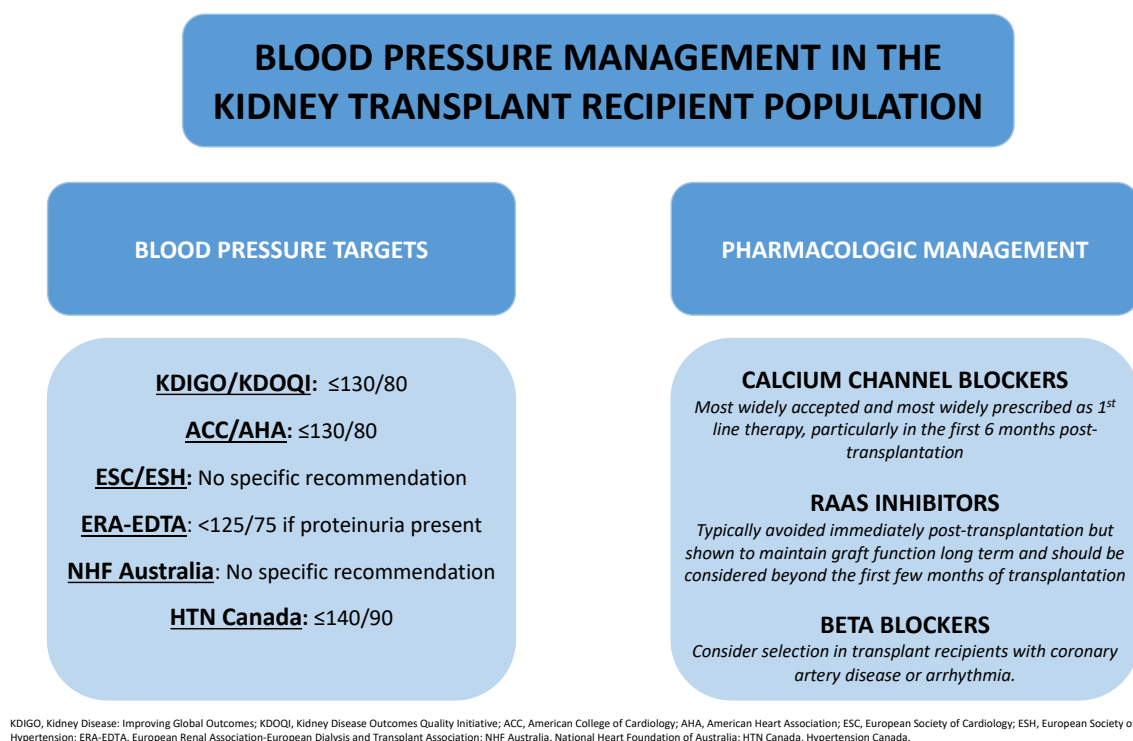


**Figure 2. Managing BP in the kidney transplant population**

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## New Dietary Approaches to Managing Kidney Disease

By Bridget M. Kuehn

**K**idney patients have long complained that the diet recommended for them is bland, tasteless, and hard to follow. But that old advice is being challenged by new research that may offer more palatable alternatives to old dietary approaches to managing kidney disease.

During the Diet and CKD [Chronic Kidney Disease]: What to Eat, When to Eat, How to Eat session at Kidney Week 2021, a panel of speakers highlighted evidence backing the health benefits of plant-based diets, time-restricted eating, and culturally sensitive dietary interventions for Black, Latinx, or Hispanic patients with kidney disease.

### Rethinking diet dogma

Juan-Jesus Carrero, PhD Medicine, PhD Pharm, MBA, MSc, professor of cardio-renal epidemiology in the Department of Medical Epidemiology and Biostatistics at the Karolinska Institute in Sweden, explained that the traditional kidney diet has emphasized avoiding plant foods because of concerns about electrolyte abnormalities, hyperphosphatemia, hyperkalemia, and protein malnutrition.

“Patients do not like these recommendations which are difficult to adhere to,” Carrero said. Patients report feeling deprived of healthy eating—lacking motivation to eat the recommended foods—and have difficulties eating away from home. “I would like us all to rethink these old dogmas and discuss whether plant-based diets can be of benefit for our patients,” he said.

Advice to restrict potassium-rich produce can inadvertently deprive patients of other nutrients that may be beneficial for patients with kidney disease, Carrero said. He noted that it may not account for hidden sources of dietary potassium from processed foods and that potassium content in foods may also vary by how much a person eats or how the food is cooked. For example, boiling food can reduce potas-

sium levels by 75%, he said. Potassium absorption may also be affected by the combination of foods that patients eat.

“Dietary potassium restriction as a means to prevent hyperkalemia and CKD may have been well intended, but it is not supported by strong evidence,” he said.

In a recent review, Carrero and colleagues highlighted the benefits of plant-based diets for patients with CKD, such as increased fiber intake, beneficial effects on gut microbiota, heart health benefits of plant-based fats, reduced acidosis, and potentially better control of hyperphosphatemia because plant phosphorous may not be as bioavailable (1).

Carrero said slow and careful changes with close monitoring may enable patients to transition to more plant-based diets. Fresh produce prepared at home is best, he said. Distributing fruits and vegetables throughout the course of the day and controlling portions may minimize risks. He said more research is needed on plant-based diets in CKD.

### On the clock

Meal timing may also be a useful intervention to improve patient health, said Michelle Gumz, PhD, associate professor in the Division of Nephrology, Hypertension, and Renal Transplantation, College of Medicine at the University of Florida, Gainesville. Gumz highlighted how disruption of the circadian clock that keeps the body entrained to the 24-hour light-dark cycle may contribute to an increased risk of CKD, hypertension, or cardiovascular disease.

We live in a 24-7 society in an environment that is not in sync with our internal [clock],” Gumz said. “These pathological states can further disrupt the clock, and this can lead to a vicious cycle.”

For example, shift work has been associated with a 2- to 3-fold increased risk of CKD, and individuals who do not have the typical nightly dip in blood pressure associated with normal circadian rhythms are at greater risk of cardiovascular and kidney events, she noted.

The body’s circadian rhythms are controlled by a central clock in the brain that is entrained to both light and the timing of food intake, Gumz explained. Peripheral clocks in the organs and tissues of the body are entrained by foods. Both the central and peripheral clock are controlled by a cycle of gene expression that regulates the expression of 50% of the genes in the body, including many important for cardiovascular and kidney health, she noted.

“If your eating circadian rhythm is out of sync with the light-dark cycle, those eating patterns can entrain the peripheral clocks,” Gumz explained. “This will result in misalignment between the brain and the peripheral clocks. This can

lead to metabolic dysfunction and is likely to increase cardio-metabolic risk factors.”

For example, a recent study showed that women who have inconsistent eating patterns have higher blood pressure, higher body mass index, and worse blood sugar control (2). But several ways to restore healthy circadian clock function have been studied, including time-restricted eating, noted Gumz. Another recent study showed that patients with metabolic syndrome who restricted their eating to a 10-hour window for 12 weeks lost weight, lowered their blood pressure, and improved their lipid profile (3).

“Timing of food intake can alter blood pressure and cardiovascular risks,” Gumz said. She said more study is needed to see if time-restricted eating helps restore a normal pattern of nighttime blood pressure dips in patients with kidney disease.

### Addressing diet disparities

Diet is considered a modifiable factor in kidney disease, but dietary modifications are not easy, said Crystal Tyson, MD, assistant professor of medicine in the Division of Nephrology at Duke University Medical Center in Durham, NC. Socioeconomic, environmental, behavioral, and cultural, as well as the patient’s kidney disease and co-morbid conditions all need to be factored into dietary interventions. Overall, she noted that Americans’ diets are poor and that Black, Hispanic, and Latinx individuals have a greater prevalence of poor dietary scores than their White and Asian counterparts.

“Improving diet in US racial and ethnic minorities may reduce disparities in kidney outcomes,” she said.

The DASH (Dietary Approaches to Stop Hypertension) diet is one of the most studied dietary patterns, particularly among people of Black race, Tyson said. A study by Tyson and her colleagues found that Black individuals with CKD who were more adherent to the diet had low blood pressure, but overall adherence was low (4). Focus groups conducted by the team at Duke with Black patients with CKD found the participants thought the DASH diet was culturally compatible, but they expressed some concern that it wasn’t consistent with previous dietary advice they had received about eating fruits and vegetables, salt, or protein. Other barriers included inadequate cooking skills and concerns about how to buy or use unfamiliar foods.

“Interventions should include cost-effective and time-efficient strategies to follow a healthy diet and emphasize food sources that are convenient and accessible in the local

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environment,” Tyson said. They should also provide instructions on measuring serving sizes, cooking tips, and resources about new foods and address kidney-related diet concerns.

Nimrit Goraya, MD, a nephrologist at Baylor Scott & White Health in Temple, TX, also highlighted some barriers to healthy food access in racial and ethnic minority communities. Food insecurity, which has been linked (5) to a higher risk of CKD and progression to end-stage kidney disease, disproportionately (6) affects Black and Hispanic or Latinx households. The pandemic has increased food insecurity in the United States, particularly among these groups, she said.

Living in “food deserts” without easy access to supermarkets can also be a barrier to healthy eating. Goraya explained that individuals who live in areas with limited access to food resources may purchase energy-dense foods from gas stations or bodegas. This leads to individuals having a higher dietary acid load, which may contribute to higher acid excretion and

CKD progression.

Making healthy foods easily available through vouchers or food banks can facilitate healthier eating, Goraya said. Family-based interventions that work to build trust in communities and engaging trusted community leaders can also help. For example, church-based programs have demonstrated success. Counseling on how to prepare healthy foods can also help, she said.

It is important to avoid stereotypes about what racial and ethnic minorities eat and to focus on individualized interventions. “Dietary patterns are diverse within cultures, and the breadth of that diversity should be recognized,” Tyson said. Because of this, it is important to address a patient’s individual needs and preferences, she said.

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# High-Impact Trials Offer Potential Solutions to Clinical Conundrums

By Bridget M. Kuehn

**A** reduced dose of the inexpensive oral methylprednisolone reduced the risk of kidney failure by 41% over 4 years in patients with immunoglobulin A (IgA) nephropathy in the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study presented during Kidney Week 2021. The drug, however, was associated with an increased risk of severe infection, particularly in the first months of treatment. The TESTING trial results were among several results that promise to help solve “clinical conundrums” in the field of nephrology, presented during the High-Impact Clinical Trials session at Kidney Week 2021.

“These are exciting times in the field of nephrology,” said Wendy St. Peter, PharmD, professor with the College of Pharmacy at the University of Minnesota in Minneapolis, who co-moderated the High-Impact Clinical Trials session at the meeting.

### Steroid balancing act

IgA nephropathy is a common cause of kidney disease in younger adults and is a consequence of autoimmune attacks on the kidneys (1). Most studies’ use of corticosteroids in these patients have not been adequately powered to assess kidney outcomes, said Vlado Perkovic, MBB, PhD, the TESTING trial’s co-senior author and dean of medicine, University of New South Wales in Australia. To help fill this gap, the trial initially planned to randomize 503 patients with IgA to a full dose of methylprednisolone starting at 0.6–0.8 mg/kg/day to a maximum dose of 48 mg/day for 2 months, followed by gradual weaning from the drug over 4 to 7 months or placebo.

However, the identification (2) of an increased incidence of serious infections, including four that were fatal, in patients taking methylprednisolone led to the change in the trial protocol in which 241 patients were randomized to a reduced dose of methylprednisolone of 0.4 mg/kg/day to a maximum of 32 mg/day, followed by weaning. When the results from both steroid groups were analyzed after an average of 4 years of follow-up, there was a 47% reduction in a composite endpoint of 40% decline in estimated glomerular filtration rate (eGFR) or kidney failure compared with the placebo group and a 41% reduction in kidney failure, according to the data presented by Perkovic. A subgroup analysis of the lower dose group compared with placebo found a 73% reduction in the composite endpoint over an average of 2.5 years’ follow-up. Perkovic noted that one patient in the lower dose group also died of a serious infection.

In the full dose group, for every 100 patients treated, methylprednisolone would precipitate about 12 fewer primary outcome kidney events but about 12 serious adverse events, Perkovic said. In the reduced dose group, for every 100 treated, there would be almost 17 fewer primary outcome kidney events with 2.4 serious events, he said. Perkovic said the results support existing guidelines that recommend nephrologists discuss the benefits and risks of corticosteroids with patients with IgA nephropathy who are at a high risk of kidney events.

“We provide additional data that will help inform those conversations by providing more precision about the risks and benefits of different approaches,” Perkovic said. “[The results] suggest this should be offered to high-risk people.”

The evidence shows that a lower dose of methylprednisolone is effective at reducing kidney-related events and resulted in fewer serious adverse events than higher doses, St. Peter said. “This is good news for patients with IgA nephropathy and their nephrologists who want them to get the benefits from an effective treatment but with less risk of a severe infection or other serious side effects that are common with higher steroid doses,” she added.

### New options for old challenges

Other high-impact studies presented during the session offered promising new options to solve longstanding challenges in nephrology, including a treatment for RNA inhibitor-reduced oxalate levels in patients with primary hyperoxaluria type 1 (PH1); a potential oral alternative to injectable therapies for anemia in patients with chronic kidney disease (CKD); and an inexpensive, older drug that may help control hypertension in patients with stage 4 CKD.

An injectable RNA inhibitor called lumasiran reduced urinary oxalate levels by one-third in patients with PH1 who were not on dialysis and by 42% among those on dialysis, according to results from the Evaluate Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C) study presented at Kidney Week by its lead author Mini Michael, MD, MMed, associate professor at Baylor College of Medicine in Houston, TX. PH1 is a rare condition associated with oxalate overproduction, kidney disease, and multi-organ damage. The trial enrolled 21 patients and followed them for 6 months.

“[Oxalate] changes of this magnitude may change long-term patient outcomes,” Michael said. She and her colleagues are continuing to follow patients to assess longer term outcomes.

“It is exciting to see a new therapy which has the potential to change the dynamic of a rare and serious disease [like PH1] that mainly affects the kidneys but can result in multi-organ damage,” St. Peter said. She noted the condition often results in the need for dialysis, kidney transplant, or liver and kidney transplant. She said one remaining question is whether lumasiran will reduce kidney disease progression, the need for dialysis, or the need for kidney and liver transplantation.

Oral daprodustat may be an alternative to injectable erythropoiesis-stimulating agents (ESAs) for treating anemia in patients with CKD, according to a presentation by Ajay Singh, MBBS, MBA, a nephrologist at Brigham and Women’s Hospital and Harvard University in Boston, MA. The results of the Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat (ASCEND) trials in patients on dialysis (3) and not on dialysis (4) were published in *The New England Journal of Medicine* simultaneously. The trials enrolled 6800 patients and showed that daprodustat was non-inferior to ESAs for treating anemia patients with CKD who were receiving dialysis and those who did not require dialysis. It was also non-inferior to ESAs when the researchers looked at major adverse cardiovascular adverse events.

In a press briefing about the results, Singh noted that many patients currently don’t have access to ESA treatment. Additionally, patients may be more likely to comply with and tolerate an oral medication, he said.

“The nephrology community has been hoping that the new hypoxia-inducible factor prolyl hydroxylase inhibitor would represent a new era in the treatment of anemia in CKD, with better efficacy and/or safety than ESAs,” St. Peter said. “It’s a little disappointing that daprodustat was only shown to be non-inferior and not superior in efficacy or safety endpoints as ESAs. Regardless, it would be nice to have an oral option for anemia management, particularly in non-dialysis-dependent patients with CKD.”

The Chlorthalidone in Chronic Kidney Disease (CLICK) study (5) randomized 160 patients with stage 4 CKD and hypertension to chlorthalidone or placebo and found the low-cost medication reduced systolic blood pressure by 11 mm Hg within 4 weeks, according to a presentation by Rajiv Agarwal, MD, of the Indiana University School of Medicine in Indianapolis. It also lowered albuminuria by one-half over 12 weeks.

“The results of the CLICK study dispelled the myth that thiazide diuretics are not effective for blood pressure man-