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Diet and the Kidney: Studies Examine Effects of Sugar-Sweetened Beverages and Fruit and Vegetable Consumption

By Tracy Hampton

New studies point to the importance of diet for kidney health in the general population as well as for the longevity of patients on dialysis. The studies, which are both published in the *Clinical Journal of the American Society of Nephrology* (*CJASN*), suggest that more research is needed to fine-tune certain dietary recommendations.

The first study, by Casey Rebholz, PhD, MPH, of the Johns Hopkins Bloomberg School of Public Health, and her colleagues, was conducted to clarify the effects of certain beverages on kidney health.

"There is a lack of comprehensive information on the health implications of the wide range of beverage options that are available in the food supply," Rebholz said. "In particular, there is limited information on which types of beverages and patterns of beverages are associated with kidney disease risk in particular."

Of note, the study focused on African Americans, who experience a disproportionate burden of kidney disease but are under-represented in clinical research. The team prospectively studied 3003 African American men and women with normal kidney function who were enrolled in the Jackson Heart Study.

Participants completed a food frequency questionnaire administered at the start of the study in 2000–2004, and they were followed until 2009–2013. Among the 3003 participants, 185 (6%) developed chronic kidney disease (CKD) over a median follow-up of 8 years. After adjustment for confounding factors, consuming a beverage pattern consisting of soda, sweetened fruit drinks, and water was associated with a higher risk of developing CKD. Participants in the top tertile for consumption of this beverage pattern were 61% more likely to develop CKD than those in the bottom tertile.

It was surprising that water was a component of the beverage pattern that was linked with a higher risk of CKD, although study participants may have reported their consumption of a wide variety of types of water, including flavored and sweetened water. The investigators did not collect information about specific brands or types of bottled water in the Jackson Heart Study.

In an accompanying editorial, Holly Kramer, MD, MPH, and David Shoham, PhD, of Loyola University Chicago, noted that the findings hold strong public health implications. "Although a few cities in the United States have reduced sugar-sweetened beverage consumption via taxation, most municipalities have resisted public health efforts to lower its consumption," they wrote. "This cultural resistance to reducing sugar-sweetened beverage consump-

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MOC Returns as a Hot Issue this Winter

A hallmark of medical care is the unwavering dedication of physicians and other health professionals to commit to lifelong learning. How physicians in the United States fulfill and document that commitment, however, has created growing concern among many clinicians.

A reflection of that concern is the decision by the American Board of Medical Specialties (ABMS) in December 2017 to establish a Vision Commission to "bring together multiple partners to vision a system of continuing board certification that is meaningful, relevant, and of value, while remaining responsive to patients, hospitals, and others who expect that physician specialists are maintaining their knowledge and skills to provide quality specialty care."

The American Board of Internal Medicine (ABIM)—the organization that certifies and recertifies internal medicine physicians, including nephrologists—is one of ABMS's 24 specialty boards. In response to a wide range of criticisms relative to recertification or maintenance of certification (MOC), ABIM announced "substantial changes" to its MOC program in February 2015.

At that time, ABIM suspended "the practice assessment, patient voice, and patient safety requirements" (Part 4 of MOC). ABIM's estimated 200,000 diplomates, including more than 10,000 nephrologists, can still receive MOC points for Part 4 activities but are not required to participate in practice improvement to maintain their certification.

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Diet and the Kidney

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tion can be compared with the cultural resistance to smoking cessation during the 1960s after the Surgeon General report was released. During the 1960s, tobacco use was viewed as a social choice and not a medical or social public health problem."

In an accompanying Patient Voice editorial, Duane Sunwold said he is a patient with CKD who changed his eating and drinking patterns to put his disease in remission. As a chef, he offers a number of recommendations to fellow patients trying to decrease their consumption of sugar-sweetened drinks.

Balancing fruit, vegetable intake and kidney failure

The second *CJASN* study examined the effects of fruit and vegetable intake in patients undergoing maintenance hemodialysis. Although higher fruit and vegetable intake is linked with lower cardiovascular and all-cause mortality in the general population and lower all-cause mortality among patients with mild to moderate CKD, kidney failure patients on hemodialysis are often discouraged from this type of diet due to its potential to cause a buildup of potassium and the development of hyperkalemia.

"Although diet is a key component of self-management and provides an important opportunity for a collaborative approach between patients and healthcare professionals to improve care, there is limited evidence on the impact of diet on patient-relevant outcomes," said lead author Valeria Saglimbene, MScMed, of the University of Sydney School of Public Health, in Australia.

In the study of 8078 hemodialysis patients who completed food frequency questionnaires, only 4% of patients consumed at least 4 servings of fruits and vegetables per day as recommended in the general population. The investigators noted that there were 2082 deaths (954 from cardiovascular causes) over a median follow-up of 2.7 years. Compared with patients who had 0–5.5 servings of combined fruits and vegetables per week, those who had 5.6–10 servings and those who had more than 10 servings had 10% and 20% lower risks of dying from any cause, respectively, as well as 12% and 23% lower risks of dying from non-cardiovascular causes.

"These findings suggest that well-meaning guidance to limit fruit and vegetable intake to prevent higher dietary potassium load may deprive hemodialysis patients of the potential benefits of these foods; however, intervention trials of fruit and vegetable intake are needed to support dietary recommendations for hemodialysis patients," said co-author Germaine Wong, MBBS, PhD, also of the University of Sydney School of Public Health. "Future studies exploring the potential benefits of a whole dietary approach in the hemodialysis setting are also warranted and we aim to pursue them," added senior author Giovanni Strippoli, MD, PhD, of Diaverum AB, in Sweden and the University of Bari, in Italy.

In an accompanying editorial, Ranjani Moorthi, MD, of Indiana University noted that the findings may spur future studies. "The hope is this excellent cohort study will form the basis of well-designed randomized controlled trials to test the effects of fruits and vegetables in patients undergoing hemodialysis, so we, their nephrologists, along with renal dietitians, can provide the details of dietary guidance they deserve."

MOC Returns as Hot Issue

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To date, neither ABMS nor the other 23 specialty boards have followed ABIM's lead and suspended Part 4. However, ABMS and all its specialty boards (including ABIM) have made major changes to Part 3 of MOC, which uses a summative (or high-stakes) process to assess the knowledge, judgment, and skills of physicians.

For example, ABIM in 2018 initiated "a two-year assessment option, called a Knowledge Check-In (KCI), for many physicians to provide them with more convenience in meeting the assessment requirement." According to ABIM, "KCIs take about three hours, and include access to UpToDate® during the exam." Nephrologists who choose "KCI can take it in either a test center or online, such as from their home or workplace," ABIM stated.

In its draft report issued in December 2018, ABMS's Vision Commission made 15 recommendations (https://visioninitiative.org/). The report received about 2000 comment letters, with the two draft recommendations relating to Parts 3 and 4 of MOC receiving the most attention:

- "Continuing certification status should not be withdrawn solely due to substandard performance on a single, infrequent, point-in-time assessment."
- "Practice improvement is an important part of continuing certification programs."

Responding to the draft report and recommendations, ASN (https://www.asn-online.org/education/moc/) agreed with many of the comments made by the Council of Medical Specialty Societies (CMSS)—which consists of 43 specialty societies, including ASN, that represent nearly 800,000 physicians—and other stakeholders. In particular, ASN and CMSS urged the commission "to propose 1) pausing the use of the high-stakes, summative examination for continuing certification and 2) suspending the practice improvement component for continuing certification."

Highlighting that "distrust exists among some diplomates regarding ABMS and its boards," ASN President Mark E. Rosenberg, MD, FASN, stated in the society's comment letter that "transparency, consistency, and uniform compliance are essential to addressing this concern." ASN "is committed to working with ABMS and its boards on a pause and suspension, proposed by CMSS (https://cmss.org/), to allow the entire physician community to reach agreement on the timeline, process, and vision for reinventing continuous certification," Dr. Rosenberg added. He concluded that ASN "stands ready to support efforts to make continuing certification a meaningful assessment program valued by physicians."

Matthew A. Sparks, MD, FASN—who facilitated a recent #AskASN Twitter chat hosted by Nephrology Journal Club about the commission's draft report and recommendations—summarized the discussion as follows: "I hope to see a solution that removes the high-stakes exam, incorporates credit for things we are already doing, and makes us all better physicians without fear of losing our livelihood."

The commission is scheduled to release its final report soon. At that time, the physician community will learn how, or if, the commission will incorporate all the feedback it received. The ABMS Board of Directors will consider the final report; if ABMS is supportive, then the 24 individual boards, including ABIM, will determine how best to move forward. Ideally, ABMS and all 24 boards will agree, as will the rest of the physician community and other stakeholders.

It's also possible that the final report will create more disagreement within ABMS, among the boards, and across the community. Even if that happens, ASN will continue to commit its resources and expertise to support nephrologists focused on maintaining excellence in care throughout their careers.

ASN Policy Statement on Maintaining Career Excellence

1. ASN endorses the role of the American Board of Internal Medicine—as one of the American Board of Medical Specialties' 24 specialty boards—to provide the initial certification for nephrologists.
2. ASN supports the lifelong learning of nephrologists through educational activities and self-assessment programs.
3. ASN believes in the right of each nephrologist to choose a process of maintaining career excellence that affirms the values of the medical profession as well as highlights to the public her/his ability to provide high-quality care.
4. ASN opposes efforts by entities outside the medical profession to weaken the public's faith in the ability of the medical profession to self-regulate.
5. ASN is committed to working for its members and their patients to:
   a. Improve all aspects of the assessment of professional competence.
   b. Explore innovative and more efficient approaches to ensuring nephrologists provide high-quality care for their patients.

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Putting Kidney Diet Apps to the Test

A growing effort is under way to produce evidence-based kidney disease nutrition apps

By Bridget M. Kuehn

Diet and other health tracking mobile applications have become a part of everyday life for many people, and patients with kidney disease are no exception. Patients can choose from numerous kidney nutrition apps available in app stores, but experts warn many contain misleading or inaccurate information and few have undergone rigorous testing to ensure they are safe and effective.

A growing number of clinicians are trying to change that by developing and rigorously testing apps that help kidney patients make dietary choices to optimize their health. In September 2018, the American Association of Kidney Patients (AAKP), the Veterans Transplantation Association, ASN, and the US Department of Veterans Affairs (VA) began recruiting patients to test the MyKidneyNutrition app. The testing collected feedback from kidney patients to ensure the app truly addresses the needs of kidney patients and serves as a resource to track daily activities including nutrition, fitness, and medication information. The MyKidneyNutrition app will become publicly available in early 2019, and was jointly developed by ASN and the VA.

"The MyKidneyNutrition app will raise awareness of patients' day-to-day activities and the impact they have on their care," said Edward V. Hickey, III, chair of AAKP's Veterans Health Initiative.

Avoiding pitfalls

Nutritionist Kelly Lambert, MSc, a renal dietician at the University of Wollongong in Australia, and her colleagues decided to take a look at the nutrition apps available on the market after getting numerous queries from patients and their families about diet tracking apps. In their review (1), they assessed the accuracy and usability of the information provided in 21 renal diet apps available for sale in Australian app stores. More than half of the apps reviewed contained inaccurate information.

"Apps shouldn't replace health professionals," Lambert said.

Lambert explained that many apps simply did not use reliable sources of information on food content, if they disclosed their source of information at all. Often apps presented information that was misleading or that might have suggested a more restrictive kidney diet than was necessary for patients with earlier stages of kidney disease. For example, an app would suggest avoiding bananas, which may be important for patients on dialysis, but isn't always necessary for other patients with CKD.

"Often it was restricting foods unnecessarily," she said. "The dietary restrictions are hard enough."

That's concerning because unnecessary food restrictions may cause frustration for patients or make it harder for them to comply. She noted that nutritionists help patients navigate food choices that are appropriate for their disease stage. Sometimes it's a matter of sticking with smaller portions of certain foods, she said.

"Patients want black and white, but dieticians work in gray," she said.

Another potential pitfall with nutrition apps is that they may provide inaccurate or outdated information about the nutritional content of foods. Lambert noted that food composition may be different in Australia compared with the United States because of differences in the way food is grown or made. For example, in the United States, many products contain significantly more phosphate than the Australian products. Also, the composition of food products changes often and databases of nutrition information may not keep up. For example, many US food producers are reducing salt in products like bread and adding potassium chlorate.

A few apps stood out for providing good information, including the National Kidney Foundation's My Food Coach app and H2O Overload. Lambert suggested that savvy patients who want to use a dietary app check who made the app and where they get their information, and then ask their clinicians about the app they are interested in.

"A good clinician should be able to recommend an app," she said.

The MyKidneyNutrition app will raise awareness of patients' day-to-day activities and the impact they have on their care

Building a better app

In light of the limitations of some of the commercially available apps, many clinicians are working to build better ones that have been carefully designed to meet patients' needs and tested in clinical trials to ensure they work.

Deborah Zimmerman, MD, associate professor of medicine in the Division of Nephrology at the Ottawa Hospital and University of Ottawa in Canada, built the OkKidney app to help her patients better manage their serum phosphate levels. She noted that it can be confusing to patients to track the phosphate content of foods.

"Despite all of our dieticians' efforts to educate them, some of them just find it completely overwhelming," she said.

Without clear information on how much phosphate patients are consuming at each meal, Zimmerman also wasn't sure if she was prescribing the appropriate amount of phosphate binding medications. So, she designed an app that would help patients count the phosphate content of their food and provide them an appropriate prescription. In her small pilot (2), she found patients' phosphate control didn't change much after using the app, but they were able to reduce the amount of phosphate binders they took. Since most Canadian patients are prescribed calcium-based binders, reducing their exposure is helpful, she noted.

"It decreases pill burden, which is huge for our patients, but may also, in the long term, perhaps have an impact on vascular calcifications," Zimmerman said. In the US, she noted use of non-calcium phosphate binders is more common, so calcifications may be less of a concern.

Now, she's begun recruitment for a larger trial. If the trial verifies the benefit of her app, it would only be available by prescription.

"We're actually asking people to use it over a longer period of time," she said. "Will they actually continue to be engaged and use it, and is it actually effective?"

Lambert has also created a free app called Easy Diet Renal, which is available only in Australia and Asia. She noted that it is very important for clinicians developing apps to involve patients in the process, and also to work with app designers and others who can make them easy to use.

The MyKidneyNutrition app

Veterans and other patients were involved in the development of the MyKidneyNutrition app, noted AAKP Past President Paul Conway. The veterans who participated saw it not only as a way to help manage their care between visits, but also as a continuation of their service to their fellow veterans, noted Hickey.

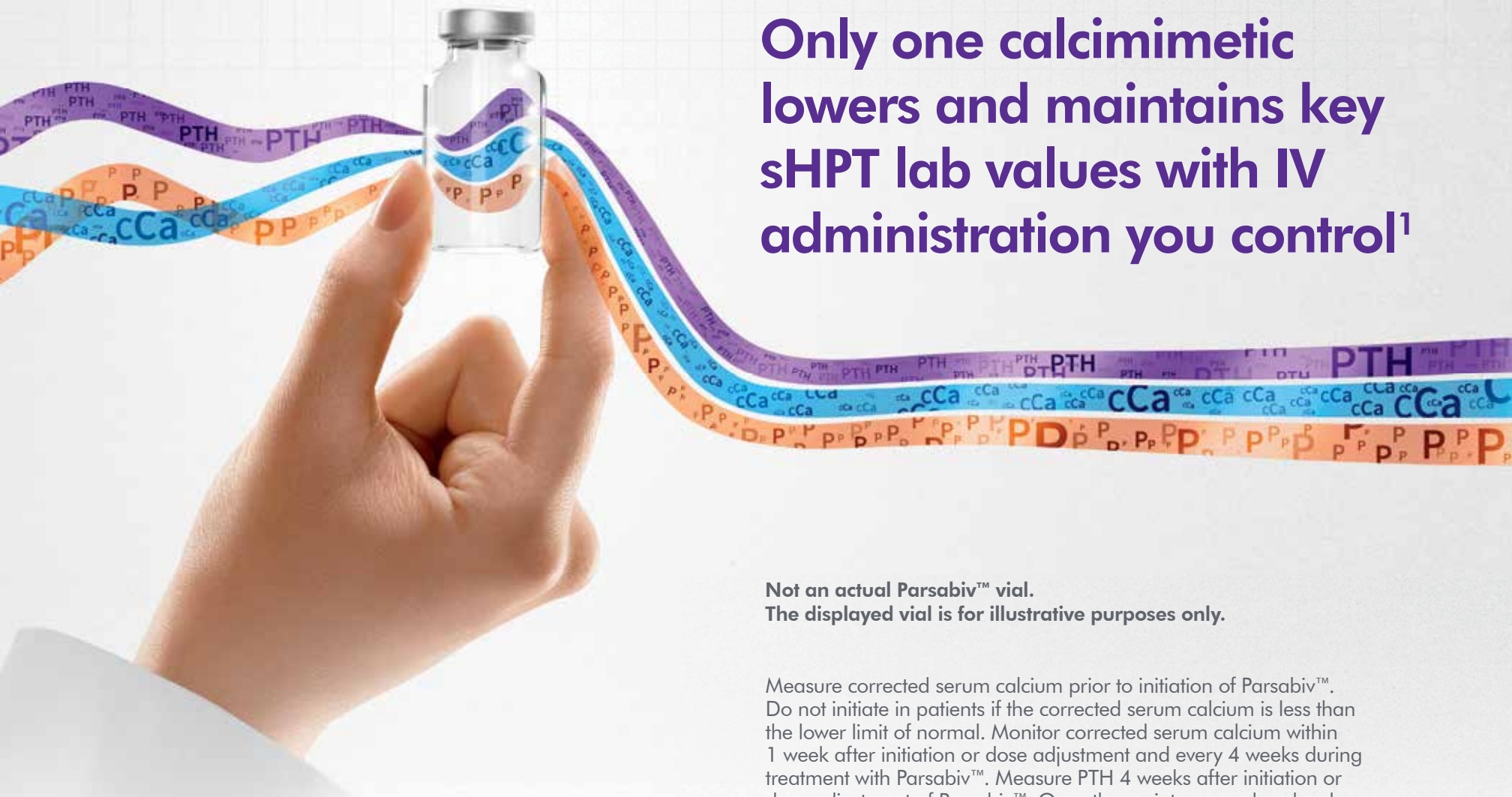
"The entire development process involved patients," Conway said. "If we're going to do it right it needs to reflect not only the needs, but the individual preferences that vets may have."

While the experts are optimistic that a growing array of evidence-based digital tools for patients are on the horizon, they are also quick to note the currently available apps aren't a replacement for working with a dietician or other clinicians.

"When it comes to our nutrition, I rely very heavily on our registered dieticians," said Zimmerman, who hasn't yet recommended any of the apps currently available.

References

1. Lambert K, et al. Should we recommend renal diet–related apps to our patients? An evaluation of the quality and health literacy demand of renal diet–related mobile applications. *J Renal Nutr* 2017; 27:430–438.
2. Imtiaz R, et al. A pilot study of OkKidney, a phosphate counting application in patients on peritoneal dialysis. *Perit Dial Int* 2017; 37:613–618.



Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

Not an actual Parsabiv™ vial.
The displayed vial is for illustrative purposes only.

Indication

Parsabiv™ (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

Hypocalcemia: Parsabiv™ lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv™. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv™.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv™. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv™.

Concurrent administration of Parsabiv™ with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv™ should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv™. Closely monitor corrected serum calcium in patients receiving Parsabiv™ and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv™. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv™. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv™. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv™ clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv™ for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv™ in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv™.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv™. Monitor patients for worsening of common Parsabiv™ GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv™ therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv™ to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.

Parsabiv™ (etelcalcetide) Injection for intravenous use

2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv™
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2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

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Moving Nephrology Care and Caregivers FORWARD

By Richard A. Lafayette

As I considered possible developments in nephrology for this coming year, I could not help but think a bit further forward to the year 2020. This led me to think more about the Centers for Disease Control and Prevention's Healthy People 2020 initiative (1), the national blueprint designed to bring about effective preventive care and improved health to the U.S. population by 2020. This ongoing initiative started decades ago, issuing 10-year plans and starting with general interventions such as ensuring a clean environment, drinkable water, good nutrition, increased exercise, and access to high-quality healthcare. The plan then moved into care for specialty areas, including acute and chronic kidney disease (CKD).

One objective of Healthy People 2010—to reduce new cases of ESRD—was retained "as is" for 2020. Others were modified, and several new objectives were added. Overall, these objectives seek to reduce the incidence of ESRD, improve the mortality rates of incident and prevalent patients receiving dialysis, improve access to and outcomes of kidney transplantation, improve the identification and care of patients with acute kidney injury (including setting standards for follow-up), include specific objectives for patients with diabetic kidney disease (reducing rates, controlling BP and lipids), and finally improve the overall awareness of patients with CKD. As an example of goal setting, Healthy People 2020 determined that fewer than 10% of adults with CKD knew they had CKD. A stated goal was to increase awareness to 13.4%.

It is always interesting to see whether and how these objectives are fulfilled years after their introduction. The objectives of Healthy People 2020 are supported by funding from the National Institutes of Health (NIH) and other government research organizations and shaped by the Centers for Medicare & Medicaid Services (CMS), which creates incentives and penalties for providers to induce them to embrace and, it is hoped, achieve these goals.

In general, it is difficult to assess how successful these programs are in changing the nation's healthcare practices because data emerge slowly and outcomes may change through other actions. Clearly, the NIH and the CMS influence physicians' and providers' practices. Incentives and penalties do get attention and results, but often they risk corresponding changes in areas that are not under immediate focus (2). For example, if dialysis access becomes a focus for measurement and intervention, sometimes areas such as bone disease may get less attention. Large numbers of studies demonstrate that guidelines are often ineffective or take a long time to affect practice (3). Nonetheless, there is inherent value in experts gathering and setting goals for general health issues of the nation and for specific health conditions, such as those facing patients in nephrology practices. Often, just identifying focus areas allows increased attention, which can yield improved outcomes.

In the latter part of this decade, however, many strong influences have had an impact on the ability of physicians and other caregivers to provide optimal care. This both generally and specifically applies to nephrology. Nationally, payment reform has taken a lot of attention and time to try to learn, and it is still unclear whether caregivers will need to work harder and longer to earn the same incomes under pay-for-performance or risky cost-sharing schemes. Electronic medical records are increasingly prevalent and require huge chunks of time in logging in and out and in providing the appropriate documentation and services. They have generally shifted more and more work to the provider rather than to support staff. With regard to maintenance of certification, physicians continue to struggle to find the right balance between ensuring community standards for knowledge and diverting provider care toward efforts that do not improve care or efficiency.

More specifically to nephrologists, care in dialysis units is increasingly deter-

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Nephrology Care and Caregivers

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mined by dialysis unit policies rather than by discussions between caregiver and patient, based on the bundle and requirements for frequent visits. Care in the hospital can be increasingly fragmented as hospitalists struggle to learn the stories of patients whom they don't care for as outpatients and as other specialists take on procedures traditionally done by nephrologists, such as biopsies, intravenous lines, and even continuous dialysis. The complexity of care of our patients seems to be ever increasing. These challenges threaten to lead to burnout and frustration, and they threaten to make the field one in which it is increasingly difficult to sustain a career. This also makes it harder to recruit future trainees.

The years 2019 and 2020 may usher in a further realization of these trends, and reform may become the new buzzword. Programs like Healthy People 2020 may actually show how nephrologists routinely improve patient care and add value to medical care, ultimately providing them a better bargaining position (4). Such programs may position nephrologists again to determine what procedures they do for their patients.

Long-promised innovations in electronic medical records may free up time for more effective face-to-face interactions and allow us to actually think about optimal care. Translational advances in dialysis, transplantation, acute kidney injury, hypertension, and glomerular disease (among others) may make nephrology ever more exciting as a field, ushering in greater joy in the profession and turning the tide on recruitment concerns.

Let's not just watch and see; let's try to make it happen.

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New Insights into Acute Kidney Injury and the Role of the Microbiome

By Sonali Gupta, Jose Pichardo, and Joseph Mattana

The gut microbiome is believed to have evolved with time and exists in symbiosis with the system in the healthy state because of its synthetic, metabolic, and immune properties. Recent studies have hypothesized that specific microbial metabolites, particularly short-chain fatty acids and D-amino acids (D-AAs), are important contributors to the maintenance of health. Disturbance of this relationship, known as dysbiosis, has been implicated in various diseases.

The emerging literature on the metabolic potential of gut microflora and its integral role in the pathogenesis of inflammatory conditions is attracting increasing interest from the nephrology community in further exploration of the gut–renal axis. For example, there is evidence that the microbiome may play a role both in the progression of chronic kidney disease (CKD) and in the uremic complications of CKD. In addition to CKD and complications of uremia, accumulating data suggest that the microbiome also plays an important role in the mediation of renal damage in acute kidney injury (AKI) (1).

Although the kidneys are generally not considered to be conventional immune organs, resident dendritic cells and macrophages play a role in the maintenance of a delicately balanced inflammatory homeostatic environment within. For example, in contrast to control mice, kidneys of germ-free (Gf) mice have been found to have lower IL-4 levels and increased natural killer T cells. After ischemia/reperfusion (I/R) injury to Gf mice, a significant accumulation of CD8 T cells within the kidneys occurs, resulting in more severe renal damage than in control mice. When Gf mice received fecal transplants from control mice, the renal damage from I/R injury was much less than, and comparable with, that in control mice, suggesting a role of gut microbiota in modulating renal inflammation (2).

However, the interaction between the gut microbiome and the kidney and the pathogenesis of renal damage in AKI is complex, and the microbiome effects on renal inflammation may not necessarily exert a general salutary effect. Emal et al. showed contrasting results in that lower expression of the chemokines CX3CR1 and CCR2 in gut flora–depleted mice resulted in attenuated renal damage after I/R injury (3). Additionally, after fecal transplantation from untreated mice, a protective effect on renal damage was lost, suggesting that depletion of gut flora after antibiotic treatment resulted in depletion of the harmful gut microflora while promoting the prevalence of AKI-protective microflora.

. . . the interaction between the gut microbiome and the kidney and the pathogenesis of renal damage in AKI is complex, and the microbiome effects on renal inflammation may not necessarily exert a general salutary effect.

After I/R injury in an AKI mouse model, there is a change in the gut microflora, with a predominance of *Lactobacillus* species, *Clostridium* species, and *Ruminococcus* species and a reduction in *Bifidobacterium* species (4). Regardless of the renal insult, the gut microflora metabolize the D-AAs, but after I/R injury only D-serine was detected in the kidney, and an elevated D-serine/L-serine ratio was found in the urine, feces, and plasma of I/R mice. It was suggested then that the gut microbiota is responsible for D-AA generation, particularly D-serine, inasmuch as no D-AAs, except D-asparagine and D-aspartic acid, were detected in the feces of Gf C57BL/6 (Gf B6) mice before and after I/R. It was also demonstrated that after renal insult, the activity of D-AA oxidase decreases and that of serine racemase increases. D-serine was shown to promote tubular cell proliferation after hypoxic damage and to mitigate hypoxia-induced tubular damage. Interestingly, the renal injury in GfB6 and D-serine–depleted mice was alleviated by the oral administration of D-serine, suggesting a potential therapeutic role of D-serine in AKI (4).

These recent studies suggest that the microbiome plays an important role in the mediation of kidney damage in AKI. However, the interplay appears to be complex, and changes in the microflora may either ameliorate or promote renal damage. It is hoped that over the several coming years, further studies of the microbiome and inflammation, and of the impact of its modulation on the development of renal damage in AKI, will better define these mechanisms and help identify effective therapies to help prevent and treat AKI.

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Novel Biomarkers to Monitor and Predict Rejection in Kidney Transplantation

By Uday Nori

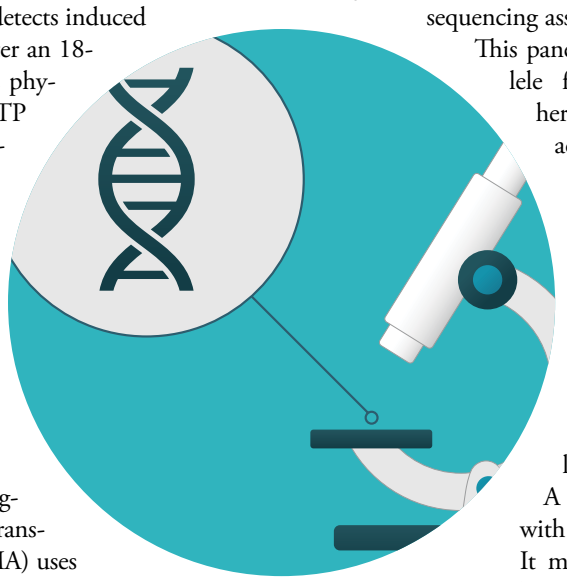
Despite the substantial successes of kidney transplantation, this field continues to be hampered by the inability to monitor the intensity of the immunosuppressive regimens. As a result, chronic antibody-mediated rejection (under-immunosuppression), as well as drug-related toxicity, malignancies, and opportunistic infections (over-immunosuppression) continue to be the leading causes of allograft loss.

In addition, counter to all the predictions, the vast improvement in the early acute rejection rate has not resulted in similar improvement in long-term allograft survival. Serum creatinine, the traditional marker to monitor kidney function, is highly unreliable in predicting renal injury of any kind. Protocol kidney biopsies, in addition to being invasive, suffer from poor inter-observer variability, sampling bias, and limited acute rejection prediction. Therefore, the majority of the above- mentioned complications are diagnosed after they have occurred. Ideally, the goal of post-transplant monitoring should be to predict and prevent such complications. Clearly, a reliable biomarker to predict acute rejection that is non-invasive and inexpensive is the most urgent need in the organ transplantation world, as long as the "holy grail," transplant tolerance, remains elusive.

The earlier years of organ transplantation employed crude immunosuppressive regimens to prevent acute rejection but resulted in mortality as high as 50% within the first year because of severe infections. Improved understanding of the biology of rejection led to the development of more sophisticated drugs during the 1980s and 1990s, mainly targeting the T and B lymphocytes. To prevent toxicity, therapeutic drug level range was identified and monitored for some drugs such as cyclosporine and sirolimus. However, the pharmacokinetics of the drugs did not serve the clinician in understanding the pharmacodynamics of the drug in the individual patient, and over- or under-immunosuppression continued to remain a problem.

Earlier, there was an interest in the role of quantitative immunoglobulins, specifically IgG, in the long-term management of the transplant recipient. Immunosuppression was slowly weaned as long as the IgG level was in the normal range. Indeed, development of hypogammaglobulinemia in immunosuppressed patients was identified as a serious risk for infectious diseases of all types. However, this method did not predict T cell behavior, which is critical in predicting acute rejection.

The previous decade saw the introduction of more advanced techniques. Numerous methods were proposed, including DNA microarray analysis in kidney biopsy specimens, to detect gene expression profiles associated with rejection; measurement of urinary cell mRNA profiles; and the ELISPOT assay. A detailed discussion about these markers is beyond the scope of this article but one of these deserves special mention. A cell-mediated immune function assay, Immuknow (Cylex Inc., Columbia, MD), was introduced in 2002. This test detects induced ATP levels in the CD4+ T cells after an 18-hour incubation with a mitogenic phytohemagglutinin. The resulting ATP level estimated the T cell alloreactivity, which is calibrated to predict infection vs. rejection. This test initially gained widespread popularity, but subsequent studies showed conflicting results. While this test is still commercially available, its role in transplant patient management remains uncertain.



Two recently introduced novel genetic methods offer hope in bridging this gap. The TruGraf test (Transplant Genomics Inc., Mansfield, MA) uses peripheral blood samples to study gene expression patterns using microarray analysis (1). The test is based on the idea that gene expression patterns within the allograft are unique for normal functioning compared to renal injury, and this pattern is detectable in the peripheral blood. In this test, RNA is extracted, amplified, and hybridized to DNA microarrays. The pattern of hybridization, or "signature," is then compared to a reference dataset using an algorithm to generate a qualitative result of "Transplant eXcellence" (TX) or "not-TX." TX indicates immune quiescence, suggesting to the clinician that the patient is adequately immunosuppressed, and not-TX suggests that immunosuppression modification is warranted. For example, patients with previous TX status that changes to not-TX status following a reduction in immunosuppression might benefit from reversing the immunosuppression change or from a diagnostic kidney biopsy. TruGraf was tested in 105 transplant patients in four medical centers and had a 73% concordance with the final diagnoses made based on other clinical data. The sensitivity of this test was 81%, specificity 70%, positive predictive value (PPV) 47%, and negative predictive value (NPV) 92%, with a false negative rate of 19%. The test will likely become commercially available soon.

Allosure® (CareDx, Brisbane, CA) is a donor-derived cell-free DNA (dd-cfDNA) measurement technique in the peripheral blood (2). The premise of the test is that injury to the transplanted kidney leads to cell death and that escape of cell DNA into the peripheral blood can be measured. The test employs targeted amplification and sequencing of single-nucleotide polymorphisms (SNPs) to quantify donor and recipient DNA contributions in each patient's blood sample. This is accomplished without requiring the donor or the recipient's DNA genotyping information. The test utilizes a next-generation sequencing assay that employs 266 SNPs. This panel was selected based on allele frequency across ancestral heritage groups, sequencing accuracy, and lack of linkage. These SNPs were also chosen not to have association with common genetic disorders to avoid reporting incidental findings. Based on several validation studies, the result of <1% dd-cfDNA is associated with high NPV and low PPV for acute rejection. A value of >1% is associated with risk of active rejection.

It must be noted that another test utilizing dd-cf DNA developed by Natera (San Carlos, CA) is being offered for transplant patients.

Despite the excitement and promise of these tests, a few important points are to be noted:

1. The test results are qualitative and not quantitative. They do not provide information on the severity of rejection.
2. Positive test results do not provide all the information that clinicians require. More clinical data including a renal biopsy are often indicated.
3. The test platforms utilizing microarrays and SNPs are FDA-approved, but the tests themselves need further validation by widespread clinical use before they become part of the standard of care.

Together, these tests offer a unique opportunity to monitor, predict, and manage acute rejection episodes in kidney transplant patients. If successful, they have the potential to bring about a long-awaited radical improvement in posttransplant outcomes. ■

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Targeting Inflammation in Autoimmune Kidney Diseases

By Andreas Kronbichler and Gert Mayer

The addition of anti-inflammatory and immunosuppressive drugs to the standard of care (SOC) treatment of systemic autoimmune disorders affecting the kidney has impressively improved outcomes over the past decades. Nonetheless, for example, the adjusted mortality rate of individuals with anti-neutrophil antibody (ANCA)–associated vasculitis is still 2.71 in comparison with the general population (1).

Uncontrolled disease activity and infectious complications are major risk factors for early mortality, but side effects of immunosuppression, and in particular corticosteroid therapy, increase long-term morbidity and mortality. Next to promoting the development of hypertension, osteoporosis, weight gain, and diabetes along with coronary heart disease (2), corticosteroids decrease patients' quality of life, inducing sleep disorders, anxiety, impaired mood, or loss of self-confidence (3). Therefore, a major goal of clinical research is to increase the array of available treatments, taking into consideration the complexity of the pathophysiology of ANCA vasculitis, to allow better tailoring of therapy to individuals' needs.

“Uncontrolled disease activity and infectious complications are major risk factors for early mortality, but side effects of mmunosuppression . . . increase long-term morbidity and mortality.”

The complement system has been recognized to play an important role in ANCA vasculitis, and C5a perpetuates inflammation by priming chemotaxis, but it also induces hypercoagulability, neutrophil extracellular traps, and neutrophil tissue factor–expressing microparticles.

In the clinical phase 2 CLEAR trial, Avacopan, an oral C5aR inhibitor, was administered without or with reduced (20 mg) corticosteroids as part of the induction therapy. In both active treatment groups there was a faster decline in the Birmingham Vasculitis Activity Score and urinary albumin/creatinine ratio (4). The larger phase 3 ADVOCATE trial will compare a steroid-free induction treatment including Avacopan with SOC. Already, more than 300 patients worldwide have been recruited, and the first results can be expected by the end of 2019. Reduction of the cumulative corticosteroid exposure has been adopted in several recent treatment protocols, including rituximab and low doses of cyclophosphamide in the induction of remission (5–7). A reduced steroid regimen alongside rituximab induction will be tested in a Japanese multicenter LoVAS trial (8).

Although considerable progress has been made in ANCA vasculitis, the situation is more complex in lupus nephritis (LN). Several recent clinical studies did not show an improved outcome, with limitations in trial design probably contributing to failure (e.g., limited follow-up time in the context of existing effective SOC induction therapy, definition of endpoints, low sample size/statistical power) (9).

With regard to long-term therapy, however, it is extremely troubling that in a real-life setting, about three-quarters of patients are still receiving corticosteroids after 10 years (10). Safe and effective corticosteroid reduction/avoidance protocols are thus also urgently needed. In an attempt to achieve this goal, pulse methylprednisolone may be effective because it not only leads to a higher complete remission rate but also lowers the risk of corticosteroid-related side effects (11). A regimen avoiding oral corticosteroids (2 doses of rituximab, 2 times 500 mg methylprednisolone and mycophenolate mofetil as maintenance treatment) achieved high remission rates in a single-center study (12).

The RITUXILUP trial aimed to investigate this strategy in comparison with an SOC arm. The trial terminated early because of slow recruitment and withdrawal of funding, but an analysis of 25 patients supported the hypothesis that a regimen without oral corticosteroids can be effective (Lightstone L, ASN Kidney Week 2018). In addition, novel strategies are currently being tested in clinical trials. In the AURA-LV study, low-dose voclosporin in addition to SOC led to higher rates of complete renal remission (13). The results are currently being tested in the large phase 3 AURORA randomized controlled trial. After B cell depletion with rituximab, a counter-regulatory increase in the B lymphocyte stimulator has been reported (14). Consequently, strategies to use rituximab followed by belimumab to suppress B cell recovery have been developed. Unfortunately, the first results from the CALIBRATE trial with a follow-up time of 24 weeks did not show a higher rate of complete remission after the addition of belimumab (Aranow C, EULAR Congress 2018) in systemic lupus erythematosus. Other promising agents are currently also being tested in LN (Figure 1). One goal is to block the “interferon signature.” Even though a trial testing of anifrolumab, a monoclonal antibody blocking the activity of all type I interferons, failed to meet the primary endpoint in the TULIP1 trial, a study including patients with LN is on its way (TULIP-LN1, NCT02547922).

On the basis of the substantial clinical need and the substantial interest from the industry and investigators to conduct clinical trials, there is hope that therapy of LN will also undergo major changes over the years to come.

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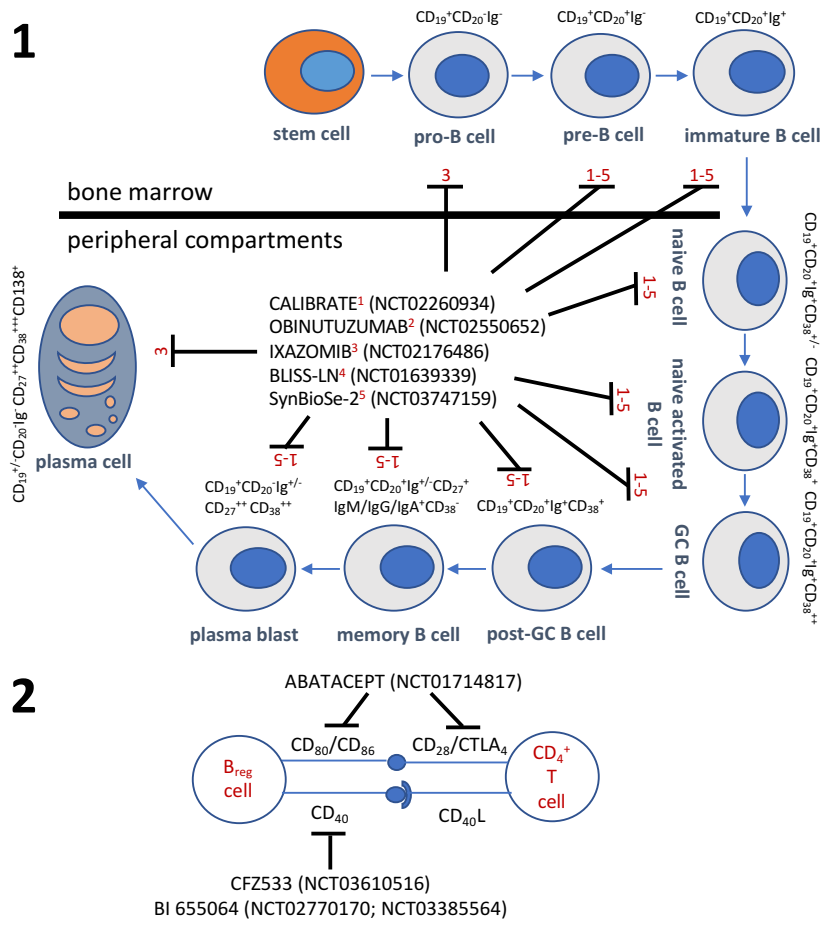
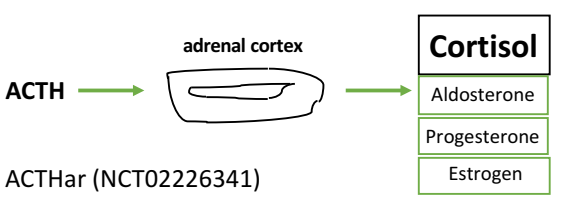
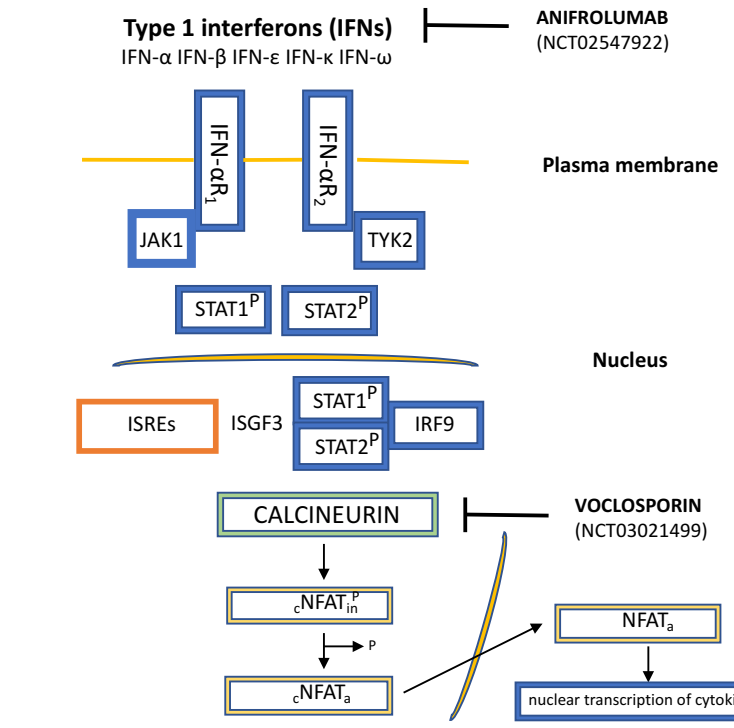
Figure 1. Selected novel strategies in the management of lupus nephritis







1. Several immunosuppressive drugs blocking differentiation steps in the B cell lineage are currently being tested. 2. Abatacept (CTLA4-Ig) has been tested in several trials in systemic lupus erythematosus (SLE) and lupus nephritis and failed to meet the primary endpoint in all clinical trials. Another strategy to impair B and T cell interaction is blockade of CD40. 3. Acthar gel is tested in several autoimmune conditions affecting the kidneys. One clinical trial in lupus nephritis is ongoing. 4. Type 1 interferons are centrally involved in SLE pathogenesis. The TULIP-LN1 trial is testing the efficacy of type 1 interferon blockade in the management of lupus nephritis. 5. Calcineurin inhibitors have been successfully and increasingly used in the management of lupus nephritis. A novel calcineurin inhibitor, voclosporin, was superior to standard of care in a recent phase 2 trial. The larger international phase 3 trial (AURORA) is currently ongoing, and results are eagerly awaited (5).

CD, cluster of differentiation; CTLA4, cytotoxic T-lymphocyte associated protein 4; GC, germinal center; IRF9, interferon regulatory factor 9; ISRE, interferon stimulated response element; JAK1, janus kinase; NFAT, nuclear factor of activated T cells; reg, regulatory; STAT, signal transducer of activation; Tyk2, tyrosine kinase 2.

New Collaborations, Shake-ups Will Shape Healthcare Business in 2019

Look for shake-ups in the business of health in 2019. Insurers, providers, and other business interests are working together to fundamentally change the way healthcare is delivered.

We can only guess what changes may lie ahead, given the combination of Aetna and CVS. Amazon's acquisition of PillPack likely signals some sort of "Prime Drug" service in the future. We also need to keep an eye on their healthcare venture with Berkshire Hathaway. Industry insiders suggest they have an eye toward mining patient data for new insights and efficiencies.

Mergers and acquisitions no longer occur just among companies producing the same products. A brave new world of vertical integration of healthcare products and delivery seems to be coming. Keep your eyes on the news for the changing landscape.

SGLT2 Inhibitors and Cardiorenal Outcomes

By Brendon L. Neuen, Edgar V. Lerma, and Joel Topf

Our top area to watch for 2019 is the advent of sodium glucose cotransporter 2 (SGLT2) inhibitors, oral anti-hyperglycemic agents that have been recently approved for the treatment of type 2 diabetes mellitus (T2DM).

Aside from their glucose-lowering effect, SGLT2 inhibitors have also been shown to reduce blood pressure, body weight, and albuminuria. These multiple beneficial metabolic effects have contributed, at least in part, to reductions in cardiovascular and renal outcomes observed in large cardiovascular outcome trials. As a result, the American Diabetes Association's 2019 Standards of Medical Care in Diabetes (1) now recommends SGLT2 inhibitors as second-line therapy after metformin in patients with T2DM and atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease (CKD).

These agents promote glycosuria by selectively inhibiting SGLT2 transporters, which are expressed in the proximal tubule and are responsible for more than 90% of filtered glucose reabsorption. In addition to this, SGLT2 inhibitors also augment urinary sodium excretion, which contributes to plasma volume contraction and alterations in intrarenal hemodynamics (discussed below).

SGLT2 inhibitors currently approved by the US Food and Drug administration include empagliflozin (Jardiance), canagliflozin (Invokana), dapagliflozin (Farxiga), and ertugliflozin (Steglatro). Combination formulations are also available: empagliflozin/metformin (Synjardy), canagliflozin/metformin (Invokamet), dapagliflozin/metformin (Xigduo XR), and ertugloflozin/metformin (Segluromet).

Several large randomized controlled trials have recently been published, demonstrating the cardiovascular and renal benefits of these new agents.

The first of these was the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Event Outcome Trial in Type 2 Diabetes Mellitus Patients) (2), reported in 2015 (Figure 1). EMPA-REG OUTCOME was a randomized double-blind placebo-controlled trial that included 7020 participants with T2DM and established cardiovascular disease. This trial demonstrated that empagliflozin reduced the risk of major adverse cardiovascular events in addition to standard of care, driven by a 38% relative risk reduction in cardiovascular death. Empagliflozin also reduced the risk of heart failure by 35% and the composite renal outcome of doubling of serum creatinine, ESKD, or renal death by 46%.

The CANVAS (Canagliflozin Cardiovascular Assessment Study) Program (4) integrated data from two parallel randomized trials involving 10,142 participants with T2DM and high cardiovascular risk (Figure 2). The CANVAS program demonstrated that canagliflozin also reduced the risk of major adverse cardiovascular events, heart failure, and adverse renal outcomes but increased the risk of amputations, mainly at the toe/metatarsal level.

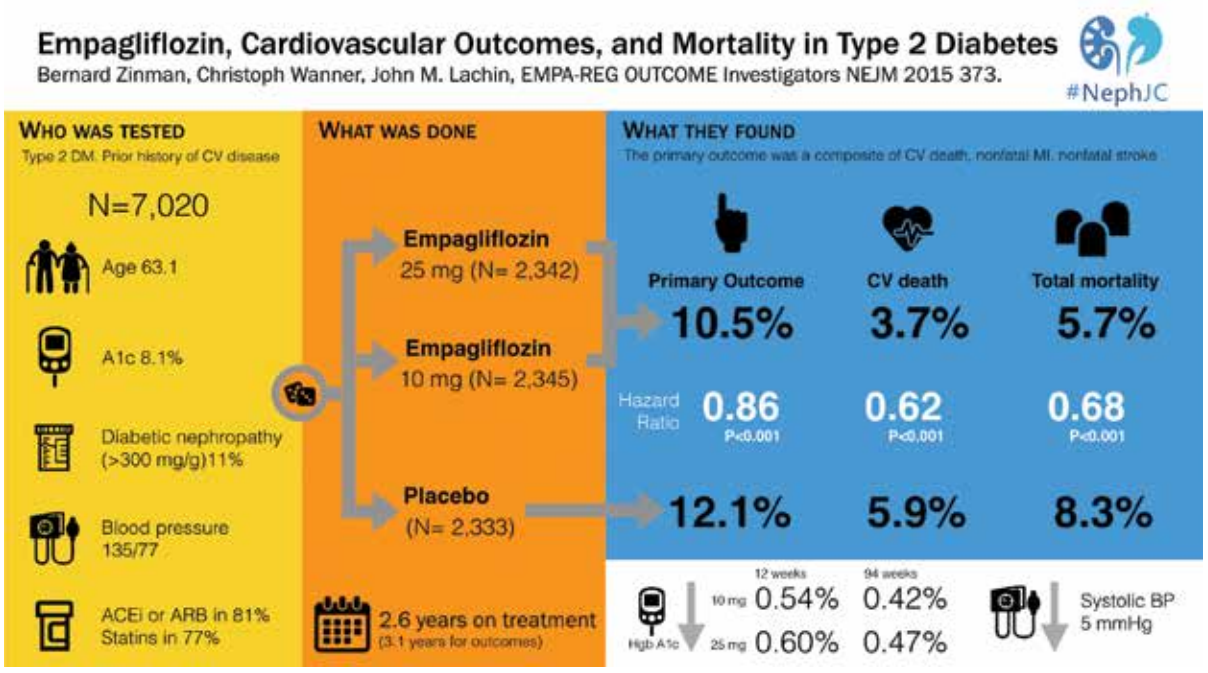
In November 2018, The DECLARE-TIMI 58 trial was published. This trial enrolled 17,160 participants with T2DM, two-thirds of whom did not have prior cardiovascular disease (i.e., a majority primary prevention cohort). While dapagliflozin did not reduce the risk of major adverse cardiovascular events, it did reduce the risk of hospitalization for heart failure and the renal composite outcome (40% decrease in eGFR, ESKD, or renal death), without any major safety concerns.

A characteristic feature of SGLT2 inhibitors is that their glycemic efficacy is dependent on glomerular filtration, and thus their effect on HbA1c diminishes with declining kidney function. In contrast, effects on blood pressure and albuminuria appear to be preserved in people with reduced kidney function, and secondary analyses of the EMPA-REG OUTCOME trial (4) and the CANVAS Program (5) suggest that the cardiovascular and renal benefits are similar regardless of baseline kidney function down to eGFR 30 mL/min per 1.73 m^2 (Figure 3).

A frequently cited explanation for the renoprotective effect of SGLT2 inhibitors is that they reduce intraglomerular pressure, which is critical in the pathogenesis of diabetic kidney disease. These agents increase distal sodium delivery to the macula densa, which activates tubuloglomerular feedback to promote afferent arteriolar vasoconstriction, and thus reduce intraglomerular pressure. This is reflected in an acute "dip" in eGFR, similar to that seen with inhibition of the renin-angiotensin-aldosterone system (RAAS). Importantly, approximately 80% of participants in these SGLT2 inhibitor trials were also receiving RAAS inhibition, which suggests that the renoprotective effects of these two classes of medications are additive, without any additional risk of acute kidney injury. However, participants with eGFR <30 mL/min per 1.73 m^2 were excluded from these trials, so the effects in this population are still unknown.

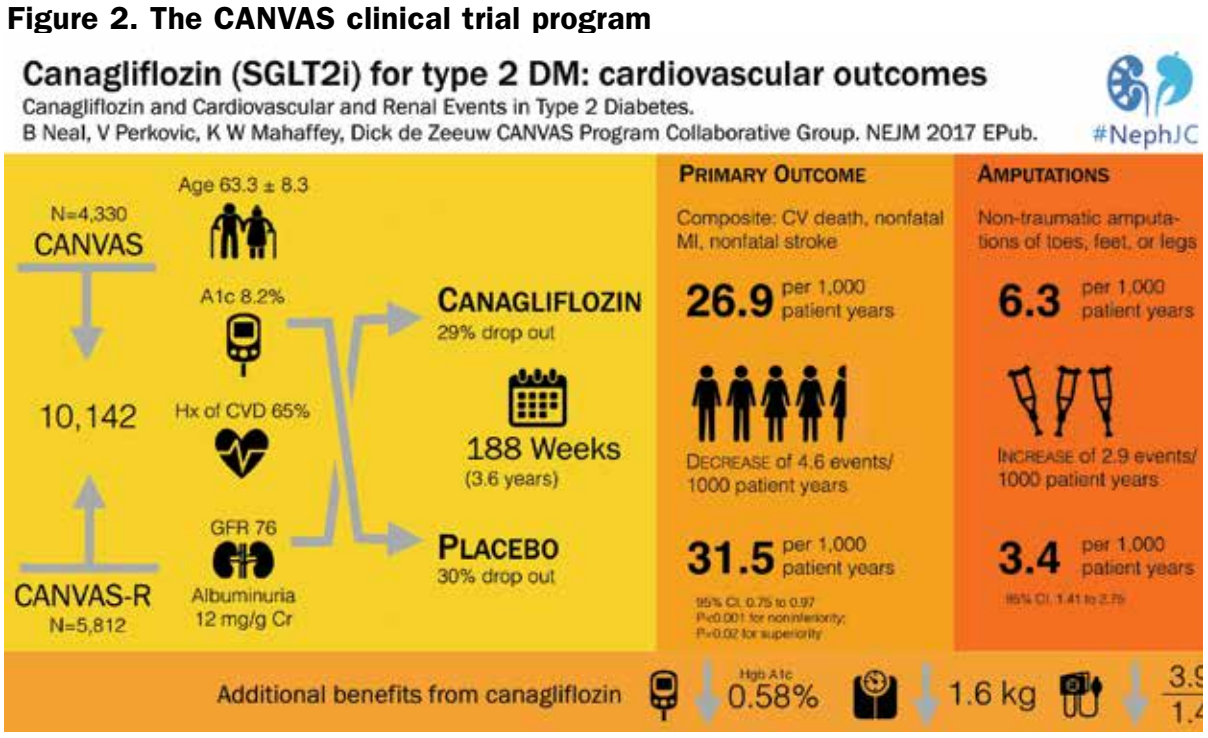
In July 2018, the CREDENCE (Canagliflozin and Renal Endpoint in Diabetes with Established Nephropathy Clinical Evaluation) trial was prematurely terminated because prespecified efficacy criteria had been achieved at a scheduled interim analysis (6). CREDENCE is a randomized double-blind placebo-controlled trial, which enrolled 4401 participants with stage 2 or 3 CKD and macroalbuminuria. Approximately 60% of these participants had an eGFR <60 mL/min per 1.73 m^2 at enrollment, and all were required to be on a maximally tolerated dose of ACE inhibitor or ARB for at least 4 weeks prior to rand-

Figure 1. The EMPA-REG OUTCOME trial



Visual abstract by Joel Topf

Figure 2. The CANVAS clinical trial program



Visual abstract by Joel Topf

omization. The results of this study will be presented on April 15, 2019, as a late-breaking clinical trial session at the World Congress of Nephrology in Melbourne, Australia.

Other dedicated CKD outcome trials that are forthcoming include EMPA-KIDNEY (7) and DAPA-CKD (8). Given the putative mechanism for renoprotection, both trials are enrolling participants with and without T2DM, and will thus provide important data on the effects of SGLT2 inhibition for cardiorenal protection in both populations. ■

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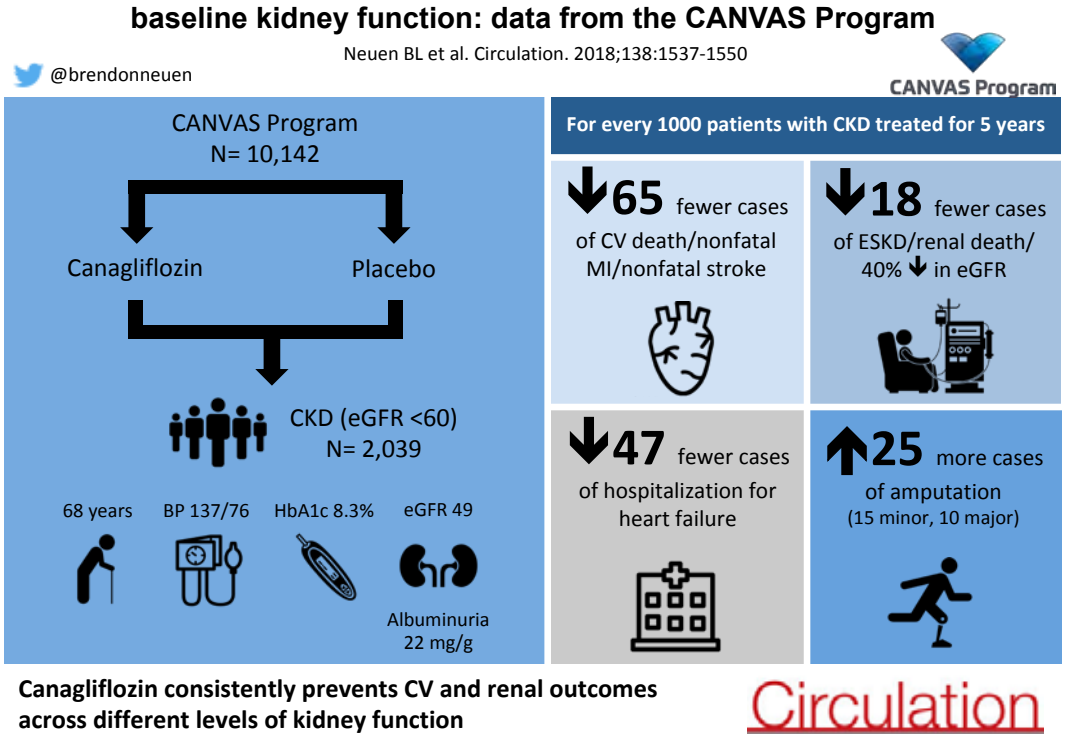
Figure 3. Cardiovascular and renal outcomes with canagliflozin



Visual abstract by Brendon Neuen

Policy Update

2019: A Lot is Happening Fast

By David White

The year 2019 promises to be a busy one in healthcare. In the face of a great deal of volatility, *Kidney News* readers can expect the following.

Mergers and acquisitions: Expect more, and sooner rather than later

A recent Capital One survey found that three-quarters of 291 senior executives across the healthcare spectrum are planning for better business performance in 2019. To exceed 2018 performance levels, 44% support more mergers and acquisitions (M&A), and 25% also expect to revamp or update existing merger offerings already on the table. In the latest figures from 2018, the third quarter saw 261 healthcare M&A deals according to PricewaterhouseCoopers (PwC). Value-based care policies and rising healthcare costs are seen as the main drivers in these deals, and 43% of the study's respondents said their greatest challenge for 2019 is regulatory and reimbursement changes.

These mergers are becoming increasingly vertical, in which the merging parties are not current competitors and are actually operating at different levels of the healthcare distribution chain. Examples include deals like UnitedHealth Group's acquisition of DaVita Medical Group; CVS and Aetna; Cigna and Express Scripts; and Humana and two private equity companies buying post-acute care provider Kindred Healthcare.

Regional hubs: A growing trend

Health systems—new mergers and existing ones—are also building regional care hubs within and across state lines. The objective is achieving a scale that can help them negotiate better rates with suppliers and payers and expanding patient access through outpatient facilities and telemedicine. Nephrology is already at the forefront of payment reforms to encourage telemedicine and support Medicare's stated goal of significantly increasing home dialysis rates. Aligning systems with regional population data can also reveal the most profitable service lines. Analysts have pointed to that approach in the Advocate Health Care and Aurora Health Care merger paving the way for a 27-hospital system spanning Illinois to Wisconsin with $10.7 billion in combined revenue.

Prescription drug prices: The fight is heating up

The midterm elections made it clear that a leading issue for the 2020 presidential race will be healthcare. The price of prescription drugs is one of the key components of that issue. There are a host of ideas that will likely be floated for 2019:

- Allowing the government to manufacture generics.
- Letting Medicare negotiate drug prices.
- Tying prescription drug prices to prices in countries like France, the United Kingdom, Germany, Japan, and Canada.
- Penalizing price gouging.
- Importing drugs from abroad—starting with Canada.
- Abolishing "pay-for-delay" deals in which a branded drugmaker pays off a generic one to keep a competing product from coming to market.

These approaches have differing ranges of support in Congress and the administration. In January 2019, Medicare closed the comment period on a proposed rule designed to lower the out-of-pocket costs of prescription drugs for Medicare beneficiaries by both prohibiting "gag clauses" in pharmacy contracts (gag clauses prohibit or penalize a pharmacy from disclosing a lower cash price to an enrollee) and removing protections from the "six protected classes of drugs." ASN supported the prohibition of "gag clauses" but strongly opposed the removal of protections for the protected classes of drugs, which include immunosuppressants,antidepressants, antipsychotics, antiretrovirals, anticonvulsants, and antineoplastics.

Repeal of the Affordable Care Act: Enter the courts

On December 14, 2018, a federal district court judge in Texas struck down the Affordable Care Act, siding with a group of 18 Republican state attorneys general and two GOP governors who brought the case. The ruling said the tax bill passed by Congress in late 2017 effectively rendered the entire health law unconstitutional. That tax bill eliminated the penalty for not having insurance.

Simultaneously, another federal district judge in Washington, DC, is presiding over a lawsuit brought by 12 Democratic state attorneys general to block a 2018 final rule issued by the Department of Labor making it easier for small firms and individuals to band together in association health plans free from many Affordable Care Act market rules. The suit maintains the rule violated the ACA, the Administrative Procedure Act, and the Employee Retirement Income Security Act. In arguments before the court in late January, it was clear the judge was skeptical of the administration's arguments in defense of Labor's actions.

The highly controversial ruling in Texas will surely make its way to the Supreme Court. In December 2018, the administration petitioned the high court to circumvent the established federal appeals process and to elevate the district court's ruling for an expedited review by the Supreme Court. While most observers think the court is unlikely to do so, readers can be assured of hearing a great more about this in 2019. ■

How Does Neighborhood Social Context Affect CKD Risk?

Neighborhood problems and social cohesion are not directly related to decline in kidney function over time—but are still linked to significant differences in chronic kidney disease (CKD) risk factors, according to a study in the A*merican Journal of Kidney Diseases*.

The study included data on 6814 men and women from the Multi-Ethnic Study of Atherosclerosis (MESA). Participants were 45 to 84 years old (mean 62 years) and free of cardiovascular disease when they enrolled in MESA in 2000-02. Forty percent of participants were white, 27% black, 22% Hispanic, and 12% Chinese.

A neighborhood problem score was calculated using participants' baseline ratings in seven domains: availability of adequate food shopping, lack of parks/playgrounds, excessive noise, poor sidewalks, heavy traffic/speeding cars, trash and litter, and violence. The study also included a social cohesion score, based on responses to questions about living in a close-knit neighborhood and having neighbors who get along, help each other, can be trusted, and share the same values. The neighborhood problem and social cohesion scores were analyzed for association with declines in estimated glomerular filtration rate (eGFR).

Twelve percent of participants had more than a 30% decline in eGFR from baseline; this outcome was most common in black participants. Income and education were higher for participants living in neighborhoods with low problem scores and high social cohesion scores. The risk of more than a 30% decline in eGFR varied only slightly between quartiles of neighborhood scores.

Neighborhood social context differed by race/ethnicity, and was associated with small differences in the prevalence of risk factors such as hypertension and diabetes. Nevertheless, after adjustment for confounders, neither neighborhood score was independently associated with decline in eGFR.

Lower socioeconomic status is significantly associated with CKD and related risk factors. However, little is known about the impact of neighborhood factors that might play an important role in earlier stages of CKD. The new study finds no independent association between neighborhood problem and social cohesion scores and the risk of eGFR decline in middle-aged and older adults.

Nevertheless, neighborhood social context is associated with many CKD risk factors, including hypertension, markers of cardiovascular disease and diabetes prevalence, and health behaviors such as smoking. The researchers conclude, "Better understanding of the role of neighborhoods is vital because neighborhood characteristics are neither random nor naturally occurring" [Hicken MT, et al. Neighborhood social context and kidney function over time: the Multi-Ethnic Study of Atherosclerosis. *Am J Kidney Dis* 2018; DOI: 10.1053/j.ajkd.2018.10.015].

High Risk of Vaccine Preventable Infections in Kids with Organ Transplants

Pediatric organ transplant recipients are at greatly increased risk of hospitalization for vaccine-preventable infections (VPIs), reports a study in *JAMA Pediatrics*.

The retrospective study included 6980 patients who were less than 18 years old (mean 6.2 years) when they underwent a solid organ transplant from 2004 through 2011. Transplants were performed at 45 not-for-profit US children's hospitals participating in the Pediatric Health Information System database. There were 2,583 kidney transplant recipients, comprising 37.0% of the sample.

Numbers of hospitalizations for VPIs in the 5 years after transplantation were analyzed, based on diagnostic codes. The morbidity, mortality, and costs of these hospitalizations were assessed as well.

A total of 1,490 VPIs occurred within 5 years after transplantation in 1,092 patients, representing 15.6% of the sample. Influenza was the most common VPI (7.4%), followed by rotavirus (3.7%), varicella (2.1%), pneumococcus (2.0%), and respiratory syncytial virus (1.8%). Risk of VPI was lowest (11.3%) for kidney transplant recipients.

Overall case fatality was 1.7%. About 13% of all infections occurred during the transplant hospitalization. Excluding these cases, 17.0% of vaccine-preventable infections required intensive care unit admission. On multivariable analysis, risk of hospitalization for VPI was higher for children undergoing lung, heart, intestine, or multiorgan transplant, relative to kidney transplant; and for those younger than 2 years at transplantation. Median cost was $120,000 higher for pediatric transplant hospitalizations complicated by VPI.

More than 15% of children undergoing solid organ transplants are hospitalized for VPI within 5 years after transplantation. The risk of hospitalization for influenza in the first year after transplantation is more than 50 times higher than in the general population, and the risk of death is four times higher. The researchers conclude, "[M]aximal efforts must be made to ensure complete immunization of transplant candidates and recipients" [Feldman AG, et al. Incidence of hospitalization for vaccine-preventable infections in children following solid organ transplant and associated morbidity, mortality, and costs. *JAMA Pediatrics* 2019; DOI: 10.1001/jamapediatrics.2018.4954].

Adiposity Markers Predict Decline in Kidney Function

Three different measures of adiposity are independent risk factors for decline in glomerular filtration rate (GFR) and death, concludes a meta-analysis in the *British Medical Journal*.

The analysis included individual-level data on nearly 5.5 million adults enrolled in 39 international general population cohorts, drawn from the Chronic Kidney Disease Prognosis Consortium. Eighteen cohorts included nearly 92,000 participants with CKD, while six cohorts included approximately 84,000 individuals at high cardiovascular risk. The study analyzed three indicators of adiposity: body mass index (BMI), waist circumference, and waist-to-height ratio. These measures were examined for association with decline in GFR—defined as eGFR decline of 40% or greater, need for renal replacement therapy, or eGFR less than 10 mL/min/1.73 m^2—and with all-cause mortality.

In the general population cohorts, average follow-up was 8 years. During this time, 5.6% of individuals met criteria for GFR decline and 14.7% died. After adjustment for age, sex, race, and smoking, hazard ratios for GFR decline were 1.18 at a BMI of 30, 1.69 at a BMI of 35, and 2.02 at a BMI of 40 (compared to a BMI of 25). The association with BMI was significant for all three criteria for GFR decline. At higher levels of BMI, the associations remained significant after adjustment for other comorbid conditions: HR 1.28 at a BMI of 35 and 1.46 at a BMI of 40. There was a J-shaped relationship between BMI and death, with the lowest risk at a BMI of 25.

Mean follow-up was 4 years in the CKD cohorts and 6 years in the cardiovascular risk cohorts. The associations between BMI and GFR decline were weaker in these risk groups than in the general population cohorts. The J-shaped association with mortality remained, being lowest at BMI between 25 and 30. In the general population, CKD, and cardiovascular risk cohorts, larger waist circumference and higher waist-to-height ratio showed associations with GFR decline similar to that of BMI. The anthropometric measures were not associated with increased mortality, however.

The association between obesity and CKD remains unclear: some studies find no association, while others show a paradoxically lower risk of death. This meta-analysis of individual-level data includes information not only on BMI, but also on measures of central adiposity.

The results show that BMI, waist circumference, and waist-to-height ratio are all independently associated with the risk of GFR decline and death. The associations are significant, although differing in strength, for general population, CKD, and high cardiovascular risk cohorts. The investigators conclude, "These findings suggest that worldwide increases in obesity prevalence could lead to future increases in CKD and ESKD prevalence" [Chang AR, et al. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ* 2019; 364: k5301].

 Continued from page 17

Can Endostatin Predict Renal Risk in Type 2 Diabetes?

Plasma endostatin might provide a useful biomarker of the risk of renal dysfunction in patients with type 2 diabetes, according to a study in Kidney International.

The study included banked specimens from 374 participants (187 matched cases and controls) from the Action to Control Cardiovascular Disease (ACCORD) trial as well as samples from a contemporary cohort of 871 patients with type 2 diabetes from the Mount Sinai BioMe Biobank. Plasma endostatin – a fragment of collagen XVIII that may reflect endothelial dysfunction, matrix remodeling after kidney injury, and angiogenesis – was evaluated for association with a composite outcome of 40% decline in estimated glomerular filtration rate (eGFR) or end-stage renal disease.

Participants who met the composite renal outcome had higher baseline plasma endostatin levels. Log2-transformed endostatin levels were associated with similar and significant increases in risk in both groups: adjusted odds ratio 2.5 in ACCORD and hazard ratio 2.6 in BioMe. Risk was also elevated for those in the highest versus lowest quartile of plasma endostatin: OR 3.6 in ACCORD and HR 4.4 in BioMe.

In the BioMe data, adding information on endostatin to a baseline clinical model improved the area under the curve for the composite renal outcome from 0.74 to 0.77. At a cutoff of 45 ng/mL, corresponding to the fourth quartile value, elevated plasma endostatin had a sensitivity of 50%, specificity of 71%, and positive and negative predictive value of 21% and 90%, respectively.

New biomarkers are needed to predict renal function decline associated with type 2 diabetes, particularly in patients with preserved GFR at baseline. This study suggests that plasma endostatin is associated with decline in kidney function over time in patients with type 2 diabetes.

Added to conventional predictors, plasma endostatin may improve risk discrimination for declining renal function. The investigators highlight the need for further validation, as well as studies to determine whether early assessment of diabetic kidney disease risk using plasma endostatin can improve clinical care [Chauhan K, et al. Plasma endostatin predicts kidney outcomes in patients with type 2 diabetes. Kidney Int 2019; DOI: 10.1016/j.kint.2018.09.019].

Combined Rituximab-Cyclophosphamide for AAV

A combined regimen of rituximab and cyclophosphamide improves long-term outcomes in patients with renal anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), reports a study in *Nephrology Dialysis Transplantation*.

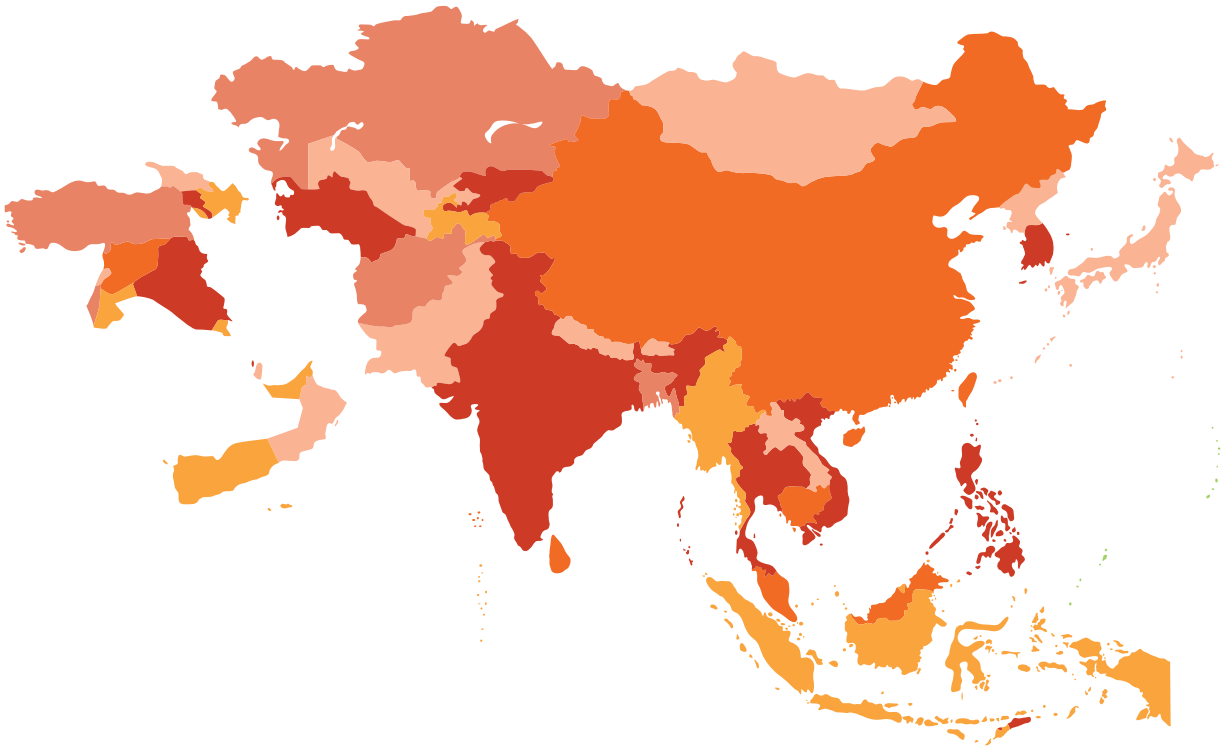
The study included 66 patients with AAV and biopsy-confirmed renal involvement. All were treated with a regimen of oral corticosteroids and rituximab plus low-dose pulsed intravenous cyclophosphamide. Maintenance therapy consisted of azathioprine and tapered steroid.

Disease activity was assessed using the Birmingham Vasculitis Activity Score (BVAS), along with monitoring of estimated glomerular filtration rate (eGFR). Median follow-up was 56 months. Outcomes were compared with those of 198 propensity-matched patients drawn from previous European Vasculitis Study Group trials.

At baseline, median BVAS score was 19 and eGFR 25 mL/min. By 6 months, patients had received median cumulative doses of 2 g of rituximab, 3 g of cyclophosphamide, and 4.2 g of corticosteroids. At that time, 94% had achieved disease remission, defined as a BVAS score of 0.

At 5 years, the patient survival rate was 84% and renal survival 95%. Eighty-four percent of patients became ANCA-negative. Fifty-seven percent of patients remained B cell-depleted (less than 10 cells/µL) through 2 years; this group had a 15% rate of major relapse at 5 years. Serious infections occurred at a rate of 1.24 per 10 patient-years. Compared to controls from previous trials, the combined rituximab-cyclophosphamide regimen was associated with lower rates of death, hazard ratio (HR) 0.29; progression to end-stage renal disease, HR 0.20; and relapse, HR 0.49.

Current guidelines for organ-threatening ANCA-associated AAV recommend the use of rituximab or cyclophosphamide. The authors call for controlled trials to evaluate the utility of combination drug regimens for treatment of AAV [McAdoo SP, et al. Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. *Kidney Int* 2019; 34:63–73].



Challenges in estimating GFR in Asia

By Vivek Kumar and Vivekanand Jha

Asia, home to 60% of the world's population, is a unique showcase of geographic, racial, and ethnic diversity that has potential implications for disease diagnosis and management. Use of serum creatinine–based estimated GFR (eGFR) equations for diagnosis and staging of chronic kidney disease (CKD) is a perfect example that exemplifies these challenges.

Kidney Disease Improving Global Outcomes (KDIGO) currently recommends Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (CKD-EPICr) for diagnosis and staging of CKD, but encourages use of a validated equation in the local population, if available.

Dietary protein intake and muscle mass, key determinants of steady state serum creatinine, have not been factored into derivation of the GFR estimating equations. Race and ethnicity are indirect determinants of body composition (muscle mass) and dietary or environmental exposure. The currently recommended creatinine-based eGFR equations show variations between different racial and ethnic populations, which resulted in the need for a correction factor for black ethnicities. Asians usually have a smaller build compared to Western populations, and their dietary patterns are also different on account of cultural and religious beliefs. The impact of these differences on the performance of the equations and on calculating CKD burden are not known.

The Asian nephrology community has investigated the accuracy of existing eGFR equations, and where needed, developed correction coefficients for eGFR equations. These studies have been done in China, Japan, Korea, Thailand, Taiwan, Pakistan, and India. The coefficients for the MDRD equation ranged from 0.808 for Japanese to 1.223 for Chinese populations, which tells us that the true GFR would be over- or under-estimated for similar serum creatinine values if the original equation were to be used. For example, in Indian subjects, the CKD-EPI$_{Cr}$ equation overestimated the true GFR (as estimated by inulin clearance) by 24.9 mL/min/1.73 m^2. Only 22% of the subjects had values within a 30% range (P30) of the true value. The Indian subjects were predominantly vegetarian, with a relatively low dietary protein intake and lower urinary creatinine excretion.

Differences in muscle mass and average dietary protein intake in different Asian ethnicities lead to different creatinine generation rates that might result in differences in performance of creatinine-based eGFR equations. Results from India suggest that measured GFR in otherwise normal predominantly vegetarian individuals of Indian ethnicity was relatively low (mean measured GFR 84 mL/min/1.73 m^2). Several completely healthy individuals exhibited GFR that would put them in stage 3 CKD! This is an interesting observation. If GFR in a healthy population is low, questions arise regarding whether these individuals suffer from kidney disease or have low, but physiologically normal GFR. In this setting, the GFR cutoffs used for diagnosis and staging of CKD or for selecting living kidney donors would require validation.

The Asian nephrology community has debated whether a single eGFR equation can provide acceptable estimates of GFR in all Asian races or ethnicities. An attempt by CKD-EPI investigators to develop and validate a separate coefficient for Asians revealed divergent results in Chinese and Japanese validation datasets thereby reflecting possible differences in non-GFR determinants of serum creatinine in these populations.

The alternative might be to find another marker that does not depend so much on patient-related factors. Cystatin C has been proposed for some time now as an alternative. Indeed, unlike serum creatinine, its generation and steady state levels are independent of muscle mass and dietary protein intake. Cystatin C–based eGFR equations have been compared with creatinine-based eGFR equations in Japan, Singapore, and China. Data from these studies consistently show that cystatin C equations perform better, either by themselves, or together with serum creatinine.

Incorrect diagnosis of CKD in otherwise normal individuals and misclassification of stages of CKD are important clinical and public health concerns. In a Thai cohort of 5525 patients, prevalence of CKD stages 3–5 changed by an order of 7 times with the use of different equations, i.e., from 5.4% with use of the Thai GFR equation to 37.9% with that of the Japanese modified CKD-EPICr. This shows a huge variation in assessment of burden of disease with unvalidated eGFR equations.

Also, the impact of so-called low normal GFR in vegetarian populations as in India needs to be assessed by a long-term, community-based, prospective cohort study. Low GFR might be normal for this population and not necessarily put them at risk of kidney disease or adverse outcomes. If it were indeed true, using current definitions of CKD would classify normal individuals as having CKD, thus over-estimating the disease burden.

As the global nephrology community calls for appropriate responses by health systems to the prevailing kidney disease burden, it is our responsibility to derive tools to accurately measure this burden.

Valid eGFR equations will help with judicious allocation of resources and adoption of public health measures toward management and prevention of kidney disease. Also, these observations manifest the need to have measured GFR as the clinically relevant end point for research studies so that applicability is wide. Overall, estimating GFR in a diverse population as in Asia is a challenge. However, it is also an opportunity for the global nephrology community to study variations and refine disease definitions through collaborative research.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Fellows Corner

My Path to Interventional Nephrology

By Crystal Farrington, MD

Crystal Farrington, MD

By my second year of internal medicine residency, I knew I wanted to be a nephrologist. Like many others who choose nephrology as a specialty, I enjoyed the challenge of solving complex acid–base problems or working up suspected glomerulonephritis. At the same time, I had grown to love procedures. My residency program was relatively small, and internal medicine residents performed nearly all of the bedside procedures in the ICU. It was satisfying to have a direct impact on the care of my patients through my ability to place a central line or endotracheal tube and deliver the treatment they needed. In researching general nephrology fellowship programs, I first learned about a specialty called interventional nephrology that connected my seemingly two disparate interests. I was intrigued.

Interventional nephrology first emerged in the 1980s when a nephrologist named Gerald Beathard grew tired of long wait times for his dialysis patients to get vascular access procedures. In response to his frustration with treatment delays, he decided to learn how to do angioplasties and other access-related procedures himself (1). Other pioneering nephrologists soon followed his lead, and it was quickly established that nephrologists were capable of performing a variety of endovascular procedures safely and effectively. What's more, dialysis patients benefited from timely treatment of their access dysfunction and continuity of care across the disciplines (2, 3).

The importance of prioritizing vascular access care really hit home during my general nephrology fellowship, when I learned how to take care of patients with ESKD. I became aware that vascular access issues were a major source of morbidity (and sometimes mortality) for dialysis patients, and that there were real consequences to delayed care, such as inadequate or missed dialysis, or unnecessary temporary catheter placement. Interestingly, I noticed that not all patients were affected equally by access-related disease. While some had used their fistulas for years with little to no problem, a significant number of others struggled almost constantly with maintaining any type of functional vascular access. I wondered about the difference, and whether I could do something about it.

This passion for vascular access led me to pursue further training at an academic interventional nephrology program, where I learn how to perform dialysis access procedures, take care of hemodialysis patients, and engage in vascular access research (4). The patients I take care of on the dialysis machine or see in the interventional suite are the very ones whose access-related problems I am trying to solve, thus my research is particularly exciting and relevant.

Academic interventional nephrology offers the chance simultaneously to do and to think: I have an immediate, direct impact on an individual patient if I angioplasty his fistula or declot her graft, but I also can have a wider, lasting impact on hemodialysis patients in general through my research. For me, it's the best of both worlds.

There are a number of challenges going forward in vascular access. In the early days of hemodialysis, those with diabetics or over age 45 were excluded from treatment, whereas elderly patients with diabetes and multiple co-morbidities constitute a significant proportion of hemodialysis patients today (5, 6).

Although the clinical characteristics of a typical hemodialysis patient in the United States have changed vastly over the last 50 years, the gold standard for vascular access (the radiocephalic fistula) has remained the same (7). In recent years, however, assumptions about the primacy of fistulas for all hemodialysis patients have been called into question, and there is a new impulse to take a patient-oriented approach to minimize access-related morbidity and increase the likelihood of vascular access success (8, 9). Nevertheless, many unanswered questions remain about how to optimize the chance that, to paraphrase, the right patient will get the right access at the right time (10). I'm eager to keep trying to find the answers, and I hope some of you reading this will join me.

Crystal Farrington, MD, is a third year interventional nephrology fellow at the University of Alabama in Birmingham.

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Industry Spotlight

Portable Dialysis News

The world is one step closer to a dialysis device that can be readily carried by a patient, while another company is working to create an ultra-thin blood filter for a wearable dialysis device.

The US FDA has granted a Breakthrough Device designation to AWAK Technologies (Singapore) for a new peritoneal dialysis (PD) device, the AWAK PD.

The device is a wearable, portable PD system that incorporates AWAK's sorbent technology. It weighs less than 2 kg, and 6 to 8 hours of therapy provide 12–16 L of total dialysate flow. The machine is small enough that it may be carried and operated in many different sites, obviating the need for a patient to report to a clinic to connect to a conventional dialysis machine or to dialyze at home. This feature will allow dialysis to be performed as a person moves through a typical day, "on-the-go," the company states.

The FDA's Breakthrough Device Designation is granted to expedite the development and review of devices that possibly could provide a more effective treatment or diagnosis for life-threatening or debilitating diseases. To be ruled a breakthrough device, the device must be for a condition with no FDA-approved alternative treatments or must offer significant advantages over the existing approved alternatives.

AWAK earned the FDA designation after the agency reviewed results from the first-in-human safety trial of the AWAK PD. The device was shown "to efficiently remove the accumulation of toxins from the body, and patients in the trial did not experience any serious adverse events during dialysis with AWAK PD," a company release stated.

A different group of engineers is tackling a portable dialysis material with its design of a blood filtration material just a few atoms thick.

The new material, called MXene, absorbs urea from blood plasma. The engineering group is led by Drexel University's Yury Gogotsi, PhD. "This material has shown a better ability to adsorb urea molecules from the blood plasma compared to other known sorbents," Gogotsi said. "This means it could one day make the wearable kidney a reality, improving quality of life for many people."

A study published in ACS Nano showed that three currently available MXene materials can remove 99% of urea from an aqueous urea solution and 94% from dialysate fluid.

Reference

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Diabetic Kidney Disease Prediction

Roche and IBM have teamed up to parse half a million electronic health records (EHRs) to create a predictive algorithm for patients with early risk of chronic kidney disease (CKD) related to diabetes. The industry duo developed the algorithm based on real-world data.

Age, body mass index, and glomerular filtration rate as well as concentrations of creatinine, albumin, glucose, and hemoglobin (HbA1c) were selected as important predictors on the basis of "a data-driven and medical selection for the study," according to the paper, published in *Nature Medicine* (1). CKD was defined as a microvascular long-term complication of diabetes.

The Indiana Bioscience Research Institute (IBRI), Eli Lilly, and Indiana University School of Medicine provided Roche and IBM with a real-world data set originating from almost 100,000 patients with diabetes obtained from the Indiana Network of Patient Care database.

Dan Robertson, PhD, director of IBRI's Applied Data Sciences Center, stated, "We are continuing our work with our industrial partners to explore disease progression, patient stratification, digital diagnostics, and eventually moving toward identifying new therapeutic targets to improve patient health."

In a comparison of clinical trials and databases with [real world data], the study authors note, "predictive analytics algorithms using [real world data] could achieve equivalent or even enhanced accuracy compared with those using clinical trial data."

The data algorithm "outperformed published algorithms derived from clinical trial data in a one-to-one comparison, as well as in cohort studies," *Health Data Management* reported.

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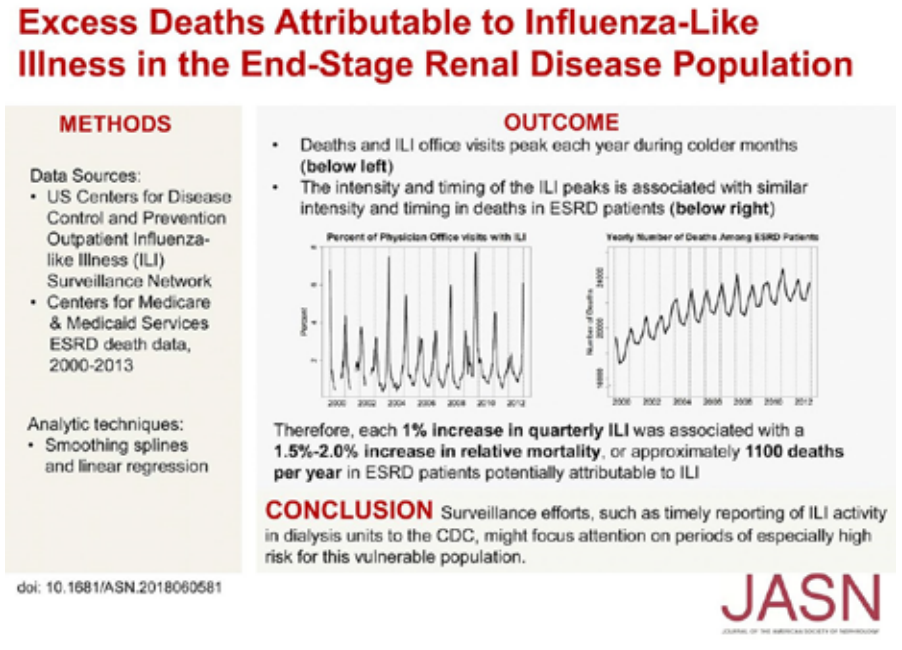
HOW MANY OF YOUR PATIENTS Received Influenza Immunization?

A recent article in JASN estimates that *more than* 1,000 dialysis patients die annually of influenza-like illness.



Flu News from the Centers for Disease Control and Prevention (CDC)
Severe flu outcomes are a somber reminder of how serious flu can be, even for otherwise healthy people. Flu vaccination protects against flu illness and reduces the risk of flu complications, including flu-associated hospitalization, admissions to the intensive care unit, and even death.

"Guidelines for Vaccinating Dialysis Patients and Patients with Chronic Kidney Disease" is available on the CDC website at *https://www.cdc.gov/vaccines/pubs/downloads/dialysis-guide-2012.pdf*

Source: Excess Deaths Attributable to Influenza-Like Illness in the ESRD Population. David T. Gilbertson, Kenneth J. Rothman, Glenn M. Chertow, Brian D. Bradbury, M. Alan Brookhart, Jiannong Liu, Wolfgang C. Winkelmayer, Til Stürmer, Keri L. Monda, Charles A. Herzog, Akhtar Ashfaq, Allan J. Collins and James B. Wetmore. JASN January 2019, ASN.2018060581; DOI: https://doi.org/10.1681/ASN.2018060581

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