ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Care After Acute Kidney Injury Falls Short for Many

Patients who survive an episode of acute kidney injury (AKI) and have persistently diminished kidney function are infrequently referred to a nephrologist, according to a recent study in the *Journal of the American Society of Nephrology*. The findings indicate that efforts are needed to identify and treat kidney injury patients who require subsequent care.

"This study is the first of its kind to demonstrate that patients who experience an acute decline in kidney function during hospitalization may not be receiving adequate attention paid to their future risk for developing kidney problems or its complications," said Michael Matheny, MD, of the Vanderbilt University Medical Center and the Tennessee Valley Healthcare System Veterans Administration. "It also highlights an opportunity to improve communication between primary care providers and nephrologists to provide a more integrated approach in caring for the kidney health of these patients."

The seriousness of AKI

AKI is increasingly common and often arises as a result of medical or surgical complications that deprive the kidneys of a normal blood flow for extended periods of time. This is why AKI is most common in people who are already hospitalized, particularly in critically ill patients who need intensive care.

The kidneys can often recover from AKI, and most patients can resume a normal life after treatment; however, they may remain at increased risk for various complications. Even mild injury, resulting in small changes in acute kidney function, can have significant short-term and long-term consequences.

For example, AKI is becoming increasingly recognized as an important determinant of incident chronic kidney disease, progression to ESRD, and long-term mortality. In fact, the current thinking regarding AKI is that it encompasses an entire spectrum of kidney disease, from its early onset as an injury, to its

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Salt in the Diet: Too Much, Too Little, Just Right?

More Data, More Questions on Sodium and Cardiovascular Risk

Questions continue to plague recommendations for daily sodium intake. Recently, both high and low sodium levels have been linked to increased cardiovascular risk in patients with established cardiovascular disease.

"We know that high sodium is certainly bad for you," said Andrew Mente, PhD, assistant professor of clinical epidemiology and biostatistics at McMaster University in Hamilton, Ontario, Canada. "What's interesting is that we also found that too little sodium was also a significant predictor of increased cardiovascular events."

Mente and Martin J. O'Donnell, MB, PhD, associate professor of medicine at McMaster, published their findings in *The Journal of the American Medical Association (JAMA)*.

High risk at both ends of the sodium range

Mente and McDonnell found a "J-shaped" relationship that included a fairly

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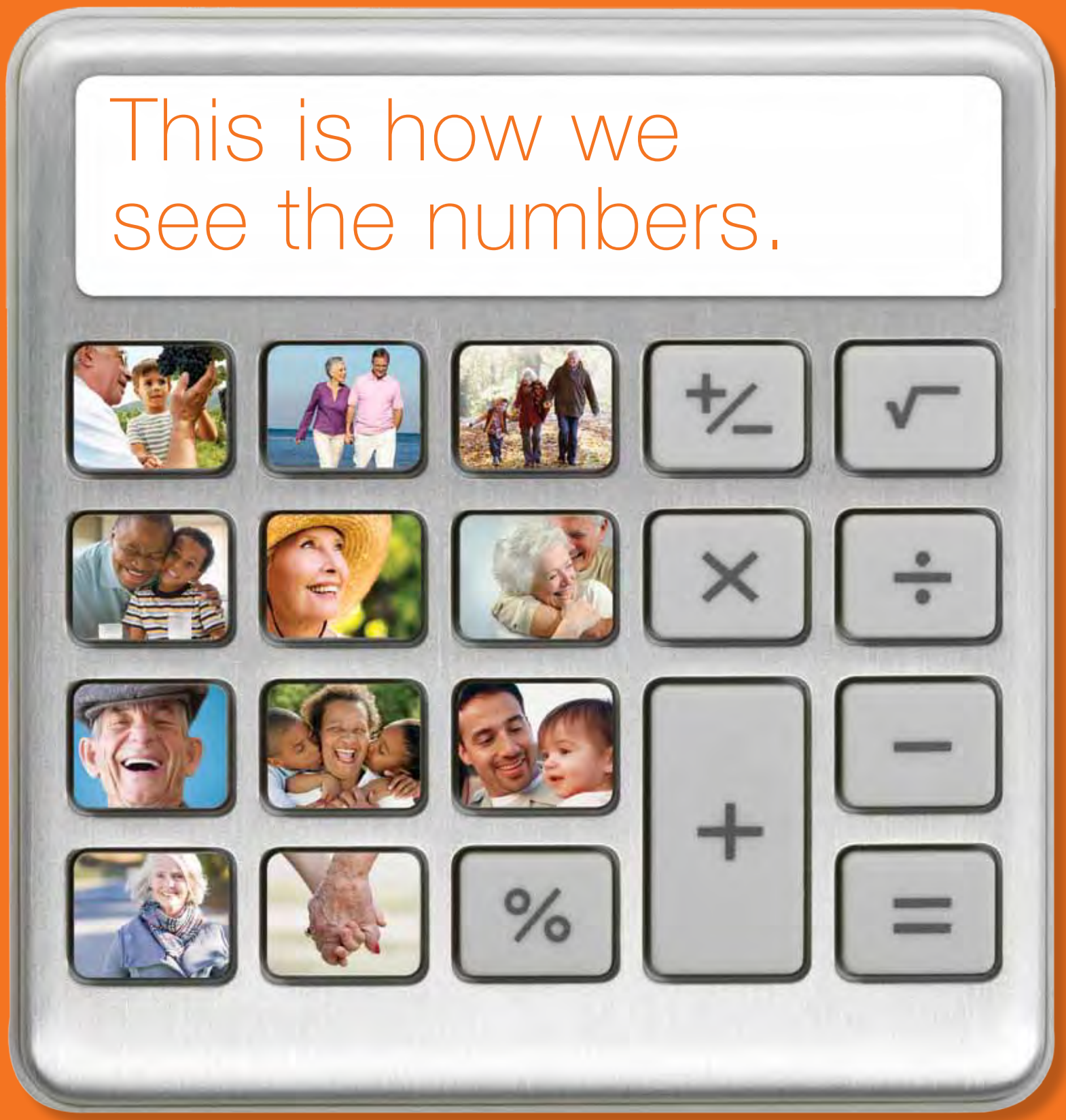

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Care After Acute Kidney Injury

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progressive loss of kidney function of increasing severity, to its development into kidney failure requiring renal replacement therapy.

Chronic kidney disease patients are especially susceptible to AKI, which in turn acts as a promoter of progression of the underlying disease. AKI is also possibly associated with an increased risk of nonkidney complications such as bleeding and sepsis as well as inflammatory effects on other organs.

As the interactions between AKI and these complications become better characterized, improving care for its survivors will depend on identifying high-risk individuals and implementing steps to prevent the progression of disease and its effects. One quality-of-care indicator for a patient with persistently diminished kidney function after an episode of AKI is the rate of nephrology referrals. When such a patient is not referred to a nephrologist, there is a missed opportunity to improve care for the patient.

Matheny, along with Edward Siew, MD, also of the Vanderbilt University Medical Center, and others examined the follow-up care received by patients who experienced AKI during hospitalization and whose information was available through a U.S. Department of Veterans Affairs database (which includes data from five Veterans Affairs medical centers in Tennessee, Kentucky, and West Virginia).

"The overarching goal of our research is to improve the care of patients with acute kidney injury. An important part of this goal is identifying what happens to these patients after leaving the hospital," Matheny said. "As almost all will be discharged to the immediate care of their primary care physician, we wanted to see if there was a potential opportunity for nephrology-based care to make a positive impact."

Post-AKI care

For their study, the researchers identified 3929 survivors of AKI who were hospitalized between January 2003 and December 2008 and who continued to have poor kidney function a month after their injury.

Over a 1-year surveillance period, 22 percent of patients died. Of the 1254 survivors with an initial baseline estimated GFR (eGFR) of at least 60 mL/min per 1.73 m^2, 50.2 percent recovered to an eGFR of at least 60 mL/min per 1.73 m^2 by the end of the 12-month surveillance period. The remainder demonstrated persistent kidney dysfunction. Among 1824 survivors with an initial baseline eGFR of less than 60 mL/min per 1.73 m^2, 50.3 percent had a last eGFR of at least 45 mL/min per 1.73 m^2, whereas the rest had lower kidney function.

"This research is an important contribution to the literature, as it highlights the course of patients who survived an episode of AKI by providing a detailed glimpse at clinical outcomes in the year following the initial event," said Ron Wald, MD, an investigator at St. Michael's Hospital in Toronto, who was not involved with the study but focuses much of his own research on AKI.

Only 8.5 percent of patients in the study were referred to a nephrologist before dying, starting dialysis, or experiencing an improvement in kidney function. Patients' severity of AKI did not affect whether or not they were referred. Also, there were no statistically significant differences in race, sex, or rates of coronary artery disease, hypertension, or peripheral vascular disease among referred and nonreferred patients.

"The relatively small number of patients who were referred for nephrology consultation, even when post-AKI kidney function was impaired, may represent an important gap in the care of these patients," Wald said.

Increasing awareness of the health risks that AKI patients face may lead to earlier and improved management of kidney-related complications.

Traditionally, physicians have not had a unified approach to categorize and treat AKI, but new guidelines being developed by Kidney Disease Improving Global Outcomes (KDIGO), an international program of the National Kidney Foundation, will soon be available and are meant to increase awareness about the prevention, recognition, and management of AKI (http://www.kdigo.org/clinical_practice_guidelines_3.php). The guidelines cover a range of topics: defining and diagnosing AKI, recognizing and modifying risk factors, and implementing treatment and follow-up. Such clinical guidelines should lead to improved outcomes and identify research questions to better understand, prevent, and manage AKI.

Study co-authors include Josh Peterson, MD, Adriana Hung, Theodore Speroff, PhD (Tennessee Valley Healthcare System Veterans Administration and Vanderbilt University Medical Center); Svetlana Eden, and T. Alp Ikizler, MD (Vanderbilt University Medical Center).

Salt in the Diet

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wide range of high but "normal" sodium levels without excess cardiovascular event rates. The findings may have implications for the management of patients at high cardiovascular risk, including those with kidney disease.

The researchers analyzed observational data on nearly 29,000 patients from two randomized trials of telmisartan: ONTARGET and TRANSCEND.

"These were people at high risk for cardiovascular disease, followed up for hard cardiovascular outcomes for an average of almost five years," said Mente.

At a 24-hour sodium excretion rate of less than 3 g/day, the investigators found increased rates of cardiovascular mortality and hospitalization from heart failure. There was also a higher burden of cardiovascular disease associated with high sodium excretion—but not until levels of greater than 6.5 g/day.

Stroke risk fell as 24-hour potassium excretion increased. There were no significant interactions between sodium and potassium excretion.

"What I found interesting is that the J-shaped curve described in this study shows increased risks starting at sodium levels of less than 3 g and more than 7 g, respectively," said Daniel Batlle, MD, professor of medicine at Northwestern University Feinberg School of Medicine and a nephrologist at Northwestern Memorial Hospital, Chicago.

"The 'safe' range where there are no excess cardiovascular events based on this study happens to be a wide one: from 3 to 7 g of urinary sodium," Batlle said. "This would encompass the average intake of sodium of most Americans—which is considered to be too high, based on current thinking."

A growing body of evidence

Other studies have reported similar relationships, Mente said. He cited the population-based European Project on Genes in Hypertension study—published in *JAMA* last spring—which also linked lower sodium to higher cardiovascular mortality.

"Some people saw that study and said, 'Well, these are people that are healthy. If we were to look at patients with cardiovascular disease, we're not going to find low sodium puts them at higher risk," he said. "But indeed, we found actually that same relationship."

Lowering sodium intake is a major focus of efforts to reduce cardiovascular risk. The current World Health Organization recommendation is less than 2 g/day. The American Heart Association advises the public, "Aim to eat less than 1500 milligrams of sodium per day."

It's especially important to clarify optimal sodium intake for patients with existing cardiovascular disease —many of whom also have chronic kidney disease—who may be more vulnerable to the effects of high and low sodium.

While most experts emphasize the importance of reinforcing advice not to eat too much salt, the evidence raises the possibility that current recommendations for sodium restriction could be causing patient harm. "Do we keep people doing what they are doing anyhow?" asked Batlle. "One could interpret the data in this way: 'Why put people on a low-salt diet when better results are seen with what we consider a normal-salt diet in the first place?'

"I am not ready to conclude at all that that's what doctors should be recommending for their patients, but this is one potential interpretation."

A key limitation of the most recent *JAMA* study was that sodium and potassium excretion were estimated from spot urine samples. "We all would agree that the way sodium was measured in the urine is not precise," said Batlle. "But having said that, the results are very thought-provoking and should be the impetus for further study, including dietary intake of sodium and potassium assessed with a timed urine collection over 24 hours."

Intriguing speculations on mechanisms

The increase in heart failure may provide a clue as to one possible mechanism by which low sodium might lead to high cardiovascular risk.

"There is some evidence that low sodium intake can trigger activation of the renin-angiotensin system and increase sympathetic nervous system activity—which is not a favorable response from a cardiovascular standpoint," said Mente.

Other studies suggest that low sodium intake can affect lipoproteins and insulin resistance and lead to a negative balance of magnesium and calcium. "So there are all these other potential unintended consequences," Mente said.

So what's the next step on sodium and cardiovascular risk?

"Certainly to answer the question definitively, we eventually need to do a randomized controlled trial," said Mente. "And not with surrogate measures like blood pressure, but with 'hard' cardiovascular disease events. But that's a challenging study in itself, because you need to get people to eat a very low sodium diet for a long period of time."

He added, "Taking the evidence in its totality, perhaps instead we should be focusing on improving the overall quality of the diet, rather than focusing on a single nutrient like sodium. Also, a high-quality diet is much more palatable and easier to maintain in the long term, and would have universal benefits beyond cardiovascular disease."

Letters

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Journal View

Genetic Score Can't Predict Stage 3 CKD Risk

A genetic risk score incorporating 16 different risk alleles doesn't add to the ability to predict advanced chronic kidney disease (CKD) in the general population, according to a report in the *American Journal of Kidney Diseases.*

The researchers created a genetic risk score from a panel of 16 single-nucleotide polymorphisms previously linked to the risk of stage 3 CKD. The observational cohort study included a total of 2489 participants from three examination cycles of the Framingham Heart Study original and offspring cohorts. The genetic risk score's ability to discriminate the risk of incident stage 3 CKD was assessed, alone and in combination with standard clinical predictors.

At a mean follow-up time of 10.8 years, 270 new cases of stage 3 CKD occurred. There was no difference in the mean genetic risk score between participants who did and those who did not develop stage 3 CKD: 17.5 versus 17.3 (on a scale of 0–32).

With adjustment for age and sex, the odds ratio for the development of stage 3 CKD was 1.06 per additional risk allele. The C statistic was 0.751 with the genetic risk score versus 0.748 without, for no discriminatory improvement. In a multivariate model adjusted for known CKD clinical risk factors, the genetic risk score was not a significant predictor.

Genome-wide association studies have identified several genetic variants associated with an increased risk of CKD. However, a risk score comprising these genetic factors cannot predict which patients are at risk for the development of stage 3 CKD, beyond the information provided by known clinical risk factors. For now, the authors believe that information on genotypes related to kidney disease is more likely to be useful for studying disease pathogenesis than for individual risk assessment [O'Seaghdha CM, et al. Performance of a genetic risk score for CKD stage 3 in the general population. *Am J Kidney Dis* 2012; 59:19–24].

Diuretic Therapy for Systolic Hypertension Increases Long-term Survival

Two decades later, patients assigned to chlorthalidone treatment for isolated systolic hypertension show significantly longer life expectancy, reports a study in the *Journal of the American Medical Association*.

The researchers analyzed very-long-term follow-up data on patients from a randomized controlled trial of treatment for isolated systolic hypertension. The patients were at least 60 years old between 1985 and 1990, when they were assigned to stepped-care treatment with the diuretic drug chlorthalidone or placebo. The original results showed a significant reduction in cardiovascular events with chlorthalidone.

The new study assessed possible differences in death resulting from cardiovascular disease and all causes at approximately 22 years' follow-up. The analysis included 2365 patients assigned to chlorthalidone and 2371 to placebo.

Patients in the chlorthalidone group had significantly increased life expectancy: 105 days for all-cause mortality and 158 days for cardiovascular mortality. For each month of chlorthalidone use, life expectancy increased by approximately 1 day. Chlorthalidone was associated with increased survival free from cardiovascular death, but no significant difference in all-cause mortality.

Absolute reductions were 2.7 percentage points for cardiovascular mortality (28.3 versus 31.0 percent) and 0.6 percentage points for all-cause mortality (59.9 versus 60.5 percent). The chlorthalidone group also had longer times to 70th percentile survival, with differences of 0.56 years for all-cause mortality and 1.41 years for survival free from cardiovascular death.

Antihypertensive therapy lowers the risk of cardiovascular events, but the effects on long-term survival remain unclear. These very-long-term follow-up data suggest that chlorthalidone treatment leads to a significant increase in life expectancy. The gain in life-years in this population of older adults may provide a strong impetus for patients to adhere to their prescribed treatment and for health care providers to overcome "therapeutic inertia." [Kostis JB, et al. Association between chlorthalidone treatment of systolic hypertension and long-term survival. *JAMA* 2011; 306:2588–2593].

Interventional Nephrology

Interventional nephrology has become a growing and distinct discipline within nephrology. The first two articles in this special section deal with everyday issues that practicing nephrologists, dialysis nurses, and technicians encounter.

In "The PICC Conundrum: Vein Preservation and Venous Access," Dr. Pflederer provides background on the increasing use of PICC lines and how their use impacts CKD patients who will require vascular access. Indeed, Dr. Pflederer's article may serve as a resource for developing a PICC line use policy.

Dr. Besarab outlines the enormous impact that the all too frequent use of central venous dialysis catheters has on the morbidity and mortality of patients. He describes the three scourges of dialysis central venous catheters: maintaining patency, catheter-related infection, and central vein stenosis. The frequent use of central venous dialysis catheters has led to what many describe as an epidemic of central venous stenosis. Unfortunately, there are no durable endovascular or surgical strategies once central vein stenosis develops, often leading to permanent vascular access loss.

Dr. Agarwal describes multiple factors favoring peritoneal dialysis. The alignment of benefits to patients (for example, better initial survival, which may be related to not using a central venous dialysis catheter) and now financial benefits derived from the changes in reimbursement may lead to an increase in peritoneal dialysis in the United States. Perhaps these changes will lead to a "PD First" approach as a corollary to "Fistula First."

Next, Drs. Rahbari-Oskoui and O'Neill outline the utility of ultrasonography when used by nephrologists. Several medical specialties have incorporated ultrasonography as part of their practice. Rahbari-Oskoui and O'Neill successfully argue that nephrologists can improve patient care by doing so. In many ways, ultrasound is supplanting the stethoscope.

In the final two articles in this issue, Dr. Dwyer discusses the development of interventional nephrology and Dr. Roy-Chaudhury discusses research opportunities in interventional nephrology.

Interventional nephrology, born in the private practice sector, has now evolved and matured with the development of formal training programs in academic medical centers. ASN has recognized the importance of these developments by establishing the Interventional Nephrology Advisory Group (INAG), which informs the ASN Council and Board of Advisors about issues of importance to the society.

Most recently, INAG has developed a comprehensive curriculum for academic-based nephrology training programs. As described by Dr. Roy-Chaudhury, INAG has also worked with other societies to recommend to the National Institute of Diabetes and Digestive and Kidney Diseases research initiatives germane to improving the care of kidney patients. This focus on research in dialysis vascular access should lead to improved patient care.

I hope that this special edition of *Kidney News* stimulates you, the reader, to learn more about interventional nephrology.

—Jack Work, MD, chair of the ASN Interventional Nephrology Advisory Group, edited this special section for ASN Kidney News, *along with* KN *editorial board member Edgar Lerma.*

The PICC Conundrum:
Vein Preservation and Venous Access

By Timothy A. Pflederer

Peripherally inserted central venous catheters (PICC lines) are being used with increasing frequency in the hospital and outpatient settings for patients who require venous access. Originally intended as a less invasive way to obtain long-term central venous access, PICC lines are now being used for a growing number of indications. Patients who require an extended course of antibiotics or other medications were often chosen to have a PICC line placed after treatment was begun with a peripheral intravenous (IV) catheter. However, PICC lines are now often chosen as the first-line access option in patients with difficult venous access regardless of the duration of therapy required.

Hospitalized patients are older and more chronically ill than in the past. Many of these patients have poor peripheral veins caused by underlying disease, repeated phlebotomy, and IV catheters. Maintaining peripheral IV access can be challenging and time consuming for hospital staff. PICC lines obviate these frustrations and have therefore become staff's preferred venous access device, often placed even when venous access may not truly be required for very much longer. Because of an increasing body of evidence that PICC lines interfere with future arteriovenous fistula placement for dialysis access, the rapid rise in the use of PICC lines has become of great concern.

PICC lines are single-lumen or dual-lumen catheters designed to be placed in a peripheral vein with the tip advanced into a central vein—typically the subclavian vein, brachiocephalic vein, or superior vena cava. They can be placed in the cephalic, median cubital, or basilic veins of the upper arm.

Ultrasound is commonly used to facilitate accurate placement, especially in the more deeply located basilic vein. PICC lines provide convenient, long-term venous access with low rates of failure from thrombosis or infection. They last longer and require less maintenance than peripheral IV catheters. And because they are placed in larger veins at the elbow or above, they can usually be successfully placed even in the most challenging patient. Hospital nursing staff can be trained to place the lines, and this often allows PICC placement to be readily available day or night. These advantages of PICC lines have led to a dramatic rise in their use, especially in the hospital setting.

Unfortunately, this increasing use of PICC lines has come with a cost for patients with chronic kidney disease who go on to require dialysis. PICC lines are associated with a 23–57 percent incidence of thrombosis of the vein in which they are inserted (1). Additionally, 7.5 percent of patients experience central venous abnormalities after the use of PICC lines (2). Loss of peripheral and central venous patency may preclude the successful placement of arteriovenous fistula access when that is necessary. This is a grave concern for these patients, in whom arteriovenous access options have a profound impact on morbidity and mortality during dialysis.

But the problem with prior venous access devices limiting future dialysis access options is not unique to PICC lines. Repeated venipuncture, peripheral IV catheters, and central venous catheters are associated with phlebitis, venous sclerosis, stenosis, and thrombosis. Central venous catheters cause endothelial denudation, smooth muscle proliferation, and pericatheter thrombus even with relatively short-term use (3,4). Not all central venous access sites are the same. Various studies have shown that central venous catheters placed in the subclavian vein are associated with a 13–42 percent incidence of venous stenosis or occlusion, whereas internal jugular catheters are associated with only a 0.3–3 percent incidence (5–7). Tunneled small-diameter catheters placed in the internal or external jugular veins may be associated with an even lower risk of catheter-related central venous complications and do not cause direct damage to peripheral veins (8).

So what are we to do to preserve the veins of patients with chronic kidney disease who may progress to a need for dialysis? PICC lines certainly have a high risk of interfering with future arteriovenous fistula placement by causing stenosis and thrombosis of both peripheral and central veins. But peripheral IV catheters and central venous catheters also carry significant risk. Several organizations have established guidelines and position statements that can be helpful in considering this issue. The Fistula First Coalition (9), the National Kidney Foundation (10), and the American Society of Diagnostic and Interventional Nephrology (11) all have provided useful direction. The Renal Network Inc. (NW 4, 9, 10) has developed a tool kit to aid in implementing a vein preservation strategy (12).

Based on these sources, several recommendations can be made. First, the actual need for venous access should be assessed carefully in all patients. Reducing the frequency of venipuncture and choosing oral medication therapy when possible can significantly reduce venous injury. When venous access is required, patients who are at risk for requiring dialysis in the future should be identified. This requires a review of their history and prior laboratory values. Patients with stage 3–5 chronic kidney disease, patients currently receiving dialysis, and patients with functioning kidney transplants should be identified before venous access is obtained. Venous access in these patients should occur with the following priority:

1. The dorsal veins of the hand are the preferred location for phlebotomy and peripheral venous access.
2. The internal jugular veins are the preferred location for central venous access.
3. The external jugular veins are an acceptable alternative for venous access.
4. The subclavian veins should not be used for central venous access.
5. Placement of a PICC should be avoided.
6. Tunneled small-bore catheters in the internal or external jugular location should be used as an alternative to PICC lines and nontunneled internal jugular central venous catheters.

For these recommendations to be implemented, processes will have to be established within the hospital to ensure that estimated GFR is determined and medical history is obtained in every patient being considered for central venous access, including a PICC line. In most instances, when the patient is at risk for future kidney failure, PICC lines should not be used. Protocols should be in place to guide decisions regarding the appropriate venous access when the patient fits one of the above categories at risk for requiring future dialysis. Finally, physicians must be available with expertise to guide these decisions and place the tunneled small-bore

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The PICC Conundrum:

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catheters. Careful attention to venous access decisions should be effective in reducing venous catheter–associated complications and in preserving the veins of patients at risk for needing dialysis in the future so that successful arteriovenous fistulae can be constructed.

Timothy Pflederer, MD, is associated with the Renal Intervention Center in Morton, IL, and is a member of the ASN Interventional Nephrology Advisory Group.

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The Scourges of the Hemodialysis Catheter

By Anatole Besarab

Hemodialysis (HD) sustains life for those with ESRD. Currently, nearly 400,000 individuals in the United States receive HD as management of ESRD (1). Sustainable vascular access that provides high-volume blood flow rates (Qb) above 300 mL/min is essential, whether through arteriovenous autologous fistulas, synthetic grafts, or tunneled dialysis catheters (TDCs) (2). Unfortunately, the overwhelming majority of incident patients begin HD treatments with a TDC: 82 percent, according to the most recent data from the U.S. Renal Data System (1). More than 20 percent of prevalent patients become or remain dependent on long-term TDC use, spanning months to years (3–5). Other nations, such as Brazil and some in Europe and the Far East, appear to be able to reduce their use of TDCs more quickly and to reduce dependence on long-term TDC use to less than 5–10 percent.

Because of the widespread use of TDCs, research efforts are focused on identifying strategies to prevent and minimize the risk of the most common catheter-related complications—thrombotic occlusion, infection, and central vein occlusion—the three catheter scourges. Proper catheter management to preserve patency and maintain high blood flow rates, reduce the risk of infection, and avoid stenosis is vital in improving patient outcomes.

The first scourge: maintaining patency

The standard procedure for maintaining patency between dialysis treatments, the instillation of heparin into the lumens in a volume sufficient to fill to the lumen tip (the lock) is being replaced by the substitution of a trisodium citrate (TSC) 4 percent lock at many centers. One large Canadian study (6) showed a lower rate of TDC exchange and tissue plasminogen activator (tPA) use without a change in hospitalization for TSC 4 percent versus heparin. On the basis of available evidence, the American Society of Diagnostic and Interventional Nephrology Clinical Practice Committee (7) recommends using a locking solution of heparin 1000 U/mL or TSC 4 percent to maintain TDC patency.

Although a larger-bore catheter design allows an initial rate of blood flow above 400 mL/min to be achieved, virtually all catheters show eventual flow dysfunction manifested as progressive blood flow reductions at prepump pressures considered safe: 200–250 mm Hg.

Prospective monitoring for blood flow dysfunction through systematic monitoring of blood flow and prepump negative arterial pressure (Pa) during HD should be a routine part of the management of patients using TDCs (8) but in many centers it is not. Most large-gauge catheters have a conductance (Qb/Pa) of 2 mL/min/mm Hg. When prescribed blood flow rate (e.g., 350–400 mL/min) is examined serially over time, an increasing negative prepump pressure over time to achieve the prescribed flow reflects alterations in inlet orifice and suggests impending access dysfunction, which may warrant intervention.

Dysfunction manifests as thrombus formation within or at the tip of an HD catheter or by its entrapment within a fibrin sleeve. Systemic anticoagulants and antiplatelet agents have proved to be ineffective in preventing such dysfunction while adding a risk of bleeding. Noninvasive pharmacotherapy with thrombolytic agents has proved to be effective in restoring catheter patency over the short term. All too often, however, adequate flow function can be restored only by catheter replacement with balloon disruption of the fibrin sheath (9), an invasive and costly procedure.

Various protocols for thrombolytic dwells are used by dialysis centers to restore TDC blood flow, usually when the situation is urgent. I favor the slow advancement of the thrombolytic by the injection of saline solution 0.2 mL/lumen behind it every 10–15 minutes to advance the lytic to the catheter tip during a 1-hour dwell, because this strategy decreases the need for repeat lytic dwells by 81 percent (10). Two alternative strategies attempt to improve flow before the development of an "emergency" TDC flow problem: so-called preemptive postdialysis thrombolytic lock or intradialysis lytic infusions. I favor the use of a thrombolytic agent as a prolonged lock of 44–68 hours, both to restore flow and to prevent flow dysfunction. Regular once-weekly use of a tPA agent as a catheter lock solution may be the most effective technique to reduce the risk of vessel occlusion between HD sessions, avoid bleeding risk, and may incur the additional benefit of lower catheter-related bloodstream infection (CRBSI) (11). However, there have been no comparative efficacy or cost studies of the various strategies.

The second scourge: CBRSI

TDCs are responsible for almost half of all infections in HD patients. The infection rates of TDC are 15- and 25-fold higher than those for grafts and native fistulas, respectively. Infection is the leading cause of catheter removal, and CRBSI is a major reason for the loss of anatomic sites for vascular access. CRBSI is associated with substantial morbidity, including metastatic infection. One can estimate from the U.S. Renal Data System and Medicare reimbursement data that there are approximately 100,000 episodes of CRBSI per year in the United States at an average cost of $22,000 per episode (1). CRBSI usually requires catheter removal and 3 weeks of appropriate antibiotics. In some circumstances, catheter removal may be avoided by adding an antibiotic lock to the systemic antibiotic therapy.

Several approaches have been used to decrease the incidence of CRBSI: the use of intravenous antibiotics around the time of catheter implantation; the use of exit-site antimicrobial agents such as honey, mupirocin, and povidone-iodine combined with nasal mupirocin; and the use of antimicrobial-impregnated catheters and antimicrobial locks (AMLs) instilled into the catheter lumen.

Of these, only AMLs and exit-site antimicrobial agents significantly reduce the risk and rate of catheter-related infection and the risk of catheter loss from any complication (12). In a metaanalysis, the use of AMLs resulted in a 75 percent reduction in the risk of CRBSI (12) and only one published study showed the emergence of resistant organisms. Despite the demonstrated effectiveness of AMLs in reducing CRBSI, there is obvious reluctance to their use because of the potential for the development of bacterial drug resistance. Given that the U.S. Food and Drug Administration is unlikely to approve an antibiotic lock, current research focuses on the use of antimicrobial agents, usually combinations of several agents that prevent biofilm formation (13).

The third scourge: central vein stenosis and occlusion

The insertion of a large-bore catheter into a central vein is all too frequently associated with the development of stenosis within that vein. Central vein stenosis is catastrophic when it develops on the side of an established or maturing permanent access, graft, or native fistula, and it all too often precludes the placement of permanent access in the ipsilateral upper extremity. When such catheters are placed in the inferior vena cava, stenosis of the iliac vein can compromise the placement of a kidney graft. Strategies considered to reduce such stenosis include self-centering catheters and catheters configured to support themselves at opposite points of the superior vena cava. Inasmuch as longer catheter dwell times increase the development of central vein abnormalities, and catheter-related infection appears to promote stenosis, it is imperative to keep a TDC as short as possible and prevent infection.

Although catheters offer several advantages in the acute setting, acting as a bridge to more permanent vascular access, continued improvement in the design and performance of catheters is needed. Future studies should focus on better defining the prophylactic use of thrombolytic agents as locking solutions and the appropriate use of AMLs. Clearly, we need improvements in the process of care to reduce the fraction of patients in whom HD is begun with a TDC.

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Peritoneal Dialysis and the Interventional Nephrologist

By Anil Agarwal

The incidence of ESRD is increasing, with a current prevalence of over half a million patients in the United States. Most ESRD patients are treated with hemodialysis (HD) and the number of patients receiving peritoneal dialysis (PD) has steadily declined over the past several decades. According to the U.S. Renal Data System 2011 annual report, approximately 7 percent of patients were being treated with PD at the end of 2009, reflecting gross underuse of this form of therapy (1). Of the incident patients, dialysis was initiated using PD in only 6.1 percent.

The growth in the number of interventional nephrologists during the past decade has established a new paradigm of approach to vascular access and to PD catheter placement. The safety of these procedures and the growth of the PD patient population in the interventional nephrology programs that perform PD catheter placement have been well documented. Interventional nephrologists are uniquely poised to improve the use of PD by highlighting and capitalizing on the following attributes.

Biological benefits of PD

PD offers several advantages over HD including better autonomy, improved patient satisfaction, superior volume control, and better initial survival. The mortality and morbidity in incident HD patients is much higher than in incident PD patients. Inasmuch as HD is started with a catheter in nearly 80 percent of patients, almost all of this early mortality has been attributed to catheters (2). Improving processes to achieve nephrology care early to avoid catheter use will be needed to decrease this early disparity in the future. Meanwhile, the ready placement of PD catheters by interventional nephrologists to initiate dialysis using PD or as a bridge access will remain an easy approach to curtail high incident mortality.

Financial benefits

The recent enactment of a prospective payment system (popularly known as the "bundle") offers even greater incentive to providers if PD is used instead of HD. Furthermore, PD catheter placement is now reimbursed at a much more favorable rate, especially if imaging is used. Given that interventional nephrologists use a peritoneoscopic or fluoroscopic approach, the financial gain should provide impetus to improve PD use.

Counteracting challenges to offering PD

Late referral, poor modality education or offering to patients, lack of new physician training in PD, and delay in PD catheter placement often result in missed opportunities. By offering PD and expeditiously placing the PD catheter without delays in scheduling, interventional nephrologists have the ability to increase PD use. Indeed, PD catheter placement by interventional nephrologists has been reported to improve PD use. Gadallah et al. reported a significant increase in the fraction of incident patients choosing PD from 19 percent to 76 percent with placement of the PD catheter by interventional nephrologists, almost tripling the prevalent PD population (3). The results were confirmed by a multicenter study that showed not only an increase in the PD population at centers providing PD catheter placement by interventional nephrologists but also a decline in the PD population when interventional nephrologists discontinued placing PD catheters (4). Perhaps the fact that the PD population increased is also a testament to the dedication of the providers of this modality.

Improving awareness and training

PD catheter placement by interventional nephrologists is also likely to result in increased awareness and interest by the provider and in better education of trainees. Because the nephrologist is likely to provide significant continuity of care to the patient, better outcomes are likely.

Technical aspects

Interventional nephrologists can place PD catheters with ease using peritoneoscopy or fluoroscopy. As opposed to open surgical dissection or laparoscopic placement, peritoneoscopic placement uses a much smaller scope (2.2 mm in diameter), a small puncture size, one peritoneal puncture site, local rather than general anesthesia, and freedom from scheduling delays, making outpatient same-day placement a possibility. As mentioned earlier, the reimbursement policy for PD catheter placement is now more favorable.

Safety of PD catheter placement by interventional nephrologists

Published data on PD catheter placement by interventional nephrologists does not indicate a higher incidence of complications than with those placed by surgeons. A randomized trial compared the peritoneoscopic and surgical techniques and found that early peritonitis episodes (occurring within 2 weeks of catheter placement) and exit-site leaks were higher in the surgical group than in the peritoneoscopic group (5). PD catheter survival with peritoneoscopic placement was significantly better at 12, 24, and 36 months, and the overall catheter failure rate was higher in the surgical group. Similar results were shown in a separate randomized study (6). The avoidance of various complications by peritoneoscopic placement may relate to the decreased tissue dissection required with this technique.

Interventional nephrologists can also manage most of the complications. Bowel perforation can be a serious complication of the peritoneoscopic technique. However, a study of 750 PD catheter insertions performed by nephrologists using this technique found a low incidence (0.8 percent) of bowel perforations. All of these events were diagnosed and managed by the nephrologists (7). When a Veress needle (blunt, self-retracting end, smaller gauge) was used instead of a trocar, a study of 82 consecutive PD catheter insertions showed no bowel perforation (8). This technical modification deserves consideration.

A PD catheter that has migrated to the upper part of the abdomen can often be repositioned with use of a Foley catheter, or a new catheter can be reinserted during the same procedure, avoiding transfer to HD, placement of a hemodialysis catheter, and interruption of PD. Catheter insertion has also been shown to be successful in patients with a history of abdominal surgery and intraperitoneal adhesions. Thus, patients with previous abdominal surgery should not be summarily denied this procedure. The peritoneoscopic technique is able to identify intraperitoneal adhesions and determine a patient's suitability for catheter placement.

In conclusion, interventional nephrologists can safely perform PD catheter insertion using imaging. This paradigm of care has great potential to improve the use of PD.

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Renal Ultrasonography for Nephrologists: Unmet Expectations

By Frederic Rahbari-Oskoui and William Charles O'Neill

Over the past four decades, ultrasonography has become an indispensable tool because of its safety, availability, and low cost. Accordingly, many specialties have incorporated ultrasonography into their core training programs for visualization of relevant organs and guidance of procedures (e.g., echocardiograms in cardiovascular medicine, pelvic ultrasounds in gynecology and obstetrics, thyroid ultrasounds in endocrinology, abdominal ultrasounds in trauma and emergency medicine).

In nephrology, ultrasonography is ideally suited for visualizing the kidneys, bladder, and blood vessels and is essential for the diagnosis and treatment of patients with kidney diseases. However, formal training in ultrasonography is rarely included in nephrology training programs. This article discusses the reasons why modern nephrologists should acquire this skill and how they can incorporate it into their daily practice.

Owing to their acoustic properties, the kidneys and urinary bladder are easily visualized by ultrasonography and present a limited spectrum of anatomic variations and pathologic conditions. The renal cortex, medulla, and collecting system are usually easily discernible, and pathologic changes correlate well with histologic findings (1). Sonography is indicated in the evaluation and diagnosis of renal failure (acute and chronic), hematuria, severe hypertension, pain, refractory urinary tract infections, and nephrolithiasis and in the screening for hereditary cystic diseases. It is particularly useful in the evaluation of chronic renal failure, where the findings of small kidneys or cortical thinning usually indicate irreversible damage, thereby avoiding further unnecessary evaluation and biopsy (2, 3).

Obstructive uropathy and polycystic kidney disease (as causes of renal failure) can be easily diagnosed or excluded, and other disorders such as nephritis, amyloidosis, and chronic pyelonephritis can be suspected. The utility of sonography is more limited in the evaluation of acute renal failure in native kidneys, when clinical and urinary sediment features strongly point toward acute tubular necrosis, volume depletion, and urinary obstruction (4). However, ultrasonography remains indicated for acute renal failure in known solitary kidneys and transplanted kidneys, where urinary obstruction is a common and unpredictable cause of renal failure (5). Sonography also plays a central role in percutaneous renal biopsy, insertion of hemodialysis catheters, preoperative vein mapping, and evaluation of arteriovenous grafts and fistulas.

Nephrologists can effectively improve patient care by incorporating sonography into their practice, thereby increasing patient convenience, expediting patient care, and providing improved scanning and interpretation (6). By performing ultrasonography during evaluation of patients in the office, nephrologists can make a prompt diagnostic assessment and take therapeutic steps that ultimately improve patient care and satisfaction by avoiding unnecessary waiting time, multiple trips to different locations, or additional testing and hospital admissions. As a simple example, urinary retention can be excluded noninvasively, eliminating the discomfort of catheterization.

Incorporating ultrasonography into nephrology practices streamlines the evaluation of the patient and increases the physician's efficiency. In the outpatient setting, delays associated with scheduling ultrasonography and obtaining results can be avoided because the sonogram can be performed and interpreted during the patient's visit.

Ultrasonography also enhances the ability of nephrologists to perform important procedures on our patients. It is indispensable for guiding central venous catheter insertion, substantially shortening the required time and significantly reducing the risks of complication. Sonography is the imaging modality of choice for performing percutaneous renal biopsies because of its low cost and lack of radiation. It also enables biopsies to be performed by nephrologists at the bedside, enhancing patient and physician convenience. Most renal biopsies are performed under computed tomographic guidance despite the increased cost and radiation exposure and the lack of data showing any advantage over ultrasound guidance (7). An additional advantage of ultrasound in this setting is that a patient whose condition is otherwise stable can be safely discharged after observation without an overnight hospital stay if a postbiopsy ultrasound is normal (8).

Knowledge of patients' personal and family histories, clinical presentation, and complementary test results enables nephrologists to appropriately focus the imaging study and also correlate ultrasound and clinical findings on a real-time basis. Visualization of dilated calyces with or without bladder distension may point toward radically different pathologic processes such as prostatic enlargement or ureteral obstruction. Absence of calyceal dilatation almost invariably rules out obstruction as a cause of acute renal failure. The finding of enlarged renal cortex may be consistent with acute tubular necrosis (in the presence of urinary granular casts) or nephritis (in the presence of proteinuria and hematuria).

Renal enlargement with increased cortical echogenicity may evoke renal vein thrombosis if new-onset hematuria and flank pain are present and should direct the imaging study toward visualization of the renal veins. The same sonographic findings may also point toward amyloidosis in the presence of other cardiac or hematologic features. Major renal asymmetry with unilateral cortical atrophy in the context of severe hypertension and bland urinary sediment strongly suggests the possibility of renovascular disease. Ultrasonography can usually identify the basis for dysfunctional or poorly maturing arteriovenous fistulae.

Finally, renal ultrasonography is an enjoyable and relatively easy skill to acquire, and the incorporation of new diagnostic and procedural modalities can improve the attractiveness of a career in nephrology. The relatively low cost of the equipment, which can be recovered with as few as two outpatient studies per week, and the availability of good-quality portable scanners should make this modality practical for any nephrology practice.

Unfortunately, very few nephrology programs offer comprehensive training in ultrasonography. The Renal Division at Emory University was the first program to provide such training, with all fellows receiving training since 1994. Since 1997, Emory has offered continuing medical education—accredited training for other nephrologists that includes a weekend didactic course held four times a year, followed by an individual week-long minifellowship that includes performance and interpretation of scans and completion of a computerized, interactive teaching file. Information on training can be obtained at http://www.medicine.emory.edu/renal/ultrasound.

Over the past 14 years, more than 1200 nephrologists have attended the didactic courses, and over 350 of them have completed minifellowships. In addition, more than 100 nephrology fellows have been fully trained. Despite the increasing interest, the number of nephrologists who have received training at our institution is still less than 7 percent of all board-certified nephrologists practicing in the United States (9). This training satisfies the didactic requirements for certification by the American Society of Diagnostic and Interventional Nephrology. Additional requirements for certification are a requisite number of ultrasound studies and submission of sample studies of different pathologic conditions. Further information on certification can be obtained at http://www.ASDIN.org.

If ultrasonography is to become an established tool for nephrologists, it must be incorporated into their training. A recent survey of renal fellowship programs (10) revealed that only 8 percent included diagnostic ultrasonography and only 42 percent included ultrasound guidance for kidney biopsies without the help of a radiologist. These numbers were slightly higher for transplanted kidneys (diagnostic: 11 percent; biopsy guidance: 51 percent).

In summary, ultrasonography is an integral part of nephrology that is clearly a feasible procedure for nephrologists, enhancing patient care and both patient and physician satisfaction. The equipment is affordable, and certification is available, but training opportunities remain limited to a very few centers that cannot accommodate the training of all nephrologists. The major obstacle remains the absence of exposure to sonography in training programs. This obstacle can primarily be surmounted by increasing the number of trained faculty members and ultimately incorporating ultrasonography training into nephrology training programs.

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Perspectives

University-Based and Non-University–Based Interventional Nephrology: Barriers and Challenges to Practice

By Amy Dwyer

Nephrologists enjoy an unusually close and extended relationship with their patients, often lasting decades through the evolution of chronic kidney disease to the eventual long-term management of ESRD. Their unique perspective on the importance of dialysis access has led to an intense interest in the field, resulting in the emergence of a distinct discipline within nephrology: interventional nephrology.

Historically, interventional nephrology began in the private practice sector. It was stimulated by a poorly functioning system that provided fragmented care, delayed treatment, and often resulted in poor vascular access care for hemodialysis patients (1). Nephrologists recognized a need for better vascular access care and seized the opportunity to intervene. Numerous outpatient vascular access centers opened up across the United States, and now there are more than 130 outpatient vascular access centers that specifically provide care for hemodialysis patients.

Although many outpatient vascular access centers were started to improve patient care, others have been motivated by the financial benefits received by performing vascular access procedures. A major barrier to starting an access center in private practice is obtaining the start-up funding to build a center. The Centers for Medicare and Medicaid Services has continued to cut reimbursement for vascular access procedures since 2005. As a result, at least 600 ESRD patients are required for an independent interventional center to make a modest profit.

The typical business model for these centers is either full ownership by the nephrology group practices or a joint venture with a vascular access management company. Unfortunately, many small practice groups simply cannot add a program to their practice and continue to rely on surgeons and radiology to provide service to their patients. In addition to financial barriers, nephrologists have difficulty obtaining the appropriate training to perform access procedures. Few training centers exist, and as a result, training for interventional nephrologists in private practice is variable. Many private training programs offer a 6-week training period, and others offer only 3 weeks. These limited programs provide inadequate training to handle complications with vascular access procedures and offer only a superficial knowledge base for the scope of interventional procedures.

The growth of interest in and need to improve patient care has also spurred growth in academic centers nationally. Currently, there are 14 academic centers in the United States that are dedicated to training fellows in the field of interventional nephrology. Academic centers have unique barriers to adding an interventional program into their nephrology divisions. Many university-based practices are challenged by barriers from hospital credentialing, lack of recognition of expertise, and turf battles with surgeons and radiologists. These issues can even delay interventional nephrologists who are certified by the American Society of Diagnostic and Interventional Nephrology from obtaining privileges at their own academic centers. This sometimes leads to nephrologists seeking privileges outside their university practices in the private setting. Private hospitals are not often swayed by egos and turf battles. They simply look for the bottom line.

A few university-based interventional practices have also started in the hospital cardiac catheterization laboratory. Given that cardiologists are also members of their departments of medicine, they are sometimes more willing to allow nephrologists time and space in their laboratories to perform procedures. However, this setting is less than ideal. Commonly, patients with ESRD are delayed in favor of patients with more acute conditions. This leads to longer wait times and extremely frustrated physicians and patients, especially when vascular access procedures are usually scheduled on the patient's day off from dialysis.

In 2009, the American Society of Nephrology (ASN) recognized the importance of interventional nephrology in the care of patients with kidney disease and convened the Interventional Nephrology Advisory Group (INAG). The first initiative of the INAG committee was to create a comprehensive interventional nephrology curriculum for academic-based nephrology training programs, which is now available on the ASN website. The importance of this standardized curriculum cannot be understated. The curriculum provides a detailed outline for an ideal academic program that includes all procedures related to the care of patients with chronic kidney disease: endovascular procedures, tunneled dialysis catheter procedures, preoperative vessel mapping, peritoneal catheter procedures, and diagnostic renal ultrasound. In addition, it also includes a strong research component, which is essential for the continued expansion of the field.

Barriers and challenges exist for private nephrologists and for academic nephrologists. Interventional nephrology began in the private practice arena. However, for the field to move forward, interventional nephrology training must continue only in the academic setting. Training must be standardized, well-designed prospective research studies must be initiated, and new academic training programs must be developed.

Amy Dwyer, MD, is associate profesor of medicine and director of interventional nephrology at the University of Louisville in Louisville, KY. She is a member of the ASN Interventional Nephrology Advisory Group.

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In Advanced Renal Cell Carcinoma...

Indication

VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Important Safety Information

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

- **Hepatic Effects:** Patients with pre-existing hepatic impairment should use VOTRIENT with caution. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended**.
- **QT Prolongation and Torsades de Pointes:** Prolonged QT intervals and arrhythmias, including torsades de pointes, have been observed with VOTRIENT. Use with caution in patients at higher risk of developing QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes within the normal range should be performed.
- **Hemorrhagic Events:** Fatal hemorrhagic events have been reported (all Grades [16%] and Grades 3 to 5 [2%]). VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.
- **Arterial Thrombotic Events:** Arterial thrombotic events have been observed and can be fatal. In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack (all Grades [3%] and Grades 3 to 5 [2%]) were observed. Use with caution in patients who are at increased risk for these events.
- **Gastrointestinal Perforation and Fistula:** Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula.
- **Hypertension:** Hypertension, including hypertensive crisis, has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite

Move Forward With VOTRIENT

In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC[1,2]

All patients
9.2 months
(95% CI, 7.4-12.9)
overall median PFS with VOTRIENT (n=290) vs **4.2 months** (95% CI, 2.8-4.2) with placebo (n=145) (*P*<0.001)[1,3]

Treatment-naïve patients
11.1 months
(95% CI, 7.4-14.8)
median PFS with VOTRIENT (n=155) vs **2.8 months** (95% CI, 1.9-5.6) with placebo (n=78) (*P*<0.001)[1,3]

Cytokine-pretreated patients
7.4 months
(95% CI, 5.6-12.9)
median PFS with VOTRIENT (n=135) vs **4.2 months** (95% CI, 2.8-5.6) with placebo (n=67) (*P*<0.001)[1,3]

NCCN Guidelines® Category 1 recommendation[4]

- As a first-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology . These Guidelines also include therapies other than VOTRIENT as first-line treatment options

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.
See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

VOTRIENT: Safety Profile Summary[1]

- Most common adverse events observed with VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  - — Grade 3/4 fatigue occurred in 2% of patients; all grades, 19% of patients
  - — Grade 3/4 asthenia occurred in 3% of patients; all grades, 14% of patients
- For any individual adverse reaction in the VOTRIENT arm, the rate of Grade 3/4 adverse events is ≤4%

Most common laboratory abnormalities were ALT and AST increases[1]

- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2% of patients
- In clinical trials, 92.5% of all transaminase elevations of any grade occurred in the first 18 weeks of treatment with VOTRIENT
- Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period

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anti-hypertensive therapy and dose reduction of VOTRIENT.

- **Wound Healing:** VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.
- **Hypothyroidism:** Hypothyroidism was reported as an adverse reaction in 26/586 (4%). Monitoring of thyroid function tests is recommended.
- **Proteinuria:** Monitor urine protein. Proteinuria was reported in 44/586 (8%) (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for Grade 4 proteinuria.
- **Pregnancy Category D:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.
- **Drug Interactions:** CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin): Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors.

  CYP3A4 Inducers (such as rifampin): Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT.

  CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

- **Adverse Reactions:** The most common adverse reactions (>20%) for VOTRIENT versus placebo were diarrhea (52% vs. 9%), hypertension (40% vs. 10%), hair color changes (depigmentation) (38% vs. 3%), nausea (26% vs. 9%), anorexia (22% vs. 10%), and vomiting (21% vs. 8%).

  Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in the VOTRIENT arm versus placebo included increases in ALT (53% vs. 22%), AST (53% vs. 19%), glucose (41% vs. 33%), and total bilirubin (36% vs. 10%); decreases in phosphorus (34% vs. 11%), sodium (31% vs. 24%), magnesium (26% vs. 14%), and glucose (17% vs. 3%); and leukopenia (37% vs. 6%), neutropenia (34% vs. 6%), thrombocytopenia (32% vs. 5%), and lymphocytopenia (31% vs. 24%).

  VOTRIENT has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients (<1%).

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. VOTRIENT Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; 2011. **2.** Sternberg CN, et al. *J Clin Oncol.* 2010;28(6):1061–1068. **3.** Data on file, GlaxoSmithKline. **4.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology® for Kidney Cancer V.1.2012. © National Comprehensive Cancer Network, Inc 2011. All rights reserved. Accessed November 17, 2011. To view the most recent and complete version of the guideline, go online to www.nccn.org.

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Oncology

Research Opportunities in Interventional Nephrology

By Prabir Roy-Chaudhury

Interventional nephrology is in the midst of an exponential growth phase, with data from the U.S. Renal Data System suggesting that at least 25 percent of total vascular access procedure costs are billed by nephrologists (1). Indeed, it is likely that the growth of interventional nephrology as a distinct discipline within nephrology has played an important role in the success of process-of-care initiatives, such as Fistula First, which has raised the arteriovenous fistula (AVF) prevalence rate from 34 percent in December 2003 at the start of this initiative to 59.5 percent as of August 2011 (2). Despite these positive indicators, however, dialysis vascular access dysfunction remains a huge clinical problem. Specifically, almost 80 percent of incident hemodialysis patients start with a tunneled dialysis catheter (TDC) (3), only 40 percent of AVFs are suitable for hemodialysis between 4 and 5 months after surgery (4), and the 1-year primary patency for polytetrafluoroethylene (PTFE) dialysis access grafts is only 23 percent (5). Clearly, we need to do better!

Although there are multiple biological and process-of-care reasons for these problems (6–10), we believe that an important underlying cause of these clinical problems is a relative lack of focused basic science, translational, clinical, and process-of-care (outcome) research in the field of dialysis vascular access.

In addition, the induction of formal, high-quality research initiatives into interventional nephrology programs in particular could potentially transform the standing of this distinct discipline within nephrology within both nephrology and internal medicine. Thus, research programs in this area could go a long way toward enhancing the standing of interventional nephrology in the eyes of nephrology program and division directors, and they could constitute an important step toward making interventional nephrology a true distinct discipline within nephrology akin to transplant nephrology. Such research programs could also help bring interventional nephrology into academic institutions. This is absolutely essential for the future of interventional nephrology. Sustained long-term growth of this distinct discipline will likely occur only if it has a solid base within academia while at the same time maintaining its close links with the community physician base that has allowed this specialty to grow so rapidly.

The first publication that attempted to identify core areas of research in vascular access was the 2006 Kidney Disease Outcomes Quality Initiative on vascular access (11), which identified several areas for possible research investigation, including patient preparation, selection and placement of hemodialysis access, cannulation of fistulae and grafts, detection of access dysfunction, treatment of fistula and graft complications, and prevention of catheter complications.

More recently, a survey sent out to the membership of the American Society of Diagnostic and Interventional Nephrology identified (a) arteriovenous fistula maturation, (b) process-of-care guidelines for the creation and maintenance of dialysis vascular access, and (c) PTFE graft stenosis as the three most pressing areas for research into dialysis vascular access, in the order described.

In addition, the ASN's Interventional Nephrology Advisory Group of the American Society of Nephrology (INAG) in combination with the council of the American Society of Diagnostic and Interventional Nephrology recently submitted several areas for research investigation to the Kidney Research National Dialogue sponsored through the National Institute of Diabetes, Digestive and Kidney Diseases. In addition to the areas described previously, improvement in long-term dialysis outcomes, optimization of endovascular and surgical

procedures, and the use of TDC coatings were highlighted as key areas for research activities in this field.

Clearly, there are many potential areas for research in this field and also at least some consensus on a priority ranking for investigative efforts. What is needed, however, is a mechanism to enable the research to be done successfully.

Although there are many approaches to investigative research in dialysis vascular access, the key issue in many ways is the establishment of a system or a process that encourages long-term research activity in this field. One approach, which has been espoused by INAG as a way to lay a firm foundation for a long-term commitment to research activity in this field, is to support the establishment of several academic dialysis access centers (ADACs). These centers will (a) establish basic or translational research programs focused on dialysis vascular access, (b) develop clinical research programs (both investigator initiated and industry sponsored), and (c) establish dedicated (1-year) interventional nephrology training programs where nephrology fellows will be trained not just to do procedures but also in the biology, epidemiology, and process of care of dialysis vascular access.

We believe that the establishment of such ADACs will not only increase the opportunities for well-funded high-quality research in this area but also play a key role in allowing interventional nephrology to grow, by establishing a place for this distinct discipline within nephrology within academic institutions. Finally, although these ADACs are likely to have a home within divisions of nephrology, it is critical that they retain a multidisciplinary nature, because dialysis vascular access dysfunction is by definition a multidisciplinary problem, which we believe can be solved only through a multidisciplinary and translational research effort.

In summary, we believe that this is the time to aggressively develop a formal structure for focused research into dialysis vascular access. We know the problems, and we are asking the questions that need to be asked. In addition, we are lucky that the past decade has seen phenomenal advances in bioengineering, drug delivery, nanotechnology, and cellular therapies, all of which could have a positive impact on dialysis vascular access. We need to apply these biological and technological advances (combined with outcomes and process-of-care research) to the clinical problem of dialysis vascular access so that we can improve on the care we provide our patients. The development of high-quality research programs focused on dialysis vascular access is essential for this to be achieved.

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vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled study *[see Clinical Studies (14) of full prescribing information]*. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%). Table 2 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Hepatic Toxicity: In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. *[See Dosage and Administration (2.2) of full prescribing information and Warnings and Precautions (5.1).]* **Hypertension:** In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. VOTRIENT has been associated with hypertensive crisis in patients with various cancer types including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. *[See Warnings and Precautions (5.6).]* **QT Prolongation and Torsades de Pointes:** In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.2).]* **Arterial Thrombotic Events:** In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). *[See Warnings and Precautions (5.4).]* **Hemorrhagic Events:** In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.3).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. **Hypothyroidism:** In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.8).]* **Diarrhea:** Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. **Proteinuria:** In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. *[See Warnings and Precautions (5.9).]* **Lipase Elevations:** In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). **Cardiac Dysfunction:** Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. **CYP3A4 Inhibitors:** Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. **CYP3A4 Inducers:** CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided *[see Dosage and Administration (2.2)]*.

Industry Spotlight

Transplant Referrals from For-Profit Versus Nonprofit Dialysis Centers Stoke Controversy

Patients with kidney disease who are treated at for-profit dialysis centers are 20 percent less likely to be informed about the transplantation option than are those at nonprofit centers, according to a study at Johns Hopkins University School of Medicine. Controversy about this finding played out recently during a forum in Oregon, when angry state insurers and others confronted representatives from for-profit dialysis centers about the transplantation option.

"In order to be transplanted, you need to be referred by your dialysis center, and in many cases that just isn't happening," said Dorry Segev, MD, PhD, who published the study in the *American Journal of Transplantation*.

Factors other than treatment at for-profit dialysis centers appeared to also affect who got information about other care or treatment options. Older, obese, uninsured, and Medicaid patients were less likely to be informed about all their options, including transplants, the study showed. These omissions have a genuine impact on health, because overall, the uninformed were 53 percent less likely to be placed on a waiting list for a new organ or to receive a kidney from a living donor, according to the study.

In Oregon, dialysis bills for the Oregon Medical Insurance Pool (OMIP) had nearly tripled from $7 million to more than $20 million in the previous 3 years, so the OMIP board in early January publicly questioned executives from the two largest for-profit dialysis companies, Fresenius and DaVita, and the American Kidney Fund (funded in part by those companies), which gives treatment-related financial assistance.

The OMIP is the high-risk health insurance pool for the state. It was established by the Oregon legislature to cover adults and children who cannot get traditional medical insurance because of their health conditions.

OMIP board members were concerned about sharply rising costs and the kidney fund's cessation of premiums for patients who went on to get transplants.

LaVarne Burton, president and CEO of the kidney fund, defended the practice, saying that the kidney fund has limited resources and could pay for dialysis premiums but not for premiums that would cover a transplant, related drugs, and subsequent care, according to Nick Budnick of the *Portland Oregonian*. Burton said that the nonprofit funding organization considers dialysis patients to be the neediest patients.

Neera Dahl, MD, PhD, and Rex Mahnensmith, MD, examine a CT scan from a PKD patient.

The genetics behind kidney disease are intricate and multi-faceted. Only a few medical institutions in the country have the commitment to understanding and treating inherited kidney diseases and the resources to house the prestigious George M. O'Brien Kidney Research Center and a Polycystic Kidney Disease (PKD) Research Center, all supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). We are one of those centers.

Research Excellence, Clinical Leadership and a Commitment to Our Patients

Our researchers have discovered over fifteen genes for human diseases affecting the kidney and blood pressure. These discoveries cover the gamut from rare disorders of blood pressure regulation through sodium and potassium handling such as Liddle's syndrome, pseudohypoaldosteronism type II and Bartter's and Gittelman's syndromes to such common inherited kidney diseases as polycystic kidney disease (PKD). While our researchers are now seeking to translate these findings to treatments for PKD and other disorders, our nephrologists are using these discoveries to help our patients lead healthy and fulfilling lives.

Being at the forefront of clinical research and treatments means that our physicians and surgeons are furthering the current understanding of kidney disease. Most importantly, it means they are positioned to provide the best care possible to our patients.

Yale-New Haven Hospital is the primary teaching hospital of Yale School of Medicine. Nephrology services at Yale-New Haven were ranked 35th by *U.S.News & World Report* in 2011-12.

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Practice Pointers

Dialysis Access Care: Are We There Yet?

This month, ASN Kidney News *editorial board member Edgar Lerma interviewed Tushar J. Vachharajani, MD, FASN, FACP, W. G. (Bill) Hefner Veterans Affairs Medical Center in Salisbury, NC, and Jack Work, MD, of Emory University in Atlanta.*

Tushar J. Vachharajani **Jack Work**

Q: Time and again we have heard the old adage that dialysis access is the Achilles heel of hemodialysis. What is currently being done to address this issue? Please discuss the Fistula First Initiative and the Kidney Disease Outcome Quality Initiative (KDOQI) Preservation of Veins.

A: The survival of patients receiving maintenance hemodialysis depends on a well-functioning vascular access, which continues to remain a weak link in our quest to provide optimal care. The arteriovenous fistula (AVF) has been recognized as the most preferred of the three commonly used vascular accesses: AVF, arteriovenous graft (AVG), and central venous catheter (CVC). A well-functioning AVF has been shown to have the lowest complication rate of stenosis/thrombosis and infection, a lower cost of maintenance, and prolonged patency compared with the other types of access.

The Fistula First Breakthrough Initiative (FFBI; www.fistulafirst.org) was implemented by the Centers for Medicare and Medicaid Services with the primary goal of increasing the use of AVF for hemodialysis. The FFBI framework provided educational materials and tools to track outcomes through 13 well-defined processes known as change concepts. As a result of the aggressive implementation of this program, the prevalent AVF rate in the United States increased from 22.8 percent in 1997 to 59.8 percent in September 2011.

The high incidence of primary AVF failure, reported as 20–60 percent, is the second major hurdle in achieving the current target of 66 percent AVF use in the prevalent hemodialysis population. Preserving veins, improving surgical skills, and educating the dialysis community have been recognized as some of the key factors in overcoming this barrier. KDOQI Guideline 7 and FFBI Concept 12 outline the role of vein preservation. An important strategy to preserve veins for future AVF creation involves the judicious use of peripherally inserted CVCs (PICCs). FFBI has a position paper on the proper use of the PICC in patients with chronic kidney disease (CKD) stages 3, 4, and 5.

Q: Where does the United States stand in comparison with other countries in terms of AVF/AVG vs. catheters? To what do you attribute this discrepancy?

A: According to U.S. Renal Data System 2011 data, 82 percent of patients in the United States have a CVC as the primary access for their first outpatient hemodialysis session, with only 14 percent beginning therapy with a functioning AVF. Catheter use in the incident population in other countries, according to data reported by the Dialysis Outcomes and Practice Patterns Study, is as follows: United Kingdom (60 percent), Sweden (58 percent), Belgium (73 percent), and Canada (70 percent), and it remains high compared with Germany (23 percent), Japan (26 percent), Spain (32 percent), France (39 percent), and Italy (40 percent).

Nearly a quarter of the prevalent population in the United States, Canada, the United Kingdom, Belgium, and Sweden remains dependent on CVCs. AVF use at first dialysis was highest in Germany (72 percent) and Japan (68 percent). The 2.5-fold increase of AVF use in the United States (22.8–59.8 percent) in the prevalent population over the past decade has been a remarkable improvement resulting from the aggressive implementation of the various guidelines, but AVS use remains low compared with Japan (91 percent), Italy (83 percent), Germany (80 percent), France (74 percent), Spain (70 percent), Australia–New Zealand (77 percent), and the United Kingdom (67 percent).

The wide discrepancy of access type in the United States arises from several barriers. Dedicated and sustained teamwork is essential to maintain the momentum achieved over the past decade. The importance of early referral to a nephrologist, better education about vascular access, improvement of surgical skills, improvement of cannulation techniques, and changing the attitude of the patient and the dialysis community can all assist with achieving the target of 66 percent AVF use. The average time from referral to AVF creation in the United States is much higher compared with 5–6 days in Italy, Japan, and Germany. According to data from the Dialysis Outcomes and Practice Patterns Study, despite seeing a nephrologist more than 4 months before starting dialysis, more than 60 percent of patients in the United States began dialysis with a CVC. In the United States, a growing obese and elderly CKD population with associated comorbidities of diabetes and peripheral vascular disease continues to pose a challenge to successful AVF creation.

Financial and regulatory barriers in the United States prevent the timely creation of AVFs. Although most uninsured or underinsured patients will eventually qualify for Medicare coverage, a patient who is unable to train for home dialysis must wait at least 3 months with a CVC before becoming Medicare eligible and before reimbursement for vascular procedures becomes available. This results in prolonged exposure to CVCs and explains the high rate of catheter use at the initiation of dialysis in the United States.

Q: Since the recognition of interventional nephrology as a subspecialty, do you think there has been a change in AVF/AVG rates?

A: The recognition of interventional nephrology (although it is important to note that interventional nephrology is not recognized as a subspecialty by the American Board of Internal Medicine) brought the issue of vascular access planning and care to the forefront. The fragmentation of access care, which was earlier considered as acceptable, has now been transformed into an organized team effort. The interventional nephrologist as a team leader can help coordinate care among the surgeon, primary care physician, interventionalist, dialysis staff, access coordinator, and patient.

The general awareness of the need to pay equal attention to establishing a successful AVF simultaneously, along with all the other issues in patients with CKD, is crucially important for the overall success of renal replacement therapy. The timely manner in which failing accesses are treated has helped reduce the hospital stay and prolong the patency of both AVFs and AVGs. The subspecialty is still young, but as more physicians (nephrologists, radiologists, and surgeons) gain interest and skills in vascular access care, the level of care will steadily improve over time.

Q: One concern during the early years of interventional nephrology was the turf war with vascular surgeons and interventional radiologists. Have there been any changes since that time?

A: The initial apprehension of the various physicians involved in vascular access care is slowly

changing with the recognition that vascular access care is better provided by a team than with a fragmented approach. Every team member has a specific role, and no individual member is dispensable.

The ever-growing CKD population, and the shortage of physicians with interventional and surgical skills, make it virtually mandatory to implement a team approach to provide optimal care. Various successful collaborations between vascular surgeons, interventional radiologists, and cardiologists have been established in the academic arena. These collaborative efforts have resulted in improved AVF rates in these institutions, as was reported in the November 2010 issue of the *Clinical Journal of the American Society of Nephrology* and the September 2011 issue of *Seminars in Dialysis*. Several national meetings have now been organized through the collaborative efforts of all these specialties. For example, the meetings of Controversies in Dialysis Access, the American Society of Diagnostic and Interventional Nephrology, and the Vascular Access Society of the Americas involve participation by all these disciplines.

Q: Please describe the growth of interventional nephrology as a distinct discipline within nephrology. What do you think are its future directions?

A: Interventional nephrology is being increasingly recognized as a necessary field not only in the United States but also globally. The American Society of Diagnostic and Interventional Nephrology (www.ASDIN.org) was established in 2000 and has seen steady growth in its membership. The American Society of Nephrology, the International Society of Nephrology, and the European Renal Association—European Dialysis and Transplant Association now recognize the field of interventional nephrology. There is growing interest in the procedural aspect of nephrology, which is being increasingly viewed as a recruiting tool for nephrology fellowship programs not only in the United States but also worldwide.

Q: Are there any screening or surveillance methods that can reliably predict AVF/AVG failure? Does Medicare cover this?

A: Monitoring and surveillance of dialysis vascular access is essential for early diagnosis and intervention to maintain patency and prevent thrombosis. Monitoring is essentially a regular and thorough physical examination of an access before each dialysis session. Surveillance is the use of sophisticated equipment to measure trends in flow or pressure and to detect access dysfunction. Physical examination alone is generally adequate, provided it is performed regularly and by an experienced person. Surveillance tests are controversial, and as yet there is no consensus regarding an ideal method or frequency at which they need to be performed. Surveillance testing requires additional personnel and equipment costs, which Medicare does not cover. Unfortunately, to date, randomized controlled trials have failed to support surveillance as a means of prolonging access survival.

Q: How do you think the bundling issue is going to affect the economics of interventional nephrology?

A: Bundling of dialysis care currently does not include the procedures performed by an interventional nephrologist. The procedures performed on a dialysis access are reimbursed separately based on specific Current Procedural Terminology codes. The use of a thrombolytic agent during a thrombectomy procedure is the only nonreimbursable cost; it is bundled in the dialysis-related reimbursement.

If vascular access care were bundled, vascular access centers would become cost centers rather than profit centers, which could lead to incentivizing optimal care rather than profitable care.

Q: What advances have been made over the past few years in terms of dialysis access?

A: The alternative to a successful AVF remains elusive. Research into synthetic and bioengineered grafts is being actively pursued. Early reports of tissue-engineered grafts from human allogeneic smooth muscle cells have been promising. Synthetic grafts coated with heparin or carbon are being studied as an alternative to the standard polytetrafluoroethylene grafts. A hybrid graft–catheter access (HeROdevice) has been recently introduced into clinical practice; experience with it so far is limited.

Q: What are the different types of hemodialysis catheters? What are the indications for, and advantages of, one over the other?

A: A plethora of tunneled catheters are available in the market. Differences in the catheters may be based on tip design (step tip, split tip, symmetrical), coatings (external or internal, antiseptic or antibiotic), shaft design (straight or curved), or placement technique (antegrade or retrograde). Each design has some advantages and disadvantages, but universally the goal should be to minimize the length of time the catheter is in place and to transition the patient to a permanent arteriovenous access as soon as possible. A catheter should be viewed as a bridging access, not as a permanent access, because of its high rate of infection-related complications and high cost of maintenance.

Q: Please tell us about the Atlas of Dialysis Vascular Access. What were the objectives in doing this project, and how do you think it will benefit the nephrology community?

A: Nephrology trainees receive limited vascular access–related education during their fellowships. Additionally, dialysis care in the United States is largely dependent on nurses and patient care technicians, who have limited training opportunities. There certainly was a need for a quick pictorial guide with easy online access to enable understanding of the basic anatomy and common access–related complications seen in clinical practice. A picture is worth a thousand words and can leave a lasting impression in a few short seconds. The ultimate goal is to provide an easy reference that will improve the awareness and understanding of the importance of dialysis vascular access to the entire dialysis community, including patients, nephrology trainees, dialysis staff, and physicians. The atlas can be easily accessed through various online sites, including ASN-online.org and www.fistulafirst.org.

Q: Do you have any Practice Pointers for our readers?

A: Routine and thorough physical examination of an AVF can help early identification of problems and enable timely intervention. Recognizing the signs of central venous stenosis (Figure 1) on inspection can potentially prevent the permanent loss of valuable limited-access sites. Monitoring pseudoaneurysms and documenting their size in the medical records can help with timely intervention and salvaging the access. A rapidly enlarging pseudoaneurysm with shiny skin and inability to tent the skin over the pseudoaneurysm in an AVF needs to be revised surgically with aneurysmorrhaphy rather than ligation (Figure 2). A pseudoaneurysm twice the size of an AVG (the normal AVG lumen size is 6 mm) can benefit from surgical revision as a primary option rather than the still controversial approach of covered stent placement.

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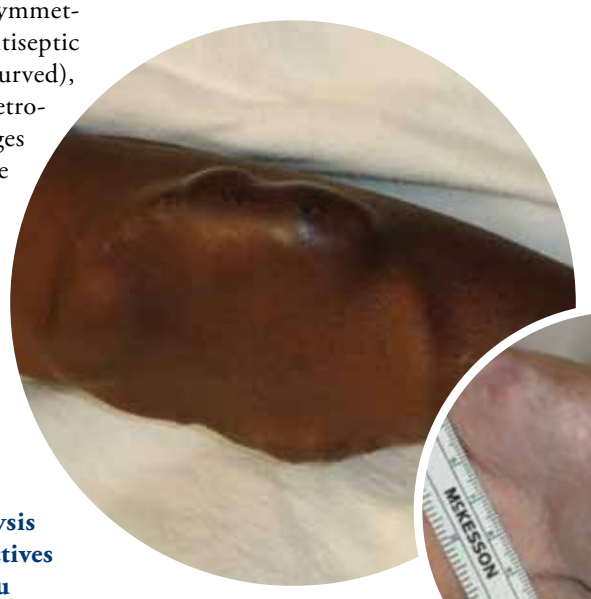


Figure 1. Tense, shiny and paper thin skin over an aneurysm from the *Atlas of Dialysis Vascular Access*

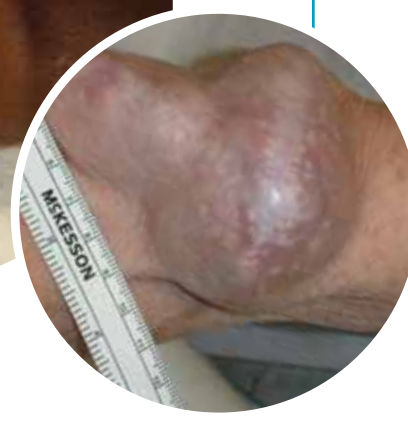


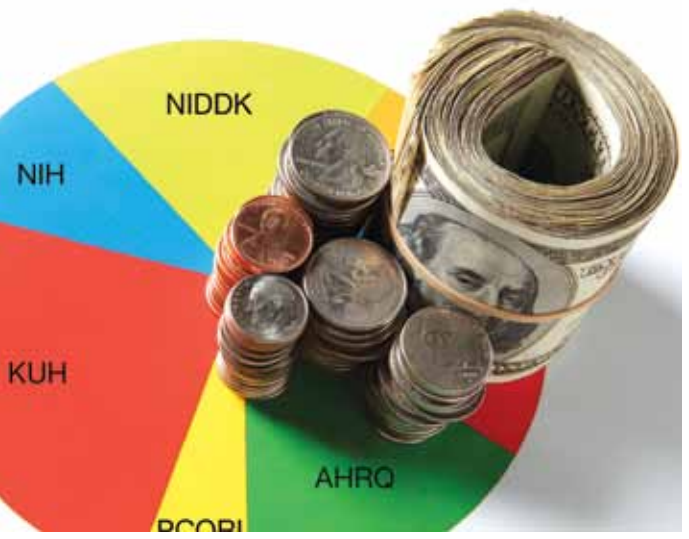
Figure 2. Large pseudoaneursym in an AVG

Policy Update

The Good, the Bad, and the Unknown: Federal Research and Healthcare Funding in 2012

By Grant Olan

After considerable party posturing and uncertainty, Congress passed a last-minute temporary 2-month physician payment patch on December 17, 2011. The patch averted a 27.4 percent cut on January 1 to Medicare reimbursements, triggered by the Sustainable Growth Rate, through February 2012. Lawmakers agreed to meet after their holiday recess to consider a longer-term patch, but concerns remain that they will scour Medicare for possible savings to pay for it. Meanwhile, hope remains that Congress will find a permanent solution for replacing the Sustainable Growth Rate.



Congress also passed an omnibus budget bill in December for fiscal year (FY) 2012. Thirteen appropriations bills fund the government. When lawmakers do not or cannot produce separate bills by the beginning of the new fiscal year on October 1, they usually roll many of the separate appropriations bills into an omnibus. The good news for 2012 is that Congress spared many health agencies from expected cuts. The bad news is that because the Joint Select Committee on Deficit Reduction failed to develop a plan to cut the federal deficit by $1.2 trillion last fall (as required by an agreement to raise the federal debt limit), deep cuts will automatically take effect (a process called sequestration) for most discretionary federal spending programs in 2013—unless lawmakers come to an alternative agreement to cut $1.2 trillion from the deficit in the interim.

At least for the moment, the nephrology care community can celebrate; although we are still waiting for final numbers, it appears that on average, federal health programs will receive a 0.3 percent increase in FY 2012 compared with a 3.84 percent reduction in FY 2011. The Indian Health Service and the Food and Drug Administration look like the biggest winners. They received overall budget increases of 6.21 percent and 2 percent, respectively. On the other side of the coin, the budgets of the Substance Abuse and Mental Health Services Administration and the Health Resources and Services Administration were reduced by 0.93 percent and 0.82 percent, respectively.

Congress also slightly reduced the National Institutes of Health (NIH) budget by 0.18 percent, although NIH is still analyzing the final numbers. However, this minor reduction was relatively small compared with early predictions. It is unclear what the National Institute of Diabetes and Digestive and Kidney (NIDDK) Division of Kidney, Urologic, and Hematologic Diseases (KUH) budget for grant allocation will look like until that number is finalized. The KUH must wait to decide on specific targets for cuts until the NIH leadership and NIDDK Council make recommendations.

As part of the omnibus bill, NIH is implementing its biggest reorganization in a decade. It is dismantling the National Center for Research Resources (NCRR) and launching a new $575 million National Center for Advancing Translational Sciences (NCATS) included in the FY 2012 budget. NCATS was designed to expedite drug development and speed the translation of basic discoveries into new therapies. The Clinical and Translational Science Awards (CTSAs), which support translational research at some 60 academic medical centers and were part of NCRR, will now be awarded through NCATS.

It is difficult to predict what effect that merger will have on the number of CTSAs awarded. The word in Washington is that most of NCATS's budget comes from the reallocation of the $487 million CTSA program. As yet, it is unclear which Institute centers will receive the remainder of NCRR's budget. Some NCATS programs also receive funding from NIH's common fund, a pot of money that the NIH director's office has to allocate. The NIH created a division of clinical innovation to oversee CTSAs in the new center. A division of preclinical innovation will house a $44-million set of mostly intramural programs, including small-molecule screening and drug development for rare diseases. These programs were previously managed by the National Human Genome Research Institute. The only new money Congress approved for NCATS was $10 million to support the center's Cures Acceleration Network.

Like NIH, the Agency for Healthcare Research and Quality (AHRQ) saw a slight budget reduction of 0.81 percent. The AHRQ announced in January 2012 that because of budget constraints, it is suspending three individual career development grants (K01, K02, and K08): the Mentored Clinical Scientist Research Career Development Award, the Independent Scientist Award, and the Mentored Research Scientist Research Career Development Award.

Despite the overall cut to AHRQ's budget, the agency did receive an increase for the Patient-Centered Outcomes Research Institute (PCORI) budget from $8 million to $24 million for FY 2012. Established by the 2010 Patient Protection and Affordable Care Act to conduct research to help patients and their health care providers make more informed health care decisions, PCORI is by law an independent, nonprofit organization. PCORI's research is intended to give patients a better understanding of the prevention, treatment, and care options available by comparing the effectiveness of drugs, medical devices, tests, surgical procedures, or ways to deliver health care.

The American Society of Nephrology (ASN) is currently accepting applications for two award opportunities: the ASN Scherbenske Grant and the ASN Student Scholar Grant. The ASN Scherbenske Grant provides bridge funding for investigators from RO1 to RO1 whose applications were not funded by the NIH. The Student Scholar Grant helps enable medical students with an interest in either basic or clinical research to spend 10–52 weeks engaged in continuous full-time research in a nephrology laboratory. For more information, visit the ASN website at www.asn-online.org.

The ASN is currently undergoing a review of its website. In a few months we hope to roll out a new public policy page that will provide up-to-date information on implementation of the Affordable Care Act and the FY 2013 budget. Although the fiscal climate is grim, ASN is committed to preserving the investigator pipeline to support innovative kidney disease research that will improve patient care and outcomes and cut costs. Stay tuned for more information in the months ahead.

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