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Intravenous Radiocontrast Exposure Not Associated with Kidney Function

Acute kidney injury associated with the administration of radiocontrast is known as contrast-induced nephropathy (CIN) and is one of the more commonly reported adverse events related to radiocontrast administration. However, according to **Robert Goulden, MBBS,** and colleagues, results of several recent observational studies have found no association between contrast exposure and adverse renal outcomes, suggesting that while agents used in the past may have contributed to CIN, modern agents and doses do not appear to be harmful.

A number of potential biases limit existing evidence, including the possibility of confounding due to baseline differences in the risk of developing kidney injury between exposure groups as well as the possibility of selection bias due to limiting study inclusion to those with appropriately timed repeat creatinine measurements.

Dr. Goulden et al. conducted a cohort study to examine whether there is an association between intravenous radiocontrast exposure and clinically significant long-term kidney impairment. The study design permitted stronger causal interpretation compared with the existing observational research. Results of the study were reported online in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2021.0916].

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Risk Factors and Outcomes Among Dialysis Patients with COVID-19 in the United States

Patients with kidney failure on maintenance dialysis are particularly vulnerable to COVID-19. The average age of patients on maintenance dialysis is 65 years. Further, patients in that population commonly have multiple comorbidities such as diabetes, obesity, and uremia-induced impaired immunity, putting them at increased risk for poor outcomes in COVID-19.

Patients with kidney failure are commonly more socioeconomically disadvantaged than the general population and live in more densely populated urban areas,

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AKI in Patients with COVID-19 Independent of Traditional Risk Factors

COVID-19 was initially considered a respiratory illness but is now recognized to affect multiple organ systems, including lungs, heart, brain, endothelium, and kidneys. During the first phase of the pandemic, acute kidney injury (AKI) was reported in 46% to 57% of patients hospitalized with COVID-19 at tertiary-care hospitals in New York, and in 32% to 37% in subsequent reports. The high rate of AKI in patients with COVID-19 has put a substantial burden on healthcare systems, including the provision of dialysis, and may be associated with long-term patient harm.

It is unknown whether the occurrence of AKI in patients with COVID-19 is independent of traditional risk factors such as hypotension, exposure to nephrotoxins, and inflammation. Previous studies have reported possible direct infection of the kidneys and glomerular disease; however, acute tubular injury is the predominant histologic lesion reported. Those findings suggest that AKI in COVID-19 is more likely to occur via pathways unrelated to direct kidney infection.

Dennis G. Moledina, MD, PhD, and colleagues conducted a multicenter, observational cohort study to test the hypothesis that AKI in patients with COVID-19 would be driven by similar risk factors as AKI in patients without COVID-19. The researchers compared the incidence of AKI in patients with and without COVID-19 overall and after controlling for quantifiable, clinically validated risk

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Should Incentives Be Introduced for Kidney Donation?

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In a thought-provoking Viewpoint article in *JAMA Surgery*[1], **Arthur Matas, MD,** makes the case for introducing a regulated system for incentives for kidney donation.

Data from the US Organ Procurement and Transplant Network (OPTN) show the extent of the kidney organ shortage in the US. More than 90,000 patients are on the kidney transplant waiting list and, since 1990, nearly 90,000 transplant candidates in the US have died waiting for a kidney, while 55,000 have been removed from the waiting list because they were too sick.

Matas proposes a vision for a regulated system of incentives to stimulate greater donation. He suggests a regulated system governed by the US government or a government-appointed agency. The regulatory framework Matas envisions would set guidelines and rules, such as acceptance criteria for donors and novel organ allocation schemes, but would also extend to pilot incentives models, such as tax benefits or provision of coverage for healthcare costs. Matas proposes that the system would be limited to citizens and legal residents so that patients could be followed for long-term assessment of outcomes.

The voices that oppose an incentive system raise ethical concerns, some legitimate, but many not. These include the potential risk to an incentivized donor and the purported complexity of obtaining consent—both easily overcome, says Dr. Matas, if one follows the same procedure as for an unincentivized donor.

Opponents of a regulated system say that a system of incentives would threaten the whole concept of altruism. Dr. Matas makes the point that kidney donation isn't really altruism in its truest sense (altruism is defined by Merriam Webster as "unselfish regard for, or devotion to, the welfare of others"), because organ donation doesn't encompass what really happens, which is that donors have complex motivations to donate. Some donate because of a family relationship, others through a sense of guilt, and some because of direct or indirect financial benefits. An excellent paper by **Mélanie Levy**[2] argues that while "altruism should remain at the heart of donation, as it reflects important community values...this does not exclude the possibility of introducing a reward." She further makes the point that based on Maussian gift exchange theory, gift giving also involves receiving and reciprocity. This gift giving concept in the context of transplantation has been further expanded by others, including Renee Fox and Judith Swazey.[3]

The other point made by opponents is that a regulated system would erode trust in government and institutions. Dr. Matas argues that there are several examples where this hasn't happened, such as sperm donation.

Another key critique of a regulated system is that incentives have the potential to exploit people with low incomes, particularly those who don't quite understand what's at stake. Dr. Matas argues that if the system works as designed, then the risk of exploitation won't occur. In fact, several examples, including Iran and Israel, demonstrate that a national regulated framework minimizes the risk of a black market for organs.

A more existential critique of a regulated system is that bioethicists are naïve in assuming a goodness in society that may not exist. **Leon R. Kass**, chairman of the President's Council on Bioethics from 2001 to 2005, writing in the *New Republic*[4]: "Part of the blame for our complacency lies, sadly, with the field of bioethics itself, and its claim to expertise in these moral matters. With its capture by analytic philosophy, however, and its inevitable routinization and professionalization, the field has by and large come to content itself with analyzing moral arguments, reacting to new technological developments, and taking on emerging issues of public policy, all performed with a naïve faith that the evils we fear can all be avoided by compassion, regulation and a respect for autonomy."

Dr. Matas and colleagues, in an earlier paper[5], make the important point that it is "underground, unregulated markets [that] have been associated with exploitation of the poor and vulnerable... Living donors who participate in these unregulated markets are often poorly informed about the procedure, deprived of appropriate screening and of quality postoperative and continuing medical care, and not compensated as agreed upon...the 'evidence' used as the basis of that argument has almost entirely been drawn from observation of unregulated organ markets."

In evaluating whether Dr. Matas is right about the wisdom of adopting a regulated system of incentives in US, it is worth looking at the experience of both Iran and Israel who have regulated systems of kidney donation.

The Iranian regulated national system for kidney donation was launched in 1988, and by 1999, according to the government of Iran, eliminated the transplant waiting list. In 1988, 245 kidney transplants were performed in Iran. By 2005 the number had grown to 1891. The Iranian system involves two tracks—living related and living unrelated. If a potential recipient doesn't have a living related donor then the patient is referred to an organization—the Dialysis and Transplant Patients Association (DATPA)—to locate a suitable living-unrelated donor. The DATPA then matches the potential donor to a potential recipient. The living unrelated donors in the system receive a payment of about USD $1200 and the government provides subsidized essential immunosuppressive drugs. More details on the Iranian system are detailed in an excellent *Clinical Journal of the American Society of Nephrology* review.[6]

In an article from the Associated Press (AP) published in *STAT News*[7], **Hashem Ghasemi**, the head of the patient-run Dialysis and Transplant Patients Association of Iran, says: "Some donors have financial motivations. We can't say they don't. If [those donors] didn't have financial motives, they wouldn't donate a kidney...And some people just have charitable motivations." According to the AP article, the Iranian system has guardrails to mitigate the risk of black market organ sales and create a regulatory framework. In Iran, nonprofit groups handle all arrangements and hold money in escrow until after the surgery. The government's Health Department also must approve the surgeries, which take place in licensed and monitored hospitals. Foreigners are now largely banned from taking part, squelching the possibility of medical tourism.

Despite its success in eliminating the transplant waiting list, the Iranian system has been criticized because of reports of donors expressing financial pressure, and the financial transaction being supplemented by other gifts. Also, there is the question of whether a regulated system that works in an authoritarian context like Iran would work in the US. Still, the Iranian experience suggests that a regulated system implemented effectively could transform the availability of kidneys for donation.

The other model that has shown impressive success is the Israeli system of regulated incentives.[2] The Israeli Organ Transplantation Law, introduced in March 2008, has countered very low kidney donation rates in Israel by creating a points-based system to designate priority on the kidney transplant waiting list. The system works by allocating priority by points that are weighted by specific circumstances. Top priority is granted to individuals with a first-degree relative who donated organs after death to non-directed and directed living donors. Second priority is granted to those who sign a donor card consenting to donate their organs after death, and third priority to individuals with a first-degree relative who has signed a donor card. For those who fall into more than one category, the highest category gets counted. Those <18 years of age also receive relative prioritization. Published data have shown that the system has resulted in a substantial increase in kidneys available for donation. In 2014, 30% of transplanted patients were advanced in line based on their priority status; in 2015, this percentage increased to 32%.[2]

My take on the Matas viewpoint article is that he does have a point. Most of the growth in kidney transplantation can be accounted for by the increase in deceased donor transplantation. If we want to increase living related transplantation, then we should think seriously about introducing a regulated system of incentives. As a nephrology and transplant community, we need to advocate for transformational change to eliminate the transplant waiting list. ■

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Risk Factors and Outcomes

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putting them at increased risk for acquiring SARS-CoV-2. The need for in-center hemodialysis and associated transportation may require patients to forego effective physical distancing. The combination of these factors is also present in individuals who reside in long-term care facilities.

As of June 2021, the Centers for Medicare & Medicaid Services reported a COVID-19 prevalence of 3.8% in the dialysis population. To provide further characterization of COVID-19 among US patients on dialysis, **Caroline M. Hsu, MD,** and colleagues conducted a retrospective cohort study to examine risk factors for COVID-19 among dialysis patients treated by Dialysis Clinic Inc. (DCI), a medium-sized national not-for-profit dialysis provider treating more than 15,000 maintenance dialysis patients at 260 outpatient dialysis clinics in 29 states. The researchers also sought to assess the risk of and risk factors for mortality in patients on maintenance dialysis. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;77(5):748-756].

The primary outcomes of interest were diagnosis of COVID-19 by nasopharyngeal or oropharyngeal swabs sent locally for reverse transcriptase-polymerase chain reaction testing, and all-cause death within 90 days of COVID-19 diagnosis among those diagnosed with COVID-19, compared with those at the same clinic without a COVID-19 diagnosis. In patients without COVID-19, all-cause death was defined by death within 90 days of the first COVID-19 diagnosis at the source clinic. Patients were followed until death or 90 days, whichever came sooner, through September 1, 2020.

Eligible study participants were maintenance dialysis patients at DCI clinics with at least one patient who tested positive for SARS-CoV-2 from February to June 2020. Clinical characteristics associated with COVID-19 and risk factors associated with mortality among patients following COVID-19 were identified using logistic regression analyses.

During the 15-week study period, 438 maintenance dialysis patients had a diagnosis of COVID-19, representing ~3% of 15,200 patients treated in DCI clinics. Not all states and clinics were exposed to COVID-19 in the early pandemic surge; the 438 patients with a positive COVID-19 diagnosis represented 5.5% of 7948 patients in impacted clinics.

Compared with patients without COVID-19 in the impacted clinics, those with COVID-19 were older, and more likely to be Black, to be treated with in-center hemodialysis, to be treated at an urban clinic, to use respiratory inhalers, and to reside in a congregate setting such as a nursing home. COVID-19 patients also had higher comorbidity burden, and higher prevalence of cardiovascular disease, diabetes, and the need for assistance with activities of daily living and/or use a wheelchair.

In multivariable models, risk factors for COVID-19 infection in patients on maintenance dialysis were male sex, Black race, being treated at an urban clinic, residing in a congregate setting, the presence of comorbid conditions, and having a diagnosis of atherosclerotic heart disease and diabetes. Patients undergoing home dialysis were less likely to have COVID-19 infection.

The 438 patients with a COVID-19 diagnosis were followed until death or censored at 90 days. Of the 438, 109 (24.9%) died, compared with 275 of 7510 (3.7%) of the dialysis patients without COVID-19. A total of 296 of the patients with COVID-19 (67.6%) received care at the emergency department or as a hospital inpatient either at the time of diagnosis or within 30 days of diagnosis. Of those 296 patients, 95 (32.1%) died. Of those deaths, 86 occurred during hospitalization and nine occurred following initial hospital discharge. The remaining 201 patients were considered recovered by the end of follow-up.

Of the 142 patients (32.4%) who were not initially hospitalized, 14 died within 30 days of diagnosis (eight of those in nursing homes, two in hospice, two had unknown site of death, and two died at home), and another nine patients were hospitalized ≥30 days after diagnosis. Three of the nine were admitted due to COVID-19 and the other six received inpatient care for various other medical conditions. As of the end of follow-up, all 128 surviving outpatients were considered recovered from COVID-19.

Mortality was higher in older patients, particularly those >80 years of age. Patients who died had higher prevalence of comorbidity related to chronic heart failure, hypertension, and other cardiovascular disease as well as peripheral vascular disease, low albumin level, and use of a wheelchair. In multivariable models, older age became strongly associated with death, with increased risk of death in each decade after the age of 50; peripheral vascular disease, chronic heart failure, hypertension, and wheelchair use also remained significantly associated with risk of death.

Citing limitations to the study findings, the researchers included the observational design of the study, focusing on data from the dialysis provider with limited details surrounding in-hospital events; extremely limited testing data early in the pandemic that may have resulted in underestimation of COVID-19 cases and misclassification of deaths; the difficulty in determining the cause of death in this population given the extensive comorbid condition burden; excluding dialysis clinics with no COVID-19 cases that may have resulted in the introduction of other biases; the inability to distinguish asymptomatic carriers of COVID-19 from those with symptomatic disease; and the small number of home dialysis patients with COVID-19 identified during the study period.

In conclusion, the researchers said, "Dialysis patients are at high risk of COVID-19, with 5.5% of patients with a diagnosis of COVID-19 in facilities with at least one COVID-19 case during the first 3 months of the pandemic in the United States. In-center dialysis, residence in a long-term care facility, and Black race are all major risk factors associated with COVID-19, suggesting that the ability to maintain physical distance is critical to controlling COVID-19. Mortality among dialysis patients with COVID-19 exceeds 20%. To address COVID-19 while awaiting availability of safe and effective vaccines and therapeutics, dialysis facilities should recognize risk factors, maximize utility of telemedicine, promote home dialysis, encourage transplantation where appropriate, and optimize socio-culturally adapted education regarding physical distancing and universal precautions including masking, not limited to the dialysis clinic but relevant to all other at-risk settings." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study characterizing the risk factors and outcomes following COVID-19 in patients receiving maintenance dialysis.
- A total of 438 of 7948 (5.5%) maintenance dialysis patients were diagnosed with COVID-19; male sex, Black race, in-center dialysis (vs home dialysis), treatment at an urban clinic, residence in a congregate setting, and greater comorbidity burden were risk factors.
- Of the 438 patients with COVID-19, 109 (24.9%) died. Factors associated with increased risk for mortality were older age, heart disease, and markers of frailty.

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factors of AKI, including time-variant factors such as demographic data and comorbidities and time-updated indicators of disease severity such as vital signs, laboratory results, use of medications, and the need for mechanical ventilation. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;77(4):490-499].

The primary outcome of interest was AKI by Kidney Disease: Improving Global Outcomes criteria. The study exposure was a positive test for SARS-CoV-2. The study cohort included patients admitted to one of six hospitals within the Yale New Haven Health System between March 10, 2020, and August 21, 2020, with results for SARS-CoV-2 testing via polymerase chain reaction of a nasopharyngeal sample.

During the study period, 38,854 patients encounters included testing for SARS-CoV-2. Of those, 22,122 patients were included in the current analysis. Of the 22,122 patients included, 2600 had tested positive for SARS-CoV-2 and 19,522 had tested negative. Hospitalized patients who tested positive were more likely to be Black (24.8% vs 19.4%) or Hispanic (27.9% vs 12.2%) and more likely to have diabetes (38.3% vs 30.5%) compared with patients who tested negative. The prevalence of congestive heart failure and liver disease was lower in patients in the positive group than in patients who tested negative. At admission, the two groups were similar in the prevalence of chronic kidney disease (16.4% vs 16.6%) and had comparable serum creatinine concentration (1 vs 1 mg/dL), estimated glomerular filtration rate (76.7 vs 76.2 mL/min/1.73 m^2), and serum urea nitrogen level (17 vs 17 mg/dL).

A higher proportion of patients with COVID-19 experienced AKI compared with patients without COVID-19 (30.6% vs 18.2%; absolute difference, 12.5%; 95% confidence interval [CI], 10.6%-14.3%). Those in the COVID-19 positive group were more likely to experience stage 2/3 AKI (11.1% vs 4.9%), and, among those with AKI, required dialysis more frequently (8.5% vs 3.6%) and for longer durations (10.1 vs 4.1 days). Due to the similarity of AKI incidence on hospital admission between the two groups (5.0% in those with COVID-19 and 4.8% in those without COVID-19), the difference in AKI was largely driven by hospital-acquired AKI.

At discharge, fewer patients in the COVID-19 group had recovered from AKI than in the non-COVID-19 group (58% vs 69.8%), and patients admitted with COVID-19 were five times as likely to die than others (14.7% vs 3.1%); those rates were higher in both groups among those who developed AKI (29.6% and 11.3%). Length of stay was longer in patients in the COVID-19 group than in the group without COVID-19 (8 vs 4 days).

Patients in the COVID-19 group had more hypotension, greater use of diuretics, and higher markers of inflammation such as C-reactive protein and ferritin. Use of radiocontrast agents was lower in patients with COVID-19 and with AKI. The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers was lower with greater AKI severity; the difference was less pronounced in patients in the COVID-19 group.

Using multivariable adjustment in time-varying Cox proportional hazards models, the researchers tested the independent association of COVID-19 with AKI. In unadjusted analysis stratified by hospital, there was an association between COVID-19 and a 81% higher rate of AKI (hazard ratio [HR], 1.84; 95% CI, 1.73-1.95). Following additional adjustment for demographic characteristics, comorbidities, and time since onset of the pandemic, the higher rate persisted (adjusted HR [aHR], 1.54; 95% CI, 1.44-1.65). The higher rate also persisted after adjustment for medication use during hospitalization (aHR, 1.64; 95% CI, 1.54-1.75) and time-varying factors such as vital signs, laboratory values, admission to the intensive care unit (ICU), and the need for mechanical ventilation (aHR, 1.40; 95% CI, 1.29-1.53). There was no change in the association between COVID-19 and AKI over the course of the pandemic (P=.4 for interaction).

In an analysis of the subgroup of patients who required admission to the ICU (25.2% in the COVID-19 positive group and 24.4% in the COVID-19 negative group), more patients in the COVID-19 positive group required ventilator support (49% vs 24%) and vasopressor support (46% vs 32%) than those in the non-COVID-19 group. Length of stay in the ICU was longer in patients with COVID-19 than in patients without COVID-19 (4.9 vs 2.3 days). Patients with COVID-19 had a higher occurrence of AKI (58% vs 32%) and higher incidences of stage 2/3 AKI (39% vs 11%), dialysis-requiring AKI (15% vs 8%), and death (30% vs 10%) compared with patients without COVID-19.

Limitations to the study cited by the authors included possible unmeasured confounders, and the possibility that selection of a control group may have influenced the association of COVID-19 with AKI.

In conclusion, the researchers said, "COVID-19 in hospitalized patients is associated with a higher rate of AKI after adjustment for a multitude of demographic and clinical variables. Analyses investigating traditional mediators of AKI, such as hypotension and nephrotoxic medications, did not abate this relationship. Further study is warranted of pathophysiologic mechanisms that may mediate kidney injury in COVID-19, as well as the long-term consequences of AKI in COVID-19." ■

TAKEAWAY POINTS

- Researchers conducted a multicenter, observational cohort study to examine the independent association of COVID-19 with acute kidney injury (AKI).
- Compared with patients who tested negative, those with COVID-19 had more AKI (30.6% vs 18.2%) and AKI requiring dialysis (8.5% vs 3.6%), and lower rates of recovery from AKI (58% vs 69.8%).
- The higher rates of AKI in patients with COVID-19 is not fully explained by adjustment for known risk factors such as hemodynamic injury or nephrotoxin exposure.

Intravenous Radiocontrast Exposure

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The study utilized regression discontinuity design (RDD) to overcome the limitations of the existing research. RDD relies on the existence of a continuous variable, the running variable, for which there is a cutoff that determines eligibility for receiving treatment. By comparing outcomes in those just either side of the cutoff, the RDD approach can provide effect estimated from observational data that are largely free from both measured and unmeasured confounding. The study assessed individuals who received D-dimer testing (the running variable) in the emergency department (ED). Suspected pulmonary embolism is the most common indication for D-dimer testing; those scoring about the cutoff (typically 500 ng/mL) more likely to receive contrast in the form of a computed tomographic pulmonary angiogram (CTPA) to rule in or rule out the diagnosis.

The primary outcome of interest was long-term kidney function, measured by estimated glomerular filtration rate (eGFR) up to 6 months following the index ED visit. Secondary outcomes were receipt of kidney replacement therapy (RRT) (dialysis or kidney transplantation) in the 6 months following the index ED visit, AKI, defined as an increase in creatinine level of 50% or 0.3 mg/dL within 7 days, and all-cause mortality at 6 months.

The primary exposure was receipt of CTPA during the index ED visit. Other covariates included in the statistical analyses were age, baseline eGFR, sex, diabetes, hypertension, cancer, coronary artery disease, ED triage score, and Charlson comorbidity index. All analyses were performed using Stata statistical software (version 15, Stata Corp.), with the primary and secondary analyses using the rdrobust package.

The study cohort included all patients ≥18 years of age in the Canadian province of Alberta presenting to the ED and undergoing D-dimer testing between April 1, 2013, and June 30, 2018. A total of 156,028 individuals met inclusion criteria and were included in the study. Mean age was 53 years, 44% (n=68,206) were men, and mean baseline eGFR was 86 mL/min/1.73 m^2. Patients just above and below the CTPA eligibility cutoff were similar in terms of measured confounders.

Fifty-four percent of the cohort (n=84,624) had data on the primary outcome (long-term eGFR) available. Median time to the last eGFR test in the 6 months after the ED visit was 3.7 months. Bandwidths of 80 ng/mL below and 1190 ng/mL above the cutoff were automatically selected by the software package, within which 29,830 patients were included.

In the local linear fuzzy RDD analysis, there was no association of intravenous contrast with long-term eGFR, with an eGFR change of –0.4 mL/min/1.73 m^2 (95% confidence interval [CI], –4.9 to 4.0 mL/min/1.73 m^2) attributable to CTPA exposure caused by crossing the D-dimer cutoff. Results of a sensitivity analysis in all 84,624 patients also found no evidence of an association, with an eGFR change of 0.4 mL/min/1.73 m^2 (95% CI, –2.1 to 2.8 mL/min/1.73 m^2) attributable to CTPA exposure. Eight sensitivity analyses used different bandwidths and polynomial orders; seven found no evidence of an association.

A total of 165 patients (0.11% of the total cohort) required RRT during the 6 months after the index ED visit (161 dialysis, four kidney transplant). There was no evidence of an association between CTPA exposure and the need for RRT (risk difference [RD], 0.07%; 95% CI, –0.47% to 0.61%). Among patients with repeated measurements of creatinine levels within 7 days, 9.7% (n=4147) developed AKI; there was no evidence of an association of contrast exposure with the risk (RD, 4.3%; 95% CI, –2.7% to 12.9%). The analysis for the association between CTPA exposure and AKI was limited by missing data.

In the 6 months following the index ED visit, 6656 patients (4.3%) died. There was no evidence of an association between death and CTPA (RD, 0.3%; 95% CI, –2.9% to 3.2%).

In the subgroup analyses, there was no evidence of an association between contrast exposure and long-term eGFR based on baseline eGFR, age, or hypertension. Among patients with diabetes, the association was potentially consistent with harm but was not statistically significant, with an eGFR change of –6.4 mL/min/1.73 m^2 (95% CI, –15.4 to 0.2 mL/min/1.73 m^2; *P* for heterogeneity=.12). The subgroup analyses were relatively underpowered, the authors noted.

In citing limitations to the findings, the researchers mentioned the generalizability of results of RDD analysis. Because the treatment effect is estimated for patients whose D-dimer value falls at the cutoff, it may not apply to patients further away from that value. The treatment effect is further restricted to those at the cutoff whose receipt of a contrast-enhanced scan is determined by the cutoff.

In conclusion, the researchers said, "To our knowledge, this study provides the strongest evidence to date that intravenous contrast is not associated with significant kidney injury, further challenging the considerable clinical preoccupation with the occurrence and prevention of CIN." ■

TAKEAWAY POINTS

- Researchers conducted a study using regression discontinuity design (RDD) to examine whether intravenous radiocontrast exposure is associated with clinically significant long-term renal impairment.
- The primary outcome of interest was estimated glomerular filtration rate up to 6 months following an index visit to the emergency department (ED) that resulted in receipt of a computed tomographic pulmonary angiogram.
- There was no evidence of an association between exposure to contrast and eGFR up to 6 months after the index ED visit or with the need for renal replacement therapy, mortality, and acute kidney injury.

CONFERENCE COVERAGE AMERICAN TRANSPLANT CONGRESS

Treating Antibody-Mediated Rejection in Kidney Transplant Recipients

The optimal regimen for the treatment of acute and chronic antibody-mediated rejection (AMR) in kidney transplant recipients is unclear. **A. Al Jurdi** and colleagues conducted a single-center retrospective study to examine the outcomes among kidney transplant recipients with acute and chronic AMR who were managed with varying treatment regimens. Results of the study were reported during a virtual presentation at the 2021 American Transplant Congress. The presentation was titled *Outcomes of Kidney Transplant Recipients with Antibody-Mediated Allograft Rejection: A Retrospective Study*.

The study cohort included all kidney transplant recipients at the center with biopsy-proven acute or chronic AMR between January 2017 and September 2020. The primary outcome of interest was allograft loss at last follow-up. Secondary outcomes were differences in allograft survival between treatment regimens, and changes in estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio (UPCR) at last follow-up.

The study included 53 kidney transplant recipients with AMR. Mean age of the cohort was 51 years, and 50% were female. The most common cause of end-stage kidney disease was glomerular disease, and 57% received living donor kidney transplants. The median number of HLA ABDR mismatches was four, and 38% had pre-transplant donor-specific antibodies. Immunosuppression regimens were anti-thymocyte globulin (61%), basiliximab (35%), and alemtuzumab (4%). Thirty-five percent of participants had acute AMR and 65% had chronic-active AMR. At the time of biopsy, mean eGFR was 32 mL/min/1.73 m^2 and UPCR was 3.0 g/g.

Treatment regimens included pulse steroids (72%), intravenous immunoglobulin (64%), plasma exchange (51%), bortezomib (43%), and rituximab (4%). Some patients received more than one treatment.

At a median follow-up of 23 months, patient survival was 94% and death-censored allograft survival was 74%, mean eGFR was 28 mL/min/1.73 m^2, and UPCR was 0.96 g/g. The risk of allograft loss was greater in patients with UPCR >3 g/g at time of biopsy compared with patients with UPCR <3 g/g (relative risk [RR], 4.3; 95% confidence interval [CI], 1.6-11.6). There was no difference in the risk of allograft loss in patients who received plasmapheresis compared with those who did not (RR, 0.97; 95% CI, 0.4-2.4). There was also no significant difference in the risk of allograft loss among patients who received bortezomib than in those who did not (RR, 0.8; 95% CI, 0.3-2.0). The risk of allograft loss was similar in patients with chronic AMR compared with those with acute AMR (RR, 1.3; 95% CI, 0.5-3.6).

"Proteinuria above 3 g/day is associated with increased risk of allograft failure in patients with AMR. Use of plasmapheresis or bortezomib was not associated with lower risk of allograft failure in kidney transplant recipients with AMR. Novel treatment regimens are needed to improve the outcomes of kidney transplant recipients with acute and chronic AMR," the researchers said.

Source: Al Jurdi A, Goldfarb L, Lafargue M, Azzi A, Riella L V. Outcomes of kidney transplant recipients with antibody-mediated allograft rejection: A retrospective study. Abstract of a presentation at the virtual 2021 American Transplant Congress (Abstract 1025), June 5, 2021.

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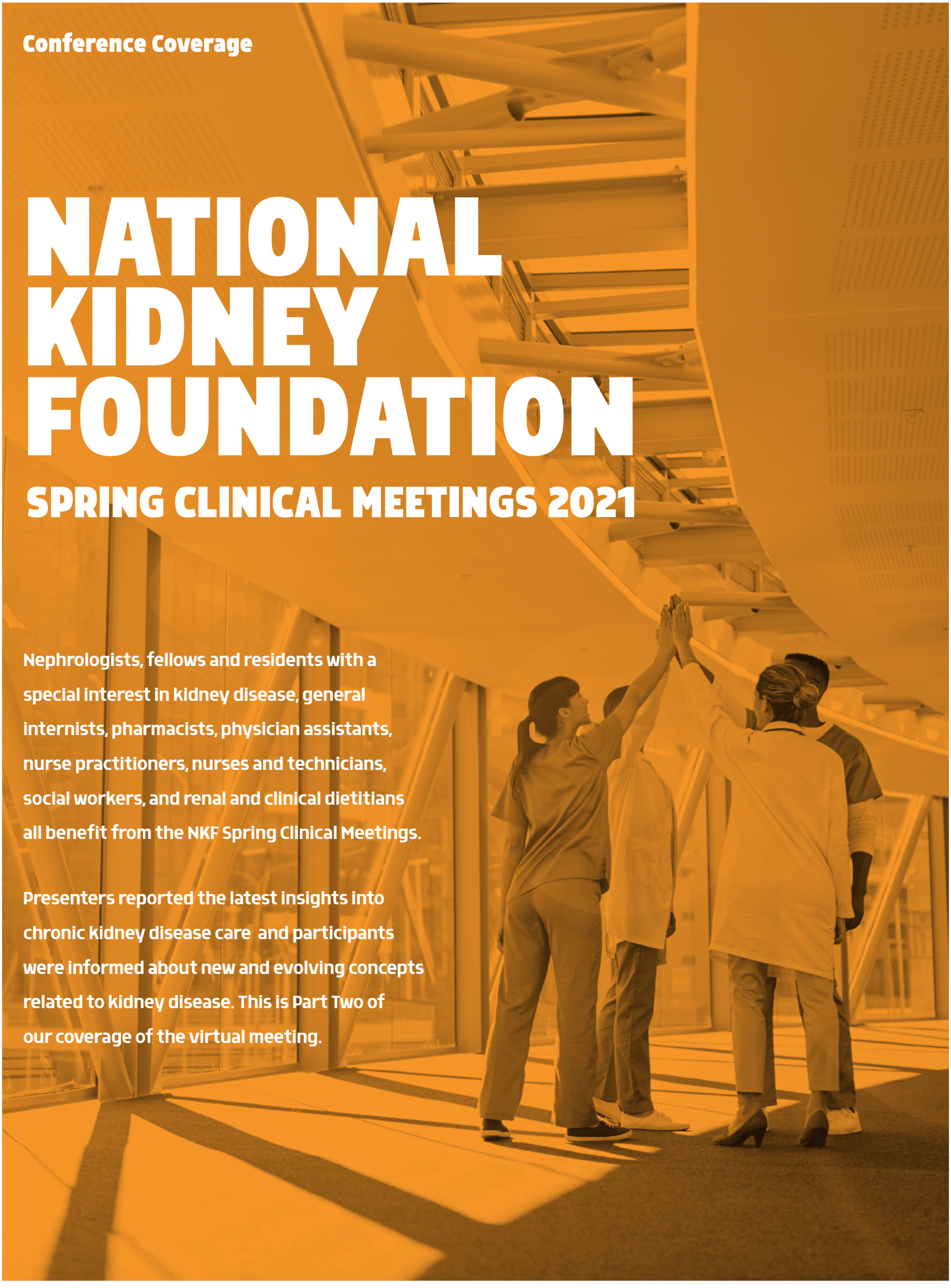


Nephrologists, fellows and residents with a special interest in kidney disease, general internists, pharmacists, physician assistants, nurse practitioners, nurses and technicians, social workers, and renal and clinical dietitians all benefit from the NKF Spring Clinical Meetings.

Presenters reported the latest insights into chronic kidney disease care and participants were informed about new and evolving concepts related to kidney disease. This is Part Two of our coverage of the virtual meeting.

DISCOVER CKD: Variations in Treatment for CKD-Related Anemia

Anemia in chronic kidney disease (CKD) commonly remains untreated until patients require dialysis. During a virtual poster session at the NKF Spring Clinical Meetings 2021, **Eric Wittbrodt, MPH, PharmD,** and colleagues described characteristics of patients with and without dialysis dependent CKD and anemia receiving a transfusion or intravenous (IV) iron in the DISCOVER CKD retrospective cohort. The poster was titled *Characteristics of Patients with and without Dialysis Dependent Chronic Kidney Disease and Anemia Receiving Blood Transfusions and Intravenous Iron: A Report from the DISCOVER CKD Retrospective Cohort*.

Data for adult patients (≥18 years of age) with CKD and anemia were obtained from the UK CPRD (United Kingdom Clinical Practice Research Datalink), Japan JMDC (Japan Medical Data Center), and US LCED (United States Limited Claims and Electronic Health Record) databases. The index date was defined as the first hemoglobin level of <12 g/dL for females and <13 g/dL for males or a prescription for anemia therapy (iron, erythropoiesis-stimulating agent, or transfusion) on or after a diagnosis code for CKD stage 3a+ or dialysis or the second of two estimated glomerular filtration rate measurements of <60 mL/min/1.73 m^2 >90 days apart between January 2008 and March 2020.

During follow-up, 27% of 72,429 patients were treated with anemia therapies, 25% of which were transfusion or IV iron. Median times from index date to initiation of blood transfusion were 285 days (US), 232 days (Japan) and 306 days (UK); for IV iron, the median times were 238 days (US), 291 days (Japan) and 929 days (UK).

Patients in the US and Japan cohorts had a higher proportion of comorbidities compared with patients in the UK cohort. Among patients receiving a transfusion, median hemoglobin ranged from 7.9 to 8.9 g/dL; among those receiving IV iron, hemoglobin range was 8.9 to 10.5 g/dL.

The researchers said, "There were clear country differences observed in the routine clinical care of anemia in patients with CKD. Transfusion and IV iron were commonly used as rescue therapies despite their invasive nature and well-recognized associations between transfusion and adverse reactions such as allosensitization and infection."

Source: Wittbrodt E, Carrero JJ, James G, et al. Characteristics of patients with and without dialysis dependent chronic kidney disease and anemia receiving blood transfusion and intravenous iron: A report from the DISCOVER CKD retrospective cohort. Abstract of a poster presented during the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #181), April 9, 2021.

Patient Education on Hypertension Often Lacks Details on CKD

Hypertension, the leading cause of chronic kidney disease (CKD), also has a significant effect on the rate of disease progression among patients with pre-existing CKD. Patient education material on hypertension, particularly in combination with a patient-provider discussion, is an important source of health information. **Katie Cardone, PharmD,** and colleagues conducted a content analysis of patient education handouts on blood pressure to increase understanding of existing materials and identify information gaps.

Results of the study were reported during a virtual poster session at the NKF Spring Clinical Meetings 2021, The poster was titled *Content Analysis of Patient Educational Materials for Hypertension.*

Online searches using the terms "blood pressure" and "hypertension" identified patient-facing handouts on hypertension; the search also included a review of relevant organization and government websites. The handouts of interest focused on hypertension education, designed for patients, and were found on .gov or .org websites and written in English.

Thematic codes were categorized under five primary codes and 35 subcodes. Following the initial review of the handouts and existing literature, the overall code frame was developed and then modified as the handouts were examined by a team of coders.

The analysis included 18 of 20 handouts identified in the search. There was no universal theme across the documents. Most offered a definition of hypertension and cited nonpharmacologic treatment options. In 16 of the 18 handouts, the most prominent theme discussed was limiting sodium intake.

Half of the handouts (n=9) included information about CKD as a consequence of hypertension; heart attack or stroke were included as consequences of hypertension more frequently. Most of the handouts included links to websites for further information; however, only five of the 18 (28%) offered suggestions for discussing hypertension with healthcare providers.

In summary, the authors said, "Patient educational materials about hypertension are readily available for providers to use in their practices. These handouts generally provide broad information about the disease, but with slightly different aspects covered. Despite CKD being a significant public health concern and consequence of hypertension, it is not consistently included in patient-facing materials about hypertension. Materials often lack advice to facilitate patient-provider communication. These information gaps should be noted by healthcare providers as they work with hypertensive patients."

Source: Cardone K, Pierce T, Reilly C, Weinkiper M, Yeung J, Parker W. Content analysis of patient education materials for hypertension. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #322), April 9, 2021.

The C5 c.55C>T (p.Gln19*) variant introduces a premature stop codon and is expected to result in the loss of function of the C5 protein that is part of the complement system.

High-Risk Genotype APOL1 and Hypertensive CKD

There is are associations between the high-risk variant alleles of apolipoprotein L1 (APOL1), G1, and G2 and rapid progression of hypertensive chronic kidney disease (CKD). However, according to **Jamrose Durrani, MD,** and colleagues, additional genetic or environmental "second hits" are required to promote the onset of kidney disease.

The researchers provided a case report of a patient with early onset treatment resistant-hypertensive CKD who was found to have homozygous APOL1 G2 variants as well as an unexpected concomitant genetic variant. The case study was reported during a virtual poster session at the NKF Spring Clinical Meetings 2021 in a poster titled *Homozygous G2 APOL1 Allele and a Heterozygous Complement 5 Variant in Hypertensive Chronic Kidney Disease*.

The patient was a 28-year-old African American male who was evaluated for maintenance hemodialysis due to CKD stage 5, secondary to uncontrolled hypertension. The patient's medical history included sickle cell trait, congestive heart failure, and longstanding hypertension (diagnosed at age 19 years). The progressive clinical course was related to medication non-adherence. HIV infection and secondary causes of hypertension, such as hyperaldosteronism or pheochromocytoma, were ruled out.

Results of genetic testing with Renasight, a 382 panel of genes associated with CKD, yielded homozygous APOL1 variants c.1164_1169del (p.Asn388_Tyr389del) (G2 allele); a heterozygous C5 variant c.55C>T (p.Gln19*); and a heterozygous HBB variant c.20A>T (p.Glu7Val).

In cohorts of African American patients, there is an association between homozygous inheritance of high-risk APOL1 variants and early onset progressive CKD. For patients who are homozygous for G1 variants, the age of onset of nephropathy is earlier than for their G2 counterparts. The patient in question had early loss of renal function with G2 homozygosity and an apparently unrelated C5 variant.

The C5 c.55C>T (p.Gln19*) variant introduces a premature stop codon and is expected to result in the loss of function of the C5 protein that is part of the complement system. There is an association between inheritance of this variant and C5 deficiency. Dysregulation of the complement system is implicated in glomerular disease; however, the role of C5 variants is unclear.

In conclusion, the researchers said, "Identification of a concomitant C5 variant, through testing with a broad renal-focused genetic panel, may reveal a potential second hit mechanism in rapidly progressing CKD that is associated with high-risk APOL1 variants."

Source: Durrani J, Kerner P, Langan L, Clark D, Tabriziani H, Yap E. Homozygous G2 APOL1 Allele and a Heterozygous Complement 5 Variant in Hypertensive Chronic Kidney Disease. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #161), April 9, 2021.

Genetic Testing and Kidney Risk Management among Black Patients

Black Americans are at increased risk for chronic kidney disease; a portion of the increased risk may be due to polymorphisms in the gene encoding apolipoprotein L1 (APOL1). Applications of *APOL1* genotyping are increasingly being utilized for evaluation of organ donors; however, there are few available data on the level of interest among Black patients in APOL1 genotyping and the implications for management of individual risk for kidney disease.

Krista L. Lentine, MD, PhD, and colleagues conducted a pilot study offering *APOL1* genetic testing to examine attitudes and concerns related to the testing and to management of kidney risk. Results were reported during a virtual poster session at the NKF Spring Clinical Meetings 2021 in a poster titled *APOL1 Genetic Testing in African American Patients with Hypertension: A Pilot Study of Attitudes and Perceptions*. Eligible patients were Black Americans treated in hypertension and nephrology clinics at a large urban medical center in the Midwest.

To date, 89 patients have genotyping results. Of those, 56% are women, mean age at testing was 58 years, 72% were obese, and participants were taking a mean of three antihypertensive agents. Mean systolic blood pressure was 146 mm Hg, mean serum creatinine level was 2.1 mg/dL, median estimated glomerular filtration rate was 43 mL/min/1.73 m^2, and median urine albumin-creatinine ratio was 89 mg/g.

A total of 13% had two *APOL1* renal risk variants (high-risk genotypes) and 42% had one risk variant. At baseline, 86% of participants reported concern regarding kidney disease, 90% thought being tested for genes that may impact kidney disease was a good idea, and 82% would want their children to be tested for the *APOL1* gene.

Only 20% indicated they would be upset if testing revealed they were at high risk. Most said they would initiate changes in health-related behaviors if they had knowledge of high-risk genotype: 62% would seek medical advice, 29% would do more research, 27% would change diet, 20% would exercise more, 19% would drink more water, and 16% would take antihypertensive medications more often. Only 2.3% said they would not change any behaviors.

In summary, the researchers said, "Black patients at a large, Midwestern medical center were receptive towards *APOL1* genetic testing and believed that testing would motivate changes in health-related behaviors. Ongoing research is needed to determine optimal patient-centered use of this emerging risk assessment tool."

Source: Lentine KL, Muiru A, Lindsay K, et al. APOL1 Genetic Testing in African American Patients with Hypertension: A Pilot Study of Attitudes and Perceptions. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #311), April 9, 2021.

Renal Outcomes in FIDELIO-DKD Trial in Subset of Black Patients

More than one third of patients in the United States receiving dialysis are Black or African American. The leading cause of kidney failure in that patient population is diabetes. Results of the FIDELIO-DKD trial of finerenone demonstrated a reduction in risk of progression of chronic kidney disease in patients with CKD and type 2 diabetes treated with finerenone.

During a virtual poster session at the NKF Spring Clinical Meetings 2021, **George Bakris, MD,** and colleagues reported results of an analysis of data from FIDELIO-DKD on outcomes among Black or African American patients. The poster was titled *Impact of Finerenone on Chronic Kidney Disease Progression in Black or African American Patients with Type 2 Diabetes–Analysis of the FIDELIO-DKD Study*.

The study randomized 5734 patients from 48 countries to receive either oral finerenone or placebo. Inclusion criteria were type 2 diabetes, urine albumin-creatinine ratio (UACR) 30-5000 mg/g, estimated glomerular filtration rate (eGFR) 25-<75 mL/min/1.73 m^2, and treatment with optimized renin-angiotensin system blockade. The primary renal outcomes of interest was time to kidney failure, sustained decline in eGFR ≥40% from baseline, or renal death. Prespecified secondary outcomes were time to kidney failure, sustained eGFR decline 57% from baseline or renal death, and change in UACR from baseline to month 4.

Of the overall cohort, 4.7% (n=264) were Black or African American. Of those, 76.5% were from North America. Median follow-up was 2.6 years.

Compared with White or Asian patients, the risk of kidney failure outcomes was higher in Black patients. In the subgroup of Black patients, the incidence rate of the primary kidney outcome was lower in the finerenone group than in the placebo group (13.9/100 patient years vs 17.2/100 patient years; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.51-1.19, respectively). The incidence rate for the secondary kidney outcome was also lower in Black patients in the finerenone group compared with the placebo group (HR, 0.76; 95% CI, 0.45-1.28). At month 4, UACR was reduced by 33% (95% CI, 43%-21%) in Black patients treated with finerenone compared with placebo.

There was no evidence of heterogeneity between Black or African American patients and other racial/ethnic groups for the kidney outcomes analyzed. In the subgroup of Black or African American patients, treatment-emergent adverse events and serious adverse events were balanced between the finerenone group and the placebo group.

In conclusion, the researchers said, "In FIDELIO-DKD there was a trend toward reducing kidney outcomes in the small subset of Black patients included in the trial."

Source: Bakris G, Joseph A, Anker S, et al. Impact of finerenone on chronic kidney disease progression in Black or African American patients with type 2 diabetes–analysis of the FIDELIO-DKD study. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #254), April 9, 2021. FIDELIO-DKD was funded by Bayer AG (NCT02540993).

Primary Care Physicians Assess Clinical Utility of KidneyIntelX™ in DKD

In patients with diabetic kidney disease (DKD), the current standard of care tests to predict the risk of kidney function decline measure estimated glomerular filtration rate (eGFR) and albuminuria to aid in chronic kidney disease risk stratification. The KidneyIntelX™ test incorporates plasma biomarkers and clinical data to predict the risk of decline in kidney function in patients with type-2 DKD.

Mansai Datar, PhD, and colleagues conducted a study to determine the clinical utility of KidneyIntelX among primary care physicians in the management of DKD. Results of the study were reported during a virtual poster session at the NKF Spring Clinical Meetings 2021 in a poster titled *Primary Care Physicians' Assessment of the Clinical Utility of a New Prognostic Test to Predict the Risk of Kidney Function Decline in Patients with Diabetic Kidney Disease*.

To estimate preferences from a convenience sample of primary care physicians, the researchers utilized conjoint analysis of results of a web survey. Hypothetical patient profiles were created with six attributes: albuminuria, eGFR, age, blood pressure, hemoglobin A1C, and KidneyIntelX result. From a fractional factorial design of 42 unique profiles, each primary care physician viewed eight randomly selected profiles. For each of the eight patients, primary care physicians indicated whether they would prescribe a sodium-glucose cotransporter-2 inhibitor (SGLT2i), increase angiotensin II receptor blocker (ARB) dose, and refer the patient to a nephrologist. The importance of each attribute was assessed using aggregate logit models.

A total of 401 primary care physicians completed the survey. The KidneyIntelX result was relatively more important than standard of care tests for prescribing an SGLT2i and increasing the dose of blood pressure medications. There was an association between the KidneyIntelX results and significantly higher odds of primary care physicians prescribing SGLT2i with a DKD indication (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.29-2.08), increasing ARB dose (OR, 1.49; 95% CI, 1.17-1.89) and referral to a nephrologist (OR, 2.47; 95% CI, 1.99-3.08) compared with no test.

In conclusion, the researchers said, "This implicit preference study indicates primary care physicians will use the results of KidneyIntelX in the management of DKD."

Source: Datar M, Ramakrishman S, Chong J, Goss T, Coca S, Vassalotti J. Primary care physicians' assessment of the clinical utility of a new prognostic test to predict the risk of kidney function decline in patients with diabetic kidney disease. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #327), April 9, 2021.

Renal Genetic Testing to Diagnose and Manage CKD

Genetic testing is increasingly being used to diagnose and manage patients with chronic kidney disease (CKD). Genetic information also has implications for family planning and biologic relatives. Renal genetic testing throughout an individual's lifespan has broad applicability, giving internal medicine physicians a potentially important tool in their practice.

During a virtual poster session at the NKF 2021 Spring Clinical Meetings, **Stacy Chronister, DO,** and colleagues described early experiences implementing a clinically available renal genetic testing, consisting of 382 genes, in an internal medicine clinic in Oklahoma. The poster was titled *Early Experiences with Renal Genetic Testing in an Internal Medicine Clinic*.

The researchers conducted a retrospective analysis on results of renal genetic testing on six patients who were tested between May and October 2020. The patients ranged from 26 to 54 years of age.

Testing was ordered for indications that included CKD with or without other health concerns (n=3), reproductive purposes (n=2), and immunodeficiency concerns (n=1). Of the six patients, three were negative and the other three had at least one genetic finding. The three patients had heterozygous variants identified in four genes: *PKDH1, ALG1, HNF4A*, and *CD2AP*.

Variants in *PKDH1* and *ALG1* were associated with an unaffected carrier status for autosomal recessive polycystic kidney disease and congenital disorder of glycosylation, type 1K, respectively. There was an association between the *HNF4A* variant and a diagnosis of Fanconi renotubular syndrome 4, with maturity onset diabetes of the young, type 1. The *CD2AP* variant was associated with a potential diagnosis of *CD2AP*-related focal segmental glomerulosclerosis.

In summary, the researchers said, "Renal genetic testing shows utility in improving the management of patients with CKD in an internal medicine setting. Early, limited use of genetic testing in this clinic identified CKD-linked genetic variants in a high proportion of patients' tests; these results were used to guide primary care, refer for specialty care, and provide reproductive risks. Expanded use and further research is needed to better understand the utility of genetic testing."

Source: Chronister S, Beretich L, McCormick S, Billings PR, Tabriziani H. Early experience with renal genetic testing in an internal medicine clinic. Abstract of a poster presented at the National Kidney Foundation virtual 2021 Spring Clinical Meetings (Abstract #203), April 9, 2021.

NEUTRALIZE Study: Assessing Efficacy and Safety of SZC in Hyperkalemia and Metabolic Acidosis

Patients with chronic kidney disease (CKD) who develop metabolic acidosis are at increased risk for cardiovascular events, mortality and progression of CKD. In previous studies, there was an association between sodium zirconium cyclosilicate (SZC), a novel potassium binder, and dose-dependent increases in serum bicarbonate.

Yasmin Brahmbhatt, MD, conducted a study to examine whether treatment with SZC can increase serum bicarbonate in a clinically meaningful way in patients with CKD-associated hyperkalemia and metabolic acidosis. The study was described during a virtual poster session at the NKF Spring Clinical Meetings 2021 in a poster titled *Effect of Sodium Zirconium Cyclosilicate on Serum Potassium and Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease: NEUTRALIZE Study.*

NEUTRALIZE is a prospective, randomized, double-blind, placebo-controlled, parallel, multicenter, phase 3b study designed to assess the ability of SZC to treat hyperkalemia and increase serum bicarbonate. The mechanism behind the increase in serum bicarbonate will be examined via measurement of changes in urine ammonium. Patients will be screened using the portable blood analyzer, i-STAT, to measure potassium and bicarbonate values for eligibility.

Inclusion criteria are i-STAT results of serum potassium 5 to 5.9 mmol/L inclusive and serum bicarbonate 16 to 20 mmol/L inclusive. Eligible consenting patients will be enrolled into the open-label correction phase and will receive SZC for up to 48 hours. Follow-up will continue for 7 days following the last administration of the study medication.

The study will be conducted in the United States at nearly 35 investigative sites; approximately 400 patients will be screened and approximately 200 will be enrolled to the open-label phase in order to achieve 182 randomly assigned to study intervention.

The study has four outcomes of interest: (1) the number of patients having normal serum potassium between 3.5 and 5.0 mmol/L at the end of treatment without the need for rescue treatment for hyperkalemia; (2) the mean change in serum bicarbonate at end of treatment compared with baseline; (3) the number of patients demonstrating an increase in serum bicarbonate of ≥3 mmol/L from baseline to end of treatment without a need for rescue treatment for metabolic acidosis; and (4) safety and tolerability.

In summary, the researchers said, "NEUTRALIZE will generate evidence intended for patients and healthcare providers regarding the efficacy and safety of SZC in treating hyperkalemia and increasing serum bicarbonate."

Source: Brahmbhatt Y, Pottorf W, Oluwatosin Y, Cooper K. Effect of sodium zirconium cyclosilicate on serum potassium and bicarbonate in patients with hyperkalemia and metabolic acidosis associated with chronic kidney disease: NEUTRALIZE study. Abstract of a poster presented at the virtual National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #265), April 9, 2021.

Variations in Kidney Function Testing in Patients with CKD and Type 2 Diabetes

There are wide variations in the prevalence of type 2 diabetes and chronic kidney disease (CKD) across geographic regions. However, despite the importance of the diagnosis and management of CKD among patients with type 2 diabetes, there are few data evaluating the geographic variations in estimated glomerular filtration rate (eGFR) and urine albumin creatinine ratio (UACR) testing in that patient population.

During a virtual poster session at the NKF Spring Clinical Meetings 2021, **Xue Feng, PhD,** and colleagues reported on an analysis of state-by-state variations in testing of kidney function in patients with type 2 diabetes. The poster was titled *Geographic Variations in Kidney Function Testing among Patients with Type 2 Diabetes.*

The researchers utilized Optum Clinformatics® claims data from 2015-2019 to identify adult patients with type 2 diabetes and patients with both type 2 diabetes and CKD. Tests of eGFR and UACR were examined by state for the two populations separately. The proportions of tested patients were summarized during the 1-year period following diagnosis of type 2 diabetes and CKD. The proportions of patients receiving adequate monitoring (defined according to Kidney Disease Improving Global Outcomes clinical guidelines) were reported in patients with type 2 diabetes and CKD.

Of the 632,105 patients with type 2 diabetes, the rate of eGFR testing was 86.0%, and the rate for UACR testing was 33.6%. There were wide variations in the testing rates across states, ranging from 68.5% in Wyoming to 93.9% in Alabama for eGFR and from 12.3% in Wyoming to 56.6% in Hawaii for UACR.

Among the patients with both type 2 diabetes and CKD (n=101,057), the testing rates were higher. The rate for eGFR testing in that patient population was 94.1%; the rate for UACR testing was 38.7%. There were cross-state variations in testing rates among patients with both type 2 diabetes and CKD, ranging from 79.5% in Colorado to 97.3% in Alabama for eGFR and from 14.0% (Maine) to 58.9% (Hawaii) for UACR.

Percentages of patients receiving adequate monitoring ranged from 64.4% in Colorado to 91.9% in Georgia for eGFR and from 7.1% in Minnesota to 30.9% in Florida for UACR.

In conclusion, the authors said, "This study showed that large geographic variations exist in kidney function testing across states. A particular concern is under testing for UACR. The association between kidney function testing and CKD-related outcomes warrants further evaluation."

Source: Feng X, Betts KA, Song J, et al. Geographic variations in kidney function testing among patients with type 2 diabetes (T2D). Abstract of a poster presented at the National Kidney Foundation 2021 Spring Clinical Meetings (Abstract #206), April 9, 2021.

Virtual Nephrology Panel to Monitor Tolvaptan Use in Patients with ADPKD

Tolvaptan has been approved by the FDA for use in patients with autosomal dominant polycystic kidney disease (ADPKD) to slow decline in glomerular filtration rate (GFR), increasing the therapeutic options for treatment of patients with the genetic kidney disease. Initiation of tolvaptan is time and resource intensive for patients and their healthcare providers. Kaiser Permanente Northern California (KPNC) established a virtual ADPKD nephrology panel to provide comprehensive care to patients with ADPKD.

During a virtual poster session at the NKF 2021 Spring Clinical Meetings, **Lin Duong, PharmD** described a model designed to leverage regional specialists to provide care for ADPKD patients spanning 15 service areas. The poster was titled *Implementing a Virtual Nephrology Panel for Tolvaptan Use in Patients with ADPKD.*

Beginning in 2019, a panel that included nephrologists and pharmacists met virtually every month to review consults for initiation of tolvaptan. The panel checked for complete work up, performed chart review, and screened candidacy criteria to establish recommendations. The patients were screened based on US expert guidelines.

Upon initiation of tolvaptan, the patients also meet virtually with the panel pharmacist who reviews and assists with risk evaluation and mitigation strategy, education, and monitoring of adverse effects and status reports. The pharmacist also works with local nephrologists to monitor for laboratory trends and dose changes. Electronic medical records provide updates to the panel. The panel also reviews complex issues such as extra-renal manifestations of ADPKD.

As of the publication of the poster, the panel had screened 34 cases. Nine of the patients initiated tolvaptan; three of those patients subsequently discontinued use. Doses were up-titrated as allowed by patient tolerance and laboratory results. Dose decreases or discontinuations were related to increases in sodium or glomerular filtration rate, liver function test, abdominal pain, or aquaretic side effects. To date, no major adverse effects have occurred. The monthly check-ins by the pharmacist in tandem with local nephrologists has ensured consistent education, care, and monitoring by the ADPKD panel.

In conclusion, the author said, "The virtual ADPKD panel provides specialized knowledge and ongoing carefully monitored care. The workflow can work for any KPNC service area and provides a seamless resource to local physicians and patients. Moreover, dedicated pharmacy support in the ADPKD panel augments patient care."

Source: Duong L. Implementing a virtual nephrology panel for tolvaptan use in patients with ADPKD. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #305), April 9, 2021.

Raising Awareness about Gout and Chronic Kidney Disease

Gout, the most common form of inflammatory arthritis, affects more than 3 million Americans. While no causal link has been established between gout and chronic kidney disease (CKD), research does demonstrate an association between gout and an increased risk of CKD progression.

Patients with gout and CKD should manage risk factors that may worsen their health. **Morenike Bello, MPH, CHES,** and colleagues conducted a study to identify opportunities to raise awareness regarding the association between gout and CKD. Results of the study were reported during a virtual poster session at NKF Spring Clinical Meetings 2021 in a poster titled *Opportunities to Raise Awareness about Gout and Chronic Kidney Disease: Findings from an Online Survey.*

The 28-item online survey, conducted by the American Kidney Fund (AKF) in 2020 among patients with gout, sought to identify participants' behaviors regarding gathering of health information as well as gaps in knowledge related to gout. The survey also covered patients' symptom management and feelings associated with talking about gout with healthcare providers, employers, and loved ones. AKF completed a descriptive analysis of 43 survey responses.

Of the survey participants, 75% reported having gout and CKD. At the onset of gout symptoms, 67% of those patients sought help within 0 to 3 months and 72% visited their physician for additional information. Patients most commonly worked with their primary care provider to manage gout symptoms rather than seeking specialist care.

More than half of respondents reported that at the time of their CKD diagnosis, no healthcare provider mentioned gout as a side effect of CKD (54%) or outlines steps to take to prevent gout (57%). In respondents with gout only, most reported that at the time of the gout diagnosis no healthcare provider mentioned the connection between gout and kidney disease (67%) or how to prevent kidney disease (73%).

In conclusion, the researchers said, "Many people are not talking to their doctors about gout and its connection to kidney disease until they experience gout symptoms. The points of gout and CKD diagnosis are a missed opportunity for prevention education. Healthcare providers are a trusted health information source for gout patients and if primary care physicians are more proactive about starting this conversation, patients may be more empowered to keep their conditions under control and mitigate their risk for developing additional comorbidities."

Source: Bello M, Alawode M, Fatima U, Spigler M, Paris M. Opportunities to raise awareness about gout and chronic kidney disease: Findings from an online survey. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings (Abstract #199), April 9, 2021.

TAME PKD Results: Phase 2 Trial of Metformin in ADPKD

Growth of kidney cysts in autosomal dominant polycystic kidney disease (ADPKD) was inhibited with metformin in both *in vitro* and *in vivo* ADPKD models. Results of TAME PKD, a phase 2, parallel-group, randomized, double-blind, placebo-controlled trial, were reported by **Ronald Perrone, MD,** during a virtual poster session at the NKF 2021 Spring Clinical Meetings. The poster was titled *A Randomized Trial of Administration of Metformin in PKD (TAME PKD).*

The primary outcomes of interest in TAME PKD were the tolerability, safety, and preliminary efficacy of metformin in ADPKD.

TAME PKD enrolled 97 participants from June 2016 to December 2018. Inclusion criteria were age 18 to 60 years, and estimated glomerular filtration rate (eGFR) >50 mL/min/1.73 m^2.

Medication tolerability was defined by (1) gastrointestinal symptoms assessed using the Gastrointestinal Symptoms Rating Scale (GSRS, range 1-7); (2) response to "Can you tolerate this dose of the study drug for the rest of your life?"; and (3) maximally tolerated dose at 24 months. Safety was defined by adverse events and serious adverse events, including prospectively defined hypoglycemia and lactic acidosis. The primary safety outcome was based on the proportion of study participants who experienced at least one serious adverse event during 24 months of study follow-up.

At baseline, the GSRS was low in both the metformin group and the placebo group; there was no significant change in GSRS over time. The highest achieved dose of 2000 mg was similar between the two groups: 67% in the Metformin group and 81% in the placebo group.

Dose was reduced in 23 participants in the metformin group (43%) due to inability to tolerate versus 14 participants in the placebo group (29%). Proportions of participants who withdrew from the study were similar in the two groups. The proportion of participants experiencing at least one serious adverse event was also similar between the groups.

Mean annual percent change in height adjusted total kidney volume was 1.68% more in the metformin group compared with the placebo group. The 24-month decline in eGFR was 2.73 mL/min/1.73 m^2 greater in the placebo group than in the metformin group.

In conclusion, the researchers said, "The TAME PKD study has demonstrated tolerability and safety of metformin in ADPKD. Demonstration of efficacy to slow progression will require a larger study enriched in participants at risk of rapid progression."

Source: Perrone R, Abebe K, Watnick T, et al. A randomized trial of administration of metformin in PKD (TAME PKD). Abstract of a poster presented at the National Kidney Foundation virtual 2021 Spring Clinical Meetings (Abstract #331), April 9, 2021.

Trends in Timing of Initiation of Long-Term Dialysis

The past 20 years have seen changes in the estimated glomerular filtration rate (eGFR) where long-term dialysis is initiated in the United States and the world. According to the US Renal Data System registry, the proportion of new patients with end-stage kidney disease (ESKD) with an eGFR of 10 to 15 mL/min/1.73 m^2 at the initiation of dialysis increased from 10% in 1996 to a peak of 28% in 2010.

Mean eGFR at initiation of long-term dialysis in 2001 to 2003 was 12.4 mL/min/1.73 m^2, rose to 16.3 mL/min/1.73 m^2 in 2010 to 2012, and did not increase through 2016 to 2018.

There are few data available on associations between changes over time in the likelihood of initiation of dialysis at any given eGFR level in at-risk patients and the population burden of ESKD. **Chi-yuan Hsu, MD, MSc,** and colleagues conducted a retrospective cohort study to examine temporal trends in initiation of long-term dialysis by eGFR level. The researchers also sought to quantify the ways the patterns are associated with the number of patients with ESKD. Results of the study were reported in *JAMA Internal Medicine* [2020;180(12):1647-1654].

TAKEAWAY POINTS

- Researchers conducted a retrospective cohort study to examine temporal trends in initiation of long-term dialysis by level of estimated glomerular filtration (eGFR) level and quantify the association of the patterns with the number of patients with end-stage kidney disease.
- Deidentified patient data from 2001 to 2018 were stratified into successive 3-year intervals. In the initial 3-year cohort, mean age was 55.4 years, 55.0% were women, and diabetes prevalence was 14.9%, characteristics that remained stable across the study period.
- The likelihood of receiving dialysis at eGFR levels of 10 to 24 mL/min/1.73 m^2 generally increased over time.

The study utilized deidentified data from Kaiser Permanente Northern California. Cohort of all adult members (≥18 years of age) with at least one valid outpatient serum creatinine measurement from 2001 through 2018 were grouped into 3-year intervals (2001-2003, 2004-2006, 2007-2009, 20120-2012, 2013-2015, and 2016-2018). Adults with ≥12 months of continuous membership in the health plan were included in 3-year cohorts on the first eligible January 1 within each 3-year interval. Patients with a prior kidney transplant or those who were already undergoing long-term dialysis were excluded.

The primary outcome of interest was 1-year risk of initiating long-term dialysis stratified by eGFR levels. After adjusting for age, sex, race, and diabetes status, multivariable logistic regression was performed to assess temporal trends in each 3-year cohort. The relative difference between the standardized risks in the initial cohort (2001-2003) and the final cohort was used to estimate the potential change in dialysis initiation in the final cohort (2016-2018).

During the study period, the size of the eligible population increased consistent with growth in overall health plan enrollment and more frequent outpatient serum creatinine testing per patient. In the 2001-2003 cohort, mean age in the eligible population was 55.4 years, 55% were women, and the prevalence of diabetes was 14.9%. Those characteristics and the distribution of index eGFR were stable across the study period. The prevalence of documented hypertension and dyslipidemia increased over the study period, and there was a higher prevalence of Asian/Pacific Islander and Hispanic patients in later years.

The temporal trend in mean eGFR at initiation of dialysis mirrored that in the general US population, with progressively higher mean eGFR through the first decade of the 21st century, followed by a plateau. Mean eGFR at initiation of long-term dialysis in 2001 to 2003 was 12.4 mL/min/1.73 m^2, rose to 16.3 mL/min/1.73 m^2 in 2010 to 2012, and did not increase through 2016 to 2018. The trends were similar for elective starts and for those initiating hemodialysis or peritoneal dialysis.

The number of eligible patients who initiated dialysis was 847 (0.086% of 983,122 at risk) in 2001 to 2003, 917 (0.074% of 1,241,537) in 2004 to 2006, 1011 (0.072% of 1,411,690) in 2007 to 2009, 1013 (0.068% of 1,482,883) in 2010 to 2012, 1092 (0.068% of 1,607,737) in 2013 to 2015, and 1224 (0.066% of 1,844,317) in 2016 to 2018. Since approximately 2008, the healthcare system has encouraged use of peritoneal dialysis as the preferred initial modality. The proportion of new cases of ESKD initiating peritoneal dialysis grew from 13.7% in 2001 to 2003 to 20.8% in 2016 to 2018.

Over time, the likelihood of long-term dialysis initiation within 1 year increased from 0.086% (95% confidence interval [CI], 0.080%-0.092%) in 2001 to 2003 to 0.103% (95% CI, 0.099%-0.107%) in 2016 to 2018 (P<.001 for trend). In analysis of the annual risk of initiating dialysis by index eGFR between 2001 and 2018, the most prominent secular trends were in those with an index eGFR of 20 to 24 mL/min/1.73 m^2 (from 3.2% to 5.1%; P=.001), those with an index eGFR of 18 to 19 mL/min/1.73 m^2 (from 8.3% to 11.0%; P=.03), those with an index eGFR of 16 to 17 mL/min/1.73 m^2 (from 12.4% to 17.9%; P=.005), and those with an index eGFR of 10 to 13 mL/min/1.73 m^2 (from 34.2% to 40.3%; P=.03). Following adjustment for age, sex, race, and diabetes, statistically significant temporal increases in 1-year odds of dialysis initiation remained among eGFR categories of 20 to 24, 16 to 17, and 10 to 13 mL/min/1.73 m^2.

Among those with an index eGFR of 20 to 24 mL/min/1.73 m^2, the 1-year odds of dialysis initiation increased for every 3-year interval by 5.2% (adjusted odds ratio [aOR], 1.052; 95% CI, 1.004-1.102); among patients with index eGFR of 16 to 17 mL/min/1.73 m^2, the 1-year odds of dialysis initiation increased by 6.6% (aOR, 1.066; 95% CI, 1.007-1.130); and among those with index eGFR of 10 to 13 mL/min/1.73 m^2, the 1-year odds of dialysis initiation increased by 5.3% (aOR, 1.053; 95% CI, 1.008-1.100).

Among patients with very low index eGFR (≤9 mL/min/1.73 m^2), the unadjusted and adjusted odds of initiation of dialysis were stable or decreased over time. Patterns were similar among a subset of patients with elective dialysis starts.

Limitations to the findings cited by the authors included limiting data to an integrated healthcare delivery system in California; lack of data on the specific system-, physician- and patient-level reasons that may have contributed to the observed trends; and no analysis of how changing the timing and threshold for dialysis initiation may have affected clinical outcomes.

"In conclusion, choices regarding the timing of dialysis initiation should be made on a patient-by-patient basis to maximize the net benefit for individual patients with kidney disease, including taking into account the results of large, randomized clinical trials, such as the IDEAL trial. Our results underscore the importance the timing of initiating long-term dialysis has on the size of the population of patients with ESKD," the researchers said. ■

Core Outcome Domains in Trials of ADPKD: Results of a Delphi Survey

The most common genetic cause of chronic kidney disease is autosomal dominant polycystic kidney disease (ADPKD). Up to 70% of patients with ADPKD progress to end-stage kidney disease (ESKD) by age 65 years. Kidney function may remain stable for years following diagnosis, however, patients with ADPKD may experience debilitating symptoms such as pain related to growth and enlargement of kidney cysts. Patients in this population are also at risk for extrarenal complications, including stroke associated with ruptured intracranial aneurysm and severe polycystic liver disease.

Lifestyle interventions such as restriction of salt intake as well as therapeutic agents such as tolvaptan have been shown to improve kidney function and total kidney volume. Other outcomes of importance to patients with ADPKD and their caregivers that include kidney pain, fatigue, and anxiety/psychosocial distress are rarely reported in trials among ADPKD patients.

The SONG-PKD (Standardized Outcomes in Nephrology—Polycystic Kidney Disease) initiative was designed to generate consensus among patients, caregivers, and health professionals on important outcomes to be reported in trials in ADPKD. The initiative aimed to inform the development of a core outcome set, defined as an "agreed minimum set of outcomes to be reported in all trials," resulting in improved consistency in outcome reporting across trials to improve shared decision making.

Yeoungipee Cho, PhD, and colleagues conducted an international two-round online Delphi survey, an internationally accepted approach to establish consensus on core outcome sets for trials in nephrology and other disciplines. The survey was conducted in English, French, and Korean languages. Results were reported in the *American Journal of Kidney Diseases* [2020;76(3):361-373].

Patients, caregivers, and health professionals with experience in ADPKD were eligible to participate in the survey. Patients and caregivers aged ≥18 years of age included patients with ADPKD across all stages of CKD (stages 1-5; hemodialysis or peritoneal dialysis; and transplantation) and family members and friends. Health professionals included physicians (nephrologists, hepatologists, surgeons, and geneticists), nurses, allied health professionals, researchers, policy makers, industry, and regulators.

The survey participants completed a 9-point Likert scale (7-9 indicating critical importance) and a Best-Worst scale (BWS). The absolute and relative importance of outcomes were assessed, and comments were analyzed thematically. The survey was administered in two rounds.

In round 1, participants scored the importance of each of 41 outcome domains. A total of 1014 participants from 56 countries completed the survey in round 1: 603 (60%) patients/caregivers and 411 (40%) health professionals. Seventeen outcomes were included in round 2; participants could review their own scores from round 1. In round 2, 713 participants (70% overall retention rate) from 47 countries completed the survey: 406 (57%) patients/caregivers and 307 (63%) health professionals.

Of the 406 patients/caregivers who completed both rounds of the survey, 74% (n=275) were not receiving kidney replacement therapy, 2% (n=7) were receiving peritoneal dialysis, 6% (n=22) were receiving hemodialysis, and 18% (n=68) were kidney transplant recipients. The patients were from 23 countries, including the Republic of Korea, United Kingdom, United States, Australia, and Canada. Of the 307 health professionals who completed both rounds, 70% (n=214) were nephrologists, 12% (n=36) were researchers, and 10% (n=32) were nurses. The health professionals were from 41 countries, including Australia, France, United States, United Kingdom, Republic of Korea, and Canada.

In round 1, the top five outcomes with the highest mean scores for patients/caregivers were kidney function, defined for participants as the ability of the kidney to remove waste from the body and balance fluids, (8.5), ESKD (8.4), cerebral aneurysm (8.0), kidney cyst size/growth (8.0), and blood pressure (7.9). For health professionals, the top 5 outcomes were kidney function (8.4), ESKD (8.4), death (7.8), cerebral aneurysm (7.5), and blood pressure (7.5). In round 2, the top five prioritized outcomes from all participants were kidney function (8.6), ESKD (8.6), death (7.9), blood pressure (7.9), and kidney cyst size/growth (7.8).

In the BWS survey, ESKD was identified by both stakeholder groups as the most important outcome; however, there were differences in the subsequent order of outcomes. The patient/caregiver groups prioritized (in descending order) ESKD, kidney function, cerebral aneurysm, cardiovascular disease, and blood pressure. Among health professionals, death was considered the second most important outcome, followed by kidney function and cardiovascular disease. Patients and caregivers identified chronic pain, kidney cyst size/growth, and kidney cyst pain/bleeding/infection as being as important as death.

The survey results identified seven themes that reflected the reasons for and changes and differences in the rating of outcomes: (1) protecting life and health; (2) directly encountering life-threatening and debilitating consequences; (3) specificity to ADPKD; (4) optimizing and extending quality of life; (5) hidden suffering; (6) destroying self-confidence; and (7) lost opportunities.

The researchers cited potential limitations to the findings, including the survey not measuring details such as ethnicity or stage of CKD to allow subgroup analysis of outcomes, and the online mode of administration of the survey not allowing for involvement from those without access to the internet or with limited computer literacy.

In conclusion, the authors said, "The most important outcomes to patients/caregivers and health professionals were ESKD, kidney function, cerebral aneurysm, and blood pressure. Kidney cyst pain and life participation were the most highly prioritized patient-reported outcomes by patients/caregivers. Before finalizing the core set of outcome domains, public consultation will be sought through a consensus workshop involving patients, caregivers, and health professionals, and any members of the public will be able to access the proposed core outcomes over a 2-week time frame and provide feedback through the SONG website. All input will be reviewed and considered by the SONG-PKD Steering Group to establish a core outcome set. Although the elements discussed as end points in this survey have been studied previously, they have generally been inconsistently reported. Therefore, when a core outcome set has been identified, outcomes measures will be developed through a systematic process (systematic review and workshop) before its implementation in trials. Establishing and implementing a core outcome set will help improve the relevance and consistency of evidence to better inform shared decision making for patients with ADPKD." ■

TAKEAWAY POINTS

- Results of an international two-round online DELPHI survey designed to identify important consensus-based core outcome domains in trials involving patients with autosomal dominant polycystic kidney disease (ADPKD) were reported.
- Survey respondents included patients and caregivers as well as health professionals; both groups identified kidney function, end-stage kidney disease, death, blood pressure, kidney cyst size/growth, and cerebral aneurysm as the top six outcomes.
- The highest rated patient-reported outcome was kidney cyst-related pain.

Outcomes in Kidney Transplant Recipients with COVID-19

COVID-19, caused by SARS-CoV-2, is primarily pulmonary, but it is now well recognized that there is significant involvement of other organs, including the kidneys and the heart, during the course of the illness. Due to immunosuppression requirements and underlying comorbidities, kidney transplant recipients are thought to be at higher risk of acquiring COVID-19 and developing severe disease requiring hospitalization.

There are few data available that compare outcomes among kidney transplant recipients with COVID-19 with those of patients receiving dialysis and waitlisted for transplant. **Mysore Phanish, MBBS, MD, FRCP, PhD,** and colleagues conducted a systematic review and meta-analysis describing 23 kidney transplant recipients who tested positive for SARS-CoV-2 infection from two tertiary care renal centers in the South London Renal Transplant Network, United Kingdom, including follow-up on five patients described in an earlier report. In addition, the researchers conducted a review and meta-analysis on 15 published studies on COVID-19 in kidney transplant recipients to examine case fatality-acute kidney injury (AKI) ratios in kidney transplant recipients hospitalized with COVID-19. Results were reported in *Kidney International Reports* [2021;6:574-585].

Data on all kidney transplant recipients who tested positive for COVID-19 during the first wave of the pandemic in the United Kingdom (March 1, 2020, to June 30, 2020) were collected. Patients were followed until October 15, 2020. COVID-19 was diagnosed via the nasopharyngeal swab polymerase chain reaction test. Data included demographics, clinical and laboratory parameters, and outcomes. The researchers also collected data on dialysis patients, including those on dialysis and those on the transplant waiting list.

Of 1494 kidney transplant recipients under follow-up care in the two renal centers, 23 tested positive for COVID-19 (1.5% of the total transplant cohort). Four were managed at home and 19 required hospitalization. Median age was 62 years, compared with a median age of 51 years in the total transplant cohort. Six of the 23 patients with COVID-19 were female, six (26%) were Black, nine (39.1%) were White, four (21.7%) were South Asian, one was East Asian, one was Hispanic, and two were other race/ethnicity. Among the overall transplant cohort, 7.7% were Black, 73.8% were White, and 15.4% were South Asian. Twenty-two of the 23 patients had hypertension, two had a history of cancer, eight had diabetes, and one had HIV.

Of the 19 hospitalized patients, median age was 64 years. Median follow-up period was 183 days (range, 169-199 days). Median transplant vintage (from transplant date to date of positive swab) was 1686 days (range, 47-12,054 days). Three of the 23 patients with COVID-19 (two hospitalized and one managed at home) were within 3 months of receipt of transplant (53 days, 56 days, and 47 days), three were between 3 and 12 months since their transplant, and the remaining patients were >12 months post-transplant.

All of the 19 hospitalized patients were managed with immunosuppression reduction, and antiproliferative agents (mycophenolate mofetil/azathioprine) were stopped on admission. In mild to moderate cases (n=11), tacrolimus dose was reduced; tacrolimus was stopped in severe cases where there was progressive clinical and radiologic deterioration (n=8). In three cases, prednisolone dose was unchanged; in 13 cases, it was increased.

Some of the patients were recruited into the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial. As part of the trial protocol, two patients received hydroxychloroquine and one received dexamethasone. Two patients received tocilizumab. Of the patients managed at home, one had his mycophenolate mofetil dose reduced by 50% and then increased back to the baseline dose after 2 weeks; the remaining three patients were managed with no change to their immunosuppression regimen.

By 2 weeks post-discharge, all patients who had tacrolimus dose reduced had the dose progressively increased to levels in a therapeutic range (5-8 ng/mL). If patients were well and fever-free and had no other symptoms of COVID-19 for at least 3 days and had normal C-reactive protein level, mycophenolate mofetil was reintroduced at 2 to 3 weeks post-discharge.

The only variables significantly different in patients who died compared with those who survived to discharge were age, admission to the intensive care unit, and type of respiratory support required. Patients who died were significantly older (59.1 vs 70.5 years; *P*=.01) and required more respiratory support (*P*=.004).

Six of the 19 hospitalized patients died. Of the total cohort of transplant recipients (1494), the six who died represent 0.4% of the total cohort. Of the 14 patients on dual immunosuppression, 12 survived (85.7%); of the nine patients on triple immunosuppression, five survived (55.6%). Thirteen of the 19 hospitalized patients developed AKI.

In comparisons of kidney transplant recipients with cohorts of patients on dialysis and those on the transplant waitlist, 123 of 1278 patients on hemodialysis tested positive for COVID-19 (1.5% vs 9.6%; *P*<.001), 12 of 253 waitlisted patients tested positive (1.5% vs 4.7%; *P*=.002), and eight of 170 patients on peritoneal dialysis tested positive (1.5% vs 4.7%; *P*=.01).

The researchers conducted a meta-analysis of 15 published studies and the data from the current analysis to determine a pooled estimate of case fatality ratio (among hospitalized patients) and AKI in kidney transplant patients who tested positive for COVID-19. A total of 871 hospitalized patients were included. The pooled case fatality ratio was 24% (95% confidence interval [CI], 19%-28%). The AKI proportion in 10 studies was 50% (95% CI, 45%-56%). There was some evidence against no heterogeneity between studies (*P*=.02).

In summary, the researchers said, "From our large cohort of transplant patients, a small proportion got COVID-19, with the proportion of infection significantly lower than that of waitlisted patients and those on dialysis. The overall case fatality ratio (26%) was comparable to that of the dialysis cohort and patients on waitlist. Thirty-one percent required intubation and ventilation, of whom 50% died. Within our entire cohort, a significantly lower proportion of transplant patients died of COVID-19 compared with hemodialysis and peritoneal dialysis patients. The case fatality ratio of hospitalized transplant patients with COVID-19 was 31.57%.

"Older age and severity of disease was associated with mortality. We observed a high proportion of AKI (68%), but the majority recovered. Meta-analysis of 16 studies including ours revealed pooled case fatality ratio of 24% for hospitalized patients, pooled AKI proportion of 50%, and pooled proportion of severe AKI of 16% to 18%. We have successfully restarted our transplant program with defined donor and recipient criteria to minimize the risk and optimize the outcomes." ■

TAKEAWAY POINTS

- Researchers reported results of an analysis of outcomes among kidney transplant patients who tested positive for COVID-19 during the early phase of the pandemic.
- Twenty-three of 1494 kidney transplant recipients tested positive for COVID-19, compared with 123/1278 hemodialysis patients and 12/253 waitlisted patients.
- Of 19 patients who required hospitalization, six died and 13 developed AKI. Patients who died were older and required more ventilatory support compared with patients who survived.

Kidney Transplantation in Patients with Sickle Cell Disease

Compared with other etiologies of kidney failure, patients who initiate dialysis due to kidney failure associated with sickle cell disease have a 1.5 to 2.8-fold hazard of mortality. Kidney transplantation is a potential treatment option to reduce the high risk of mortality in this patient population. However, it is unclear whether transplantation is desirable in patients with kidney failure associated with sickle cell disease due to higher post-transplant mortality.

Access to transplantation may be affected by the high post-transplant mortality rate in patients with sickle cell disease and, according to **Sunjae Bae, MPH, PhD,** and colleagues, transplant centers are disincentivized to perform transplantation in those patients due to the close monitoring of each center's aggregate post-transplant mortality rate.

While post-transplant mortality is higher in recipients with sickle cell disease, the decrease in mortality associated with transplantation may be similar or greater in that patient population due to the significant increase in dialysis mortality compared with non-sickle cell counterparts. There are few available data on lower mortality associated with transplantation in patients with sickle cell disease.

The researchers conducted a national cohort study to (1) examine mortality rates and measured decreased in mortality associated with transplantation in patients with kidney failure due to sickle cell disease compared with other etiologies, and (2) compare access to transplantation between populations with and without sickle cell disease, from initiation of dialysis to transplant waitlist registration, to receipt of a kidney transplant. Results of the study were reported online in the *Clinical Journal of the American Society of Nephrology* [doi:10.2215/CJN.02720320].

To quantify the decrease in mortality associated with transplantation, the researchers measured the absolute risk difference and hazard ratio for mortality in matched pairs of transplant recipients versus waitlisted candidates in the sickle cell and control groups. To compare the chance of receiving transplantation, hazard ratios (HRs) for receiving transplantation in the sickle cell and control groups were estimated, treating death as a competing risk.

The study utilized data from the United States Renal Disease System (USRDS) and the Scientific Registry of Transplant Recipients (SRTR). The dialysis cohort included all adults ≥18 years of age who initiated maintenance dialysis with incident diagnosis of kidney failure between January 1, 1998, and December 31, 2017, from USRDS data. Patients who had sickle cell disease as the "primary cause of renal failure" on the end-stage kidney disease Medical Evidence Report (Form CMS-2728), with *International Classification of Diseases, Ninth Edition, Clinical Modification* diagnosis code 282.6 or *International Classification of Diseases, Tenth Edition, Clinical Modification* diagnosis code D57. All others were included in the controls. The waitlist cohort included all adults added to the national kidney transplant waiting list between January 1, 1998, and December 31, 2017, from SRTR data. Candidates whose primary diagnoses were sickle cell disease (diagnosis code 3029) or other (diagnosis code 99), were identified. All others were included in the controls.

The dialysis cohort included 1970 patients in the sickle cell group and 2,047,790 in the control group. Compared with controls, the sickle cell group was younger (median, 44 vs 65 years), more likely to be Black (92% vs 27%), and had fewer comorbidities. The waitlist cohort included 507 patients in the sickle cell group and 463,298 in the control group. The sickle cell group was younger (median, 39 vs 53 years), more likely to be Black (94% vs 28%) or have panel reactive antibody ≥80% (19% vs 10%), and less likely to have diabetes (3% vs 42%) compared with the control group.

In all analyses, the sickle cell group showed higher mortality. The 10-year Kaplan-Meier estimates for dialysis, waitlist, and post-transplant mortality were 85%, 61%, and 50%, respectively, in the sickle-cell group, and 81%, 41%, and 32%, respectively, in the control group.

In model 1 (before any adjustments), the sickle-cell group showed 1.21-fold (95% confidence interval [CI], 1.15-1.27) dialysis mortality, 1.98-fold (95% CI, 1.75-2.23) waitlist mortality, and 1.81-fold (95% CI, 1.45-2.27) post-transplant mortality. Model 3 (fully adjusted) indicated greater differences in mortality, with adjusted HRs of 2.14 (95% CI, 2.03-2.25) for dialysis mortality, 3.21 (95% CI, 2.84-3.62) for waitlist mortality, and 3.03 (95% CI, 2.42-3.80) for post-transplant mortality.

Of the 507 patients with sickle cell disease in the waitlist cohort, 192 subsequently received a transplant. Of the 463,298 candidates from the controls, 243,045 received a transplant. There was an association between kidney transplantation and similar decreases in mortality in the sickle cell and control groups.

In the sickle cell group, transplant recipients had lower mortality, with absolute risk differences of 6.1 (98.75% CI, –0.8 to 13.0) percentage points at 1-year post-transplant, 15.3 (98.75% CI, 3.9-26.7) at 3 years post-transplant, 23.8 (98.75% CI, 9.6-38.0) at 5 years post-transplant, and 20.3 (98.75% CI, 0.9-39.8) at 10 years post-transplant as compared with candidates on the waitlist. In the control group, transplantation was associated with absolute risk differences at 1, 3, 5, and 10 years post-transplant of 0.7 (98.75% CI, 0.5-0.8), 6.6 (98.75% CI, 6.4-6.9), 12.7 (98.75% CI, 12.4-13.1), and 19.8 (98.75% CI, 19.2-20.4), respectively. Following adjustment for race and clinical characteristics, the estimates remained overall similar.

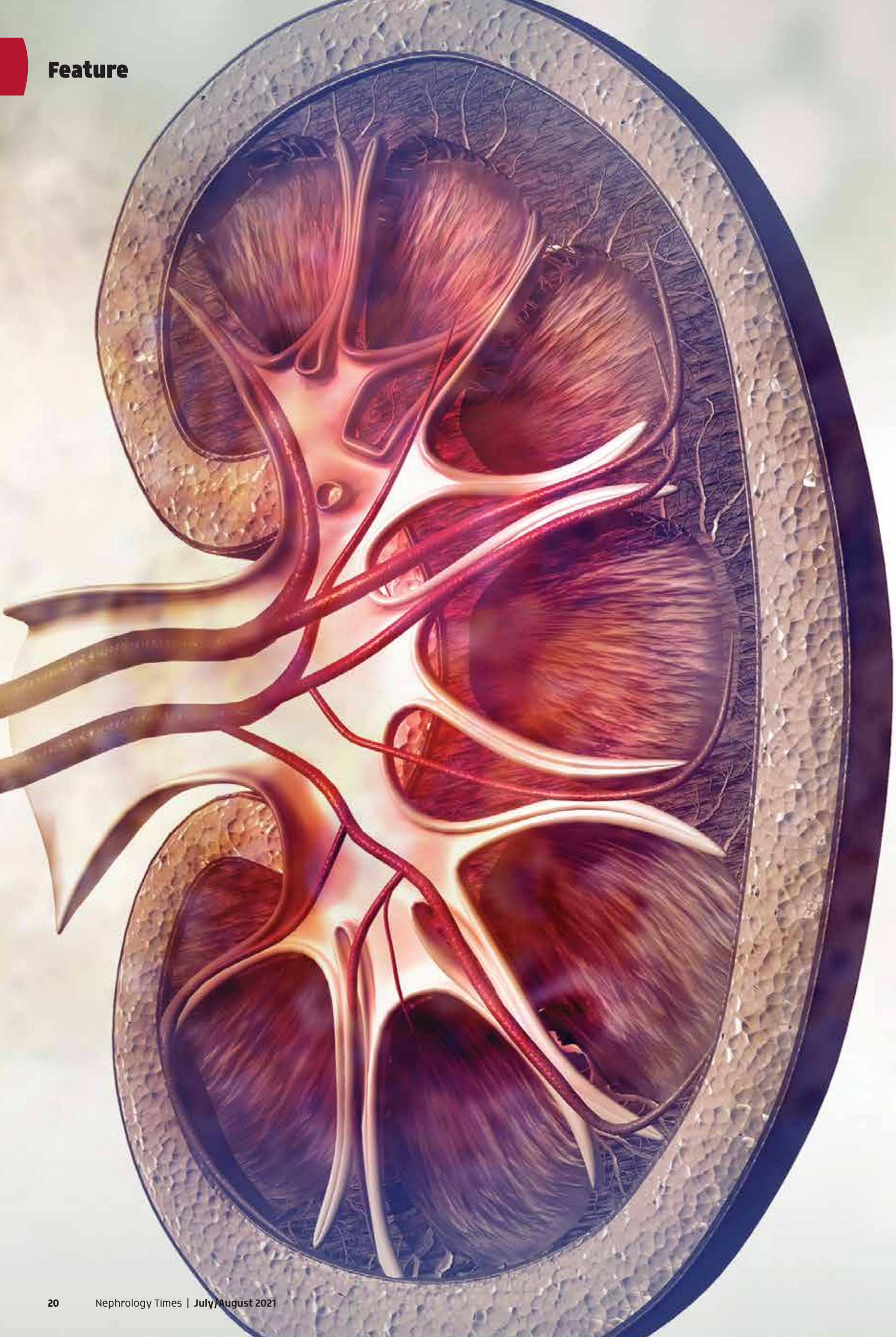
The sickle cell group had lower access to transplantation overall. Beginning at initiation of dialysis, the sickle cell group was less likely to receive a transplant (subdistribution HR, 0.73; 95% CI, 0.68-0.97). After waitlist registration, the sickle cell group was also less likely to receive a transplant compared with the control group (subdistribution HR, 0.62; 95% CI, 0.53-0.72).

Limitations to the study cited by the authors included the possibility of confounding due to the observational study design, restricting the analyses on the decreases in mortality associated with transplantation to waitlisted candidates, and the lack of details on certain clinical factors.

In conclusion, the researchers said, "In this national study, kidney transplantation was associated with similar and substantial decreases in mortality in the sickle cell and control groups. Nonetheless, the sickle cell group had worse access to transplantation compared with the control group, even after being placed on the national kidney transplant waiting list. Our findings suggest that access to transplantation in the sickle cell population should be improved." ■

TAKEAWAY POINTS

- Researchers conducted a national, observational cohort study to examine the decrease in mortality associated with kidney transplantation in patients with kidney failure associated with sickle cell disease.
- Compared with matched candidates on the kidney transplant waitlist, transplant recipients with sickle cell disease and a group of controls with other kidney failure etiologies had similar post-transplant mortality.
- Even after waitlist registration, patients with sickle cell disease were less likely to receive transplantation compared with the control group.



Terlipressin with Albumin for Patients with HRS-1: CONFIRM Trial Results

Patients with decompensated cirrhosis and ascites may develop type 1 hepatorenal syndrome (HRS-1), characterized by rapidly progressing kidney failure. If left untreated, HRS-1 is often fatal, with a median duration of survival of weeks to months. Reversal of the hemodynamic abnormalities associated with advanced cirrhosis may be achieved with pharmacotherapy with vasopressors to improve renal perfusion and function in patients with HRS-1.

Terlipressin is a synthetic vasopressin analogue with vasoconstrictor activity in the splanchnic and systemic vasculature. The efficacy and safety of terlipressin in patients with HRS-1 have been examined in previous, multicenter, placebo-controlled trials. It is used to treat patients with HRS-1 in many parts of the world and is part of the clinical practice guidelines in Europe.

Florence Wong, MB, BS, MD, and colleagues conducted the CONFIRM trial to confirm the efficacy and safety of terlipressin plus albumin, compared with placebo plus albumin, in adults with cirrhosis and HRS-1. Results of the phase 3 trial were reported in the *New England Journal of Medicine* [2021;384(9):818-828].

Patients were randomly assigned in a 2:1 ratio to receive terlipressin or placebo for up to 14 days. Concomitant use of albumin was strongly recommended for both groups. The primary end point of interest was verified reversal of HRS-1, defined as two consecutive serum creatinine measurements of 1.5 mg per deciliter or less at least two hours apart up to day 14 and survival without renal replacement therapy (RRT) for at least 10 days following treatment completion. To account for multiple comparisons, four prespecified secondary end points were analyzed with the Hochberg procedure: (1) HRS reversal, defined as serum creatinine level of 1.5 mg per deciliter or less; (2) durability of HRS reversal, defined as HRS reversal without RRT to day 30; (3) HRS reversal among patients with systemic inflammatory response syndrome; and (4) verified HRS without recurrence of HRS by day 30.

Data on nonserious adverse events were collected up to 7 days following the end of the treatment period, and data on serious adverse events were collected up to 30 days following the end of the treatment period. Mortality was documented for up to 90 days following the first dose of terlipressin or placebo.

The trial was conducted from July 13, 2016, to July 24, 2019, at 60 sites in the United States and Canada. The total cohort included 300 patients who were randomized to the terlipressin group (n=199) or the placebo group (n=101). The two groups were generally well balanced at baseline in clinical and demographic characteristics.

Concomitant albumin was administered in 165 patients (83%) in the terlipressin group (mean total dose per person, 199.4 g over a median of 5.0 days) and 92 patients (91%) in the placebo group (mean total dose, 239.5 g over a median of 5.5 days). Sixty-one percent of the terlipressin group (n=121) and 60% of the placebo group (n=61) had previously received midodrine and octreotide.

The primary end point (verified reversal of HRS) was achieved by a significantly higher percentage of patients in the terlipressin group than in the placebo group (32% [63 patients] vs 17% [17 patients]; *P*=.006); 17 patients in the terlipressin group and nine in the placebo group were considered to be unclassifiable with respect to the primary end point.

Three of the four secondary end points reached statistical significance: HRS reversal, defined as any serum creatinine level of 1.5 mg per deciliter or less during the first 14 days, was reported in 39% (78 patients) of the terlipressin group and 18% (18 patients) in the placebo group; *P*<.001; HRS reversal without RRT by day 30 was reported in 34% (68 patients) of the terlipressin group and 17% (17 patients) of the placebo group; *P*=.001; HRS reversal among patients with systemic inflammatory response syndrome (84 patients in the terlipressin group and 48 patients in the placebo group) was reported in 31 patients in the terlipressin group (37%) and three patients in the placebo group (6%); *P*<.001. The fourth secondary end point, verified HRS reversal without recurrence by day 30, was reported in 26% (52 patients) of the terlipressin group and 17% (17 patients) of the placebo group; *P*=.08.

Over a mean duration of follow-up of 55.3 days, 23% of patients (n=46) in the terlipressin group received a liver transplant; in the placebo group, 29% (n=29) of patients received a liver transplant over a mean duration of follow-up of 56.1 days. There were no differences between the two groups in overall or transplantation-free survival up to 90 days.

By day 90, 101 patients in the terlipressin group (51%) died, compared with 45 patients in the placebo group (45%) (difference, 6 percentage points; 95% confidence interval, –6 to 18).

Adverse events of any severity were reported in 88% of patients in the terlipressin group (176/200) and 89% of the placebo group (88/99). In the overall safety population (299 patients), the most frequently reported adverse events were abdominal pain, (45 patients [15%]), nausea (42 patients]14%]), diarrhea (33 patients [11%]), hepatic encephalopathy (33 patients [10%]), and dyspnea (30 patients [10%]).

More patients in the terlipressin group reported abdominal pain, nausea, diarrhea, or respiratory failure, compared with the placebo group (14 % [28 patients] vs 5% [5 patients]). The two groups were similar in percentage of patients who had dose interruptions associated with adverse events (7% in each group); the percentage of patients with permanent discontinuation of the assigned regimen due to adverse events was higher in the terlipressin group compared with the placebo group (12% [24 patients] vs 5% [15 patients]). Death within 90 days due to respiratory disorders occurred in 11% of the terlipressin group (22 patients) and 2% of the placebo group (2 patients).

Limitations to the trial cited by the authors included the inability to assess between-group differences in survival, and the lack of an assessment of prespecified outcomes after liver transplantation was not performed.

In conclusion, the authors said, "In the CONFIRM trial, the use of terlipressin plus albumin was more efficacious than placebo plus albumin in producing verified reversal of HRS in patients with decompensated cirrhosis and HRS-1. Terlipressin was associated with serious adverse events, including respiratory failure." ■

Alan Mendelson Appointed to NKF Board

Alan C. Mendelson has been appointed to the national Board of Directors of the National Kidney Foundation (NKF). Mr. Mendelson retired as a senior partner from Latham & Watkins LLP in December 2020. He also served as secretary and acting general counsel at Amgen earlier in his career.


Alan C. Mendelson

One of Amgen's focuses was a partnership with Johnson & Johnson on a new drug treatment for kidney patients, giving Mr. Mendelson an awareness of the burden kidney disease puts on patients and their families. He later served as president of NKF's then Northern California affiliate for 3 years, was on the local Board of Directors for 12 years, and has worked to support NKF events in the Bay Area for more than 35 years.

In a press release from NKF, **Anthony E. Tuggle,** board chair and president of consumer operations at Afiniti and a kidney transplant recipient, said, "Alan has helped numerous companies grow through every stage of the business life cycle. He brings decades of experience counseling boards and executives of emerging and public companies and will be an integral advisor helping us accelerate innovation in kidney disease and transplantation. The wealth of business acumen Alan brings from advising startups to working with venture capital firms and investment banks and helping them through a full range of transactions will definitely add value to the work we do every day on behalf of the 37 million Americans who have kidney disease."

Mr. Mendelson said, "I'm honored to join the National Kidney Foundation Board of Directors and share my perspective as a lawyer with 40+ years of experiences in the life sciences industry. My association with Amgen led to a career dominated by representation of emerging biotechnology companies. I've seen the continuing development of relationships between academic and research institutions, non-profits and emerging biotechnology companies, and I want to do all that I can to use the knowledge I've acquired to help advance innovation in the treatment of those who have kidney disease."

CHF Solutions Changes Name to Nuwellis, Inc.

CHF Solutions has announced it is now Nuwellis, Inc. According to a press release, the change reflects the company's core therapeutic focus areas of pediatric, critical care, and heart failure fluid imbalance. The benefits of the company's Aquadex SmartFlow® System, originally used to remove excess fluid in patients with heart failure, is also clinically proven to improve outcomes in critical care and pediatric patients weighing ≥20 kg, the press release stated.

Nestor Jaramillo, Jr., president and CEO, said, "2020 was a transformational year for our company, we grew in unexpected ways and expanded our therapeutic focus areas. We are no longer exclusively a heart failure company, as our prior name suggested. Nuwellis represents our mission to better adhere to the needs of all patients suffering from fluid imbalance and reflects our new commercial focus. This is an exciting time for our company and represents the growth we have seen and strive to continue to achieve. We will continue to evolve in order to give patients and their providers the best technology to restore fluid balance, and rebranding is a high-level change that reflects our commitment."

Nuwellis, Inc. Announces ULTRA-Peds Registry

In a recent press release, Nuwellis, Inc. (formerly CHF Solutions) announced the enrollment of the first patient in the ULTRA-Peds Registry (Ultrafiltration Therapy Registry Using Aquadex). The registry will collect real-world evidence on the safety, efficacy and utilization of Aquadex SmartFlow® in children who weigh ≥20 kg with fluid overload. Nuwellis is the registry sponsor, in collaboration with the Acute Kidney Injury Critical Care Research Foundation.

The registry will include approximately 500 patients; key clinical data of interest include treatment course survival, intensive care unit (ICU) survival, ICU length of stay, change in kidney function, hemodynamic stability, change in percentage of fluid overload, and complications and adverse events.

Alex R. Constantinescu, MD, chief of pediatric nephrology at Joe DiMaggio Children's Hospital, Hollywood, Florida, said, "Maintaining fluid balance and hemodynamic stability are imperative to minimize the risk of increased morbidity and mortality. This involves selecting the appropriate treatment for fluid overload states. Because the majority of medical products are designed for and tested in adults, having clinical outcomes data supporting a device's use in children has an immeasurable value. I'm honored to support the collection of pediatric data on Aquadex because I know the therapy works, and data will support clinical adoption meaning more kids can benefit from this therapy."

The president and CEO of Nuwellis, **Nestor Jaramillo, Jr.,** said, "We are grateful to partner with organizations like Joe DiMaggio's Children's Hospital as part of our commitment to improve and customize pediatric care with the Aquadex SmartFlow system. As part of our continued growth, we are committed to finding ways to advance future technology and progress our pipeline, while demonstrating that this innovative and gentle therapy is safe, effective, and beneficial for pediatric patients who are suffering from fluid overload."

App to Manage Hb in CKD-Related Anemia in Development

AstraZeneca and Sanguina have announced a collaboration on a study to develop a custom version of AnemoCheck Mobile, an application for a smartphone that provides noninvasive and equipment-free hemoglobin (Hb) levels for patients with anemia associated with chronic kidney disease (CKD). Sanguina is a research-based health platform company.

According to a press release, AnemoCheck Mobile is the first application to estimate Hb levels using a snapshot of a fingernail, applying an algorithm based on the pallor of the nailbed, eliminating the need to draw blood. The app has the potential to be personalized to allow patients with CKD-related anemia to manage measurements at home.

The study, in collaboration with AstraZeneca and NephroNet, will examine the accuracy and reproducibility of data to assess the practicality of the new custom tool for patients with CKD. The study will enable training of the AnemoCheck algorithm

with complete blood count Hb level measurements and the app's analysis of images of fingernails. Following training, the study will test the custom algorithms in patients by comparing app results against complete blood count Hb levels. The algorithm is being tested in an ethnically diverse cohort of patients with CKD-related anemia.

Sanguina founder and CEO, **Erika Tyburski,** said, "This partnership will allow us to further test and demonstrate the unique capabilities of AnemoCheck Mobile so that we can empower patients with innovative solutions to help manage their health. As someone who has experienced anemia, I know personally the impact it has on quality of life and peace of mind. I look forward to helping improve other patients' lives for the better."

Tarek Rabah, vice president, AstraZeneca US Renal-Cardio, said, "This collaboration reinforces our shared commitment to helping revolutionize kidney care through innovative approaches for the millions of patients living with CKD. In these times, when patients with chronic illness are faced with more challenges than ever, AnemoCheck offers a personalized solution and increased access for patients."

Results from the AnemoCheck study are expected in the third quarter of 2021.

First-Year Results of Cricket Health's Patient Support Platform

In a recent press release, Cricket Health announced results from the first year of deployment of StageSmart™, a proprietary machine learning disease identification model, and MyCricket™, a patient support program. The programs have seen a 65% reduction in hospital admissions among enrolled members, a 94% patient satisfaction rate, and a 90% patient retention rate.

Andrew Schutzbank, chief product officer at Cricket Health, said, "Managing a complex condition like chronic kidney disease requires doing little things every day to stay healthy, which is difficult if you are trying to go it alone. Our goal at Cricket Health is to give people with kidney disease the support they need to live their best lives. The frequent engagement we're seeing in the MyCricket platform is making a real difference."

The platform connects patients with kidney disease with peer support, a peer mentor, a multidisciplinary care team, and educational resources available 24/7. In the first year of the program, members interacted with their Cricket care teams weekly on average, with 40% of members connecting an average of 10 times a month, every 2 or 3 days. MyCricket has also hosted 25,000 interactions with clinicians, 2900 interactions with peer mentors, and more than 10,000 views of the educational content.

StageSmart uses predictive GFR (pGFR™) to identify people with kidney disease and determine the stage of their disease. Stag-

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eSmart has helped health plans identify patients at risk for kidney failure who have not yet been diagnosed.

Robert Sepucha, CEO of Cricket Health, said, "StageSmart allows health plans to deliver stage-specific care to their population diagnosed with kidney disease, as well as intervene in kidney disease in earlier stages, avoiding costly complications like hospital visits. This proactive care transforms the status quo of largely waiting to treat a patient's kidney disease until after their kidneys have failed, fundamentally changing what a kidney disease diagnosis means for patients."

Both platforms, StageSmart and MyCricket, are available to commercial health plans, nephrology practices, and Medicare Advantage plans.

GWAC to RenalytixAI for KidneyIntelX Testing

RenalytixAI has received a 10-year Governmentwide Acquisition Contract (GWAC) to provide KidneyIntelX™ early stage kidney disease bioprognostic testing services. The contract was granted through the US General Services Administration and covers testing services that can be provided through more than 140 US government departments, agencies, and affiliates, including the US Veterans Administration (VA), Department of Defense military branches (Army, Navy, Air Force, Marines), and Indian Health Services.

According to a press release from RenalytixAI, the contract has a term of 5 years, with an option for an additional 5-year extension. KidneyIntelX is now available through the Federal Supply Schedule and physicians working within government-sponsored healthcare programs can order KidneyIntelX testing for their patients with diabetic kidney disease. The contract simplifies structuring service agreements with VA facilities, military installations, and tribal nations, and facilitates contracting with the VA's regional healthcare networks to cover KidneyIntelX testing for eligible patients.

Tom McLain, RenalytixAI president, said, "This provides the opportunity for RenalytixAI to support our veterans, active military, and Native American communities, and to expand our health system care delivery model. Achieving this contracting milestone allows us to make KidneyIntelX available to patients throughout the US government healthcare system. Executing on our market access strategy represents a substantial commercial opportunity for RenalytixAI.

James Post, MD, nephrologist and chief of internal medicine at the James J. Peters VA Medical Center in Bronx, New York, said, "Access to KidneyIntelX testing represents a significant development in the early detection, intervention, and management of patients at risk for chronic kidney disease. With the clinical information provided by the KidneyIntelX risk score report, primary care physicians can identify and intervene early in the management of patients who are on a path for renal failure prior to direct involvement of a nephrologist or the need for dialysis."

Bayer Announces Phase 3 Results of FIGARO-DKD

Bayer has announced phase 3 results of FIGARO-DKD, a study of cardiovascular outcomes assessing the efficacy and safety of finerenone versus placebo. The results demonstrated that finerenone, an investigational drug added to standard of care for patients with chronic kidney disease (CKD) and type 2 diabetes, has met the study's primary end point. In the finerenone group, the composite risk of time to first occurrence of cardiovascular death or nonfatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure) was significantly reduced compared with placebo.

Compared with the FIDELIO-DKD study, the first of two phase 3 studies, FIGARO-DVD included more patients with earlier stage CKD and diabetes. FIGARO-DKD, a randomized, double-blind, placebo-controlled, parallel-group, event-driven phase 3 study included ~13,000 patients across a broad range of disease severity, from early kidney damage to more advanced stages of kidney disease.

Coprincipal investigator, **Luis M. Ruilope, MD, PhD,** said, "Up to 40% of people with type 2 diabetes develop chronic kidney disease, and they are at high risk of experiencing cardiovascular events, as well as progressing to kidney failure. The FIGARO-DKD study delivers important insights into the potential effects on cardiovascular outcomes of finerenone in the management of people with chronic kidney disease and type 2 diabetes."

The clinical data from FIGARO-DKD will be presented at an upcoming scientific meeting, according to a press release from Bayer.

Connected Health Platform for Home Dialysis Management

The Renal Therapies Group of Fresenius Medical Care North America (FMCNA) has introduced a new connected platform for home dialysis that supports the management of a patient's peritoneal dialysis therapy on the Liberty® Select cycler. According to a press release from FMCNA, the Kinexus™ Therapy Management Platform "is designed to enhance clinical workflows enabling advanced therapy programming capabilities that aim to improve patient outcomes and nurse productivity."

Mark Costanzo, president of the FMCNA Renal Therapies Group, said, "The Kinexus platform is an important step to further accelerating the adoption of home dialysis by enabling patient treatment data to flow more easily and simply to care teams. Our new connected health system is compatible, agile, and scalable, which will allow for an evolution of new features."

The platform is available for all dialysis providers. The cloud-based system enables the management of patient care anytime via timely, automatic transmission of patient treatment data to the care team, and reduced reliance on paper flow sheets, improving clinicians' workflow and productivity.

"By making recent treatment data more easily accessible to clinicians, we hope to empower care teams to resolve treatment issues earlier as well as reduce unnecessary hospitalizations," **Mike Anger, MD,** chief medical officer for FMCNA's Renal Therapies Group, said. "This is a significant and important upgrade that will make the home dialysis experience even better for patients and providers."

Single 1000 mg Dose Injector® Option Approved by FDA

In a recent press release, Daiichi Sankyo, Inc. and American Regent, Inc., a Daiichi Sankyo Group company, announced approval from the US FDA of a single 1000 mg dose option of Injectafer® (ferric carboxymaltose injection), an iron replacement product for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron, have had unsatisfactory response to oral iron, or have non-dialysis-dependent chronic kidney disease.

Linda Mundy, chief medical officer at American Regent, Inc., said, "We are pleased to build on the proven, mainstay Injectafer 1500 mg two-dose course of treatment with the approval of this new 1000 mg single dose option. More than 1.7 million patients have been treated with Injectafer in the United States and healthcare providers now have an additional dosing option for adult patients with IDA who may not be appropriate for oral iron or who have non-dialysis-dependent CKD." ■

Pennsylvania Enacts Living Donor Legislation

In late April, Pennsylvania Governor **Tom Wolf** signed HB 203, the Living Donor Protection Act, into law. In a press release, the American Kidney Fund (AKF) applauded the enactment of the law that will increase the availability of organs for transplant from living donors in Pennsylvania.

AKF worked with HB 203 sponsor **Rep. Tarah Toohil** (115th Legislative District) to help move the bill through the legislature. Provisions in HB 203 prohibit insurance companies from denying or limiting coverage for living organ donors and charging higher premiums. It also calls for job-protected leave through the Family and Medical Leave Act to individuals who choose to become living organ donors.

AKF is leading a nationwide effort to pass laws that protect living donors; to date 13 states have enacted such legislation.

LaVarne A. Burton, president of AKF, said, "With the passage of this bill, Pennsylvania joins a growing list of states that have enacted these commonsense, lifesaving policies in recent years. Ultimately, living donor protection laws will save lives by shortening the transplant waiting list."

COVID-19

Incidence and Outcomes of AKI in Pediatric Patients with COVID-19

Pediatric Nephrology. doi.org/10.1007/s00467-021-05084-x

There are few data available on the epidemiology of acute kidney injury (AKI), associated risk factors, treatment, and mortality among pediatric patients with COVID-19 admitted to the intensive care unit (ICU). AKI is recognized as a severe complication among children and adolescents with COVID-19. **Rupesh Raina, MD,** and colleagues conducted a comprehensive literature search to identify published literature related to AKI in pediatric COVID-19 patients, including incidence and outcomes.

The researchers searched PubMed, MEDLINE, and Cochrane Center Trials and identified 24 studies that reported outcomes of interest. Across all 24 studies, there were 1247 children who tested positive for COVID-19. Median age of the population was 9.1 years. AKI incidence was 30.51%; only 0.56% required kidney replacement therapy. The mortality rate was 2.55%, and the incidence of multisystem inflammatory syndrome was 74.29%.

"AKI has shown to be a negative prognostic factor in adult patients with COVID-19 and now also in the pediatric cohort with high incidence and mortality rates," the researchers said. "Additionally, our findings show a strong comparison in epidemiology between adult and pediatric COVID-19 patients; however, they need to be confirmed with additional data and studies."

Survival and Recovery in COVID-19 Patients Requiring CRRT

Journal of Critical Care. doi: 10.1016/j.jcrc.2021.04.002

Karin E. Eriksson, MD, and colleagues conducted an observational study at a university hospital in Sweden to describe mortality and renal outcomes in critically ill patients with COVID-19 who were treated with continuous renal replacement therapy (CRRT). The study cohort included 451 patients.

Of the 451 patients, 43.7% developed acute kidney injury and 18.2% received CRRT. Median age of the CRRT group was 60 years, 90% were male, median body mass index was 29, 23.2% had diabetes, 37.8% had hypertension, and 6.1% had chronic kidney disease prior to hospital admission. All required mechanical ventilation and 8.5% received extra corporeal membrane oxygenation.

Median length of stay was 23 days. ICU mortality was 39% and 90-day morality was 45.1%. There were associations between age, baseline creatinine values, and change in body weight and 60-day mortality. Of those who survived, none required dialysis at hospital discharge, 73.8% recovered renal function, and patients lost a median of 10.5% of body weight during admission.

In conclusion, the researchers said, "Critically ill COVID-19 patients with AKI who received CRRT had a 90-day morality rate of 45.1%. At follow-up, three quarters of survivors had recovered renal function. This information is important in the clinical management of COVID-19."

CONFERENCE COVERAGE **AMERICAN TRANSPLANT CONGRESS**

Kidney Paired Donation in Pediatric Recipients

Kidney paired donation allows for ABO-mismatched or HLA-incompatible pairs to receive a living donor kidney transplant. Among the pediatric kidney transplant population who will likely require multiple transplants in their lifetime, the superior graft survival among recipients of living donor kidneys is of particular importance. According to **J. Smith** and colleagues, kidney paired donation represents a strategy to increase living donation among pediatric kidney transplant candidates. The use of kidney paired donation is on the increase among adults; the use of the strategy in the pediatric population is not well outlined.

The researchers utilized data from the Scientific Registry of Transplant Recipients to examine the population of pediatric living donor transplant recipients from 2014 to 2019 by kidney paired donation status. The researchers performed chi-squared tests for difference by kidney paired donation status, and compared the proportion of pediatric and adult kidney paired donation recipients during the study period. Results were reported during a virtual session at the 2021 American Transplant Congress in a presentation titled *Kidney Paired Donation in Pediatrics: An Underused Opportunity?*

The number of kidney paired donation kidney transplants has increased from 8 (3.3% of living donor recipients) in 2014 to 18 (7.5%) in 2019, with a peak of 25 (9.1%) in 2018. Use of kidney paired donation is higher in adults and has been steadily increasing since 2014.

Characteristics that were more common to pediatric kidney paired donation recipients than to other pediatric living donor recipients were: Black race (18.0% vs 8.3%); previous transplant (15.7% vs 6.5%), panel reactive antibodies >20% (33.7% vs 13.8%), and donor <10 years older than the recipient (6.7% vs 2.7%).

In conclusion, the researchers said, "Participation in kidney paired donation presents logistical and financial challenges for pediatric kidney programs, but an increasing number have been performed in recent years. This program could provide increased transplant opportunities for pediatric recipients, especially for disadvantaged groups."

Source: Smith J, Skeans M, Engen R, Bartosh S. Kidney paired donation in pediatrics: An underused opportunity? Abstract of a presentation at the virtual 2021 American Transplant Congress (Abstract 77), June 5, 2021.

CHRONIC KIDNEY DISEASE

Use of ACEi/ARB in Patients with Proteinuric CKD

Mayo Clinic Proceedings. doi.org/10.1016/j.mayocp.2020.12.038

Researchers, led by **Ian E. McCoy, MD, MS,** conducted an analysis to examine use of angiotensin-converting inhibitors (ACEi) and angiotensin receptor blockers (ARB) in patients with proteinuric chronic kidney disease (CKD). The researchers also sought to describe barriers that limit use of this guideline-concordant care.

The researchers utilized a nationwide database that included patient-level claims and integrated clinical information to identify ACEi/ARB prescriptions on the index date of April 15, 2017, as well as prior ACEi/ARB use in 41,743 insured adults with proteinuric CKD. Multivariable logistic regression was used to estimate adjusted associations between current ACEi/ARB use and putative barriers, including past acute kidney injury (AKI), hyperkalemia, advanced CKD, and lack of nephrology care.

On the index date, 20,641 patients (49%) had an active prescription; 36,199 (87%) had been previously prescribed an ACEi/ARB. Use was lower in patients with past AKI (adjusted odds ratio [aOR], 0.61; 95% confidence interval [CI], 0.58-0.64), in patients with hyperkalemia (aOR, 0.76; 95% CI, 0.72-0.80), in patients with CKD stages 4 or 5 (aOR, 0.48; 95% CI, 0.45-0.51), and in those with a lack of nephrology care (aOR, 0.85; 95% CI, 0.81-0.89).

In conclusion, the researchers said, "Discontinuing, rather than initiating, ACEi/ARB treatment limits guideline-concordant care in proteinuric CKD. Past AKI, hyperkalemia, advanced CKD, and lack of nephrology care were associated with lower use of ACEis/ARBs, but these putative barriers may in many instances be inappropriate (AKI and advanced CKD) or modifiable (hyperkalemia and lack of nephrology care).

Outcomes in Patients with Prior Renal Dysfunction Undergoing Liver Transplant

Transplantation. doi: 10.109.1097/TP.0000000000003728

There are few data available on the significance of pretransplant kidney disease on outcomes in recipients of living donor liver transplantation.

Therese Bittermann, MD, and colleagues conducted a retrospective cohort study of 2806 adult recipients of living donor liver transplant between January 2019 and June 2020.

The study compared transplant recipients with estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 m^2 (eGFR-low) with recipients requiring dialysis. In multivariable survival analyses, eGFR-low was evaluated as a predictor of post-living donor liver transplant survival. The study also assessed the survival of living donor liver transplant versus deceased donor liver transplant alone with eGFR-low.

Prior to living donor liver transplant during the study period, 5.0% of the 2806 recipients (n=140) had eGFR-low and 0.6%

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(n=18) required dialysis. Between 2017 and 2020, the number of living donor liver transplant recipients requiring dialysis outnumbered the previous 7 years. Living donor liver transplant recipients with eGFR-low had longstanding renal dysfunction: mean eGFR 3 to 6 months before liver transplant was 42.7 mL/min/1.73 m^2.

Five of 12 of patients in the eGFR-low group with active kidney transplant listing at time of liver transplant experienced renal recovery. Under the new "safety net" policy, five patients underwent early kidney transplant after living donor liver transplant.

In unadjusted analysis, survival after living donor liver transplant was worse with eGFR-low (hazard ratio [HR], 2.12 vs eGFR ≥40 mL/min/1.73 m^2; 95% confidence interval [CI], 1.47-3.05; *P*<.001). After accounting for mean eGFR 3 to 6 months pre-living donor liver transplant, the relationship was attenuated (HR, 1.27; 95% CI, 0.82-1.95; *P*=.3). There was no difference in adjusted survival in patients with eGFR-low receiving living donor liver transplant versus deceased donor liver transplant alone (*P*=.08).

"Overall, outcomes after living donor liver transplant with advanced renal dysfunction are acceptable. These findings are relevant given the recent 'safety net' kidney transplant policy," the researchers said.

Factors Associated with Risk of Falls in Elderly Patients with CKD

International Urology and Nephrology. doi.org/10.1007/s11255-021-02884-w

Patients with chronic kidney disease (CKD) commonly represent an aging population. There are associations between CKD and older age and an increased risk of falling. According to **Cihan Heybeli, MD,** and colleagues, there are few data available on risk factors for falls among elderly patients with CKD.

The researchers retrospectively reviewed records of outpatients from a geriatric clinic in Turkey. A high risk of falls was defined as a result of ≥13.5 seconds on the timed up-and-go test. Logistic regression models were used to identify independent predictors of an increased risk of falls among patients with CKD (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2).

Two hundred and five patients had CKD, representing 20.2% of the overall cohort. CKD was identified as an independent predictor of increased fall risk (odds ratio, 2.59). Among the 205 patients with CKD, serum folic acid levels and frailty were independent predictors of increased fall risk.

Patients in the CKD/fall risk group were older, had lower median years of education, lower levels of vitamin D, and lower serum folic acid levels than those in the CKD/non-fall risk group. In addition to higher serum creatinine and potassium levels, the only significant difference between patients with CKD/fall risk and a matched non-CKD/fall risk was a lower median folic acid level in the CKD/fall risk group.

In conclusion, the researchers said, "Frailty and low folic acid levels are independently associated with an increased risk of falls among elderly patients with CKD. Prevention of frailty may reduce the risk of falls in these subjects. Possible benefit of folic acid supplementation requires further studies."

DIABETES

No Association Between SGLT2 Inhibitors and Risk of AKI

Journal of Clinical Endocrinology & Metabolism. doi.org/10.1210/clinem/dgab274

Donna Shu-Han Lin, MD, and colleagues at National Taiwan University Hospital, Taipei, Taiwan, conducted a meta-analysis to examine the occurrence of adverse events associated with the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) for the treatment of type 2 diabetes. The researchers also sought to examine the level of risk of adverse events in patients with various underlying diseases.

The researchers conducted the quantitative meta-analysis of randomized controlled trials retrieved from the MEDLINE and EMBASE databases. The search also included the Cochrane Library. The outcomes of interest were four overall safety outcomes and 12 specified safety outcomes. Subgroup analyses were performed based on patient status of diabetes mellitus, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease, and congestive heart failure, and by dosage of SGLT2i (high dose vs low dose).

The ten eligible studies represented 71,553 participants. Results of the meta-analysis suggested that SGLT2i use was associated with increased risk of genital infection (risk ratio [RR], 3.56; 95% confidence interval [CI], 2.84-4.46), urinary tract infection (RR, 1.06; 95% CI, 1.00-1.12), diabetic ketoacidosis (RR, 2.23; 95% CI, 1.36-3.63), and volume depletion (RR, 1.14; 95% CI, 1.06-1.23).

Conversely, there were associations between use of a SCLT2i and reduction in risk of any serious adverse event (RR, 0.92; 95% CI, 0.90-0.94), acute kidney injury (AKI) (RR, 0.84; 95% CI, 0.77-0.91) and hyperkalemia (RR, 0.84; 95% CI, 0.72-0.99). In subgroup analysis, the risk of amputation was higher in patients with ASCVD than in those without ASCVD (RR, 1.44 vs 0.96; *P*=.066).

In conclusion, the researchers said, "The use of SGLT2i is generally safe. SGLT2i may be associated with increased risks of genital infection but is protective against AKI. Of note, the risk of amputation was higher in patients with ASCVD. The key to safe use of SGLT2i lies in the identification of high-risk populations and close surveillance of patients after treatment."

Dapagliflozin in Patients with and without Type 2 Diabetes

The Lancet. 2021;9(1):22-31

In patients with chronic kidney disease (CKD), treatment with dapagliflozin reduces the risk of kidney failure and heart failure. **David C. Wheeler, MD,** and colleagues reported the results of an analysis of data from the DAPA-CKD study. The analysis was designed to examine the effects of

dapagliflozin on kidney, cardiovascular, and mortality outcomes according to the presence or absence of type 2 diabetes and according to the underlying cause of CKD (diabetic nephropathy, chronic glomerulonephritides, ischemic or hypertensive CKD, or CKD of other or unknown cause).

DAPA-CKD was a multicenter, double-blind, placebo-controlled, randomized trial conducted at 386 study sites in 21 countries. Patients with a urinary albumin-to-creatinine ration of 200 to 5000 mg/g and an estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min/1.73 m^2 were randomly assigned in a 1 to 1 ratio to dapagliflozin 10 mg once daily (n=2152) or a matching placebo (n=2152) in addition to standard care.

The primary outcome of interest was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or kidney-related or cardiovascular death. Secondary outcomes were a kidney-specific composite (the same as the primary outcome but excluding cardiovascular death), a composite of cardiovascular death or hospital admission for heart failure, and all-cause mortality.

In the total cohort (n=4304), 68% (n=2906) had a diagnosis of type 2 diabetes. Of those participants, 14% (n=396) had CKD ascribed to causes other than diabetic nephropathy. The relative risk reduction for the primary composite outcome with dapagliflozin was consistent among participants with and without type 2 diabetes (hazard ratios [HR], 0.64; 95% confidence interval [CI], 0.52-0.79 and 0.50; 95% CI, 0.35-0.72; respectively; *P* for interaction=.24).

Findings were similar for secondary outcomes: kidney-specific composite (HR, 0.57; 95% CI, 0.45-0.73 vs 0.51; 95% CI, 0.34-0.75; *P* for interaction=.57), cardiovascular death or hospital admission for heart failure (HR, 0.70; 95% CI, 0.53-0.92 vs 0.79; 95% CI, 0.40-1.55; *P* for interaction=.78), and all-cause mortality (HR, 0.74; 95% CI, 0.56-0.98 vs 0.52; 95% CI, 0.29-0.93; *P* for interaction=.25).

The effect of dapagliflozin on the primary outcome was also consistent in patients with diabetic nephropathy, ischemic or hypertensive CKD, or unknown cause, with similar consistency across the secondary outcomes. There were no variations in the proportions of participants in the dapagliflozin and placebo groups with serious adverse events or discontinuation of the study drug due to adverse events between those with and those without type 2 diabetes.

"Dapagliflozin reduces the risks of major adverse kidney and cardiovascular events and all-cause mortality in patients with diabetic and non-diabetic chronic kidney disease," the researchers said.

Funding for this analysis was provided by AstraZeneca. ■

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Sarah Tolson

Understanding the Importance of Billing Compliance

Compliance officer is one of the hats I wear at the company I work for, Sceptre Management. Part of my role as compliance officer is providing training about fraud, waste, and abuse to our staff and assisting our clients with their billing compliance. I have always been a rule follower (when I was younger, this often resulted in being teased by my peers), so helping others to be compliant with all applicable regulations is something I wholeheartedly enjoy.

Recently, a reader of this column sent me an email with an issue that made the compliance officer in me cringe. The email was from a biller at a small practice who was reaching out for guidance and insight about a challenge she had encountered with her supervisor. The supervisor had instructed the biller to submit claims to Medicare for a service that the biller believed was included in the Medicare Capitated Payment (MCP). The biller had told her supervisor that she believed the service in question was included in the MCP, but the supervisor instructed her to, "Just bill it and see if it gets paid. If it gets paid, that means it's not included."

The biller, due to her reservations, had not yet submitted the claims to Medicare that she believed were not payable outside of the MCP. Rather, she decided to research the issue to determine the appropriate action. Questioning the supervisor's instruction was absolutely the correct action in this instance. In fact, at Sceptre Management we encourage our staff to question instruction they receive if they feel it does not align with their understanding of our compliance program. This helps everyone to have a better understanding of our compliance program and take ownership in maintaining compliance with all applicable regulations.

The biller and I corresponded about the issue and were able to identify the section of the Medicare manual that discussed the coverage and reimbursement for the services the biller's supervisor had instructed her to bill to Medicare. The biller took the documentation to her supervisor to discuss the services. The two determined that reimbursement inside of the MCP was already being received and it would have been both unnecessary and inappropriate to submit a claim to Medicare, as the service was not separately payable.

This situation had a great outcome, but it could have ended much differently. Had the biller submitted the claims to Medicare without performing additional research, it is quite possible that Medicare would have issued payment in error for the services. If Medicare had issued an erroneous payment for the services, the supervisor may have believed the services were separately payable. In this situation, the practice likely would have continued to bill and receive payment until the payment error was discovered by Medicare, at which time Medicare would require the practice to repay all of the funds it had received for claims paid in error. ■

FRAUD, WASTE, AND ABUSE

Regardless of a person's role in a medical practice or entity that is involved with billing and obtaining reimbursement for medical services, everyone is responsible for preventing fraud, waste, and abuse. My experience has been that most people want to avoid fraud, waste, and abuse and welcome any assistance in maintaining their compliance.

Fraud is knowingly and willfully executing, or attempting to execute, a scheme or artifice to defraud any health care benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any health care benefit program.

Waste includes practices that, directly or indirectly, result in unnecessary costs to the Medicare Program, such as overusing services. Waste is generally not considered to be caused by criminally negligent actions but rather by the misuse of resources.

Abuse includes actions that may, directly or indirectly, result in unnecessary costs to the Medicare Program. Abuse involves paying for items or services when there is no legal entitlement to that payment, and the provider has not knowingly or intentionally misrepresented facts to obtain payment.

Questioning the supervisor's instruction was absolutely the correct action in this instance.

Sarah Tolson is the director of operations for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD dialysis programs, nephrology practices, and vascular access. Your questions are welcome, and she can be reached at stolson@sceptremanagement.com, 801.775.8010, or via Sceptre's website, www.sceptremanagement.com.

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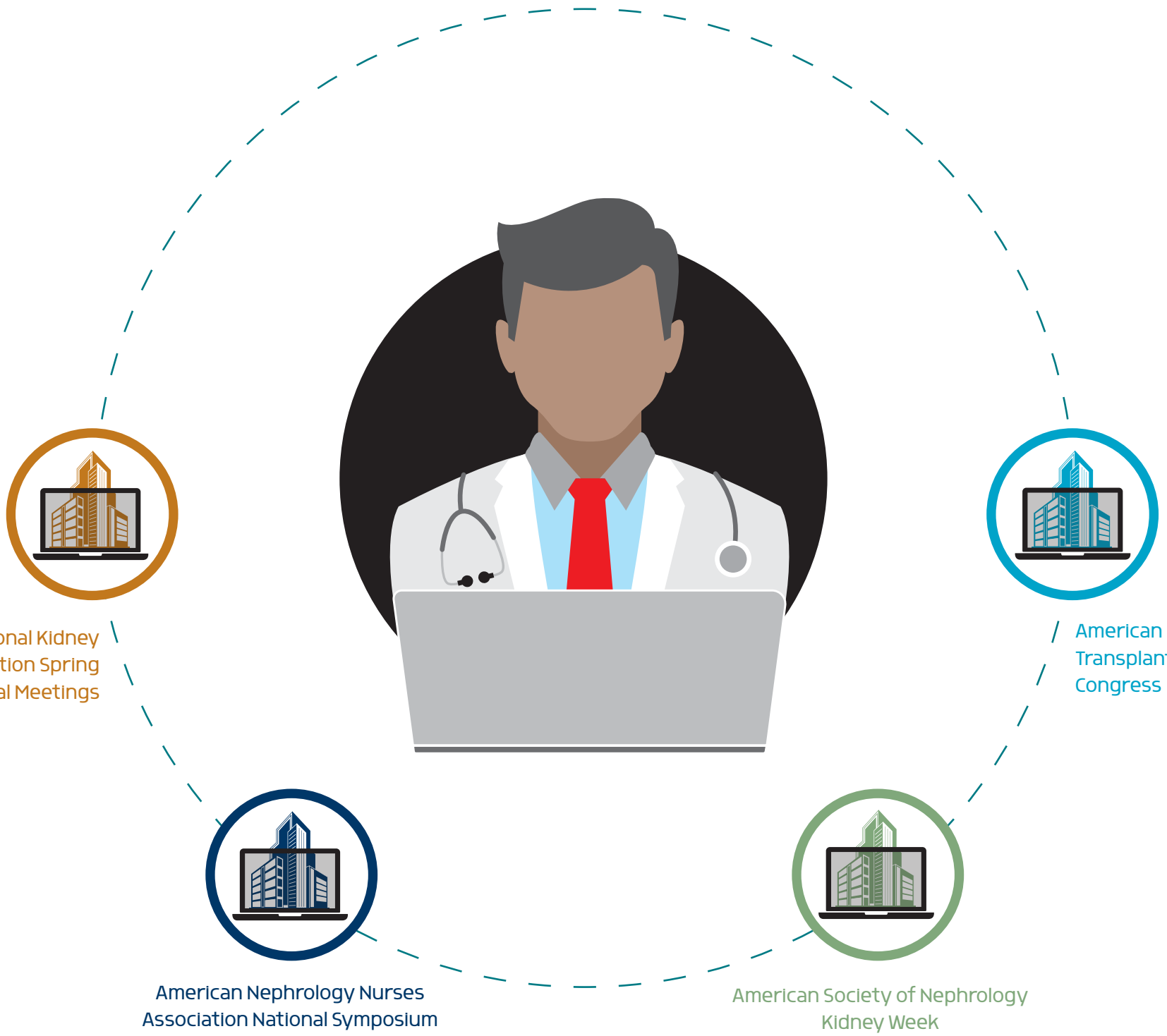

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