Global Trials Focus

January-February 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!
@ISNeducation

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ISN-ACT Clinical Trials Toolkit
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*ISN Academy: **Dialysis***

Apixaban demonstrates comparable safety and efficacy to vitamin K antagonism among dialysis patients

A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 Study

Reinecke et al, Circulation (2023).

R A BP BO CD CR B

Reviewed by Daniel V O'Hara

Summary: The study randomized 97 patients with atrial fibrillation (AF) on hemodialysis to the direct oral anticoagulant apixaban 2.5mg twice daily or to the vitamin K antagonist (VKA) phenprocoumon with a target international normalized ratio of 2.0-3.0. The median follow-up time was 429 days for apixaban and 506 days for phenprocoumon. Across participants receiving phenprocoumon, the median proportion of time in the target range was 51%. The composite primary efficacy outcome of all cause-death, ischemic stroke, myocardial infarction, deep vein thrombosis or pulmonary embolism occurred in 21% of those receiving apixaban and 31% of those receiving phenprocoumon (p value for a difference on log-rank testing = 0.508). The composite primary safety outcome of all-cause death, the first event of major bleeding or clinically relevant non-major bleeding, occurred in 46% of those receiving apixaban and 51% of those receiving phenprocoumon (hazard ratio [HR] 0.93, 95% CI 0.53–1.65, p test for non-inferiority = 0.157). The rates of major bleeding were similar at 10% for apixaban versus 12% for phenprocoumon.

Discussion: Determining appropriate anticoagulation among patients on dialysis remains a very common and difficult problem. The three primary issues are whether to commence anticoagulation at all, which agent to use, and what dose is most suitable. The evidence for commencing anticoagulation is primarily based upon observational data, with conflicting results among different cohorts. For determining which agent to select, in this study, apixaban showed similar efficacy and safety event rates to phenprocoumon, the most commonly used VKA in Germany, but did not meet statistical criteria for non-inferiority. The efficacy events were primarily cardiovascular deaths, where the benefits of anticoagulation may be less apparent than for ischemic stroke or pulmonary embolism, and hence using this outcome for event-driven recruitment criteria may lead to underpowering to detect a difference between agents. There was some baseline imbalance in important prognostic characteristics, as is not infrequent in smaller trials, including the proportion of males (65% vs 76%) and the mean time on dialysis (1329 vs 2673 days). Another recent trial testing apixaban in dialysis patients with AF (RENAL-AF) to warfarin use among 154 participants, was also underpowered to demonstrate non-inferiority. The optimum dosing of apixaban has also not been determined, with

the RENAL-AF trial using 5mg twice daily as a standard dose but reducing to 2.5mg twice daily in people ≥80 years of age, or weight ≤60kg, compared to a set 2.5mg twice daily dosing in the present trial. Further anticoagulation studies with larger sample sizes and longer follow-up to detect a greater number of thromboembolic events, and with inclusion of a non-anticoagulation arm, are needed to better understand the risk/benefit profile, including among subgroups such as the elderly.

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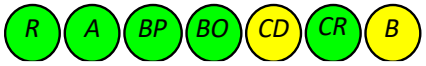
*ISN Academy: **Glomerular Diseases***

Bardoxolone methyl may not have a role in treating Alport syndrome

Effects of bardoxolone methyl in Alport syndrome

Warady et al, Clin J Am Soc Nephrol (2022).



Reviewed by Daniel V O'Hara

Summary: There are very limited treatment options for Alport syndrome, where inherited abnormalities of type IV collagen lead to a defective glomerular basement membrane and kidney dysfunction. Bardoxolone methyl activates a transcription factor (NF erythroid 2-like 2; or Nrf2) that alters the expression of genes contributing to inflammation, cellular energy metabolism and oxidative stress, and treatment reduces kidney re-modelling and fibrosis in animal models. The CARDINAL phase 3 trial tests the use of bardoxolone methyl among 157 participants aged 12-70, with Alport syndrome confirmed on either biopsy or genetic testing, with eGFR 30-90mL/min/1.73m^2, and on maximal renin-angiotensin-aldosterone (RAAS) blockade. Those receiving bardoxolone methyl demonstrated greater preservation of eGFR at both 48 weeks and at 100 weeks (between group difference at 100 weeks 7.4mL/min/1.73m^2, 95%CI 3.1-11.7, p<0.001) compared to placebo. Four weeks after completion, the between group difference was not significant using available data, although with imputation of missing eGFR data was significant at 4.4mL/min/1.73m^2 in favor of bardoxolone. There was no increase in serious adverse events. Reversible transaminase elevation was common with bardoxolone methyl, at 47% of participants for alanine aminotransferase (ALT) and 25% for aspartate aminotransferase (AST). The increased risk of heart failure hospitalizations or related death previously seen in the BEACON study was not observed, although patients with a history of heart failure or brain natriuretic peptide (BNP) >200 ng/ml were excluded. In total, 34% discontinued bardoxolone methyl, compared to 16% for placebo, largely driven by protocol-specified aminotransferase criteria.

Discussion: Bardoxolone methyl has early-phase evidence of benefit in reducing chronic kidney disease progression (BEACON study), particularly for diabetic kidney disease (TSUBAKI study). Assessment of potential benefit is complicated by bardoxolone methyl's recognized effect in causing an acute reversible rise in eGFR that persists while on treatment. The benefit off treatment was not clearly established in this study without imputation of data. The reversible increase in albuminuria on treatment is also concerning, and is consistent with pre-clinical studies that suggest bardoxolone methyl increases glomerular pressure. In light of the uncertain efficacy, and the safety concerns, the authors note that the risk benefit profile observed in this study does not support the use of bardoxolone methyl in Alport syndrome at this point.

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

Decision aids appear helpful for older adults with advanced CKD

Effectiveness of an intervention to improve decision making for older patients with advanced chronic kidney disease: a randomized controlled trial

Ladin et al., Ann Intern Med (2023).

Reviewed by Neeru Agarwal

Summary: In a multicenter trial across 8 outpatient nephrology units in the USA, 363 older participants (age ≥70years) with advanced CKD (mean age 78yrs, 58% male, 78% White, mean eGFR 23ml/min/1.73m^2) were randomized to an interactive, web-based Decision-Aid for Renal Therapy (DART, n=183) or usual care (n=180). DART provided information about kidney therapy options including conservative kidney management, and helped participants explore their values. The primary outcome was a change in the decisional conflict scale (DCS) from baseline, on a scale of 0 to 100, with lower scores representing less decisional conflict. The intervention was associated with a reduction in mean DCS compared to usual care at 6 months (mean difference -8.5 points [95% CI -12.0 to -5]; P <0.001); however, the effects attenuated at the 12- and 18-month follow up. There was also significant improvement in knowledge scores on a 12-point test at 3 months (mean difference 9.0 percentage points higher [CI 4.6 to 13.4]; P <0.001) with DART compared to usual care, which persisted through to the 18-month follow up. Importantly, the proportion of people who were "unsure" about their treatment choice was lower at each time point

with DART than with usual care - 59% vs 51% at baseline, 28% vs 38% at 3 months, 20% vs 35% at 6 months, 23% vs 32% at 12 months, and 14% vs 18% at 18 months.

Discussion: This large multicenter trial demonstrated that a decision aid can improve decisional conflict, knowledge and decision-making among older adults with stage 4 and 5 CKD. This was an important study as previous decision aids are often dialysis-focused, without specifically addressing the needs of older patients, such as a thorough discussion of the option for conservative kidney management without dialysis. Interventions such as this will hopefully encourage the ongoing shift towards shared decision-making, rather than the current model in many places where dialysis is considered the default therapy, and where patients may face a higher risk of loss of autonomy and decisional regret. Further studies would help to improve generalizability of the intervention such as among non-English speaking individuals, those of diverse ethnicities, and those with low health and/or digital literacy. The DART content is available at www.goemmi.com/DART, with the code "TEST".

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*ISN Academy: **Glomerular Diseases***

Targeted release steroid reduces proteinuria in IgA nephropathy

An additional dose of viral vector COVID-19 vaccine and mRNA COVID-19 vaccine in kidney transplant recipients: Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

Barratt J. et al. JASN 2022.

R A BP BO CD CR B

Reviewed by Megan Borkum

Summary: In this international phase 3 trial, 306 patients with biopsy-proven (within the last 10 years) primary IgA nephropathy and eGFR 35-90ml/min/1.73m^2 with proteinuria ≥1g/24 hr despite maximal RAAS inhibition were randomized to receive 9 months of treatment with 16mg/d of a targeted release oral budesonide formulation (Nefecon) or placebo and were observed for a further 3 months off treatment. At 9 months, 24hr proteinuria was reduced by 27% in the budesonide group, compared with the placebo group (95%CI 13%–39% lower, p=0.0003). Proteinuria further improved in budesonide patients 3 months after study drug discontinuation. The mean fall in eGFR was 3.9mL/min/1.73m^2 less for those receiving budesonide (p=0.0014), which was maintained 3 months later. The UPCR benefit was seen regardless of baseline proteinuria severity, or baseline eGFR or HbA1c. At 12 months, however a post hoc analysis showed a statistically significant (*p*=0.0429) relationship between the eGFR treatment effect and baseline UPCR, with benefit only in those with baseline UPCR >1.5g. There was no increase in the risk of infectious events, with no serious infections requiring hospitalization, and there were no deaths. A further follow-up observational period, Part B, is ongoing and is expected to be reported later in 2023.

Comment: Compared with systemic steroids, targeted release budesonide is designed to act specifically in the ileocecal region of the intestines to suppress the gastrointestinal immune response in the Peyer's patches, which is thought to be a trigger contributing to IgA nephropathy pathogenesis. Although budesonide safely decreased proteinuria in all subgroups studied and appeared to preserve eGFR at 12 months in all groups except those with low baseline proteinuria, there was an unexpected rise in eGFR at 3 months in the budesonide group which is as yet unexplained. The trial also has several limitations identified by the authors: included patients were primarily Caucasian with ~12% of Asian ethnicity (who have a high prevalence of IgA nephropathy), correlation with recent histological severity scoring was not performed, and the location and mechanism of action of this budesonide formulation is "still speculative at this time"; mechanistic studies are currently ongoing. The anticipated follow-up study will help to identify whether an increased risk of systemic steroid side effects is observed over time, as was seen in the phase 2b study. Direct comparisons between targeted and systemic steroids would also be of interest.

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*ISN Academy: **Obstetrics and Pregnancy***

Intrapartum extended-release nifedipine prevents severe hypertension in women with preeclampsia with severe features

Trial of intrapartum extended-release nifedipine to prevent severe hypertension among pregnant individuals with preeclampsia with severe features

Cleary et al. Hypertension (2023).

R A BP BO CD CR B

Reviewed by Maria Chiara Pelle

Summary: The study recruited 110 pregnant women with preeclampsia and severe features who were admitted to the labor and delivery unit for a trial of labor. Severe features were defined as either severe hypertension (systolic blood pressure [SBP] ≥160mmHg or diastolic blood pressure [DBP] ≥110mmHg, sustained over ≥10minutes and requiring acute therapy, or two separate measurements at least 4 hours apart), or mild hypertension (SBP≥140mmHg or DBP ≥90mmHg) together with pre-eclampsia symptoms or laboratory tests consistent with severe disease. Participants were randomized to receive 30mg slow release nifedipine daily until delivery, or placebo. The daily study drug was withheld with SBP <120mmHg or DBP <70mmHg. No other new long-acting antihypertensive agents were commenced until after delivery, although long-acting beta-blockers were continued among those with chronic hypertension. All participants received an intravenous magnesium sulfate bolus and infusion. The primary outcome was the need to administer parenteral labetalol, parenteral hydralazine, or oral immediate-release nifedipine, for the acute treatment of severe blood pressures in the period between study drug initiation and delivery. This outcome was observed in 34.0% of individuals in nifedipine group versus 55.1% in placebo group (relative risk [RR] 0.62, 95% CI 0.39-0.97). The number needed to treat to prevent receipt of acute treatment was 5 (95%CI 3-44). The need for caesarean delivery was lower in nifedipine group (20.8% vs 34.7%), as was the NICU admission rate (29.1% vs 47.1%), although neither demonstrated a statistically significant reduction. There were no differences in the rates of maternal symptomatic hypotension, or neonatal outcomes such as altered Apgar score, low birth weight, or severe hyperbilirubinemia.

Comment Preeclampsia complicates about 8% of pregnancies, causing major maternal and perinatal morbidity, with ~70,000 women dying each year worldwide, and ~500,000 neonates born prematurely due to preeclampsia. Finding effective and safe treatments of hypertension during delivery is crucial. This well-conducted trial suggests that slow release nifedipine intrapartum is effective in reducing the need for acute therapy of hypertension. While there may be a particular benefit to the long-acting medication approach, the study also likely highlights the overall importance of pre-emptive management of intrapartum hypertension, rather than a reactive approach to each rise in blood pressure, where blood pressure can continue to escalate while awaiting the onset of action of immediate-release medications. Further individualization of care is likely required, including to account for differences in drug metabolism as identified by the authors.

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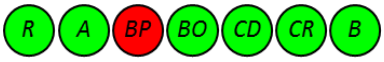
*ISN Academy: **Pediatric Nephrology***

Tight blood pressure control not shown to alter cardiac remodeling in children with chronic kidney disease

Intensive compared with less intensive blood pressure control to prevent adverse cardiac remodeling in children with chronic kidney disease (HOT-KID): a parallel-group, open-label, multicenter, randomised, controlled trial

Sinha et al. Lancet 2023.



Reviewed by Michele Provenzano

Summary: In the HOT-KID trial, 124 children aged 2–15 years with stage 1–4 chronic kidney disease (CKD) were randomized to either intensive treatment for blood pressure control (systolic target <40th percentile for age) or standard treatment (systolic target between the 50th and 75th percentiles). Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) were used as first-line agents, with the dose titrated every 2–4 weeks. Sixty five percent of patients were already on antihypertensive medications at baseline. The primary outcome was the difference in left ventricular mass index (LVMI, expressed in g/m$^{2.7}$) between the intensive versus standard treatment groups, determined with a transthoracic echocardiogram acquired at baseline and at annual intervals. Median follow-up was 38.7 months. As expected in the intensive treatment group, blood pressure was lower than in standard treatment group (mean 4mmg lower), but in both groups was close to the 50th percentile. There was no significant difference between the two groups for the primary outcome (p=0.76). A reduction in relative wall thickness was greater for the intensive treatment group than for the standard treatment (p=0.0019). Renal outcomes and adverse events were similar between groups.

Comment: CKD is associated with a greater likelihood of left ventricular hypertrophy in children, which confers an increased long-term cardiovascular risk. Current recommendations regarding the management of blood pressure in children are largely influenced by a single trial, ESCAPE, which showed that targeting a mean arterial pressure below the 50th percentile for age was associated with better preservation of kidney function, but showed no difference in LVMI among a subset of study participants. HOT-KID is the first randomized controlled trial dedicated to studying

the effect of different targets of blood pressure control on left ventricular remodeling in children with CKD. No significant difference was shown between the two groups regarding LWMI, perhaps because left ventricular hypertrophy was only present in a small proportion of the subjects, and blood pressures were relatively well-controlled at baseline. Relative wall thickening, which can precede left ventricular hypertrophy, was elevated at baseline and was significantly reduced by intensive blood pressure reduction, which provides some support for tighter blood pressure control.

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