PRESS RELEASE

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HIGH-IMPACT CLINICAL TRIALS YIELD RESULTS THAT COULD IMPROVE KIDNEY CARE

Orlando (November 4, 2022) — The results of numerous high-impact clinical trials that could affect kidney-related medical care will be presented in-person and online at ASN Kidney Week 2022 November 3–November 6.

- Saline (0.9% sodium chloride) is the most widely used intravenous fluid in kidney transplantation but may increase the risk of delayed graft function (defined as the need for dialysis within 7 days of transplant) due to its high chloride content. Investigators analyzed data from 807 participants in the BEST-Fluids trial who were randomized to receive a balanced low-chloride crystalloid solution (Plasma-Lyte 148) or saline solution during and after transplant surgery. Fewer participants in the balanced crystalloid group needed dialysis after transplant surgery due to poor kidney function compared with those in the saline group (30.0% vs. 39.7%). The effect was consistent across pre-specified subgroups of deceased donor type, kidney donor risk index, machine perfusion, and ischemic time. The incidence of hyperkalemia, or high potassium, was similar in both groups, and there were no significant differences in acute rejection, graft failure, or mortality up to 52 weeks. Numbers of serious adverse events were also similar in both groups. “Reducing dialysis with this simple, low cost-intervention should improve patient recovery after transplant, lower healthcare costs, and may improve long-term outcomes for patients,” said corresponding author Michael Collins, MBChB, PhD, of the Royal Adelaide Hospital and the Australasian Kidney Trials Network, in Australia. “Based on the results of this trial, we believe that peri-operative balanced crystalloid fluid should become the standard of care in deceased donor kidney transplantation.” *The BEST-Fluids Trial: A Randomized Controlled Trial of Balanced Crystalloid Solution vs. Saline to Prevent Delayed Graft Function in Deceased Donor Kidney Transplantation*

- Oxidative stress can contribute to the development and progression of diabetic kidney disease. In a phase 2 trial, 140 patients with type 2 diabetes and chronic kidney disease were randomized to receive isuzinaxib (an inhibitor of nicotinamide adenine dinucleotide phosphate-oxidase and a modulator of oxidative stress) or placebo for 12 weeks. At week 12, the average change of urine albumin-to-creatinine ratio (UACR)—a marker of kidney damage, with a high value indicating higher

damage—was -21% in the isuzinaxib group and -2.5% in the placebo group. In patients with especially low kidney function at the start of the study, the average UACR change was -36% in the isuzinaxib group compared with +11% in the placebo group. Interestingly, KIM-1, a urinary marker of kidney injury, was reduced significantly in the isuzinaxib group. “This study demonstrates the first clinical evidence of isuzinaxib’s effectiveness in diabetic kidney disease. Future clinical development will likely be focused on patients with advanced chronic kidney disease,” said corresponding author Dae Ryong Cha, MD, of the Korea University College of Medicine and School of Medicine.
Effect of Isuzinaxib, Pan NOX Inhibitor in Patients With Type 2 Diabetes and CKD in a Randomized, Double Blind, Placebo Controlled Phase 2 Trial

- Certain medications, including non-steroidal anti-inflammatory drugs (NSAIDs), renin-angiotensin-aldosterone system inhibitors (RAASis), and proton pump inhibitors (PPIs) can contribute to the development of acute kidney injury in hospitalized patients. In an open-label, parallel group, randomized controlled trial conducted from August 2020 to November 2021 at 4 hospitals in a large, regional US health system, investigators tested an automated, electronic “pop-up” alert that appeared during medication order entry and flagged the NSAIDs, RAASis, and PPIs for potential discontinuation. In the trial that included 5,060 hospitalized individuals with acute kidney injury and an active order for one of these drugs, the drug was discontinued in 61.1% of the alert group vs. 55.9% of the usual care group within 24 hours (a significant difference). The primary outcome—a composite of progression of AKI, dialysis, or death within 14 days or hospital discharge—occurred in 585 (23.1%) of individuals in the alert group and 639 (25.3%) of patients in the usual care group (not a statistically significant difference). A pre-specified subgroup analysis found a significant benefit of alerting among those exposed to PPIs, however. “This suggests that patients on PPIs may be a population in whom AKI alerts and discontinuation of potentially toxic medications is effective,” said corresponding author F. Perry Wilson, MD, MSCE, of Yale University.
  Automated, Medication-Targeted Alerts on AKI Outcomes: A Multi-Center Randomized, Controlled Trial

- Black Americans are disproportionately affected by hypertension and chronic kidney disease, with inequitable access to healthy foods and knowledge gaps about healthy eating playing potential roles. In a recent trial, 150 Black adults with hypertension and chronic kidney disease were randomized to a Self-Shopping Dietary Approaches to Stop Hypertension (S- DASH) diet with a $30/week grocery allowance for 4 months but no guidance on purchases, followed by no grocery allowance for 8 months or to a Coaching (C-DASH) diet advice group with a $30/week food allowance and assistance in purchasing high potassium foods for 4 months, followed by coaching without food allowance for 8 months. The C-DASH group had increased

dietary potassium and fruit/vegetable consumption compared with the S-DASH group; and the C-DASH group had declines in UACR (urine albumin-to-creatinine ratio)—a marker of kidney damage, with a higher value indicating more damage—that did not differ statistically from the S-DASH group, except among the subgroup with especially high UACR, where the C-DASH group had a 73.3% decrease in UACR and the S-DASH group had a 20.5% increase. There was also a suggestion of benefit for those with diabetes. “We found several benefits for Black Americans with high blood pressure and early kidney disease who were coached one-on-one on selecting healthy foods that were then delivered to them by a local grocer. People who received the coaching improved the quality of their eating habits compared with those who shopped on their own using gift cards from the same grocer; and we saw some signs of improvements in kidney health, particularly for people who at the beginning of the study were losing high amounts of protein in their urine and for those with diabetes,” said corresponding author Deidra Crews, MD, ScM, of Johns Hopkins University School of Medicine. “Our next steps will be to try to expand the program to support more populations disproportionately affected by kidney disease.”
Dietary Intervention Trial for Hypertensive Black Adults With CKD

- Metabolic acidosis—when there is too much acid in the body fluids—is a common complication of chronic kidney disease (CKD), and it can lead to poor outcomes, such as bone demineralization, muscle mass loss, and worsening of kidney function. The VALOR-CKD trial is an international, phase 3, randomized, multicenter, double-blind, placebo-controlled study evaluating the effect of once-daily veverimer on kidney disease progression in patients with CKD and chronic metabolic acidosis. Veverimer is a novel hydrochloric acid binder that removes acid from the gastrointestinal tract. A total of 1,480 patients from 34 countries and 191 sites were randomized to veverimer or placebo. Investigators assessed whether veverimer affected the primary endpoint of kidney disease progression and the secondary endpoints of physical function decline, cardiovascular death, and all-cause death. “We found that in this study, treatment with veverimer did not result in a slowing of CKD progression or improvement in physical function. The lack of a clinically meaningful difference in serum bicarbonate levels between the active and placebo patients may have limited our ability to detect a benefit from the treatment of metabolic acidosis,” said lead author Navdeep Tangri, MD, PhD, of the University of Manitoba, in Canada.
  VALOR-CKD: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial Evaluating Veverimer in Slowing Progression of CKD in Patients With Metabolic Acidosis

- Conventionally, dialysis centers have provided maintenance hemodialysis using a standard dialysate temperature for all patients. Many centers now use cooler

dialysate in patient care, but this practice change is based on limited evidence. In the open-label MyTEMP trial, 84 of Ontario's 97 hemodialysis centers were randomized to use cooler temperature dialysate (0.5°C below each patient's body temperature) or standard temperature dialysate (36.5°C). Over 4 years, 15,413 patients were treated with hemodialysis. The primary outcome—a composite of cardiovascular-related death or hospital admission with myocardial infarction, ischemic stroke, or congestive heart failure—occurred in 1,711 of 8,000 patients (21.4%) in the cooler dialysate group vs. 1,658 of 7,413 patients (22.4%) in the standard-temperature group (not a significant difference). Patients in the cooler dialysate group were more likely to report feeling uncomfortably cold during dialysis. "What is innovative about the MyTEMP trial is the methods we used. Because we embedded the trial into existing healthcare, we were able to determine whether the intervention would improve outcomes in a real-world setting that included all dialysis patients. Based on the trial's findings, dialysis centers that are currently providing cooler dialysate as a center-wide policy should consider using a standard dialysate temperature of 36.5°C for the comfort of their patients, as cooler dialysate did not improve patient outcomes," said corresponding author Amit Garg, MD, PhD, of Western University, the Lawson Health Research Institute, and ICES in Ontario. "We intend to conduct more large-scale high-quality clinical trials in this way to efficiently identify those treatments that improve the outcomes and health care of patients with kidney disease. We can conduct these trials better, faster, and cheaper than traditional trials by integrating them in routine healthcare and using information from existing data sources to efficiently study patient outcomes.
Personalized Cooler Dialysate for Patients Receiving Maintenance Hemodialysis

- Activation of complement pathways, which are part of the innate immune system, contributes to the development of IgA nephropathy. A phase 2 study assessed the effects of cemdisiran, an investigational RNA interference therapy that suppresses liver production of complement component 5, in patients with IgA nephropathy. A total of 31 patients were randomized 2:1 to subcutaneous cemdisiran 600 mg or placebo once every 4 weeks alongside standard care. The primary endpoint was the change from baseline to week 32 in 24-hour urine protein/creatinine ratio—a marker of kidney damage, with a high value indicating more damage. Cemdisiran led to a 37.4% adjusted geometric mean reduction in 24-hour urine protein/creatinine ratio compared with placebo at week 32. Cemdisiran also led to a 98.7% average reduction from baseline in serum C5 at week 32. Cemdisiran was generally well tolerated with no treatment-related serious or severe adverse events. "IgA nephropathy is an important cause of kidney failure and in 2022 we have severely limited treatment options for our patients. This study shows for the very first time that we can specifically target the genetic machinery that makes a key component of the immune system and thereby successfully block activation of the complement system," said corresponding author Jonathan Barratt, PhD, FRCP, of Leicester

General Hospital, in the UK. “Activation of the complement system is a key driver for kidney damage in IgA nephropathy and this study shows that by blocking complement with cemdisaran we can begin to see signs of reduced kidney inflammation and damage in patients with IgA nephropathy.”
Exploratory Results From the Phase 2 Study of Cemdisiran in Patients With IgA Nephropathy

- More evidence was needed on the effects of sodium glucose co-transporter-2 (SGLT2) inhibitors on kidney and cardiovascular health in patients with chronic kidney disease, especially in patients without diabetes, and patients with the levels of low kidney function cared for in specialist kidney clinics. Therefore, the EMPA-KIDNEY trial investigators randomized 6,609 adults who were at risk of kidney disease progression from a range of different kidney conditions to the SGLT2 inhibitor empagliflozin 10mg once daily or matching placebo. Empagliflozin showed significant benefit, reducing the risk of kidney disease progression or death from cardiovascular disease by 28%. “Treatments such as empagliflozin should be offered to all patients with chronic kidney disease who may benefit from reduced risk of kidney disease progression and cardiovascular complications, regardless of whether they have diabetes or not, and even at low kidney function,” said corresponding author Will Herrington, MA, MBBS, MD, FRCP, of the Medical Research Council Population Health Research Unit at the University of Oxford, in the UK. “The EMPA-KIDNEY trial not only confirms the results of previous trials among particular groups of patients with chronic kidney disease (such as those with diabetes or with high levels of protein in their urine), but also shows that the benefits extend to a much broader group of patients. These exciting results will substantially increase the benefit for patients’ and population health,” added senior author Richard Haynes, DM, FRCP, also of the Medical Research Council Population Health Research Unit.
Empagliflozin in Patients With CKD

- Investigators recently collated and reanalyzed kidney outcome data from all large randomized clinical trials that have studied sodium-glucose co-transporter-2 (SGLT2) inhibitors. These drugs were originally developed to treat people with diabetes, but the most recent trials have also included large numbers of people without diabetes. After analyzing data from 13 trials, the team found that SGLT2 inhibitors safely reduced the risk of progression of kidney disease by approximately 40% and acute kidney injury by nearly a quarter. “The results were similar in patients with and without diabetes and across the different kidney disease diagnoses studied in the trials,” said presenting author Natalie Staplin, PhD, of the Medical Research Council Population Health Research Unit at the University of Oxford, in the UK.
Sodium Glucose Cotransporter-2 (SGLT2) Inhibitors Among Patients with and without Diabetes: Collaborative Meta-Analysis of Large Placebo-Controlled Trials

ASN Kidney Week 2022, the largest nephrology meeting of its kind, will provide a forum for nephrologists and other kidney health professionals to discuss the latest findings in research and engage in educational sessions related to advances in the care of patients with kidney diseases and related disorders.

Since 1966, ASN has been leading the fight to prevent, treat, and cure kidney diseases throughout the world by educating health professionals and scientists, advancing research and innovation, communicating new knowledge, and advocating for the highest quality care for patients. ASN has more than 20,000 members representing 132 countries. For more information, visit www.asn-online.org and follow us on Facebook, Twitter, LinkedIn, and Instagram.

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