

Kidney News

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Revolt against Maintenance of Certification Makes Legislative Gains

By Eric Seaborg



A physician rebellion against maintenance of certification (MOC) is spreading nationwide, with legislation introduced in a dozen states and laws that limit the use of MOC in licensure, hospital privileges, and insurance reimbursement enacted in Texas and Georgia.

Bills similar to, or more limited than,

the laws enacted in Texas and Georgia have been introduced in a dozen states, with varying levels of success. The process often starts with a resolution from the state medical society, and the legislation is often introduced by a legislator who is a physician. The movement has been spurred by doctors who say the MOC process is dominated by the member boards of the American Board of Medical Specialties (ABMS), with an overemphasis on high-stakes tests every 10 years that impose too great a burden in time and money in a process that has not been proven to improve patient outcomes. They seek alternative methods—such as state requirements for continuing medical education (CME)—to show that physicians are keeping up with current evidence and best practices.

At the national level, the June 2017 American Medical Association (AMA) meeting in Chicago featured a panel of physicians from different states who shared their experiences working to pass legislation. And the House of Delegates held a contentious hearing on a resolution

that called for greater AMA involvement in state efforts to rein in MOC.

Georgia moves forward; support and opposition in Texas

Enacted in May 2017, the Georgia law will prevent the use of MOC as a condition of licensure, for employment by a state medical facility, for participation in insurance panels, or for malpractice insurance, according to the Medical Association of Georgia website.

The Texas law is similar, but had some amendments added to assuage the Texas Hospital Association in a process that illustrates the fault lines the movement has exposed—often pitting physicians against hospital organizations, health insurers, and ABMS.

The effort began with a unanimous resolution by the Texas Medical Association in support of a bill that would ensure that MOC “does not allow the [specialty] boards to prevent licensure, credentialing, employment, or contracts for insurance.”

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Serum Phosphorus Affects Long-Term Kidney Transplant Outcomes

Serum phosphorus levels have a significant impact on outcomes after kidney transplantation—especially the risk of transplant failure, suggests a study in the *American Journal of Kidney Diseases*.

Despite a “marginal” effect on the risk of cardiovascular disease (CVD) events, higher phosphorus levels are associated with substantial increases in the risk of

dialysis-dependent transplant failure and all-cause mortality, according to analysis of prospective data from a large sample of kidney transplant participants.

The study included data on more than 3000 kidney transplant participants enrolled in the “Folic Acid for Vascular Outcome Reduction in Transplantation” (FAVORIT) Trial—a randomized trial of homocysteine-lowering therapy with

high-dose vitamin B. The lead author and senior author, respectively, were Basma Merhi, MD, and Andrew Bostom, MD, both of Rhode Island Hospital.

The primary results, published in *Circulation* in 2011, showed no significant difference in fatal and nonfatal CVD events, transplant failure, or mortality for kidney transplant participants assigned to high-dose versus low-dose B vitamins. That was so even though high-dose vitamin B successfully lowered homocysteine levels.

The new analysis examined associations between posttransplant hyperphosphatemia and the risk of adverse graft and patient outcomes. As kidney disease ad-

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Revolt against MOC

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said Ray Callas, MD, an anesthesiologist in private practice in Beaumont who headed the medical association's council on legislation. Introduced by a physician-legislator, the bill sailed through the Texas Senate, but "right before the bill went to the floor of the House, lobbyists were coming out of the woodwork. The ABMS was the biggest one trying to stop legislation," Callas told *Kidney News*. "The Texas Hospital Association didn't like it at all."

One physician-legislator objected to "state legislation getting in the way of physicians making decisions on maintenance of certification," Callas said, so the bill was amended to say that hospital "medical staff have to be the ones to decide [whether a facility would] opt in or opt out of maintenance of certification." Other exceptions were made for level one trauma centers and advanced cancer centers like MD Anderson, Callas said.

These kinds of amendments made the legislation acceptable to the Texas Hospital Association, according to Lance Lunsford, the association's vice president for strategic communications.

But ABMS remained firm in opposition: "The American Board of Medical Specialties believes that such legislation lowers the standards for medical specialty care, undermines professional accountability for medical specialty practice, and interferes with the right of medical staffs to set their own quality standards. It is bad for the profession and bad for patient care," according to a statement supplied by Susan Morris, ABMS director of communications.

After a frenetic amendment process at the end of the session, the bill passed. Given the state's size, the Texas law could have a significant impact on the debate.

Oklahoma trips on a technicality

The Texas Medical Association's approach benefited from the experience in Oklahoma, the first state to adopt similar legislation, in 2016. Jack Beller, MD, an orthopedic surgeon in Norman and former president of the Oklahoma State Medical Association, said that a bill passed aimed at forbidding the use of MOC for condition of licensure, reimbursement, employment, or hospital admitting privileges. But hospitals in the state claimed that a technicality in the wording and the title in state codes meant the law did not apply to them.

The state medical association returned this year with clarifying legislation, but that legislation ran into a buzzsaw of opposition from the Oklahoma Hospital Association (OHA), Oklahoma Association of Health Plans, and ABMS.

"We got caught by surprise that ABMS hired four powerful lobbyists to fight it," said the bill's sponsor, family practice

physician and Republican legislator Mike Ritze, DO.

"OHA opposed the bill because it interferes with a hospital's right to contract with a physician and set appropriate conditions," said Susie Wallace, OHA's director of communications.

"The hospitals came out big time against it," said Beller. "It is not our intention to take the granting of hospital privileges away from the medical staff. We think that if the medical staff wants to require recertification then that is their prerogative. Our problem is the hospital entities requiring recertification without input from the hospital staff."

Michigan scales back

The Michigan State Medical Society has been pursuing similar legislation and framing the effort as a "Right-2Care" campaign because, as its website puts it: "a bureaucratic nightmare known as 'Maintenance of Certification' ... could cut off patients' access to the physicians they know and trust!"

This year, the society is backing two bills. One prohibits the use of MOC in licensure. Another prohibits insurers and health maintenance organizations from requiring certifications not specifically required for licensure. The bills' sponsor, Republican Rep. Edward Canfield, DO, a retired family physician, said that the second bill focuses on insurers because it would be "too heavy a lift" to also include hospitals, and perhaps raise their opposition. He notes that doctors can affect hospital by-laws to influence MOC requirements.

AMA: action or inaction

Those supporting the MOC-limiting legislation often give the impression that physicians are united in supporting their efforts, but the outcome at the recent AMA meeting reveals the uncertainty the issue presents to the medical community. A group that included the delegations of the large states of California, Florida, New York, Pennsylvania, and Texas; American College of Radiation Oncology; and American Society of Interventional Pain Physicians presented a resolution on "Action Steps Regarding Maintenance of Certification" to the House of Delegates to increase the association's activism on the issue.

Although the AMA affirmed the resolution's provision of "lifelong learning" as "a fundamental obligation of physicians" that is "best achieved by ongoing participation in a program of high-quality CME," the most contentious provisions of the resolution were held in deference to existing policy or for future consideration. Among the measures sent back to Council for future consideration was that AMA "join with state medical associations and specialty societies in directly lobbying state licensing boards, hospital associations, and health-care insurers to accept the satisfactory demonstration of lifelong learning through high-quality CME ... for credentialing,"

State Legislation on Physician Maintenance of Certification

State legislatures are abuzz with legislation concerning maintenance of certification, with varying levels of success.

Legislation enacted

- Georgia prohibited the use of MOC in licensure, insurance reimbursement, and employment.
- Texas passed similar legislation, with less restrictive provisions leaving hospital privileges in the hands of medical staff.
- In 2016, Kentucky and Missouri prohibited the use of MOC to deny licensure; in 2017, Maryland did the same.
- In 2016, North Carolina passed a bill stating: "The [North Carolina Medical] Board shall not deny an application for licensure based solely on the applicant's failure to become board certified."
- Tennessee passed a bill that prevents MOC from being required for state licensure. As introduced, it would have prevented hospitals from denying admitting privileges and insurance companies from denying participation in a network based on MOC participation. The bill was amended to create a task force of legislators to study MOC as it relates to these topics.

Bills introduced

- Missouri restricted the use of MOC in licensure last year, but this year an attempt to restrict insurance companies and hospitals from considering MOC in creating networks or staff privileges did not pass.
- Similar legislation was introduced this year in Alaska, Florida, Maine, Massachusetts, Maryland, Michigan, New York, and Rhode Island without passing, generally not making it out of committee.

instead of "the ABMS-sponsored MOC process using ... high-stakes testing."

The snowballing state efforts and recent AMA House of Delegates debate about MOC raise questions about physician self-regulation versus turning over control of recertification to state regulators.

Norman Kahn Jr., MD, CEO, of the Council of Medical Specialty Societies, said he does not want state regulation to supplant the profession's own efforts. Dr. Kahn, a family physician, said it is understandable that physicians can feel overwhelmed by the demands and burdens placed on them, but this legislative approach may be "self-destructive in the long run" because physicians have a responsibility to self-regulate the profession: "It's a part of professional self-regulation, and if it's not right, it's our responsibility to fix it."

Objections to MOC

The objections to MOC are well-known in the medical community: The tests are an outsized burden in terms of money and time; the thousands of doctors grandfathered in are performing well without being subjected to the tests; and MOC has not been shown to improve patient outcomes or quality measures. A recent study in the *Journal of the American Medical Association* found that almost a third of questions on the ABIM Maintenance of Certifi-

cation (IM-MOC) examination were not relevant to general practice during the 2010–2013 testing period.

Texas' Callas notes that the challenge is not against certification: "We 100% agree that ABMS or any board is very important to make sure that we have standardization and specialization related to getting board-certified."

But recertification is a different matter, said Oklahoma's Beller: "The problem is that all of these doctors have gotten their board certification, and now they are having to spend days and thousands and thousands of dollars every 10 years to maintain that certification. It has just become such a financial burden and a time burden out of their practices." He notes that he is exempt from the testing because he is grandfathered in, and CME has proven sufficient for him and his peers.

"There isn't data that shows [that MOC] improves patient outcomes," said Megan Edison, MD, a Grand Rapids, Mich., pediatrician who has been a prominent MOC critic. "Continuing education has been shown to improve patient outcomes, but ... ABMS' education product has not been shown to do it. [CME] has worked pretty well for grandfathered doctors. Over half of doctors ... passed their boards once, and then they do continuing education. Every state has their own requirements."

Kevin McFatridge, director of market-

ing, communications, and public relations at the Michigan State Medical Society, said his organization agrees with this perspective: “The MOC requirement is not increasing the quality of care at all, and there are many studies that prove that. Michigan is one of the states that have the most CME hours required by law for physicians to complete for their [licensure]. So, for a health plan to tack on the MOC process is duplicative.”

Of course, it was the perception among many specialty boards that CME is too passive and not effective enough that led to the increase in MOC requirements, said Kahn of the Council of Medical Specialty Societies.

And ABMS disagrees strongly about MOC’s utility: “There is evidence that board certification and MOC are associated with higher standards, better quality care, and improved patient outcomes. There is evidence that physicians participating in MOC provide care at lower cost, mostly by ordering fewer tests and more efficient patient management.”

Alternative path?

One response to dissatisfaction with ABMS has been the establishment of a continued certification program by the National Board of Physicians and Surgeons that is less costly and requires a fraction of the time of the ABMS program. The organization’s website says it is “currently accepting applications for all ABMS and American Osteopathic Association specialties.”

Dissatisfied with the pace of change at ABIM, the American Association of Clinical Endocrinologists sent a letter to its members in 2015 inviting them to explore this alternative path to MOC.

At least one other professional organization is also pushing ABIM to reform its MOC process. The American Gastroenterological Association has proposed an alternative to the “high-stakes, every 10-year exam,” which the organization opposes, according to its website. The Gastroenterologist-Accountable Professionalism in Practice (G-APP) Pathway would replace the test with “active, adaptive, self-directed learning modules that allow for continuous feedback.”

Boards respond with changes

For their part, ABMS and its member boards are responding to physician concerns and complaints about the burden of MOC by proposing and implementing changes. Last year, ABIM said it would begin offering a second option in addition to the exam taken every 10 years.

The new option would allow physicians to take more frequent, shorter assessments on their personal or office computers. The process, which would allow ABIM’s diplomates to use an open-book resource, “would provide feedback on important knowledge gap areas so physicians can better plan their learning,” according to an ABIM press release. ABIM plans to pilot this two-year option in internal medicine

and nephrology starting in spring 2018.

The American Board of Anesthesiology has already dropped its 10-year test and replaced it with an online test and learning modules.

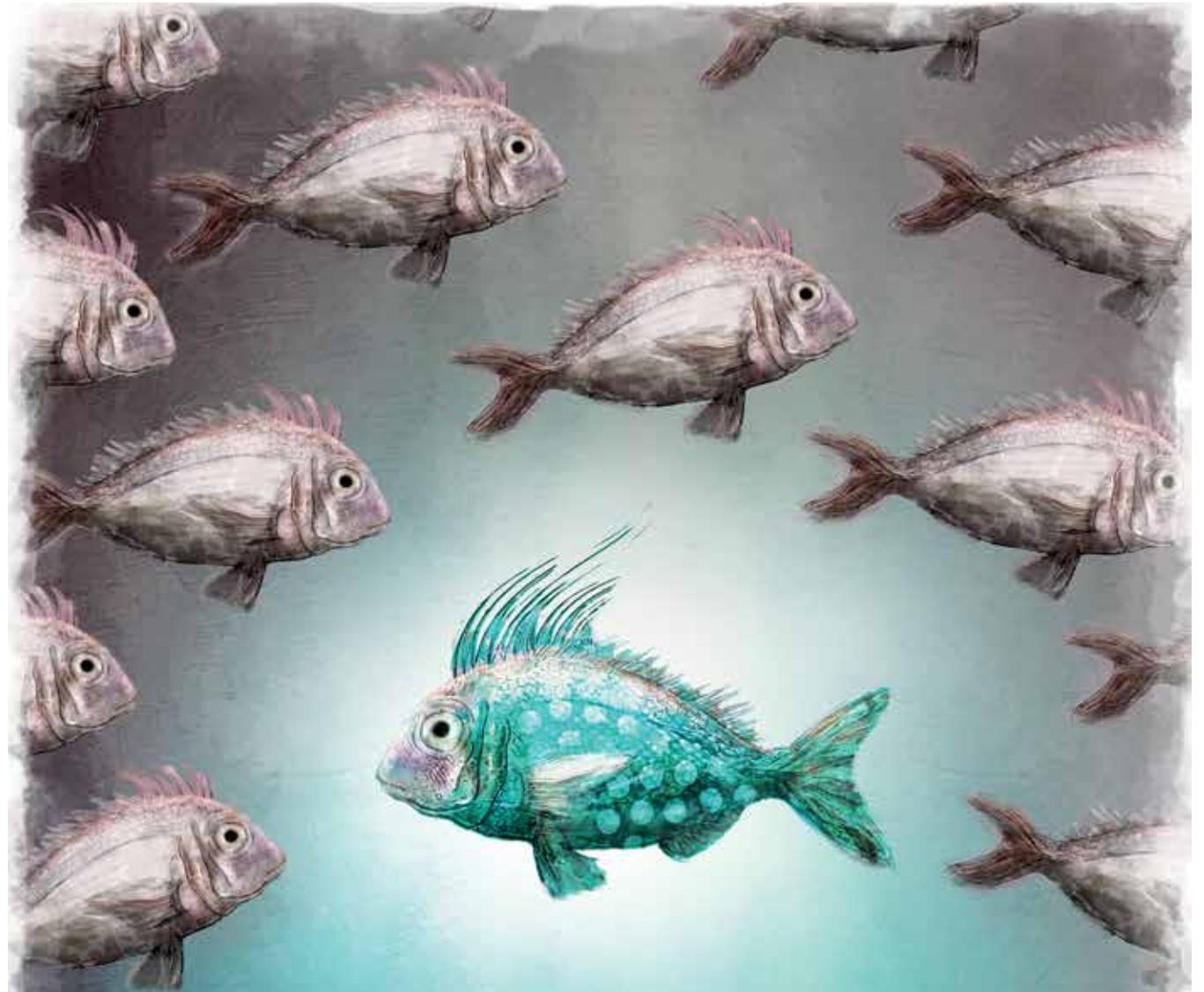
“An overwhelming majority of our diplomates are actively using the tool, which means they are continuously engaging in building and retaining their medical knowledge,” said Deborah J. Culley, MD, secretary of the American Board of Anesthesiology. “They’ve told us we’re moving in the right direction. Since longitudinal assessment is a new approach to physician

assessment, we have had a few challenges. For instance, diplomates have told us some questions were not relevant, poorly written, or repeated too often. We’ve revised or pulled questions based on this feedback, and continue to develop new items to build our question bank.”

“I give ABA very big credit, because they listened to their anesthesiologists,” said Callas, the anesthesiologist and MOC critic from Texas. “They did away with the high stakes test. We have to answer 30 questions every quarter, and we are not scored in a negative or derogatory way.

They give you the answer at the end after you assess your question, and you read about it. They try to make sure that we maintain a high level of care, and they also try to gear the questions toward your type of practice.”

The anesthesiology board is often cited as a leader in exploring this new approach to physician education and re-assessment. As other specialty boards adapt to the shifting landscape, the pace of their innovations could determine how much they are challenged by dissatisfied physicians pushing legislation to force change. ●



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CKD=chronic kidney disease.

Reference: 1. Ganz T, Nemeth E. Iron balance and the role of hepcidin in chronic kidney disease. *Semin Nephrol.* 2016;36(2):87-93.



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Serum Phosphorus

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vances, patients often develop deranged calcium-phosphorus metabolism, which is not fully reversed after kidney transplantation.

The study included 3138 FAVORIT subjects with complete data, representing about three-fourths of the study sample. Mean age was about 52 years and mean time since transplantation was 4 years. Thirty-nine percent of patients had a history of diabetes while 19% had a history of CVD.

Mean serum phosphorus level was 3.07 mg/dL, with a range of 0.79 to 8.32 mg/dL. Patients with higher phosphorus levels differed in some important baseline characteristics, including lower estimated glomerular filtration rate (eGFR) and higher urine albumin/creatinine ratio (UACR). They also had a longer time since transplantation and a higher rate of cadaveric transplant. Hyperphosphatemia was also associated with older age, male sex, and higher rates of smoking, higher blood pressure, and higher chole-

sterol.

During follow-up, a total of 436 CVD events occurred, including 135 deaths. There were also 238 transplant failure events and 348 total deaths. On unadjusted analysis, the risk of incident or first recurrent CVD—the primary outcome—was 25% higher per 1 mg/dL increase in serum phosphorus.

However, on an initial multivariable analysis, the increase in CVD risk significantly weakened: to 14% per increment in phosphorus level. After further adjustment for eGFR and UACR, the association became nonsignificant. The association became nonsignificant after further adjustment for eGFR and UACR.

In contrast, serum phosphorus was more strongly related to the risk of transplant failure. Risk increased by 72% per 1 mg/dL increment in phosphorus in the “almost fully adjusted” model, and remained significant at 36% after further adjustment for kidney measures. From the lowest quintile to the highest decile of serum phosphorus—2.51 mg/dL or less versus 3.83 mg/dL or higher—risk for transplant failure increased by

215%.

Serum phosphorus was also associated with all-cause mortality, with risk increases of 43% and 34% in the mostly and fully adjusted models. An association with cardiovascular death became nonsignificant after adjustment for eGFR and UACR. For a composite outcome of transplant failure and death, the hazard ratio in the fully adjusted model was 1.25. The pattern of associations was significant on competing risk analysis.

The authors note that their findings are consistent with the “phosphate toxicity hypothesis,” as previously reported in CKD patients who have not undergone transplantation. However, the pathways responsible for the cytotoxic effect of extracellular phosphate remain far from clear. One possible mechanism that warrants further study is the formation of insoluble calciprotein particles, formed by combination of extracellular phosphorus with calcium and fetuin A.

The FAVORIT investigators also point out some key weaknesses of their study—including the lack of data on other FGF-23, parathyroid hormone, and vitamin D status. While the study adjusted for eGFR and

UACR, there may be residual confounding from other measures of kidney function.

Of course, given its observational nature, the study permits no conclusions about the potential benefits of phosphorus-lowering therapy for kidney transplant recipients.

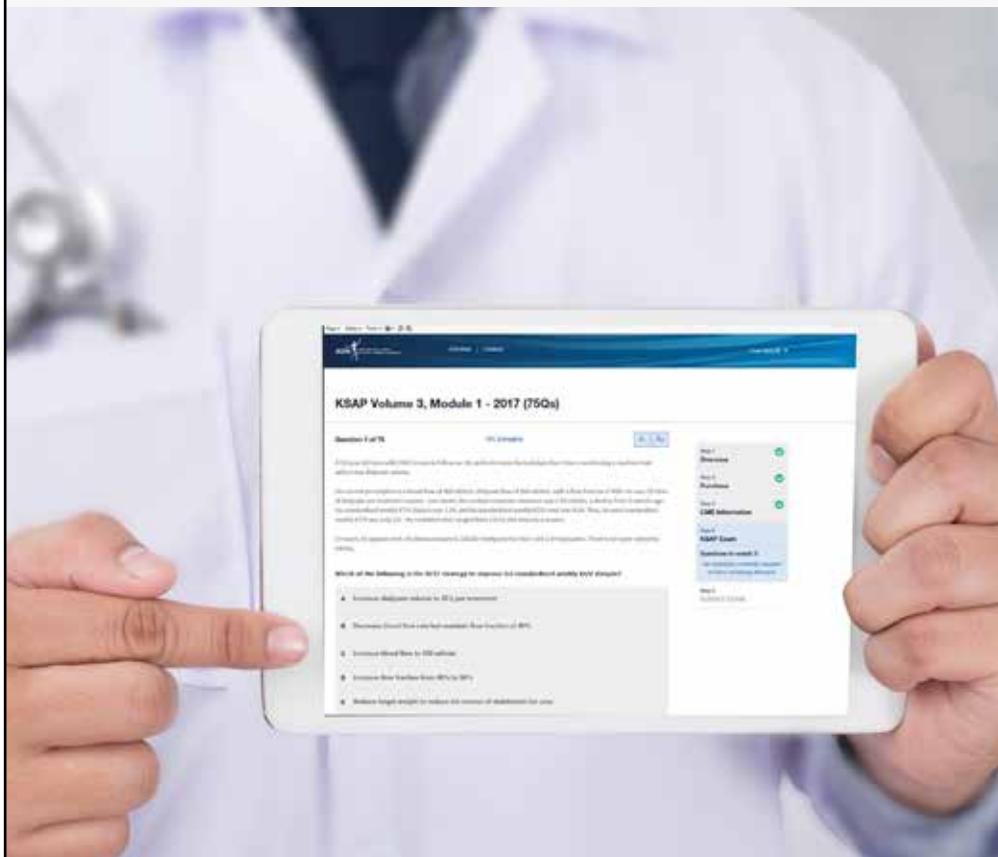
“Our data suggest that kidney transplant participants merit a randomized controlled clinical trial that assesses the potential impact of phosphorus-lowering therapy on hard outcomes in this CKD population, such as CVD, all-cause mortality, and the development of kidney transplant failure—the last outcome, especially,” the authors said. ●

Bostom AG, et al. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the Folic Acid for Vascular Outcome Reduction in Transplantation Trial. *Circulation* 2011; 123:1763–1770.

Kuro-O M. A phosphate-centric paradigm for pathophysiology and therapy of chronic kidney disease. *Kidney Int Suppl* 2011; 3:420–426.

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Findings

APOL1 Improves Risk Prediction in African American Deceased Donors

A revised Kidney Donor Risk Index (KDRI) incorporating *APOL1* genotype rather than race improves prediction of allograft survival of kidneys from African American deceased donors, reports a study in *American Journal of Transplantation*.

The study included data on 622 African American deceased kidney donors from three southern US centers. The researchers used a series of models to analyze the impact of a revised KDRI substituting

APOL1 genotype for race.

For all donors, mean current KDRI was 1.4930. With the revised KDRI, the risk score decreased to 1.2518 for 529 donors with no or one *APOL1* risk variant, but increased to 1.8527 for 93 donors with two risk variants. Posttransplant survival prediction errors were comparable for the original and revised equations. However, there was a 37-percentage point spread in the Kidney Donor Profile Index score,

based on the presence or absence of two *APOL1* risk variants.

Time to allograft failure is shorter in kidneys from African American deceased donors with two *APOL1* risk variants. The new analysis suggests that using *APOL1* genotype instead of race as a risk factor in the KDRI might give a better prediction of the risks associated with transplanting organs from these donors.

The revised model using *APOL1* geno-

type improves KDRI score for 85% to 90% of kidneys from African American deceased donors. While emphasizing the need for further research, the authors discuss the implications for improving the link between the quality of donor organs and the need of the recipient [Julian BA, et al. Effect of replacing risk with apolipoprotein L1 genotype in calculation of Kidney Donor Risk Index. *Am J Transpl* 2017; 17:1540–1548]. ●

Prolonged Total Ischemic Time Leads to Worse Transplant Outcomes

Particularly in interaction with donor age and pathway of death, total ischemic times of 14 hours or longer are associated with increased rates of adverse allograft outcomes in deceased donor kidney recipients, reports a study in *Transplantation*.

The researchers analyzed the impact of total ischemic time and graft outcomes in 7542 patients receiving their first deceased donor kidney transplant in Australia and New Zealand between 1994 and 2013. Total ischemic time included warm and cold ischemia: from the time of donor renal artery interruption/clamping to release of the renal artery clamp in the recipient. The authors hypothesized

that donor characteristics and the pathway of donor death would affect graft outcomes. Median follow-up time was 5.3 years, with an interquartile range of 8.2 years.

Prolonged ischemia of 14 hours or longer was recorded for 48.7% of recipients. At follow-up, graft loss occurred in 59.6% of patients with prolonged total ischemic time and 40.4% of those with a shorter ischemic time. Rates of graft loss were 99.4 versus 58.7 per 1000 person-years, respectively.

Delayed graft function (DGF) occurred in 13.5% of recipients with total ischemic times of 14 hours or longer ver-

sus 10.9% of those with shorter ischemic times. This effect was greatest for those with donors aged 55 years or older. The adjusted odds ratio (OR) for DGF associated with prolonged ischemic time was 1.79 with older donors versus 1.45 with younger donors.

Prolonged total ischemic time was also associated with an increased risk of overall graft loss, OR 1.09, and increased overall mortality, OR 1.13. The pathway of donor death also had a significant impact: among recipients of kidneys from older donors with donation after cardiac death, the risk of allograft loss was at least three times higher for those with total ischemic

times of 14 hours or longer.

Prolonged total ischemic time is associated with an increased risk of adverse outcomes in recipients of deceased donor kidneys. The effect is even greater with organs from older donors—especially those with circulatory death. The authors discuss the implications for “appropriate and optimal use” of kidneys from older donors and those with comorbid conditions [Wong G, et al. The impact of total ischemic time, donor age and the pathway of donor death on graft outcomes after deceased donor kidney transplantation. *Transplantation* 2017; 101:1152–1158]. ●

Varying Use of Growth Hormone for Children with CKD

Pediatric nephrology centers vary in their use of growth hormone therapy for children with chronic kidney disease (CKD) and short stature, reports a study in *BMC Nephrology*.

The authors report an online survey distributed to US pediatric nephrologists, via the Midwest Pediatric Nephrology Consortium and the American Society of Pediatric Nephrology. Respondents were asked about their approach to recombinant human growth hormone (rhGH) therapy in short children with CKD. The analysis included 73 responses, 30 from small (4 or fewer pediatric nephrologists) and 43 from

large practices. One-third of physicians and more than half of centers responded to the survey.

The initial workup for rhGH therapy varied considerably: 95% of pediatric nephrologists routinely obtained bone age, but only 40% obtained hip and knee x-rays. The workup included thyroid function assessment for 58% of respondents, insulin-like growth factor-1 measurement for 40%, and ophthalmologic evaluation for 7%.

Just over half (52%) of respondents said they rarely involve endocrinologists in managing rhGH therapy. However, more than one-fourth (27%) said that

endocrinologists managed most aspects of rhGH therapy. While 68.5% of centers had a dedicated renal dietitian, 21% reported that the nephrologist was the main resource for nutritional support.

At both large and small centers, family refusal was the most common reason why children with growth failure did not receive rhGH. Ninety-five percent of pediatric nephrologists believed rhGH improved quality of life, 44% that it improved lean body mass, and 24% that it improved physical function.

Use of rhGH in children with CKD and short stature is thought to be low. Decision-making about growth hor-

mone therapy is complicated by a lack of high-quality evidence.

This study shows significant variability concerning the use of rhGH for children with CKD at US pediatric nephrology centers. The researchers write, “Our data suggests that opportunities are available to standardize care to improve growth outcomes in children with CKD” [Akchurin OM, et al. Approach to growth hormone therapy in children with chronic kidney disease varies across North America: the Midwest Pediatric Nephrology Consortium report. *BMC Nephrol* 2017; doi: 10.1186/s12882-017-0599-1]. ●

Quarter-Dose Antihypertensive Therapy—Meta-Analysis

Especially in combination, quarter-dose medication regimens may provide a safe and effective alternative for blood pressure-lowering therapy, according to a meta-analysis in *Hypertension*.

A literature review identified 42 randomized trials of quarter-dose therapy with major classes of antihypertensive drugs. Comprising a total of 20,284 patients, all studies included at least one quarter-dose arm and one placebo and standard-dose monotherapy arm. On average, the studies were published 17 years ago. Data were pooled for meta-analysis

of safety and efficacy outcomes.

On analysis of 36 comparisons with placebo, quarter-dose therapy was associated with a 4.7/2.4 mm Hg reduction in blood pressure. With dual quarter-dose therapy, based on six comparisons with placebo, the reduction in blood pressure was 6.7/4.4 mm Hg. In a single placebo-controlled study, quadruple quarter-dose therapy reduced blood pressure by 22.4/13.1 mm Hg.

Analysis of 37 comparisons of single quarter-dose therapy versus standard monotherapy suggested a blood pressure

increase of +3.7/+2.6 mm Hg. Data from seven comparisons of dual quarter-dose therapy versus monotherapy showed no significant difference. In one study, quadruple quarter-dose therapy reduced blood pressure by 13.1/7.9 mm Hg. Adverse events of single and dual quarter-dose therapy were no different from placebo, and less frequent than with standard-dose monotherapy.

For many patients, combinations of antihypertensive drugs are needed to achieve good blood pressure control with minimal side effects. The new meta-anal-

ysis suggests potential clinical advantages of quarter-dose antihypertensive regimens.

Based on just two trials, quadruple quarter-dose combinations may significantly increase efficacy. The authors conclude, “This review suggests a potentially broader clinical role for low-dose blood pressure-lowering drugs” [Bennett A, et al. Efficacy and safety of quarter-dose blood pressure-lowering agents: a systematic review and meta-analysis of randomized controlled trials. *Hypertension* 2017; 70:85–93]. ●

Sodium in Packaged Foods—12% Decrease Over 15 Years

The sodium content of packaged foods and beverages purchased by Americans has decreased substantially over the past several years, reports a study in *JAMA Internal Medicine*.

In the 2000–2014 Nielsen HomeScan Consumer Panel, a nationally representative sample of 172,042 US households used a barcode scanner to report all packaged food purchases. The researchers examined trends in the sodium content of purchased foods, and in the percentage of households buying products with optimal sodium density (1.1 mg/kcal or less).

During the period studied, the amount of sodium obtained from pack-

aged foods and beverages decreased by 396 mg/d—from 2363 to 1967 mg/d. Sodium from packaged foods (as opposed to beverages) decreased by 260 mg/d while table salt purchases decreased by 111 mg/d.

The sodium content of packaged food purchases decreased by 12% (49 mg/100 g), with reductions starting in 2005 and continuing through 2014. The reductions were significant in all the most important sources of sodium, including condiments, sauces, and dips (by 114 mg/100 g) and salty snacks (by 142 mg/100 g). The percentage of US households with optimal sodium density in total food purchases remained very low, but increased

from 0.6% to 1.2%.

Reduction in the sodium content of packaged foods is an essential recommendation to reduce excessive sodium intake. Reflecting voluntary initiatives by food manufacturers, this study finds a 12% reduction in the sodium content of packaged foods and beverages purchased by US households. The continued high rate of excessive sodium density highlights the need for “more concerted” sodium reduction efforts [Poti JM, et al. Sodium reduction in US households’ packaged food and beverage purchases, 2000 to 2014. *JAMA Inter-*



nal Med 2017; doi:10.1001/jamainternmed.2017.1407]. ●

Early Diabetic Kidney Disease Shortens Life Expectancy

Early diabetic kidney disease (DKD)—often clinically expressed as proteinuria—is associated with a 16-year reduction in life expectancy, reports a study from Taiwan in *Kidney International*.

The prospective cohort study included 512,700 adults participating in a comprehensive health surveillance study between 1994 and 2008. Of these, 9067 patients had early DKD, defined as stage 1 to 3 chronic kidney disease (CKD) based on estimated glomerular filtration rate and/or albuminuria. Another 50,977 patients had early CKD without diabetes and 18,388 had diabetes without CKD.

Life expectancy was compared among groups and with the reference group of individuals who had neither diabetes nor CKD.

One-third of those with diabetes had early DKD. Proteinuria was present in 72.3% of subjects with early DKD, compared to 60.8% of nondiabetic subjects with early CKD. Over an average 8 years’ follow-up, all-cause mortality in the early DKD group was three times higher than in the reference group, hazard ratio (HR) 3.16; twice as high as in the early CKD group, HR 2.01; and nearly twice as high in diabetic patients without CKD, HR

1.79. Ninety-eight percent of subjects with early DKD were unaware of their condition.

Life expectancy was 16 years shorter in patients with early DKD, compared to the reference group. Early DKD was also associated with a 10-year reduction in life expectancy compared to diabetes and six years compared to early CKD. The early DKD group had a high rate of lifestyle risk factors such as inactivity and obesity, which greatly amplified the reduction in life expectancy.

Early DKD is potentially controllable and even reversible. However, outside of

nephrology specialty care, awareness of this condition is limited.

The study highlights the dramatic reduction in life expectancy associated with early DKD, even compared to nondiabetic CKD or diabetes without kidney involvement. The authors conclude, “[I]dentifying early proteinuria among diabetic patients and realizing the importance of reducing lifestyle risks like inactivity is a clinical challenge, but can save lives” [Wen CP, et al. Diabetes with early kidney involvement may shorten life expectancy by 16 years. *Kidney Int* 2017; doi: 10.1016/j.kint.2017.01.030]. ●

In Black Patients with Type 1 Diabetes, HbA1c Underestimates Mean Glucose

Glycated hemoglobin (HbA1c) levels may underestimate mean glucose level in African Americans with type 1 diabetes, reports a study in *Annals of Internal Medicine*.

The T1D Exchange Racial Differences Study Group analyzed data on 104 non-Hispanic black and 104 non-Hispanic white patients with type 1 diabetes, enrolled at 10 US centers. (Individuals with anemia or hemoglobinopathy were excluded.) All subjects were at least 8 years old and had had type 1 diabetes for at least 2 years. Mean glucose concentration was measured by continuous glucose monitor-

ing, and racial differences in the relationship between glucose and HbA1c were assessed.

In this population with type 1 diabetes, mean HbA1c was 9.1% in black subjects compared to 8.3% in white subjects; mean glucose concentration was 191 versus 180 mg/dL, respectively. At a given mean glucose concentration, HbA1c was 0.4 percentage point higher in blacks compared to whites. The results were similar on analysis of subjects with a higher number of continuous glucose monitoring measurements.

The racial difference in mean glucose–HbA1c relationship also persisted on stratified analysis by age under 18 years versus age 18 or older. Glycated albumin and fructosamine were highly correlated with HbA1c, with no clinically significant difference by race.

Studies have consistently reported higher HbA1c levels in black compared to white adults and children with type 1 or 2 diabetes. Although this could indicate poorer glycemic control in black patients, it might also reflect racial differences in glycation of hemoglobin.

This study suggests that HbA1c overestimates mean glucose concentration in black patients with type 1 diabetes. While this could reflect racial differences in hemoglobin glycation, race only partly explains the observed difference in HbA1c. The authors write, “Future research should focus on identifying and modifying barriers impeding improved glycemic control in black persons with diabetes” [Bergental RM, et al. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. *Ann Intern Med* 2017; doi:10.7326/M16-2596]. ●



Want to learn even more about how changes in health care policy, the kidney workforce, and new research will affect you?

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We are pleased to present this pair of articles as part of an occasional series in *Kidney News*, “Controversies in Nephrology.” The series will highlight common clinical issues in the care of patients with kidney diseases that may be more controversial than we would like and will provide some further basis for rational, evidence-, and experience-based care. We thank Drs. Parfrey and Goldsmith for their contributions to this issue and for setting an initial gentle tone for future pro and con presentations. We hope you will enjoy the series and welcome your suggestions for future articles (kidneynews@asn-online.org).

Richard Lafayette, MD, Editor-in-Chief, *Kidney News*

The Case for Earlier/Targeted Treatment of Hyperparathyroidism with Cinacalcet: Calcimimetics Have Much to Offer the “Right” Patient

By David Goldsmith, MD

In the therapy of hypertension, diabetes, or dyslipidemia or the attempt to prevent solid organ transplant rejection, it is a well recognized strategy to use a number of complementary pharmacologic approaches to address the fundamental goal, whether it is achieving better control of blood pressure (BP), blood sugar, or blood lipids, or long-term allograft survival. Monotherapy can work well, of course, in all of these settings, but usually only with milder disease states and only with good patient adherence and responsiveness to that single intervention. More often than not, we blend synergistic approaches, maximizing response while minimizing toxicity.

One has to wonder, just from first principles, whether in nephrology we have grasped this, or do we still think and prescribe largely in silos?

The use of vitamin D therapy is now well established in the medical management of secondary hyperparathyroidism. It has been part of good clinical practice for about three decades, and many guideline statements and other documents attest to its importance (1). However, it must be said that there is no evidence of worth anywhere that the use of vitamin D improves the quality and length of life in patients with chronic kidney disease (CKD) (2).

Sadly, this is the rule and not the exception in nephrology. From the birth of the use of erythropoiesis-stimulating agents with epoetin in 1989 to 2009 and the TREAT Study (Trial to Reduce Cardiovascular Events with Aranesp Therapy), it had been regarded as self-evident that erythropoietin prolonged patients’ lives on the basis of spin and assertion, not resting securely on randomized, controlled trial data (3). We may well be in the same situation with vitamin D and its expensive analogues for exactly the same reasons. This is not, in 2017, a comfortable position to be in.

The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events Trial, of course, has told us (or certainly me) that the use of cinacalcet in the attempt to prolong the life of CKD patients with mild to moderate secondary hyperparathyroidism was both expensive and futile (4). This is not the fault of cinacalcet but more of a failure to design and undertake a clinically relevant trial. However, what should not be forgotten is the prodigious and impressive effect that cinacalcet has on plasma calcium and parathyroid hormone (PTH). Both with the actual speed and extent of the effect on PTH and the fact that the plasma calcium falls with cinacalcet but hypercalcemia is the main reason for vitamin D-related treatment failures, it is clear that cinacalcet is the perfect tool

to use alongside vitamin D compounds to synergize with and complement the actions of vitamin D on the parathyroid glands and, therefore, better control hyperparathyroidism in the medium term (5).

The way, however, that the regulatory pathways and some other influences compel innovators or new product manufacturers to work is to show that their product adds something of value to the previous gold standard. Although technically correct as an approach, this tends to lead to negation of the possibility that, by adding additional or novel therapies at an earlier stage in a chronic disease’s evolution, there could be longer-term benefit to the patient. Conditions that tend to progress with age or time, such as diabetes and complications of CKD, definitely fall into this category in my opinion. Therefore, with the introduction of cinacalcet, what was demanded by regulators was the demonstration of the ability of the drug to improve the biochemical profiles of patients already taking vitamin D but failing to meet guideline-recommended serum PTH concentrations. This is useful and valid information indeed, but the companies have also failed to do trials that accurately reflect real patients and always preferred to pretend that diverse biochemical or hematologic manipulations are somehow meaningful for patients.

I think there are three reasons we should consider cinacalcet to be of great value to nephrology and in the treatment of secondary hyperparathyroidism. The first is in the prevention, or at least delay, of surgical parathyroidectomy in patients truly not medically or psychologically fit enough for surgical intervention (the words that I have used are important here—I am not advocating the abolishment of parathyroid surgery) (6).

The second is in situations where patients show vitamin D sensitivity with hypercalcemia, hyperphosphatemia, and raised Ca × P product. Here, cinacalcet is really important to help restore some biochemical balance and permit ongoing vitamin D-based therapy (one is contemplating here that cinacalcet’s value is in being permissive of continued use of vitamin D) (7).

The third state where cinacalcet is of value is postrenal transplantation in controlling serum calcium and preventing major hypercalcemia (e.g., >3 mmol/L or 12 mg percent) (8). In these circumstances in the past, we were often forced to use big doses of intravenous bisphosphonates (with several short- and medium-term risks) or resorted to early post-renal transplant parathyroidectomy, which is associated with some loss of kidney function (bearing in mind that vitamin D itself can be so associated and that vitamin D doses after successful parathyroidectomy are often prodigious in

the short term at least).

Cinacalcet in my view is “more sinned against than sinning,” and we should thus rethink its potential roles in nephrology more carefully now, rejecting the Lorelei siren calls coming from the commercial drive for more widespread, indiscriminate prescription. However, in selected patient groups for better bone and mineral metabolism control (for whatever reason), it is close to indispensable (pun not intended). ●

Professor David Goldsmith, MA, MB BChir, FRCP (Lond), FRCP (Ed), FASN, is a consultant nephrologist, Guy’s and St Thomas’ Hospitals, and professor, Cardiovascular and Cell Sciences Institute, St George’s University of London.

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What Groups of Patients on Dialysis Who Have Secondary Hyperparathyroidism Might Not Benefit from Calcimimetics?

By Patrick Parfrey, MD

In the assessment of chronic kidney disease–mineral bone disorder (CKD-MBD), serial measurements of serum calcium, phosphorus, and parathyroid hormone (PTH) occur, and attempts are made to bring these levels into the normal range. However, the optimal level of PTH in dialysis patients is not known. Kidney Disease Improving Global Outcomes recommends that, in dialysis patients requiring PTH-lowering therapy, calcimimetics, calcitriol, vitamin D analogs, or a combination of these drugs be prescribed (1). However, which patients need these drugs? The indications may include prevention or treatment of severe unremitting hyperparathyroidism (hyper-PTH) or prevention of major clinical events (cardiovascular events or fractures). Calcimimetics may be given orally (cinacalcet) or intravenously (etelcalcetide). Recently, it was reported that etelcalcetide in one trial of patients on dialysis with secondary hyper-PTH reduced PTH from a baseline of 849 to 384 pg/mL after 20 to 27 weeks of therapy and in a second trial, from 845 to 363 pg/mL (2).

Prevention of severe, unremitting hyper-PTH

Cinacalcet is approved for the treatment of secondary hyper-PTH, and it is very effective in the prevention of severe unremitting hyper-PTH. This has been defined as plasma PTH >1000 pg/mL with sustained hypercalcemia or a decision to undertake a parathyroidectomy (PTX). The relative hazard comparing patients randomized to cinacalcet compared with those randomized to placebo in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) Study was 0.31 and significant regardless of whether the baseline PTH was 300 to 600, 600 to 900, 900 to 1200, or >1200 pg/mL (3).

However, in patients with PTH levels below 900 pg/mL, these hyper-PTH events took time to occur and were relatively infrequent in the first 2 years. Consequently, I would not prescribe cinacalcet for PTH levels below 900 pg/mL if the intent was the prevention of severe unremitting hyper-PTH.

Treatment of severe hyper-PTH

In patients with PTH >900 pg/mL, severe unremitting hyper-PTH is highly likely to occur, and treatment choices are PTX or cinacalcet. PTX is clearly a more definitive treatment than cinacalcet, but its harms may outweigh its benefits in some subgroups, particularly the frail elderly and those with severe comorbidity. There is no head-to-head randomized, controlled clinical trial of PTX versus calcimimetics. Consequently, I would likely not prescribe cinacalcet in those patients who can undergo an invasive surgery and are at mild to moderate surgical risk. However, these patients should be permitted to choose their preferred therapy when provided information on harms and benefits of each choice.

Prevention of cardiovascular events

In the EVOLVE Study of cinacalcet versus placebo for the treatment of secondary hyper-PTH, the unadjusted primary composite end point (death or nonfatal cardiovascular events) showed a nonsignificant reduction (relative risk [RR] = 0.93) but when adjusted for imbalances in baseline characteristics, showed a nominally significant reduction in the primary composite end point (RR = 0.88; $p = 0.007$) (4). Of particular

interest was the observation in a pre-specified analysis of age that cinacalcet in patients ≥ 65 years old reduced the primary end point by 26% ($p < 0.001$) and mortality by 27% ($p < 0.001$) but had no effect on the primary end point in patients younger than 65 years old (5). In my opinion, trials should not be judged by the result of a single analysis and a single p value, but inferences should be on the basis of the totality of the data (6). Consequently, I would not prescribe cinacalcet in patients younger than 65 years old with PTH levels <900 pg/mL.

In older patients with PTH levels <900 pg/mL, I would prescribe cinacalcet, but I would not prescribe it in patients with substantial comorbidity and a short life expectancy.

Prevention of fractures

In the EVOLVE Study, the results for fractures were very similar to those for the primary end point: nonsignificant reduction in the risk of clinical fractures in the unadjusted analyses (RR = 0.93), nominally significant reduction in risk when adjusted for age (RR = 0.88; $p = 0.007$), and a treatment effect that was strongly age dependent (7). The adjusted RR for clinical fracture was 0.92 (NS) in patients younger than 65 years old and 0.69 (95% confidence interval, 0.49 to 0.95) in patients 65 years or older. These data support the recommendations for limiting cinacalcet use in younger patients discussed in the previous paragraph.

Treatment of calcific uremic arteriopathy

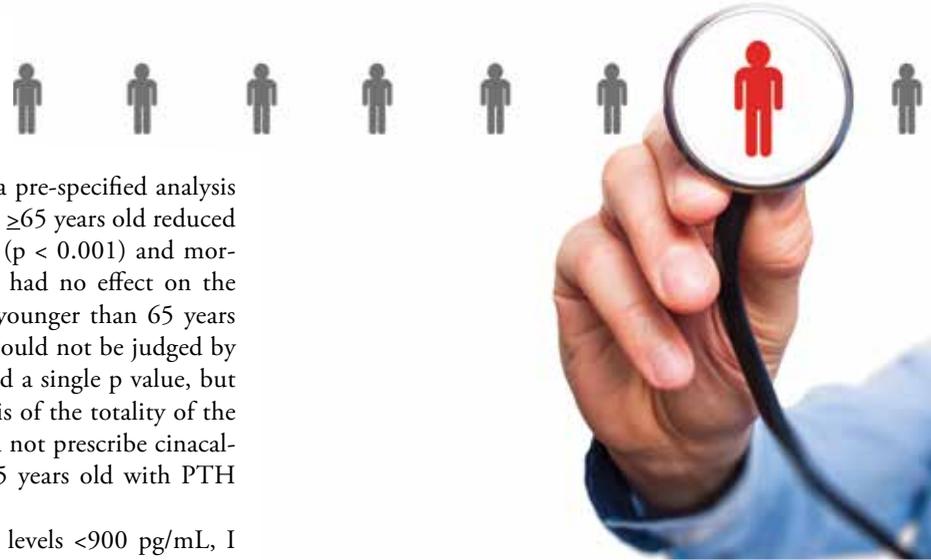
Cinacalcet reduced the incidence of calcific uremic arteriopathy in the EVOLVE Study, implying that hyper-PTH was implicated in its cause (8). However, that does not mean that cinacalcet would be an effective treatment of calcific arteriopathy.

Balance of benefits versus harms

Nausea and vomiting occur quite frequently when using either oral cinacalcet (4) or intravenous etelcalcetide (2). Of interest, with the intravenous compound, nausea occurred in 12% of patients (compared with 7% of controls), and vomiting occurred in 9% of patients (compared with 5% of controls) (2). This may be occasionally severe enough to withdraw calcimimetics (9). Furthermore, hypocalcemia may occur (8), although it is usually asymptomatic, and in the EVOLVE Study, rarely engendered a therapeutic response (P. Parfrey, unpublished data). Consequently, the decision to prescribe or maintain cinacalcet requires an assessment of the likelihood that potential important clinical benefits will be achieved and that the drug will be tolerated in individual patients.

Economic evaluation of cinacalcet in the US

Cinacalcet does not represent a cost-effective use of health care resources when using the unadjusted intention to treat analysis from the EVOLVE Study and a willingness to pay a threshold of \$100,000 (10). However, when using the covariate-adjusted treatment effect, which probably represents the least biased estimate, cinacalcet is a cost-effective therapy for patients with moderate to severe hyper-PTH. If used in the more targeted manner described above, cinacalcet becomes much more cost effective.



Conclusion

Calcimimetics are unlikely to provide important clinical benefits in patients younger than 65 years old, other than those who have severe hyper-PTH and cannot have a PTX. In older patients, treatment of moderate to severe hyper-PTH may be more beneficial, but prescription of calcimimetics should take account of life expectancy. ●

Patrick Parfrey, MD, is professor with the John Lewis Paton Distinguished University Memorial University, St John's, NL, Canada.

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Policy Update

Legislation Targets Kidney Disease Research, Treatment Access, and Medicare ESRD Program Stability

By Rachel Meyer

While the news cycle in recent weeks has been laser-focused on Senate efforts and intra-party debates surrounding repeal and replacement of the Affordable Care Act, bright spots of bipartisan collaboration on other healthcare legislation are quietly proceeding on Capitol Hill.

The Chronic Kidney Disease Improvement in Research and Treatment Act of 2017, introduced in late May 2017, tackles three distinct areas of interest to the kidney community: research, access to treatment, and stability for the Medicare ESRD program. Introduced in the House by Rep. John Lewis (D-GA), Rep. Tom Marino (R-PA), and Rep. Peter Roskam (R-IL), the bill is a focal point for Kidney Care Partners (KCP)—a broad advocacy coalition of which ASN is a member. The ambitious legislation includes several provisions ASN advocated for. The society will be emphasizing these areas as it works in partnership with fellow KCP members and other stakeholders to raise awareness and build support for the bill in the coming months:

Eliminating barriers to transplantation

Calls on the Secretary of Health and Human Services to

conduct a study on any disincentives in Medicare that create barriers to kidney transplants and to examine best practices to increase deceased and living organ donation rates.

Fostering adoption of new technology

Commissions the National Academy of Sciences to evaluate the ESRD payment system to identify barriers to adopting innovative technologies and make recommendations to eliminate the barriers.

Assessing palliative care opportunities

Requires the Government Accountability Office (GAO) to issue a report on the use and impacts of palliative care on those with ESRD.

Improving minority health

Tasks the Secretary of Health and Human Services to conduct a study to better understand the progression of kidney disease and treatment of kidney failure in minority populations.

Ensuring equitable access to transplantation

Guarantees patients with ESRD who are under 65 the ability to enroll in Medigap plans, secondary coverage without

which many patients cannot become active on the transplant wait list (Medigap for patients under 65 is currently not available in 19 states).

Promoting access to home dialysis

Allows home dialysis patients to interact with their nephrologist (and allows the nephrologist to be paid) from their home via telehealth if they both so choose.

Increasing access to kidney disease education

Only 2% of eligible patients currently receive the kidney disease education benefits for which they are eligible; this bill would expand the providers who can offer the education and allow people with stage 5 CKD not yet on dialysis to access it.

Creating loan repayment for nephrologists

Permits nephrology health professionals in underserved rural and/or urban areas to participate in the National Health Service Corps loan forgiveness program.

Join ASN in advocating for enactment of this legislation: Contact your congressional representative at <https://www.asn-online.org/policy/lac.aspx> ●

NIH Pivots from Grant Support Index to Next Generation Researchers Initiative

By Ryan Murray

There have been concerns for years that the National Institutes of Health (NIH) has limited resources for too many researchers applying for grant funding. This situation has created a competitive environment as applications go unfunded, which is particularly challenging for many new- and mid-career investigators to navigate. In passing the 21st Century Cures Act, Congress gave NIH an edict to promote policies that support early-career investigators. To that end, NIH announced a major policy change in May 2017 titled the Grant Support Index (GSI) that aimed to cap the number of research grants an investigator may hold.

GSI proposed measuring grant support not solely by the amount of funding received but rather assigned different types of grants points based on type, complexity and size.

Investigators were limited to a GSI of 21 points, which equated to three R01s. NIH noted that only 6% of investigators receive support above the proposed GSI limit of 21 points and that as funds are freed up, 1600 new grants would be created and steered toward early- and mid-career investigators. By increasing the number of investigators conducting NIH research, NIH sought to improve the stability of the enterprise.

The plan drew criticism for potentially cutting funding for productive labs and for discouraging collaborative research, complex trials, and research networks. Responding to the feedback received from the medical research community, NIH altered the point system, which scaled back the number of principal investigators over the cap to 3% and decreased the number of new grants to 900.

Despite the NIH's efforts to revise the proposed GSI policy, it remained a topic of controversy, with the medical research community providing comments and concerns to NIH through its Open Mike blog, council meet-

ings, and other discussions with stakeholders.

NIH was receptive to the feedback it received and in June announced that the proposed GSI would not be implemented. In the same announcement, NIH shared that it has shifted to launching the Next Generation Researchers Initiative. The Initiative went into effect immediately and supports early and mid-career investigators by:

- Allocating approximately \$210 million in 2017, ramping up to nearly \$1.1 billion per year after five years (pending availability of funds) to support additional early-stage investigators and mid-career investigators;
- Tracking NIH Institute and Center funding decisions for early- and mid-career investigators and assessing their impact;
- Emphasizing current NIH funding mechanisms for early- and mid-career investigators with a goal of funding applications that score in the top 25th percentile from early-career investigators; and
- Developing and testing multiple methods to evaluate the impact of NIH grant support on scientific progress.

“Like many of my colleagues, I was hesitant when NIH proposed the new GSI policy and the tradeoffs that it entailed, including potentially limiting the amount of funding that highly productive labs could receive and impacting collaborative projects across sites,” said Daniel E. Weiner, MD, FASN, chair of the ASN Quality Committee. “I am pleased that NIH heard the concerns of the community and were still able to support early- and mid-career investigators by launching the Next Generation Researchers Initiative, which prioritizes researchers whomay be faced with leaving research for financial reasons.”



The American Society of Nephrology applauded NIH for being receptive to the medical research community throughout the process and will continue to advocate for increased resources for NIH so that funding can be used to tackle tough research questions and improve the health of all Americans.

Individuals are encouraged to continue to provide their feedback to the NIH through the Open Mike blog or by sending an email to publicinput@od.nih.gov. More information on the Next Generation Researchers Initiative can be found by visiting <https://grants.nih.gov/ngri.htm>. ●

Continued on page 13



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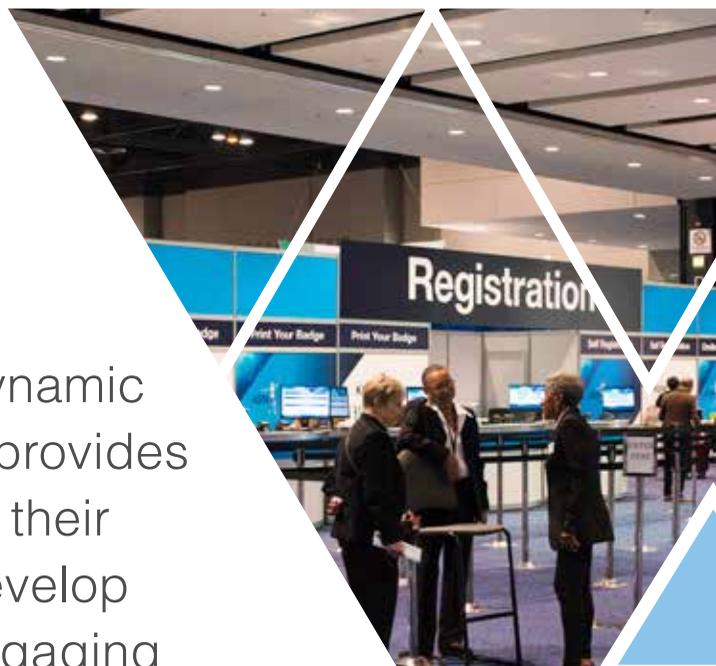


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Policy Update

Continued from page 11

VA Center for Innovation Announces Funding for Innovative Kidney Projects

By Ryan Murray

The Department of Veterans Affairs (VA) Center for Innovation (VACI), the innovation hub within the department, recently released a Broad Agency Announcement (BAA). The announcement seeks to source and fund early stage research, development, prototyping, and piloting of innovative ideas in the kidney space.

VA BAAs are competitive procedures in which proposals from outside groups are solicited and contracts are awarded for research and development.

One in 6 veterans have chronic kidney disease and more than 13,000 veterans experience kidney failure each year, according to the VA's announcement. To address the need for innovation in kidney disease prevention, care coordination, and treatment, the BAA announced a competition cycle that seeks applications across the following primary topic areas:

- Kidney Disease Prevention and Treatment
- Data Science Advances to Improve Health Care of People with Kidney Disease
- Rehabilitation of Patients with Kidney Failure
- Education for People with or at Risk for Kidney Disease and/or their Caregivers

The VA is seeking solutions that can be developed, tested, and evaluated within a 12–24 month period that will consist of a Development Phase and a Field Test Phase.

No funding has been reserved for this BAA at this time; however, the VA intends to award multiple contracts and has established the following contract funding limits:

- Development Phase—maximum funding of \$250,000
- Field Test/Piloting Phase—maximum funding of \$500,000
- Combined Development Phase and Field Test/Piloting Phase—maximum funding of \$750,000 ●

METABOLIC ACIDOSIS IN CKD IS A SIGNIFICANT PREDICTOR OF ESRD

CLINICAL SCENARIO:

A 70 year old male with CKD stage 4 (eGFR 25 ml/min), hypertension (BP well controlled at 122/76), diabetes (controlled), proteinuria (managed with ACEi therapy, last UACR of 30 mg/g) and hyperlipidemia (managed with statin therapy). Laboratory studies show normal serum sodium, potassium, calcium, phosphorus and albumin.

What would be the ideal serum bicarbonate for this patient?

Using the 8 variable kidney failure risk equation,* here is the ESRD risk for this patient at different levels of serum bicarbonate:

Risk of Progression to Kidney Failure Requiring Dialysis or Transplantation		
Serum Bicarbonate (mEq/L)	2-year Risk (%)	5-year Risk (%)
17	9.2	26.9
23	6	18.2
26	4.8	14.9

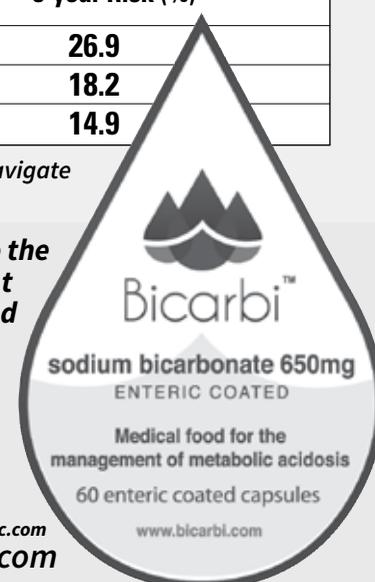
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Industry Spotlight

Baxter News in Peritoneal Dialysis, Mayo Partnership

Baxter International (Deerfield, IL) is developing a system to produce sterile solutions for peritoneal dialysis (PD) in patients' homes. The company said it received FDA guidance about the regulatory pathway for the system, which would be integrated into Baxter's Amia PD System with a small water-filtration device.

Baxter notes that the system for PD solutions plus the Amia PD system would be considered a combination product and was placed in the specific regulatory approval pathway the FDA uses when a product comprises a device plus a pharmaceutical product.

Baxter plans to begin a clinical trial in 2018, with regulatory submission to the FDA sometime in 2019. Laura Angelini, general manager of Baxter's Chronic Renal business, said, "These technology advancements have the potential to greatly enhance home dialysis therapy for pa-

tients by providing solution generation on-demand."

The Amia system is currently in about 1700 US homes where patients undertake home dialysis, and the system has provided a total of 250,000 dialysis treatments. The Amia system integrates with a telehealth platform called SHARESOURCE, allowing health care providers to manage patients remotely. With the addition of a pharmaceutical system for on-demand PD solution, physicians would have the flexibility to prescribe different dextrose concentrations as needed for each cycle that the solution dwells in the cavity before draining, usually three or four times, depending on a patient's needs, Baxter said.

The home solution system would reduce storage and weight handling requirements that come with traditional PD therapy. Patients typically must have space to store approximately a one-month supply of PD solutions—up to

40 boxes. Each box of PD solution weighs approximately 30 pounds and can be burdensome for patients and care givers.

In other Baxter news, the company recently partnered with Mayo Clinic, headquartered in Rochester, MN, in a five-year research and development partnership that will begin with a focus on kidney disease.

"We are excited about combining Mayo's clinical and research expertise with Baxter's ability to apply scale and innovation," Gianrico Farrugia, vice president of Mayo Clinic and CEO of Mayo Clinic in Florida, said in a statement. "We are confident that this collaboration will help accelerate discoveries, development, and application of life-changing therapies for patients." The agreement includes a five-year renewal option and the work will be performed in Mayo's Florida clinic in Jacksonville. ●

Royaldee Making Inroads in its CKD Niche

One year after US Food and Drug Administration (FDA) approval of Royaldee (calcifediol), Miami-based OPKO Health in June 2017 announced new agreements for the drug with several large Medicare Part D (prescription drug coverage) plan sponsors. The drug helps treat secondary hyperparathyroidism (SHPT) in patients with stages 3–4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D less than 30 ng/mL.

The FDA in 2017 issued a complete response letter, indicat-

ing deficiencies at OPKO's third-party contract manager, which were corrected. No issues were cited about the safety, efficacy, or labeling of Royaldee.

According to OPKO, "approximately 68% of all insurers have access to Royaldee. The company notes that it is on track to "reach 75% of all insured lives by year end." The company expects to expand its sales force into certain geographic areas as reimbursement is secured.

"We are particularly pleased to have Royaldee covered by an increasing number of Medicare Part D plan sponsors as a large percentage of SHPT patients with CKD stage 3 or 4 are Medicare beneficiaries," noted Phillip Frost, MD, chairman and chief executive officer (CEO) of OPKO. "The additional coverage recognizes the potential benefits of Royaldee in this patient population and should enhance our commercial efforts as we seek to fill the treatment void for this large unmet medical need." ●

Continued on page 19

Practice Pointers

Diabetic Kidney Disease

By Caroline Gluck, MD, and Katalin Susztak, MD, PhD

Kidney disease remains a leading cause of mortality in patients with diabetes

Diabetes is pandemic. Globally, diabetes affects up to half a billion people. In the US, one in 10 people have diabetes. Moreover, for Americans born in the year 2000, the lifetime risk of diabetes is a staggering 25% to 45%.

Diabetes care has significantly improved over the past few decades. Patient education, support, provider role changes, and telemedicine are consistently shown to improve glycemic indices. In response to the diabetes epidemic, the rate of diabetes drug approvals has accelerated. Since January 2013, nine new diabetes products have been approved, including a new inhaled insulin (Afrezza); a new DPP4 inhibitor, alogliptin (Nesina, Kazano, and Oseni); new inhibitors of the sodium glucose transporter 2 (SGLT2) transporter canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance); and a glucagon-like peptide 1 (GLP-1) receptor agonist, albiglutide (Tanzeum).

Despite improvements in diabetes care, the American Diabetes Association estimates that a person diagnosed with diabetes mellitus at age 50 years old dies 6 years earlier than a person without diabetes. Kidney disease shows the strongest correlation with mortality. During the past 20 years, kidney disease incidence only declined by 28% compared with a dramatic more than 70% decline in cardiovascular mortality. Better understanding of diabetic kidney disease (DKD) (1) will likely be essential to decrease not only the number of ESRD patients but also diabetes-associated mortality (2).

We need clarity in diagnosis and better prognostic markers for DKD

The gold standard diagnosis of DKD still relies on comprehensive histopathologic analysis of kidney biopsy samples. Recently, the American Renal Pathology Society (RPS) recommended a histopathologic-based staging (RPS classification) of DKD. The diagnosis is on the basis of the presence of glomerular basement membrane thickening (>395 nm in women and >430 nm in men). Greater than 25% expansion of the mesangial space is the most commonly used criterion to define class II disease according to this RPS classification. Nodular sclerosis is a highly specific but not very sensitive criterion to represent class III lesions. Finally, global sclerosis or class IV is mostly seen in patients with advanced disease (3).

Although biopsy remains the gold standard and the only specific criterion for diagnosis, in practice, DKD remains a clinical diagnosis. Most practitioners use the Kidney Disease Outcomes Quality Initiative guidelines: "In most people with diabetes, CKD should be attributable to DKD in the presence of: 1) macroalbuminuria (i.e., albumin to creatinine ratio [ACR] > 300) or microalbuminuria plus retinopathy, and 2) in people with type 1 diabetes, in the presence of microalbuminuria plus duration of diabetes longer than 10 years" (4). This recommendation is on the basis of old observational studies of patients with type 1 diabetes, in whom microalbuminuria preceded macroalbuminuria followed by functional decline, chronic kidney disease (CKD), and ESRD development. Although patients

with type 2 diabetes show much greater heterogeneity in their clinical manifestation, the same paradigm has been used to describe their disease manifestation.

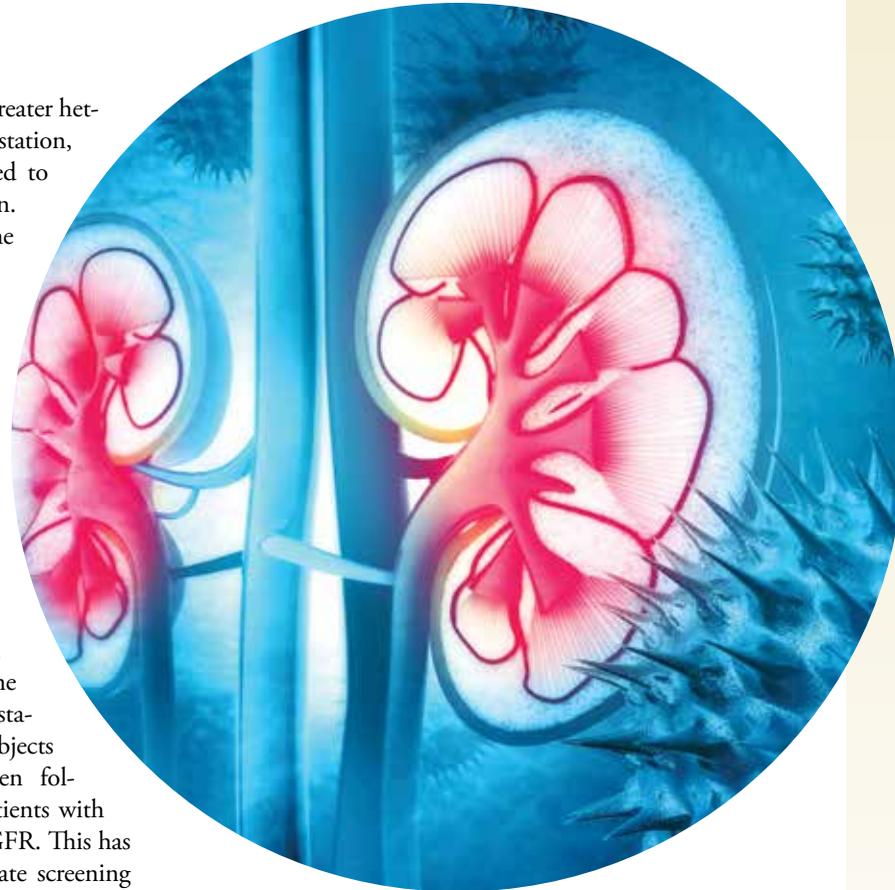
Reports originating from the 1990s began to indicate that the clinical manifestation of DKD is more complex. Large numbers of patients with type 2 diabetes and microalbuminuria, even those with biopsy-proven DKD, actually revert to normoalbuminuria. Moreover, this observation has been made independent of renin-angiotensin-aldosterone system (RAAS) blockade (5). As a consequence, it is being increasingly recognized that albuminuria and GFR decline might be complementary manifestations of DKD. Although some subjects manifest with albuminuria, often followed by GFR decline, other patients with diabetes only manifest with low GFR. This has led several investigators to advocate screening for both GFR and albuminuria to diagnose DKD.

There are significant regional differences in clinical practice patterns with regard to kidney biopsy for patients with diabetes. Studies from the Columbia Pathology Group indicate that urine sediment and serologies are actually poor predictors of histologic manifestations of DKD on biopsy (6). I believe that, until we develop better clarity of the clinical manifestations and markers of DKD, it is probably best to increase reliance on renal biopsies.

RAAS blockade and glucose control remain the mainstays of DKD therapeutics, but targets remain unclear

Hyperglycemia plays a key role in DKD development. Early studies from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study indicated that early tight glucose control decreases the incidence of diabetic nephropathy in patients with types 1 and 2 diabetes. We also learned that DKD can be reversed in select patients who undergo pancreatic transplantation. This critical observation translated to the recommendations to normalize serum glucose levels in patients with diabetes.

Despite this clear rationale, multiple large trials (the VA-DT, ACCORD, and ADVANCE trials) have now established that intensive glycemic control (to the level of almost normalization of glycohemoglobin levels) does not improve cardiovascular and renal outcomes (7). In these studies, targeting glycohemoglobin levels of 6.5% did not improve survival in patients with type 2 diabetes. A secondary analysis indicated a potential minor benefit for young and relatively healthy individuals. It remains unclear why improved glycemic control did not lead to improved outcomes. Many have speculated that diabetes induces an irreversible change at the cellular level, so-called metabolic memory, which leads to disease development.



Overall, most guidelines recommend keeping hemoglobin A1c (HbA1c) levels around 7%. Making matters more complicated, HbA1c measurements in patients with CKD are less precise owing to decreased red blood cell half-life in individuals with CKD.

In addition to glycemic control, inhibition of the RAAS remains the mainstay of DKD therapy. Both angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) effectively and significantly reduce albuminuria and slow the progression of DKD. However, combined therapies failed to show reductions in doubling of serum creatinine, dialysis, or death. This may be, in part, due to increased adverse effects, such as hyperkalemia, in patients who are on double therapy.

BP reduction is just one critical mechanism of action whereby ACEis and ARBs slow kidney disease progression. The usual goal is 130/80 mg Hg; unfortunately, there remains a lack of consensus among policy organizations regarding BP targets. In addition, results from several recent hypertension studies have shown improved outcomes with intensive BP control. These results may influence future organization and expert guideline recommendations for DKD BP goals.

The future could be bright: new therapies with promising outcomes

The year 2016 seemed to be a paradigm shift in DKD therapeutics. Several trials have shown positive outcomes using various newer diabetes drugs (Table 1). The LEADER Trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) investigated the effects of liraglutide, a glucagon-like peptide-1 (GLP-1) analogue shown to improve glycemic control in patients with diabetes (8). The trial was a double-blind, placebo-controlled study that included subjects with high cardiovascular risk. Results showed that fewer patients died from cardiovascular

causes in the liraglutide group (hazard ratio = 0.78). Nephropathy was analyzed as the secondary end point in this study. Kidney disease development was significantly lower (hazard ratio = 0.78) in the liraglutide-treated group compared with the placebo group, indicating a likely benefit of GLP-1 analogues in DKD. Further studies are needed to determine the effect and role of GLP-1 analogues in DKD, but these results are very encouraging.

More great news came with the positive outcome of two trials using newly registered drugs, empagliflozin and canagliflozin, which are inhibitors of the renal-specific SGLT2. SGLT2 is expressed in the proximal tubules, and genetic deletion of the transporter causes renal glucosuria without any other systemic effect. SGLT2 inhibitors block both glucose and sodium reabsorption in the proximal tubule and thereby result in significant weight loss as well as reduction of systemic BP. Further studies are needed to understand the mechanism of action of SGLT1 in renal physiology. However, one postulated mechanism is attributed to the tubule-glomerular feedback mechanism. Decreased proximal tubule reabsorption of sodium leads to increased distal tubule sodium delivery, resulting in increased GFR. Side effects of the drugs include urinary infection and ketoacidosis. Further studies are needed to clarify its benefits.

The first trial, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG), investigated the effect of empagliflozin on hard DKD outcomes (9, 10). Remarkably, the EMPA-REG trial reported a statistically significant

difference in doubling of serum creatinine, dialysis, and even death in patients treated with empagliflozin compared with controls. Patients treated with empagliflozin were 38% less likely to die from cardiovascular-related events. Interestingly, empagliflozin is a derivative of phlorizin, a dietary constituent found in a number of fruit trees.

Finally, Heerspink et al. (11) compared canagliflozin with glimepiride in a randomized, double-blind trial. They showed that patients receiving canagliflozin showed significantly slower GFR decline and decreased albuminuria (in patients with ACR \geq 30 mg/g), which were independent of improved glycemic control. Stay tuned for results from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial, which is aimed at answering whether this drug prevents ESRD and cardiovascular death. ●

Caroline Gluck, MD, is a Pediatric Nephrology Fellow in the Division of Nephrology at the Children's Hospital of Philadelphia, and Katalin Susztak, MD, PhD, is affiliated with the Renal Electrolyte and Hypertension Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

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Table 1: Diabetes drug trials with positive cardiovascular and renal outcomes

Drug	Mechanism	Trial	Outcome
Liraglutide	Glucagon-like peptide 1 analogue	Marso et al. (8): Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)	Decreased death from cardiovascular causes (HR = 0.78); decreased nephropathy
Empagliflozin	Sodium glucose transporter 2 inhibitor	Wanner et al. (9) and Zinman et al. (10): Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)	Decreased death from cardiovascular causes (38% relative risk reduction); decreased progression of nephropathy (HR = 0.61); decreased initiation of RRT (55% relative risk reduction)
Canagliflozin	Sodium glucose transporter 2 inhibitor	Heerspink et al. (11): Ongoing Trial: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Trial	Improved annual eGFR decline (0.5 mL/min per 1.73 m ² per year compared with 3 mL/min per 1.73 m ² per year in patients treated with glimepiride)

Abbreviations: eGFR = estimated GFR; HR = hazard ratio; RRT = renal replacement therapy.



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Fellows Corner

Ultrasound: Demand It.

By Nathaniel Reisinger, MD



Improvised hastily by a young physician to avoid the embarrassment from direct auscultation of a particularly buxom patient's chest, the stethoscope recently celebrated its 200th anniversary. After initial resistance, it has since become standard of care and a ubiquitous icon of the physician (1).

Technology has improved since the Napoleonic era, and more sophisticated devices are now available to augment the physical exam. Ultrasound was originally applied as sonar to hunt submarines in the First World War, but was quickly co-opted into the medical field. Early machines occupied entire rooms, but now powerful imaging devices are handheld and can be paired wirelessly with smartphones allowing ultrasound to be used on bedside rounds (2).

Point-of-care ultrasound (POCUS) has been used by obstetricians, cardiologists, and emergency medicine physicians for more than 20 years to answer focused questions and expedite clinical decision-making. In this time, POCUS has become increasingly incorporated into medical school curricula across the country. Some schools even provide point-of-care devices for all of their medical students; an entire generation of young physicians is training with concept of the ultrasound-stethoscope (2, 3).

Nephrologists have not fallen behind in this trend. Many already use ultrasound for dialysis catheter placement and percutaneous kidney biopsy. Interventional nephrologists are using ultrasound to look at fistula stenoses and renal intensivists have taken it a step further, bringing a suite of simple ultrasound tests to the bedside to diagnose undifferentiated shock.

Nephrology fellows are already demanding formal training in ultrasound. It was true in 2008 (4) and confirmed in a recent survey of fellows conducted in 2016. Whereas only 12% of fellows reported having formal ultrasound training, 44% wanted additional instruction in ultrasound interpretation (5).

Some uses of POCUS have intuitive value. For instance, immediate detection of hydronephrosis or a distended bladder in a new consult with acute kidney injury can rapidly change management and has the potential to improve outcomes.

Other uses of POCUS are of less obvious value. The volume exam is one of these. While no physical exam finding is entirely sensitive or specific for volume depletion or volume overload, and even central venous pressure has fallen out of favor as a marker for volume responsiveness, ultrasound for determining volume status is still in its nascency. Inferior vena cava (IVC) collapse as a marker of volume responsiveness is interesting, but it is of uncertain value as a marker of volume overload in dialysis patients (6).

One bright spot is lung ultrasound for quantification of extravascular lung water (EVLW) in patients with end stage renal disease (ESRD) on hemodialysis (HD). Fluid overload in these patients is a well-known yet underdiagnosed independent risk factor for adverse cardiovascular outcomes and death (7).

When applied to the lung, ultrasound was initially thought to be valueless as reverberation artifacts termed "A-lines"—viewed as serial horizontal reflections of the pleural line—obscured anatomic visualization of the lung parenchyma (Figure 1). It was soon realized that as alveoli fill with fluid and the alveolar interstitium thickens, this A-line pattern gives way to another pattern of hyperechoic lines, termed "B-lines," which radiate perpendicular to the pleural line (Figure 2).

The converse is also true, B-lines disappear dynamically during dialysis correlating with ultrafiltration volume (8). A total B-line score can be measured serially over 4, 8, or 28 intercostal spaces and this score correlates with EVLW as measured by thermodilution (9).

What's more, B-line score diagnoses subclinical pulmonary congestion more often than physical exam (10). As expected, B-line score correlates with cardiovascular outcomes, death, and even readmissions, the bane of fellows everywhere (11). A multi-center, prospective, randomized clinical trial (LUST trial) is ongoing in Europe using a B-line score directed ultrafiltration algorithm to mitigate fluid overload in patients on HD. This trial uses a well-validated web-based tutorial to ensure interobserver agreement among nephrology and cardiology attendings (12).

The first question I'm asked by attendings is how to bill for this. It's possible to bill for a limited ultrasound and for some a bedside ultrasound can add to critical care time to enhance relative value unit generation. Where I see lung ultrasound being most valuable is on the population level.

The LUST trial is powered to detect a 33% reduction in cardiovascular events. Such a powerful and cost-effective technique to improve patient outcomes is sure to garner attention from large dialysis organizations (LDOs). LDOs have the economies of scale needed to implement the technique broadly.

As our health system moves from fee-for-service payments toward performance-based metrics, LDOs stand to realize shared savings through ESRD Seamless Care Organizations (ESCOs) if they can demonstrate strategies to reduce cost to Medicare.

For the individual, the benefit of POCUS is clear: to answer focused clinical questions to enhance the physical exam. Basic competency in POCUS will become a necessary skill for practicing nephrologists as trainees from medical students to fellows start to demand training. ●

Nathaniel Reisinger, MD, is a fellow with the Renal-Electrolyte and Hypertension Division, Perelman School of Medicine at the University of Pennsylvania, Hospital of the University of Pennsylvania & Penn Presbyterian, Philadelphia.

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Figure 1. Lung ultrasound obtained using a curvilinear wireless ultrasound device paired with a smart phone. A-line pattern. Note the serial echogenic lines evenly spaced running parallel to the pleural line. This image depicts normal healthy lung obtained from the author.

Photo Credit: Nathaniel Reisinger, MD



Figure 2. Lung ultrasound obtained using a curvilinear wireless ultrasound device paired with a smart phone. B-line pattern. Note the echogenic lines emanating from the pleural line and running deep to the edge of the image. This image is obtained from a young woman who presented with dyspnea and was found to have pulmonary edema due to volume overload related to advanced lupus nephritis. Following dialysis and ultra-filtration, the B-line pattern reverted to an A-line pattern. Reproduced with patient's permission.

Photo Credit: Nathaniel Reisinger, MD

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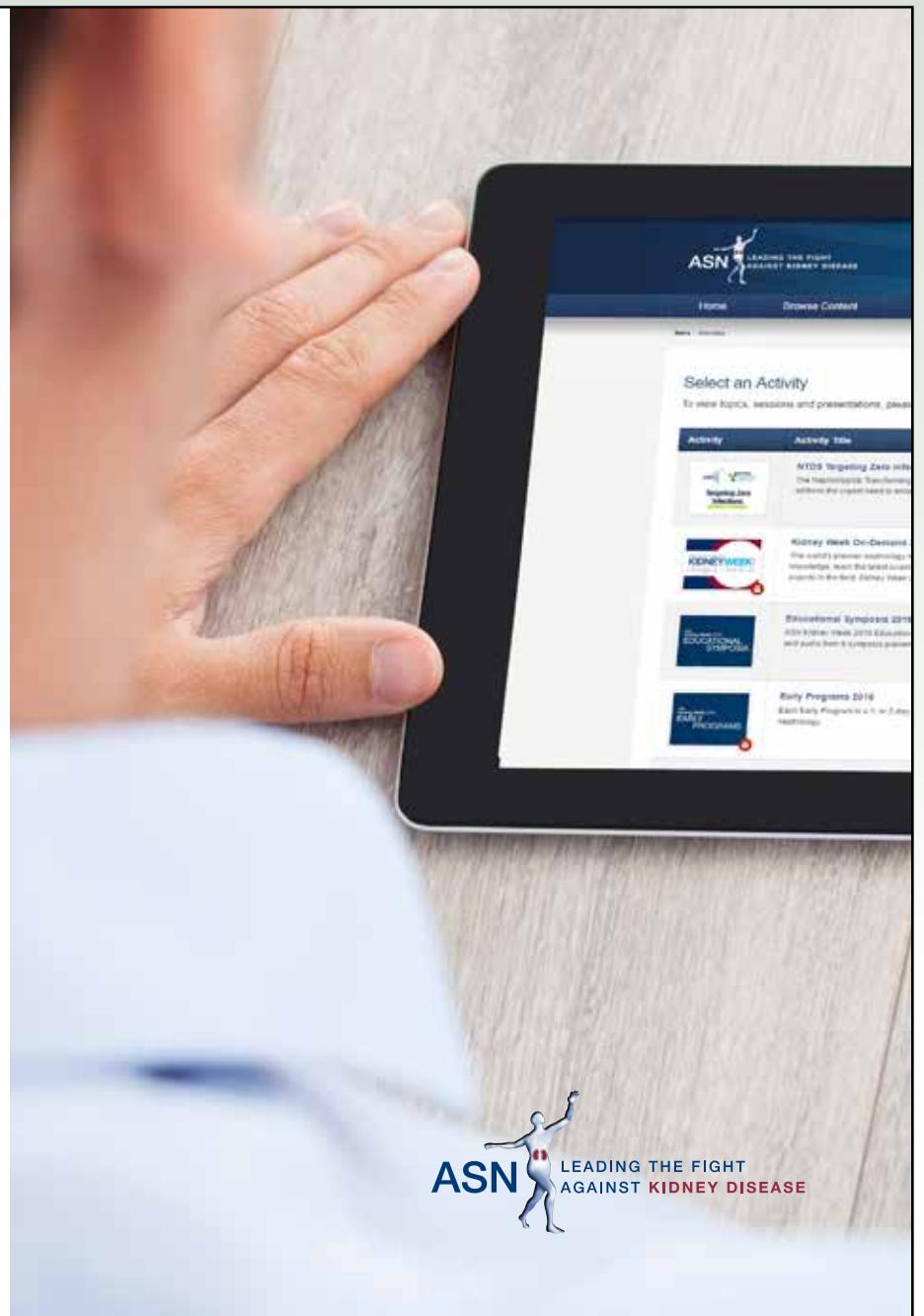
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Industry Spotlight

Distribution of Anemia Drug through Dialysis Centers

Vifor Pharma, a global specialty pharmaceuticals company in Zurich, Switzerland, that develops its own products and also partners with other companies, in May 2017 agreed to invest in and sell Akebia Therapeutics' Phase 3 anemia drug vadadustat through its network of dialysis centers. Vadadustat is an oral hypoxia-inducible factor (HIF) stabilizer in development for treatment of anemia associated with chronic kidney disease (CKD).

According to Fierce Biotech, Vifor is making a \$50 million (€45 million) investment in Akebia (in Cambridge, MA) at \$14 a share to secure the right to exclusively distribute vadadustat in the US through its network of Fresenius Medical Care dialysis facilities.

Akebia and Vifor will share the profits. The FDA still needs to approve vadadustat, and the drug also must be included in a bundled reimbursement model in order for Akebia to receive a \$20 million payment from Vifor.

The agreement gives Vifor another potential source of

revenue at a time when it is trying to organize as an independent company, Fierce Biotech reports, citing "three years of intense investment to cement its position."

"Vadadustat could represent a significant advancement in the treatment of renal anemia with the potential to establish a new treatment paradigm and overcome the limitations of current therapies for patients with chronic kidney disease," Vifor COO Stefan Schulze said. Schulze also foresees vadadustat as a therapy in hyporesponding patients, those for whom erythropoiesis-stimulating agents are ineffective.

The agreement with Akebia follows deals Vifor completed to add OPKO's Rayaldee (see above), Relypsa's Veltassa (a hyperkalemia treatment), and other drugs to its pipeline, Fierce Biotech notes.

Akebia is racing against FibroGen (San Francisco) to bring a HIF drug to market. In early June, Akebia prevailed over two patent claims made by FibroGen in the Opposition Division (OD) of the European Patent Office. ●

Quick test for PD patient infections

A new rapid, noninvasive test that can detect infections among peritoneal dialysis (PD) patients has earned the "Conformité Européene" (CE) mark. This mark means that a product may be marketed within the European Economic Area.

The regulatory submissions are supported by positive results from a Phase 3 S-TRAC, (Sunitinib Trial in Adjuvant Renal Cancer) study.

Mologic (Thurleigh, Bedfordshire, UK) has launched the point-of-care test PERiPLEX. The test was created for use in the home by PD patients or their caregivers, and takes 10 minutes for a result.

Peritonitis at the PD catheter insertion site traditionally has been detected when the patient or caregiver notices a change in the color, opaqueness, or aroma of PD fluid when it is being disposed. Patients with advanced infection may detect a change in their sense of well-being if there is an infection. If infection is suspected, a microbiologic test is ordered, Mologic says.

The company notes that traditional microbiological methods can take at least 24 hours for a result. Because of the rapid results from the PERiPLEX test, antibiotic treatment may begin sooner. Quick treatment is crucial in warding off further problems, including damage to the peritoneal membrane used in PD.

PERiPLEX finds two recognized markers of infection using a lateral flow immunoassay system. The markers are interleukin 6 (IL6) and matrix metalloproteinase 8 (MMP8).

The test includes a hypodermic needle that pierces a PD waste bag to gather and pass waste peritoneal dialysate from the patient to the test strip. When present in the patient's dialysate, MMP8 and IL6 are picked up by antibodies carried on the surface of gold nanoparticles. The nanoparticles carrying MMP8 or IL6 are then captured and appear as up to two separate lines across the strip, colored red in positive samples. The test is the first of several point-of-care tests that Mologic has in its pipeline, CEO Mark Davis said. ●

Drug updates for common and rare forms of RCC

Pfizer Inc. announced that the FDA and the European Medicines Agency (EMA) accepted the company's regulatory submission for label expansion of its renal cell carcinoma (RCC) drug, Sutent (sunitinib). The FDA's response is expected in January 2018.

The EMA validated the new indication request as a type II variation application for Sutent in the same patient population using it now. Sutent is already approved for advanced RCC, imatinib-resistant or intolerant gastrointestinal stromal tumors, and advanced pancreatic neuroendocrine tumors. The EMA validation is the initiation of the EMA's centralized review process.

The company is looking to expand Sutent's label for adjuvant treatment of adult patients at high risk of recurrent RCC after surgery. There are no approved therapies for patients with kidney cancer after surgery, Zacks.com wrote.

The regulatory submissions are supported by positive results from a Phase 3 S-TRAC, (Sunitinib Trial in Adjuvant

Renal Cancer) study. The S-TRAC trial comprised two cohorts: Global and China. The most recent results are from the Global cohort.

A rare form of renal cancer now has a drug treatment in Phase 2 study. In May 2017, Peloton Therapeutics (Dallas, TX) announced that patient dosing had begun in a Phase 2 study of treatment for patients with von Hippel-Lindau (VHL) disease-associated kidney cancer.

VHL is a hereditary form of cancer caused by the mutation in or deletion of the VHL gene, which can cause blood vessel cells in particular to grow, resulting in the tumors. These tumors can appear in up to 10 different areas of the body, including the kidneys, brain, and spine.

The orally administered drug, PT2385, targets hypoxia-inducible factor 2a, Peloton said in a statement. The study will evaluate the overall response rate of VHL disease-associated clear cell renal cell carcinoma (ccRCC) tumors in VHL patients. ●

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