Global Trials Focus

December 2023 - January 2024

The ISN-ACT (Advancing Clinical Trials) team presents the January 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

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ISN Academy: Glomerular Diseases

Sparsentan decreased proteinuria, but failed to slow eGFR decline in FSGS: data from the DUPLEX trial

Sparsentan versus Irbesartan in Focal Segmental Glomerulosclerosis

Rheault et al., N Engl J Med 2023.

R A BP BO CD CR B

Reviewed by Anastasiia Zykova

Summary: The DUPLEX study is a phase 3 multicenter double-blind trial that compared the efficacy of sparsentan, a dual endothelin-angiotensin receptor antagonist, to active control, irbesartan, in individuals with biopsy-proven focal segmental glomerulosclerosis. A total of 371 participants were randomized to sparsentan (n = 184; target dose, 800 mg/day) or irbesartan (n = 187; target dose, 300 mg/day) for up to 108 weeks. The primary efficacy endpoint of eGFR total slope (day 1 to week 108) was not statistically significant between the two groups (between-group difference of 0.3 ml/min/ 1.73 m^2 per year; 95% confidence interval [CI], −1.7 to 2.4; P=0.75). Similarly, the eGFR chronic slope (week 6-108) was not significant (between-group difference of 0.9ml/min/ 1.73 m^2 per year; 95% CI, −1.3 to 3.0; P=0.42). However, at 36 weeks, treatment with sparsentan resulted in greater proteinuria reduction than irbesartan, and this was sustained over 108 weeks. At 108 weeks, the least-squares geometric mean reduction in the urinary protein-to-creatinine ratio was 50.0% (95% CI, 40.8 to 57.7) with sparsentan and 32.3% (95% CI, 20.2 to 42.6) with irbesartan. There was also higher incidence of partial remission (37.5% vs. 22.6%) and complete remission (18.5% vs. 7.5%) in proteinuria with sparsentan than with irbesartan. In terms of safety, the rate of serious treatment-related adverse events were similar between the two groups (37.0% in the sparsentan group and 43.9% in the irbesartan group). Although there were more episodes of hyperkalemia (16.8% vs 10.7%) and hypotension (17.9% vs 11.2%) in the sparsentan group, there was no increased risk of peripheral oedema (19.6% vs 21.9%).

Comment: FSGS is a rare kidney disorder that is challenging to manage as there are limited treatment options, and despite treatment, many patients progress to kidney failure. The authors should be commended on conducting the largest FSGS trial to date demonstrating that evidence generation is feasible even in rare conditions. Sparsentan seemed a promising treatment option in FSGS based on the significant reduction of proteinuria in the DUET trial, and the beneficial anti-proteinuric and kidney preservation effects in the treatment of IgA nephropathy in the PROTECT study. However, sparsentan failed to significantly slow eGFR total or chronic slope in people with FSGS over two years in the DUPLEX trial. The negative results were found despite the trial being larger than the IgA nephropathy trial, and despite recruitment of a high risk population losing 5.7ml/min/1.73m^2/year (95% CI -7.2 to -

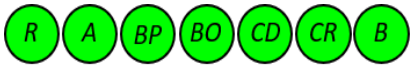
4.3) in total eGFR slope in the irbesartan group. The study population was also heterogenous for some known poor prognostic clinical factors: 20% had a FSGS-associated genetic variant and 26% were on concomitant immunosuppressive therapy during the trial. It remains possible there could be a smaller benefit than the study was powered to find, or a larger benefit for an unindentified subgroup. The open-label extension trial will seek whether longer follow-up reveals a delayed response. For now though, the absence of a statistically significant difference in eGFR total slope in the presence of decreases in proteinuria at the end of follow-up is disappointing.

ISN Academy: Glomerular Diseases

PROTECTing IgA nephropathy patients: sparsentan reduces proteinuria AND preserves kidney function through to 2 years

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Rovin et al., Lancet 2023.



Reviewed by Neeru Agarwal

Summary: The PROTECT Trial is a phase 3 double-blind study that randomised 404 adults with biopsy-proven IgA nephropathy (IgAN) to either sparsentan (target dose 400mg/day, n = 202), or to the active comparator, irbesartan (target dose 300mg/day, n = 202). Participants with eGFR ≥30mL/min/1.73m^2 and proteinuria ≥1.0g/day despite maximally tolerated renin-angiotensin system blockade for at least 12 weeks were enrolled in this study. The study mets its primary efficacy endpoint with sparsentan-treated participants having a significantly greater reduction in proteinuria from baseline (-49.8%) versus irbesartan (-15.1%) at week 36 (prespecified interim analysis). This reduction in proteinuria was sustained over the 2-year follow-up period (geometric least-squares mean reduction of urine protein-to-creatinine ratio from baseline to week 110 was -42.8% [95% CI -49.8 to -35.0] with sparsentan versus -4.4% [95% CI -15.8 to 8.7] with irbesartan). Sparsentan-treated participants also had a higher incidence of complete proteinuria remission (urine protein excretion <0.3g/day) compared to irbesartan alone (31% vs 11%, relative risk [RR] 2.5, 95% CI 1.6-4.1). While eGFR total slope (day 1 to week 110) was not statistically significant between the two groups (between-group difference of 1.0 ml/min/1.73 m^2/year; 95% CI, −0.03 to 1.94; P=0.058), the eGFR chronic slope (weeks 6-110) showed a statistically significant rate of decline in eGFR (between-group difference of 1.1 ml/min/1.73 m^2/year; 95% CI, 0.1 to 2.1; P=0.037). Moreover, in the sparsentan group, 18/202 (9%) participants reached the composite kidney failure end point of 40% eGFR reduction, end-stage kidney disease or all-cause mortality, compared with 26/202 (13%) in the irbesartan group (RR 0.7, 95% CI 0.4-1.2). Sparsentan was well tolerated, and adverse events were comparable across both groups, with no discontinuations due to heart failure or oedema.

Comment: IgAN is the most common primary glomerulonephritis worldwide, and risk of progression to kidney failure is strongly associated with persistent proteinuria (>0.75-1 g/day). In recent years there has been a growing interest in discovering effective therapeutic approaches to manage this disease, including systemic steroids (TESTING trial), targeted-release formulation of budesonide (NeflgArd) and SGLT-2 inhibitors (DAPA-CKD, EMPA-KIDNEY). The 2-year follow up results of the phase 3 PROTECT trial confirmed the significant reduction of proteinuria in sparsentan-treated participants compared to irbesartan, with kidney preservation suggested by benefits in chronic eGFR slope, although it narrowly fell short of reaching the total eGFR slope endpoint. Given that sparsentan is not an immunosuppressive agent, it may appeal as standard-of-care supportive therapy in patients with persistent proteinuria despite RAS bloakade. The open-label extension trial with concomitant use of sparsentan and SGLT-2 inhibitor (NCT05856760) will provide further benefit and safety information.

ISN Academy: Dialysis

Better AV Access patency and longevity following Drug-Coated Balloons Angioplasty versus Traditional Percutaneous Angioplasty

IN.PACT AV Access Randomized Trial of Drug-Coated Balloons for Dysfunctional Arteriovenous Fistulae: Clinical Outcomes through 36 Months

Lookstein et al., J Vasc Interv Radiol 2023.

R A BP BO CD CR B

Reviewed by Lin Lin Myat

Summary: Various percutaneous treatment modalities have been investigated to enhance the primary patency rates of dysfunctional arteriovenous fistulas (AVF) in patients undergoing haemodialysis. The IN.PACT AVF access single-blind trial evaluated whether the IN.PACT AV drug-coated balloon (DCB) would improve the longevity and patency rates in new or non-stented restenotic lesions up to 100mm in length in AVFs of the upper extremity compared with percutaneous transluminal angioplasty (PTA). The DCB carried a paclitaxel dose of 3.5 µg/mm² with a urea excipient. This study randomized 330 participants in a 1:1 ratio to receive DCB (n=170) or undergo PTA (n=160). Target lesion primary patency (TLPP) was significantly higher in the DCB group compared with the PTA group through 24 months (52.1% vs 36.7%, log-rank P<0.001), and this persisted through 36 months (43.1% vs 28.6%, log-rank P<0.001). Participants in the DCB group also had a delay in reintervention time of approximately 14.7 months. Moreover, the access circuit primary patency (ACPP) was higher in the DCB group than in the PTA group through to 36 months (26.4% vs 16.6%, log-rank <0.001). The cumulative incidence of access circuit thrombosis was also lower in the DCB group than in the PTA group through 36 months (8.2% vs 18.3%, log-rank P=0.04). Importantly, there was no significant difference in mortality between the two groups (26.6% with DBC and 30.8% with PTA, log-rank P=0.071).

Comment: AVFs are the preferred choice for establishing long-term haemodialysis access for patients with kidney failure. AVF creation causes vascular remodelling resulting in wall shear stress and strain, with expected neointimal hyperplasia and dysfunction over time. This large multicentre RCT has demonstrated significantly improved outcomes using the IN.PACT AV DCB compared with PTA through to 36 months. While the cost of DCBs are higher than PTA, the cost-effectiveness of this intervention needs to be considered including the increased morbidity and mortality associated with access circuit thrombosis including consequences of missed dialysis sessions, additional procedures of thrombectomy, increased hospital stays, and central venous catheter placement. However, this trial is limited in its generalizability due to the exclusion of high risk patients such as those with target lesions in the graft, central veins or within a stent, as well as history of current circuit thrombosis. The single-blinded design also precludes researchers from preventing certain types of biases such as observer bias, treatment administration bias and data analysis bias, although an attempt is made to address this concern by incorporating independent adjudication for outcome analysis in this trial. Nevertheless, this study supports the use of IN.PACT AV DCBs for dysfunctional AVFs given its sustained and superior effectiveness over PTA.

ISN Academy: Dialysis

Risk of developing catheter-related bloodstream infections in hemodialysis patients is reduced with a tauroldine solution compared to heparin: insights from the LOCK-IT 100 trial

Taurolidine/heparin lock solution and catheter -related bloodstream infection in haemodialysis

Agarwal et al., CJASN 18: 1446–1455, 2023.

R A BP BO CD CR B

Reviewed by Nayef Habbashi

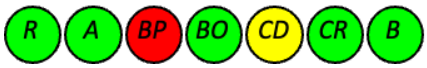
Summary: The LOCK-IT 100 trial was a phase 3, double-blind, active-control trial where catheter lock solution with antimicrobial and antifungial properties containing taurolidine 13.5mg/ml and heparin 1000 units/ml was compared to heparin control catheter lock solution (1000 units/ml). Participants with a central venous catheter (CVC) implanted ≥ 14 days with at least 2 successful dialysis episodes were enrolled. Catheter-related bloodstream infections (CRBSI) were defined as growth of the same organism obtained from ≥1 blood culture from a peripheral site or bloodline sample, and either the arterial or venous catheter hub, with presence of clinical signs. This trial was terminated early after the planned interim analysis of the first 28 cases of CRBSI favoured the intervention arm due to an observed 72% reduction in the risk of CRBSI with the taurolidine/heparin compared to heparin. At study completion (n=795), nine participants in the taurolidine/heparin arm (n=397; 2%) had a CRBSI compared to 32 participants in the heparin arm (n = 398; 8%). There was also a clinically significant lower event rate per 1000 catheter days for taurolidine/heparin (0.13 vs 0.46, respectively; P<0.001), with a hazard ratio of 0.29 (95% CI 0.14 to 0.62), corresponding to a 71% reduction in CRBSI risk with taurolidine/heparin vs heparin alone. There were no significant differences in the rate of catheter removals for any reason or loss of catheter patency between the two arms. There were no special safety concerns attributed to the treatment.

Comment: CRBSI are associated with increased mortality, morbidity and treatment costs among patients undergoing hemodyalsis with central venous catheters (CVC). A previous meta-analysis of RCTs looking at alternative anticoagulant containing locking solutions (ALSs), systemic warfarin and low/no dose heparin showed they have been relatively small (median participant number 62, IQR 42-174) with short follow up (median 6 months, IQR 2.95-11.05). It also showed that CRBSI were reduced by ALSs, including citrate locking solutions, some of which had taurolidine. The LOCK-IT 100 trial adds to this literature, being the largest study comparing taurolidine and heparin, with heparin alone. This study found a 71% reduction in the risk of developing a CRBSI in participants receiving taurolidine/heparin compared to heparin alone, with no special safety concerns. The early termination of the trial due to the efficacy of the intervention speaks to the importance of these results which has subsequently received FDA approval. Considering that some patients need to dialyse through a CVC, this safe and effective antimicrobial catheter lock solution will play an important role in reducing CRBSI, and hopefully this will translate to improved morbidity, mortality and healthcare utilization in this patient population.

A ray of light for people living with chronic kidney disease: a promising digital physical activity intervention

Evaluating the effect of a digital health intervention to enhance physical activity in people with chronic kidney disease (Kidney BEAM): a multicentre, randomised controlled trial in the UK

Greenwood et al. Lancet Digit Health 2024.



Reviewed by Megan Borkum

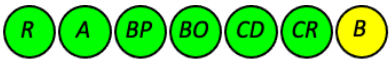
Summary: The single-blind Kidney BEAM study investigated the impact of a 12-week physical activity digital health intervention on health-related quality of life. Adult participants with chronic kidney disease (CKD) from 11 UK sites were enrolled. A total of 340 participants (mean age 53.8 years, 46% female, 75% White, median creatinine 159umol/L) were randomly assigned to either the Kidney BEAM intervention (n=173) or the waitlist control (n=167). The intervention, led by trained kidney-specific exercise professionals, involved moderate-intensity aerobic and resistance exercise sessions with a brief educational element. A physiotherapist assistant, skilled in motivational interviewing, utilized phone calls or emails to motivate participants to reach their goals. At 12 weeks, the intervention group demonstrated a significant improvement in the patient-reported Kidney Disease Quality of Life Short Form version 1.3 Mental Component Summary (KDQoL-SF1.3 MCS) score (from mean 44.6 AU [SD 10.8] at baseline to 47.0 AU [10.6] at 12 weeks) compared to the control group (from 46.1 AU [10·5] to 45.0 AU [10.1]), with a between-group difference of 3.1 AU (95% CI 1.8-4.4; P<0.0001). In the intervention arm, the median adherence rate was 63% (IQR 38-92), involving a median of 44 minutes/week of structured physical activity. Of the secondary outcomes, there was a significant improvement at 12 weeks in PAM-13 patient activation score (p<0.0001) and the 60-second sit-to-stand test (remotely conducted) of physical function (p<0.0001) in the Kidney BEAM group compared with the control group. There were no significant between-group differences at 12 weeks for Work and Social Adjustment Score, EQ-5D-5L clinical utility score, Global Physical Activity Questionnaire measures, fatigue (Chalder Fatigue Scale score) and anxiety and depression (PHQ-4 score). Median adherence to education sessions was 50% (8-83). No serious adverse effects related to the trial were reported.

Comment: This work contributes to the growing body of evidence supporting the benefits of physical activity interventions in managing CKD. Kidney BEAM offers live and on-demand physical sessions, educational blogs and videos, and peer support. The novelty of this trial lies in the feasibility and benefits demonstrated by a digital intervention versus traditional, in-person exercise training. Cost-effectiveness and patient experience data, along with 6-month follow-up results, are anticipated in subsequent publications. Given the propensity of CKD patients towards physical inactivity, frailty, and sarcopenia, this trial suggests that digital interventions, particularly when exercise professionals are not routinely part of kidney care teams, offer a pragmatic and promising alternative to enhance access to rehabilitation care. Nevertheless, digital interventions assessing mental health-related quality of life in larger, more diverse groups, over a longer period and assessing if motivation and adherence are sustained are required to confirm these findings.

Combined endothelin receptor antagonist (ERA) and SGLT-2 inhibition reduces albuminuria and has a safety profile equivalent to SGLT-2i alone

Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial

Heerspink et al. Lancet 2023.



Reviewed by Megan Borkum

Summary: The ZENITH-CKD trial is a phase 2b, double-blind active-controlled study that randomised 447 adults aged 18-90 years with an eGFR of at least 20mL/min/1.73m^2 and urinary albumin:creatinine ratio (uACR) of 150-5000mg/g in a 2:1:2 ratio to high-dose zibotentan (1.5mg daily) plus dapagliflozin 10mg (n=179), or low-dose zibotentan (0.25mg daily) plus dapagliflozin 10mg (n=91), or dapagliflozin 10mg plus placebo (n=177), on top of maximally tolerated renin-angiotensin-system inhibition. Majority of participants in this study were male (69%) and White (68%) with a mean age of 62.8 years (SD 12.1), median uACR of 565.5mg/g (IQR 243-1212.6) and mean eGFR 46.7mL/min/1.73m^2 (SD 22.4). At the end of the 12-week study period, the difference in uACR between the dapagliflozin and placebo group was -33.7% (90% CI -42.5 to -23.5; P<0.0001) for the high-dose zibotentan plus dapagliflozin group, and -27% (90% CI -38.4 to -13.6; P=0.002) for the low-dose zibotentan plus dapagliflozin group. Systolic and diastolic blood pressure, HbA1c% and LDL cholesterol were also reduced in both doses of zibotentan plus dapagliflozin compared to dapagliflozin monotherapy. More patients in the high-dose zibotentan plus dapagliflozin group reached the pre-specified fluid-retention endpoint compared to those in the low-dose zibotentan plus dapagliflozin and dapagliflozin monotherapy groups (18% vs 9% vs 8%, respectively).

Comment: This is the first randomized trial evaluating the addition of zibotentan, an endothelin receptor antagonist (ERA), to the new standard of care for treatment of CKD, consisting of SGLT-inhibitors and renin-angiotensin blockade. In this study, both high- and low-dose zibotentan plus dapagliflozin demonstrated reduction in albuminuria compared to dapagliflozin alone. While increased fluid retention was observed in the high-dose zibotentan plus dapagliflozin group, there was no difference between the low-dose zibotentan plus dapagliflozin and dapagliflozin monotherapy groups. This study is limited by its short follow up of 12 weeks, and it is not possible to draw conclusions about long-term efficacy on eGFR decline or other clinical kidney endpoints. A planned phase 3 trial (NCT06087835) will help further establish the efficacy and safety of SGLT2/ERA combination therapy for patients with CKD and increased albuminuria.

ISN Academy: Transplant

Continuous glucose monitoring improves early posttransplant glycemic control

A randomized trial of continuous glucose monitoring to improve post-transplant glycemic control

Jandovitz et al. Clin Transplant. 2023.

Reviewed by Nikolina Basic-Jukic

Summary: In this single-site, single-blinded study, 40 adult kidney transplant (KT) recipients with diabetes were randomized in a 1:1 ratio to receive continuous glucose monitoring (CGM) using the Medtronic Guardian Sensor 3 or standard point-of-care glucose monitoring that involved finger prick test pre-meals and before bed during the first five days post-transplant. All patients received standard induction immunosuppression along with methylprednisone, followed by a rapid steroid taper over 7 days to prednisone 5mg daily. The median glucose level throughout the first five days post-transplant was significantly lower in the intervention group compared to the control group (185.0 [158.0–220.0] mg/dL vs. 198.2 [165.6–236.7] mg/dL, P=0.037). Although there were no significant differences in daily median glucose levels between the groups, there were significantly fewer hyperglycemic episodes in the intervention group compared to the control group on post-operative days 2 to 5, with no differences in hypoglycamic episodes through out the five days. In addition, there were no differences in the amount of both short- and long-acting insulin injected in hospital post-transplant, length of hospitalization following the transplant, nor infections rates in the first 30 days post-transplant.

Comment: Hyperglycemia is commonly observed following KT and may occur in both diabetic and non-diabetic KT recipients. Early post-transplant hyperglycemia has been associated with numerous complications, including cardiovascular, respiratory, neurologic, and infectious morbidities, but also with worse KT outcomes. This study showed that continuous glucose monitoring (CGM) post-KT was feasible and associated with better glycaemic control than with the standard finger-prick tests, in particular in reducing episodes of hyperglycaemia. However, this study is limited by its small sample size and is not generalisable given that non-diabetic KT receipeints were not included even though they may experience new onset perioperative hyperglycaemia. Moreover, further studies should test the efficacy of CGM by looking at other statistical measures of glucose variability, not just the median value. In future studies, it would also be important to assess the use of CGM beyond the hospital setting, and assess its long-term impacts on glycaemic control, hypoglycaemic detection and transplant outcomes.

ISN Academy: Transplant

mTOR inhibitors (Sirolimus or Everolimus) with low-dose Tacrolimus reduce incidence of CMV infections in Renal Transplant recipients

A Head-to-head Comparison of De Novo Sirolimus or Everolimus Plus Reduced-dose Tacrolimus in Kidney Transplant Recipients: A Prospective and Randomized Trial

De Rezende Freschi et al. Transplantation. 2024.

Reviewed by Bassem Tanios

Summary: In this single centre, open label trial, 268 kidney transplant recipients with low immunological risk, were randomized in a 1:1:1 ratio to 3 groups: Sirolimus (SRL), Everolimus (EVR) and Mycophenolate Sodium (MPS). All participants received a 3mg/kg single anti-thymocyte globulin dose as induction therapy with tacrolimus and prednisone, without cytomegalovirus (CMV) prophylaxis. SRL and EVR were adjusted to maintain whole blood trough concentrations (C0) between 4-8ng/ml, and tacrolimus was adjusted to maintain C0 between 3-5ng/ml. In the MPS group, tacrolimus was adjusted to maintain C0 between 5-10ng/ml. At 12 months, both SRL and EVR had significantly reduced incidence of CMV infection/disease (10.5% with SRL vs 10.1% with EVR vs 15.1% with MPS, P<0.0001) corresponding to a relative risk reduction of 76% [95% CI, 53%-87%; *P* < 0.0001) with SRL and 82% [95% CI, 62%-95%; *P* < 0.0001] with EVR as compared to MPS. There was no difference in the incidence of BK polyomavirus viremia, treatment failure (composite endpoint of biopsy proven acute rejection, graft loss or recipient death), de novo donor specific antibodies, delayed graft function, nor kidney allograft function and proteinuria at 12 months. In addition, more treatment discontinuations due to side effects or lack of efficacy were noted in participants receiving SRL or EVR as compared to the MPS group (18.6% vs 15.6% vs 6.7%, p=0.054).

Comment: CMV infection is associated with increased morbidity, risk of graft loss, and increased mortality in kidney transplant recipients. The current study suggests that patients receiving de novo mammalian target of rapamycin inhibitor (mTORi) such as SRL or EVR, targeting similar therapeutic blood concentrations, have reduced CMV incidence compared to those who receive MPS. However, this study has multiple limitations. First, this is a single-center study with a small sample and limited follow up. The premature termination of the study due to the COVID-19 pandemic further limited the power to detect differences in secondary endpoints like acute rejection, treatment failure and kidney allograft function at 12 months due to the small sample size. As a result, the safety and efficacy profile of SRL or EVR vs MPS as initial immunosuppression remains unanswered. Second, this study is limited in its generalizability given the utilization of a different induction regimen to many other countries, the use of a pre-emptive CMV strategy rather than universal anti-viral CMV prophylaxis, and the enrolment of patients with low immunological risk only. In addition, the effectiveness of this strategy in patients with the highest risk for CMV (Donor CMV positive/Recipient CMV negative) remains unanswered due to the limited number of patients in this category. To address these gaps, future studies with a larger sample size, longer follow-up, and with patients receiving CMV prophylaxis, would be needed to confirm the clinical benefit of using de novo mTORi with reduced dose tacrolimus, as compared with the more widely used regimen of MPS with regular dose tacrolimus. Therefore, the current proposed intervention does not appear to enhance our available treatment options for post-transplant CMV which remains an important challenge.

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