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Practical News, Trends, and Analysis

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FEATURE

Estimates of Shortages in Capacity for CKRT during the Pandemic

Developing models of CKRT demand and capacity to inform emergency planning. **22**

NEWS

ADPKD Patients Experience Broad and Variable Trial Outcomes

A total of 1413 outcomes were reported across 68 trials. **14**

CONFERENCE COVERAGE

Kidney Week 2020

Abstracts of selected posters presented at the virtual ASN Kidney Week 2020 Reimagined. **10**

FOCUS ON TRANSPLANTATION

Stroke-Related Deaths among Kidney Transplant Recipients

The cumulative incidence for stroke-related mortality was higher among patients with pre-existing cerebrovascular disease. **21**

PLUS....

FROM THE FIELD

2021 Changes to ESRD PPS

Final rule changes to reimbursement and billing requirements. **30**

Drug-Coated Balloon Angioplasty for Dysfunctional Arteriovenous Fistulas

Worldwide, approximately 850 million individuals have chronic kidney disease and nearly 4 million receive renal replacement therapy. Among those 4 million, 520,000 Americans are undergoing dialysis, and fewer than 225,000 have a functioning kidney transplant. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative is working to develop an individualized, patient-driven life plan that will address disease progression among dialysis patients.

At present, preference is given to arteriovenous fistulas or grafts for most patients undergoing dialysis due to the lower risk of infection associated with those treatment methods compared with the use of a central venous hemodialysis catheter. However, according to **Robert A. Lookstein, MD, MHCDL,** and colleagues, the high incidence of dysfunction caused by vascular stenosis within the fistula circuit can lead to inadequate hemodialysis. The percentage of patients who undergo repeat intervention within 6 months is approximately 50%.

The current recommended treatment for dysfunctional hemodialysis fistulas is standard percutaneous transluminal angioplasty. However, that treatment yields poor long-term outcomes. Outcomes may be improved with the use of drug-coated balloons delivering the

continued on page 7

Belimumab plus Standard Therapy for Treatment of Active Lupus Nephritis

Among patients with systemic lupus erythematosus (SLE), 25% to 60% develop lupus nephritis, the most common severe manifestation of SLE and a major cause of illness and death. The percentage of patients with lupus nephritis who have a positive renal response is low despite aggressive treatment. Ten to 30% of patients with lupus nephritis progress to end-stage kidney disease (ESKD). The risk of ESKD in this patient population has remained unchanged for the past 30 years.

The US FDA approved belimumab, a recombinant human IgG-1A mononclonal antibody that inhibits B-cell activating factor, for patients ≥5 years of age with active autoantibody-positive SLE. Patients with acute severe lupus nephritis were excluded from the trials used for the FDA approval; thus, there are few data available on the efficacy and safety of belimumab in patients with lupus nephritis.

Richard Furie, MD, and colleagues conducted BLISS-LN (Belimumab International

continued on page 6

Racial/Ethnic Disparities in Anemia Complications in Patients with ESKD after 2011

In 2016, more than half a million people in the United States were affected by end-stage kidney disease (ESKD). ESKD represents a significant economic burden on the healthcare system. Anemia is a common modifiable complication of chronic kidney disease (CKD) and is more pronounced in later CKD stages. Patients with anemia are at increased risk for left ventricular hypertrophy, heart failure, cognitive impairment, and poorer quality of life; anemia is also a key predictor of mortality.

Erythropoiesis-stimulating agents (ESAs) are first-line treatments for anemia; however, use of those agents is associated with safety concerns. In 2011, a series of policy changes adopted in the United States combined to change incentives around the use of ESAs. The Centers for Medicare & Medicaid Services implemented the Medicare ESKD prospective payment system (PPS) that altered financial incentives by allowing providers to retain payments above Medicare's reimbursement level while providing dialysis services. The system reduced the incentive to provide

continued on page 8

Print-only Content

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The Dawn of a New Era in Renoprotection: SGLT2 Inhibitors and Mineralocorticoid Antagonists

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as essential agents in our battle to slow the progression of kidney disease, especially in patients with chronic kidney disease (CKD) from type 2 diabetes. While it made sense that they would be effective in renoprotection in these patients due to their effectiveness in lowering blood glucose and blood pressure, their ability to slow kidney progression in patients without diabetes had not been previously established until an important clinical trial, the DAPA-CKD, was published in the *New England Journal of Medicine* in October 2020.[1]

Likewise, the importance of mineralocorticoid hyperactivity in the progression of kidney disease has been discussed for many years, because of hemodynamic and potentially antifibrotic effects of these agents. However, trial data had been lacking. That was until the publication of the FIDELIO-DKD in the *New England Journal of Medicine* in December 2020.[2]

These two new trials—one using dapagliflozin, an SGLT2 inhibitor, and the other, finerenone, a selective mineralocorticoid antagonist—are discussed here and will almost certainly usher in a new era in kidney protection.

The background on how SGLT2 inhibitors and selective mineralocorticoid inhibition cause renal protection is reviewed in detail elsewhere.[3-6] SGLT2 inhibitors lower the Tmax or threshold for urinary glucose excretion in the kidney and thus cause urinary glucose excretion.[2-3] These inhibitors also result in sodium excretion due to the linkage of glucose with sodium transport. Conversely, aldosterone binds to the mineralocorticoid receptor located in the distal convoluted tubule, connecting segment and cortical collecting duct (aldosterone-sensitive distal nephron) where it modulates sodium reabsorption and potassium excretion.[6] Several preclinical studies reviewed in reference 6 have suggested a hemodynamic role for mineralocorticoid antagonism in slowing the progression of kidney disease.

Of growing interest is the antifibrotic effect of both SGLT2 inhibition and mineralocorticoid antagonism on the kidney as a mechanism for kidney protection.[7]

In the DAPA-CKD trial[1], Heerspink and colleagues randomized 4304 participants to receive either dapagliflozin (10 mg once daily) or placebo. Key eligibility criteria for entry to the study included an estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min/1.73 m,^{2} a urinary albumin-to-creatinine ratio of 200 to 5000 mg/g creatinine. Patients with type-1 diabetes were excluded. Randomization was stratified by two factors: a history of type 2 diabetes and the level of albuminuria (less or greater than 1 g/d of albumin excretion). The primary outcome was a composite of a >50% lowering in eGFR, end-stage kidney disease (ESKD), or death from renal or cardiovascular causes. The trial was stopped early by the data monitoring committee, which saw an early benefit of the treatment.

At a median follow-up of 2.4 years, there was a 39% reduction in the risk of the composite renal/cardiovascular disease (CVD) outcome that was highly significant ($P<.001$). When the investigators looked at the renal outcome separate from CVD outcomes, the composite renal outcome (>50% reduction in eGFR, ESKD, or death from renal causes) demonstrated a reduction in risk of approximately 44% ($P<.001$).

The bottom line from the DAPA-CKD trial is that SGLT2 inhibitors are beneficial when added to renin-angiotensin blockade as part of a multipronged strategy to slow the progression of kidney

disease. Indeed, the US FDA in October 2020 granted dapagliflozin Breakthrough Therapy Designation (BTD) for use in slowing kidney progression in patients with CKD, with and without type 2 diabetes.

The second agent, a mineralocorticoid antagonist, has received much attention since its recent publication. The agent is finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist that blocks excess mineralocorticoid activity in CKD patients.

FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease)[2] was a randomized double-blind placebo-controlled trial in which 5734 patients with CKD and type 2 diabetes received either finerenone (at a dose of 10 or 20 mg/day depending on eGFR) or placebo. Enrolled patients had type 2 diabetes and moderately advanced CKD. The primary outcome was a composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over at least 4 weeks, or death from renal causes.

Following a median follow-up of 2.6 years, patients randomized to the finerenone arm showed an 18% reduction in the composite renal outcome. The patients in the finerenone group also had a significant reduction (~14%) in CVD outcomes compared with control. A potential reason for the comparatively modest effect of finerenone compared with an SGLT2 inhibitor was thought to be concurrent treatment with SGLT2 inhibitor in a small subset of patients (and about 4% were on an SGLT2 inhibitor).[8]

So, what should we know about SGLT2 inhibitors and finerenone?

First, because of the risk of diabetic ketoacidosis (DKA), patients with type-1 diabetes mellitus and kidney disease should not be treated with SGLT2 inhibitors. That said, among CKD patients with type 2 diabetes or those patients without diabetes, SGLT2 inhibitors are usually well tolerated, as suggested by the DAPA-CKD trial (none of the patients with or without type 2 diabetes developed ketoacidosis). There is no known concern with finerenone causing DKA, but it has also not been tested in patients with type 1 diabetes.

Second, because of glucosuria induced by SGLT2 inhibition, patients are at a higher risk of developing genital infections.[9-10] Infections include genital candidal infections, vaginitis, or vulvovaginitis in women, and genital candidal infections, penile infections, and phimosis in men. Risk factors for infection include female sex and prior history of a genital infection.[9] Prevention is key and good genital hygiene is very important. Because finerenone does not act through this pathway, genital infections are not a concern.

Third, it is important to be aware of the effects of SGLT2 inhibitors on fluid balance and electrolytes. Due to SGLT2 inhibition, modest sodium wasting is observed. Chronically, SGLT2 induced natriuresis causes mild volume-depletion. However, hyponatremia is not observed. Nor do SGLT2 inhibitors cause significant changes in serum potassium, calcium, phosphate, or magnesium levels. The main issue with using finerenone is the higher incidence of hyperkalemia (twice as high [15.8%] in the finerenone vs control arm)—not surprising because of antagonizing mineralocorticoid action on the distal nephron. It is certainly possible that when additional trials are done in patients with milder CKD, hyperkalemia will be less common. The FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trial is ongoing.

SGLT2 inhibitors have been tested more widely, and more information on them has been published than on mineralocorticoid receptor antagonists. From the DAPA-CKD trial, we know that dapagliflozin works well in both older and younger patients, men and women, White, Black and Asian patients, and in patients with or without heavy proteinuria. Dapagliflozin was also well tolerated in patients on other antihypertensive or diuretic medications. Experience with finerenone is less robust and based primarily on the FIDELIO-DKD trial. Not much is known about subgroups—these data will likely be published elsewhere.

An important collateral benefit from the DAPA-CKD and FIDELIO-DKD trials were the CVD benefits. The finding with respect to dapagliflozin was consistent with similar results reported in the DECLARE–TIMI 58 and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trials.[11-12]

In summary, SGLT2 inhibitor therapy should be considered in all CKD patients, with the exception of patients with type-1 diabetes. In this regard, dapagliflozin has been approved by the FDA. Finerenone, on the other hand, is efficacious in patients with CKD and type-2 diabetes but has not been approved by the FDA as yet. In the future, once FDA approval comes through for finerenone, it is likely that both of these agents will be (should be) used in conjunction with an inhibitor of the renin-angiotensin system, such as an ACE inhibitor or angiotensin receptor blocker.

A new era of kidney protection begins!

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Belimumab plus Standard Therapy

continued from page 1

Study in Lupus Nephritis), a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of belimumab in combination with standard therapy (mycophenolate mofetil or cyclophosphamide-azathioprine) in patients with lupus nephritis. Results of the study were reported in the *New England Journal of Medicine* [2020;383(12):1117-1128].

Adult patients with biopsy-proven, active lupus nephritis were assigned in a 1:1 ratio to receive intravenous belimumab (at a dose of 10 mg per kilogram of body weight) or matching placebo in addition to standard therapy. The primary end point at week 104 was a primary efficacy renal response, defined as a ratio of urinary protein to creatinine of ≤0.7, an estimated glomerular filtration (eGFR) that was no worse than 20% below the renal flare (pre-flare value) or ≥60 mL/min/1.73 m^2 of body surface area, and no use of rescue therapy. The main secondary end point was a complete renal response, defined as a ratio of urinary protein to creatinine of <0.5, an eGFR that was no worse than 10% below the pre-flare value or ≥90 mL/min/1.73 m^2, and no use of rescue therapy.

A total of 797 patients underwent screening from July 2012 through July 2017. The final cohort included 448 patients who underwent randomization, 224 to the belimumab group and 224 to the placebo group. The modified intention-to-treat population included 223 patients in each group. Randomization was stratified according to induction regimen (59 patients in each group had received cyclophosphamide and 164 in each group had received mycophenolate mofetil) and race (31 patients in the belimumab group and 32 in the placebo group were Black and 192 patients in the belimumab group and 191 in the placebo group were not Black). Through week 100, 65% of the belimumab group (n=146/223) and 59% of the placebo group (n=132/223) received a trial agent.

The two groups were balanced in baseline characteristics. Mean age was 33.4 years and median duration of lupus nephritis was 0.2 years. Of the total cohort, 58% (n=258/446) had a kidney-biopsy specimen classified according to International Society of Nephrology and Renal Pathology Society criteria as class III or IV lupus nephritis, 26% (n=116) had class III or IV coexisting with class V, and 16% (n=72) had pure class V.

At 104 weeks, a primary renal response was observed in significantly more patients in the belimumab group than in the placebo group (43% [96/223) vs 32% [72/223]; odds ratio [OR], 1.6; 95% confidence interval [CI], 1.0-2.3; *P*=.03). Individual components of the primary efficacy renal end point at week 104, including a decrease in the ratio of urinary protein to creatinine to 0.7 or less and no treatment failure, occurred more often in the belimumab group than in the placebo group.

More patients in the belimumab group than in the placebo group had a primary efficacy renal response earlier (week 52) (47% [104/223] vs 35% [79/223]; OR, 1.6; 95% CI, 1.1-2.4; *P*=.02). At each visit, starting at week 24, more patients in the belimumab group had a primary efficacy renal response than those in the placebo group. The chance of having a primary efficacy renal response that was sustained through week 104 was higher in the belimumab group than in the placebo group (hazard ratio, 1.46; 95% CI 1.07-1.98).

At week 104, significantly more patients in the belimumab group than those in the placebo group had a complete renal response (30% [67/223] vs 20% [44/223]; OR, 1.7; 95% CI, 1.1-2.7; *P*=.02). More patients in the belimumab group compared with patients in the placebo group had components of a complete renal response at week 104, including a decrease in the ratio of urinary protein to creatinine of less than 0.5 and no treatment failure. From week 12 onward, more patients in the belimumab group had a complete renal response than those in the placebo group. The chance of a complete renal response that was sustained through week 104 was higher with belimumab than with placebo (hazard ratio [HR], 1.58; 95% CI, 1.08-2.31).

The risk of a renal-related event or death during the study period was significantly lower in the belimumab group than in the placebo group (HR, 0.51; 0.34-0.77; *P*=.001). Those results were due primarily to increased proteinuria, impaired kidney function, or both (in 17 patients in the belimumab group and 39 patients in the placebo group) or kidney-related treatment failure (16 in the belimumab group and 20 in the placebo group).

The safety profile for belimumab plus standard therapy was similar to that of standard therapy alone. There were no anti-belimumab antibodies detected. Infection-associated deaths were balanced between the two groups, and there were no deaths directly attributed to lupus nephritis by the investigators.

Limitations to the study findings included the low enrollment of Black patients and patients receiving cyclophosphamide-azathioprine, and only allowing two induction and maintenance regimens as background therapy.

In summary, the researchers said, "The current international trial involving 448 patients showed that belimumab plus standard therapies for lupus nephritis enhanced renal responses; furthermore, the risk of a renal-related event during the trial was almost 50% lower among patients who received belimumab than among those who received standard therapy alone. Up to 3 g of mycophenolate mofetil or cyclophosphamide-azathioprine was combined with belimumab in our trial, and we did not observe adverse events that differed from those in previous trials involving patients with SLE who received belimumab or other trials involving patients with lupus nephritis." ■

TAKEAWAY POINTS

- Researchers reported results of a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled trial designed to examine the efficacy and safety of intravenous belimumab plus standard therapy in patients with active lupus nephritis.
- At week 104, significantly more patients in the belimumab group had a primary efficacy renal response and a complete renal response compared with patients in the placebo group.
- The risk of renal-related event or death was lower in the belimumab group than in the placebo group. The safety profile for belimumab plus standard therapy was similar to that of standard therapy alone.

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Drug-Coated Balloon Angioplasty

continued from page 1

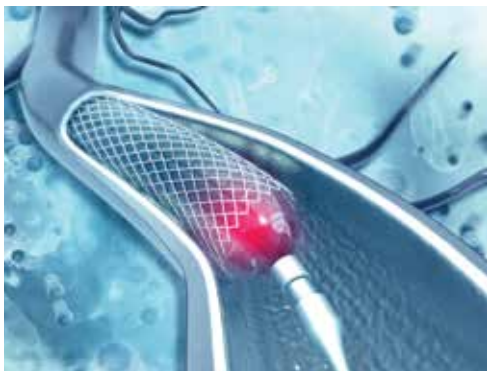
antirestenotic agent paclitaxel. Dr. Lookstein et al. conducted a prospective, global, multicenter, single-blind, 1:1 randomized clinical trial to evaluate the IN.PACT AV drug-coated balloon (Medtronic) in comparison with standard (non-drug-coated) balloon angioplasty for the treatment of new or nonstented restenotic lesions up to 100 mm in length in arteriovenous fistulas. Results were reported in the *New England Journal of Medicine* [2020;383(8):733-742].

The trial was conducted at 29 sites in the United States, Japan, and New Zealand. The primary effectiveness end point was target-lesion primary patency, defined as freedom from clinically driven target-lesion revascularization or access-circuit thrombosis measured during the 6 months following the index procedure. The primary safety end point was defined as serious adverse events involving the arteriovenous access circuit within 30 days following the procedure.

Eligible patients were at least 21 years of age and presented with a new or nonstented restenotic native arteriovenous dialysis fistula that had at least 50% stenosis. The trial device was a drug-coated balloon that carried a paclitaxel dose of 3.5 mg per square millimeter with a urea excipient.

A total of 330 participants underwent randomization: 170 were assigned to receive treatment with a drug-coated balloon and 160 were assigned to receive treatment with a standard balloon. Of the total cohort, 204 participants were treated in the United States, 112 in Japan, and 14 in New Zealand. Baseline characteristics were similar in the two groups; as expected, a high percentage of participants had diabetes, hypertension, or cardiovascular disease. The distribution of forearm (radiocephalic) and upper-arm (brachiocephalic and brachiobasilic) arteriovenous access lesions treated was even between the groups. Common presenting clinical symptoms of arteriovenous fistula dysfunction included decreased blood flow and elevated venous pressure. In most participants, the target lesions were in the venous outflow, including the cephalic arch, with the lesion in 25.5% (n=84/330) located at the arteriovenous anastomosis.

During the 6 months following the index procedure, 82.2% of participants in the drug-coated-balloon group had target-lesion primary patency compared with 59.5% in the standard-balloon group.



The mean length of the balloons used in the index procedure was greater in the drug-coated-balloon group than in the standard-balloon group (50.0 mm vs 47.4 mm). The final mean percent diameter stenosis was similar in the two groups, as was antiplatelet therapy use after the procedure.

During the 6 months following the index procedure, 82.2% of participants in the drug-coated-balloon group had target-lesion primary patency compared with 59.5% in the standard-balloon group (risk difference, 22.8 percentage points; 95% confidence interval [CI], 12.8 to 32.8; $P<.001$). When the effect of missing data was examined in sensitivity analyses, conclusions were consistent with those of the primary analysis. In the drug-coated-balloon group, the percentage of participants with clinically driven target-lesion revascularization was 16.4% compared with 38.5% in the standard-balloon group (risk difference, –22.1 percentage points; 95% CI, –31.9 to –12.3).

In safety end point analyses assessing the percentage of participants with a serious adverse event involving the arteriovenous assess circuit within 30 days, the drug-coated balloon was noninferior to the standard balloon (4.2% and 4.4%, respectively; risk difference, –0.2 percentage points; 95% CI, –5.5 to 5.0; with a noninferiority margin of 75 percentage points, $P=.002$ for noninferiority). In sensitivity analyses, the conclusions were consistent with those of the primary analysis.

The researchers cited some limitations to the trial, including the inability to utilize a double-blind trial design because the drug-coated balloon has a different appearance than a standard balloon, and the fact that repeat intervention rates may be biased. Other limitations were only reporting short-term outcomes, and possible confounders due to between-group differences in the number of inflations and the maximum inflation pressures.

"Treatment of dysfunctional native hemodialysis arteriovenous fistulas with a drug-coated balloon provided primary patency, including freedom from clinically driven target-lesion revascularization that was superior to that provided by standard balloon angioplasty. The drug-coated balloon was noninferior to standard balloon angioplasty with respect to safety," the researchers said. ■

TAKEAWAY POINTS

- Standard recommended treatment for dysfunctional hemodialysis fistulas is percutaneous transluminal angioplasty; however, that treatment is associated with poor long-term outcomes.
- Results of a prospective 1:1 randomized trial comparing standard balloon treatment with drug-coated balloon treatment demonstrated that target-lesion primary patency was maintained during the 6 months after the procedure more often in participants in the drug-coated-balloon group than in the standard-balloon group.
- In analyses of the primary safety end point, drug-coated balloons were noninferior to standard balloons.

CONFERENCE COVERAGE AMERICAN TRANSPLANT CONGRESS

JC Virus and Development of BK Virus in Kidney Transplant Recipients

Researchers at the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, led by **G. Huang,** conducted a study to examine the effect of JC [John Cunningham] virus (JCV) on the development and prognosis of BK virus (BKV) infection and polyomavirus nephropathy (PVN) in renal transplant recipients. Results of the study were reported during a virtual poster session at the American Transplant Congress in a poster titled *Effect of JC Virus on Polyomavirus Nephropathy in Renal Transplant Recipients.*

The study included 196 renal transplant recipients who underwent graft biopsy at the First Affiliated Hospital from May 2017 to December 2018. The patients were divided into a PVN group (n=69) and a non-PVN group (n=127). The researchers compared differences in infection rate and replication of JCV and BKV between the two groups. They also examined the effects of JCV on the pathologic degree of PVN and the relationship between JCV and graft survival rate and function of PVN recipients.

In the PVN group, 100% of cases were infected with BKV, compared with 27.6% in the non-PVN group ($P<.001$). There were 22 cases (31.9%) infected with JCV in the PVN group compared with 48 cases (37.8%) in the non-PVN group.

In the PVN and non-PVN groups, median level of BKV-DNA in plasma was 4.06×10^4 and 2.49×10^3 ($P=.014$), respectively. BKV-DNA in urine was 1.4×10^9 and 2.64×10^6 ($P<.001$) in the PVN group and non-PVN group, respectively.

The median level of JCV-DNA in urine was 1.3×10^8 in the PVN group and 2.87×10^6 ($P=.065$) in the non-PVN group. In plasma, the median level of JCV-DNA was 2.43×10^4 in the PVN group and 0 in the non-PVN group ($P=.016$).

There was no significant correlation between JCV level and scores of main pathologic parameters. The creatinine level in PVN recipients with JCV viremia 1 year after biopsy was significantly higher compared with non-JCV viremia recipients ($P=.041$).

"JCV plays a positive role in promoting BKV replication among PVN recipients. It is recommended to monitor plasma JCV-DNA in recipients with PVN," the authors said.

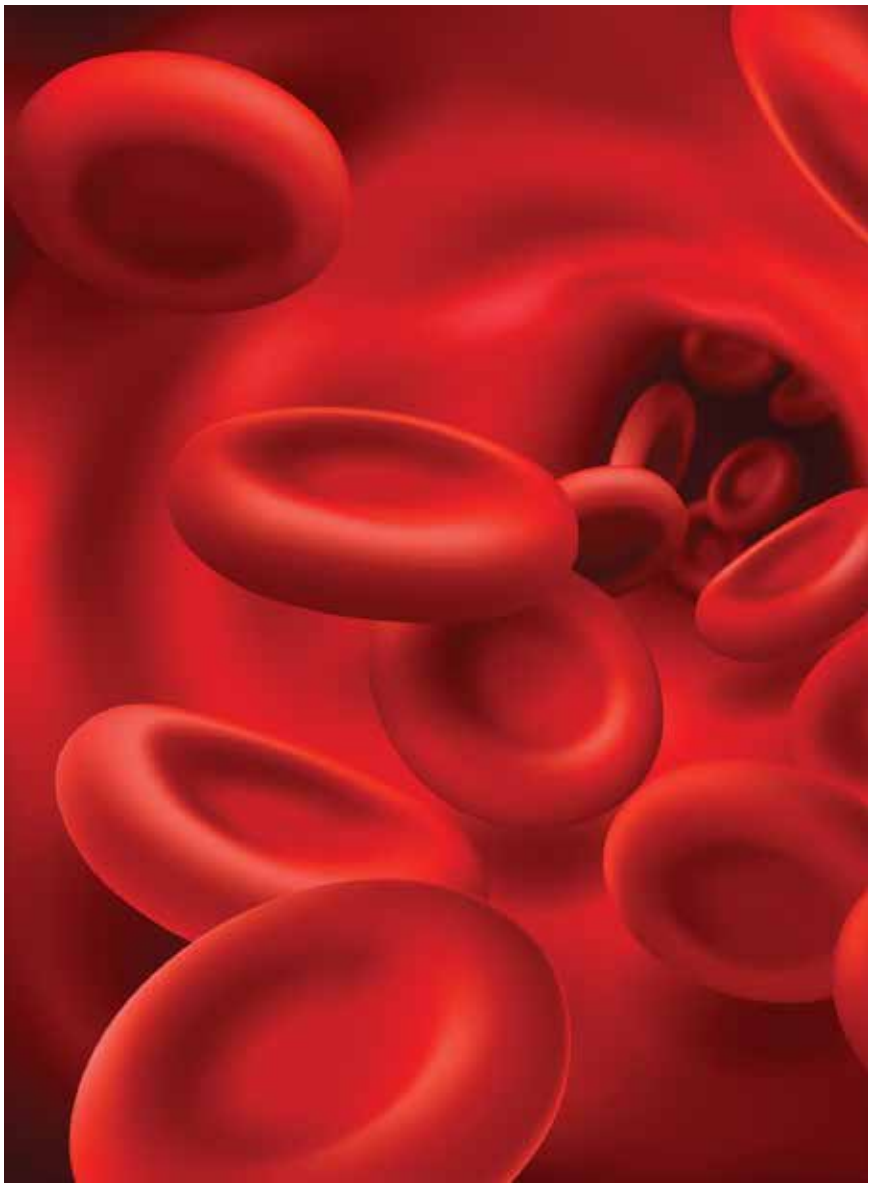
Source: Huang G, Huang Y, Chen X, et al. Effect of JC virus on polyomavirus nephropathy in renal transplant recipients. Abstract of a poster presented at the virtual American Transplant Congress 2020 (Abstract D-181), May 30, 2020.

continued from page 1

treatments that had been reimbursed on a fee-for-service basis, including injectable medications such as ESAs.

Also in 2011, the US FDA revised the prescribing advice for ESAs with guidance on a more conservative use of the agents for renal anemia. That same year, the ESKD Quality Incentive Payment was implemented to improve quality of care by applying a penalty for poor management of dialysis patients, including the overuse of ESAs. The three policy changes resulted in a shift in transfusions from an outpatient to an inpatient setting. However, there are few data available on the effect of the changes on care and outcomes in an inpatient setting.

According to **Nga TQ Nguyen** and colleagues at the Centre for Public Health School of Medicine, Dentistry, and Biomedical Sciences, Queens University Belfast, Belfast, UK, race/ethnicity adds a layer of complexity to the potential impact of the policy changes. The researchers conducted a study aimed at examining the impact of PPS on the likelihood of an inpatient episode for ESRD being recorded with anemia following the adoption of PPS as well as its effect on hospital costs, inpatient mortality, and discharge destination. The second outcome of interest was the impact of PPS on ethnic disparities with a particular focus on the experience of Native Americans. Results of the study were reported online in *BMC Nephrology* [doi.org/10.1186/s12882-020-02081-4].



The researchers utilized data from the National Inpatient Sample–Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. All admissions with a primary diagnosis of ESKD and a procedure/diagnosis code referring to any type of renal replacement therapy were identified using *International Classification of Diseases (ICD) Ninth and Tenth Revision* codes. Episodes with a code indicating acute kidney injury were excluded. From the resulting cohort, episodes that involved anemia due to CKD were identified using ICD codes.

Over a 9-year period (2008-2016), there were 591,683 admissions with ESRD. Of those, the proportions of episodes of care related to White, Native, Black, Asian, and Hispanic Americans were 39.8%, 0.95%, 36.6%, 3.4%, and 16.4%, respectively. In 2008, the percentage of inpatient episodes with recorded anemia arising from CKD was 26.2%; in 2016, the percentage was 50.0%.

At admission, mean age ranged from 57.0 years among Black Americans to 64.8 years among Asian Americans. The predominant insurance was Medicare; only a small percentage in each racial group had private insurance (the smallest percentage was among Native Americans, 7.1%).

Black Americans had the highest percentage of patients receiving hemodialysis as RRT modality (92.8%), followed by Native Americans (92.5%). Diabetes was most prevalent in admissions who were Native American; 42.7% had diabetes with complications and 29.2% had diabetes without complications. Approximately 42.3% of episodes among Native Americans with ESKD and 37.8% of those among White Americans with ESKD had anemia recorded as a diagnosis.

In the fully adjusted model, compared with White Americans, the odds of anemia were highest for Native Americans (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.15-1.25) and Asian Americans (OR, 1.20; 95% CI, 1.17-1.22), followed by Hispanic Americans (OR, 1.12; 95% CI, 1.10-1.13) and Black Americans (OR, 1.04; 95% CI, 1.03-1.05). The risk of anemia was higher in patients with iron deficiency, diabetes with complications, lower age-adjusted Charlson comorbidity index score, age ≤50 years or ≥80 years compared with other groups.

Over the 9-year study period, all ethnicities have a higher likelihood of a diagnosis of anemia compared with White American admissions. In 2011, there was a sharp increase in the likelihood of anemia for all ethnicities, followed by a steady increment in subsequent years.

Results from the fully adjusted regression model of the impact of PPS on recorded anemia found that the odds ratio of recorded anemia after PPS was 1.42 (95% CI, 1.40-1.44) compared with the preceding period. Following PPS, the odds of inpatient mortality for admissions with anemia compared to admissions without anemia increased; the odds ratio for admissions with anemia dying in the hospital rose from 0.61 (95% CI, 0.56-0.67) to 0.72 (95% CI, 0.68-0.76) between 2008 and 2010 and 2011-2016. The likelihood of discharge to another healthcare facility increased, and costs per inpatient episode fell during the same periods. Minorities, including Native American admissions, were less likely to die in the hospital, less likely to be discharged to another healthcare facility, and, with the exception of Black American admissions, were more expensive to treat.

The researchers cited some limitations to the study findings, including the significant increase in the number of individuals in the United States identified as mixed race, the use of *ICD* codes to identify health status, outpatient data not collected on the same annual basis as inpatient data, and the cross-sectional nature of the data based on each single hospitalization limiting the ability to examine patterns related to factors such as readmissions.

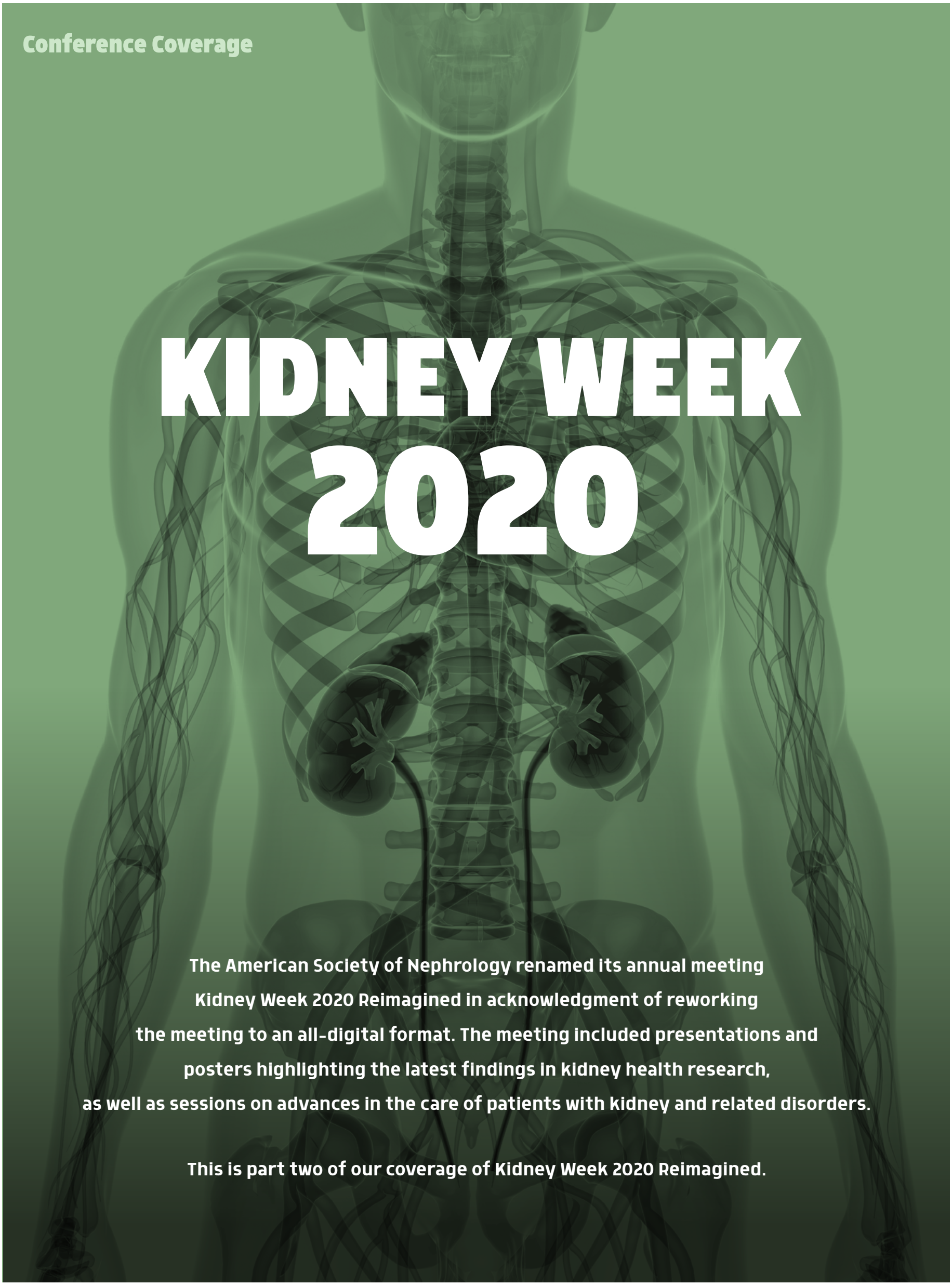
In conclusion, the researchers said, "We found a significant increase in anemia recorded as a complication among ESKD hospitalizations in the US following the adoption of PPS. We found ethnic disparities in the recorded anemia as a complication among ESKD admissions, a gap that was most evident among Native American admissions and that widened for all racial/ethnic groups following the introduction of the PPS. The study demonstrated the potential unintended consequence of measures targeting behavior in one part of the healthcare system to have a material impact on other parts in terms of both equity and efficiency." ■

TAKEAWAY POINTS

- A series of policy changes in 2011 changed reimbursement arrangements and guidance on the use of erythropoiesis-stimulating agents for the treatment of patients with end-stage renal disease with anemia.
- Researchers conducted a study to examine trends in anemia in ESRD hospitalization and to analyze disparities in inpatient outcomes among ethnic groups following the changes.
- Following the changes, there was an increase in anemia recorded as a complication among ESRD admissions. The study also demonstrated the existence of ethnic disparities that widened following the policy changes.

Print-only Content

KIDNEY WEEK 2020



The American Society of Nephrology renamed its annual meeting Kidney Week 2020 Reimagined in acknowledgment of reworking the meeting to an all-digital format. The meeting included presentations and posters highlighting the latest findings in kidney health research, as well as sessions on advances in the care of patients with kidney and related disorders.

This is part two of our coverage of Kidney Week 2020 Reimagined.

Incidence of AKI in Patients Hospitalized with COVID-19

An estimated 8% to 18% of hospitalized patients develop acute kidney injury (AKI). Hospitalized patients who develop AKI are at increased risk for mortality; however, it is unknown whether there is an association between AKI and increased risk for mortality in patient hospitalized with coronavirus disease 2019 (COVID-19). **Panupong Hansrivijit, MD,** and colleagues conducted a study designed to examine the incidence of AKI and its association with mortality in COVID-19 patients.

The study utilized a systematic literature review and meta-analysis. Results were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Incidence of AKI and Its Association with Mortality in Coronavirus Disease 2019 (COVID-19) Patients: A Meta-Analysis*.

The search included Ovid MEDLINE, EMBASE, and the Cochrane Library for eligible publications (without language restriction) that reported the clinical characteristics of patients with confirmed COVID-19. Eligible studies reported the incidence of AKI and mortality. Due to the emerging nature of the COVID-19 pandemic, there were a large number of studies published in a short time period. To avoid studies with duplicated patient populations, valid Institutional Review Board number or approval by the National Health Commission of the study's country was screened.

From 26 eligible studies, representing 5497 patients, the pooled incidence of AKI in patients with COVID-19 was 8.4% (95% confidence interval [CI], 6.0%-11.7%), with a pooled incidence of renal replacement therapy of 3.6% (95% CI, 1.8%-7.1%).

The incidence of AKI was higher in critically ill patients (19.9%) compared with non-critical hospitalized patients (7.3%). Mortality was higher among critically ill patients with COVID-19 than in non-critically ill hospitalized patients with COVID-19 (33% vs 16.1%). The pooled estimated unadjusted odds ratio for mortality from AKI was 13.33 (95% CI, 4.05-43.91).

In meta-regression analysis, there was a positive association between the incidence of AKI and mortality in an adjusted model (Q 26.18; P=.02). Further, the adjusted model also demonstrated positive associations between age (P<.01), diabetes (P=.02), hypertension (P<.01), and baseline serum creatinine levels (P=.004) and the incidence of AKI.

In summary, the researchers said, "AKI is present in 8.3% of overall COVID-19 patients and in 19.9% of critically ill COVID-19 patients. Presence of AKI is associated with 13-fold increased risk of mortality. Age, diabetes, hypertension, and baseline serum creatinine levels are associated with increased AKI incidence. More studies, including the ones from multinational databases, are encouraged to confirm our findings."

Source: Hansrivijit P, Boonpheng B, Thongprayoon C, Cheungpasitporn W, Ghahramani N. Incidence of AKI and its association with mortality in coronavirus disease 2019 (COVID-19) patients: A meta-analysis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00664), October, 22, 2020.

Anemia Associated with Low Muscle Mass and Strength in Transplant Recipients

Kidney transplant recipients often develop anemia, a complication that has a negative impact on quality of life, particularly on physical functioning. There are few data available regarding decreased physical functioning among kidney transplant recipients. **Joanna Sophia J. Vinke** and colleagues at the University Medical Center Groningen, Netherlands, conducted a prospective study designed to examine the association between anemia and muscle mass and muscle strength in kidney transplant recipients.

The researchers reported results of the study during a virtual poster session at ASN Kidney Week 2020. The poster was titled *Anemia and Decreased Muscle Mass and Muscle Strength in Kidney Transplant Recipients*.

The analysis included kidney transplant recipients in the TransplantLines Biobank and Cohort Study. Eligible participants were those who were 1 year post-transplant and had data on hemoglobin (Hb) levels and muscle mass.

Muscle mass was assessed two ways: (1) using 24-hour urinary creatinine excretion and (2) using bioelectrical impedance analysis (BIA). Muscle strength was measured via hand grip strength using a dynamometer. Mean overall hand grip strength was calculated from three attempts of both hands for 30 seconds recovery time in between each attempt. The researchers defined anemia as Hb <12 g/dL for women and <13 g/dL for men, according to World Health Organization definitions. Associations between anemia and muscle mass and strength were examined using multivariable linear regression analyses.

The cohort included 824 kidney transplant recipients. Median age was 56 years, 60% were male, median estimated glomerular filtration rate (eGFR) was 52 min/1.73/m^2, and median serum Hb was 13.5 g/dL. Thirty percent of the cohort had anemia.

There was an association between HB level and creatinine excretion, independent of age, sex, eGFR, body mass index, high-sensitivity C-reactive protein, smoking status, alcohol use, and use of renin-angiotensin-aldosterone system inhibitors, statins, calcineurin inhibitors, proliferation inhibitors, or prednisolone (P=.001). There was also an independent association between the presence of anemia and lower creatinine excretion (P=.021).

There was an independent association between Hb levels and muscle mass, estimated using BIA resistance measurements (P<.001). Hb and anemia were both associated with handgrip strength, independent of potential confounders (P<.001 and P=.005, respectively).

In conclusion, the researchers said, "Low hemoglobin levels and anemia are strongly associated with lower muscle mass and muscle strength in kidney transplant recipients, likely impairing physical functioning. Future research is needed to address whether correction of anemia improves physical performance in kidney transplant recipients."

Source: Vinke JSJ, Wouters HJ, Post A, et al. Anemia and decreased muscle mass and muscle strength in kidney transplant recipients. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P02502), October 22, 2020.

Treatment of Anemia Due to Chronic Kidney Disease

The prevalence of chronic kidney disease (CKD) is greater in individuals ≥65 years of age compared with those 45 to 64 years of age and those 18 to 44 years of age (38% vs 13% vs 7%, respectively). Anemia is a common sequela of CKD patients, affecting 8% to 53%; anemia is more common as CKD progresses.

Patients with anemia associated with CKD are at increased risk for emergency department visits and hospital admissions. **Jill Davis** and colleagues conducted a retrospective cohort study to examine patient characteristics, treatment rates, and time to treatment among Medicare Advantage Prescription Drug Plan (MAPD) non-dialysis-dependent (NDD) patients with CKD stage 3-5 and severe anemia. Results of the study were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Understanding Treatment of Severe Anemia Due to CKD: A Descriptive Study in Non-Dialysis Medicare Advantage Prescription Drug Plan Patients*.

Severe anemia was defined as laboratory measurement of hemoglobin <10 g/L. Humana claims data (medical, pharmacy, laboratory) from 2016 to 2019 were used in the analysis. The index date was the first diagnosis of anemia following diagnosis of CKD. CKD stage and dialysis independent status were classified in the 12 months pre-index. At 12 months post-index, treatments (intravenous [IV)] iron, oral iron, erythropoiesis-stimulating agents [ESA], red blood cell transfusions [RBCT]), and all-cause healthcare resource use were examined.

The study identified 31,026 NDD-CKD patients with anemia. Of those patients, mean age was 75 years, 60% were female, and overall 36% had an anemia treatment. As CKD progressed, the percentages of treated patients increased (32%, 39%, and 50% in stage 3, 4, and 5, respectively). The use of ESA increased as CKD progressed (7%, 17%, and 34% in stage 3, 4, and 5, respectively), as did use of IV iron (11%, 15%, and 21%). Rates of RBCT and oral iron use were consistent across all stages of CKD.

The median number of days from diagnosis of anemia to first anemia treatment was 48 days. As CKD progressed, all-cause healthcare resource use increased. In the 12-months post-index period, inpatient admissions in stage 3, 4, and 5, respectively were 46%, 53%, and 59%. ED visits were 64%, 70%, and 72% in the same period.

In conclusion, the researchers said, "This descriptive examination of treatment by CKD stage for NDD patients with anemia found that anemia was oftentimes left untreated, especially in the stage 3-4 CKD patients. After NDD-CKD patients were diagnosed with anemia, it was almost 1.5 months before treatment was initiated. In NDD-CKD patients with anemia, as stage increased, healthcare resource use increased, highlighting the importance of care coordination as CKD progresses."

Source: Davis J, Suehs, Xu Y, et al. Understanding treatment of severe anemia due to CKD: A descriptive study in non-dialysis Medicare Advantage Prescription Drug Plan patients. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00273), October 22, 2020. Funding for this poster was provided by AstraZeneca.

Double-Dose plus Booster of Influenza Vaccine in Patients on Hemodialysis

Patients with end-stage kidney disease receiving maintenance hemodialysis may be at increased risk of illness and death from influenza. There are few data available on the efficacy of increased dose of influenza vaccine among dialysis patients. **Ekapol Ritveeradej** and colleagues in Bangkok, Thailand, conducted a prospective, open-label, randomized study to examine the efficacy of double-dose and booster influenza vaccines compared with standard-dose vaccine in patients on hemodialysis.

The researchers reported results of the study during a virtual poster session at ASN Kidney Week 2020. The poster was titled *Efficacy of Double-Dose Influenza Vaccine with a Booster Compared with Standard Dose in Hemodialysis Patients: Randomized Controlled Trial.*

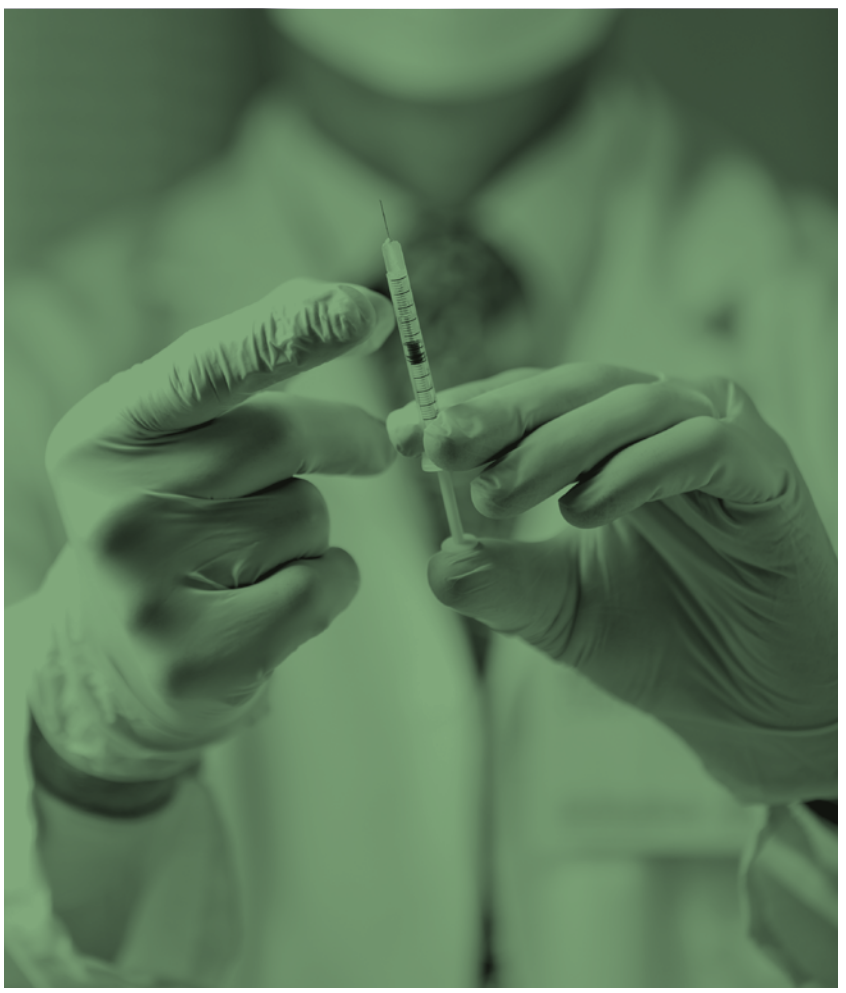
The study enrolled 100 hemodialysis patients who were randomized to receive double-dose and a booster of intramuscular inactivated seasonal quadrivalent influenza vaccine and a booster in the following 2 weeks (double-dose group, n=50) or one dose of the vaccine (standard-dose group, n=50). Demographics and comorbidity data were collected at baseline. Hemagglutination inhibition (HAI) titers were assessed prior to vaccination and at 14 and 28 days post-vaccination.

The two groups were similar in baseline laboratory measurements and comorbidities. Mean age was 61 years. The double-dose group had a higher rate of seroprotection than the standard group (100% vs 86%; *P*=.006) and seroconversion (84% vs 60%, *P*=.008) measured using HAI against H3N2. Further, those in the double-dose group had higher rates of sustained antibody level at 4 weeks after the initial vaccination compared with the standard-dose group, measured by HAI against H1N1 (88% vs 52%, *P*=.006) and against H3N2 (84% vs 72%, *P*=.003).

There were no differences in HAI against B strains. At 4 weeks after the initial vaccination, HAI against H1N1, H3N2, B/Colorado, and B/Yamagata were similar in the two groups.

In conclusion, the researchers said, "The double dose with booster influenza vaccine can provide higher seroprotection and seroconversion rates of HAI against H3N2 but no difference in other strains compared with standard dose."

Source: Ritveeradej E, Boonnak K, Yoowannakul S. Efficacy of double-dose influenza vaccine with a booster compared with standard dose in hemodialysis patients: Randomized controlled trial. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P01067), October 22, 2020.



Those in the higher dose group had higher rates of sustained antibody level at 4 weeks after the initial vaccination compared with the standard-dose group, measured by hemagglutination inhibition against H1N1 (885 vs 52%; *P*=.006) and against H3N2 (84% vs 72%; *P*=.003).

Hypokalemia Risk in Dialysis Patients with Hyperkalemia

Patients with combined predialysis and postdialysis hypokalemia are at increased risk for mortality. Results of the phase 3 DIALIZE study (NCT03303521) demonstrated that sodium zirconium cyclosilicate (SZC) reduces predialysis serum potassium and is well tolerated in patients on hemodialysis with hyperkalemia. **Steven Fishbane, MD**, and colleagues conducted a post hoc safety analysis of DIALIZE data to assess hypokalemia events in both the SZC arm and the placebo arm of DIALIZE.

Results of the post hoc analysis were reported during a virtual poster session at ASN Kidney Week 2020. The poster was titled *Risk of Hypokalemia in Hyperkalemia Hemodialysis Patients.*

A total of 191 patients were randomized blindly in a 1:1 ratio to receive placebo (n=99) or SZC (n=97) 5 g starting dose once daily on nondialysis days, 4 days per week for 8 weeks. The 8-week period comprised a 4-week SZC or placebo dose-titration phase (max 15 g) to achieve target predialysis serum potassium level 4.0-5.0 mmol/L and a 4-week stable-dose evaluation phase.

In the current analysis, the proportions of patients with hypokalemia, defined as serum potassium level <3.5 mmol/L, predialysis, postdialysis, and combined predialysis and postdialysis at the same visit were tabulated by visits. Patients' current predialysis serum potassium stratified by postdialysis serum potassium (≥3.5 vs <3/5 mmol/L) at the previous visit was also assessed.

The frequency of predialysis hypokalemia was similar between the two groups: five patients in the SZC arm accounted for seven events and five patients in the placebo arm accounted for five events. The proportion of patients with postdialysis hypokalemia at each visit was greater in the SZC group than in the placebo group. Predialysis serum potassium returned to ≥3.5 mmol/L at the next visit for all but two SZC patients with postdialysis hypokalemia. One patient in each arm had combined predialysis and postdialysis hypokalemia.

In conclusion, the researchers said, "Despite the efficacy of SZC in lowering predialysis serum potassium, SZC was not associated with a clinically significant increase in the frequency of predialysis hypokalemia. Treatment with SZC versus placebo did not increase the frequency of combined predialysis and postdialysis hypokalemia which is associated with increased mortality risk."

Source: Fishbane S, Ford ML, Fukagawa M. et al. Risk of hypokalemia in hyperkalemic hemodialysis patients. Abstract of a poster at the American Society of Nephrology virtual Kidney Week 2020 (P01051), October 22, 2020. Funding for this poster was provided by AstraZeneca.

Limited Physical Function among Patients with CKD and Metabolic Acidosis

The loss of physical function in patients with chronic kidney disease (CKD) is due, in part, to the development of sarcopenia associated with metabolic acidosis. Decline in the ability to rise from a seated position is one measure of the risk of loss of independence among patients with CKD. However, according to **Vandana S. Mathur, MD, FASN,** and colleagues, physical performance is not part of a routine office visit in CKD clinical practice.

The Kidney Disease and Quality of Life Physical Function Domain (KDQOL-PFD) is a 10-item survey in which responses include "not limited at all," "limited a little," and "limited a lot." Dr. Mathur and colleagues conducted a study to evaluate the correlation between patient-reported limitation on daily activities on the KDQOL-PFD and the standardized 5-times repeat chair stand time (RCS) test. The researchers used data from a 1-year randomized trial of patients with metabolic acidosis in CKD.

Results of the current analysis were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Correlation Between Patient-Reported Physical Limitation and Objective Physical Performance on the Repeated Chair Stand Time Test among Patients with Non-Dialysis Dependent CKD and Metabolic Acidosis.*

There was a significant, direct correlation between improvement (higher score) over 1 year on the KDQOL-PFD total score and improvement on the RCS (faster time) (Pearson's product-movement correlation, 0.33; $P<.001$) In addition, there was significant correlation between five of the 10 individual KDQOL-PFD activity limitations and RCS time: (1) lifting or carrying groceries; (2) bending, kneeling, or stooping; (3) walking one block; (4) walking several blocks; and (5) bathing or dressing yourself (P for correlation for all questions, <.050).

In a linear model, there was an association of each category of decline in the KDQOL-PFD for the individual questions and significant deterioration of RCS time in the range of 3.29 to 3.80 seconds, exceeding the minimally clinically important difference of 1.7 seconds.

In conclusion, the researchers said, "Our findings suggest that asking patients if they are limited in their ability to do daily activities such as walking one block or lifting or carrying groceries may be a practical way to screen for significant physical performance declines known to have important health, social, and economic consequences. Routine identification of patients with physical functional decline might allow for earlier implementation of interventions to forestall further impairment."

Source: Mathur VS, Walker M, Klaerner. Correlation between patient-reported physical limitation and objective physical performance on the repeated chair stand test among patients with non-dialysis dependent CKD and metabolic acidosis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (PO1687), October 22, 2020. Funding for this poster was provided by Tricida, Inc.

Warfarin and Risk of Vascular Calcification in Dialysis Patients

Patients receiving maintenance hemodialysis commonly experience vascular calcifications, a recognized risk factor for increased mortality risk. Results of previous studies have demonstrated the association between warfarin, frequently prescribed among dialysis patients, and vascular calcifications. **Eren Sadioglu, MD,** and colleagues recently conducted a study to examine the association between vascular calcification and use of warfarin in patients on hemodialysis.

Results of the cross-sectional, observational, multicenter study were reported during a virtual poster session at ASN Kidney Week 2020. The poster was titled *Warfarin Increased the Risk of Vascular Calcification in Hemodialysis Patients: A Multicenter Case-Control Study.*

Vascular calcification was assessed using the Adragao calcification score (AS; pelvis and hands) and Kauppila score (KS; lateral lumbar spine) in 76 hemodialysis in patients from six centers. Of a total of 711 hemodialysis patients, 32 (4.5%) were being treated with warfarin for at least 1 year; the study also included 44 control patients with matching parameters of age, sex, and dialysis vintage. Clinical characteristics, concomitant treatments, and laboratory results were recorded; the study was designed to analyze possible risk factors related to vascular calcification.

Of the total cohort, 47% were female, mean age was 65.8 years, 23% had diabetes, mean dialysis vintage was 68.39 months, and mean Kt/V was 1.66. There were no significant differences between the warfarin group and the control group in clinical characteristics and basic laboratory results.

Median Kauppila score was higher in the warfarin group than in the control group (11 vs 6.5 [%25, %75 percentile, 5 vs 15]; $P=.032$). Percentages of Kauppila score >6 patients were also higher (76.6% vs 50%; $P=.029$). There were no significant differences in median Adragao score between the two groups (7 vs 6 [%25, %75 percentile 6 vs 8]; $P=.177$).

Results of logistic regression analysis demonstrated an independent association between warfarin treatment and Kauppila scores of >6 (odds ratio, 3.28; 95% confidence interval, 1.17-9.22; $P=.024$).

"The results of this study showed that warfarin is a strong risk factor for vascular calcifications, especially in aorta of hemodialysis patients," the researchers said.

Source: Sadioglu E, Ustuner E, Ergun I, Ecder T, Nergizoglu, Keven K. Warfarin increases the risk of vascular calcification in haemodialysis patients: A multicenter case-control study. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (PO1035), October 22, 2020.

ADPKD Patients Experience Broad and Variable Trial Outcomes

The most common cause of genetic kidney disease is the potentially life-threatening autosomal dominant polycystic kidney disease (ADPKD). The course of ADPKD is progressive, leading to kidney failure and the need for dialysis or kidney transplantation. Approximately 70% of patients with ADPKD require renal replacement therapy (RRT) by age 65. The psychosocial well-being and lifestyle of patients with ADPKD and related complications that include cardiovascular, hepatic, digestive, and neurologic disease, as well as symptoms that include pain, are severely impaired.

During the past two decades, there has been an increase in the number of randomized trials in patients with ADPKD. The choice of outcomes of trials in that patient population is challenging due to the lengthy natural history of the disease. Trials in the ADPKD population have often focused on surrogate outcomes such as kidney volume and function. Detailed empirical evidence of outcome reporting in trials is not available in the context of ADPKD. **Bénédicte Sautenet, PhD,** and colleagues and members of the SONG-PKD (Standardized Outcomes in Nephrology—Polycystic Kidney Disease) Initiative, conducted a systematic review to assess the range and variability of outcome domains and measures reported in trials of ADPKD. Results of the review were reported in the *American Journal of Kidney Diseases* [2020;76(2):213-223].

The researchers searched MEDLINE, EMBASE, the Cochrane Kidney and Transplant Specialized Register, Australian and New Zealand Clinical Trials Registry, the European clinical trials register, and ClinicalTrials.gov to identify all randomized controlled trials in patients with ADPKD up to October 1, 2019. For trials that included patients without ADPKD, only trials with at least 50% of patients with ADPKD were eligible to be included in the analysis.

Nine trial characteristics were extracted for each eligible trial: first author, year of publication, participating countries, sample size, mean age of participants, study duration, intervention type, primary outcome, and all discrete outcome measures. A discrete outcome measure was defined as any measurement or event reported separately for all trial arms.

A total of 68 trials involving 10,750 participants were identified. Of those, 36 (53%) were published, one (1%) was a protocol, and 31 (46%) were unpublished registered trials. The publication/registration year ranged from 2001 to 2019. Median duration of the trials was 18 months, and median sample size was 50 participants. Of the 68 trials, 86% (n=59) investigated a pharmacologic intervention, 5% (n=3) evaluated a surgical intervention, and 9% (n=6) examined a dietary intervention.

A total of 1413 outcomes were reported across the 68 trials. The median number of outcome measures (a different measurement, aggregation, metric, and time point) was 11 per trial. Exclusive of time points, the median number of outcome measures was seven per trial. The analysis classified

continued on page 16

The Liver Meeting

Terlipressin in Patients with HRS-AKI

Hepatorenal syndrome (HRS) is a type of functional acute kidney injury (AKI) resulting from portal hypertension leading to decreased effective circulating arterial volume and renal vasoconstriction. The European Association of the Study of Liver Diseases recommends the use of terlipressin as a first-line vasopressor to treat patients with HRS-AKI.

Kevin Moore, PhD, MBBS, FRCO, BSc, and colleagues recently performed a post hoc analysis of a retrospective chart review study that was conducted in 26 hospitals in the United Kingdom. The study included 250 adult patients hospitalized with a diagnosis of HRS-AKI between January 1, 2013, and December 31, 2017. Results of the analysis were reported during a virtual poster session at The Liver Meeting, the annual meeting of the American Association for the Study of Liver Diseases in a poster titled *Predictors of Response to Terlipressin in Patients with Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI): A Multicenter Study.*

Outcomes of interest were clinical response at end of treatment. Complete response was defined as serum creatinine ≤1.5 mg/dL; partial response was defined as a reduction in serum creatinine of ≥20% but serum creatinine level >1.5 mg/dL. Mortality was also an outcome of interest.

In the subset of patients who received terlipressin (n=203), backwards-selected logistic regression and Cox proportional hazards models were used to evaluate predictors of response (complete and partial) and mortality, respectively. Evaluated predictors were age, severity of AKI at baseline (mild, serum creatinine <2.25 mg/dL; moderate, serum creatinine ≥2.25 mg/dL and <3.5 mg/dL; and severe, serum creatinine ≥3.5 mg/dL), presence of a precipitating event, concomitant use of albumin, presence of encephalopathy, and infection during the HRS-AKI hospitalization.

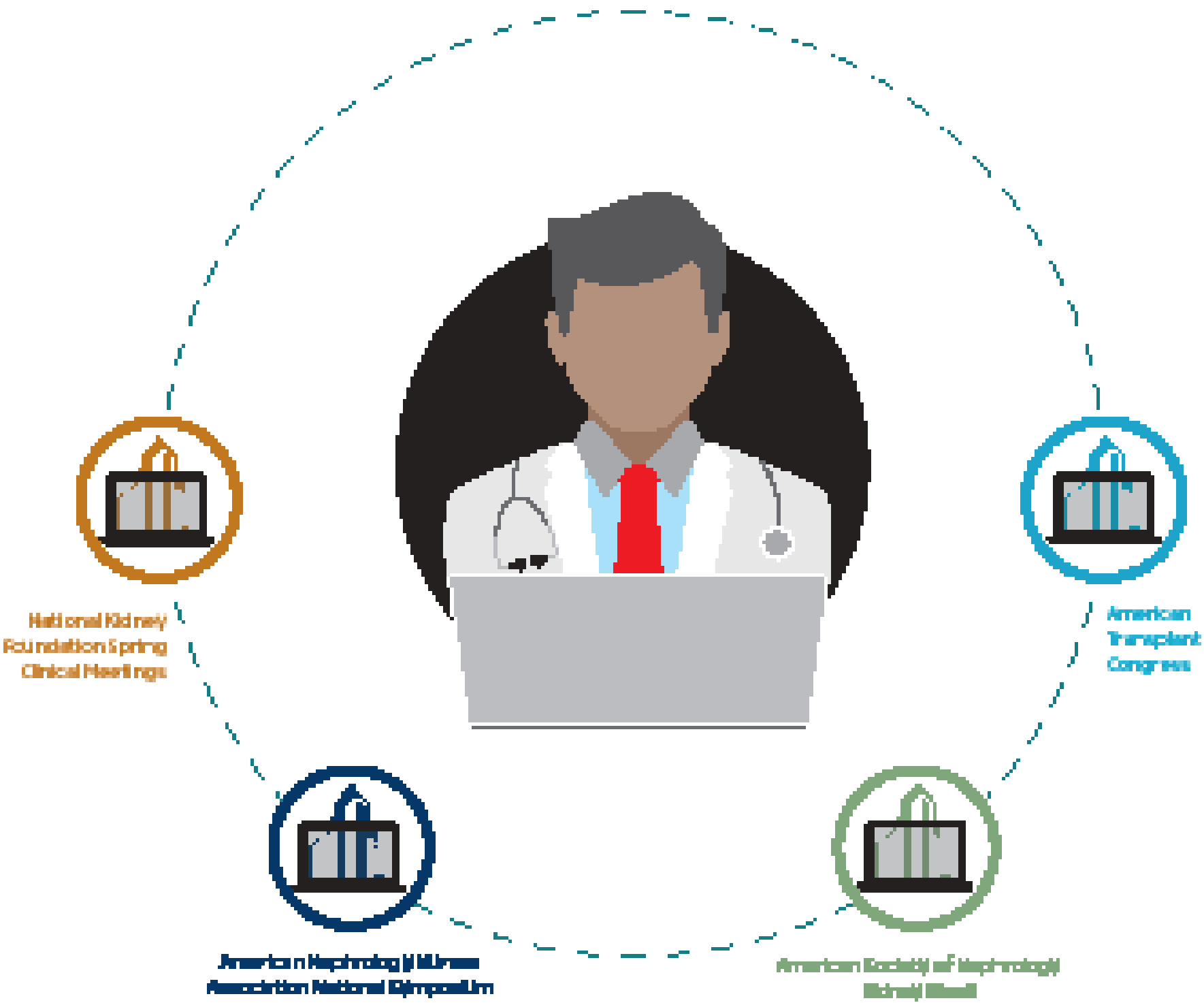
Mean age of the 203 terlipressin patients was 53.9 years. The patients were evenly distributed by baseline AKI severity (mild, 33%; moderate, 36%; severe, 31%). Eighty-four percent of the cohort had more than one precipitating event, 33% had comorbid encephalopathy, and 49% had infection during the HRS-AKI hospitalization. Concomitant albumin was administered to 72% of patients.

The overall response rate was 73% (mild AKI, response rate 79%; moderate AKI, response rate 78%; and severe AKI, response rate 60%). In the logistic regression model, absence of a precipitating event (odds ratio [OR], 0.288; 95% confidence interval [CI], 0.10-0.87; *P*=.027), concomitant use of albumin (OR, 2.717; 95% CI, 1.29-5.70; *P*=.008), and mild baseline AKI (OR, 2.481 [ref, severe]; 95% CI, 1.11-5.44; *P*=.026) or moderate baseline AKI (OR, 2.288; 95% CI, 1.06-4.95; *P*=.036) were identified as significant predictors of overall response. The only significant predictor of mortality was the presence of encephalopathy (hazard ratio, 2.77; 95% CI, 1.56-4.92).

In conclusion, the researchers said, "The results of this study highlight the importance of albumin use and timely treatment with terlipressin when serum creatinine is mildly or moderately elevated in patients with HRS-AKI to optimize patient outcomes."

Source: Moore K, Jamil K, Verleger K, et al. Predictors of response to terlipressin in patients with hepatorenal syndrome-acute kidney injury (HRS-AKI): A multicenter study. Abstract of a virtual poster at The Liver Meeting, the annual meeting of the American Association for the Study of Liver Diseases (Poster 1831), November 13-16, 2020. This poster was supported by Mallinckrodt Pharmaceuticals.

Whether in person or virtual, we have you covered.



Nephrology Times goes to meetings!

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Nephrology Times

continued from page 14

the 1413 outcome measures into 97 outcome domains: 42% (n=41) were surrogate; 31% (n=30) were clinical; and 27% (n=26) were patient-reported outcomes.

The top six most frequently reported outcomes were: (1) kidney function, n=54, 79% of trials; (2) kidney and cyst volumes, n=43, 63% of trials; (3) blood pressure, n=27, 42% of trials; (4) proteinuria and albuminuria, n=22, 32% of trials; (5) unspecified adverse events, n=20, 29% of trials; and (6) pain (kidney, abdominal, and epigastric), n=16, 24% of trials. In <20% of trials, 90 outcome domains were reported. Mortality and kidney failure requiring RRT were reported in 9% (n=6) and 12% (n=8) of the trials, respectively.

Of the 41 surrogate outcomes, the three most frequent were kidney function (n=54; 79% of trials), which had 46 outcome measures (131 when timepoints were included); kidney and cyst volume (n=43; 63% of trials), which had 52 outcome measures (88 when timepoints were included); and blood pressure (n=28; 41% of trials), which had 30 outcome measures (65 when time points were included).

Of the clinical outcomes, the three most frequently reported were infection (n=10; 15% of trials), which had 21 measures (33 including time points); cardiovascular event (n=9; 13% of trials), which had six different outcome measures (14 including different time points); and end-stage kidney disease (n=8; 12% of trials), which had five (17 including time points) outcome measures.

Of the 26 patient-reported outcomes, the three most frequently reported were pain (kidney, abdominal, and epigastric; n=16; 24% of trials), which had 26 outcome measures (42 including time points); pain (other; n=11; 16% of trials), which had 11 (18 including time points) outcome measures; and diarrhea/constipation/gas/bloating (n=10; 15% of trials), which had nine (16 including time points) outcome measures.

Of the 68 total trials, 56 specified a primary outcome; of those, 47 specified a single primary outcome, and nine specified multiple primary outcomes. In 45 of the 47 studies specifying a single primary outcome, the majority of the reported outcomes were surrogate, compared with one with a clinical primary outcome and one with a patient-reported primary outcome. The two most frequently reported single primary outcomes were kidney and cyst volumes (n=17) and kidney function (n=13).

The researchers cited some limitations to the analysis results, including only assessing outcomes measures in the top three domains in each category, excluding non-English trials, and not analyzing all the reported measures.

In conclusion, the authors said, "The outcomes reported in ADPKD trials are varied, heterogeneous, and focused on surrogate outcomes related to progression to kidney failure requiring kidney replacement therapy (KRT). Clinical and patient-reported outcomes such as KRT requirement and pain are seldom reported. The development of a core outcome set for ADPKD will improve outcome reporting, which will be of relevance and importance to all stakeholders in clinical trials and ultimately will strengthen trial-based evidence to inform decision making in ADPKD based on the outcomes that matter to patients, caregivers, and health professionals." ■

TAKEAWAY POINTS

- Researchers conducted a systematic review of randomized controlled trials among patients with autosomal dominant polycystic kidney disease (ADPKD) to assess the range and variability of reported outcomes.
- The outcomes in ADPKD trials were both broad and highly variable.
- The three top outcome domains were surrogate, clinical, and patient-reported outcomes. Surrogate outcomes were the most widely reported.

The Liver Meeting

Practice Patterns and Outcomes in Patients with HRS and AKI

As per a 2019 presidential executive order, advancing kidney health in the United States has been identified as a key public health priority. Patients with liver disease may develop hepatorenal syndrome (HRS), a life-threatening complication. In 2007, the International Club of Ascites classified HRS; since then, new definitions and diagnostic criteria have been proposed. It is a challenge to identify a diagnosis of HRS from a large database, limiting the ability to understand national practice patterns and outcomes.

In a virtual poster presented at The Liver Meeting, **Andrew Allegretti, MD, MSc,** and colleagues described two approaches to capturing HRS and/or acute kidney injury (AKI) from a large inpatient database. The poster was titled *Hepatorenal Syndrome and Acute Kidney Injury in Patients with Liver Disease: National Practice Patterns and Outcomes from a Large US Database.*

The researchers used the Premier Healthcare Database to identify patients hospitalized between January 1, 2107, and December 31, 2018, with an *International Classification of Diseases* diagnosis of HRS (HRS cohort) or AKI and liver cirrhosis (AKI cohort). The database included data from more than 1000 contributing hospitals. Patients with HRS and acute tubular necrosis were excluded from the AKI cohort and patients with total hospital length of stay <2 days were excluded from both cohorts.

The study evaluated patient demographics, clinical characteristics, treatments, and outcomes in the HRS cohort (n=13,061) and the AKI cohort (n=41,884). In the HRS and AKI cohorts, mean age was 60 years versus 65 years, 60.6% versus 57.5% were male, and 75.4% versus 76.0% were White, respectively. In each cohort, more than 90% of patients were admitted to the hospital via emergency or urgent care.

Of note, 90.2% of patients in the HRS cohort also had a diagnosis of AKI; midodrine and octreotide were administered in 36.2% of the patients in the HRS cohort. In comparisons of the HRS cohort to the AKI cohort, in-hospital mortality rates were 26.4% versus 9.1%, respectively. In the HRS cohort, the rate of discharge to hospice care was 19.0% and the rate of discharge to home or self-care was 21.4%. The rates of discharge to hospice or home/self-care in the AKI cohort were 6.9% and 39.2%, respectively. The average hospital length of stay was 10.9 days in the HRS cohort and 8.1 days in the AKI cohort.

In conclusion, the researchers said, "This study reports the real-world patient profile and outcomes of patients hospitalized with HRS and AKI. Descriptive data on HRS and AKI in patients with liver disease from a large database may help advance kidney health, consonant with a recent executive order. Further work to identify healthcare resource utilization and costs in this population is forthcoming."

Source: Allegretti A, Boing E, Ahn S-W, et al. Hepatorenal syndrome and acute kidney injury in patients with liver disease: National practice patterns and outcomes from a large US database. Abstract of a virtual poster at The Liver Meeting, the annual meeting of the American Association for the Study of Liver Diseases (Poster 650), November 13-16, 2020. Support for this poster was provided by Mallinckrodt Pharmaceuticals.

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ABO-Incompatible Living Donor Kidney Transplantation and Patient Survival

As one method of accommodating the increasing shortage of organs available for transplant, blood group ABO-incompatible (ABOi) living donor kidney transplantations have been increasing. However, ABOi transplant recipients are at approximately 2-fold higher risk of antibody-mediated rejection than ABO-compatible (ABOc) transplant recipients.

Among ABOi transplant recipients, the risks of developing other post-operative complications are also higher than among ABOc transplant recipients, including a 2.1-fold higher risk of pneumonia, a 3.5-fold higher risk of a wound infection, a 1.5-fold increase in urinary tract infection/pyelonephritis, and a 1.8-fold higher risk of post-operative hemorrhage. ABO incompatibility also adds $32,000 to the cost of living donor kidney transplantation over the costs of blood group-compatible transplantation.

Data regarding differences in graft survival between the two groups are inconsistent, according to **Allan B. Massie, PhD, MHS,** and colleagues. Some previous single-center studies have reported comparable graft survival between ABOi and ABOc kidney transplant recipients. ABOi experiences in the United States, Europe, Japan, and Korea have also demonstrated the feasibility of obtaining equivalent graft-survival outcomes. However, a retrospective study of US patients in the Scientific Registry of Transplant Recipients (SRTR) reported higher risk for graft loss within the 2 weeks following transplant in recipients in the ABOi patient population. The 2-week post-operative period is associated with a 2.3-fold higher risk for graft loss in the ABOi group.

Transplantation programs are graded by the SRTR and the Centers for Medicare & Medicaid Services for 1-year patient and graft survival; however, performance grading does not adjust for ABO incompatibility. Dr. Massie and colleagues recently conducted a retrospective cohort study designed to assess the difference in patient survival between ABOi living donor kidney transplantation and waiting for an ABOc living donor kidney transplant or undergoing an ABOc deceased donor kidney transplant. Results were reported in the *American Journal of Kidney Diseases* [2020;76(5):616-623].

The study participants were 808 ABOi living donor kidney transplant recipients who were matched to 2423 controls; controls were identified from 245,158 adult first-time kidney-only waitlist registrants who did not receive an ABOi living donor kidney transplant and who remained on the waitlist or received either an ABOc living donor transplant or an ABOc deceased donor transplant from 2002 to 2017. The outcome of interest was death.

Cox proportional hazards regression and Cox models that accommodated for changing hazard ratios over time were used to compare mortality among ABOi living donor kidney transplant recipients versus a weighted matched comparison population.

Compared with the control group (general waitlist population), ABOi recipients were slightly younger at the first active date (median age 51 years vs 54 years), more likely to have private insurance (67.2% vs 48.5%), more likely to list preemptively (52.7% vs 23.8%), less likely to be Black (18.2% vs 29.1%) or Hispanic (15.1% vs 17.2%), and more likely to have blood type O (70.4% vs 50.7%) ($P<.001$ for all comparisons).

At 30 days following living donor kidney transplantation, cumulative survival was lower in the ABOi group than in the matched controls receiving conservative therapy (99.0% vs 99.6%). At 1-year following living donor kidney transplantation, cumulative survival was comparable between the two groups: 97.0% in the ABOi living donor recipient group versus 96.4% in the matched controls receiving conservative therapy.

However, at 5 and 10 years post procedure, cumulative survival was substantially higher for ABOi transplant recipients (90.0% vs 81.9% and 75.4% vs 68.4%, respectively). The increase in survival for transplant recipients in the ABOi group during the study period was statistically significant. During the observed follow-up time, results of a stratified Cox model showed a significant association between ABOi living donor kidney transplant and an average 25% lower mortality risk (hazard ratio, 0.67; 95% confidence interval, 0.53-0.84; $P<.01$).

Among the matched controls who did not undergo ABOi transplantation, median time to kidney transplantation, either living donor or deceased donor, was 4.2 years. Accounting for the competing risk of waitlist mortality, the cumulative incidence of kidney transplantation at 1, 3, and 5 years was 21.2%, 41.4%, and 53,7%, respectively. Accounting for the competing risk of kidney transplantation, cumulative risk of waitlist mortality at 1, 3, and 5 years was 3.3%, 10.8%, and 15.0%, respectively.

The researchers cited some limitations to the study findings, including the unavailability of desensitization regimens and methods to detect and measure ABO antibody titers, and not accounting for the possibility of kidney paired donation (KPD) due to unavailability of KPD registry status.

In conclusion, the researchers said, "We report that ABOi living donor kidney transplantation is associated with a substantial survival benefit compared with waiting for a compatible deceased donor organ. Although these findings are not surprising, we have quantified this survival benefit: ABOi living donor kidney transplantation confers an ~35% reduction in mortality over the long term compared with waiting for ABOc living donor kidney transplant or deceased donor kidney transplant. The survival benefit of ABOi living donor kidney transplant compared favorably with other types of kidney transplantations. ABOi living donor kidney transplantation remains a viable treatment option for patients with a willing but incompatible living kidney donor." ■

TAKEAWAY POINTS

- In Cox proportional hazards regression and Cox models that accommodated for changing hazard ratios over time, compared with matched controls, there was an association between ABOi living donor kidney transplantation and greater mortality risk in the first 30 days following the procedure.
- However, mortality was lower in the ABOi group than in the control group beyond 180 days post-transplantation. Patients in the ABOi group had higher cumulative survival at 5 and 10 years post-transplant compared with patients who remained on the waitlist or received an ABOc living or deceased donor transplant.

Stroke-Related Deaths among Kidney Transplant Recipients

The most effective treatment option for kidney failure is kidney transplantation, which is associated with improved long-term outcomes in appropriately selected patients. While patients with end-stage kidney disease are at increased risk for stroke and stroke-related mortality, recipients of kidney transplantation have a lower risk of cardiovascular disease compared with patients on dialysis. The lower cardiovascular risk is due, in part, to improved kidney function and selection bias related to extensive cardiovascular risk screening in potential kidney transplant recipients.

In the past 10 years in Australia and New Zealand, preventive treatment and improved risk factor control have halved the stroke mortality rates in the general population. However, according to **Nicole L. De La Mata, PhD,** and colleagues, it is unclear whether kidney transplant recipients have benefited from stroke prevention and management at levels similar to those in the general population over the past 20 years.

The researchers conducted a population-based retrospective cohort study designed to compare stroke mortality among kidney transplant recipients to that of the general population and define the risk factors associated with stroke-related mortality in kidney transplant recipients in Australia and New Zealand. The study also sought to examine whether the rate of stroke-related mortality and the risk factors for stroke death differed in kidney transplant recipients with polycystic kidney disease. Results of the study were reported in *Transplantation* [2020;104(10);2129-2138].

The cohort included all adult and pediatric kidney transplant recipients in Australia (January 1, 1980, to December 31, 2013) and New Zealand (January 1, 1988, to December 31, 2012). Both countries have similar demographics, including life expectancies and racial background, as well as universal healthcare systems, where free medical care is provided in public health systems. The study used data linkage between kidney transplant recipients in the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) and the national death registries in both countries. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* codes were used to determine the primary cause of death.

The analysis included data on 17,628 kidney transplant recipients. Over 175,084.3 person-years with a median 8.3-year follow-up posttransplant, there were 158 stroke deaths and 5126 other deaths. The remaining 12,344 recipients (70%) were in active follow-up. Of the total study population, 15,579 recipients underwent their first kidney transplant, 1798 underwent their second kidney transplant, and 251 underwent their third or more kidney transplant.

Graft failure occurred in 3733 recipients, 518 experienced two graft failures, and 79 experienced three or more graft failures. The agreement for fact of death between ANZDATA and the death register was nearly perfect in Australia (Kappa statistic, 0.89; 95% confidence interval [CI], 0.88-0.90) and New Zealand (Kappa statistic, 0.93; 95% CI, 0.91-0.95).

More than half (60%) of the study population were <50 years of age at time of transplantation (median, 45 years of age). Most of the transplants were conducted in Australia (88%) and during 2000 or later (56%). Sixty-one percent were male, 36% had normal weight body mass index (BMI), and 25% were overweight. BMI was not collected for 17% of the cohort.

Of the 158 stroke deaths, 36% (n=57) were intracerebral hemorrhages, 7% (n=11) were intracranial hemorrhages, 13% (n=20) were ischemic strokes, 12% (n=19) were subarachnoid hemorrhages, and 32% (n=51) were unspecified strokes. An additional 76 stroke deaths were listed in the secondary causes of death where kidney disease was the primary cause. The leading underlying causes of death in the remaining 5126 deaths were coronary heart disease (n=787), diabetes (n=440), and kidney failure (n=427).

Among patients with preexisting cerebrovascular disease, the cumulative incidence for stroke morality was higher than among those without preexisting cerebrovascular disease ($P<.001$). At 5-years posttransplant, the incidence was 0.49% for patients with and 0.15% for patients without cerebrovascular disease.

The overall mortality rate for stroke was 90.2 per 100,000 person-years (95% CI, 77.2-105.5). Subgroup mortality rates were: intracerebral hemorrhage, 32.6 per 100,000 person-years (95% CI, 25.1-42.2) and 11.4 per 100,000 person years (95% CI, 7.4-17.7) for ischemic stroke. During the first year posttransplant, there was no discernible pattern in stroke mortality rates over time, unlike rates for other deaths which were highest in the first 3 months following transplant. After the first 3 months, there was a steady increase in stroke mortality rates from 47.7 per 100,000 person years (95% CI, 23.9-95.5) in the first year to 140.0 per 100,000 person years (95% CI, 77.5-252.8) in the 10th year after transplant. For other deaths, rates declined after the first year posttransplant and steadily increased thereafter.

In the multivariate model, risk factors for stroke mortality included older age at transplant, having ever had a kidney transplant fail, earlier era of transplant, preexisting cerebrovascular disease, and not previously having had cancer. There was no association between previous duration of dialysis and risk of stroke death.

Among the 2196 transplant recipients with polycystic kidney disease who were followed over 19,491.2 person-years, there were 28 stroke deaths and 608 other deaths. The overall stroke mortality rate in that subgroup was 143.7 per 100,000 person-years (95% CI, 99.2-208.1), and the overall stroke standardized mortality ratio was 4.2 (95% CI, 2.9-6.0).

Limitations to the study cited by the researchers included the inability to include data on concurrent medications or other relevant stroke risk factors in the analyses, and using the underlying cause of death from the national death registries to determine stroke deaths.

In conclusion, the researchers said, "Kidney transplant recipients have a high excess of stroke death, particularly young recipients, and risk factors for stroke death include preexisting cerebrovascular disease and graft failure. While there were improvements over time, it is unclear whether kidney transplant recipients have access to stroke prevention or are receiving effective stroke prevention. Preexisting cerebrovascular disease being a risk factor presents an opportunity for secondary prevention. Further studies are needed to assess the benefits and harms of current stroke management in kidney transplant recipients or determine whether specialized strike prevention and intervention need to be developed through novel clinical trials." ■

TAKEAWAY POINTS

- There are few data available on the risk of stroke among kidney transplant recipients; researchers reported results of a population-based retrospective cohort study.
- The cohort included 17,628 kidney transplant recipients in Australia and New Zealand. There were 158 stroke deaths and 5126 nonstroke deaths in 175,084.3 person-years.
- Risk factors for stroke included older age at transplant, ever graft failure, earlier era of transplant, preexisting cerebrovascular disease, and no previous malignancy.

Estimates of Shortages in Capacity for CKRT during the Pandemic

During the coronavirus disease 2019 (COVID-19) pandemic, there was a surge in patients requiring intensive care. Among patients with COVID-19 who are critically ill, 4.8% to 6.9% develop acute kidney injury stage 3 requiring dialysis (AKI 3D). AKI 3D is commonly managed with continuous kidney replacement therapy (CKRT) in the intensive care unit (ICU).

Anticipating a surge in patients with AKI 3D, the healthcare system underwent crisis capacity activation for inpatient CKRT, an adjustment to standards of care. Various strategies were implemented to improve capacity for CKRT, including procuring additional CKRT machines from manufacturers, decreasing the dose and duration of CKRT, and expanding use of hemodialysis and peritoneal dialysis. However, there were CKRT shortages in hospitals in New York during the initial wave of the pandemic.

To inform planning for current and future crises, **Yuvaram N. V. Reddy, MBBS,** and colleagues conducted a study designed to develop mathematical models of CKRT demand and capacity to inform emergency planning, identify areas where more data are needed, and mitigate CKRT shortages during the current pandemic and future crises. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;76(5):696-709].

The researchers developed mathematical models to predict nationwide and statewide CKRT demand and capacity. The model utilized data from the Institute for Health Metrics and Evaluation model, the Harvard Global Health Institute model, and the published literature. The study population included patients in the United States hospitalized during the initial wave of the COVID-19 pandemic (February 6, 2020, to August 4, 2020). The outcomes of interest were demand and capacity of CKRT and the number of states projected to encounter shortages in CKRT.

The models projected that, during the study period, cumulatively 28,479 (95% uncertainty interval [UI], 21,974-39,338) patients with COVID-19 in the United States would require CKRT. The researchers estimated a nationwide daily capacity of 7032 CKRT machines. In a state-by-stage comparison of CKRT demand and capacity, there was a combined shortage of 1088 (95% UI, 910-1568) machines. There were shortages projected in six states (Connecticut, Maryland, Massachusetts, Michigan, New Jersey and New York) at peak resource use during the initial wave of the pandemic. Possible shortages were projected in eight other states (Arizona, Colorado, Louisiana, Nebraska, New Mexico, Rhode Island, South Carolina, and Wyoming).

Results of multiway sensitivity analysis in the best case scenario, defined as lowest demand and higher capacity, projected that from February 6, 2020, to August 4, 2020, a total of 26,053 (95% UI, 20,229-35,523) patients with COVID-19 in the United States would require CKRT. The models estimated a nationwide daily capacity of 10,254 CKRT machines. In a state-by-state comparison, results demonstrated a combined shortage of 614 (95% UI, 498-834) machines. Shortages were projected in Connecticut, New Jersey, and New York at peak resource use during the initial wave of the pandemic. The model also projected possible shortages in Arizona and Colorado.

In the worst-case scenario, defined as highest demand and lowest capacity, the projections demonstrated that from February 6, 2020, to August 4, 2020, CRKT would be required by a total of 38,013 (95% UI, 29,208-52,978) patients with COVID-19 in the United States. The model estimated a nationwide daily capacity of 4395 CKRT machines. Results of a state-by-state comparison demonstrated a combined shortage of 4540 (95% UI, 3886-6692) machines. Shortages were projected in 26 states at peak resource use during the initial wave of the pandemic. Possible shortages were projected in 13 additional states.

The researchers cited some limitations to the analyses, including the model results being subject to simplifications and assumptions, the dynamic nature of the COVID-19 pandemic, the assumption that all patients with AKI 3D in the ICU would receive CKRT, and the tendency of multiway sensitivity analyses to overweight extremes.

"In conclusion," the researchers said, "several US states could encounter CKRT shortages at peak response use during the initial wave of the COVID-19 pandemic. More complete and reliable data on CKRT demand and capacity would improve the estimates of future model-based analyses. Strategies such as the creation of an inpatient CKRT national registry and a national stockpile to bolster state capacity should be considered to mitigate CKRT shortages during the COVID-19 pandemic and future healthcare crises." ■

TAKEAWAY POINTS

- Researchers in New York performed an analysis to estimate shortages in capacity for continuous kidney replacement therapy (CKRT) for patients with acute kidney injury stage 3 requiring dialysis during the initial wave of the coronavirus disease 2019 (COVID-19) pandemic.
- In base-case model assumptions, there was a nationwide capacity of 7032 machines, an estimated shortage of 1088 machines, and shortages in six states at peak resource use.
- The findings suggest a need to establish an inpatient CKRT national registry and maintain a national stockpile of CKRT equipment.

Fresenius Announces Partnership with Livongo Health

Fresenius Medical Care North American (FRCNA) has announced a partnership with Livongo Health, Inc. The partnership will enable Fresenius Health Partners, a division of FRCNA, to deliver targeted, real-time care coordination services through Livongo Health, Inc. Through Livongo Whole Person for CKD [chronic kidney disease], patients with CKD who are managed by Fresenius Health Partners will have access to Livongo's solutions for management of diabetes and hypertension.

In a press release, CEO of FMCNA, **Bill Valle,** said, "By adding Livongo to our value-based care services, we can make a positive impact in the lives of people living with kidney disease. We are excited to add this proven suite of technologies and services as we expand our leadership in renal care management and work to slow the progression of kidney disease."

Livongo provides a connected ecosystem for members to manage their health that includes cellular-connected devices and integration with continuous glucose monitors, access to health coaches, and real-time health insights delivered through Health Nudges.

Glen Tullman, Livongo founder and executive chairman, said, "Through Livongo's advanced data science engine and clinically based approach, we can effectively use our proven solutions to empower individuals living with chronic kidney disease. We are excited about our innovative partnership with Fresenius Medical Care North American to offer people living with chronic kidney disease a better care experience that is personalized to them and addresses all aspects of their health."

Vifor Pharma and Cara Therapeutics Sign License Agreement for IV Korsuva™

In a press release in late fall, Vifor Pharma and Cara Therapeutics, Inc. announced a license agreement for commercialization of intravenous (IV) Korsuva™ (CR845/difelikefalin) for the treatment of pruritus associated with chronic kidney disease (CKD-aP) in the US dialysis market for non-Fresenius Medical Care (FMC) clinics under a Cara 60%, Vifor Pharma 40% profit-sharing agreement.

Stefan Schulze, CEO of Vifor Pharma Group, said, "Vifor Pharma has a strong market position and deep expertise in the nephrology space. This agreement further strengthens our US nephrology presence. We now have commercialization rights for IV Korsuva in the full dialysis segment by adding all non-FMC dialysis clinics, representing approximately 66% of the US market."

Derek Chalmers, PhD, DSc, president and CEO of Cara Therapeutics, said, "With an established fully dedicated nephrology sales force in the US, Vifor Pharma is an ideal commercialization partner to bring IV Korsuva to dialysis patients across the country. In addition, we believe Vifor Pharma's existing relationships with US dialysis providers will provide significant momentum for the launch and adoption of ICV Korsuva, if approved."

AKF and Tricida Partner in Educational Effort on Metabolic Acidosis

The American Kidney Fund (AKF) has announced a partnership with Tricida, Inc., to help increase understanding of chronic metabolic acidosis, a serious complication of kidney disease that can lead to progression of chronic kidney disease (CKD), muscle atrophy, and cardiovascular issues. With Tricida's support, the AKF will develop and disseminate information about the role of metabolic acidosis in CKD progression.

LaVarne A. Burton, president and CEO of AKF, said, "Complications of CKD, such as metabolic acidosis, create serious health problems, including patients' kidney disease getting worse. We are extraordinarily grateful to Tricida for its partnership in working with us to encourage patients to take metabolic acidosis management seriously."

Gerrit Klaerner, PhD, CEO and president of Tricida, said, "Tricida is honored to partner with the American Kidney Fund on this critical effort to increase awareness and understanding of metabolic acidosis in those with kidney disease. We estimate that in the US, approximately 3 million patients with CKD have metabolic acidosis, and this initiative aligns with our goal to slow CKD progression by reducing the prevalence and severity of metabolic acidosis in these patients with kidney disease."

Biofine® Dialysis Solution Bag Material Approved by US FDA

The Renal Therapies Group of Fresenius Medical Care North America (FMCNA) has announced US FDA approval of its DELFLEX® peritoneal dialysis solutions in Biofine®, an innovative bag material. The approval is another step in FMCNA's commitment to grow home dialysis via new and improved products.

In a press release, **Mark Costanzo,** president of FMCNA's Renal Therapies Group, said, "The new Biofine peritoneal dialysis solutions line is part of our ongoing commitment to expand supply of peritoneal dialysis solutions and make home dialysis available to more patients with kidney failure. We are excited to bring this innovative new product, which aims to make home treatment even easier, to market."

There are three advantages for peritoneal dialysis patients and their clinicians associated with the Biofine line of products: additional capacity to support patient growth; built in convenience for patients; and being environmentally friendly.

The Biofine bag material is up to 60% thinner than alternative materials, saving raw materials and reducing waste; Biofine degrades on incineration with no release of hydrochloric acid and eliminates DEPH plasticizers.

Mike Anger, MD, chief medical officer for FMCNA's Renal Therapies Group, said, "After transplantation, home therapy has repeatedly been demonstrated as the preferred alternative for many end-stage renal disease patients and the healthcare system. This expansion of Fresenius Medical Care's capacity with an innovative new product marks another step toward improving the quality of life for dialysis patients."

Cricket Health Announces Leadership Change

In late fall, Cricket Health announced that cofounder **Arvind Rajan** was named executive chairman of the board of directors and **Robert Sepucha** was named CEO. Cricket Health is a comprehensive kidney care provider that utilized a personalized, evidence-based approach to management of patients with kidney disease.

In a press release from Cricket Health, Mr. Sepucha said, "I look forward to leading the company as we enter the next phase of growth, expanding relationships with existing partners and forming new partnerships to improve care for more people with kidney disease in our current markets in California, Texas, and beyond."

The change in leadership coincided with $15 million in debt financing from K2 HealthVentures. The financing will be used to support Cricket's growth as the company adds more payer customers, supports more nephrology practices, and serves more people with kidney disease, the press release added.

Strive Health Aids Nephrologists in CKCC

In a press release, Strive Health announced partnerships with nearly 200 physicians and advanced practitioners from 20 nephrology groups across several states to participate in the Centers for Medicare & Medicaid Services Comprehensive Kidney Care Contracting (CKCC) options of the Kidney Care Choices Model. Strive Health is a national care delivery system known for value-based kidney care.

CKCC is a new Center for Medicare and Medicaid Innovation (CMMI) payment model that incentivizes healthcare providers to manage the care of Medicare beneficiaries with chronic kidney disease (CKD) stages 4 and 5 and end-stage kidney disease (ESKD). The model addresses both beneficiaries with CKD and ESKD and aligns patients based on nephrology care rather than on dialysis treatments. The program's implementation period began on October 15, 2020; the official launch of the performance period will occur on April 1, 2021.

Gary Singer, MD, a nephrologist in St. Louis, Missouri, said, "New payment models like CKCC are putting nephrologists at the center and creating meaningful opportunities to transform care for our patients. We looked for a partner whose incentives align with our goal of delaying the progression of kidney disease, and whose model blends technological innovation with high-touch care. We believe Strive is well positioned to support us in CKCC and beyond."

Strive Health cofounder and CEO, **Chris Riopelle,** said, "Our company is the market leader in transformative, value-based kidney care. The new CMMI models take an exciting step in the right direction and create unprecedented opportunities for nephrologists to innovate and be rewarded for high-quality, long-term care goals over individual treatments."

By early 2021, Strive will be managing, or supporting the management of, more than 30,000 patients in 12 states in the United States. The company is launching new value-based kidney care arrangements with commercial payers, health systems, and medical groups and engaging local nephrologists as central care providers within those models.

White Paper on Rare Kidney Disease Released

In late fall, NephCure Kidney International and Retrophin, in partnership with the American Association of Kidney Patients (AAKP), released a five-point paper outlining policy recommendations for areas to bring innovation and equity in diagnosis, treatment, and education about rare kidney disease.

In a press release, **Lauren Lee,** executive vice president, stakeholder engagement for NephCure Kidney International, said, "We're proud to work with Retrophin and AAKP to convene leaders in the community to address the needs of rare kidney disease patients and families. The changes proposed in this comprehensive paper are critical to creating a better future for patients who have endured their conditions with limited treatment options."

The five recommendations are: (1) increase awareness and education about rare kidney disease; (2) improve diagnosis of rare kidney disease through enhanced tools and protocols; (3) provide patient access to community-level information and platforms to connect with healthcare providers and other patients; (4) educate healthcare providers on rare kidney disease to create a standard of care; and (5) provide earlier patient access to specialists and designated patient advocates.

Eric Dube, CEO of Retrophin, said, "We are excited to be part of this effort to kickstart a reimagining of how society approaches rare kidney disease education and care. The workgroups and roundtable discussion presented actionable recommendations to address the gaps in innovation and inclusion in rare kidney disease that have been absent for decades. We look forward to continuing the collaboration with leaders in the space as we aim for a better future for patients affected by rare kidney disease."

AKF and VA Work to Increase Awareness of Kidney Disease among US Veterans

The American Kidney Fund (AKF) has announced a partnership with the US Department of Veterans Affairs (VA) Veterans Health Administration (VHA). The partnership is aimed at increasing awareness of kidney disease among US veterans and supporting veterans diagnosed with kidney disease.

As a group, veterans have higher rates of chronic kidney disease compared with the general population in the United States; kidney disease affects one in seven Americans but one in six veterans. More than 40,000 veterans in the VHA have end-stage kidney disease and rely on dialysis or kidney transplant for survival.

The partnership will enable AKF and the VA to identify opportunities for improvement of kidney disease resources, programs, and support for veterans. The two organizations will also work together to provide educational materials and resources for veterans diagnosed with kidney disease and their families and caregivers.

In a recent press release, **LaVarne Burton,** president and CEO of AKF, said, "The American Kidney Fund shares the VA goal of supporting veterans with kidney disease by helping them live healthier lives through early identification and referral for appropriate treatment. Working together, we can leverage each other's strengths to address the unique challenges veterans face in managing their kidney health."

American Kidney Fund Responds to CBO Score of H.R. 5534

LaVarne A. Burton, president and CEO of the American Kidney Fund (AKF), responded to the Congressional Budget Office's (CBO) scoring the H.R. 5534, the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2020. The CBO estimates that the bill will reduce federal spending on Medicare benefits for some kidney transplant patients by $400 million over 10 years.

In a recent statement, Ms. Burton said, "H.R. 5534 will add a new Medicare coverage option solely to cover immunosuppressive drugs used by kidney transplant patients under age 65. People with transplants must take immunosuppressive drugs or their body will reject the transplanted organ. For people with a kidney transplant, the devasting impact of losing their kidney means they will have to go on dialysis or try another kidney–a daunting task with close to 100,000 people on the wait list.

"AKF has been tirelessly advocating for H.R. 5534 because of the terrible impacts that follow patients' inability to afford critical antirejection medications after Medicare coverage ends. According to the *New England Journal of Medicine,* nearly 70% of kidney transplant programs reported either a death or transplant loss because patients were unable to pay for their antirejection medications.

"The CBO score brings us this much closer to creating a new, limited benefit under Medicare that will cover most of the cost of immunosuppressive drugs for people who have had a kidney transplant but whose post-transplant coverage under Medicare has ended. This bill will provide a vital safety net for low-income end-stage renal disease patients for whom access to healthcare is a matter of life and death. We urge Congress to move forward immediately with the debate and passage of this critical legislation."

Fresenius Kabi to Distribute Veltassa® in China

In a recent press release, Vifor Fresenius Medical Care Renal Pharma (VFMCRP) and Fresenius Kabi announced an agreement to develop register, and distribute Veltassa® (patiromer) for the treatment of hyperkalemia in the People's Republic of China. Fresenius Kabi will have exclusive rights to distribute and sell the drug across China. Fresenius Kabi is among the top 10 multinational pharmaceutical companies in China.

Stefan Schulze, CEO of Vifor Pharma group said, "We are delighted to expand VFMCRP's collaboration with Fresenius Kabi. There is a high prevalence of CKD [chronic kidney disease] and heart failure in China and hyperkalemia is one of the most common complications associated with these two conditions. As a result there is a high demand for an effective, proven hyperkalemia treatment. The excellent commercial infrastructure, the well-established relationships in nephrology and our existing successful collaboration make Fresenius Kabi our partner of choice to provide Veltassa to patients."

Oskar Haszonitis, president, region Asia Pacific of Fresenius Kabi, said, "This agreement is an important step in intensifying our collaboration and relationship with VFMCRP in nephrology. We believe Veltassa has the potential to provide many benefits to patients across the country, and we look forward to adding it to our portfolio and working with VFMCRP."

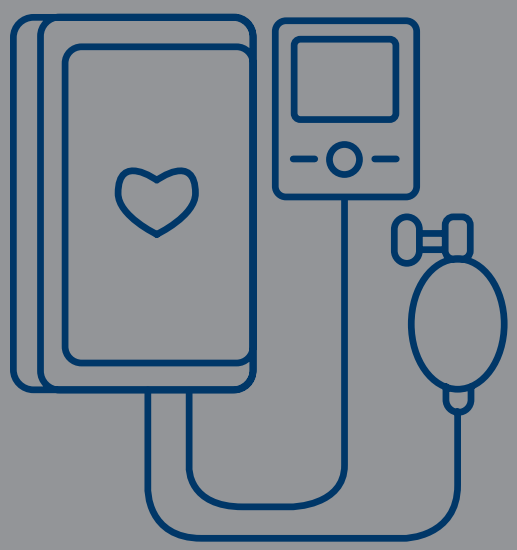
At-Home uACR Test Available

The National Kidney Foundation (NFK) has partnered with Healthy.io to offer a home urine albumin-to-creatinine ratio (uACR) test kit. The kit, which is free, helps detect early signs of kidney disease. Individuals who complete a 1-minute quiz that is part of the NKF's Are You the 33% public awareness campaign to assess risk for kidney disease, are eligible for the kit.

In a press release from NKF, **Joseph Vassalotti, MD,** chief medical officer at NKF, said, "Diagnosing kidney disease early is key to staving off its life-long complications, and if you have diabetes, you are at risk. We're pleased to partner with Healthy.io to help increase diagnosis of kidney disease through their unique at-home test and encourage patients with diabetes to work with their clinicians to take the necessary follow-up seps."

Among patients at risk for kidney disease, fewer than 50% with diabetes and fewer than 10% with hypertension complete the recommended annual uACR test. In a study completed by Healthy.io with NKF and Geisinger in 2019, 71% of previously untested, consenting individuals used the at-home kit, and 89% said they preferred home testing to traditional testing.

Paula LeClair, US general manager of healthy.io, said, "Now more than ever, we need to enable more people to screen for conditions like kidney disease from the comfort of home. We're proud to partner with NKF and to offer our kits to people at risk for kidney disease, so they can get on a path to better health soon." ■



Surgeon General Issues *Call to Action to Control Hypertension*

In an editorial in *JAMA* in October, **Jerome M. Adams, MD, MPH,** and **Janet S. Wright, MD,** both of the Office of the Surgeon General, Department of Health and Human Services, Washington, DC, defended the release of the Surgeon General's Call to Action to Control Hypertension.

According to the authors, "Hypertension is common, costly, and controllable...Uncontrolled blood pressure can lead to largely preventable events such as myocardial infarction, stroke, and maternal mortality, as well as debilitating and expensive conditions such as kidney disease, heart failure, and cognitive decline."

The three goals in the Call to Action provide a national roadmap to drive change in strategies to improve blood pressure control: (1) make hypertension control a national priority; (2) ensure that communities support hypertension control; and (3) optimize patient care for hypertension control.

Drs. Adams and Wright said, "The time for action is now. Implementing the goals and strategies in the Call to Action, together as a nation, could help patients, clinicians, and communities achieve the health, wealth, and equity benefits that national hypertension control can bring."

COVID-19

AKI in Kidney Transplant Recipients with COVID-19

Transplantation. https://bit.ly/3ow1jr7

Patients with severe or critical acute respiratory syndrome coronavirus 2 (SARS-CoV-2) frequently experience renal involvement. There are few data available on acute kidney injury (AKI) in Black kidney transplant recipients with coronavirus disease 2019 (COVID-19). **Pritika Shivastava, MD,** and colleagues conducted a retrospective, single-center study with a predominately Black cohort (79%) of kidney transplant recipients with COVID-19 infections in the Detroit metropolitan area.

The study included 39 kidney transplant recipients who tested positive for COVID-19 between March 16, 2020, and April 25, 2020. The researchers retrieved data from electronic medical records to compare outcomes between kidney transplant recipients with COVID-19 without AKI and those with COVID-19 with AKI.

The final analysis was conducted on 38 patients; of those 30 (79%) were Black. AKI occurred in 27 (71.1%) of kidney transplant recipients with COVID-19; six of those patients required hemodialysis. The overall AKI incidence rate was 71%. The rate among Black patients was 76.7% compared with 50% among non-Black patients.

In univariate logistic regression analysis, there was no significant association between Black race and AKI (odds ratio [OR], 3.4; 95% confidence interval [CI], 0.68-17.4). Following risk adjustment by race, patients with diabetes had a significantly higher risk of AKI (adjusted OR, 19.85; 95% CI, 1.65-58.66; *P*=.012). Kidney transplant recipients with AKI had higher preexisting renin-angiotensin-aldosterone system inhibitor use than those without AKI (*P*=.03).

In conclusion, the researchers said, "Kidney transplant recipients infected with SARS-CoV-2 have a high incidence of AKI, with associated increased morbidity and mortality. Though no racial differences in mortality were noted in our kidney transplant recipients with AKI, we await data from registries to help elucidate this difference."

Acute Kidney Injury in COVID-19 and Hospital Mortality

Nephrology Dialysis Transplantation. 2020;35(10):1652-1662

In late summer 2020, more than 21 million people worldwide had been infected with coronavirus disease 2019 (COVID-19). At that time, the occurrence of acute kidney injury (AKI) in patients hospitalized with COVID-19 was as high as 43%, comparable to AKI in other forms of pneumonia requiring hospitalization.

John A Kellum, MD, FACP, FCCM, and colleagues provided a review of the association between AKI and mortality in patients hospitalized with COVID-19.

At present, there are few data available on the impact of AKI on COVID-19 outcomes; however, as in other forms of sepsis, there is a strong association between AKI and hospital mortality. Mortality in COVID -19 patients without AKI has been low to date.

The pathophysiologic mechanisms of AKI in COVID-19 are thought to be multifactorial and include systemic immune and inflammatory responses associated with viral infection, systemic tissue hypoxia, reduced renal perfusion, endothelial damage, and direct epithelial infection with severe acute respiratory syndrome coronavirus 2.

Mitochondria play a central role in the metabolic deregulation in the adaptive response to the systemic inflammation and are also known to be vital in response to direct viral damage as well as tissue reperfusion. There is an association between those stress conditions and increased glycolysis and reduced fatty acid oxidation.

"Thus, there is a strong rationale to target AKI for therapy in COVID-19. Furthermore, many approaches that have been developed for other etiologies of AKI such as sepsis, inflammation, and ischemic-reperfusion, have relevance in the treatment of COVID-19 AKI and could be rapidly pivoted to this new disease," the researchers said.

CHRONIC KIDNEY DISEASE

Characteristics of Participants in the DAPA-CKD Trial

Nephrology Dialysis Transplantation. 2020;35(1):1700-1711

The DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial (NCT03036150) was designed to examine the effect of dapagliflozin in kidney and cardiovascular events in patients with CKD both with and without type 2 diabetes. Dapagliflozin is a sodium-glucose cotransporter 2 inhibitor. **David C. Wheeler, MD,** and colleagues conducted an analysis to examine the baseline characteristics of patients recruited for the DAPA-CKD study and compare them to participants enrolled in other trials.

The trial enrolled 4304 participants with a urinary albumin to creatinine ratio (UACR) ≥200 mg/g and estimated glomerular filtration rate (eGFR) 25 to 75 mL/min/1.73 m^2; participants were randomized to either dapagliflozin 10 mg once daily or placebo. Mean eGFR was 43.1 mL/min/1.73 m^2 and median UACR was 949 mg/g (108 mg/mmol).

A total of 2906 participants (68%) had type 2 diabetes; of those, 396 had CKD due to a cause other than diabetes. Following diabetes (n=2510), the most common causes of CKD were ischemic/hypertensive nephropathy (n=687) and chronic glomerulonephritis (n=695). Immunoglobulin A nephropathy was the most common form of glomerulonephritis (n=270). Ninety-seven percent (n=4174) of participants were receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; 43.7% (n=1882) were receiving diuretics, 5.3% (n=229) were receiving mineralocorticoid receptor antagonists, and 2.8% (n=122) were receiving glucagon-like peptide 1 receptor agonists.

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial limited enrollment to participants with CKD due to diabetes. Mean eGFR of participants in the DAPA-CKD trial was 13.1 mL/min/1.73 m^2 lower than in CREDENCE, and similar to that in the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in DKD) trial and SONAR (Study of Diabetic Nephropathy with Atrasentan).

In conclusion, the researchers said, "Participants with a wide range of underlying kidney diseases receiving renin-angiotensin system blocking therapy have been enrolled in the DAPA-CKD trial. The trial will examine the efficacy and safety of dapagliflozin in participants with CKD stages 2-4 and increased albuminuria, with and without type 2 diabetes."

Variations in Blood Pressure and Development of CKD

Nephrology Dialysis Transplantation. 2020;35(10):1739-1746

There are limited data on the association between visit-to-visit variability in blood pressure and the risk of chronic kidney disease (CKD) in patients treated for hypertension. **Youbao Li, MD,** and colleagues conducted a post hoc analysis of data from the Renal Sub-Study of the China Stroke Primary Prevention Trial to examine the relationship of visit-to-visit variability in blood pressure with the development of CKD, and identify potential effect modifiers in hypertensive patients with no prior cardiovascular diseases.

The analysis included 10,051 hypertensive patients with and without CKD. Patients with a minimum of six visits of blood pressure measurements from randomization to the 24-month visit were eligible. The main visit-to-visit variability in blood pressure was expressed as a standard deviation (SD). The primary outcome of interest was the development of CKD, defined as a decrease in estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 and to a level of <60 mL/min/1.73 m^2, or end-stage kidney disease.

Median treatment duration was 4.4 years. Following multivariable adjustment, including baseline systolic blood pressure and mean systolic blood pressure during the initial 2-year treatment period, there was a significant positive relationship of SD of systolic blood pressure and the risk of development of CKD (per SD increment; odds ratio, 1.27; 95% confidence interval, 1.10-1.46). Results across subgroups, including age, sex, systolic blood pressure at baseline, treatment compliance, concomitant antihypertensive medications, and mean systolic blood pressure during the first 2 years of treatment, were consistent.

In conclusion, the researchers said, "Systolic blood pressure variability, irrespective of mean blood pressure level, was significantly associated with the development of CKD in general treated hypertensive patients."

DIABETES

Resting Heart Rate and Development of Microalbuminuria

Diabetic Medicine. doi.org/10.1111.dme.14436

Microalbuminuria is an indicator of chronic kidney disease (CKD) as well as adverse cardiovascular events. Results of previous studies have suggested an elevated resting heart rate is a risk factor for microalbuminuria in patients with cardiovascular disease. However, there are few data available on the role of elevated resting heart rate in the development of microalbuminuria in patients with type 2 diabetes. **Y. K. Chang, PhD,** and colleagues conducted an analysis to examine the association between resting heart rate and new-onset microalbuminuria in type 2 diabetes.

The analysis included 788 individuals from a glycemic control trial in Taiwan. Microalbuminuria was defined as a fasting urine albumin-to-creatinine ratio ≥30 mg/g in two consecutive urine tests. Resting heart rate and other covariates were measured at baseline. Quartiles of resting heart rates (<70, 70-74, 75-80, and >80 beats/min) were used in the analysis. The association between resting heart rate and risk of microalbuminuria was assessed using Cox proportional hazard models.

A total of 244 participants developed microalbuminuria during follow-up. Those who developed microalbuminuria had longer diabetes duration (3.0 vs 2.0 years; *P*<.001), higher rate of hypertension (77% vs 66%; *P*=.003), higher rate of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use (50% vs 38%); *P*=.001), and higher baseline hemoglobin A1c level (70 vs 64 mmol/mol; *P*<.001).

Following adjustment for demographic characteristics, metabolic profiles, and inflammatory markers, there was a significant association between developing microalbuminuria and baseline resting heart rate of 70-74 (hazard ratio [HR], 2.05 95% confidence interval [CI], 1.32-3.18), 75-80 (HR, 2.10; 95% CI, 1.32-3.23), and ≥80 (HR, 1.62; 95% CI, 1.01-2.59) beats per minute, compared with resting heart rates <70 beats per minute. In the multivariable Cox model, the average increased risk of microalbuminuria for increments of 10 beats per minute was ~24% among patients with hypertension (HR, 1.24; 95% CI, 1.05-1.47).

"This prospective cohort study showed that resting heart rate may be an associative risk factor for developing microalbuminuria in type 2 diabetes," the researchers said.

Home-Based Kidney Care Intervention Effect Modified by Diabetes Status

Journal of Diabetes and Its Complications. https://bit.ly/34C9gDe

Home-based kidney care is a treatment approach that addresses issues of patient preferences as well as cultural barriers to healthcare. Researchers, led by **V. Shane Pankratz, PhD,** previously conducted a study of home-based kidney care versus usual care in a cohort of Zuni Indians in New Mexico. A recent analysis examined the potential for differential efficacy of home-based kidney care versus usual care according to type 2 diabetes status.

The analysis utilized data from all participants in the randomized clinical trial comparing home-based kidney care to usual

care among patients with chronic kidney disease (CKD), and determined whether the effect of the home-based kidney care intervention affected the subset of patients with type 2 diabetes differently than those without type 2 diabetes. Linear regression models were used to estimate the effect of home-based kidney care on improvement in Patient Activation Measure (PAM) total scores within the groups of participants defined by type 2 diabetes status, and to compare the effects between those two groups. Generalized estimating equations were used to account for household clustering.

The original study included 63 participants in the home-based kidney care group and 62 in the usual care group. Of those, 98 completed the 12-month intervention (50 in the home-based care group and 48 in the usual care group). The current analysis compared the effect of the intervention in the 56 participants with type 2 diabetes (24 in the home-based care group and 32 in the usual care group) to the intervention effect in the 42 participants without type 2 diabetes (26 in the home-based care group and 16 in the usual care group).

Participants with type 2 diabetes in the home-based care group experienced an average increase in PAM total score of 16.0 points (95% confidence interval [CI], 8.8-23.1) greater than those with type 2 diabetes in the usual care group. The intervention had essentially no effect for those without type 2 diabetes: participants in the home-based care group had average PAM scores 1.4 points (95% CI, –12.4 to 9.6) lower than those in the usual care group. There was a significantly different home-based kidney care treatment effect by type 2 diabetes status (P=.02).

In conclusion, the researchers said, "This secondary analysis suggests that the effectiveness of this home-based kidney care intervention on increasing patient activation is most notable among those CKD patients who also have type 2 diabetes." ■

PEDIATRIC NEPHROLOGY

Healthcare Utilization in Children with CKD in the United States

American Journal of Kidney Diseases. doi.org/10.1053.j.ajkd.2020.07.024

Zubin J. Modi, MD, and colleagues recently conducted a study designed to examine the prevalence of pediatric chronic kidney disease (CKD) among children hospitalized in the United States and examine the association of CKD on hospital outcomes. The cross-sectional national survey of pediatric hospital discharges utilized data from the Health Cost and Utilization Project Kids Inpatient Database for the years 2006, 2009, 2012, and 2016 to identify hospital discharge of children ages >28 days to 19 years with a chronic medical discharge.

Outcomes of interest were length of stay, costs, and mortality. Multivariable analysis using Poisson, Gamma, and logistic regression were performed for length of stay, cost, and mortality, respectively.

During the study period, a chronic medical condition was present in 6,524,745 estimated discharges; CKD was present among 3.9% of discharges. Those with CKD had longer length of stay: median, 2.8 days with CKD versus 1.8 days without CKD (P<.001). Median costs were higher in the CKD group compared with the non-CKD group: $8755 per hospitalization versus $5016, respectively ($P$<.001).

There was an association between the presence of CKD and longer length of stay (29.9%; 95% confidence interval [CI], 27.2%-32.6%), higher cost (61.3%; 95% CI, 57.4%-65.4%), and higher risk of mortality (odds ratio, 1.51; 95% CI, 1.40-1.63).

In conclusion, the researchers said, "Pediatric CKD was associated with longer length of stay, higher costs, and a higher risk of mortality compared to hospitalizations with other chronic illnesses. Further studies are needed to better understand the healthcare needs and delivery of care to hospitalized children with CKD."

CONFERENCE COVERAGE **AMERICAN TRANSPLANT CONGRESS**

High eGFR Associated with Worse Long-Term Graft Survival

Cardiovascular morbidity and mortality is associated with high estimated glomerular filtration rate (eGFR) as well as low eGFR. In recipients of kidney transplantation, the transplanted kidney is exposed to hyperfiltration-mediated injury. Those nonimmunological injuries, as well as immunological injuries, further accelerate poor graft outcome in transplant recipients.

H. Choi and colleagues in Korea conducted a study to examine whether high levels of eGFR at post-transplantation in the first year are a risk factor for long-term graft survival in kidney transplantation patients. Results of the study were reported during a virtual poster session at the American Transplant Congress 2020 in a poster titled *High Estimated Glomerular Filtration Rate in the First Year after Kidney Transplantation Is Associated with Worse Long-Term Graft Survival in Kidney Recipients*.

The single-center study included 1692 adult kidney transplant recipients with more than 1 year of follow-up. Serum creatinine level was measured throughout the study period. Cox regression model covariates included duration of dialysis prior to transplantation, recipient age and sex, related status, acute rejection status, diabetes status, and GFR at 1 year after kidney transplantation. Study participants were stratified into four groups according to GFR level: (1) 60 to 75 mL/min/1.73 m^2; (2) 76 to 90 mL/min/1.73 m^2; (3) 91 to 105 mL/min/1.73 m^2; and (4) 106 to maximum mL/min/1.73 m^2. Participants with eGFR <60 mL/min/1.73 m^2 were excluded.

The rate of graft survival, as estimated by the Kaplan-Meier estimator, was significantly lower in participants in the eGFR 106 to maximum mL/min/1.73 m^2 category (log-rank test P=.016). In multivariable Cox regression models, following adjustment for recipient age and sex, related status, acute rejection status, and diabetes status, there was a significant association between the highest eGFR group and higher graft failure (hazard ratio, 1.629; P=.014).

"Our data support that the higher eGFR at 1 year after kidney transplantation is associated with poor outcome for long-term kidney graft survival in kidney transplant recipients," the researchers said.

Source: Choi H, Huh K, Kim M, Kim S, Kim Y, Kim B. High estimated glomerular filtration rate at the first year after kidney transplantation is associated with worse long-term graft survival in kidney recipients. Abstract of a poster presented at the virtual American Transplant Congress (Abstract C-066), May 30, 2020.

Sarah Tolson

2021 Changes to the ESRD PPS

A little more than 12 years ago, I began my career in the renal billing field. At that time, dialysis was reimbursed under the composite rate and medications such as ESAs, IV iron, and vitamin D were separately reimbursed. During those days, the reimbursement for a billable unit of epoetin was around a dollar and Medicare controlled overuse by leveraging a patient's hemoglobin and hematocrit readings. As administration of epoetin has a direct impact on a patient's hemoglobin and hematocrit readings, Medicare used these lab values, among other things, to determine the medical necessity of ESA administration.

As a biller, I learned to be proficient in identifying a hemoglobin over 13 or a hematocrit over 39 and subsequently assessing the ESA utilization and past months' hemoglobin and hematocrit readings to determine if a claim may be subject to a reduction in ESA reimbursement. During the years I billed for dialysis under the composite rate reimbursement system, it was not unheard of to see billing sheets for patients that were administered more than 400,000 units of epoetin in a calendar month. This also happens to be the Medicare medically unlikely edit (MUE) for epoetin on a dialysis claim.

In 2010, I learned of the end-stage renal disease (ESRD) prospective payment system (PPS), or the ESRD bundle for the first time. I remember my predecessor, Rick Collins, conducting analyses on our client's utilization of medications that were separately reimbursable under the composite rate system to help them prepare financially for life under the ESRD PPS. We prepared extensive training materials for our staff, as the reimbursement change also came with changes in billing requirements, and we provided clients with modified billing forms to assist in capturing all the information necessary to meet the new billing requirements.

Each year since the inception of the ESRD PPS, the Centers for Medicare & Medicaid Services (CMS) have made changes to the components of the ESRD PPS to align the cost of a dialysis treatment to reimbursement. Most years, these changes were small; increases or decreases in the fixed dollar loss amount or a change to the low volume payment adjustment (LVPA) amount or qualification thresholds, etc. That is, until the implementation of the Transitional Drug Add-On Payment Adjustment (TDAPA) in January of 2018: this change to the ESRD PPS allowed dialysis facilities, for the first time in 8 years, to bill

TABLE | **Comparison of ESRD PPS 2011-2021**

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
ESRD PPS Base Rate	$251.60	$234.45	$240.36	$239.02	$239.43	$230.32	$231.55	$232.77	$235.27	$239.33	$253.13
LVPA	18.90%	18.90%	18.90%	18.90%	18.90%	18.90%	23.90%	23.90%	23.90%	23.90%	23.90%
Onset of Dialysis Adj.	51%	51%	51%	51%	51%	32.70%	32.70%	32.70%	32.70%	32.70%	32.70%
Home Training Add-on	$33.44	$33.44	$33.44	$50.16	$50.16	$50.16	$95.60	$95.60	$95.60	$95.60	$95.60
Pediatric MAP	variable	$45.44	$41.39	$40.49	$43.57	$39.20	$38.29	$37.31	$35.18	$32.32	$30.88
Pediatric FDL	$195.02	$71.64	$47.32	$54.01	$54.35	$62.19	$68.49	$47.79	$57.14	$41.04	$44.78
Adult MAP	variable	$78.00	$59.42	$50.25	$51.29	$50.81	$45.00	$42.41	$38.51	$35.78	$50.92
Adult FDL	$155.44	$141.21	$110.22	$98.67	$86.19	$86.97	$82.92	$77.54	$65.11	$48.33	$122.49
Rural Dialysis Facility Adj.	0%	0%	0%	0%	0%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
LVPA Common Ownership Radius	25 miles	25 miles	25 miles	25 miles	25 miles	5 miles	5 miles	5 miles	5 miles	5 miles	5 miles
Acute - GI Bleed	18.30%	18.30%	18.30%	18.30%	18.30%	8.20%	8.20%	8.20%	8.20%	8.20%	8.20%
Acute - Bacterial Pneumonia	13.50%	13.50%	13.50%	13.50%	13.50%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Acute - Pericarditis	11.40%	11.40%	11.40%	11.40%	11.40%	4.00%	4.00%	4.00%	4.00%	4.00%	4.00%
Chronic - Sickle Cell Anemia	7.20%	7.20%	7.20%	7.20%	7.20%	19.20%	19.20%	19.20%	19.20%	19.20%	19.20%
Chronic - Monoclonal gammopathy	18.90%	18.90%	18.90%	18.90%	18.90%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Chronic - Myelodysplastic Syndrome	9.90%	9.90%	9.90%	9.90%	9.90%	9.50%	9.50%	9.50%	9.50%	9.50%	9.50%

separately for and obtain additional reimbursement for a medication on a claim for dialysis services.

One stipulation of TDAPA was that CMS will separately reimburse for medications qualified for reimbursement under TDAPA for a minimum of 2 years to allow CMS to obtain sufficient utilization data for reimbursement under the bundle. In 2018, when calcimimetics became available for purchase, many but not all, the facilities my company billed for began utilizing them in their facilities. Over the last three years, we have seen stabilization in the utilization of calcimimetics, in those facilities that utilize them.

As for the new billing requirement, CMS now requires dialysis facilities to report the total number of hours that a patient spends dialyzing each month.

The 2021 ESRD PPS final rule contains changes to reimbursement and billing requirements that remind me, in some ways, of big, sweeping changes to dialysis reimbursement and billing requirements. Rather than reimbursing calcimimetics on a fee for service basis, CMS increased the bundle to account for the average expenditure per treatment for calcimimetics, based on the most recent claims data available. As for the new billing requirement, CMS now requires dialysis facilities to report the total number of hours that a patient spends dialyzing each month.

The 2021 ESRD PPS base rate is just about $14.00 more than the 2020 ESRD PPS base rate. For those facilities that do not use or have a very low utilization of calcimimetics, this increase in the ESRD PPS base rate will likely be a welcome increase in reimbursement. However, based on the history of the ESRD PPS base rate, I would suspect that the base rate in 2022 decreases significantly based on the likely decrease in utilization of calcimimetics just as the 2012 base rate decreased due to the significant reduction in ESA utilization.

Over the years, I have kept a table of the base rate and many of the adjustment factors that impact the final payment amount to help me keep track of how claims were reimbursed in any given year. In light of the similarities of the 2011 and 2021 reimbursement changes, I find this chart more beneficial than I have in years past; I hope you find it beneficial as well. ■

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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