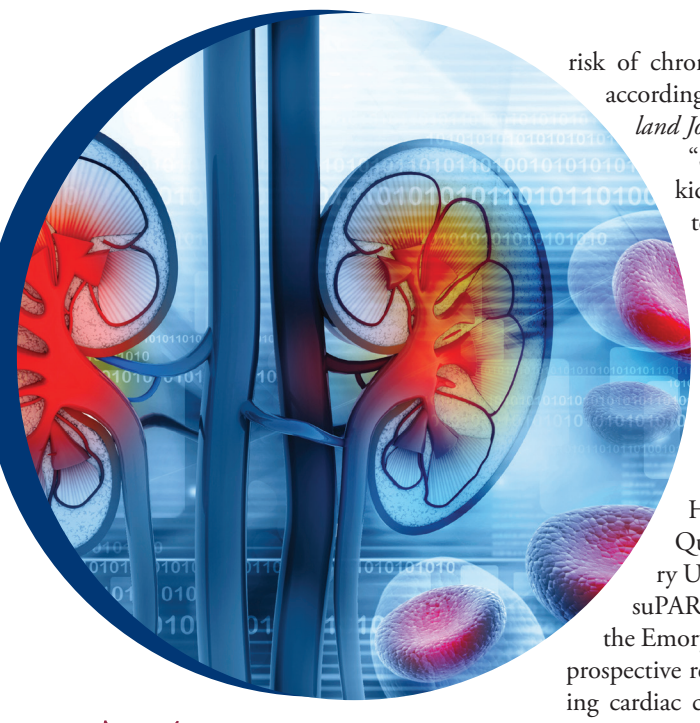
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

# KidneyNews

December 2015 | Vol. 7, Number 12

## New, Early Marker of Kidney Disease Said to Predict Development of CKD



The inflammatory/immune biomarker soluble urokinase receptor (suPAR) may offer a valuable new tool for identifying patients at increased risk of chronic kidney disease (CKD), according to a study in *The New England Journal of Medicine*.

"SuPAR promises to do for kidney disease what cholesterol has done for cardiovascular disease," commented senior author Jochen Reiser, MD, PhD, who is Ralph C. Brown, MD, professor and chairman of medicine at Rush University Medical Center in Chicago.

Lead researchers Salim Hayek, MD, and Arshed Quyyumi, MD, both at Emory University, Atlanta, measured suPAR in 3683 individuals from the Emory Cardiovascular Biobank, a prospective registry of patients undergoing cardiac catheterization. Median age was 63 years; about two-thirds of those studied were men.

In this cohort of patients with cardiovascular disease, the median suPAR level was 3040 pg/mL. As a group, patients with higher suPAR levels had a lower estimated glomerular filtration rate and a higher rate of proteinuria.

SuPAR was then evaluated for association with change in eGFR over time and with incident CKD in 2292 participants. In adjusted models, higher baseline suPAR was associated with a faster decline in eGFR: median annual change -4.2 mL/min/1.73 $m^2$ for those in the highest quartile of suPAR versus -0.9 mL/min/1.73 $m^2$ for those in the lowest quartile. Five-year decline in eGFR was about 20 percent for subjects in the highest quartile of suPAR and 15 percent for those in the third quartile, compared to 7 percent in the two lower quartiles.

The suPAR-related decline in eGFR was greatest among subjects with a normal baseline value (greater than 90 mL/min/1.73 $m^2$). The association was independent of race, diabetes, or proteinuria.

Of 1335 participants with a normal baseline eGFR (60 mL/min/1.73 $m^2$), 24 percent developed CKD during follow-

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## *NIH, VA Research Poised to Win in 2016 Budget*

By Grant Olan

On November 2, 2015, President Barack Obama signed into law the Bipartisan Budget Act, a top ASN policy priority that opens the door for a funding increase for kidney research at the National Institutes of Health (NIH) and Department of Veterans Affairs (VA). The act raises the overall federal discretionary spending levels for 2016 and 2017. However, Congress still needs to pass a budget for 2016 that details exactly how much funding all the federal agencies—including NIH and the VA—can spend.

Congress avoided a government shutdown at the start of the 2016 fiscal year by passing a short-term appropriations bill that funds the government until December 11. Congress must pass another funding bill to avoid a government shutdown by December 11; they can either enact another short-term appropriations bill or an appropriations bill that funds the government through the end of the 2016 fiscal year.

"The Bipartisan Budget Act was a victory, but it is not complete until Congress passes a year-long 2016 budget that increases federal funding for NIH and VA research," Frank "Chip" Brosius, MD, ASN Research Advocacy Committee Chair commented. "I urge lawmakers to work together to ensure

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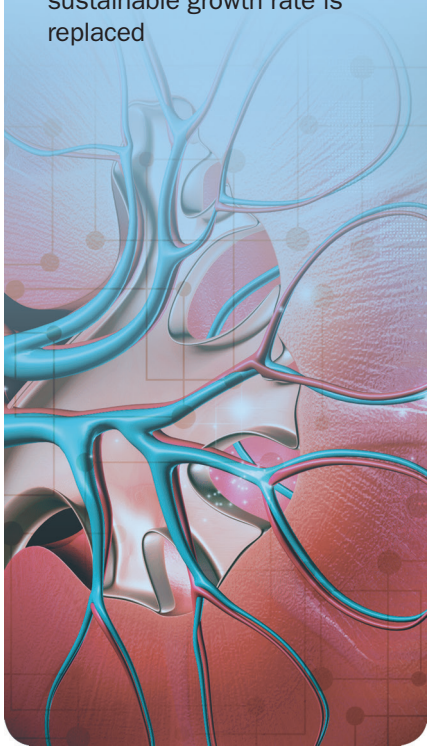

# TINY CRYSTALS.
# BIG PROBLEM.

**Gout preys on more than just bones and joints—** monosodium urate (MSU) crystals can deposit in the kidneys, spine, and soft tissues, including ligaments or tendons.[1,2] Even when patients are not flaring, these crystals can be associated with chronic inflammation, bone erosion, organ damage, and other systemic diseases.[2-6]

Keeping uric acid levels consistently <6 mg/dL—below the MSU saturation point—can dissolve existing crystals and prevent new crystal formation.[7-10]

## Take a deeper look at TheRealGout.com

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## New, Early Marker

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up. Relative to the lowest quartile of suPAR, risk of CKD was about three times higher for subjects in the highest quartile and twice as high for those in the third quartile.

Forty percent of patients with suPAR levels above the median developed CKD, compared to 10 percent of those with lower levels. For subjects with very high suPAR levels—greater than 4020 pg/mL—estimated 10-year risk of CKD was about 80 percent.

In validation studies in a cohort of women from the Women's Interagency HIV Study, the association between suPAR and kidney disease was still significant, but weaker. This likely reflected the younger age and better health of women in the validation group.

SuPAR, as well as its membrane-bound form, plays a direct role in regulating cell adhesion and migration via integrin binding. Reiser's lab has previously presented evidence that suPAR is involved as a circulating blood factor in the pathogenesis of focal segmental glomerulosclerosis and diabetic kidney disease. These findings prompted the researchers to suspect that suPAR may play a broader role in the development of CKD.

Could suPAR testing to assess kidney disease risk really become as familiar as cholesterol testing for cardiovascular disease risk? While not yet FDA-approved for use in direct patient care, the suPAR blood tests are relatively inexpensive and are already being used in Europe for other purposes.

"One characteristic of suPAR is that it is unmodifiable to some degree by lifestyle— for example by stopping [smoking]," said Reiser. "Also, if suPAR is high, we can particularly watch those patients and be more aggressive in terms of giving proper medications to control high blood pressure and diabetes, which contribute to CKD."

Sanja Sever, PhD, co-first author of the study, commented: "SuPAR testing could also be useful for stratifying nephropathy risk in patients with diabetes—for example, in clinical trials testing nephropathy drugs." Sever is associated with Harvard Medical School.

Hayek and Reiser agree as to the next steps toward routine testing of suPAR:

- Exploring whether a change in suPAR is associated with reclassification of risk
- Determining what lifestyle or therapeutic measures lead to a change in suPAR levels
- Designing a trial in which subjects are randomized according to their suPAR levels to usual care versus therapies shown to modify suPAR

Answers to these points will also provide insights as to whether suPAR might be a new therapeutic target in CKD. If so, "We may envision an injectable antibody that binds to suPAR and basically neutralizes it," Reiser said.

## NIH, VA Research

*Continued from page 1*

these programs have the resources everyone broadly agrees are needed. The US scientific workforce, research enterprise, and patients depend on it."

Given the widespread bipartisan support NIH and VA research enjoys, as well as the recognition that NIH and VA research is underfunded, expectations are that lawmakers will boost funding for the programs. However, Democrats are threatening to oppose 2016 budget bills that include ideological policy riders—controversial provisions that would not pass as their own bills—such as limits on US Environmental Protection Agency regulations under the Clean Air and Water acts.

If Congress is able to pass a budget for all of 2016, it is especially likely that NIH and VA kidney research would benefit. Both the House and Senate Appropriations Committees' 2016 budget proposals would raise funding for NIH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and VA research. Under the House proposal, NIH and NIDDK would see increases of 5.9% and 1.71%, respectively. Under the Senate proposal, NIH and NIDDK would receive increases of 8.96% and 2.85%, respectively. The House and Senate proposals would increase VA research by 5.6% and 7.08%, respectively (Table 1).

If Congress does not pass a budget bill by December 11, a government shutdown would bring significant consequences for some researchers. During the last shutdown in 2013, which lasted 16 days, research programs that are funded through annual appropriations were affected. NIH, for instance, was unable to fund new grants and contracts during that time. ASN has been urging lawmakers to come to agreement, support medical research and other important public health programs, and avert a government shutdown.

### ASN budget advocacy

ASN has been actively campaigning for NIH and VA budget increases, along with the Coalition for Health Funding, the coalition NDD United, and Friends of VA Medical Care and Health Research. The society met with 57 congressional offices during ASN Kidney Health Advocacy Day in April 2015 and organized Kidney Community Advocacy Day, which brought together 16 kidney patient and health professional organizations this past September for 112 congressional office meetings.

ASN has also organized and participated in congressional briefings. ASN sponsored a Coalition for Health Funding and Congressional Public Health Caucus Leadership briefing on November 18. Benjamin L. Margolis, MD, a nephrologist at the University of Michigan, spoke to a packed audience about the impact of federal austerity on his own research, as well as the future of medical research and healthcare.

"Due to the current funding environment, we are at risk of losing a whole generation of scientists and severely impairing our ability to respond to the country's healthcare needs in the future," Dr. Margolis said. Research yields critical new therapies patients desperately need and helps our economy. Investing more in medical research is smart for patients and smart for our country."

### What's next?

The budget battles do not end with passage of the 2016 budget. The Bipartisan Budget Act only provides budget relief in 2016 and 2017, but federal austerity measures capped federal discretionary spending through 2021. ASN will continue to work with stakeholders in the kidney and research communities to campaign for budget relief in years 2018 to 2021, as well as steady and sustained funding increases for NIH, NIDDK, and VA research.

**Table 1**
**House and Senate Appropriations Committees 2016 budget proposals**

| | 2015 Budget | House 2016 Budget Proposal | Change from 2015 | % Difference | Senate 2016 Budget Proposal | $ Difference | Change from 2015 |
|---|---|---|---|---|---|---|---|
| **NIH** | $29,446,000,000 | $31,184,000,000 | $1,738,000,000 | 5.90% | $32,084,000,000 | $2,638,000,000 | 8.96% |
| **NIDDK** | $1,889,000,000 | $1,921,388,000 | $32,388,000 | 1.71% | $1,975,162,000 | $53,774,000 | 2.85% |
| **VA Research** | $589,000,000 | $622,000,000 | $33,000,000 | 5.60% | $630,700,000 | $41,700,000 | 7.08% |

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# ASN's Options for Helping Nephrologists Maintain Career Excellence

By Mark E. Rosenberg and Tod Ibrahim on behalf of the ASN Council

For nearly 50 years, the American Society of Nephrology (ASN) has supported the American Board of Internal Medicine's (ABIM's) efforts to certify nephrologists. Championing every aspect of certification—including continuing medical education, continuous professional development, and lifelong learning—ASN is committed to ensuring nephrologists provide the highest-quality care possible throughout their careers.

ASN dedicates intellectual capital, member and staff time, and financial resources to making sure every aspect of certification is meaningful for nephrologists and improves care for the more than 20 million Americans with kidney diseases. This commitment includes supporting nephrology fellowship programs, extending free membership to fellows, offering an in-training examination, holding a board review course, providing the Nephrology Self-Assessment Program (NephSAP) as a free benefit to ASN's nearly 16,000 members, launching the Kidney Self-Assessment Program (KSAP) earlier this year, and developing two practice improvement modules.

On behalf of the broader kidney community, however, ASN must now join much of internal medicine—particularly professional societies that represent internal medicine specialists—in questioning ABIM's ability to meet its mission: "To enhance the quality of health care by certifying internists and subspecialists who demonstrate the knowledge, skills, and attitudes essential for excellent patient care" (1–12).

In response to growing criticisms of the 2014 changes to the Maintenance of Certification (MOC) program, ABIM suspended its Practice Assessment, Patient Voice, and Patient Safety MOC requirements earlier this year. ASN supports this decision, even though it rendered the society's two practice improvement modules mostly obsolete. ASN will terminate these modules on December 31, 2015.

Additionally, ABIM in 2015 released "A Vision for Certification in Internal Medicine in 2020," a report developed by the Assessment 2020 Task Force. The task force recommended ABIM replace its 10-year secure exam with more frequent assessments (with the potential for some portion to be open book), focus MOC on cognitive and technical skills, recognize specialization, and consider certification in specialized areas without requiring maintenance of underlying certificates (13). Supporting these recommendations—which the ABIM leadership is still considering—ASN requests that ABIM also address the fact that more internists (including specialists, such as nephrologists) than ever before are failing the MOC examination the first time they take it (14).

Beyond the uncertainty surrounding MOC, changes to the practice environment and the proliferation of institutional quality improvement programs have raised questions about the need for a recertification process. The Medicare Access and CHIP Reauthorization Act (PL 114-10) created the Merit-Based Incentive Payment System (MIPS) in addition to repealing the Sustainable Growth Rate (SGR). Increasing the relationship between assessment and payment, the mandatory MIPS will integrate several government programs (Meaningful Use, the Physician Quality Reporting System, and the Value Based Payment Modifier).

To help implement the new law, ASN provided guidance to the Centers for Medicare & Medicaid Services regarding the practice improvement activities that Medicare should incorporate into MIPS and encourage as part of outcomes-based alternative payment models. ASN strongly supports the concept that physicians should receive credit for meeting existing requirements, such as the forthcoming MIPS for MOC or vice versa.

In fact, the kidney community is ahead of other specialties in this arena, because nephrologists must navigate bundled payment, a quality incentive program, other federal mandates (such as Quality Assurance and Performance Improvement in dialysis units), and a "model" evaluating a specialty-specific accountable care organization (15, 16). Besides increasing the regulatory burden on nephrologists, these programs often shift assessment from individual physicians to health care institutions, making much of MOC duplicative.

An additional challenge occurred when ABIM ended a 25-year-old commitment to lifetime certificate holders. Starting with the 1990 examination, ABIM implemented a certificate that was "time limited" for 10 years. ABIM considered all certified internists (including nephrologists) "grandfathers" or "grandmothers," allowing each to remain certified as long as he or she maintained a valid medical license. With little feedback from the internal medicine community, ABIM last year tried to change the lexicon describing time-limited certificate holders to either "meeting" or "not meeting" MOC requirements. Responding to protests from internists certified before 1990, ABIM revised the terminology this year to "participating" or "not participating" in MOC.

While supporting this revised terminology, ASN is disappointed that ABIM withdrew its pledge to certificate holders with so little input from the community. ASN also rejects the argument that ABIM was forced by the American Board of Medical Societies (ABMS) to make this change, because ABIM certifies nearly 25% of the physicians in the United States and ABIM revised the terminology earlier this year without first consulting ABMS (17).

With virtually no feedback from the internal medicine community, ABIM fundamentally changed its governance structure in 2014. Previously, the ABIM Board of Directors comprised the chairs of each test-writing committee (including nephrology) and other selected leaders, such as internal medicine department chairs or chief executive officers of health care systems. This structure guaranteed every internal medicine specialty was represented on the ABIM leadership and resulted in a reasonable balance among general internists, hospitalists, geriatricians, and specialists.

Today, ABIM's Board of Directors is much smaller with representation from fewer specialties; no nephrologist currently serves on the board of directors, but the Chair of the Nephrology Specialty Board is a member of a recently formed ABIM Council that includes the chairs of all of the specialty boards. The charges to, purposes of, and relationships among the ABIM Board of Directors, Council, specialty boards, and test-writing committees are unclear, as is the link between these entities and the many internal medicine professional societies, including ASN.

Confusion surrounds the specialty boards. What is their charge? Does this charge encompass the entire mission of ABIM or just MOC? Should each specialty board have the same charge, have parallel memberships, and function similarly? How are the specialty boards supposed to relate to the professional societies?

This lack of clarity has left societies such as ASN unsure of how to interact effectively with ABIM. Due to a combination of uninspired agendas and choreographed meetings, the ABIM Liaison Committee for Certification and Recertification is currently not a meaningful forum for dialogue between ABIM and the internal medicine community. Even though ABIM held three summits with internal medicine leaders during the past 18 months, these discussions have failed to accomplish much. ABIM scheduled the third such summit the day before ASN Kidney Week 2015, virtually guaranteeing no nephrologist would participate in the discussion.

Recently, the ABIM Nephrology Specialty Board approached the directors of the US nephrology fellowship training programs about fundamentally changing the documentation requirements for fellows regarding procedures, including recording the number of inpatient dialysis orders and outpatient home dialysis encounters. The fact that the nephrology specialty board could consider this proposal raises troubling boundary questions about the responsibilities of ABIM, the Accreditation Council for Graduate Medical Education (ACGME), and the kidney community (as represented by ASN in this situation).

These boundary questions highlight the fact that members of the specialty boards brandish remarkable power in their fields, despite the fact that they were appointed and not elected by a broad membership, unlike the leaders of societies such as ASN. In light of the firestorm over MOC, concerns about the changes to ABIM's governance, and lack of clarity concerning the role of the specialty boards, ASN currently lacks confidence in ABIM's direction, focus, and leadership.

Finally, investigative journalist Kurt Eichenwald has questioned the organizational relationship between ABIM and the ABIM Foundation, the transfer of reserves from ABIM to the Foundation, ABIM's approach to estimating deferred revenue, and ABIM's dependence on future revenue from MOC (18–20). Given the gravity of these accusations, ASN has been deeply disappointed with ABIM's response. ABIM's reaction reduced trust across internal medicine, including in the kidney community.

ABIM has invited ASN and other professional societies to "co-create" a meaningful MOC program that supports lifelong learning and practice improvement while achieving public accountability. ASN will continue to address the multiple concerns raised by the society's members, along with much of organized medicine, regarding the direction, focus, and leadership of ABIM, with a particular focus on MOC reform.

As part of this process, ASN will request that ABIM:

1. Suspend all MOC-related activities until the ABIM implements a completely new approach to MOC that is far less onerous to physicians. The entire internal medicine community must fully vet and approve this new direction. Pausing MOC would allow the community to work with ABIM to co-create an ideal approach to continuous professional development.
2. Include in its new approach to MOC recommendations outlined by the ABIM Assessment 2020 Task Force that have already been embraced by the internal medicine community. These recommendations include replacing the 10-year secure exam with more frequent assessments (with the potential for some portion to be open book), focusing MOC on cognitive and technical skills, recognizing specialization, and considering certification in specialized areas without requiring maintenance of underlying certificates.
3. Return its governance structure to the previous model, eliminate the specialty boards, and name "sponsors" (such as the Alliance for Academic Internal Medicine, the American College of Physicians, and the specialty societies) to increase organizational oversight.
4. Allow ASN's leaders and auditor to meet with ABIM Chief Financial Officer Vincent J. Mandes to review the finances of both ABIM and the ABIM Foundation in light of Mr. Eichenwald's accusations. ASN thanks ABIM President and Chief Executive Officer Richard J. Baron, MD, for extending this offer to ASN shortly before press time.

While continuing to address these issues and reinvent every aspect of MOC, ASN has a responsibility to its members to explore at least four other pathways in 2016 to ensure nephrologists have the tools to continue to provide high-quality care to the more than 20 million Americans with kidney diseases.

**Option 1: ASN could request that ABMS create two boards.** The first board (ABIM) would focus solely on general internal medicine, hospital medicine, and geriatrics; the second board (the proposed American Board of Specialty Medicine) would focus on specialty internal medicine, including nephrology. Some may argue ABIM is "too big to fail," but the nation's 9,771 urologists, 9,320 otolaryngologists, and 8,832 dermatologists each have independent boards. The 9,394 nephrologists in the United States are massed into ABIM along with more than 200,000 generalists, hospitalists, geriatricians, and other specialists (21).

**Option 2: ASN could promote competition by partnering with ABIM, the National Board of Physicians and Surgeons (NBPAS), and any other qualified entity to certify nephrologists and provide continuous professional development.** Ideally, this option would result in improving coordination among the myriad entities that assess physicians and institutions. It should also eliminate the unacceptable variability among ABMS's 24 specialty-specific boards.

**Option 3: ASN could sever ties with ABIM (and ABMS) and partner with NBPAS or any other qualified entity to certify nephrologists and provide continuous professional development.** This option is tricky, because the approximately $9,500,000,000 annually in Medicare funding for graduate medical education (including nephrology fellowship programs) has two criteria. First, the residency or fellowship program must be accredited by ACGME. Second, the training program's residents or fellows must be eligible to take an ABMS-sanctioned certification examination.

**Option 4: ASN could recognize that changes to the practice environment eliminate the need for ABIM/ABMS MOC.** Under this option, ABIM/ABMS could focus on initial certification while the specialty societies provided continuous professional development. ASN commends the American Gastroenterological Association (AGA) for beginning to explore this possibility in the Gastroenterologist: Accountable Professionalism in Practice (G-APP) Pathway (22). In theory, societies like ASN and AGA could band together to provide lifelong learning.

Committed to ensuring nephrologists provide the highest quality care possible throughout their careers, ASN will consider every aspect of certification and continuous professional development in 2016. (To suggest other potential approaches, please contact ASN at education@asn-online.org by January 31, 2016.) During this assessment—which will include a survey of US nephrologists—ASN will determine the future of its relationship with ABIM, ABMS, NBPAS, and other entities. ASN will continue to do what is best for patients, for the relationship between patients and their physicians, and for ensuring nephrologists maintain excellence throughout their careers.

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# Late-Breaking Trials Provide New Insights for Improving Clinical Care

By Kurtis Pivert

The late-breaking clinical trials presented at ASN Kidney Week 2015 featured research that could help advance patient care in a wide range of clinical areas—from uremic pruritus in dialysis patients to acute kidney injury (AKI) in the hospital setting to the next frontier in renal replacement therapy. Although some trial outcomes were unfavorable or unexpected, Lynda Szczech, MD, FASN, told *ASN Kidney News* they still provide an important contribution to the medical literature and clinical care. "Negative trials have value too. They will prevent patient exposure where there's no benefit," said Szczech.

## Randomized trials address multiple facets of AKI

Several trials focused on preventive treatments and protocols for reducing AKI incidence in the hospital setting. AKI is estimated to complicate the postoperative course of 20 to 30 percent of patients undergoing cardiac surgery, and is associated with a 5-fold increase in premature death.

Frederic T. Billings, MD, presented results from the Statin AKI Cardiac Surgery trial, a prospective, double-blind, placebo-controlled clinical trial of high-dose perioperative atorvastatin for prevention of AKI associated with cardiac surgery (1). Because statins can affect some underlying mechanisms of AKI, the researchers wanted to determine if a short-term high dose of perioperative atorvastatin would reduce postoperative AKI.

The 820-participant randomized trial was terminated early after researchers determined high-dose perioperative statin use did not decrease postoperative AKI risk following cardiac surgery in patients with chronic kidney disease, and could increase AKI risk in patients naïve to statin therapy. However, the short-term withdrawal or continuation of statins around the time of cardiac surgery did not appear to affect AKI risk.

A substudy of the SIRS (Steroids In caRdiac Surgery) trial—a multinational placebo-controlled, randomized trial of 7286 patients at high risk of perioperative mortality undergoing cardiac surgery—investigated whether corticosteroids could reduce the patient's AKI risk (2). Because corticosteroids have been successful in treating acute inflammation in the kidney, the authors, led by Amit Garg, MD, PhD, hypothesized they could suppress the systemic inflammatory response syndrome activated by the use of cardiopulmonary bypass pump in cardiac surgery.

The researchers found that high doses of the corticosteroid methylprednisolone did not reduce AKI risk regardless of whether the patient had preexisting CKD. The results would suggest that prophylactic steroids not be used to prevent AKI in patients undergoing cardiac surgery with cardiopulmonary bypass, said Garg.

Another clinical trial investigated contrast-induced AKI, a complication in medical imaging estimated to affect between 2 and 20 percent of patients. Investigators at the Charité Hospital in Berlin led by Eva Schönenberger, MD, conducted the first randomized comparison between CT angiography and invasive contrast-enhanced angiography (the standard test for diagnosing a blocked coronary artery) to determine which method was the most accurate and safest for detecting coronary disease (3).

In the study, 318 patients with suspected coronary disease were randomized to undergo either invasive angiography or CT angiography. Both arms received the same contrast agent administered directly into the coronary arteries for angiography or superficial veins for CT. AKI was 2 to 3 times more likely to occur with invasive angiography compared with CT angiography. "The diagnosis of coronary disease by CT may thus offer two advantages—noninvasiveness and at the same time reduced risk of AKI," Schönenberger told *Kidney News*.

## New understandings in dialysis care

Researchers led by Ashley Irish, MBBS, MD, conducted the FAVOURED (Fish oils and Aspirin in Vascular access OUtcomes in REnal Disease) trial to investigate ways to potentially overcome the 30 to 50 percent attrition rate of newly created arteriovenous fistulae (AVF), considered the optimal vascular access for hemodialysis (4). Because of the anti-inflammatory, antiplatelet, antihypertensive effects of fish oil and aspirin, investigators conducted a randomized, placebo-controlled trial to determine if they could reduce AVF access failure.

After randomizing 567 hemodialysis patients to fish oil or placebo, with a subset of patients randomized to additionally receive aspirin or placebo, the researchers found that neither omega-3 polyunsaturated fatty acids nor aspirin had any effect in preventing AVF failure. "It's disappointing we didn't see a benefit because these therapies are cheap, safe, and readily available," said Irish. Yet he added that such trials generate a huge amount of knowledge about the natural history of AVFs and other aspects that can inform practice and drive future trials.

Another randomized trial investigated whether nalbuphine, a κ-opioidagonist/μ-opioid antagonist, was safe and effective in reducing the itching intensity of uremic pruritus, a common side effect of hemodialysis that affects a patient's sleep, quality of life, and social functioning (5). Because κ receptors mediate anti-pruritic effects, researchers led by Vandana Mathur, MD, FASN, hypothesized the opioid nalbuphine could reduce the itching associated with uremic pruritus.

A total of 373 patients on dialysis were randomized to one of two doses of nalbuphine or placebo. After 8 weeks, the high-dose (120 mg) group demonstrated a significant reduction in itch intensity. "Other quality of life measures, such as sleep, also seemed to improve," said Mathur.

## Tacrolimus more effective in steroid-resistant nephrotic syndrome

A new prospective open-label randomized controlled trial found tacrolimus was superior to mycophenolate mofetil (MMF) in maintaining remission in children with steroid-resistant nephrotic syndrome (6). Led by Aditi Sinha, MD, researchers from the All India Institute of Medical Sciences in New Delhi conducted a trial to determine if MMF would enable remission while avoiding the toxicity associated with calcineurin inhibitors, such as tacrolimus.

A total of 60 patients were randomized to either tacrolimus and prednisone or MMF and prednisone. After 12 months, MMF was inferior to tacrolimus with 51.7 percent of patients on MMF experiencing treatment failure (recurrence of steroid resistance, frequent relapses, or more than one serious adverse effect) compared to 9.7 percent in the tacrolimus group. Ninety percent of patients receiving tacrolimus demonstrated a favorable outcome (sustained remission and infrequent relapses) compared with 48 percent in the MMF group. "In patients with steroid-resistant nephrotic syndrome and remission with 6-month therapy with tacrolimus therapy, MMF was associated with a higher risk of treatment failure," said Sinha.

## A new frontier: the Wearable Artificial Kidney (WAK) trial

The first human trial of the WAK, invented by UCLA/Cedars Sinai nephrologist Victor Gura, MD, FASN, demonstrated the proof of concept of the device (7). The WAK is a miniaturized, battery-operated, belt-like device that removes excess salt, water, and accumulated toxins that allows patients to undergo dialysis at a natural rate while ambulating or working and without the customary dietary restrictions required by hemodialysis.

Five of the seven patients in the pilot study completed the 24-hour trial, conducted at the University of Washington at Seattle. The WAK was well tolerated and effective in maintaining electrolyte homeostasis, solute clearance, and volume removal. "The data provides proof of concept that the WAK is an effective and safe dialysis device that will greatly improve quality of life for ESRD patients," said Gura. "The results suggest that the WAK has the potential to reduce patient mortality and cut the exorbitant cost of treating kidney failure."

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# Maternal Prenatal Lead Exposure Linked with Early Childhood High Blood Pressure in Offspring

Exposure to lead during pregnancy was linked with higher blood pressure in young children in a study presented at Kidney Week 2015. Exposure to lead during infancy did not seem to impact later blood pressure.

Alison Sanders, PhD, of the Icahn School of Medicine at Mount Sinai and her colleagues examined the effect of exposure to lead during pregnancy or in infancy on blood pressure in 4-year-old children. The analysis included 397 children and their mothers, with maternal blood samples previously collected at the 2nd trimester, 3rd trimester, and at delivery. Children's blood samples were collected at birth, 1 year, and 2 years of age.

The team found that exposure to lead during pregnancy was tied to higher blood pressure in the 4-year-olds, but the effects of lead exposure on blood pressure did not show up during infancy.

"There is growing awareness that adult hypertension has origins in childhood. These findings support the role of lead exposure in the developmental origins of disease, possibly even adult hypertension," said Dr. Sanders. "If so, the prenatal period may be a susceptible window for the development of mechanisms that regulate blood pressure and may be an appropriate timeframe during which interventions to prevent hypertension should occur."

"Effect of Prenatal and Childhood Lead Exposure on Blood Pressure at 4 Years of Age" (Abstract SA-PO644).

# African Americans with Uncontrolled Hypertension Often Lack Healthy Foods

Many African Americans with uncontrolled hypertension do not have recommended food choices in their homes. They also often do not have adequate discussions with their doctors about diet, especially the Dietary Approaches to Stop Hypertension (DASH) diet, according to findings from two studies presented at ASN Kidney Week 2015.

The DASH diet is recommended for the treatment of hypertension, especially among African Americans.

To assess barriers to following the DASH diet, Deidra Crews, MD, ScM, FASN, of Johns Hopkins University School of Medicine and her colleagues conducted interviews and inspected the homes of 159 African Americans with uncontrolled hypertension living in Baltimore, MD. They found that those with chronic kidney disease (CKD) were less likely to have fresh fruits than those with normal kidney function and that young African Americans were less likely to have plant proteins available. Those who were both young and with lower incomes were less likely to have whole grains in their homes.

Overall, only 14.5% of patients had all 5 of the DASH food categories in their homes (fruits, vegetables, low-fat dairy, whole grains, and plant proteins).

Beyond looking at food availability, Crews and her team also looked at the homes' capacity for preparing adequate meals. While more than 80% had full-sized ovens and refrigerators to allow for DASH meal preparation, low health literacy was associated with a lower likelihood of having these appliances.

"The homes of urban African Americans with risk factors for chronic kidney disease were often lacking either the foods or needed appliances for preparing DASH diet–accordant meals," said Dr. Crews. "Interventions to improve the dietary quality of this high-risk group should consider these factors."

Dr. Crews and her colleagues also looked at how often diet discussions occurred among primary care physicians and African Americans with uncontrolled hypertension at increased risk for CKD.

For this study, the investigators audio-recorded 127 patients' routine visits with their primary care physicians at the first visit following study enrollment. Diet was discussed in 73% of visits, but only 12% of visits included discussion of the DASH diet. Discussions about diet were more likely to occur when the visits were longer, were centered on patient priorities, and were attended by patients with higher incomes.

"DASH Diet Accordant Foods in the Homes of Urban African Americans at Risk for CKD" (Abstract SA-PO711).

"Engaging Urban African Americans at Risk for CKD in Discussions about their Diet" (Abstract SA-PO715).

# Longer Survival for Kidney Transplants Compared with Home Hemodialysis

Patients who received kidney transplants survived longer than age-matched patients who underwent home hemodialysis in two studies presented at Kidney Week.

Previous studies found that kidney failure patients on long-term dialysis tend to die earlier than patients who receive kidney transplants, but none of the studies considered death rates in US patients using alternative forms of dialysis such as home hemodialysis.

To help shed light on that question, Miklos Zsolt Molnar, MD, PhD, FASN, of the University of Tennessee Health Science Center and his colleagues compared information on 2000 patients who started home hemodialysis with 2000 patients who received kidney transplants in the US between 2007 and 2011. Over 5 years of follow-up, home hemodialysis patients were 4 times more likely to die than kidney transplant recipients.

Also, there was an interaction with race in the association of treatment modality with mortality," said Dr. Molnar. "In African Americans, mortality risk increased after the first year as the survival lines were separated only after this time-point, while in whites the survival lines were separated from the beginning of the follow-up." More research is needed to elucidate the reasons underlying racial differences in the risk of premature death in home hemodialysis vs. kidney transplant patients, Dr. Molnar said.

In a second study, Dr. Molnar and his team compared mortality rates in 480 elderly (>65 years old) patients using home hemodialysis with 480 matched kidney transplant recipients. The home hemodialysis patients had nearly a 5-times higher risk of dying during follow-up than did kidney transplant patients. Results were consistent across different types of kidney donors and subgroups divided by various recipient characteristics.

Still to be determined is whether kidney transplantation provides better quality of life or lower hospitalization rates compared with home hemodialysis in elderly individuals with end stage renal disease, Dr. Molnar said.

"Racial Differences in Survival of Incident Home Hemodialysis and Kidney Transplant Patients" (Abstract FR-PO1007).

"Survival of Elderly Incident Home Hemodialysis and Kidney Transplant Patients" (Abstract FR-PO1008).

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## Focus on Donors

# African Americans Often Have Complications after Living Kidney Donation

In a study that looked at the frequency and severity of early complications after living kidney donation, African Americans had a 26% increased risk of experiencing any complication and a 56% increased risk of experiencing major complications, after appropriate adjustment was made for other factors.

Krista Lentine, MD, PhD, FASN, of Saint Louis University and her colleagues integrated national US donor registry data from 2008 to 2012 with administrative records from a consortium of 98 academic hospitals. They found that 16.8% of donors experienced complications, most commonly gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), and surgical- or anesthesia-related injuries (2.4%). Major complications affected 2.5% of donors.

In addition to African American race, other significant correlates of major complications included obesity, predonation blood disorders and psychiatric conditions, and robotic nephrectomy. Greater annual hospital volume of living kidney donations predicted lower risk for major complications after the surgery.

"As policies for informed consent, medical evaluation, and follow-up of living organ donors are receiving increased attention and formalization by the organizations that guide and regulate transplantation practice, ongoing efforts to improve the understanding of outcomes after living donation are needed," said Dr. Lentine. "Ultimately, by improving understanding of the short- and long-term health outcomes among representative, diverse samples of living donors, the transplant community can strengthen the processes of consent, selection, and clinical management that are vital priorities."

"Racial Disparities in Perioperative Complications after Live Kidney Donation" (Abstract FR-OR071).

# New Equations May Help Predict Lifetime Risk of Kidney Failure in Kidney Donor Candidates

A team of investigators led by Morgan Grams, MD, of the CKD Prognosis Consortium recently developed equations to help predict potential kidney donors' lifetime risk of end stage renal disease (ESRD) on the basis of their demographic and health characteristics before kidney donation.

"We suggest consideration of predonation lifetime ESRD risk in the evaluation and counseling of potential living kidney donors," the authors of the study said. "Our equations estimate a person's lifetime incidence of ESRD in the absence of donation according to multiple demographic and clinical characteristics."

The team found that the predicted predonation lifetime incidence of ESRD varied by age, race, and sex. Incidence was 2.7% for 20-year-old black men, 1.1% for 20-year-old black women, 0.9% for 20-year-old white men, and 0.6% for 20-year-old white women. For 60-year-olds, predonation lifetime ESRD incidence was 0.6 percent for black men, 0.3% for black women, 0.3% for white men, and for 0.2% for white women.

Lifetime incidence of ESRD increased with additional risk factors, especially low kidney function. The predicted lifetime incidence of ESRD before donation was <1% in 88% of recent US donors.

"Predicting the Lifetime Risk of End-Stage Renal Disease in Kidney Donor Candidates" (Abstract FR-OR068).

# Postdonation Hypertension, Diabetes May Affect ESRD Development and Risk of Death

Twenty-seven percent of kidney donors surveyed in a recent study reported at Kidney Week developed new-onset hypertension after donation.

Hassan Ibrahim, MD, FASN, of the University of Minnesota and his colleagues followed 3638 kidney donors for 13 +/– 11 years through surveys about hypertension and kidney disease, and also through laboratory testing. They found that predonation risk factors for development of hypertension included older age as well as higher BMI, systolic blood pressure, and serum glucose at donation. White donors were found to be 40 percent less likely to develop hypertension.

The team also found that kidney donors who developed hypertension had a nearly fourfold increased risk of premature death, proteinuria, and estimated glomerular filtration rate <30 mL/min or end stage renal disease (ESRD).

In a second study by Ibrahim and his colleagues, development of diabetes was determined in 3874 kidney donors who were followed for a mean of 16 +/– 12 years. Among the 7 percent who developed diabetes, predonation risk factors included older age, tobacco use, as well as higher BMI and fasting serum glucose.

The investigators also found that postdonation diabetes was associated with a twofold increase in ESRD and a nearly fivefold increase in proteinuria.

Ibrahim and his team used information from the studies to develop individualized risk calculators for development of postdonation hypertension and diabetes.

"ESRD and Post Donation Hypertension and Risk of Death and ESRD" (Abstract FR-OR069).

"Post Donation Diabetes and Risk of Death" (Abstract SA-PO1020).

# Living Kidney Donation Rates Lower Among African Americans

Living kidney or kidney-pancreas donation rates were highest among Caucasians followed by Hispanics and Asians in a study that looked at the impact of organ transplant candidates' socioeconomic environment on living donation rates. The findings were reported by Douglas Keith, MD, of the University of Virginia Medical Center at Kidney Week 2015.

Keith and his team identified all candidates listed for kidney or kidney-pancreas transplant in the Scientific Registry of Transplant Recipients database from 2000 to 2010. They then linked their information to US census data on median income by zip code.

The researchers found that increasing median income levels of candidates' zip codes were associated with higher rates of living donation for all racial and ethnic groups.

African Americans had by far the lowest overall living donation rates. Rates of living donation for African American candidates living in the wealthiest neighborhoods were only slightly higher than rates seen among the lowest quintile median income areas for Caucasians.

"The finding could reflect lower levels of wealth for African Americans, which are probably similar to Caucasians living in low income communities," said Keith Norris, MD, PhD, clinical professor specializing in health policy and nephrology at UCLA. "It could also reflect distinct health beliefs and behaviors for African Americans rooted in a historical distrust of American institutions based on years of disenfranchisement."

Likewise, said Dr. Norris, who was not associated with the study: "This finding suggests that people living in communities with lower median income may have lower levels of disposition to philanthropic giving, but more likely suggests that either there are higher rates of co-morbidity leading to exclusion for being a donor and/or the nonreimbursed costs related to donation—such as time off work for evaluation and follow-up, parking, and child or elder care—may preclude many from participating.

"Association of Neighborhood Poverty and Living Donor Kidney Transplant Rates by Race" (Abstract FR-PO1002).

# Acid Reflux Medications May Increase Kidney Disease Risk

New research presented at ASN Kidney Week 2015 found that use of proton pump inhibitors (PPIs) is associated with increased risk for chronic kidney disease (CKD). PPIs are commonly used to treat acid reflux, stomach ulcers, and other acid-related gastrointestinal conditions.

In one study, PPI users were between 20% and 50% more likely to develop CKD than non-PPI users, even after accounting for baseline differences between users and non-users.

For this study, Benjamin Lazarus, MBBS, of Johns Hopkins University and his colleagues followed 10,482 adults with normal kidney function from 1996 to 2011.

They found similar results in a second study in which over 240,000 patients were followed from 1997 to 2014.

In both studies, individuals who used H2-blockers to suppress stomach acid did not have a higher risk of developing kidney disease, according to Dr. Lazarus. "If we know the potential adverse effects of PPI medications we can design better interventions to reduce overuse," he said.

In another large study, Pradeep Arora, MD, of SUNY, Buffalo, and his team found that PPI use was linked with a 10% increased risk of CKD and a 76% increased risk of dying prematurely. They looked at records of 24,149 patients who developed CKD between 2001 and 2008—out of a total of 71,516 patients—25.7% of whom were treated with PPIs. Among all patients studied, those who took PPIs were less likely to have vascular disease, cancer, diabetes, hypertension, and chronic obstructive pulmonary disease, despite their increased risk for CKD and for dying prematurely.

"As a large number of patients are being treated with PPIs, health care providers need to be better educated about the potential side effects of these drugs, such as CKD," said Dr. Arora. "PPIs are often prescribed outside of their approved uses, and it has been estimated that up to two-thirds of all people on PPIs do not have a verified indication for the drug."

"Proton Pump Inhibitor Use is Associated with Incident Chronic Kidney Disease" (Abstract SA-OR005).

"Proton Pump Inhibitors Are Associated with Increased Risk of Development of Chronic Kidney Disease" (Abstract TH-PO574).

# Hypertension Underdiagnosed in Overweight, Obese Teens

Despite evidence supporting hypertension in overweight and obese adolescents as risk factors for heart disease, high blood pressure is underdiagnosed in these teenagers. New research presented at Kidney Week examined the extent of the underdiagnosis.

Brian Sykes, MD, a pediatrician with Nemours/A.I. duPont Hospital in Wilmington, DE, and his colleagues looked at hypertension diagnoses in overweight and obese adolescents cared for by Nemours Health Care System. They examined electronic medical records within Nemours and identified 6604 youth 12 to 17 years old with a BMI above the 85th percentile and with more than 3 documented blood pressure readings >120/80 mm Hg between 2010 and 2014. Only 3.8% (255) of these adolescents received a diagnosis of hypertension during the study period, while 96.2% (6349) were undiagnosed. Adolescents who were undiagnosed had lower BMIs and blood pressure readings. They were also less likely to be African American, have Medicaid, or be seen by subspecialists who manage blood pressure monitoring and treatment.

"In a large pediatric health care system, hypertension in overweight and obese adolescents remains underdiagnosed despite evidence supporting both as independent risk factors for cardiovascular disease," said Dr. Sykes. "It is crucial that additional resources and future efforts focus on improving detection and early recognition of hypertension in order to reduce cardiovascular morbidity and mortality in this at-risk population."

Potential initiatives might include alert flags in electronic medical records for this at-risk population and additional educational workshops or seminars for clinicians.

"Under-Diagnosis of Hypertension in a Large Cohort of Overweight/Obese Adolescents" (Abstract SA-PO666).

*Kidney Week 2015 stories continue on p. 17*

# Industry Spotlight

## Vascular Access News

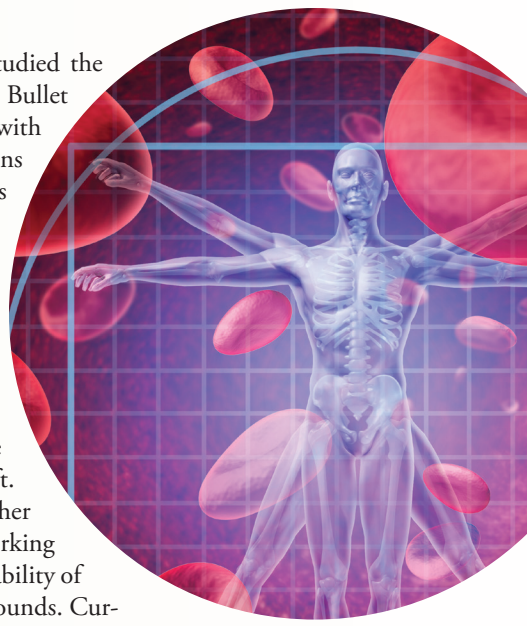
New approaches to long-term vascular access problems are arriving. One group is working in trials to get approval for its system for creating vascular access. The other team is working to prevent needle sticks that penetrate into and through the vascular graft walls, causing profuse bleeding.

TVA Medical( Austin, TX), is developing minimally invasive therapies for patients with ESRD. TVA has completed $15 million in financing with new investors Baxter Ventures (lead) and Boston Scientific, as well as existing strategic investors. TVA hopes to accelerate its market development for the everlinQ endoAVF system, a catheter-based technology that is designed to create hemodialysis access for patients with chronic kidney disease using a minimally invasive procedure.

The system creates an arteriovenous fistula for hemodialysis. During the access procedure, two thin, flexible magnetic catheters are inserted into an artery and a vein in the arm. A small burst of radiofrequency energy into the catheter area connects the artery and vein to create the fistula, and the catheters are removed. The system has been studied outside the US and has received a CE mark in Europe. It is not currently available, however, in the US and has not yet been approved for commercial use by the Food and Drug Administration.

Funding will support the ongoing Novel Endovascular Access Trial (NEAT) clinical study; completion of the 12-month follow-up is expected in 2016.

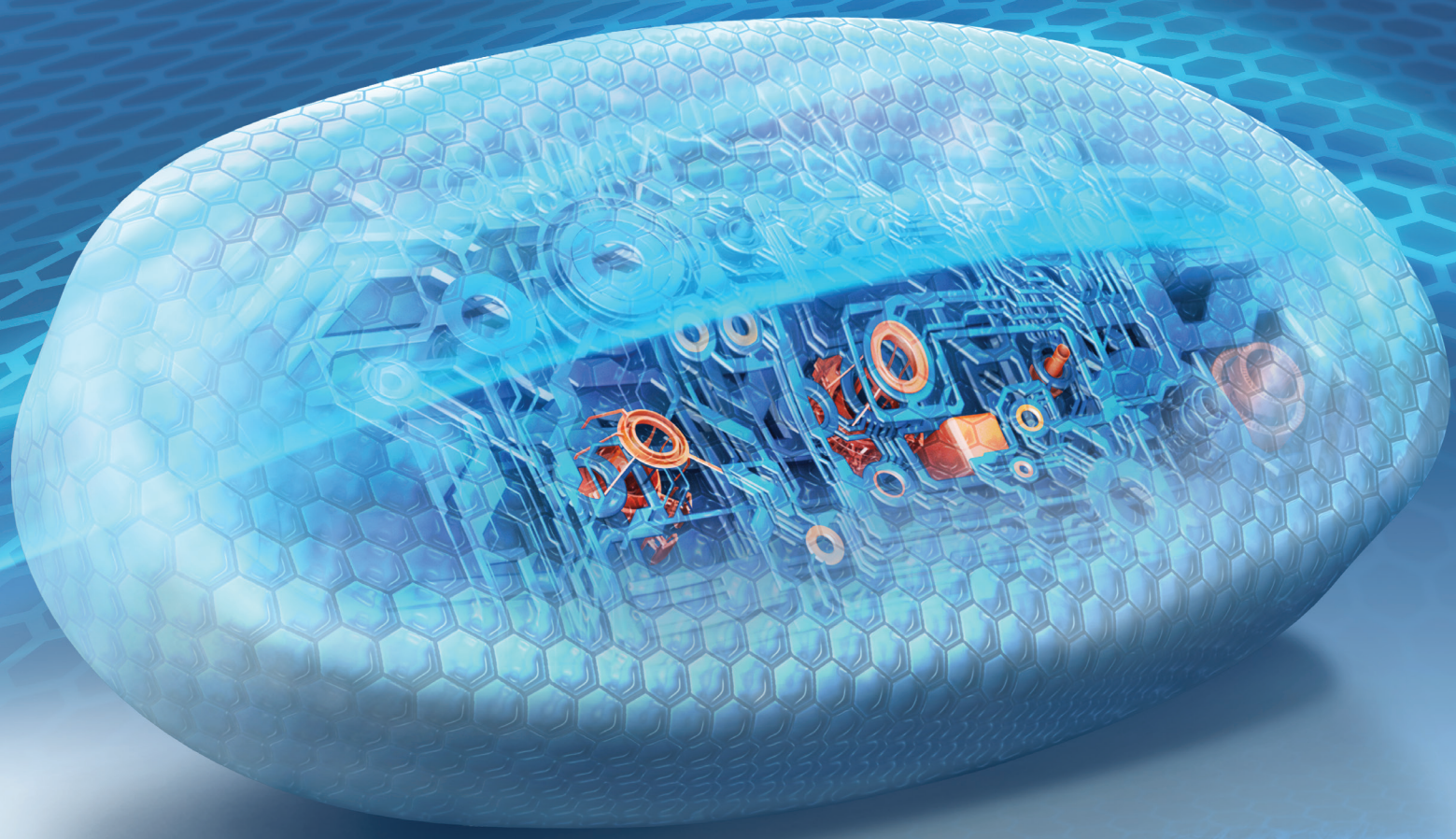
Needle pokes constitute another problem. Because patients receiving dialysis often have painful bruising and infections from needles that overreach (entering one side of the vascular access and exiting from the other), a system that prevents bleeding from such needle insertions would be welcome.



Duke University physicians who have studied the problem have created a new device, called Bullet Proof. Their new vascular graft is identical with those conventionally used but also contains two penetration-resistant chambers. One is for the needle that sends blood out of the body; the other is for the needle that sends the blood back in. Each chamber is built with a "window of material that seals itself after each needle poke," according to an article published by the Duke Translational Medicine Institute. Along the back of the tube is a rigid plate that makes it impossible for a needle to go straight through the graft. When a needle is pushed too far, it bends rather than penetrating the wall. The doctors are working to finalize their device design and to test the ability of the device to resist punctures and self-seal wounds. Currently the investigators are conducting a large-animal study and implanting grafts to learn how well they will work in vivo.

The Duke team has already fabricated simple prototypes of their new device and has launched a company called InnAVasc (http://innavasc.com) with a goal of marketing the graft.

**NEW!** ENVARSUS XR, the only once-daily tacrolimus for



## INDICATIONS AND USAGE

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants.

Limitation of Use: ENVARSUS XR extended-release tablets are not interchangeable or substitutable with other tacrolimus products.

## IMPORTANT SAFETY INFORMATION

**WARNING: MALIGNANCIES AND SERIOUS INFECTIONS**
**Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death**

## CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

## WARNINGS AND PRECAUTIONS

**Lymphoma and Other Malignancies:** Immunosuppressants, including ENVARSUS XR, increase the risk of developing lymphomas and other malignancies, particularly of the skin. Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients.

**Serious Infections:** Immunosuppressants, including ENVARSUS XR, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes.

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All other trademarks are property of their respective owners.

**Graft Rejection and Other Serious Adverse Reactions due to Medication Errors:** Medication errors, including substitution and dispensing errors, between tacrolimus immediate-release products and tacrolimus extended-release products were reported outside the U.S. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under- or over-exposure to tacrolimus. ENVARSUS XR is not interchangeable or substitutable with tacrolimus immediate-release products or other tacrolimus extended-release products.

**New Onset Diabetes After Transplant:** ENVARSUS XR caused new onset diabetes after transplant (NODAT) in kidney transplant patients, which may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk.

**Nephrotoxicity:** ENVARSUS XR, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity. Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range. The risk for nephrotoxicity may increase when ENVARSUS XR is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity.

**Neurotoxicity:** ENVARSUS XR may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions.

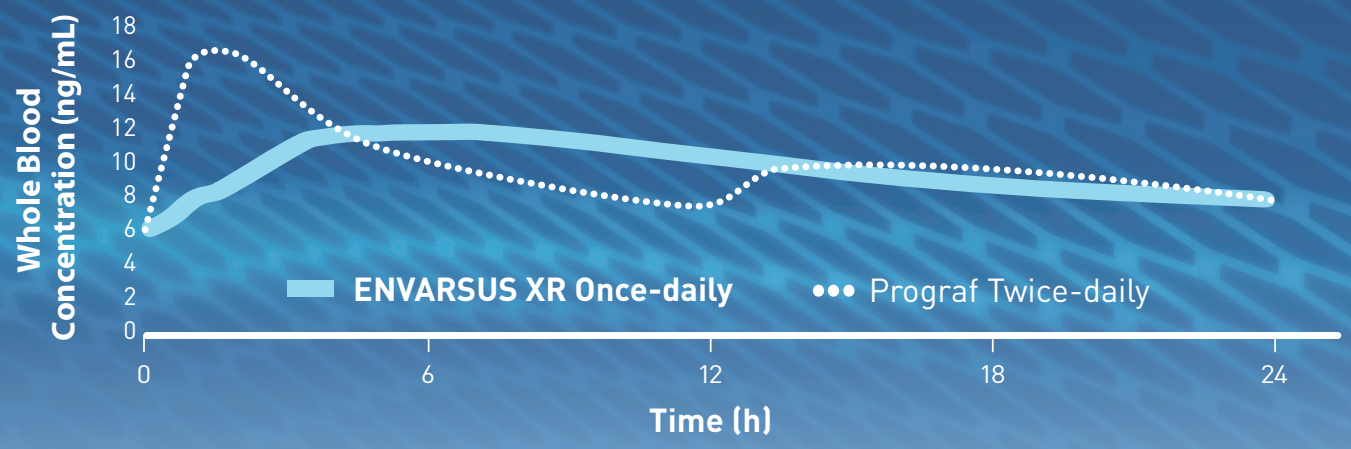
**Hyperkalemia:** Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ENVARSUS XR. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

**Hypertension:** Hypertension is a common adverse reaction of ENVARSUS XR therapy and may require antihypertensive therapy.

kidney transplant patients converted from twice-daily Prograf®

## Designed for the narrow therapeutic window of tacrolimus

# Delivery Re-engineered




**The innovative delivery technology of ENVARSUS XR increases tacrolimus bioavailability and enables a smoother pharmacokinetic curve, with comparable efficacy at a 20% lower dose than Prograf.[1-3]**

**Study Design:** Phase 2, open-label, multicenter, prospective study of adult stable kidney transplant patients (N=47) who were converted from Prograf capsules twice-daily to ENVARSUS XR tablets once-daily at least 6 months post-transplant. Primary objective of the study was to demonstrate the steady-state tacrolimus exposure and trough levels on Days 7, 14, and 21.[1,3]

**Clinical benefit of the differences in ENVARSUS XR pharmacokinetics has not been established.**

COMING SOON Once-daily **Envarsus XR™**

(tacrolimus extended-release tablets)

**Risk of Rejection with Strong CYP3A Inducers and Risk of Serious Adverse Reactions with Strong CYP3A Inhibitors:** The concomitant use of strong CYP3A inducers may increase the metabolism of tacrolimus, leading to lower whole blood trough concentrations and greater risk of rejection. In contrast, the concomitant use of strong CYP3A inhibitors may decrease the metabolism of tacrolimus, leading to higher whole blood trough concentrations and greater risk of serious adverse reactions. Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR with strong CYP3A inhibitors or strong CYP3A inducers.

**QT Prolongation:** ENVARSUS XR may prolong the QT/QTc interval and cause Torsade de Pointes. Avoid ENVARSUS XR in patients with congenital long QT syndrome. Consider obtaining electrocardiograms and monitoring electrolytes periodically during treatment in patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other products that lead to QT prolongation, and those with electrolyte disturbances. When coadministering ENVARSUS XR with other substrates and/or inhibitors of CYP3A, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended.

**Immunizations:** Whenever possible, administer the complete complement of vaccines before transplantation and treatment with ENVARSUS XR. Avoid the use of live attenuated vaccines during treatment with ENVARSUS XR. Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with ENVARSUS XR.

**Pure Red Cell Aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. If PRCA is diagnosed, consider discontinuation of ENVARSUS XR.

## ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10%) reported with ENVARSUS XR include: diarrhea and blood creatinine increased.

## USE IN SPECIFIC POPULATIONS

**Pregnancy:** Based on animal data may cause fetal harm. Use only if the potential benefit justifies the risk.

**Nursing Mothers:** Tacrolimus is present in human milk. Discontinue drug or nursing, taking into account the importance of drug to the mother.

**Pediatric Use:** The safety and efficacy of ENVARSUS XR in pediatric patients have not been established.

**Geriatric Use:** Clinical studies of ENVARSUS XR did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

**Renal Impairment:** Frequent monitoring of renal function is recommended. Lower doses may be required.

**Hepatic Impairment:** Frequent monitoring of tacrolimus trough concentrations is recommended. With greater tacrolimus whole blood trough concentrations in patients with severe hepatic impairment, there is a greater risk of adverse reactions and dosage reduction is recommended.

**Race:** African-American patients may require higher doses to attain comparable trough concentrations compared to Caucasian patients.

**Please see Brief Summary, including Boxed Warning, on adjacent pages.**

**To report SUSPECTED ADVERSE REACTIONS, contact Veloxis Pharmaceuticals, Inc. at 1-844-VELOXIS (835-6947) or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.**

**References: 1.** ENVARSUS XR [prescribing information]. Edison, New Jersey: Veloxis Pharmaceuticals; 2015. **2.** Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. *Am J Transplant.* 2013;13(3):760-769. **3.** Gaber AO, Alloway RR, Bodziak K, et al. Conversion from twice-daily tacrolimus capsules to once-daily extended-release tacrolimus (LCPT): a phase 2 trial of stable renal transplant recipients. *Transplantation.* 2013;96:191-197.

**ENVARSUS XR**™ (tacrolimus extended-release tablets) for oral use.
**Brief Summary: For full Prescribing Information see package insert.**

**WARNING: MALIGNANCIES AND SERIOUS INFECTIONS**
**Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death**
***[see Warnings and Precautions (5.1, 5.2)]***

## 1 INDICATIONS AND USAGE

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants

Limitation of Use

ENVARSUS XR extended-release tablets are not interchangeable or substitutable with other tacrolimus extended- release or immediate-release products *[see Warnings and Precautions (5.3)]*.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Administration Instructions

- Take ENVARSUS XR on an empty stomach at the same time of the day, preferably in the morning (to ensure consistent and maximum possible drug exposure) *[see Clinical Pharmacology (12.3)]*.
- Swallow ENVARSUS XR whole with fluid (preferably water); do not chew, divide, or crush the tablets.
- If a dose is missed, take it as soon as possible within 15 hours after missing the dose; beyond the 15-hour time frame, wait until the usual scheduled time to take the next regular daily dose. Do not double the next dose.
- Avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ENVARSUS XR *[see Drug Interactions (7.2)]*.
- African-American patients, compared to Caucasian patients, may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations *[see Use in Specific Populations (8.8) and Clinical Pharmacology (12.2)]*.

### 2.2 Conversion from Tacrolimus Immediate-Release Formulations

To convert from a tacrolimus immediate-release product to ENVARSUS XR, administer an ENVARSUS XR once daily dose that is 80% of the total daily dose of the tacrolimus immediate-release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve target whole blood trough concentration ranges of 4 to 11 ng/mL.

### 2.3 Therapeutic Drug Monitoring

Measure tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after any change in dosage, after a change in co-administration of CYP3A inducers and/or inhibitors, or after a change in renal or hepatic function. When interpreting measured concentrations, consider that the time to achieve tacrolimus steady state is approximately 7 days after initiating or changing the ENVARSUS XR dose.

Monitor tacrolimus whole blood trough concentrations using a validated assay [e.g., immunoassays or high-performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS)]. The immunosuppressive activity of tacrolimus is mainly due to the parent drug rather than to its metabolites. Immunoassays may react with metabolites as well as the parent drug. Therefore, whole blood tacrolimus trough concentrations obtained with immunoassays may be numerically higher than concentrations obtained with an assay using HPLC/MS/MS. Comparison of the whole blood tacrolimus trough concentrations of patients to those described in the prescribing information and other published literature must be made with knowledge of the assay method(s) employed.

## 3 DOSAGE FORMS AND STRENGTHS

Oval, white to off-white uncoated extended-release tablets debossed with "TCS" on one side:

- 0.75 mg extended-release tablet: debossed with "0.75" on the other side.
- 1 mg extended-release tablet: debossed with "1" on the other side.
- 4 mg extended-release tablet: debossed with "4" on the other side.

## 4 CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Lymphoma and Other Malignancies

Immunosuppressants, including ENVARSUS XR, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Examine patients for skin changes and advise to avoid or limit exposure to sunlight and UV light.

Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients. The risk of PTLD appears greatest in those individuals who are EBV seronegative. Monitor EBV serology during treatment.

### 5.2 Serious Infections

Immunosuppressants, including ENVARSUS XR, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:

- Polyomavirus-associated nephropathy (especially due to BK virus infection),
- JC virus-associated progressive multifocal leukoencephalopathy (PML), and
- Cytomegalovirus (CMV) infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor are at highest risk of CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection *[see Adverse Reactions (6.1)]*.

### 5.3 Graft Rejection and Other Serious Adverse Reactions due to Medication Errors

Medication errors, including substitution and dispensing errors, between tacrolimus immediate-release products and tacrolimus extended-release products were reported outside the U.S. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under- or over-exposure to tacrolimus. ENVARSUS XR is not interchangeable or substitutable with tacrolimus immediate-release products or other tacrolimus extended-release products. Instruct patients and caregivers to recognize the appearance of ENVARSUS XR tablet *[see Dosage Forms and Strengths (3)]*.

### 5.4 New Onset Diabetes After Transplant

ENVARSUS XR caused new onset diabetes after transplant (NODAT) in kidney transplant patients, which may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk. Monitor blood glucose concentrations and treat appropriately *[see Adverse Reactions (6.1) and Use in Specific Populations (8.8)]*.

### 5.5 Nephrotoxicity due to ENVARSUS XR and Drug Interactions

ENVARSUS XR, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity. Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range. The risk for nephrotoxicity may increase when ENVARSUS XR is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors) *[see Drug Interactions (7.2)]*. Monitor renal function and consider dosage reduction if nephrotoxicity occurs.

### 5.6 Neurotoxicity

ENVARSUS XR may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions *[see Adverse Reactions (6.1, 6.2)]*. As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of ENVARSUS XR if neurotoxicity occurs.

### 5.7 Hyperkalemia

Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ENVARSUS XR.Concomitant use of agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) may increase the risk for hyperkalemia *[see Adverse Reactions (6.1)]*. Monitor serum potassium levels periodically during treatment.

### 5.8 Hypertension

Hypertension is a common adverse reaction of ENVARSUS XR therapy and may require antihypertensive therapy *[see Adverse Reactions (6.1)]*. Some antihypertensive drugs can increase the risk for hyperkalemia *[see Warnings and Precautions (5.7)]*. Calcium-channel blocking agents may increase tacrolimus blood concentrations and require dosage reduction of ENVARSUS XR *[see Drug Interactions (7.2)]*.

### 5.9 Risk of Rejection with Strong CYP3A Inducers and Risk of Serious Adverse Reactions with Strong CYP3A Inhibitors

The concomitant use of strong CYP3A inducers may increase the metabolism of tacrolimus, leading to lower whole blood trough concentrations and greater risk of rejection. In contrast, the concomitant use of strong CYP3A inhibitors may decrease the metabolism of tacrolimus, leading to higher whole blood trough concentrations and greater risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.10)]* Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR with strong CYP3A inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., rifampin, rifabutin) *[see Dosage and Administration (2.3) and Drug Interactions (7.2)]*.

### 5.10 QT Prolongation

ENVARSUS XR may prolong the QT/QTc interval and cause Torsade de Pointes. Avoid ENVARSUS XR in patients with congenital long QT syndrome. Consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment in patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other products that lead to QT prolongation, and those with electrolyte disturbances (e.g., hypokalemia, hypocalcemia, or hypomagnesemia).

When coadministering ENVARSUS XR with other substrates and/or inhibitors of CYP3A, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended *[see Drug Interactions (7.2)]*.

### 5.11 Immunizations

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with ENVARSUS XR.

Avoid the use of live attenuated vaccines during treatment with ENVARSUS XR (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with ENVARSUS XR.

### 5.12 Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All of these patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. A mechanism for tacrolimus-induced PRCA has not been elucidated. If PRCA is diagnosed, consider discontinuation of ENVARSUS XR.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. In addition, the clinical studies were not designed to establish comparative differences across study arms with regards to the adverse reactions discussed below.

In an open label, randomized, multinational conversion study, stable kidney transplant patients on a tacrolimus immediate-release product and concomitant immunosuppressants were randomized to treatment with ENVARSUS XR (N=162) or to continued treatment on the tacrolimus immediate-release product (N=162) and treated for a duration of 12 months *[see Clinical Studies (14)]*.

The proportion of patients who discontinued treatment due to adverse reactions was 7.4% and 1.2% in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group was cardiac arrest (2 events).

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in stable kidney transplant recipients treated with ENVARSUS XR or tacrolimus immediate-release product are shown in **Table 1.**

**Table 1. Percentage of Stable Patients with Infections Through One Year Post- Treatment in the Conversion Study[a]**

| | ENVARSUS XR ± steroids, MMF/MPS or AZA N=162 | Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA N=162 |
|---|---|---|
| All infections | 46% | 48% |
| Respiratory Infections | 26% | 28% |
| Urinary Tract Infections | 10% | 14% |
| Bacterial Infections | 7% | 5% |
| Fungal Infections | 4% | 4% |
| Gastrointestinal Infections | 4% | 5% |
| BK virus[b] | 2% | 2% |
| Cytomegalovirus Infections | 2% | 1% |
| Serious Infections | 8% | 9% |

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

[b] BK virus associated nephropathy (BKVAN) occurred in 1.2% (2/162) and 0.6% (1/162) in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

New Onset Diabetes After Transplantation (NODAT)

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post baseline, insulin requirement for ≥31 days, an oral hypoglycemic agent use ≥31 days, or $HbA_{1c}$ ≥6.5% (at least 3 months after randomization) among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for the stable kidney transplant study through one year post-transplant is summarized in **Table 2** below *[see Warnings and Precautions (5.4)]*.

**Table 2. Percentage of Stable Patients with NODAT Through 1 Year Post-Treatment in the Conversion Study [a]**

| | ENVARSUS XR ± steroids, MMF/MPS or AZA (N=90) | Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA (N=95) |
|---|---|---|
| Composite NODAT[b] | 10% | 11% |
| $HbA_{1c}$ ≥6.5% | 3% | 7% |
| Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences | 8% | 6% |
| Oral hypoglycemic use | 1% | 1% |
| Insulin Use ≥31 days | 1% | 0% |

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

[b] Analyses restricted to patients at risk for NODAT.

Common Adverse Reactions

The incidence of adverse reactions that occurred in ≥5% of ENVARSUS XR-treated patients compared to tacrolimus immediate-release product through one year of treatment in the conversion study is shown by treatment group in **Table 3**.

**Table 3. Adverse Reactions ( ≥5%) in Stable Kidney Transplant Patients Through 1 Year Post-Treatment in the Conversion Study 1[a]**

| Adverse Reaction | ENVARSUS XR N=162 | Tacrolimus immediate-release product N=162 |
|---|---|---|
| Diarrhea | 14% | 9% |
| Blood Creatinine Increased | 12% | 9% |
| Urinary Tract Infection | 9% | 14% |
| Nasopharyngitis | 9% | 11% |
| Headache | 9% | 7% |
| Upper Respiratory Tract Infection | 7% | 9% |
| Peripheral Edema | 7% | 6% |
| Hypertension | 4% | 6% |

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release for the adverse reactions reported in this table.

### 6.2 Postmarketing Experience

The following adverse reactions have been reported from marketing experience with tacrolimus in the U.S. and outside the U.S. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Blood and Lymphatic System Disorders:* Agranulocytosis, decreased blood fibrinogen, disseminated intravascular coagulation, hemolytic anemia, hemolytic uremic syndrome, pancytopenia, prolonged activated partial thromboplastin time, pure red cell aplasia *[see Warnings and Precaution (5.12)]*, thrombocytopenic purpura, thrombotic thrombocytopenic purpura

*Cardiac Disorders:* Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial hypertrophy, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, supraventricular extrasystoles, supraventricular tachycardia, Torsade de Pointes, deep limb venous thrombosis, ventricular fibrillation

*Ear Disorders:* Hearing loss including deafness

*Eye Disorders:* Blindness, photophobia, optic atrophy

*Gastrointestinal Disorders:* Colitis, dysphagia, gastrointestinal perforation, impaired gastric emptying, intestinal obstruction, mouth ulceration, peritonitis, stomach ulcer

*Hepatobiliary Disorders:* Bile duct stenosis, cholangitis, cirrhosis, fatty liver, hepatic cytolysis, hepatic failure, hepatic necrosis, hepatic steatosis, jaundice, hemorrhagic pancreatitis, necrotizing pancreatitis, venoocclusive liver disease

*Hypersensitivity Reactions:* Hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

*Immune System Disorders:* Graft versus host disease (acute and chronic)

*Metabolism and Nutrition Disorders:* Glycosuria, increased amylase, pancreatitis

*Musculoskeletal and Connective Tissue Disorders:* Myalgia, polyarthritis, rhabdomyolysis

*Neoplasms:* Lymphoma including EBV-associated lymphoproliferative disorder, PTLD [*see Warnings and Precautions (5.1)*]; leukemia

*Nervous System Disorders:* Carpal tunnel syndrome, cerebral infarction, coma, dysarthria, flaccid paralysis, hemiparesis, mental disorder, mutism, nerve compression, posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions (5.6)]*, progressive multifocal leukoencephalopathy (PML) sometimes fatal *[see Warnings and Precautions (5.2)]*, quadriplegia, speech disorder, status epilepticus, syncope

*Renal and Urinary Disorder:* Acute renal failure, hemorrhagic cystitis, hemolytic uremic syndrome, micturition disorder

*Respiratory, Thoracic and Mediastinal Disorders:* Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, pulmonary hypertension, respiratory distress, respiratory failure

*Skin and Subcutaneous Tissue Disorders:* Hyperpigmentation, photosensitivity

## 7 DRUG INTERACTIONS

### 7.1 Mycophenolic Acid

When ENVARSUS XR is prescribed with a given dose of mycophenolic acid (MPA) product, exposure to MPA is higher with ENVARSUS XR coadministration than with cyclosporine coadministration because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA associated adverse reactions and reduce the dose of concomitantly administered mycophenolic acid products as needed.

### 7.2 Effects of Other Drugs/Substances on ENVARSUS XR

**Table 4. Effects of Other Drugs/Substances on ENVARSUS XR[a]**

| Drug/Substance Class or Name | Drug Interaction Effect | Recommendations |
|---|---|---|
| Grapefruit or grapefruit juice[b] | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.10)]* | Avoid grapefruit or grapefruit juice |
| Alcohol | May modify the rate of tacrolimus release | Avoid alcoholic beverages |
| Strong CYP3A Inducers[c] such as: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's Wort | May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see Warnings and Precautions (5.9)]* | Increase ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.2)]* |
| Strong CYP3A Inhibitors[c], such as: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.9, 5.10)]* | Reduce ENVARSUS XR dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.2)]* |
| Mild or Moderate CYP3A Inhibitors, such as: antibiotics (e.g., erythromycin), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole, azole antifungals (e.g., clotrimazole, fluconazole) | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [*see Warnings and Precautions (5.6, 5.10)]* | Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.3), Clinical Pharmacology (12.2)]* |
| Other drugs, such as: Magnesium and aluminum hydroxide antacids<br>Metoclopramide | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.10)]* | Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.3), Clinical Pharmacology (12.2)]* |
| Mild or Moderate CYP3A Inducers, such as:<br>Methylprednisolone, prednisone | May decrease tacrolimus concentrations | Monitor tacrolimus whole blood trough concentrations and adjust ENVARSUS XR dose if needed *[see Dosage and Administration (2.3)]* |

[a] ENVARSUS XR dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures *[see Clinical Pharmacology (12.2)]*, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status

[b] High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor

[c] Strong CYP3A inhibitor/inducer, based on reported effect on exposures to tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate)

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Pregnancy Category C*

There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy in humans has been associated with neonatal hyperkalemia and renal dysfunction.

Tacrolimus given orally to pregnant rabbits at 0.7 times the maximum clinical dose and pregnant rats at 1.1 times the maximum clinical dose was associated with an increased incidence of fetal death *in utero*, fetal malformations (cardiovascular, skeletal, omphalocele, and gallbladder agenesis) and maternal toxicity. ENVARSUS XR should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant rabbits, tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.7 and 2.3 times the maximum clinical dose based on body surface area, respectively) was associated with maternal toxicity as well as an increased incidence of abortions. At the 1 mg/kg dose, fetal rabbits showed an increased incidence of malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosis, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg (3.7 times the maximum clinical dose) was associated with maternal toxicity, an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally to pregnant rats after organogenesis and during lactation at 1.0 and 3.2 mg/kg (1.2 and 3.7 times the maximum recommended clinical dose, respectively) was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.

### 8.3 Nursing Mothers

Tacrolimus is present in breast milk. Because of the potential for serious adverse drug reactions in nursing infants from ENVARSUS XR, a decision should be made whether to discontinue nursing or to discontinue ENVARSUS XR, taking into account the importance of drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness of ENVARSUS XR in pediatric patients have not been established.

### 8.5 Geriatric Use

Clinical studies of ENVARSUS XR did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In the stable kidney transplant study, there were 17 patients 65 years of age and older, and no patients were over 75 years *[see Clinical Studies (14)]*. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### 8.6 Renal Impairment

The pharmacokinetics of tacrolimus in patients with renal impairment was similar to that in healthy subjects with normal renal function. However, due to its potential for nephrotoxicity, monitoring of renal function
in patients with renal impairment is recommended; tacrolimus dosage should be reduced if indicated
*[see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)]*.

### 8.7 Hepatic Impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy subjects with normal hepatic function [*see Clinical Pharmacology (12.2)*]. With greater tacrolimus whole blood trough concentrations in patients with severe hepatic impairment, there is a greater risk of adverse reactions and dosage reduction is recommended [*see Dosage and Administration (2.2)*]. For patients with moderate hepatic impairment, monitor tacrolimus whole blood trough concentrations. For patients with mild hepatic impairment, no dosage adjustments are needed.

### 8.8 Race

African-American patients may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations compared to Caucasian patients *[see Dosage and Administration (2.1), Clinical Pharmacology (12.2)]]*

## 10 OVERDOSAGE

Postmarketing cases of overdose with tacrolimus have been reported. Overdosage adverse reactions included:

- nervous system disorders (tremor, headache, confusional state, balance disorders, encephalopathy, lethargy and somnolence)
- gastrointestinal disturbances (nausea, vomiting, and diarrhea)
- abnormal renal function (increased blood urea nitrogen and elevated serum creatinine)
- urticaria
- hypertension
- peripheral edema, and
- infections [one fatal postmarketing case of bilateral pneumopathy and CMV infection was attributed to tacrolimus (extended-release capsules) overdose].

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

# Electronic Alert Protocol Reduces In-Hospital AKI Mortality in Pilot Study

By Kurtis Pivert

A new streamlined approach for early detection and treatment of acute kidney injury (AKI) reduced mortality by 23 percent in a pilot study presented at ASN Kidney Week 2015 (1). AKI is frequently encountered in the hospital setting, complicating approximately 20 percent of cardiac surgeries worldwide. The STOP-AKI protocol—a combination of electronic alerts, a standardized intervention bundle, and staff and patient engagement—is a replicable model that could help to reduce the global burden of AKI.

AKI is common and costly, estimated to affect 21 percent of hospitalized adults and 33 percent of hospitalized children worldwide. Despite a high mortality rate—as high as 30 percent, deadlier than either heart attack or stroke—AKI deaths can often be prevented when detected early.

To reduce AKI's toll and raise awareness of the importance of its prevention and early detection, researchers from the University Hospital Aintree in Liverpool, UK, developed a model to quickly identify and treat AKI in the hospital setting. The goal of the project, led by Thangavelu Chandrasekar, MRCP, and Hsu Pheen Chong, MbChB, was to decrease AKI mortality rates (26 percent in the period before the study) in their institution by 30 percent. STOP-AKI is one of several Avoidable Mortality Reduction projects underway at University Hospital Aintree, the others focused on reducing the incidence of deaths caused by sepsis and pneumonia.

Chandrasekar used a Plan-Do-Study-Act methodology to develop a multidisciplinary streamlined approach for AKI prevention, detection, and treatment (Figure 1). The final STOP-AKI model incorporates assessment and screening for patients at risk for AKI; early detection using automated electronic alerts triggered by serum creatinine changes using a standardized algorithm; and effective intervention using an evidence-based AKI treatment bundle (a modified version of the ABCDE checklist for AKI management) (2). Staff engagement, including training to raise clinical suspicion of AKI in at-risk individuals, as well as patient educational materials were other key components of the program.

In STOP-AKI, alerts are distributed by phone to the ward staff and electronically on the dashboard of the Outreach Team, who are highly trained nursing staff with critical care background. The Outreach Team visits the ward to review the patient and implement the AKI treatment bundle, which is simple, retainable, and has clear instructions to the medical staff based on evidence-based AKI management guidance, said Chandrasekar (Figure 2). The Outreach Team facilitates discussions with the renal or critical care team where appropriate, and supports education of patients and staff.

After implementation of STOP-AKI, AKI-associated mortality fell by 27 percent (to 19 percent) and length of hospital stay decreased by 13 percent, equivalent to a 2.7-day reduction. "Improving staff and patient awareness through education, effective monitoring, and handover to primary care on discharge has ensured continuity of care that will hopefully reduce readmissions with AKI," said Chandrasekar. He added this required multiple changes to the system at different levels to achieve the reductions in mortality and length of stay.

Chandrasekar noted that the simple, straightforward STOP-AKI protocol model is reproducible in other environments that utilize electronic health records. "The key components are identifying patients at risk and real-time automated e-alerts which then trigger implementation of an effective treatment regimen," he added.

Because AKI affects patients across all specialties, an emphasis on teamwork is important in successfully identifying and treating AKI in the hospital setting. "This needs a whole system approach with multiple interventions at different levels that dovetail with each other," Chandrasekar emphasized. "Health care workers across all levels play an important role in improving care provision and hence positive outcomes."

Because of STOP-AKI's success, the system is being rolled out throughout the hospital and in primary care, with Chandrasekar anticipating further reductions in mortality.

In addition to an institution-wide implementation of STOP-AKI, the next phase of their research is development of assessment tools. "We are in the process of developing metrics to assess AKI progression and its predictors, and have rolled out our AKI alerts and management guidelines to the community, enabling much earlier intervention," Chandrasekar added.

**References**


1. Chong HP, Chandrasekar T. STOP-Acute Kidney Injury (AKI): A Streamlined Approach to the Management of AKI Leads to Reduction of Mortality Rates [Abstract]. *J Am Soc Nephrol* 2015; 26:471A.
2. Forde C, et al. Acute Kidney Injury: It's as easy as ABCDE. *BMJ Quality Improvement Reports* 2013; doi: 10.1136/bmjquality.u200370.w326.


**Figure 1**
**Flowchart of the STOP-AKI protocol development**

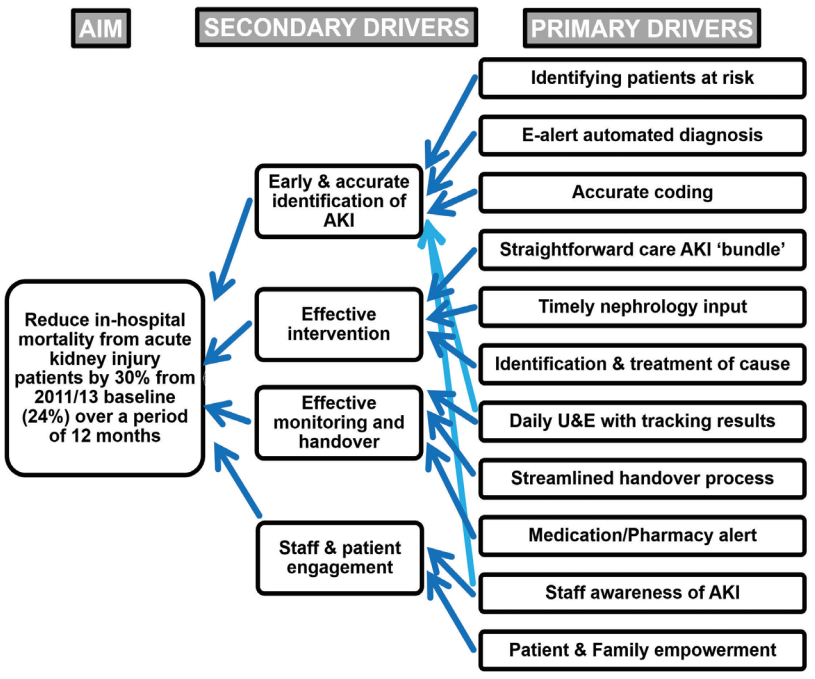
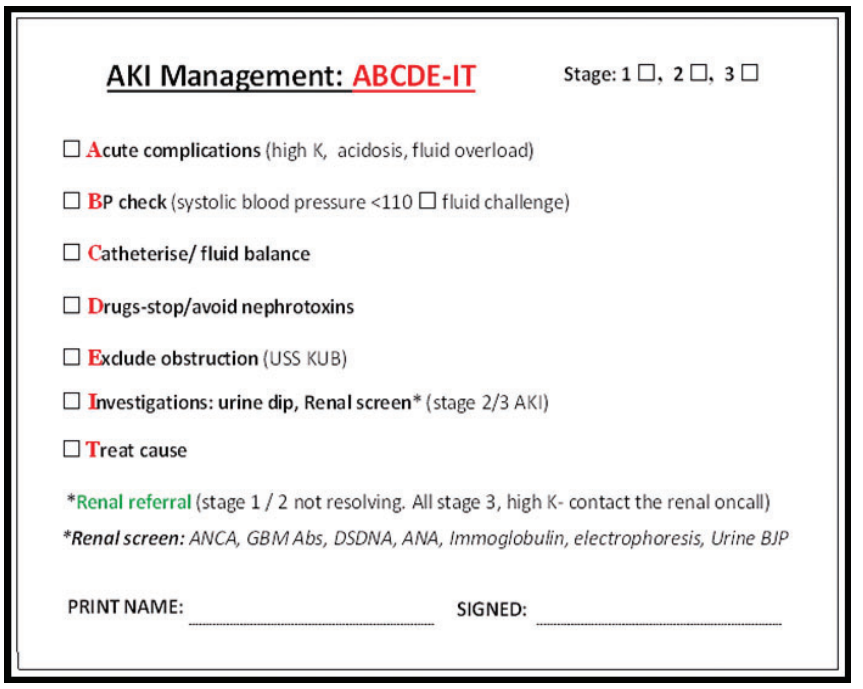



**Figure 2**
**The ABCDE-IT AKI treatment protocol**



# Policy Update

## Kidney Community Advocacy Day 2015: 16 Organizations Unite to Demand Action from Congress

By Mark Lukaszewski

On Thursday, September 10, 2015, the American Society of Nephrology (ASN) convened Kidney Community Advocacy Day 2015. An unprecedented group of more than 100 representatives of 16 kidney patient and health professional organizations banded together to demand Congress support legislation that would increase kidney research funding and remove barriers for people considering living kidney donation (Table 1). Altogether, advocates met with over 120 congressional offices.

Now in ASN's third year of hosting the event, members of the kidney community united on Capitol Hill to underscore the need for this vital legislation by emphasizing the scope of the public health burden to Congress, including that more than 20 million Americans have kidney diseases, nearly 650,000 of these with end stage renal disease (ESRD).

### Increasing kidney research funding

Organizations called on Congress to strengthen kidney research funding, critical for the development of new treatments and cures for the millions of Americans suffering with kidney diseases. More investments in kidney research and innovation are needed to reduce the significant burden of kidney diseases on both patients and Medicare. Currently, NIH invests less in kidney research than other major diseases both in terms of absolute numbers and per patient.

Yet, as of 2013, federal investments in kidney research were less than 1 percent of Medicare costs for patients with kidney disease. Advocates emphasized they didn't want Congress to take money away from other medical research. Instead they conveyed the fact that since 1972 the federal government has paid nearly all the costs of care for ESRD patients on dialysis ($80 billion annually), yet a commensurate investment to slow or cure kidney diseases hasn't occurred. Last year, 1 percent of Medicare patients accounted for nearly 8 percent of Medicare expenditures. Yet the government hasn't committed the necessary capital for research funding to develop the most cost-efficient therapies to reduce the burden of kidney diseases on patients and Medicare.

"The kidney community has come together to ensure patient voices are heard in Congress," said ASN Past President Jonathan Himmelfarb, MD, FASN. "We're committed to providing better care and treatments for patients with kidney disease. Congress can do that by bolstering kidney research investments and enacting legislation that promotes organ donations."

### Removing barriers to living donation

Kidney Community Advocacy Day representatives also emphasized the importance of transplantation in context of the forthcoming Living Donor Act (LDA) (Table 2). Each congressional office learned that every 14 minutes a patient is added to the kidney waitlist and 12 Americans die each day waiting for a transplant. Advocates noted that transplantation is cost-effective for Medicare, with annual costs of $32,922 per transplant patient vs. $87,845 per hemodialysis patient.

"Kidney transplants are the best treatment option for most patients with kidney failure, yet there aren't enough donated kidneys for everyone who needs them," said ASN Secretary-Treasurer and Public Policy Board Chair John R. Sedor, MD, FASN. "More than 100,000 people are on the waiting list for a kidney transplant," Dr. Sedor added. "Congress can help them by enacting commonsense legislation that promotes organ donations by ensuring insurance coverage and job security for donors."

The LDA would help to increase the number of kidney transplants by eliminating barriers to donation. The legislation would prohibit insurers from denying or limiting coverage or from charging higher premiums to living organ donors; ensure living organ donors can use "time off" protected by the Family and Medical Leave Act (FLMA) to recover from donation surgery and maintain job security; and require that the Department of Health and Human Services (HHS) update its education programs to include and explain the new changes for donors.

This unified advocacy day built tremendous momentum on Capitol Hill and showed members of Congress that while organizations may have different goals they are able to unify to promote change. ASN will continue to work with other members of the community in order to advance shared goals, and will keep *ASN Kidney News* readers updated. To learn more about ASN policy, please visit https://www.asn-online.org/policy/.

**Table 1**
**Kidney Community Advocacy Day 2015 participating organizations**

- Alport Syndrome Foundation
- American Association of Kidney Patients
- American Kidney Fund
- American Nephrology Nurses Association
- American Society of Nephrology
- American Society of Pediatric Nephrology
- American Society of Transplant Surgeons
- American Society of Transplantation
- Home Dialyzors United
- IgA Nephropathy Foundation of America
- National Kidney Foundation
- National Renal Administrators Association
- NephCure Kidney International
- Oxalosis and Hyperoxaluria Foundation
- Polycystic Kidney Disease Foundation
- Society for Transplant Social Workers

**Table 2**
**Key benefits of the Living Donor Act**

Ensure living organ donors have access to life, disability, and long-term care insurance:

- Banning this discriminatory behavior would eliminate an unnecessary hurdle for living donors. Currently, 11 percent of living organ donors experience difficulty securing or paying for insurance after their procedures.

Allow living organ donors Family and Medical Leave Act "time off" to recover:

- Without this guarantee, many people who want to be living donors simply cannot afford the risk of unemployment. Kidney donor hospitalization averages 3 to 7 days and donors typically do not return to work sooner than 4 weeks postdonation.

Educate and encourage more Americans to consider living donation via a HHS campaign:

- Making more people aware of the benefits of living kidney donation to those in kidney failure and the new ways this law protects donor rights would help boost transplant rates overall.
- Raising awareness is imperative: the number of kidney transplants performed in the US is equal to less than 1 percent of the number of patients on dialysis annually.

# SGR Replacement: Opt for Merit-Based Incentive Pay or Join Alternative Payment Model

In spring 2015, a multiyear advocacy effort to motivate Congress to repeal and replace the dated, flawed physician payment system—known as the Sustainable Growth Rate—succeeded with passage of a new law: the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Having worked in close collaboration with other medical societies and with Congress to advance this ASN advocacy priority, the society is now focusing efforts on working in partnership with the Centers for Medicare & Medicaid Services (CMS) as the agency implements the law.

In contrast to the old payment system, which called for substantial cuts to physician reimbursement on an annual basis, MACRA establishes predictable, positive payment updates through 2019. More important, the law was designed to transition physician reimbursement away from a fee-for-service model—paying for quantity of care—to a value-based model that pays for quality of care. Physicians will have choices regarding how they participate in the new reimbursement system, opting either to participate in the "Merit-Based Incentive Payment System," (MIPS) or to participate in an "Alternative Payment Model," (APM).

## Merit-based incentive payment system

Taking effect in 2019, MIPS will consolidate three existing Medicare programs: the Physician Quality Reporting System, the Value-Based Modifier, and the EHR Meaningful Use program. The single MIPS program will evaluate similar aspects of care as do the three programs that will sunset, assessing physicians in four categories:

- Clinical practice improvement activities
- EHR adoption and use
- Quality
- Resource use

CMS will combine physicians' performance in each category to calculate a total performance score that can adjust reimbursement levels up or down. The maximum effect the total performance score can have on reimbursement is set at +/- 4% for the 2019 payment year and increases to +/- 9% for the 2022 payment year and in subsequent payment years.

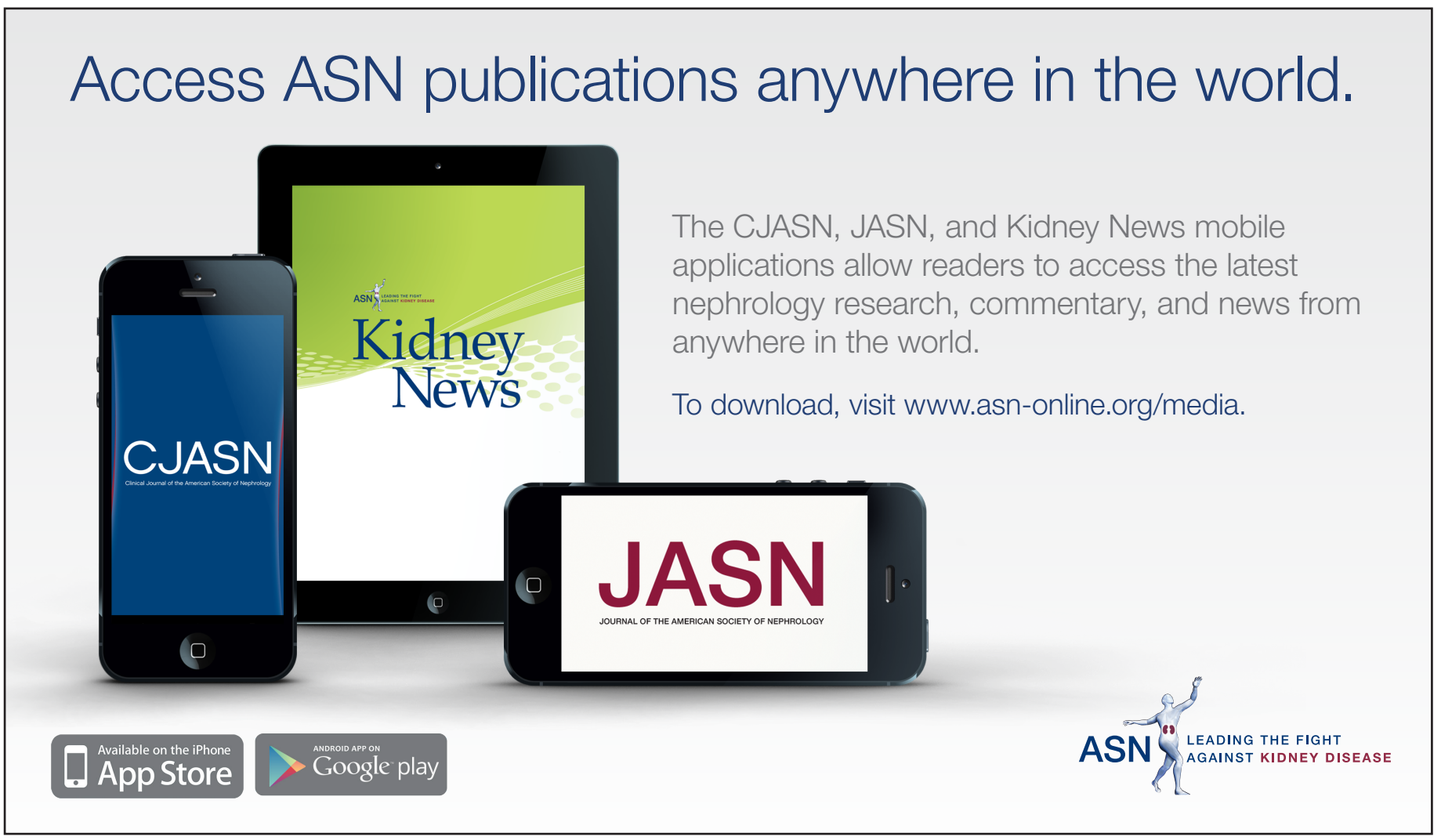
Based on prior experience with CMS programs such as Meaningful Use and the Quality Incentive Program, there is typically a two-year lag from "performance year" to payment year, which means that the payment adjustments physicians see when the program takes effect in 2019 will actually be based on their performance in 2017. ASN urges CMS to ensure that physicians have as much notice as possible regarding the standards and expectations of the MIPS program prior to 2017 so they can prepare accordingly.

## Alternative payment models (APMs)

MACRA also calls on CMS to facilitate the creation of Alternative Payment Models (APMs). Physicians who participate in APMs are not only exempted from participation in the MIPS program, but can also earn a 5% annual bonus update designed to help them establish the infrastructure for their new care delivery models. Participants must receive at least 25 percent of their Medicare revenue through an APM in 2019–2020 to quality for the bonus. This threshold will increase to 50 percent in 2021–2022, and to 75 percent in 2023 and beyond.

Although the details of what constitutes or qualifies as an APM is still being defined by CMS, in partnership with stakeholders including ASN, there will likely be many different types of APMs. In general, APMs will aim to deliver more coordinated, comprehensive care that focuses on population health and value. The three basic principles that every APM must have are 1) receiving payment based on performance on quality measures (which must be comparable to the quality measures in the MIPS program), 2) bearing financial risk "in excess of a nominal amount" (CMS is still determining the definition of "nominal amount") and 3) making use of certified EHR technology. It is clear that existing Accountable Care Organization programs, the Medicare Shared Savings Program, and the Health Care Quality Demonstration Program, will all count as APMs. "Demonstrations required by federal law," can also count as APMs, and it's possible that CMS will open the door to allow many other care delivery models to count as APMs in the future.

MACRA also calls for the creation of "physician focused payment models," including models for specialists, and in the future these models may also quality as APMs. ASN is actively considering potential models for nephrologists and will continue to work with CMS to ensure the new payment and care delivery system models account for the unique needs of patients with kidney disease and the health professionals who serve them.

# Findings

## Better Outcomes with HHD versus Peritoneal Dialysis

In comparison with peritoneal dialysis, patients using daily home hemodialysis (HHD) have lower mortality, fewer hospitalizations, and a lower rate of technique failure, reports a study in the *American Journal of Kidney Diseases*.

Using the US Renal Data System database, the researchers identified matched groups of 4201 patients starting HHD and PD from 2007 through 2010. In both groups, the average mean time from the onset of ESRD to the start of home dialysis therapy was about 44 months.

Throughout follow-up, mortality was significantly lower for patients using daily HHD than for those using PD: hazard ratio (HR) 0.80. Daily HHD was also associated with lower rates of hospitalization: HR 0.92; and technique failure, HR 0.63.

On a subset analysis of 1368 patients starting home dialysis within 6 months of ESRD onset, there was no overall difference in mortality between HHD and PD. The overall hospitalization rate was similar as well: HHD patients were at lower risk of hospitalization for cardiovascular disease and dialysis access infection, whereas PD patients were less likely to be hospitalized for bloodstream infection. The HHD group remained at lower risk of technique failure: HR 0.70.

As more patients in the US begin to use daily HHD, there are few direct comparisons of important clinical outcomes compared with PD. This matched cohort study found lower overall rates of mortality, hospitalization, and technique failure with HHD versus PD. More research is needed to clarify the interaction between home dialysis modality and duration of ESRD [Weinhandl ED, et al. Mortality, hospitalization, and technique failure in daily home hemodialysis and matched peritoneal dialysis patients: a matched cohort study. *Am J Kidney Dis* 2015 Aug 26. DOI: http://dx.doi.org/10.1053/j.ajkd.2015.07.014].

## Good Outcomes with SLED in Critically Ill Patients with AKI

Sustained low-efficiency dialysis (SLED) is an "acceptable alternative" for the treatment of critically ill patients with acute kidney injury (AKI), concludes a study in *BMC Nephrology*.

The retrospective study included patients with AKI treated at four intensive care units at a Canadian academic medical center between 2007 and 2012. Seventy-four patients were treated with SLED, with a target of 8-hour dialysis sessions at a blood flow rate of 200 mL/min, generally without anticoagulation. The 30-day mortality and other outcomes were compared with those of 158 AKI patients beginning continuous renal replacement therapy (CRRT) at the same intensive care units. The analyses were adjusted for demographic factors, comorbid conditions, baseline kidney function, and Sequential Organ Failure Assessment (SOFA) score.

The two approaches yielded similar 30-day mortality rates: 54 percent with SLED and 61 percent with CRRT. There was also no significant difference in the specified secondary outcomes of dependence on renal replacement therapy at 30 days or early clinical deterioration, defined as an increased SOFA score or death within 48 hours after the start of therapy.

Sustained low-efficiency dialysis is increasingly used as an alternative to CRRT for patients with AKI in hemodynamically unstable condition. Within the study limitations, the new results show similar clinical outcomes for critically ill AKI patients treated with SLED versus CRRT. Pending the outcomes of a definitive noninferiority trial, the researchers conclude, "SLED appears to be an acceptable alternative to CRRT for hemodynamically unstable patients with AKI" [Kitchlu A, et al. Outcomes of sustained low efficiency dialysis versus continuous renal replacement therapy in critically ill adults with acute kidney injury: a cohort study. *BMC Nephrol* 2015; 16:127].

## Finerenone Reduces Albuminuria in Diabetic Nephropathy

Finerenone, a new nonsteroidal mineralocorticoid receptor antagonist, can improve albuminuria in patients with diabetic kidney disease, reports a trial in the *Journal of the American Medical Association*.

The randomized controlled trial included 823 patients with type 2 diabetes; persistent albuminuria, urinary albumin–creatinine ratio (ACR) 30 mg/g or higher; and current treatment with a renin-angiotensin system (RAS) blocker. The mean age was 64.2 years, and 78 percent of patients were men. The baseline ACR was 300 mg/g or higher in 36.7 percent of patients, and 40.0 percent had an estimated GFR of 60 mL/min/1.73 $m^2$ or less.

The patients were assigned to treatment with oral finerenone, in doses ranging from 1.25 to 25 mg/d, or placebo, while continuing their RAS blocker. The changes in urinary ACR at 90 days were compared between groups. Serum potassium level and kidney function were assessed as safety outcomes.

Finerenone reduced ACR in a dose-dependent fashion. The placebo-corrected mean ratio of ACR at 90 days (compared with baseline) was 0.79 with finerenone at a dose of 7.5 mg/g, 0.76 at 10 mg/d, 0.67 at 15 mg/d, and 0.62 at 20 mg/d. At the 10 mg/d dose, there was no difference in the rate of hyperkalemia leading to treatment discontinuation in comparison with placebo. The rates of this safety outcome were 2.1 percent with finerenone at a dose of 27.5 mg/d, 3.2 percent at 15 mg/d, and 1.7 percent at 20 mg/d. There were no differences in the rate of a 30 percent or greater drop in estimated GFR or in serious adverse events.

Adding a steroid mineralocorticoid receptor antagonist to a RAS blocker reduces proteinuria in patients with chronic kidney disease, but with a high risk of adverse events. A previous trial found that finerenone decreased albuminuria in patients with CKD and heart failure, with a lower rate of hyperkalemia in comparison with spironolactone.

This placebo-controlled trial shows a reduction in urinary ACR in patients with diabetic nephropathy assigned to finerenone, added to a RAS blocker. Further trials of finerenone are needed, including comparison with other active treatments [Bakris GL, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy. *JAMA* 2015; 314:884–894].

## Excess Mortality from Type 2 Diabetes: Rates and Risk Factors

Interactions among age, glycemic control, and kidney disease have a major influence on risk of death for patients with type 2 diabetes, according to a study in *The New England Journal of Medicine*.

The researchers matched 435,369 patients with type 2 diabetes, drawn from the Swedish National Diabetes Register, to 2.1 million population controls without diabetes. Excess mortality associated with type 2 diabetes was analyzed, including the role of glycemic control and renal complications.

At a mean follow-up of nearly five years in both groups, mortality was 17.7 percent in patients with type 2 diabetes versus 14.5 percent in controls. Excess mortality from type 2 diabetes was "historically low": the adjusted hazard ratio (HR) for all-cause mortality was 1.15. Cardiovascular mortality was 7.9 versus 6.1 percent, respectively: HR 1.14.

For both all-cause and cardiovascular mortality, risk increased with younger age, worse glycemic control, and more severe kidney complications. For diabetic patients under 55 with a glycated hemoglobin level of 6.9 percent or less, the HR for death from any cause was 1.92, compared to controls. In contrast, for patients 75 or older at the same level of glycemic control, all-cause mortality was somewhat lower than in controls: HR 0.95.

For patients younger than 55 with normoalbuminuria and a glycated hemoglobin level of 6.9 percent or less, the HR for death was 1.60, compared to controls. Again, older diabetics with normoalbuminuria and good glycemic control had lower all-cause mortality than controls: HR 0.76 for patients aged 75 or older and 0.87 for those aged 65 to 74.

The data suggest wide variation in excess mortality among patients with type 2 diabetes, based on age, glycemic control, and renal complications. Patients under age 55 are at substantially higher risk, even if they have good glycemic control and normoalbuminuria.

Discussing the implications for efforts to reduce excess mortality among patients with type 2 diabetes, the authors highlight the importance of reducing renal complications in all age groups. They write, "Excess mortality among younger patients with chronic kidney disease was approximately 15 times as high as that in controls" [Tancredi M, et al: Excess mortality among persons with type 2 diabetes. *N Engl J Med* 2015;373:1720–1732].

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| Monthly | 12 | 12.00 |

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Contact Person: Bob Henkel
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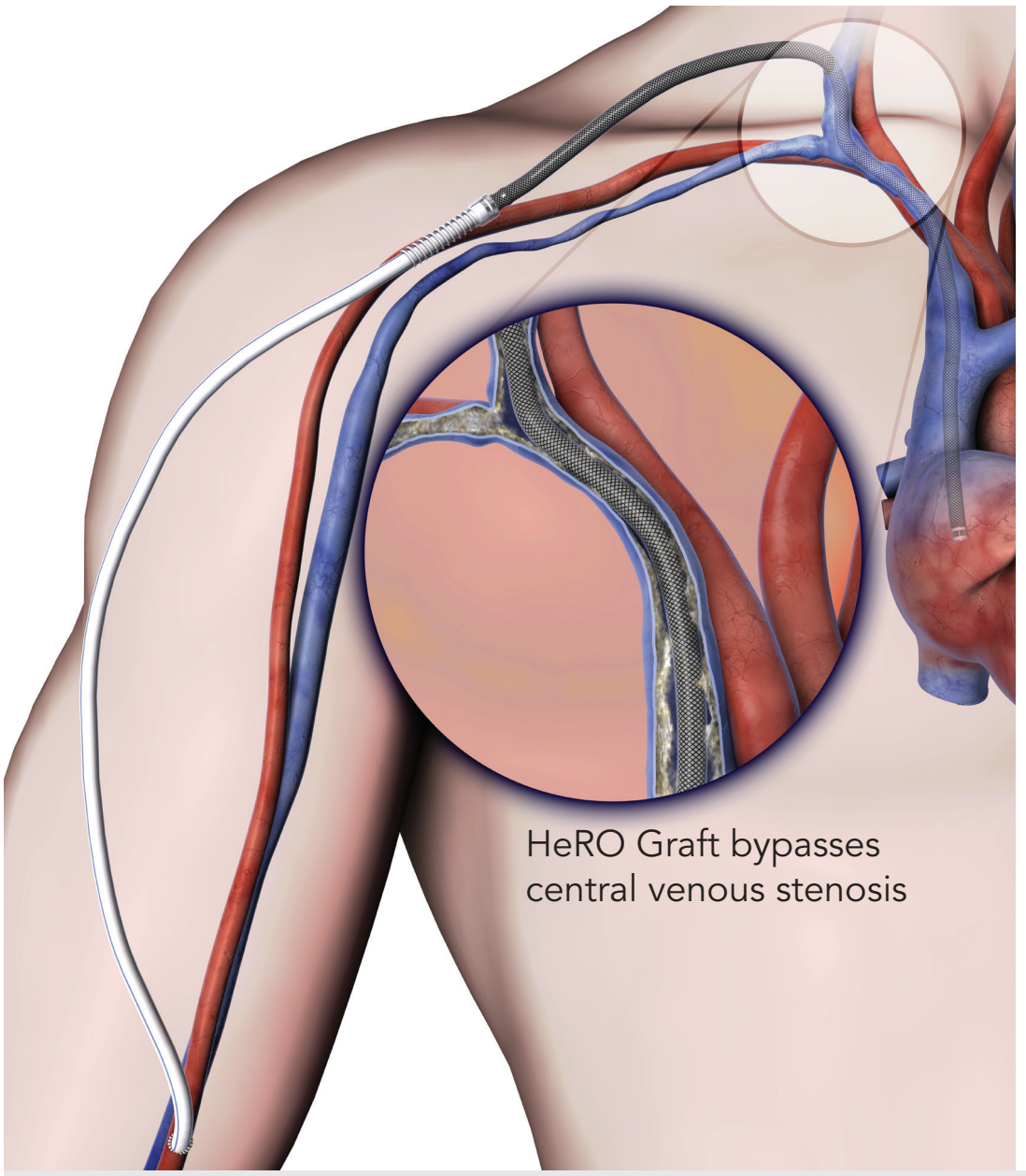

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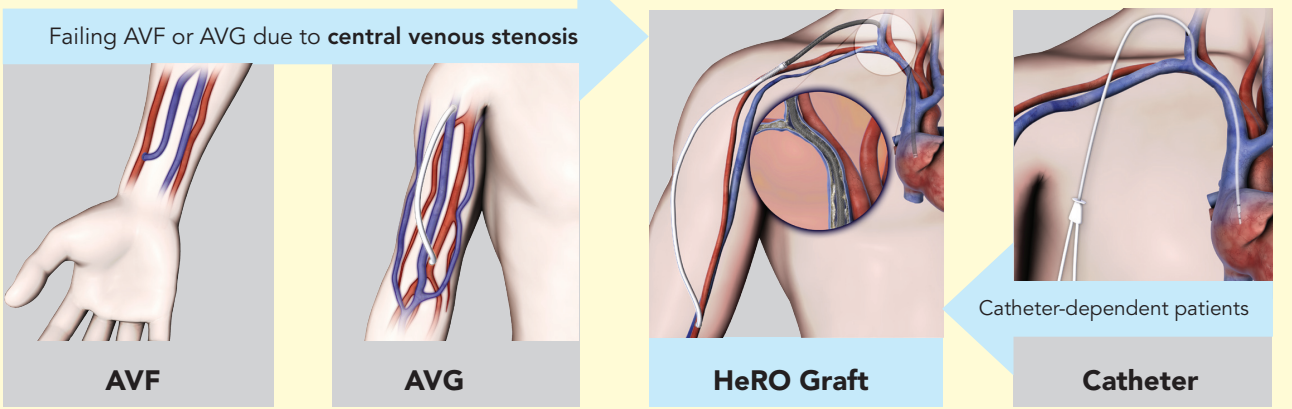


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