Kidney News

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Less Than Perfect Kidneys May Help Expand Transplant Access

By Bridget M. Kuehn

Kidneys from donors with acute kidney injury (AKI) are often discarded, but a recent study suggests that transplant patients who receive donor kidneys with AKI do as well as those who receive comparable kidneys without AKI.

The findings are the latest in a growing body of evidence that suggests using more donor kidneys that are less than perfect may help increase access to transplantation. Transplantation is considered the best treatment option for most patients with kidney disease because it can improve their quality of life and help them live longer, according to the National Kidney Foundation. But with about 100,000 patients on the waiting list for transplantation and only about 20,000 kidney transplants completed each year, many patients end up waiting years for a kidney. Currently, about one-third of donor kidneys with AKI are discarded, noted Chirag Parikh, MBBS, PhD, Director of the Division of Nephrology at Johns Hopkins Medicine in Baltimore. Other studies have suggested that donor kidneys that are seropositive for hepatitis C virus (HCV) or kidneys from older donors might also be underutilized options.

“We and other groups are looking at opportunities where there are kidneys in the discard pool [that] can potentially work well and can benefit more people who are on the waiting list,” Parikh said.

Currently, many deceased donor kidneys with AKI are discarded because patients and nephrologists fear they may not last as long, explained Parikh. But some evidence suggests that these fears may be misplaced. With their recent study, Parikh and his colleagues strengthened the case for using donor kidneys with AKI.

In the study, they analyzed data from DonorNet on transplant outcomes in 12,810 patients who received deceased donor kidneys with AKI and 12,513 patients who received kidneys without AKI from donors with similar characteristics. They found that there wasn’t a significant difference in all-cause graft failure or death-censored graft failure in the two groups. Although more patients who received AKI kidneys experienced delayed graft function (29% vs. 22%), Parikh said the rigorous design of the study and the fact that it included all kidneys transplanted between Jan. 1, 2010, and Dec. 31, 2013, bolster the evidence base.

Based on the evidence, Parikh said he thinks between 500 and 700 deceased donor kidneys with AKI could be used for transplantation each year.

Does Fistula Creation for Dialysis Access Have its Own Benefits?

Because patients often resist surgery to create recommended arteriovenous fistulas for dialysis, some researchers have hoped to find advantages

By Eric Seaborg

An arteriovenous fistula (AVF) is the guideline-recommended vascular access for hemodialysis, yet a large majority of patients in the US and Canada begin dialysis using catheter access, despite its higher rates of complications. Because patients resist having the AVF surgical procedure, many nephrologists have looked to the results of observational studies that led to the hypothesis that AVF creation could affect kidney function—and even lead to benefits that could postpone the need for dialysis.

Definitive evidence for such a benefit remains elusive, however, with two new studies contributing to the discussion.
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Less Than Perfect Kidneys

added to the donor pool each year. This could be beneficial for both patients and society, he said, noting the huge costs of maintaining patients on dialysis. “Taking these people off dialysis and giving them a meaningful life back makes a huge difference,” he said.

Another potentially underutilized pool of deceased donor kidneys are HCV-positive organs. Until recently, HCV-positive donor kidneys could not be used for transplantation because peginterferon plus ribavirin, the gold standard treatment, could cause rejection, said Xingqiu Cheng, MD, a transplant nephrologist and clinical assistant professor at Stanford University in California. But the emergence of direct-acting antiviral drugs that have been shown to eliminate the HCV virus in up to 100% of patients after transplant has changed the landscape. The number of HCV seropositive donors has also increased from 181 to 661 per year between 2000 and 2016 as opioid overdose deaths have increased, a recent study co-authored by Cheng showed. The study showed the number of HCV-positive donor kidneys transplanted increased from 165.4 to 334.7. Most are transplanted into HCV-positive patients, but some centers are also transplanting them into patients without HCV. Cheng noted. Both groups of patients are treated with direct-acting antivirals after transplant.

But the use of HCV-positive donor kidneys has lagged behind the use of HCV-positive donor livers, the study found. Cheng said there are several likely explanations for this. Kidney patients can stay on dialysis while they wait for a kidney, while liver transplant patients don’t have such an option. Hepatologists also may be more experienced and comfortable using direct-acting antivirals than their nephrologist counterparts. Another potential concern is whether patients have access to direct-acting antiviral medications, which can cost as much as $94,000 per treatment. Cheng said she and her colleagues seek preapproval for coverage of direct-acting antivirals for prospective kidney transplant patients who are already HCV-positive.

“I think there is a great role for [HCV positive donor kidneys],” she said. The biggest thing that needs to be overcome is the financial hurdle of financing the treatments, so that we don’t create two classes of kidney transplant recipients, ones who have good insurance that can afford the treatment, and ones who can’t.

Another group of kidneys that may be underutilized are those from older donors, as studies have found that older recipients may benefit from a transplant from older donors. Stephen Pastan, MD, Associate Professor of Medicine and Medical Director of the Kidney and Pancreas Transplant Program at Emory University School of Medicine, explained that a kidney from an older donor may not last as long—perhaps 5 years rather than 8—but getting a transplant from an older donor is still much better than staying on dialysis.

There are several national efforts underway to increase access to transplantation and increase the number of organs available from both deceased and living donors.

Among the aims of the US Department of Health and Human Services Advancing American Kidney Health program launched in 2019 are increasing the number of donors kidneys available, reforming the organ procurement system, and removing financial and other barriers to living organ donation. The United Network for Organ Sharing is developing systems that would more quickly match donor kidneys to centers that will use them in order to decrease discards of donor kidneys that spend too much time on ice during the allocation process.

A report from the National Kidney Foundation’s Consensus Conference to Decrease Kidney Discards highlighted the need to change regulations or payer incentives that may unfairly penalize transplant centers that use lower quality kidneys, Cheng noted.

“We’re trying to identify things that should be done to try to remove those kinds of barriers,” he said. “We do a lot about patient education to make sure that patients are ready and willing to accept whatever kidney comes their way because it would be in their best interest to get a transplant rather than staying on the waiting list.”

Patients and physicians must also weigh the potential benefits and risks of accepting a particular kidney for each patient, Cheng noted. She explained there can be “tension between what is best for the community and what is best for an individual patient.” For example, using an older donor kidney in an older patient may be beneficial, if it fails, an older patient may be less likely to get a second chance. “It’s a great idea to try to expand the usage of [marginal] kidneys,” Cheng said. “But there are a lot of just unknowns and ethical questions in finding the proper patients to get these organs to. I’ve personally in my practice seen great successes with these and I’ve also seen some really bad failures.”

References:

ASN Executive Vice President Tod Ibrahim Named President of CMSS

Tod Ibrahim, ASN executive vice president, has been named president of the Council of Medical Specialty Societies (CMSS). His term took effect in November 2019.

“CMSS is uniquely positioned to help address pressing clinical topics, research-related issues, and educational topics common to its members,” Ibrahim said. “There is an opportunity to think creatively across specialties, and that was really appealing to me.”

Founded in 1965, CMSS provides an independent forum for the discussion by medical specialists of issues of national interest and mutual concern. The organization currently has 46 national medical society members representing more than 800,000 physicians. ASN has been a member of CMSS for nearly 10 years.

Ibrahim succeeds Ken Bertka, MD, FFAFP, CPHM, a past member of the board of directors of the American Academy of Family Physicians, and David B. Hoyt, MD, FACS, executive director of the American College of Surgeons. Dar-
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.

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 spasm (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.

Visit ParsabivHCP.com for more information.
Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE
PARSABIV is indicated for the treatment of secondary hyperparathyroidism (SHPT) 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 urticaria, 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 arrhythmias. 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 mcg in the QTcF interval (0.5% placebo versus 3.4% 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 arrhythmias 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.

Decrease in corrected serum calcium below the lower limit of normal or symptoms of hypocalcemia 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 (5.4) 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 (5.1) 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 to 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 53 years, and 64% 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N = 513)</th>
<th>PARSABIV (N = 503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood calcium decreased&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10%</td>
<td>64%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypocalcemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.2%</td>
<td>7%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1%</td>
<td>6%</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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)
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:

- Hypercalcemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hyperkalemia: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hyperphosphatemia: 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 prolongation 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 based on AUC. 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 1.4 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 11), 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 an in-vitro 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 [14C]-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 [14C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [14C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Other adverse reactions not specifically mentioned are:

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

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 overdose. Overdose 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 overdose. In the event of overdose, 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).

PARSABIV™ (etelcalcetide)

Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
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Patent: http://pat.amgen.com/Parsabiv/

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Fistula Creation
Continued from page 1

Reasons for eGFR benefit

Two broad categories of explanations have been proposed for how AVF placement could contribute to flattened eGFR decline: first, by contributing to physiological changes that benefit kidney function, and second, through ancillary improvements in care or patient actions.

Several physiological reasons—or at least possibilities—have been proposed for how AVF placement could be associated with reduced eGFR decline [with] no significant difference in eGFR decline between the two procedures.

Patient compliance and other effects

The study from the Karolinska Institute calls into question the impact of a physiological reason for stabilization of eGFR because the results were the same for the AVF and peritoneal dialysis catheter groups, but rather appears to bolster a “process of care” and compliance explanation, according to Prabir Roy-Chaudhury, MD, of the University of North Carolina Kidney Center in Chapel Hill.

Because patients resist having the AVF surgical procedure, many nephrologists have looked to the results of observational studies that led to the hypothesis that AVF creation could affect kidney function—and even lead to benefits that could postpone the need for dialysis.

Roy-Chaudhury notes that as their disease progresses, patients will have more interactions with their healthcare providers. Patients resist the idea of going on dialysis, and don’t want to give in to their situation, but faced with the grim reality of having a procedure, their compliance might increase: “When the patient asks, ‘Is there any chance that I can prolong the time to dialysis even with the fistula placed?’ The physician is going to say, ‘Do all the things that you were doing before,’ which the patient may not have been doing. So now suddenly the patient starts doing all of those important things they have been neglecting, like taking their medicine, controlling their blood pressure, coming to appointments, and listening to the nurse.”

Similarly, the patient receives stepped-up care and closer attention from providers when preparing to have a procedure, which could also have beneficial effects on the patient’s condition. “It could be a result of the process of care, . . . which is important because it means that one way of reducing the decline of GFR is to enhance the process of care,” Roy-Chaudhury said.

Another confounding factor could be that the reasons and timing of preparing for dialysis play into a statistical phenomenon known as regression to the mean related. “The accelerated decline in kidney function leads to the decision to begin dialysis and implant a fistula, but such declines tend not to be linear. The decline tends not to occur at a consistent rate, but flattens out over time—regresses to the mean rate of decline,” Roy-Chaudhury told ASN Kidney News.

Effects of AVF maturation

Casha P. Kovovsky, MD, of the University of Tennessee Health Science Center in Memphis, said there are now three or four observational studies that show an association of AVF placement with the benefit of a flatter trajectory of eGFR decline. The Swedish study shows no difference between AVF and catheters, but is like the Canadian study in that both “show a benefit from intervention,” Kovovsky said.

Kovovsky and colleagues published the largest study to date of the potential AVF effect in Nephrology Dialysis Transplantation in 2017. They compared more than 3000 patients with chronic kidney disease who had a pre-dialysis AVF or arteriovenous graft (AVG) with a 3500-patient comparator cohort who started dialysis with a central venous catheter. They found a deceleration of eGFR decline in the AVF/AVG group compared with an acceleration of eGFR decline in the catheter group.

The benefit in the AVF/AVG group occurred independent of the AVF/AVG maturation, however, which led the researchers to “consider the possibility that the deceleration of eGFR decline . . . may be attributable to factors unrelated to the physiological effects of a mature vascular access, such as more attentive nephrologist care and improved patient health status or behavioral compliance with therapy. Nonetheless, there still seem to be other plausible physiological mechanisms that could explain the potential renoprotective effects of AVF/AVG creation even in those patients whose vascular access is not mature enough for standard hemodialysis cannulation.”

These findings did not support that these physiological mechanisms were related to cardiac improvements, but the researchers noted the “growing evidence from experimental and clinical studies” of benefits from RIPC. The process of AVF surgery involves “repetitive clamping of the feeding artery and permanent ligation of small arterial branches. It has been postulated that even a brief ischemic stimulus of a remote site releases RIPC-induced humoral factors such as adenosine, erythropoietin, or nitric oxide into the systemic circulation, which subsequently protects other target organs, including the kidney,” the researchers wrote.

“Local limb ischemia would occur in all patients who underwent an AVF procedure, so the potential benefit would apply regardless of whether the fistula matured.”

No definitive answers

Kovovsky bemoaned the “inertia or lack of trust” encountered when trying to convince a patient it is time to place an AVF to prepare for dialysis, and sees the advantage of having another reason to encourage a patient to proceed. But, “this is observational data, so the level of evidence is not high enough to truly implicate at this point. And there are several aspects of that data which suggest that it may indeed be some kind of an unmeasured confounder” leading to the benefit, he said.

Nadeau-Fredette said that she would like to see more patients using AVFs because “it is the best access,” and a link to another benefit might help convince them—but the evidence of cause and effect is not there. “This is only observational, so I cannot say that it is directly related. There are some hemodynamic reasons that could be involved, but it is very difficult to know if it is really the cause or just kind of an observation,” she said.

There is one point on which everyone agrees: More direct evidence on the level that randomized clinical trials could provide would be a tremendous help. But it would be ethically difficult to design a clinical trial in which a tranche of patients were denied the recognized standard of care of AVF placement.
Changes to Organ Procurement Organization Measures Garner ASN’s Support, with Recommendations for Improvement

By David White

The American Society of Nephrology (ASN) provided comments of support and recommendations for improvement in February 2020 on the proposed rule for Organ Procurement Organizations (OPOs) Conditions for Coverage: Revisions to the Outcome Measure Requirements for Organ Procurement Organizations proposed by the Centers for Medicare & Medicaid Services (CMS). The proposed rule intended to require transparent, verifiable, and uniform metrics by which CMS can evaluate OPO performance.

ASN supported the proposal, writing “[W]ith 115,000 Americans waiting for an organ, ASN supports the proposed rule to establish both transparent, uniform metrics to help assess the performance of each of the 58 OPOs and clear procedures for evaluating those organizations including processes for improvement and re-certification. ASN believes that reforming the current system of OPO performance oversight is necessary to enable the Advancing American Kidney Health goal of doubling the number of kidneys available for transplant by 2030 as well as to approach the proposed target transplant rate described in the ESRD Treatment Choices proposed model and the four tracks of the voluntary model.”

In July 2019, President Donald J. Trump issued the Executive Order 13879 titled Advancing American Kidney Health (1), aspects of which are addressed in the proposed rule. The Executive Order specifically calls on the Secretary of Health and Human Services to “propose a regulation to enhance the procurement and utilization of organs available through deceased donation by revising Organ Procurement Organization (OPO) rules and evaluation metrics to establish more transparent, reliable, and enforceable objective metrics for evaluating an OPO’s performance.”

In highlights summarizing the major points in its comment letter, ASN stated its support for the following:

- Using the inclusionary Cause, Age, and Location Consistent (CALC) metric described in the Proposed Rule, as opposed to the proposed denominator that uses exclusionary diagnosis.
- Avoiding penalties for “zero organ donors,”
- Opposing risk adjustment based on race and ethnicity,
- Creating a system that transparently evaluates OPO performance with clear pathways to addressing improvement and consequences for not improving,
- Reporting outcome measures of organ transplant rates by type of organ, and
- Taking future steps in other proposed rules to address waitlist criteria, less than ideal organs and patients, and payment issues for less than ideal patients.

CMS proposed to replace the existing outcome measures for OPO recertification with two new outcome measures that would be used to assess an OPO’s performance: “donation rate” and “organ transplantation rate,” effective beginning in 2022. The “donation rate” would be measured as the number of actual deceased donors as a percentage of total inpatient deaths in the donation service area (DSA) among patients 75 years of age or younger with any cause of death that would not be an absolute contraindication to organ donation. The “organ transplantation rate” would be measured as the number of organs procured within the DSA and transplanted as a percentage of total inpatient deaths in the DSA among patients 75 years of age or younger with any cause of death that would not be an absolute contraindication to organ donation (2).

Cause, Age, and Location Consistent (CALC) donation measure

CMS proposed two methodologies for calculating the denominator in these measures: 1) the Cause, Age, and Location Consistent (CALC) donation measure that uses ICD-10 codes to identify deaths that are consistent with donation (that is, inclusion criteria) and 2) an alternative where CMS would exclude ICD-10 codes that are absolute contraindications to organ donation (that is, exclusion criteria).

ASN supported using the inclusionary CALC metric described in the Proposed Rule, as opposed to the proposed denominator that uses exclusionary diagnosis. Although CMS has shown that the net result in terms of among-OPO comparisons is similar, “the CALC metric has superior face validity, because it restricts the denominator to inpatient deaths from causes that are consistent with donation, rather than the exclusionary measure, which includes causes of death that never lead to donation,” ASN commented.

As lead researcher on the CALC metric David Goldberg, MD, and his colleagues accurately summarize, “compared to the current metric that relies on eligible deaths, the benefits of our proposed donation metric are that it:

- Does not rely on self-reported data,
- Utilizes a uniform process of estimating the donation potential within each donor service area,
- Includes potential DCD donors that are excluded from the eligible death definition, and
- Provides a reliable year-to-year measure of OPO performance to track changes in performance.” (3)

The researchers also write, “[T]hese conclusions should provide CMS, and the transplant community, with comfort that the proposed CMS metric using CDC inpatient death data as a tool to compare OPO is not compromised by its lack of inclusion of ventilation or other comorbidity data.” (4)

Donation rate numerator (or definition of donor)

ASN encouraged CMS to avoid penalizing OPOs under the scenarios when extensive efforts are made to procure organs for transplant, but ultimately no organs are placed for transplant (so called “zero organ donors”). ASN outlined the following scenario as an example that could occur, and credit for the attempt would be denied if only donors from whom organs are transplanted are considered donors:

1. A deceased (brain-dead or donation after cardiac death) donor is identified that matches a locally available potential recipient.
2. There is preliminary determination of medical suitability, and preliminary offer acceptance by a transplant center.
3. The donor is taken to the operating room, but during organ procurement the transplant surgeon unexpectedly finds an unacceptable situation (such as unsuspected intra-abdominal cancer).
4. The surgeon appropriately cancels use of the organs for transplant.

ASN maintained that the effort and expense to reach this stage is unlikely to lead to “gaming” to obtain credit for donation noting “more aggressive pursuit of higher risk and older donors will likely lead to more identification of medical contraindications at later stages. Aggressive pursuit of organ donors will always be accompanied by some medically appropriate non-utilization.”

Risk adjustment

ASN supported CMS’ decision to not risk adjust based on race, quoting Janice E. Whaley, MPH, CTBS, CPTC, Chief Executive Officer of Donor Network West from the organization’s comment letter to CMS in September 2019 on its proposed rule on “Organ Procurement Organizations Conditions for Coverage: Proposed Revision of the Definition of Expected Donation Rate.”

“As [P]ast-President of the Association for Multicultural Affairs in Transplant (AMAT) and deeply steeped in mi-
Organ Procurement
Continued from page 9

nority and ethnic concerns during my nearly 30-year ca
reer in donation and transplantation, I would like to offer a
word about donation and communities of color. Increased
focus has been given recently to minority authorization
rates and a perceived burden of producing good results in
these measures based on the racial and ethnic composition of
the OPO service area. This increased attention has been a
positive development because it allows for a full-throated
discussion about race, ethnicity, and the nexus of organ
donation. The view of race and ethnicity needs to evolve
in our community much the same as it has for our na
tion across various assets and services. Minorities donate.
Further, in some parts of the country, minorities donate at
the same rate as do Caucasians. Thus, it can be done, and
when the DSA functions as a true community, it is done.”

Success threshold and expected donation rate/decertification
ASN supported redefining the definition of success and
basin that success on how OPOs perform on the outcome
measures of donation rate and organ transplantation rate
compared with a top percent of donation and transplantation
rates for all OPOs.

Currently, CMS conducts recertification inspections of
OPOs for compliance with requirements and performance
standards every four years as a condition of Medicare and
Medicaid participation.

In addition to those periodic recertification inspections,
the rule proposed a review of OPO performance every 12
months to provide more frequent feedback to all OPOs. If
an OPO’s outcome measures—its donation and trans-
plantation rates—fall statistically significantly below the
top 25% of OPOs (as defined by a given OPO’s upper
limit of the one-sided 95% confidence interval falling
lower than the threshold rate), CMS would require that
OPO to revise its quality assurance and performance im-
provement (QAPI) program in order to improve. ASN
requested “further information from CMS on the pro-
cess by which OPO underperformance would be reme-
diated after the new metrics go into effect and whether
the top 25% rate is static or reoccurring.”

ASN recommended that CMS “should stagger the
end of the four-year deadline so that not all 58 OPOs are
on the same deadline—for example, 1/3, 1/3, 1/3 as the
elections for the United States Senate are structured”—
to ensure that as some OPOs are potentially decertified,
other higher-functioning OPOs are in existence to main-
tain the supply of procured organs as well as bid for the
contracts of any OPOs that have failed to improve their
performance during their four-year window.”

While mindful of the need to ensure access to organs and transplantation, ASN reminded CMS that “[O]verall, however, stakeholders’ fear of change should be
weighed against the very real fear, lived and expressed
by the patients ASN members serve, that their lives will
end before they can access a transplant because OPOs are
underperforming. These patients might not receive a
transplant because the system has not asked every OPO
to meet an objective, verifiable standard of performance
with an evidence-based standard of practice.”

Organ transplantation rates by type of organ
ASN supported reporting outcome measures of organ
transplant rates by type of organ. The criteria for qualify-
ing for a transplant not only differ based on transplant
center, but also on the type of organ. In reporting these
data, ASN suggested that CMS consider how to distin-
guish the rate of organs transplanted versus those that
were expected to be transplanted by organ type as well.

This ratio would likely differ based on type of procure-
ment, such as thoracic and abdominal organ procure-
ment; donor management factors prior to procurement
as these can affect usability and transplant success; and
other factors.

Other regulatory steps to improve access to trans-
plantation are expected this year. Follow Kidney News for
more details.

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utive-order-advancing-american-kidney-health/
pdf
+deb.pdf

Organ Procurement

ASN believes that reforming the current system of OPO
performance oversight is necessary to enable the
Advancing American Kidney
Health goal of doubling the
number of kidneys available
for transplant by 2030 . . . .

Nationwide Campaign Aims to Mobilize Public, Kidney Community to Encourage Early Detection and Management of Kidney Disease

A nationwide public awareness campaign to pro-
mote early detection, treatment, and management
of kidney disease is launching in March 2020 in
conjunction with National Kidney Month.

The campaign, called “Are You the 33%?” aims to engage
every adult to learn more about their risk for kidney disease
by taking a simple, one-minute online quiz at MinuteforY-
ourKidneys.org.

One in three adults in the United States is at risk for kid-
ney disease.

“Look around the next time you’re sitting in a school au-
ditorium or even in a giant professional sports stadium; one-
third of every adult in there with you is at risk of developing
kidney disease,” said Kevin Longino, CEO of the National
Kidney Foundation (NKF) and recipient of a kidney trans-
plant.

Launched by NKF, the campaign is among the first
steps in a collaborative partnership among the Department
of Health and Human Services (HHS), NKF, and ASN to
raise awareness about kidney disease and improve patient out-
comes. The Public Awareness Initiative was outlined in the
Executive Order on Advancing American Kidney Health, the
historic action to transform kidney health signed by President
Donald J. Trump in July 2019. The National Kidney Foundation has entered into strate-
gic alliances with CVS Kidney Care, HealthYio and Labora-
tory Corporation of America in order to carry out the cam-
paign with Otsuka America Pharmaceutical, Inc. serving as a
Campaign Sponsor.

In its partnership with HHS and NKF, ASN will fulfill
the Public Awareness Initiative outlined in the Executive
Order by educating clinical professionals and spurring inno-
vations by entities serving the kidney community. Officially
launching in fall 2020, ASN’s campaign will target and in-
form kidney care professionals about how to succeed in a fu-
ture where the practice of nephrology includes more home-
based therapies and transplantations. In addition, ASN will
build off its efforts in 2019 and continue to engage capital
capital markets to dispel myths, encourage prioritizing the kidney
space for investment, and advocate that nephrology is open
for business.

The public awareness “Are you the 33%?” campaign will include “compelling visuals, a thought-provoking social
media campaign, and a broadcast PSA launching later this
month with television and film star Wilmer Valderrama,
[and will focus] on the 33% of American adults at risk for
developing dangerous, life-threatening kidney disease,” ac-
cording to a press release issued by NKF: “Risk factors in-
clude diabetes, heart disease, high blood pressure, obesity and
family history of kidney disease.”

The campaign microsite will be available in Spanish start-
ing in September 2020.

“More than 90% of the 37,000,000 Americans and
850,000,000 individuals worldwide affected with kidney
disease are unaware that they are even sick,” said Anupam
Agarwal, MD, FASN, ASN President. “This silent epidemic
often strikes without symptoms. Millions of people won’t
know they have kidney disease until their kidneys stop work-
ing and it’s too late.”
Preventing Bloodstream Infections in Hemodialysis Patients

By Michele H. Mokrzycki

In 2017, approximately 459,000 patients in the United States received in-center hemodialysis (HD), and more than 108,000 new patients began renal replacement with HD (1). HD catheters were the most common form of vascular access in new patients, accounting for 80% of all accesses. Therefore, more than 86,000 new HD patients began treatment with a catheter in 2017 (1). Among prevalent HD patients, catheter use was lower: approximately 20%. Unfortunately, catheter use in patients receiving both incident and prevalent HD has remained unchanged over the past 6 years. Patients receiving in-center HD are a unique patient population and are at risk for infections because of the shared treatment setting and frequent accessing of the bloodstream. Catheter-dependent patients are particularly vulnerable because of the potential for direct entry of skin bacteria from the catheter entrance site into the tunnel and bloodstream, and during catheter connection and disconnection. In fact, the rate of bloodstream infection is nine times higher for catheter-dependent HD patients than in those using arteriovenous fistulas (2).

Core interventions for preventing infections in HD

A recently published review, “Prevention of bloodstream infections in patients undergoing hemodialysis” by Fisher et al. (3), in the January 2020 issue of CJASN examines both established and novel strategies available for the prevention of bloodstream infections in patients receiving HD (Figure 1).

The CJASN review highlights the Centers for Disease Control and Prevention’s core interventions for preventing HD catheter infections, which are also available on the CDC’s website. The CDC’s core interventions were initially published in 2013 and were last updated in 2016 (4). An important recent additional recommendation to the updated 2016 CDC core interventions was on the preferred use of chlorhexidine as a skin antiseptic agent for care of the catheter exit site.

Chlorhexidine-alcohol antiseptic solution has been shown to be significantly superior to povidone iodine–alcohol in preventing catheter infections in the intensive care unit. In a 2013 study, patients randomized to the chlorhexidine-alcohol arm experienced an 80% lower rate of catheter-related bloodstream infections than did those in the povidone iodine–alcohol arm (5). The CDC also recommends the use of a topical antimicrobial ointment as an important part of routine care of the HD catheter exit site. Triple antibiotic ointment and povidone-iodine ointment are the recommended antimicrobial agents, and both are associated with marked reductions in bloodstream infections of approximately 75% to 93%. The application of mupirocin to the catheter exit site, although effective, may have the potential for microbial resistance with long-term use, and its routine use is not recommended.

New chlorhexidine-containing products

Chlorhexidine-based products are now widely used in the HD setting. They include chlorhexidine-impregnated sponges (Biapatch CHG, Johnson and Johnson, Inc.) and dressings (Tegaderm CHG, 3M), which may be alternatives to antimicrobial ointments for routine catheter exit site care. More recently, a novel catheter hub device (ClearGuard HD Antimicrobial Barrier Cap, Pursuit Vascular, Inc.) has been shown to reduce central catheter–associated bloodstream infections in HD patients and was approved by the US Food and Drug Administration in 2018 (6–9). It is designed with a chlorhexidine-coated rod, which provides antiseptic delivery directly into the HD catheter lumen between HD sessions (6–9). Although the upfront costs of these novel products are higher, the long-term projected savings attributable to lower rates of bloodstream infections and hospitalizations may be substantial.

Progress in catheter lock research

Antibiotic catheter locking solutions have been used for prevention of bloodstream infections and are highly effective, achieving a reduction of 50% to 100% in infections. Gentamicin is the most frequently prescribed antibiotic catheter lock; however, a report of gentamicin resistance in one series, which used a relatively high concentration of gentamicin (4 mg/mL) has warranted caution about its routine use (10). More recent studies of gentamicin lock, using lower concentrations (0.32 mg/mL), reported either no change or a decline in gentamicin resistance during long-term follow-up and without loss of efficacy (11, 12).

To avoid the risk of selection for antibiotic-resistant microbes, recent efforts have focused on the development of novel nonantibiotic catheter locking agents, including tissue plasminogen activator, taurolidine, ethanol, and sodium bicarbonate. The instillation of tissue plasminogen activator into the catheter lumen as a lock once weekly, in addition to heparin lock twice weekly, has been shown to significantly reduce bloodstream infection rates; however, the immediate costs are a concern and have hindered its routine use (13). Taurolidine, which has a low potential for resistance, is widely used as a catheter locking agent in the European Union and is effective for prevention of HD catheter-related bloodstream infections, but it has not yet been approved for use in the United States. A phase 3 trial, the Lock-It 100 study of taurolidine-heparin-citrate lock (Neutrolin, CorMedix, Inc.) in the United States, reported a significantly lower rate of catheter-associated bloodstream infec-
Developing an electronic catheter checklist

Implementing the CDC’s core interventions to clinical practice in the HD setting has been shown to reduce the bloodstream infection rate associated with vascular access by 54% (Figure 2) (18). Partnerships between the CDC and the dialysis community (Making Dialysis Safe for Patients Coalition), and more recently with the American Society of Nephrology (Nephrologists Transforming Dialysis Safety, NTDS) have increased awareness about the evidence-based tools available to reduce preventable infections in HD, but there is still a need for improvement to achieve the NTDS’s goal to “target zero infections.”

One of the components of the CDC’s core interventions is the recommendation that observations of vascular access care and catheter access by the HD staff be performed quarterly. Catheter checklists are available on the CDC’s website to assess staff adherence to recommended aseptic technique when connecting catheters, when disconnecting catheters, and during dressing changes. The NTDS’s Vascular Access Workgroup and the CDC have developed the Electronic Chairside Catheter Checklist (Figure 3). This is an electronic web-based version of the CDC’s checklists available on a handheld tablet, and it is currently being evaluated as a pilot in seven outpatient HD units in the United States.

The Electronic Chairside Catheter Checklist also includes resources for patients in a video format, which address another one of the CDC’s core interventions: providing patient education and increasing patient engagement (Figure 4). The embedded videos include the following topics: 1) the importance of hand hygiene, 2) catheter-associated bloodstream infections, 3) proper technique to prevent infection, and 4) the clean hands count campaign for dialysis. The pilot will run from January through April 2020 to determine the feasibility of its use in the busy outpatient HD setting, and feedback will be collected from staff members and patients about the tool. We hope to make the results of the Electronic Chairside Catheter Checklist pilot available in the latter half of 2020.

Conclusion

Bloodstream infection is potentially preventable in the HD population. A significant percentage of such infection is related to vascular access. Interventions to reduce infections in the HD setting include new tools to improve compliance with the CDC’s existing core interventions for catheter care, improving patient involvement and staff education, and the development of novel products and devices for preventing catheter-associated infections.

Acknowledgment: Kerry Leigh, RN, project specialist, NTDS, for the images of Electronic Chairside Catheter Checklist.

Michele H. Moberg, MD, FASN, is chair of the vascular access committee, Nephrologists Transforming Dialysis Safety Initiative of the American Society of Nephrology, and a professor of medicine at the Mount Sinai Einstein College of Medicine.

References

Figure 2. Access-related bloodstream infection rates before and after intervention in 17 hemodialysis facilities participating in the CDC Dialysis Bloodstream Infection Prevention Collaborative

Figure 3. Example of the Electronic Chairside Checklist 2020, which is in development by the Nephrologists Transforming Dialysis Safety (NTDS) Vascular Access Workgroup of the American Society of Nephrology and the Centers for Disease Control and Prevention
Community-Acquired Acute Kidney Injury in Asia

By Vivek Kumar and Vivekanand Jha

Asia is synonymous with diversity, which is reflected in the epidemiology of kidney diseases, especially acute kidney injury (AKI). In contrast to people in the industrialized developed countries, most Asian people, especially those living in rural areas with relatively limited access to healthcare, continue to bear a large burden of AKI. This condition develops in three communities secondary to locally prevalent health issues of public health importance.

The 0by25 Global Snapshot study by the International Society of Nephrology showed that 80% of the burden of AKI in low- and middle-income countries of Asia is community acquired. Community-acquired AKI (CA-AKI) predominantly affects young, previously healthy individuals who often work outdoors in rural areas and are exposed to a variety of occupational, environmental, or sociocultural risk factors that predispose or lead to the development of AKI. These factors are often the culmination of a complex interplay between geographic, ecological, social, and economic conditions prevalent in those regions. They include exposure to tropical infections like malaria, leptospirosis, dengue, or acute diarrheal illnesses; toxic误用mation after animal or insect bites (e.g., snakebite); the use of unproven traditional or local systems of medicine that frequently include nephrotoxic compounds; delays in seeking appropriate care; and lack of hygiene, sanitation, or an adequate supportive healthcare infrastructure.

This pattern of development for CA-AKI is in striking contrast to that for hospital-acquired AKI, which is seen in developed regions and high-income countries. The usual prototype of a patient at risk of AKI in such regions is an individual with preexisting comorbidities like chronic kidney disease, diabetes, or hypertension who is admitted to the hospital for complications related to chronic disease, or in whom AKI develops after a healthcare intervention like major surgery. The fact that mortality in children with AKI is 55 times higher in low- and middle-income countries than in high-income countries reflects the public health importance of addressing AKI in such settings.

Infections are the leading cause of CA-AKI in Asia. The tropical Asian climate favors the persistence and growth of microbes and disease vectors. Although most countries have undertaken community-based measures to control and prevent tropical infections through national programs and international collaborative efforts, the absolute burden remains very high. At one end, Sri Lanka and the Maldives have recently declared malaria free, whereas at the other end, southeast Asia still reports the second highest number of malaria cases after Africa.

The epidemiology of infectious diseases has changed in Asia over recent decades, reflecting the changing host-pathogen interactions resulting from habitat destruction, industrialization, climate change, and indiscriminate use of drugs. Examples include the recognition of human Plasmodium knowlesi malaria, previously seen only in Old World monkeys in countries like Malaysia, Cambodia, and Indonesia; the identification of semi-domestic farm animals as maintenance or accidental hosts for leptospirosis in Sri Lanka; the dramatic increase in dengue viral infections; and the reemergence of rickettsial diseases like scrub typhus across India and China. All of these infections can cause AKI.

Other important risks for CA-AKI are animal or insect bites—occupational hazards for those living in rural areas and working outdoors for their livelihood. South Asia and southeast Asia report the highest number of snakebite-related envenomation and deaths in the world. AKI is common in vasculotoxic viper bites. Stinging insects like wasps, hornets, and bees can also cause AKI, especially when a swarm attacks an individual and injects large doses of venom.

Finally, AKI after the consumption of exotic tropical plants continues to be encountered in Asia. The development of acute oxalate nephropathy leading to AKI after star fruit juice consumption is a classic example. Other plants whose consumption has been reported to lead to AKI include Gloriosa superba and Cleistanthus collinus. The unregulated and easy availability of chemicals, insecticides, and pesticides allows their abuse for homicidal or suicidal intent. AKI can develop after the ingestion of copper sulfate, paraquat, or aluminum phosphide. A lack of healthcare facilities, and reliance on unproven traditional or indigenous medicines owing to social or cultural beliefs, frequently expose underprivileged people to local drugs that contain nephrotoxic compounds and heavy metals.

AKI in obstetric patients in the settings of puerperal sepsis, unsupervised pregnancies, unsafe deliveries, or illegal abortions by untrained personnel is still common among young women from poor socioeconomic groups. Acute cortical necrosis is a dreaded complication especially associated with obstetric AKI, which portends poor renal recovery.

Despite the nonmodifiable nature of a few risk factors (e.g., geographic and ecological factors), a vast majority of CA-AKI cases in Asia are potentially preventable. Convergent efforts over three decades in Bangladesh have almost eliminated a mortality rate of 27% that was previously seen with AKI and acute diarrheal illnesses during floods. Such successes underlie the need to adopt public health approaches to the elimination of preventable mortality due to AKI—the mission behind the 0by25 initiative of the International Society of Nephrology. Awareness among the general public, focused social groups, administrative stakeholders, and various healthcare professionals, and collaborative efforts to implement measures for preventing CA-AKI by early identification in the community and timely referral to appropriate healthcare facilities, are keys to improving outcomes.

Vivek Kumar, MD, DM, is assistant professor, Department of Nephrology, PGIMER, Chandigarh, India. Vivekanand Jha, MD DM FRCP FAMS, is executive director, The George Institute for Global Health, India, professor of nephrology and James Martin Fellow, University of Oxford; consultant nephrologist, University of New South Wales, Sydney, and president, International Society of Nephrology.

Figure 4. Example of the patient education tools embedded in the Electronic Chairside Checklist. These include videos produced by the Centers for Disease Control and Prevention (CDC). In development by the Nephrologists Transforming Dialysis Safety (NTDS) Vascular Access Workgroup of the American Society of Nephrology with the CDC.
Community House Hemodialysis Reduces Hurdles to Home Dialysis

By Bridget M. Kuehn

Undergoing home dialysis in a shared house with other patients of Māori or Pacific ethnicity without medical supervision provided patients with flexibility and support, and enabled them to overcome obstacles to home dialysis, according to a recent study.

New Zealand, where the study was conducted, has long embraced home dialysis. But not all patients are able to or want to do dialysis at home. To help meet their needs, an initiative launched in 2004 to set up community dialysis homes across the country where patients can go to dialyze on their own schedule. The local kidney societies own the homes and manage their day-to-day operations with help from the patients, explained lead author Rachael Walker, PhD, associate professor of Postgraduate Nursing Programs and a nurse practitioner at the Eastern Institute of Technology in Napier, New Zealand. The primary dialysis provider in the area installs the machines and maintains them.

“It’s a way to provide independent hemodialysis close to the patient’s own home, when otherwise they wouldn’t have access to appropriate housing or utilities that would enable them to do home dialysis,” she said. She explained that renters may not be able to install the necessary plumbing, some individuals may lack the room for the machines or supplies, or the costs may be prohibitive. Additionally, many patients may wish to dialyze away from home to maintain their privacy or reduce their family’s exposure to their care.

Walker described a qualitative interview study with 25 patients of Māori or Pacific ethnicity who use the community dialysis houses. The study, which was published in Kidney Medicine, found that patients said the model reduced the burden on their families and offered freedom and flexibility, control of their health, and community support.

“Being able to come whenever you feel like it instead of having to fit into the hospital routine,” was important to one woman in her 40s who participated in the study. “I come whenever it suits me. Those reasons make dialysis a lot more double and livable and part of your life as opposed to attending a dialysis appointment. It makes it feel like it is just one section of your life rather than a hospital taking over your life.”

People who are Māori or other Pacific ethnicities are disproportionately affected by kidney failure. They are also under-represented among the ranks of patients on home dialysis, Walker noted. Yet the study found this model worked well for them.

“The community houses, as well as meeting their cultural preferences, allow the patients to achieve best practice by actually enabling them to have more dialysis hours,” she said. “The majority of the patients were doing over 20 hours of dialysis a week.”

Having more flexibility with timing also allowed more than half of the patients to work, which is often impossible for patients on hospital-based dialysis, noted Walker. Additionally, they found the group environment more supportive, less lonely, and they had fewer concerns about safety. More experienced patients often helped less experienced ones, she said.

“The houses provided more psychosocial support and also allowed them to be able to continue employment, and social, cultural, and community responsibilities and preferences,” Walker said.

Jenny Shen, MD, assistant professor of medicine in the Division of Nephrology at the David Geffen School of Medicine at the University of California–Los Angeles, said community home dialysis...
CONTRAINDICATION:

AURYXIA® (ferric citrate) is contraindicated in patients with iron overload syndromes.

IMPORTANT SAFETY INFORMATION

PREGNANCY AND LACTATION: Patients with gestational diabetes at increased risk of developing cardiovascular disease (CVD) at follow-up through young adulthood, reports a study in the British Medical Journal.

The prevalence of CVD among children and young adults has increased in recent decades. Rates of pregestational and gestational diabetes have been rising as well; a growing body of evidence suggests that offspring of women with diabetes are at increased risk of metabolic syndrome and congenital heart disease. This population-based study sought to determine the extent to which exposure to maternal diabetes increases the lifetime risk of diabetes in offspring.

The BMJ study used Danish national health registry data on liveborn children without congenital heart disease between 1977 and 2016. The researchers identified three groups of children exposed to maternal diabetes during gestation: type 1 diabetes, 22,055 children (0.9%); type 2 diabetes, 6537 children (0.3%); and gestational diabetes, 26,272 children (1.1%). Mothers with diabetes were more likely to be older, to have higher parity, to live alone, and to smoke less during pregnancy.

Follow-up data for up to 40 years were analyzed to examine associations between maternal diabetes and early-onset CVD, defined by hospital diagnosis. Analyses included adjustment for potential founders including calendar year, sex, singleton birth, maternal risk factors, and paternal history of CVD before childbirth. Cumulative incidence of early-onset CVD was averaged across individuals and adjusted for competing causes of death.

During follow-up, CVD was diagnosed in 11,533 offspring whose mothers had diabetes and 91,311 without such exposure: rates per 1000 person-years were 2.02 versus 2.01, respectively. The offspring exposed to maternal diabetes were more likely to have a parental history of CVD and were also at higher risk of developing diabetes, obesity, hypertension, hypercholesterolemia, and chronic kidney disease. Exposed offspring had a significantly higher overall risk of CVD: hazard ratio (HR) 1.29. The increase in CVD risk was greater for offspring exposed to pregestational diabetes, with a HR 1.54; but remained significant for those exposed to gestational diabetes, HR 1.19.

At age 40, cumulative incidence of CVD was 13.07% in the exposed group versus 2.01, respectively. The offspring exposed to maternal diabetes were more likely to have a parental history of CVD and were also at higher risk of developing diabetes, obesity, hypertension, hypercholesterolemia, and chronic kidney disease.
Approval for First Triple Combination Pill for Type 2 Diabetes

The US Food and Drug Administration (FDA) recently approved a new pill containing three type 2 diabetes medications: Trijardy XR (extended release). The triple-combination pill is marketed through a partnership of Boehringer Ingelheim and Eli Lilly and includes the following medications:

- The SGLT-2 inhibitor empagliflozin, which helps your kidneys push more sugar out of your body
- The GLP-1 receptor agonist lixisenatide, which helps control the appetite and blood sugar levels
- The metformin hydrochloride extended release formulation (ER). Empagliflozin (brand name Jardiance), and lixisenatide (Tradjenta) are each manufactured and sold through a partnership between Boehringer Ingelheim (Ridgefield, CT) and Eli Lilly (Indianapolis, IN).

Metformin hydrochloride ER has been available since 1995 in the United States and is sold under brand names (e.g., Glucophage) and generic formulations. It is the most commonly prescribed oral treatment for type 2 diabetes (1).

Multiple medications may be needed to treat type 2 diabetes. The triple combination pill simplifies patient management of their diabetes.

“Many adults living with type 2 diabetes who are already on a treatment plan including multiple medications still struggle to keep their blood sugar under control, and may require additional agents to reach their A1C targets,” said Ralph DeFronzo, MD, professor and diabetes division chief at University of Texas Health in San Antonio. “Adding new medicines to an individual’s plan can be challenging for some, which is why new treatment options that can help improve blood sugar without the burden of an increased pill count are important…. Having three different diabetes medications in a single tablet is an important advance in diabetes treatment.”

The side effects list for Trijardy XR incorporates effects of the individual drugs involved, according to a media release from Boehringer Ingelheim. Common side effects include upper respiratory tract infection, urinary tract infections, stuffy or runny nose and sore throat, constipation, headache, and gastrointestinal.

Among the serious side effects of the new triple-combination drug are lactic acidosis; pancreatitis; heart failure; a rare but serious bacterial infection of the peritoneum, necrotizing fasciitis; acute kidney injury; serious urinary tract infections; leukocytosis; dehydration; and hypoglycemia. 1

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The Science of Learning: How it Can Help Improve Nephrology Education

"Leveraging the Science of Learning to Elevate Your Teaching" was the topic of an inaugural faculty development workshop for medical educators at Kidney Week 2019. The workshop showcased high-yield strategies to optimize participants' teaching, enhance the experience of learners, and translate teaching innovations into education scholarship for dissemination and academic credit. Advancing education in nephrology has long been a focus of ASN Past President Mark E. Rosenberg, MD, FASN.

Suzanne Norby, MD, FASN, chair of the ASN Continuous Professional Development Committee, and Melanie Hoenig, MD, developed and moderated the session, which featured a cast of education rock stars and provided an opportunity for participants to brainstorm together and network. Norby is affiliated with the Mayo Clinic College of Medicine and Science Division of Nephrology & Hypertension in Rochester, MN, and Hoenig is affiliated with Beth Israel Deaconess Medical Center in Boston.

Keynote speaker Peter Brown, author of Make It Stick: The Science of Successful Learning, shared big ideas, including the role of retrieval in learning. He explained that long-term memory develops from encoding, consolidation, and then retrieval—in other words, "get it out to get it in." He stressed the effectiveness of low-stakes spaced quizzes and of mixed practice: the process of alternating different topics and skills during the same study session. Although these strategies may take some learners out of their comfort zones, this can be desirable to promote growth, Brown said.

Exploring approaches to unpack the core concepts in teaching kidney physiology was the focus of Joel Michael, PhD, an educator and physiologist from Rush University, who has worked with the National Science Foundation and the American Physiological Society to improve learning in physiology. He noted that different aspects of physiology and pathophysiology are too often taught in silos, making it difficult for learners to absorb material. When different symbols and terminology are used to reflect the same concept, the parallels can be unrecognizable for students, he said. For example, Fick's law, Poiseuille’s law, and airflow in airways are all examples of flow-down gradients, but this key concept can be missed by students. Communication among educators is the key to limiting this confusion and facilitating students’ ability to make these connections.

Kris Gorman, an education program specialist from the University of Minnesota’s Center for Educational Innovation, helped the group contemplate metacognition. Metacognition means "thinking about thinking" and is used to consider how to assess cognitive processes and promote higher-order thinking skills. Gorman demonstrated how these strategies may be used both in the classroom and in the clinical arena to encourage learning.

To address the challenge of engaging digital natives and meet their learning needs, David Roberts, MD, dean of external education at Harvard Medical School, spoke about harnessing technology in medical education. He emphasized that good teaching is still about the content; technology is only a tool. When electronic content is created, however, it should be accessible on all platforms, especially by cell phones. He acknowledged that because modern learners are so accustomed to finding instant answers online, they have had fewer opportunities to experience the "productive frustration" that can lead to learning, reinforcing Brown’s point about thoughtfully leading learners out of their comfort zones.

Because the impact of the learning environment should always be considered in the complex system of medical education, Thomas Viggiano, MD, former associate dean of faculty affairs at Mayo Clinic Alia School of Medicine, highlighted the challenges learners face in clinical settings and how these challenges may affect the decision to pursue nephrology. He also offered solutions to common learning environment problems, including creating a positive and supportive climate when teachers work with learners of all levels.

Grace Huang, editor-in-chief of MedEdPortal, noted the importance of educators disseminating their teaching successes and promoting scholarship, including publication in the medical education literature. She said there are a surprising number of journals and sites interested in publishing medical education content.

To conclude the session, Hoenig and Gorman facilitated small-group discussions to stimulate formulation of tangible ways participants can apply concepts from the workshop in their own teaching practices. Participants who shared their ideas will receive an e-mail from Norby and Hoenig asking how they implemented their strategies.

Kidney Education Website Goes “Viral,” Generating Over 60 Million Hits Worldwide

By Karen Blum

About 15 years ago, nephrologist Sanjay Pandya, MD, noticed that his patients were facing difficulties understanding their kidney diseases, including what to eat or not eat, and what other care they needed. He thought that if there were a book that spelled everything out in a single source, it would be useful to his patients, and he could then reduce the amount of time he spent counseling about these topics.

So, in 2006, Pandya, who has a private practice in Gujarat, India, wrote a book, “Save Your Kidneys,” in his native Gujarati language. The 200-page text, given free to patients, contained basic information about kidneys and how they function, advice on how to help prevent kidney disease, information about various kidney diseases and their causes and treatment, and comprehensive information about dialysis and transplantation. The book became so popular that he then thought to prepare a second version translated into Hindi, the national language of India, to make the information accessible to a wider audience. That, too, became popular among patients.

Then he dreamed bigger, and by 2010 had created the nonprofit Kidney Education Foundation and posted the information to a website he established, called KidneyEducation.com. Shortly thereafter, he developed an English version of the information. That’s when things really took off. Tushar Vacharajani, MD, a nephrologist in Cleveland, joined the project as an international liaison officer and, with Pandya, contacted other nephrologists around the globe asking for help.

Within a span of about eight years, they amassed a team of about 100 nephrologists, who together have made the information available in 37 languages, including Italian, Chinese, Spanish, French, Arabic, Russian, Portuguese, German, and Japanese, through KidneyEducation.com. The project has attracted the attention of some notable leaders in the world kidney community, including Giuseppe Remuzzi, a past president of the International Society of Nephrology, who prepared the Italian version of the book and website, and Guillermo Garcia-Garcia, a past president of the International Federation of Kidney Foundations, who prepared the Spanish versions. Books in Chinese were printed and distributed free to patients by Ho Chung Ping in Hong Kong. The educational resource is now available to read online, through the WhatsApp mobile application, and through free book downloads.

The website has been accessed over 60 million times, Pandya said. In 2017, the Golden Book of World Records awarded the foundation a certificate for having an e-book in the most languages.

The number of patients suffering from chronic kidney disease is on the rise, Pandya noted. However, he said, ig-
Although being passionate about a mission is essential, teaching skills education and continually refine your passion alone is not enough. During my training I have actively worked to develop my teaching skills by delivering lectures to medical students and residents. I have tried to expand my skill sets by learning how to make animated videos, writing short blogs, micro-mentoring, and developing apps and websites. Learning a new skill can sound intimidating, but it can also become a very empowering tool for connecting with trainees.

Use social media as a teaching platform

The medical community on social media (#medtwitter) is growing exponentially. Being part of the #medtwitter family helped me connect with others who have similar interests and goals and led to collaborations with other institutions. As we all know, being active as a physician on social media comes with some rules. To better understand the medical media world, I did a one-year internship as part of the Nephrology Social Media Collective and later joined the executive team. Apply for internships, workshops, and volunteer activities to improve or add to your skill sets. These opportunities will keep you updated and help you have an open mind for new methods of teaching.

Develop passion and a progressive mindset about medical education

We need to continually make learning interactive and engaging. The right mindset is the crucial to make changes and improve the medical education system. Even in a short interaction with a trainee about a consult, it is important to endeavor to leave the trainee with a stimulating pearl that can become a topic for future conversation.

Actively involve yourself in medical education and continually refine your teaching skills

Although being passionate about a mission is essential, passion alone is not enough. During my training I have actively worked to develop my teaching skills by delivering

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**Figure 1. Trends in inpatient admission comorbidity and electronic health data: implications for resident workload intensity**

Clark AV, et al. Aug 2018

@Visual Abstract by @WrayCharles

Reprinted with permission from Clark et al. (1). (Visual abstract by @WrayCharles.)
High Diabetes Rates in Hispanic and Asian Americans

Hispanic Americans have the highest racial/ethnic prevalence of diabetes, while diabetes prevalence is similar in Asian and black Americans, according to a nationally representative study in *The Journal of the American Medical Association*. The study included data on 7575 US adults aged 20 years or older (mean 47.5) from the National Health and Nutrition Examination Surveys 2011–16. Participants were asked if they had been diagnosed with diabetes by a physician; undiagnosed diabetes was assessed by measurement of hemoglobin A1c, fasting plasma glucose, or 2-hour fasting plasma glucose. Racial/ethnic differences in diabetes prevalence were assessed, including selected subgroups within the Hispanic and Asian populations.

Sixty-five percent of participants were non-Hispanic white, 15% non-Hispanic black, 6% non-Hispanic Asian, and 3% other race/ethnicity. Crude prevalence of diabetes was 14.6% overall, including diagnosed diabetes in 10.0% of participants and undiagnosed diabetes in 4.6%. Another 37.5% of participants had prediabetes. There were significant racial/ethnic variations in age, body mass index, and education.

After adjustment for age and sex, weighted total diabetes prevalence was 12.4% for white adults compared to 22.1% for Hispanic, 20.4% for black, and 19.1% for Asian adults. Within the Hispanic population, total diabetes prevalence was 24.6% for the Mexican, 21.7% for Puerto Rican, 20.5% for Cuban/Dominican, 19.3% for Central American, and 12.3% for South American subgroups. Prevalence was 22.4% for Southeast Asian, 22.3% for South Asian, and 14.0% for East Asian subgroups.

Non-white racial/ethnic groups had higher prevalences of undiagnosed diabetes: 3.9% for white, 5.2% for black, and 7.5% for both Hispanic and Asian Americans. A high percentage of cases of undiagnosed diabetes were identified by 2-hour fasting plasma glucose.

Hispanic and Asian individuals now account for 23% of the US population. Both of these racial/ethnic groups have been reported to have a higher prevalence of diabetes compared with European and African populations. The new study of racial/ethnic differences includes current, nationally representative estimates of diabetes prevalence among Hispanic and Asian Americans.

The results suggest that Hispanic Americans have the highest total prevalence of diabetes. Asian and black Americans also have increased diabetes prevalence, compared to their white counterparts.


Treatment for HCV Slows Progression of CKD

Direct-acting antiviral therapy for hepatitis C virus (HCV) slows the decline in kidney function for patients with chronic kidney disease (CKD), reports a study in *Kidney International*. The retrospective study included 1178 HCV-infected patients who started DAA therapy between 2013 and 2017. All included patients were compliant with DAA treatment, had not undergone organ transplantation or started dialysis, and had available data on baseline characteristics and change in estimated glomerular filtration rate (eGFR) at 12 months.


References:


4. Groopman E, Goldstein D, Gharavi A. March 2020 | ASN Kidney News | It’s time for kidney talk

When you see unexplained signs of kidney disease, think Alport syndrome. It can filter through a family.

Incurable disease

• Alport syndrome (AS) is a permanent, hereditary condition responsible for a genetically defective glomerular basement membrane, causing chronic kidney inflammation, tissue fibrosis, and kidney failure.

• Across the entire range of AS genotypes, patients are at risk of progressing towards end-stage kidney disease (ESKD).

Hidden signs

• Patients often go undiagnosed, as the clinical presentation of AS is highly variable and family history may be unavailable.

• Persistent, microscopic hematuria is the cardinal sign of AS and should prompt immediate diagnostic investigation—particularly when combined with any family history of chronic kidney disease.

Early action

• Expert guidelines published in the Journal of the American Society of Nephrology now recommend genetic testing as the gold standard for diagnosing Alport syndrome.

• Early AS detection via genetic diagnosis, and its ability to guide a patient’s treatment decisions, demonstrates the powerful impact of precision medicine in nephrology.

Reata and Invitae have collaborated to offer no-charge genetic testing for rare chronic kidney disease diagnosis and greater clinical insights. For more information regarding the KIDNEYCODE program or to order a test, please visit www.invitae.com/chronic-kidney-disease or contact Invitae client services at clientservices@invitae.com or 800-436-3037.

Abnormal kidney function can have a strong family connection—Alport syndrome

Learn more about Alport syndrome at ReataPharma.com.

Peripheral Artery Disease Increases Adverse Outcomes in CKD

Patients with moderate to severe kidney disease have a higher risk of peripheral artery disease (PAD) with an increased risk of lower-limb complications and other adverse outcomes, reports a study in the American Journal of Kidney Disease.

The retrospective analysis used administrative data on nearly 454,000 adult residents of Manitoba, Canada, who had at least one serum creatinine measurement between 2007 and 2014. Based on hospital discharge diagnostic codes and medical claims, 4.5% of patients had a diagnosis of PAD. Associations between PAD and CKD were analyzed, including the impact on lower-limb complications, cardiovascular events, and mortality.

Patients with PAD were older (69.0 versus 50.7 years) and more likely to be male (52.4% versus 44.8%). Grade 3 to 5 CKD was present in 30.0% of patients with PAD, compared to 10.1% of the non-PAD group. Rates of grade 5 CKD requiring dialysis were 3.1% versus 0.4%, respectively. Periperal arterial disease was also associated with high rates of other comorbid conditions, including chronic pulmonary disease, diabetes, and cardiovascular/cerebrovascular disease.

Patients with PAD were at increased risk for all-cause mortality, cardiovascular events, and lower-limb complications, in all eGFR categories. The risk of lower-limb complications was 10 to 12 times higher for patients with grade 5 CKD requiring dialysis, compared to patients with normal kidney function who were free of PAD. Among patients with CKD grade 3 to 5, the hazard ratio for lower-limb complications increased from 2.12 for patients without CKD to 6.61 for those with CKD.

Peripheral artery disease is a common and burdensome complication among patients with CKD—largely related to foot complications. Few studies have examined the prevalence of PAD and associated adverse outcomes among patients with CKD not requiring kidney replacement therapy.

The new findings show a high prevalence of PAD among patients with grade 3 or higher CKD. The presence of PAD in patients with CKD is a “potent risk factor” for lower-limb complications, cardiovascular events, and death. The authors call for trials of screening and treatment strategies to address the “extreme risk” of lower-limb amputation or ulceration in dialysis patients with PAD [Bourrier M, et al. Peripheral artery disease: its adverse consequences with and without CKD. Am J Kidney Dis 2019; DOI: 10.1053/j. ajkd.2019.08.028].

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