

ISN Trial-List

October 2017



Once a month, the ISN-ACT (Advancing Clinical Trials) team collects and publishes a list of important nephrology trials from the latest medical literature.

Glomerular disease

ISN Academy: [Glomerular Disease](#)

C5a inhibition may be effective for ANCA vasculitis

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

[Jayne, et al. J Am Soc Nephrol. 2017;28\(9\):2756-2767](#)

The activation of neutrophils in ANCA-associated vasculitis leads to the generation of inflammatory complement components such as C5a. Jayne, et al. tested a novel oral small molecule C5a receptor inhibitor - avacopan – in a double-blind trial of 67 participants with newly diagnosed or relapsing vasculitis who were concurrently treated with cyclophosphamide or rituximab. Patients were randomized to either high dose prednisone (initial dose 60mg), avacopan or avacopan plus moderate dose prednisone (starting at 20mg) and followed for 12 weeks. The primary outcome was achieving a $\geq 50\%$ reduction in Birmingham Vasculitis Activity Score (BVAS) without a worsening of disease in any organ. This outcome was reached in 70% of the high dose prednisone group, 81% in the avacopan group and 86.4% in the combination group. Both avacopan alone and avacopan plus moderate dose prednisone were found to be non-inferior to high-dose prednisone alone ($p=0.01$ and $p=0.002$, respectively). Remission (BVAS 0) at weeks 4 and 12 was seen in 9/43 (21%) of the participants treated with avacopan and 1/20 (5%) participants on prednisone alone ($p=0.1$). Adverse events were common in all groups with no significant differences between them. While this trial was small and excluded those with rapidly progressing glomerulonephritis or an eGFR < 20 ml/min/1.73m², it does pave the way for further studies to explore the potential of this new therapeutic approach.

Hypertension, Chronic Kidney Disease

ISN Academy: [Hypertension, Chronic Kidney Disease](#)

Tight BP control reduces mortality in patients with CKD but may not improve renal outcomes

Effects of Intensive BP Control in CKD

[Cheung, et al. J Am Soc Nephrol. 2017;28\(9\):2812-2823.](#)

The SPRINT Trial of intensive blood pressure control was a landmark study showing that targeting a systolic blood pressure < 120 mmHg in patients at high cardiovascular risk was safe, prevented cardiovascular events and reduced mortality compared to a usual target of < 140 mmHg. It is worth noting that the BP was measured by an automated BP machine, which may result in a lower reading than a casual office measurement. The secondary analysis presented by Cheung, et al focuses on the 2646 participants with CKD at baseline (mean eGFR 47.9ml/min/1.73m², median urinary ACR 13.3mg/g (1.5mg/mmol)). Reassuringly, the reduction in all-cause mortality was maintained in those with CKD, and the effects on cardiovascular events were consistent in those with and without CKD. The primary renal outcome of a $\geq 50\%$ rise in creatinine or end-stage kidney disease was uncommon (1.2%) and did not differ between groups. As expected, there was an early lowering of eGFR in the tight treatment target group attributed to the haemodynamic effects of lower blood pressure. Beyond this point, there remained a slight, but significant, increase in the rate of eGFR decline in the treatment group (-0.47 ml/min/1.73m² per year vs -0.32 ml/min/1.73m², $p=0.03$), however, as the authors note, this is consistent with the -0.5 ml/min/1.73m² per year decline attributed to ageing. Finally, the rate of serious adverse events was not different between groups. In summary, these results suggest that lower BP targets are effective in reducing cardiovascular and all-cause mortality in patients with CKD, but there is no evidence that this improves long-term renal outcomes. These conclusions may not apply to patients with proteinuric renal disease.

Tight BP control may increase the risk of new CKD

Effects of Intensive Systolic Blood Pressure Control on Kidney and Cardiovascular Outcomes in Persons Without Kidney Disease

[Beddhu, et al. Ann Intern Med. 2017 Sep 5; doi: 10.7326/M16-2966](#)

This secondary analysis of the SPRINT trial focussed on the 6662 participants without CKD at baseline (i.e. with an eGFR \geq 60ml/min/1.73m²). The prespecified outcomes were incident CKD (a > 30% decrease in eGFR to a value < 60ml/min/1.73m²), incident albuminuria (a doubling of albumin:creatinine ratio to a value > 1mg/mmol) and end-stage kidney disease (ESKD). Tight BP control (target < 120mmHg) was associated with an increased incidence of CKD compared to standard BP control (target < 140mmHg) of 1.3 versus 0.4 events per 100 patient-years ($p < 0.001$). There was no difference in the incidence of albuminuria and no cases of end-stage kidney disease were observed in either group. A significant difference in mean eGFR of 3.3 ml/min/1.73m² between the two groups appeared by 6 months and this widened to approximately 4.5 ml/min/1.73m² by 18 months. However, after this point the between group difference in eGFR remained stable. These findings may raise concern about intensive BP lowering, however the longer term impact of these changes in eGFR on renal outcomes such as the development of advanced CKD or ESKD is not clear. Further analysis of the rate of decline in eGFR and the change in CKD stage may help clarify their likely clinical importance. Overall, the main cause of mortality in patients with CKD is cardiovascular disease and the primary results of the SPRINT trial (demonstrated again in this substudy) were that tight BP control (target < 120mmHg, measured by automated BP machine) was associated with a reduction in cardiovascular events and all-cause death.

Chronic Kidney Disease

ISN Academy: [Chronic Kidney Disease](#)

Better communication between community pharmacies and CKD clinics may reduce medication errors

Community Pharmacist Training-and-Communication Network and Drug-Related Problems in Patients With CKD: A

Multicenter, Cluster-Randomized, Controlled Trial

[Lalonde, et al. Am J Kidney Dis. 2017;70\(3\):386-396.](#)

The potential role of community pharmacists in preventing drug-related adverse events in patients with CKD was examined in this cluster randomized controlled trial in Quebec, Canada. Participating patients from 6 hospital-based CKD clinics were recruited along with the 207 community pharmacies that supplied them. Each cluster of one pharmacy and its regular patients was randomized. The intervention consisted of a 90-minute online learning module to pharmacists and the provision of patient medical summaries developed by the patient's CKD clinic comprising medical history and selected laboratory results. The primary outcome was the number of potential drug-related problems assessed by a pair of independent assessors (blinded to study allocation) who reviewed the patient history and medication summary at baseline and 12 months. From baseline to 12 months, the mean number of drug-related problems per patient fell from 2.16 to 1.60 in the intervention group as compared to 1.70 to 1.62 in the control group. After adjusting for baseline values and clustering, the difference in change over time was significant ($p < 0.001$). There were no significant changes in patient eGFR, blood pressure, cholesterol or HbA1c. Although this study did not examine actual drug-related adverse events, it does highlight the potential benefits of improved communication between prescriber and community pharmacies. Further studies exploring the effects of wider integration of healthcare records between providers is warranted.

Diabetes

ISN Academy: [Diabetes](#)

Benefits of SGLT2 inhibitors confirmed, but with caveats

Canagliflozin and cardiovascular and renal events in type 2 diabetes

[Neal, et al. N Engl J Med. 2017;377\(7\):644-657.](#)

The sodium-glucose transporter 2 (SGLT2) inhibitor, empagliflozin, was recently reported to reduce mortality and improve renal outcomes in patients with diabetes. The CANVAS trial, reports similar outcomes in a pair of double-blind trials of over 10,000 participants with type 2 diabetes and elevated cardiovascular risk recruited from 30 countries. Those with an eGFR < 30ml/min/1.73m² were excluded. Participants were randomized to canagliflozin 300mg, canagliflozin 100mg or placebo for a median follow up was 2.4 years. Fewer patients in the canagliflozin group suffered the primary outcome of major cardiovascular events (2.7 vs 3.2 per 100 patient-years, $p = 0.02$ for superiority) and the rate of hospitalisation for heart failure was also lower (0.6 vs 0.9 per 100 patient years, hazard

ratio 0.7; 95% CI 0.52-0.97). Moreover, the renal composite outcome of a 40% reduction in eGFR, need for renal-replacement therapy or death from renal causes occurred less often in the treatment group (0.6 vs 0.9 per 100 patient-years, hazard ratio 0.6; 95% CI 0.47-0.77). There was no increase in hypoglycaemia, hyperkalaemia or acute kidney injury but there was an increase in the frequency of lower limb amputation (0.6 vs 0.3 per 100 patient years, hazard ratio 2.0; 95% CI 1.41-2.75) and, although rare, there was a non-significant increase in diabetic ketoacidosis (0.06 vs 0.03 per 100 patient years, hazard ratio 2.3; 95% CI 0.76-7.17). The risk of fracture was increased overall (1.5 vs 1.2 per 100 patient years, hazard ratio 1.3; 95% CI 1.04-1.52), but this was only seen in the CANVAS and not the CANVAS-R study. Overall, this important trial demonstrated that canagliflozin reduces the risk of major cardiovascular events and reduces adverse renal and heart failure outcomes – but it also highlighted the potential increased risk of amputation and possibly fracture. These results will help clinicians individualise therapy for diabetes and cardiovascular disease.

Liraglutide reduces new onset macroalbuminuria when added to usual care for type 2 diabetes

Liraglutide and Renal Outcomes in Type 2 Diabetes

[Chen, et al. N Engl J Med. 2017;377\(9\):839-848](#)

The LEADER trial showed that the glucagon-like peptide-1 inhibitor, liraglutide, reduced cardiovascular outcomes in patients with type 2 diabetes. Chen, et al. present the results of pre-specified secondary analysis of the renal outcomes. This randomized, double-blind placebo controlled trial randomised 9340 patients, 23% of whom had an eGFR < 60ml/min/1.73m², microalbuminuria was present in 26% and macroalbuminuria in 10%. The renal outcome (new onset macroalbuminuria, doubling of creatinine, end-stage kidney disease and death from a renal cause) occurred at a rate of 1.5 per 100 patient years in those treated with liraglutide compared with 1.9 per 100 patient years in the placebo group (p=0.003). This was primarily driven by a reduction in the rate of new macroalbuminuria (0.9 per 100 patient years vs 1.2 per 100 patient years; hazard ratio 0.78, 95% CI 0.67-92; p=0.004). There was no difference in the rate of ESKD, although this outcome was less common (0.3 per 100 patient years in the whole cohort). These effects were similar in the subgroup with renal disease (albuminuria or eGFR < 60ml/min/1.73m²) at baseline. The extent to which these effects depend on improved glycaemic control remains unclear, the authors report that the renal benefits of liraglutide remained after statistical analysis adjusting for changes in HbA1c over the course of the trial. Whatever the mechanism of action, this trial supports a role for liraglutide in managing selected patients with type 2 diabetes.
