresses may assist with cramps on dialysis

Effects of warm or cold compresses applied to the legs during hemodialysis on cramps, fatigue, and patient comfort: A placebo-controlled randomized trial

Kesik G et al. Hemodial Int 2023. 27(2):117-125.



Reviewed by Mohamed Elrggal

Summary: This trial of 74 hemodialysis patients compared the effects of warm, cold, and room temperature compresses on muscle cramps, fatigue, and patient comfort during hemodialysis treatment. While the inclusion criteria did not require symptoms at baseline, participants had a mean ~3.5 cramps of >1min duration per session at the time of enrolment. Thermal gel compresses measuring 27 x 35 cm were used across the 3 treatment arms, including being warmed to 38–39°C, cooled to 15–16°C, or standardized to a control temperature of 24–25°C. They were applied to the shins for 2 x 15-minute intervals in the last 2 hours of each dialysis session, over a period of 4 weeks. Patients were followed using Cramp Episode Follow-up Chart (CEFC), Piper's Fatigue Scale (PFS), and Hemodialysis Comfort Scale (HCS). The study found that both warm and cold compresses significantly reduced muscle cramps, fatigue, and improved patient comfort compared to the placebo controls. However, warm compresses were found to be more effective than cold compresses in reducing these complications.

Comment: Muscle cramps and fatigue are common complications in hemodialysis patients and have been associated with reduced patient comfort. The results of this study suggest that the application of warm or cold compresses to the extremities during hemodialysis treatment may be a useful complementary therapy to improve patient comfort and reduce cramps and fatigue. This intervention, which could be applied by patients, caregivers or dialysis nursing staff, could represent a simple maneuver to reduce these complications. Further studies with a larger sample size, and targeted to those with significant cramping at baseline, would help to provide further support for this approach.

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