

KidneyNews

January 2020 | Vol. 12, Number 1

Mediterranean Diet May Help Preserve Kidney Function in Transplant Recipients

By Tracy Hampton



Diet plays an important role in the health of patients with chronic kidney disease, even after transplantation. New research published in the *Clinical Journal of the American Society of Nephrology* indicates that following the Mediterranean diet may help kidney transplant recipients maintain normal kidney function.

The Mediterranean diet—which focuses on high intake of fish, fruit, vegetables, legumes, nuts, and olive oil together with lower intake of dairy and meat products—has been linked with reduced risks of cardiovascular disease and early death in the general population, and a reduced risk of diabetes after kidney transplantation; however, whether the diet is also associated with kidney function preservation in kidney transplant recipients is unknown.

To investigate, António Gomes-Neto, MD, of the University of Groningen, in the Netherlands, and his colleagues provided a food-related questionnaire to adult kidney transplant recipients from their medical center who had a functioning donor kidney for at least one year. After assessing answers to the questionnaire, which inquired about intake of 177 food items during the last

month, the researchers assessed adherence to the Mediterranean diet using a 9-point score.

During an average follow-up of 5.2 years, 119 of the 632 participants in the study experienced kidney function decline (76 of whom developed kidney failure). The Mediterranean Diet Score was inversely associated with kidney function decline and kidney failure. Each 2-point increase in the score was associated with a 29% lower risk of kidney function decline and a 32% lower risk of kidney failure.

“Increasing scientific evidence has demonstrated health benefits of the Mediterranean diet on cardiovascular and kidney health. In this study, we show that kidney transplant recipients with higher adherence to the Mediterranean diet are less likely to experience function loss of their kidney transplant,” Gomes-Neto said. “Moreover, this association was strongest in patients with greater proteinuria and patients transplanted more recently.”

The findings are important because, despite improvements in the survival of transplanted kidneys in the early years after transplantation, loss of kidney function

Continued on page 3 ➤

Desmopressin and Bleeding after Kidney Biopsy

Creatinine Level May Affect Risk

By Tim O’Brien

The clot-promoting drug desmopressin is commonly used with the goal of reducing bleeding complications in patients undergoing percutaneous kidney biopsy. But the evidence supporting this practice is weak—particularly in patients with decreased kidney function.

Desmopressin’s impact on bleeding risk after kidney biopsy depends on the patient’s creatinine level, reports

a paper in the open-access journal *BMC Nephrology* (1). In a retrospective analysis, Ambarish Athavale, MD, and colleagues of Cook County Health, Chicago, report that desmopressin is associated with fewer bleeding events in patients with elevated serum creatinine—but with a spuriously increased bleeding risk in those with lower creatinine values.

Continued on page 3 ➤

Inside

KDIGO

Our special section looks at KDIGO’s history, current guidelines, and vision moving forward.



Policy Update

KidneyX receives \$5 million in funding; OPO accountability and living donor incentives get boost.



Kidney Health Initiative

2019 was a banner year for kidney medicine, and KHI will continue to catalyze innovation in 2020.



Exercise and Kidney Disease

Can exercise training affect cardiovascular morbidity in patients with CKD?





KidneyNews

EDITORIAL STAFF

Editor-in-Chief: Richard Lafayette, MD
Executive Editor: Dawn McCoy
Design: Lisa Cain

EDITORIAL BOARD

Joseph Mattana, St. Vincent's Medical Center, Bridgeport, CT
Andrew King, MD, Scripps, San Diego, CA
Vivek Kumar, MD, Post Graduate Institute of Medical Education and Research, Chandigarh, India
Pascale Lane, MD, FASN, University of Oklahoma Health Sciences
Edgar V. Lerma, MD, FASN, University of Illinois – Chicago /Associates in Nephrology, SC
Gert Mayer, MD, Medical University of Innsbruck
Uday S. Nori, MD, Ohio State University Wexner Medical Center
Glenda Payne, MS, RN, CNN, Nephrology Clinical Solutions
Jeffrey Petersen, MD, Amgen
Amy Williams, MD, Mayo Clinic, Rochester, MN

ADVERTISING SALES

The Walchli Tauber Group
2225 Old Emmorton Road, Suite 201, Bel Air, MD 21015
443-252-0571 Mobile
214-704-4628 Phone
kelley.russell@wt-group.com

CLASSIFIED ADVERTISING

443-512-8899 *106
rhonda.truitt@wt-group.com

ASN COUNCIL

President: Anupam Agarwal, MD, FASN
President-elect: Susan E. Quaggin, MD
Past-President: Mark E. Rosenberg, MD, FASN
Secretary-Treasurer: Keisha L. Gibson, MD, MPH
Councilors: Barbara Murphy, MD, David H. Ellison, MD, FASN,
Prabir Roy-Chaudhury MD, PhD, Crystal A. Gadegebeku, MD, FASN

Executive Vice President: Tod Ibrahim
Senior Director of Communications: Robert Henkel

ASN Kidney News is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

ASN Kidney News is the authoritative source for analysis of trends in medicine, industry, and policy affecting all practitioners in nephrology. The statements and opinions expressed in *ASN Kidney News* are solely those of the authors and not of the American Society of Nephrology (ASN) or the editorial policy of the editors. The appearance of advertisements in *ASN Kidney News* is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. The American Society of Nephrology disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

The American Society of Nephrology is organized and operated exclusively for scientific and educational purposes, including enhancing the field of nephrology by advancing the scientific knowledge and clinical practice of that discipline through stimulation of basic and clinical investigation, providing access to new knowledge through the publication of journals and the holding of scientific meetings, advocating for the development of national health policies to improve the quality of care for renal patients, cooperating with other national and international societies and organizations involved in the field of nephrology, and using other means as directed by the Council of the Society.

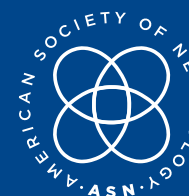
Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service,
American Society of Nephrology 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to
PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: \$12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include \$12 for *ASN Kidney News* subscription.

Copyright © 2020 All rights reserved

★ WINNER OF 2 DESIGN AWARDS ★



CORPORATE SUPPORTERS

ASN gratefully acknowledges the Society's Diamond and Platinum Corporate Supporters for their contributions in 2019.

DIAMOND LEVEL

AstraZeneca

Baxter

FRESENIUS
MEDICAL CARE

relypsa
A Vifor Pharma Group Company

TRICIDA

PLATINUM LEVEL

ALEXION®

Mallinckrodt
Pharmaceuticals

Otsuka

REATA
PHARMACEUTICALS

Mediterranean Diet

Continued from page 1

within 10 years still occurs in more than one-third of recipients. Identifying modifiable risk factors may help to improve organ survival. “The observational design of this study precludes us from drawing conclusions of causality, and residual confounding may exist despite adjustments for potential confounders in our analyses,” noted Gomes-Neto.

In addition, no conclusions can be made concerning any potential mechanisms behind the associations seen in the study, but the authors offer several hypotheses, including effects on oxidative stress, inflammation, endothelial dysfunction, dietary acid load, lipid profiles, protein intake, and glycemic index.

Casey Rebholz, PhD, who is an assistant professor of epidemiology at the Johns Hopkins Bloomberg School of Public Health and was not involved with the research, noted that the study is a useful contribution to a growing literature on diet as a modifiable risk factor for kidney disease outcomes.

“These findings align well with the new draft guidelines on nutrition in chronic kidney disease from the Kidney Disease Outcomes Quality Initiative and the Academy of Nutrition and Dietetics, which recommend the Mediterranean diet for chronic kidney disease patients who are not on dialysis,” Rebholz said. “This study provides evidence to support the extension of this recommendation to kidney transplant recipients.”

The article, entitled “Mediterranean Style Diet and Kidney Function Loss in Kidney Transplant Recipients,” will appear online at <http://cjasn.asnjournals.org>. ■

Desmopressin and Bleeding

Continued from page 1

“Desmopressin should not be used routinely prior to percutaneous kidney biopsy in patients at low risk for bleeding but should be reserved for patients who are at high risk for bleeding,” the researchers write.

Desmopressin before kidney biopsy: Which patients do (and don't) benefit?

Athavale is a nephrologist and director of clinical research at Cook County Health. His coauthors are Hemant Kulkarni, MD, of M&H Research, San Antonio, Texas; and Cagil D. Arslan, MD, and Peter Hart, MD, of Cook County Health.

Their study included 269 patients who underwent percutaneous kidney biopsy at the authors' urban public hospital from 2014 through 2018. All patients had available data on bleeding time; patients with bleeding time over 10 minutes, platelet counts under 50,000, or evidence of coagulopathy were excluded from the analysis. Indications for biopsy (nonexclusive) included nephritis in 122 patients, nephrotic syndrome in 122, and chronic kidney disease in 85. Biopsy was performed on an emergency basis in 56 patients.

At the discretion of the nephrologist performing the biopsy, 37.17% of patients received desmopressin (0.3 µg/kg IV). There were some significant differences in patient characteristics, including potential risk factors for bleeding events: Patients receiving desmopressin had lower baseline hemoglobin, lower platelet count, lower estimated glomerular filtration rate, higher bleeding time, higher blood urea nitrogen, and higher serum creatinine.

Athavale and colleagues looked at whether desmopressin achieved the goal of reducing bleeding risk, and whether this effect differed for patients with decreased versus normal kidney function. The primary outcome was a composite of a 1 g/dL or greater decrease in hemoglobin, gross hematuria, and need for angiogram or red blood cell transfusion. Overall, patients in the desmopressin group had a higher rate of bleeding events: 59.46%, compared to 31.75% in those who did not receive desmopressin.

A propensity score was generated to account for variables that differed between groups. In this analysis, the odds of postbiopsy bleeding were nearly four times higher in patients receiving desmopressin: odds ratio 3.88. Most of the difference was related to higher rates of decreased hemoglobin (44.14% versus 18.96%) and hematoma (18.02% versus 15.17%) in desmopressin-treated patients. Rates of gross hematuria and need for red blood cell transfusion were similar between groups.

On subgroup analysis, two factors contributed to the desmopressin-related increase in bleeding events: high baseline eGFR and low serum creatinine. None of the other factors analyzed—including gender, emergent versus elective biopsy, acute kidney injury, diabetes, hypertension, or bleeding time—were significantly related to bleeding risk.

For patients with high baseline creatinine (1.8 mg/

dL or greater), there was a trend toward reduced bleeding complications after desmopressin administration: OR 2.11 (95% confidence interval 0.87 to 5.11). In contrast, administration of desmopressin to patients with low baseline creatinine (less than 1.8 mg/dL) was associated with a large increase in bleeding risk: OR 9.2 [95% confidence interval 2.95 to 31.96].

“This increased odds of bleeding was driven mainly by a drop in hemoglobin in patients with relatively preserved kidney function,” Athavale said. “Because these patients did not need blood transfusion or angiographic embolization and the absolute magnitude of hemoglobin drop was small, we felt that this decrease in hemoglobin reflected dilution effect after desmopressin administration and not true bleeding from kidney tissue.”

New questions on routine desmopressin before kidney biopsy

Bleeding is the most frequent complication of percutaneous kidney biopsy and is more common in patients with decreased kidney function. Several abnormalities may contribute to platelet dysfunction in patients with kidney disease. The rationale for using desmopressin is to improve platelet aggregation by increasing release of von Willebrand factor.

Desmopressin should not be used routinely prior to percutaneous kidney biopsy in patients at low risk for bleeding but should be reserved for patients who are at high risk for bleeding.

“However, there is sparse data to support routine use of desmopressin, and it is not known if there is a subset of patients who will benefit the most from administration of desmopressin,” Athavale and coauthors write.

Some studies have reported lower bleeding risk in patients receiving desmopressin. In a 2004 study, Manno et al. reported a significant reduction in postbiopsy bleeding with desmopressin: 13.7% versus 30.5%, relative risk 0.45 (2). However, the only benefit was in the number and size of hematomas, with no significant effect on hard endpoints such as transfusion and angiographic intervention.

In a registry study, Peters et al. found a lower overall rate of complications (3.4% versus 8.4%, odds ratio 0.39) with desmopressin before native kidney biopsy in patients with serum creatinine over 150 µmol/L, particularly in women (3).

However, other studies have yielded conflicting results. A recent retrospective study by Lim et al. found no significant difference in bleeding risk for patients who did and did not receive desmopressin (15.0% vs. 13.3%) (4).

However, these authors observed a sharply increased risk of severe hyponatremia in patients receiving desmopressin: 10.7% versus 3.0%, adjusted odds ratio 4.02. Athavale and colleagues found no episodes of symptomatic hyponatremia, nor any other adverse events or side effects attributable to desmopressin.

In a study in *CJASN*, Moledina et al. found an 8% rate of transfusion, a 7% rate of hematoma, and a 2% rate of angiographic intervention in a cohort of 256 patients undergoing kidney biopsy (5). Hospitalized patients were at higher risk of complications; other risk factors included lower platelet count, female sex, and higher blood urea nitrogen (BUN). In this analysis, desmopressin was associated with a lower risk of transfusions after controlling for BUN level: odds ratio 0.24.

The new study suggests that desmopressin reduces post-biopsy bleeding in patients with elevated serum creatinine (1.8 mg/dL) or higher but is not useful in patients with normal creatinine levels. Athavale and colleagues note that most of the desmopressin-related increase was driven by an increase in postbiopsy hemoglobin, which doesn't necessarily reflect true bleeding from the kidney. However, a drop in hemoglobin may lead to additional and unnecessary testing, leading to increased costs and patient anxiety. The authors add that desmopressin has been linked to other adverse events, including increased thrombotic risk when given to reduce bleeding risk in non-uremic patients undergoing major cardiovascular surgery.

Athavale and colleagues note some strengths of their study, including the inclusion of many patients with common risk factors: elevated serum creatinine in about 70%, high body mass index in 40%, and acute kidney injury in 4%. The experience reflects contemporary kidney biopsy practice. All procedures were performed using an 18-gauge biopsy needle; the findings may not be applicable to biopsies performed using a 16-gauge needle.

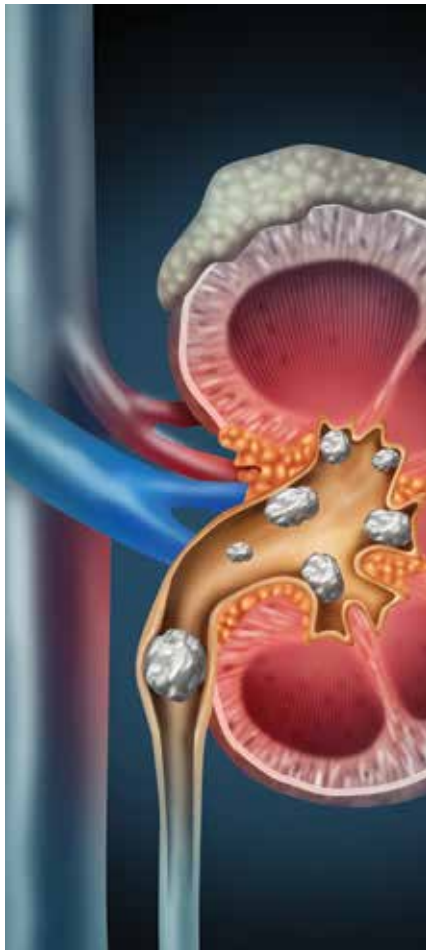
These limitations, together with the mixed findings and sparse evidence on bleeding risk associated with kidney biopsy in general and the effects of desmopressin in particular, highlight the need for definitive studies of assessing and reducing bleeding risk. Athavale and coauthors conclude, “A randomized trial is needed to further evaluate the efficacy and safety of desmopressin in high-risk patients.” ■

References

1. Athavale A, et al. Desmopressin and bleeding risk after percutaneous kidney biopsy. *BMC Nephrol* 2019; 20:413. doi: 10.1186/s12882-019-1595-4.
2. Manno C, et al. Predictors of bleeding complications in percutaneous ultrasound-guided renal biopsy. *Kidney Int* 2004; 66:1570–1577.
3. Peters B, et al. Desmopressin (Octostim®) before a native kidney biopsy can reduce the risk for biopsy complications in patients with impaired renal function: a pilot study. *Nephrology (Carlton)* 2018; 23:366–370.
4. Lim CC, et al. Desmopressin for the prevention of bleeding in percutaneous kidney biopsy: efficacy and hyponatremia. *Int Urol Nephrol* 2019; 51:995–1004.
5. Moledina DG, et al. Kidney biopsy-related complications in hospitalized patients with acute kidney disease. *Clin J Am Soc Nephrol* 2018; 13:1633–1640.

Policy Update

KidneyX Receives \$5 Million in Funding to Spur Innovation



KidneyX Innovation Accelerator (KidneyX)—a public-private partnership between ASN and the US Department of Health and Human Services—would receive \$5 million in funding to continue its work to spur innovation in kidney care as part of the compromise US government spending package proposed in late 2019.

This first-time Fiscal Year 2020 funding for KidneyX came after months of advocacy by ASN and its members and as the innovation accelerator recently opened the second phase of Redesign Dialysis and announced the intent to launch a prize focused on the development of an artificial kidney.

Redesign Dialysis Phase 2 challenges participants to build and test prototype solutions, or components of solutions, that can replicate normal kidney function or improve dialysis access. Up to three winners will be awarded \$500,000 each. Submissions to the prize challenge are due at 5 p.m. EST on January 31, 2020, and awardees will be announced by May 2020.

Among the prototype solutions KidneyX is looking for in Redesign Dialysis Phase 2 are blood filtration, electrolyte homeostasis, volume regulation, toxin removal and secretion, filtrate drainage, and dialysis access.

To further advance innovation in the field, KidneyX issued and received comments on a Request for Information (RFI), now closed, about an Artificial Kidney Prize being put forth in order to fulfill the goals set by KidneyX and Section 6 of the Executive Order on Advancing American Kidney Health. The Arti-

ficial Kidney Prize intends to build on Redesign Dialysis and to advance the development of an artificial kidney that can replace physiological kidney function to sustain life and improve patient quality of life. KidneyX will make changes to the Artificial Kidney prize announcement based on constituents' feedback to the RFI, and the submission period will be announced later this year.

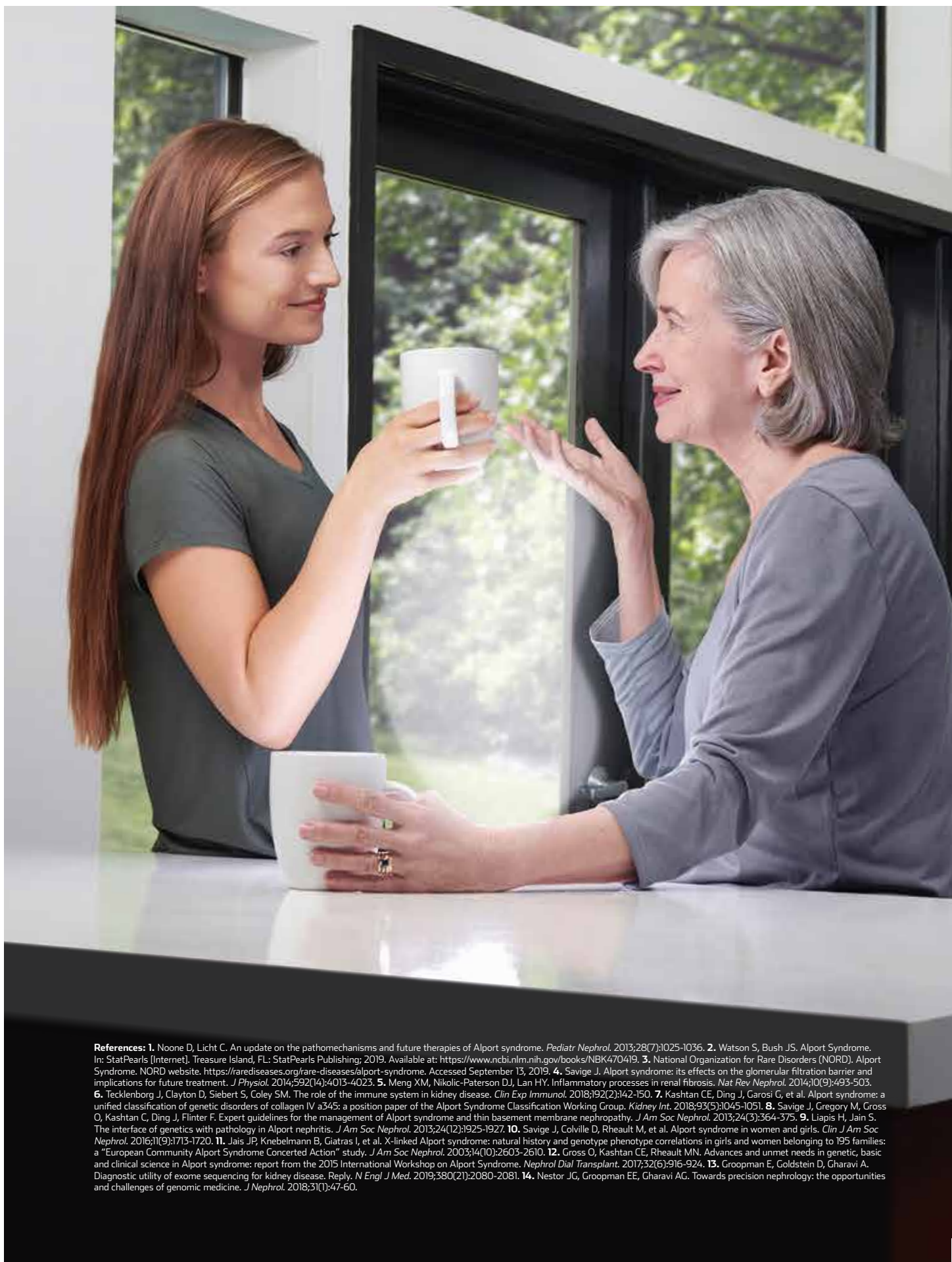
"This is a breakthrough moment for not only KidneyX but the entire kidney community," said ASN President Mark E. Rosenberg, MD, FASN, in response to the announcement of the KidneyX

appropriations funding. "For the first time Congress has called for and provided critical funding for prize competitions aimed at spurring innovation and improving kidney care for the 37 million Americans with kidney disease."

The \$5 million of funding for KidneyX in the compromise spending package represents the culmination of a year of rigorous advocacy and robust support for KidneyX funding by ASN members, the kidney care community, and members of Congress. In March, the Congressional Kidney Caucus—led by Reps. Suzan DelBene (WA) and Larry Bucshon

(IN)—and nearly 60 members of Congress signed a letter encouraging House appropriators to fund KidneyX, and a similar letter led by Sens. Todd Young (IN) and Ben Cardin (MD) urged Senate appropriators to do the same. Securing KidneyX funding has also been the primary focus of numerous policy initiatives by ASN, including Kidney Health Advocacy Day, as reported by Kidney News Online earlier this year.

The comprise funding package passed the House on Tuesday, December 17, and President Trump was expected to sign the agreement into law. ■



References: 1. Noone D, Licht C. An update on the pathomechanisms and future therapies of Alport syndrome. *Pediatr Nephrol*. 2013;28(7):1025-1036. 2. Watson S, Bush JS. Alport Syndrome. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK470419>. 3. National Organization for Rare Disorders (NORD). Alport Syndrome. NORD website. <https://rarediseases.org/rare-diseases/alport-syndrome>. Accessed September 13, 2019. 4. Savage J. Alport syndrome: its effects on the glomerular filtration barrier and implications for future treatment. *J Physiol*. 2014;592(14):4013-4023. 5. Meng XM, Nikolic-Paterson DJ, Lan HY. Inflammatory processes in renal fibrosis. *Nat Rev Nephrol*. 2014;10(9):493-503. 6. Tecklenborg J, Clayton D, Siebert S, Coley SM. The role of the immune system in kidney disease. *Clin Exp Immunol*. 2018;192(2):142-150. 7. Kashtan CE, Ding J, Garosi G, et al. Alport syndrome: a unified classification of genetic disorders of collagen IV α345: a position paper of the Alport Syndrome Classification Working Group. *Kidney Int*. 2018;93(5):1045-1051. 8. Savage J, Gregory M, Gross O, Kashtan C, Ding J, Flinter F. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. *J Am Soc Nephrol*. 2013;24(3):364-375. 9. Liapis H, Jain S. The interface of genetics with pathology in Alport nephritis. *J Am Soc Nephrol*. 2013;24(12):1925-1927. 10. Savage J, Colville D, Rheault M, et al. Alport syndrome in women and girls. *Clin J Am Soc Nephrol*. 2016;11(9):1713-1720. 11. Jais JP, Knebelmann B, Giatras I, et al. X-linked Alport syndrome: natural history and genotype phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study. *J Am Soc Nephrol*. 2003;14(10):2603-2610. 12. Gross O, Kashtan CE, Rheault MN. Advances and unmet needs in genetic, basic and clinical science in Alport syndrome: report from the 2015 International Workshop on Alport Syndrome. *Nephrol Dial Transplant*. 2017;32(6):916-924. 13. Groopman E, Goldstein D, Gharavi A. Diagnostic utility of exome sequencing for kidney disease. Reply. *N Engl J Med*. 2019;380(21):2080-2081. 14. Nestor JG, Groopman EE, Gharavi AG. Towards precision nephrology: the opportunities and challenges of genomic medicine. *J Nephrol*. 2018;31(1):47-60.

Trump Administration Proposes Measures to Overhaul Organ Procurement and Incentivize Living Donors

ASN Advocacy Efforts Bear Fruit

Making more organs available by strengthening the accountability of organ procurement organizations (OPOs) and removing financial barriers to living organ donation are the aims of two proposed rules released by the US Department of Health and Human Services (HHS) in December 2019.

Increasing the availability of organs for transplantation and supporting living donors have been long-standing priorities of

ASN. The society has called for the use of objective and verifiable metrics to assess OPO performance in several communications to the Centers for Medicare & Medicaid Services (CMS) and supported legislation by Sen. Todd Young (IN) that establishes similar practices. ASN has similarly advocated for the expansion of assistance offered to living donors, who often face steep financial barriers to being an organ donor.

The proposal for OPOs would improve current methods of measuring OPO performance by using “objective and reliable data, incentivize OPOs to ensure all viable organs are transplanted, and hold OPOs to greater oversight while driving higher OPO performance,” stated CMS, which contracts with and funds OPOs. Currently, OPO performance is measured using non-standardized and self-reported data, mak-

ing it hard to differentiate between high- and low-performing OPOs and determine areas for improvement.

To further encourage the dissemination of best practices among OPOs, CMS has proposed that all OPOs must meet the donation and transplantation rate of the top 25% of OPOs in a process that is transparent to the public. CMS estimates that “if all OPOs were to meet both the donation and transplantation rate measures in their donation service area, the number of annual transplants would increase from about 32,000 to 37,000 by 2026, for a total of almost 15,000 additional transplants during [the time between finalization of the proposed rule in 2022 and 2026],” according to an agency release. In addition, OPOs would be evaluated each year throughout their four-year recertification cycle, instead of at the four-year mark, as is currently the case, allowing for earlier identification of opportunities for improvement.

“Today’s tremendous news truly transforms the landscape for kidney patients, providing hope and a path to positive change for the future,” said Michelle A. Josephson, MD, FASN, transplant nephrologist and incoming ASN Policy and Advocacy Committee chair. “Bringing transparency to organ procurement organizations’ performance opens the door to improving transplant availability and access for patients.”

“This is a strategy that will help increase the number of kidneys available to patients,” said Richard A. Knight, president of the American Association of Kidney Patients (AAKP). “AAKP will continue to educate patients so they understand how the system works.” Knight also serves on the HHS Health Resources and Services Administration (HRSA) Scientific Registry of Transplant Recipients, which provides oversight for OPOs.

The Association of Organ Procurement Organizations (AOPO), representing the 58 federally designated OPOs across the country, responded in a statement: “The AOPO welcomes today’s rulemaking from CMS as an opportunity to drive meaningful changes that will increase the availability of organs for transplant and save more lives.”

The proposed rule for living kidney donors incentivizes donation by “expanding the scope of reimbursable expenses incurred by living organ donors to include lost wages and childcare and elder care expenses incurred by a primary caregiver,” according to HRSA, which issued the rule.

Many of the proposed changes would not take effect until 2022, but they garnered high praise from the kidney community.

“These changes are great for nephrology and, more importantly, are a tremendous boost for patients, their families, and potential American donors,” said ASN President Mark E. Rosenberg, MD, FASN. “Living donors literally give the gift of life when they donate a kidney and they deserve our society’s complete support. Today’s proposal to reimburse their lost wages and help with child and elder care costs during donation are long overdue.” ■

It’s time for kidney talk

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

Incurable disease

- Alport syndrome (AS) is a **permanent, hereditary condition** responsible for a genetically defective glomerular basement membrane, causing chronic kidney inflammation, tissue fibrosis, and kidney failure¹⁻⁶
- Across the entire range of AS genotypes, **patients are at risk of progressing towards end-stage kidney disease (ESKD)**^{3,7,8}

Hidden signs

- **Patients often go undiagnosed**, as the clinical presentation of AS is highly variable and family history may be unavailable^{3,9-11}
- **Persistent, microscopic hematuria is the cardinal sign of AS** and should prompt immediate diagnostic investigation—particularly when combined with any family history of chronic kidney disease^{8,11,12}

Early action

- Expert guidelines published in the *Journal of the American Society of Nephrology* **now recommend genetic testing as the gold standard for diagnosing Alport syndrome**⁸
- Early AS detection via genetic diagnosis, and its ability to guide a patient’s treatment decisions, demonstrates the **powerful impact of precision medicine in nephrology**¹²⁻¹⁴

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

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

Learn more about Alport syndrome at
ReataPharma.com.



© 2019 Reata Pharmaceuticals, Inc. All Rights Reserved. US-NON-1900031 10/19

Delivering on the Opportunities of 2019

How the Kidney Health Initiative Will Provide Innovation for People with Kidney Disease

By Raymond C. Harris, MD, FASN

Nephrology has constantly fought against, and sometimes succumbed to, a narrative of decline and stagnation. There is a complaint that new therapies are not being developed or approved, there has been a paucity of successful clinical trials, and in-center dialysis remains the standard of care for kidney failure. It is time to put this negative narrative to rest. Over the past year, I have had the privilege of leading the Kidney Health Initiative (KHI) and from that vantage point have seen firsthand that today is a new day for innovation in kidney diseases.

Yes, many challenges remain for our specialty, but the actions of the federal government and the kidney community over the past year give me confidence that kidney health professionals today operate in a new world of possibilities.

The *Advancing American Kidney Health* initiative set the priorities for a renaissance in our field. Never before had the federal government signaled such concern for the state of kidney care or proposed such bold solutions to its problems. Promoting prevention, providing alternatives to dialysis, and increasing transplantation rates are all goals that KHI supports. As a public-private partnership with the US Food and Drug Administration (FDA), KHI is in a unique position to do the translational work necessary to deliver on the promises of *Advancing American Kidney Health*.

The kidney community was primed to take advantage of this new environment. As the largest consortium in the kidney community, with over 100 member organizations, KHI observes and leverages the contributions that every stakeholder group makes to catalyzing innovation. This past year, I have seen every member organization engage in new activities and renew investments into bringing new drugs and devices to people living with kidney diseases.

The year 2019 is filled with examples (Figure 1). Neph-Cure Kidney International is investing in a clinical trial discovery tool for glomerular diseases and matching people with glomerular disease with specialists and clinical trials. In the last two years, the National Kidney Foundation (NKF) hosted patient-focused drug development meetings with the FDA on Alport syndrome and IgA nephropathy. Additionally, NKF is developing a first-of-its-kind patient registry for people living with kidney diseases. Diabetic kidney disease received increased attention this year because of the results of the CREDENCE trials. The possibilities of

SGLT2 inhibitors led the American Society of Nephrology (ASN) to establish the Diabetic Kidney Disease Collaborative to help prepare kidney health professionals to use these new drugs. In total, 23 pharmaceutical companies that are KHI members are conducting clinical trials today.

Today, the kidney community is benefiting from years of KHI investment into catalyzing innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases (Table 1). This investment has resulted in a positive impact on the quality and quantity of clinical trials in kidney disease since its founding.

That impact is in part a result of the projects we conduct with volunteer subject matter experts from across the community to catalyze drug and device development. KHI has four ongoing projects related to catalyzing drug development that address a variety of topics:

- 1 **Overcoming Barriers to Involving Kidney Patients in Cardiovascular Trials**
Many people living with kidney disease are unaware of their associated risk of cardiovascular disease. This project addresses barriers and identifies innovative solutions to involving people living with kidney diseases in cardiovascular clinical trials.
- 2 **Endpoints for Clinical Trials in FSGS**
This project is working to provide information about currently accepted endpoints for FSGS trials and exploratory endpoints that, with further research, could potentially be used in future trials for innovative new therapies.
- 3 **Endpoints for Clinical Trials in Primary and Enteric Hyperoxaluria**
This project is evaluating potential surrogate endpoints for these rare kidney diseases that could provide sponsors with the information needed to accelerate drug development in this area.
- 4 **Pediatric Drug Development**
This project is developing recommendations for fostering drug development in children with kidney diseases and has launched a clearing house to identify available sites and refer sponsors to expert consultants to conduct feasibility assessments, assist with pre-protocol development, and conduct protocol reviews for pediatric clinical trials.

This year KHI also completed a project that identified surrogate endpoints for clinical trials in IgA nephropathy, the most common form of glomerular disease worldwide.

KHI's insights into device development fall into three interconnected clusters. The first is technology roadmapping. This is a strength for KHI because of its unique ability to convene disparate stakeholder groups and experts from across the community. The keystone output in this cluster is the *Technology Roadmap for Innovative Approaches to Renal Replacement Therapy* released in 2018 and considered a foundation for future efforts to develop an artificial kidney. The *Innovations in Fluid Management* report, released in the fall of 2019, was the first KHI output that could be considered a supplement to the first Roadmap. It extended the conceptual framework of the Roadmap to a specific area necessary for the development of an artificial kidney.

The second device development cluster is around the patient perspective. KHI's foundational contribution in this area is a 2015 workshop on patient engagement in device development that, among other impacts, informed FDA guidance for home hemodialysis. In 2019, KHI disseminated a Patient Edition of the Roadmap to help educate and inspire people with kidney diseases about future treatment options.

The final cluster is endpoints in device development. In 2017, KHI published a series of seminal papers on endpoints for vascular access devices, a critical technology area for the development of an artificial kidney. In 2019, KHI extended its endpoints work to patient-reported outcomes (PROs) projects for novel renal devices, muscle cramping, and vascular access.

Our insights and publications in drug and device development have placed KHI at the cutting edge of innovation during this historic moment. In the remaining two years of my term as co-chair, I plan on continuing to move innovation forward, to build on KHI's success, and to capitalize on the opportunities presented to the kidney community over the past year in four ways.

First, refocus KHI's project portfolio to tackle issues that are relevant to a broad spectrum of the kidney community. In 2020, KHI will continue to endorse and complete projects related to surrogate endpoints and clinical trial

Figure 1.

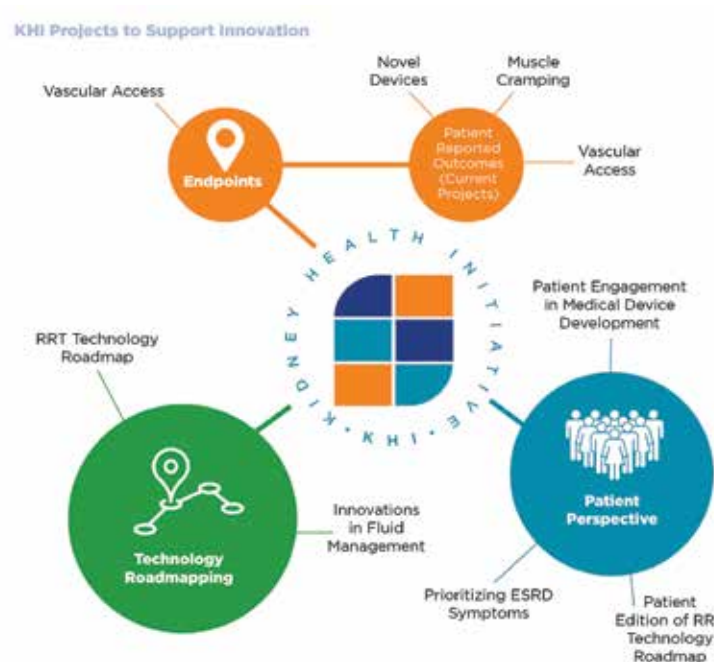


Table 1.

KHI Projects to Support Innovation			
Project Topic	Current Project	Workshop	Publication
Prioritizing ESRD Symptoms			
IgA Nephropathy Surrogate Endpoints			
Lupus Nephritis Surrogate Endpoints			
Cardiovascular Disease Trials			(Forthcoming)
FSGS Surrogate Endpoints			(Forthcoming)
Hyperoxaluria Surrogate Endpoints			(Forthcoming)
Pediatric Drug Development			(Forthcoming)

design, with a focus on barriers that impact a broad group of member organizations.

Second, support an on-study culture in kidney care. This is a new focus for KHI and ASN. I believe KHI has a role to play in supporting new and exciting clinical trials and developing innovative trial design. This year, ASN is rolling out a new organizational structure, part of which will be a center with programs addressing “Research, Discovery, and Innovation,” of which KHI will be a part. Research readiness is a primary focus of this center and will provide KHI more resources to have an impact on revolutionizing the clinical trial landscape.

Third, invest in technology roadmapping. As KidneyX continues to mature, KHI will have a role in identifying barriers that need to be overcome, disseminating guidance to innovators, and providing the intellectual foundation for prize competitions. This year, KHI is launching a new roadmapping project for AKI Biomarkers that will con-

vene experts from many stakeholder groups to outline the path forward for this important clinical area. Additionally, KHI recently announced a project extending the work of our original Roadmap to the issue of identifying endpoints and clinical trial design for innovative renal replacement therapy (RRT) products.

Last, KHI is committing to amplifying the patient perspective in 2020. During Kidney Week 2019, Health and Human Services Secretary Alex Azar II called out a new KHI project that will develop a patient preference survey for novel RRT devices. This project supports the *Advancing American Kidney Health* initiative and will provide the community a prioritization of benefits and risks of novel devices and additional patient preference information innovators can use to develop an artificial kidney.

Follow our progress on these goals at www.kidney-healthinitiative.org and on social media with #KidneyHealthInitiative.

Let’s not allow the cynicism of the old narrative to again become the norm in the kidney community. 2019 was a historic year and 2020 is our chance to deliver on the opportunities we have been handed. There are significant obstacles to be overcome, but the environment has never been more primed for change. KHI is available to help the community do the translational work necessary to make innovative therapies a reality for the people we serve. We have all seen too many of our patients die without new treatment options. Catalyzing innovation must no longer be just a catchphrase but an imperative to deliver new therapies for our patients. People living with kidney diseases have waited long enough. ■

Raymond C. Harris, MD, FASN, is the ASN Co-Chair for the Kidney Health Initiative and the Director of Research in the Division of Nephrology and Hypertension at the Vanderbilt University School of Medicine.

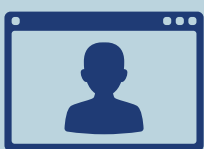
nephSAP

COMING SOON

Welcome to the **NEW** *nephSAP*. Experience the new platform and enhanced mobile-friendly design.

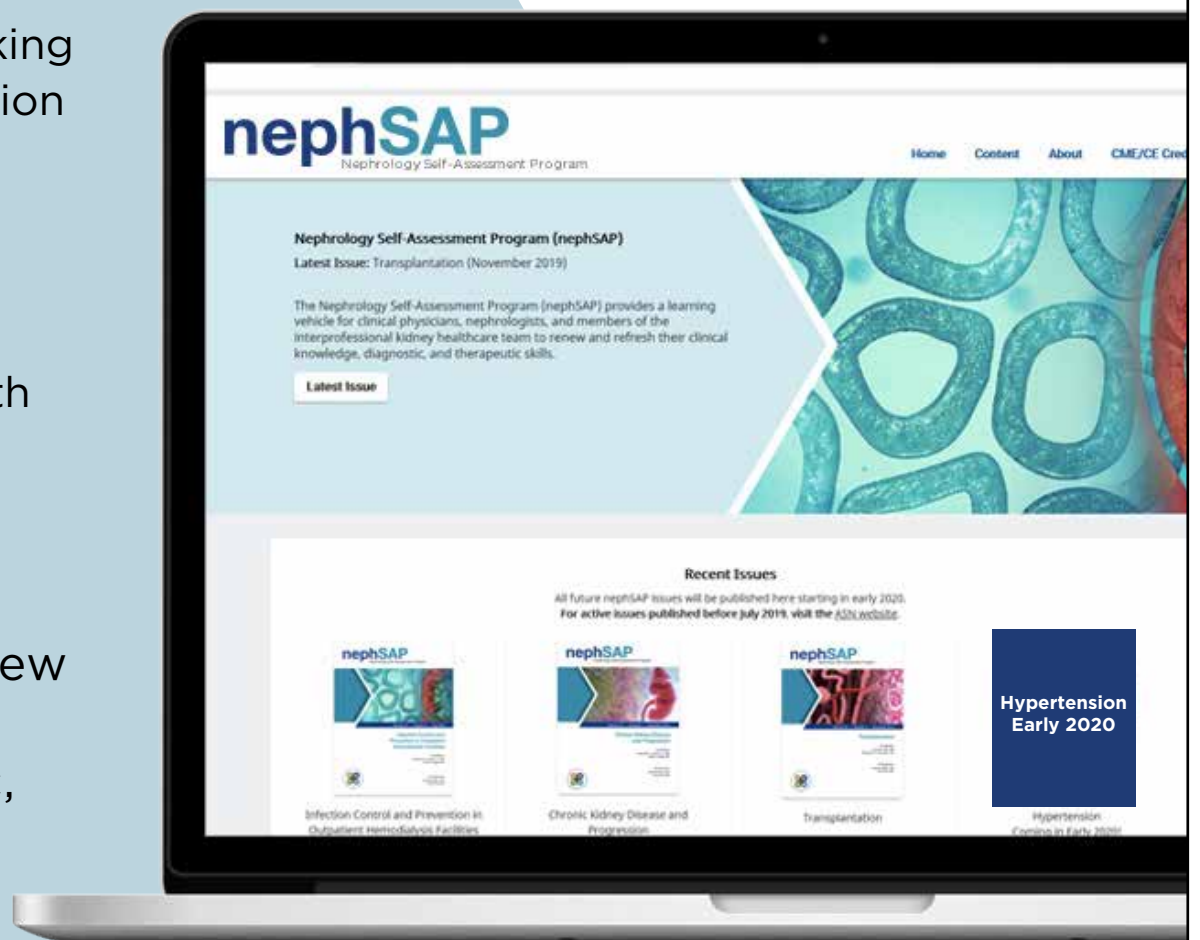



Social networking and collaboration tools



Personalized experience with *My nephSAP*

nephSAP provides a learning vehicle to renew and refresh clinical knowledge, diagnostic, and therapeutic skills. Rigorously assess your strengths and weaknesses in the broad domain of nephrology.





Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control¹

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

Indication

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

Limitations of Use:

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

 **Parsabiv™**
(etelcalcetide) Injection for
intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION



Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

Hypersensitivity

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

WARNINGS AND PRECAUTIONS

Hypocalcemia

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

QT Interval Prolongation and Ventricular Arrhythmia

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

Seizures

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

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

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

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

Worsening Heart Failure

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

Upper Gastrointestinal Bleeding

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

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

Adynamic Bone

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased ^a	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia ^b	0.2%	7%
Paresthesia ^c	1%	6%
*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group		
^a Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)		
^b Symptomatic reductions in corrected serum calcium < 8.3 mg/dL		
^c Paresthesia includes preferred terms of paresthesia and hypoesthesia		

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

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

Description of Selected Adverse Reactions

Hypocalcemia

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

Hypophosphatemia

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

QTc Interval Prolongation Secondary to Hypocalcemia

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

Hypersensitivity

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

Immunogenicity

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Data

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

Pediatric Use

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

Geriatric Use

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

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

OVERDOSAGE

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

AMGEN[®]

PARSABIV[™] (etelcalcetide)

Manufactured for:

KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.

One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: <http://pat.amgen.com/Parsabiv/>

© 2017 Amgen, Inc. All rights reserved.

ASN Kidney News gratefully acknowledges the editors of this special section, Kidney News Editorial Board member Edgar V. Lerma, MD, and KDIGO Chief Scientific Officer Michael Cheung, for their invaluable expertise in the preparation of this issue.

A Brief History of KDIGO: Now in Our Seventh Year of Independence

Since its founding in 2003, KDIGO has been inextricably linked with the development of global clinical practice guidelines in nephrology. Significant advances in guideline methodologic approaches and in our understanding of kidney disease pose new challenges on how best to synthesize and appraise the ever expanding data and distill expert guidance into guidelines that are most useful to clinicians. In the following series of articles, we present brief summaries of KDIGO's recent accomplishments and outline their vision plan for maintaining guidelines up-to-date and improving their knowledge translation.

By John Davis

KDIGO's history is a history of guidelines in nephrology. There were none in 1994 when a conference called Controversies in the Quality of Dialysis Care was held under the auspices of the National Kidney Foundation (NKF, United States). It was co-chaired by Dr. Gary Eknoyan. One recommendation from that event was the call for the development of nephrology guidelines. That thought resonated with various stakeholders, who provided funding and expertise to enable the NKF to develop evidence-based clinical practice guidelines. Four guidelines under the banner of the DOQI (Dialysis Outcomes Quality Initiative) were published in 1997.

Those guidelines made a major impression on American nephrologists and were used in everyday practice. The government data entity, the United States Renal Data System (USRDS), tracked areas covered by the guidelines and reported significant improvement in the uniformity of care. The NKF continued to develop guidelines, although Dr. Eknoyan amended the name to KDOQI (Kidney Disease Outcomes Quality Initiative) to better reflect on all aspects of chronic kidney disease (CKD) care rather than just dialysis care. Several more guidelines were produced between 1997 and 2002.

Publication of the Chronic Kidney Disease Guideline in 2002 strengthened the concept that guidelines should be developed globally, rather than country by country. Care was taken to vet this idea with non-American opinion leaders, and after 2 years of study, their opinions were enthusiastically positive. So, the concept for an international nephrology guideline body—KDIGO (Kidney Disease: Improving Global Outcomes)—was born. It was to be truly global, not just the expansion of an American effort. Thus, the organization was incorporated in Brussels and became a foundation in the public interest under Belgian law, with NKF continuing to provide management support.

KDIGO's first guideline on the management of hepatitis C in patients with CKD was published in 2008. It was followed by Mineral and Bone Disorders and Care of the Transplant Recipient in 2009. During these years KDIGO's other core program, Controversies Conferences, began to thrive. The format was established where 60 to 70 international experts were brought together to discuss and debate important issues that weren't totally resolved and these conferences were well known for not only providing clinical guidance in controversial areas but helped advance the fu-

Table 1.

KDIGO Guidelines published since independence	
Topic	Year
Evaluation and Management of Chronic Kidney Disease	2013
Lipid Management in Chronic Kidney Disease	2013
Evaluation and Care of Living Kidney Donors	2017
Diagnosis, Evaluation, Prevention and Treatment of CKD–MBD	2017
Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease	2018
Upcoming	
Evaluation and Management of Candidates for Kidney Transplantation	2020
Management of Diabetes and Chronic Kidney Disease	2020
Update: Management of Blood Pressure in Chronic Kidney Disease	2020
Update: Glomerulonephritis	2020
Update: Anemia	2021 (Initiating work)
Diagnosis, Evaluation, Management and Treatment of ADPKD	2021 (Initiating work)

KDIGO Controversies Conferences held since independence	
Topic	Year
Revisiting CKD–MBD	2013
Supportive Care in Chronic Kidney Disease	2013
ADPKD	2014
ADTKD (Consensus Conference)	2014
Cystinosis	2014
Iron Management in Chronic Kidney Disease	2014
Complement-Mediated Kidney Disease: C3G and aHUS	2015
Diabetes and Chronic Kidney Disease	2015
Fabry Nephropathy	2015
Understanding Kidney Care Needs and Implementation Strategies in Low- and Middle-Income Countries	2015
Challenges in Conducting Clinical Trials in Nephrology	2016
Chronic Kidney Disease and Arrhythmias	2016
Common Elements in Rare Kidney Diseases	2016
Gitelman and Tubulopathies	2016
Improving the Prognosis of Patients with Advanced Chronic Kidney Disease	2016
Blood Pressure in Chronic Kidney Disease	2017
Heart Failure in Chronic Kidney Disease	2017
Kidney Disease in the Setting of HIV infection	2017
Management and Treatment of Glomerular Diseases	2017
Coronary Artery & Valvular Disease and Chronic Kidney Disease	2018
Dialysis Initiation, Modality Choice, Access, and Prescription	2018
Onconeurology	2018
Potassium Homeostasis and Management of Dyskalemia	2018
Acute Kidney Injury	2019
Blood Pressure and Volume Management in Dialysis	2019
Early Identification and Intervention in Chronic Kidney Disease	2019
Nomenclature for Kidney Function and Disease (Consensus Conference)	2019
Optimal Anemia Management in Chronic Kidney Disease	2019
Upcoming	
Central and Peripheral Arterial Diseases in Chronic Kidney Disease	2020
Genetics and Kidney Disease	2020
Home Dialysis	2020
Novel Therapies for Treatment of Anemia in Chronic Kidney Disease	2020
Dialysis Innovation	2021
Role of Complement in Kidney Disease	2021
Management of Symptom-Based Complications in Dialysis	2021

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; aHUS, atypical hemolytic uremic syndrome; C3G, C3 glomerulopathy; CKD-MBD, chronic kidney disease-mineral bone disorder.

History of KDIGO

Continued from page 11

ture evidence base by identifying the key research agenda.

By 2009 KDIGO had become a global leader in nephrology guidelines designed to inform clinical decisions.

The economic downturn in 2009 and 2010 caused the NKF to rethink its priorities. One area to be cut back was global guidelines. This came at a time when KDIGO's reputation was growing. Two landmark Controversies Conferences were held during this time: Definition, Classification, and Prognosis in CKD, and Cardiovascular Disease in CKD.

KDIGO's Mineral and Bone Disorder guideline created CKD-MBD as a near-universal term and had major global impact, and work began on other new guidelines. In 2011 John Davis left the NKF but retained the title of Chief Executive Officer of KDIGO. A meeting was held in the Netherlands with Bert Kasiske, Kai-Uwe Eckardt, David Wheeler, and John to discuss KDIGO's future. The decision was made to go at it alone. Negotiations began to terminate KDIGO's management contract with the NKF, and plans were made for moving forward. John continued to manage KDIGO and recruited Danielle Green to join him. With great help from Dr. Yusuke Tsukamoto in Tokyo, some money was raised to bridge this critical period of transition.

KDIGO officially became an independent Belgian corporation on October 1, 2012. It had €19,000 in the bank. Bert and David were the co-chairs, with John and Danielle

as the staff. A small but excellent executive committee was recruited to provide governance and guidance. KDIGO then began a steady building process that was directed at sustaining its place in global nephrology.

To reassert the organization's standing in the nephrology community, KDIGO published four original guidelines in 2012. Two more guidelines came in 2013, along with two Controversies Conferences. Michael Cheung and Tanya Green were subsequently recruited to the staff, and efforts were made to bring all of KDIGO's operations into full compliance with Belgian regulations and standard nonprofit practices.

KDIGO's goal in those early years was simply to get better every day and to strengthen its independent status. Being self-governed, self-managed, and self-funded were important elements of KDIGO's growth. The guideline on the Evaluation and Care of Living Kidney Donors was the first to be wholly developed under its independence, as was the Controversies Conference on CKD-MBD: Back to the Future, and KDIGO has been remarkably active since then (Table 1).

KDIGO began an emphasis on implementation programs and developed a presence in major congresses, both globally and locally. New volunteers were brought in, and previous volunteers were recognized as members of the KDIGO global network. A reception in Philadelphia in 2015 attracted over 200 people. KDIGO is continuing to be innovative and transparent while experimenting with new technologies like electronic guideline publishing. Naturally, KDIGO also pays

more attention to updating its existing guidelines and is increasingly focusing on a more robust and streamlined guideline development process and methodology.

Corporate support has always sustained KDIGO's growth. While KDIGO does not solicit or accept funding for the development of guidelines or its updates, KDIGO has attracted several major sustaining partners which provide the resources needed to conduct all of its programs. KDIGO especially appreciates the long-term commitments of companies like Fresenius, Boehringer-Ingelheim, and AstraZeneca. KDIGO takes pride in our transparency and full disclosure policy while striving to enhance its conflict of interest safeguards.

KDIGO now has three guidelines in development at all times and holds four or five Controversies Conferences each year. Implementation presentations and tools, along with an improved website and app, are part of a concerted effort to make the work more accessible to clinicians everywhere. KDIGO's vision focuses on its core programs while seeking appropriate collaborations and strengthening its volunteer base.

Although still relatively young, KDIGO has come a long way. It has taken a few risks but remains dedicated to its only mission: to improve outcomes for patients. It is with this optimism and commitment that KDIGO builds on the past and looks toward the future with enthusiasm. ■

John Davis is Chief Executive Officer of Kidney Disease: Improving Global Outcomes.

New Guideline Update: Hepatitis C in Patients with Chronic Kidney Disease

By Michel Jadoul

The 2008 KDIGO guideline on the prevention, diagnosis, evaluation, and treatment of hepatitis C virus (HCV) infection in patients with chronic kidney disease (CKD) was the very first guideline produced by KDIGO. Since then, there have been dramatic changes in the field of antiviral treatments, which prompted a timely reassessment and publication of this guideline update in 2018 (1). The purpose of this short review is to summarize the key recommendations from this important guidance document.

As in the previous guideline edition, Chapter 1 addresses the detection and evaluation of HCV in CKD. It should be stressed that the guideline now recommends that all patients be screened once for HCV at the time of initial CKD evaluation. This new recommendation is based on multiple large observational studies that have consistently identified HCV positivity as a risk factor for adverse clinical outcomes, independently of classic CKD and cardiovascular risk factors. These adverse outcomes include CKD onset, rapid CKD progression, and development of ESKD and cardiovascular complications.

Recent evidence further shows that in patients with various causes of CKD, including diabetic nephropathy or nephrosclerosis, and thus not just HCV-associated membranoproliferative glomerulonephritis, HCV treatment is associated with delayed onset of CKD (2) and cardiovascular complications. The cost of a single immunoassay for HCV

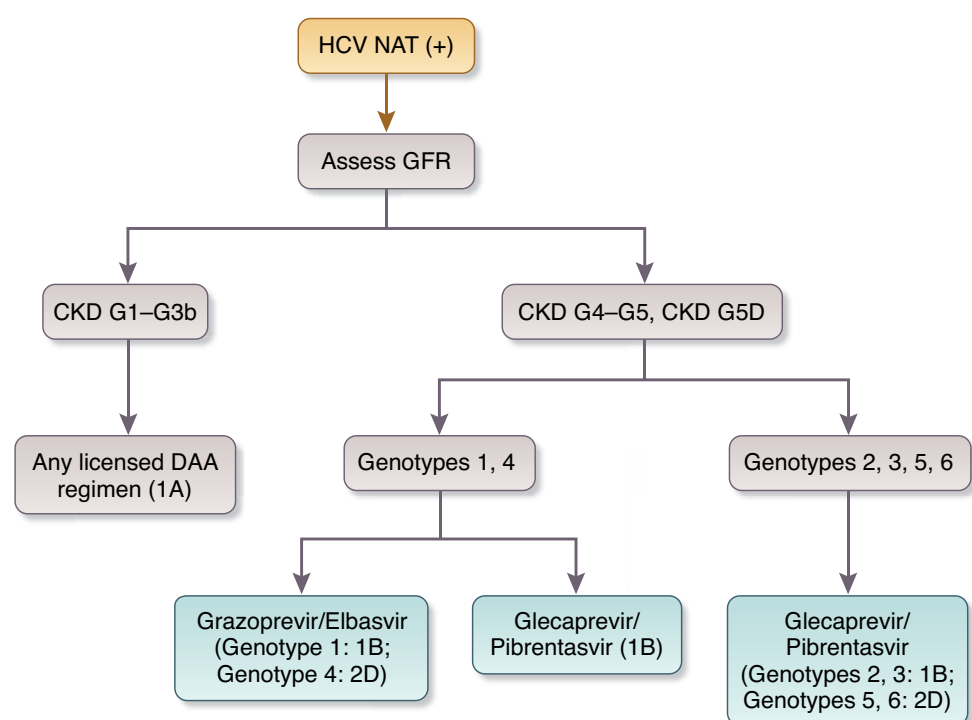
thus appears small in comparison with the potential clinical benefit(s). A second key change in this chapter is the recommendation to start investigating HCV-positive patients via non-invasive means such as transient elastography (e.g., FibroScan) and/or biochemical indexes. These have indeed been shown, even in late CKD patients including candidates for kidney transplantation, to accurately quantify noninvasively the extent of liver fibrosis. Thus, a liver biopsy is now required only if there is a high suspicion of another cause of liver disease than HCV, and/or if noninvasive results are discordant (1).

Chapter 2 addresses HCV antiviral treatments, also known as direct-acting antiviral agents (DAAs), which can

effectively cure HCV infections in more than 95% of cases over a course of 12 weeks. DAA treatments thus now become the rule rather than the exception in CKD patients as well, if life expectancy is reasonable (no uniform minimum threshold can be proposed, although a life expectancy of at least 12 months appears reasonable). As highlighted in Figure 1, certain DAA regimens can be used even in patients with an eGFR <30 mL/min per 1.73 m². Similarly, prevalent kidney transplant recipients can also be treated effectively and safely with DAA regimens (Figure 2), with careful attention to the level of immunosuppressive agents during DAA treatment so as to minimize the risk of drug–drug interactions.

Chapter 3 deals with the prevention of nosocomial HCV

Figure 1. Algorithm showing treatment scheme for chronic kidney disease (CKD) G1 to G5D



Recommendation grades (1–2) and strength of evidence (A–D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype. Pangenotypic sofosbuvir/velpatasvir-based regimens are not listed because they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However, FDA has recently indicated that no dose adjustments are required for these regimens in CKD patients including those on dialysis. These regimens may be considered pending their availability in various jurisdictions. Abbreviations: CKD G, chronic kidney disease GFR category; FDA, Food and Drug Administration; DAA, direct-acting antiviral agent; GFR, glomerular filtration rate; NAT, nucleic acid testing. Reproduced with permission from reference 1.

transmission within hemodialysis units. This risk remains significant, as shown by a very recent Dialysis Outcomes and Practice Patterns Study report (3). Thus, the guideline still recommends meticulous attention to hygienic precautions and regular auditing of infection control procedures. Also, in line with the 2008 KDIGO guideline and the recommendations by the United States Centers for Disease Control and Prevention, the guideline still does not advocate the use of dedicated dialysis machines for HCV-positive patients or the isolation of HCV-positive patients in a specific ward. These are indeed unnecessary and may tend to reduce the attention devoted to proper infection control practices.

Chapter 4 addresses the management of HCV before and after kidney transplantation. The key point here is that as a result of the ongoing opioid epidemic, there is currently a significant number of HCV-positive organs available for transplantation, whose acceptance by HCV positive recipients may markedly shorten their waiting time for a graft. This calls for a collaboration with transplantation centers in decisions about the timing of HCV treatment in potential candidates for a kidney transplant.

The decision to treat HCV before versus after kidney transplantation will therefore be dependent on the severity of liver disease (which may prompt a simultaneous kidney-liver transplantation in cases of decompensated cirrhosis) but will also be markedly influenced by the expected waiting time for a kidney graft, as detailed in Figure 3. Interestingly, recent evidence shows that HCV-negative recipients who are willing to accept HCV-positive organs may also undergo transplantation much more rapidly than otherwise and have good outcomes. However, given the unknown long-term safety of this approach, the KDIGO Work Group thought that this practice should remain strictly investigational pending further studies.

Chapter 5 discusses the management and treatment of HCV-associated glomerulonephritis. In patients with rapidly progressive glomerulonephritis, severe cryoglobulinemia or nephrotic syndrome, the guideline now recommends immunosuppressive treatment with rituximab in addition to DAA treatment. This recommendation is based on two randomized controlled trials, admittedly relatively small, demonstrating the efficacy and superiority of rituximab over alternative regimens (5).

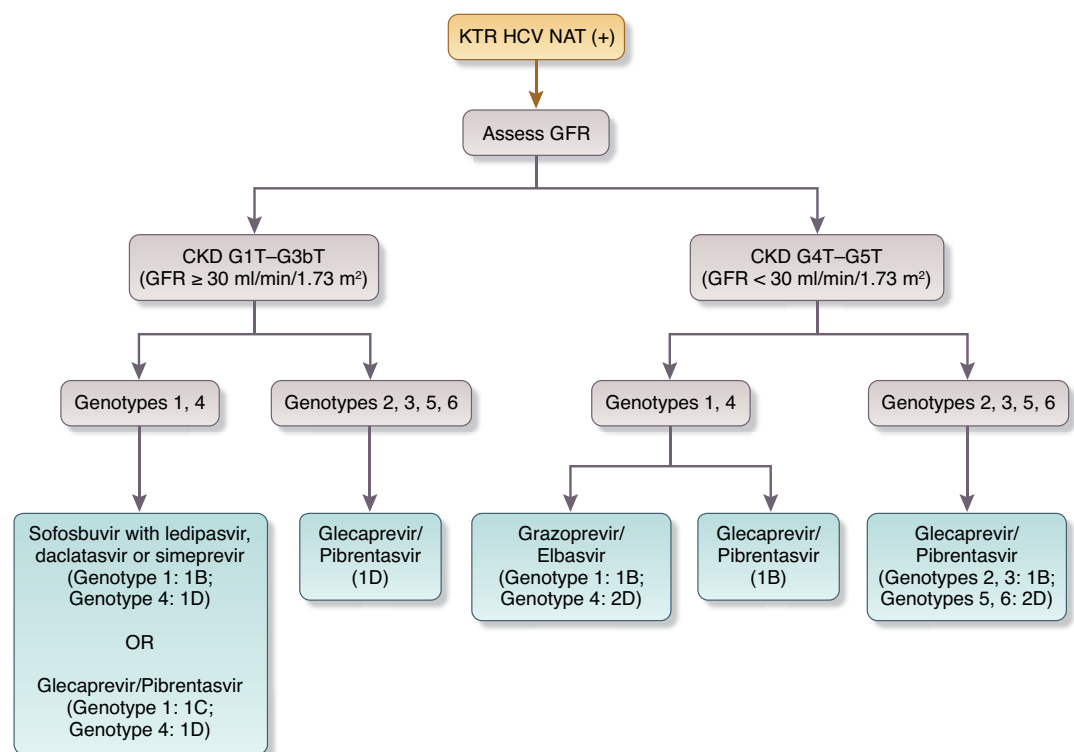
Over the past decade, remarkable progress has been achieved in the management of HCV. The shift from weaker guideline statements a decade ago to the present strong recommendations on HCV treatment can be attributed to the arrival of these highly effective and well-tolerated DAA regimens. As such, this is the right time for nephrologists to greatly reduce the burden of HCV in CKD patients in line with the World Health Organization's commitment to eliminate viral hepatitis as a significant public health problem by 2030 (6). ■

Michel Jadoul, MD, is head of Nephrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

References

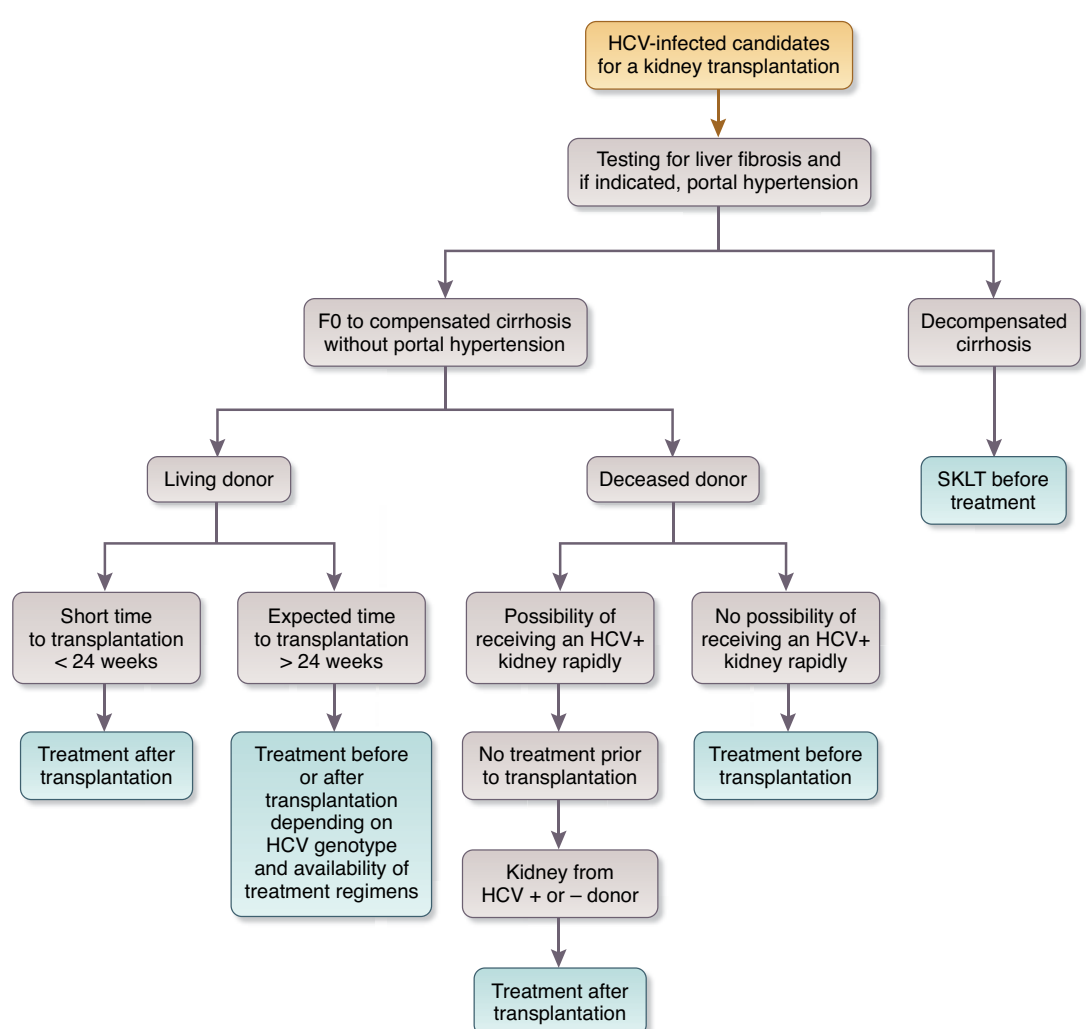
1. KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. *Kidney Int Suppl* 2018; 8:91–165.
2. Park H, et al. Chronic hepatitis C virus (HCV) increases the risk of chronic kidney disease (CKD) while effective HCV treatment decreases the incidence of CKD. *Hepatology* 2018; 67:492–504.
3. Jadoul M, et al. Prevalence, incidence, and risk factors for hepatitis C virus infection in hemodialysis patients. *Kidney Int* 2019; 95:939–947.
4. Pol S, et al. Hepatitis C virus and the kidney. *Nat Rev Nephrol* 2019; 15:73–86.
5. De Vita S, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012; 64:843–853.
6. Towards elimination of viral hepatitis by 2030. *Lancet* 2016; 388:308.

Figure 2. Algorithm showing treatment scheme for kidney transplant recipients (KTRs)



Recommendation grades (1–2) and strength of evidence (A–D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype. Pangenotypic sofosbuvir/velpatasvir-based regimens are not listed because they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However, FDA has recently indicated that no dose adjustments are required for these regimens in CKD patients including those on dialysis. These regimens may be considered pending their availability in various jurisdictions. However, readers are encouraged to consult <https://www.hep-druginteractions.org/> for drug-drug interactions, particularly with immunosuppressants (e.g., cyclosporine, sirolimus, and tacrolimus). Abbreviations: CKD G, chronic kidney disease; FDA, Food and Drug Administration; GFR category (suffix T denotes transplant recipient); NAT, nucleic acid testing. Reproduced with permission from reference 1.

Figure 3. Algorithm showing proposed strategy in a kidney transplantation candidate infected with hepatitis C virus (HCV)



Abbreviation: SKLT, simultaneous kidney-liver transplantation. Reproduced with permission from reference 1.

Chronic Kidney Disease–Mineral and Bone Disorder

Personal Perspective after the 2017 KDIGO CKD-MBD Guideline Update

By Markus Ketteler

The Kidney Disease: Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) represented a selective update of the prior CKD-MBD guideline published in 2009 (1, 2). The guideline update, along with the original 2009 publication, is intended to assist physicians, especially nephrologists, who care for CKD patients, including those using long-term dialysis therapy and individuals with a kidney transplant.

The 2017 guideline update focused on recommendations for the diagnosis of bone abnormalities in CKD-MBD; treatment of CKD-MBD by lowering serum phosphate and maintaining serum calcium; treatment of parathyroid hormone abnormalities in CKD-MBD; treatment of bone abnormalities by the use of antiresorptive agents and other osteoporosis therapies; and the evaluation and treatment of kidney transplant bone disease.

Although a reasonable number of high-quality studies were published between 2009 and 2017, significant gaps in the knowledge base about the optimized treatment approaches for patients with features of CKD-MBD still exist.

Although a reasonable number of high-quality studies were published between 2009 and 2017, significant gaps in the knowledge base about the optimized treatment approaches for patients with features of CKD-MBD still exist. Nevertheless, I would like to briefly feature three developments that were stimulated by the recent KDIGO CKD-MBD update publication that may improve the treatment of patients in the future, at least from my subjective point of view:

- Diagnosis and management of osteoporosis in CKD patients
- Fibroblast growth factor-23 (FGF23) as a biomarker
- Role of nutritional vitamin D in CKD

Osteoporosis in CKD

Among the most prominent changes in the 2017 guideline update were recommendations about the clinical handling of suspected osteoporosis in patients in all stages of CKD. First, dual-energy X-ray absorptiometry for determining bone mineral density became recommended as a reasonable diagnostic test for assessing fracture risk, if the results may affect treatment decisions. Second, the caution and reservation against classic anti-osteoporosis medications (especially antiresorptive agents) was partially relieved by the accumulating evidence supporting potential clinical benefits under defined circumstances.

The KDIGO update release was consequently followed by the publication of two remarkable and well-balanced review articles that both presented clinical algorithms for two different settings:

1. Patients in all stages with low bone mineral density (T score ≤ -2.5), or with T score > -2.5 plus a low-impact fracture according to the World Health Organization's definition of osteoporosis (3)
2. Dialysis patients (CKD G5D) with low-impact fractures (4)

The first algorithm (Figure 1) suggested using cutoff levels of bone-specific alkaline phosphatase as a pragmatic approach to more appropriately stratifying patients into high, normal, or low bone turnover groups, and it assigned treatment modalities accordingly (3). In essence, proper management of CKD-MBD phenotypes is warranted before more specific therapeutic approaches should be considered.

The second algorithm (Figure 2) for dialysis patients suggested a two-step approach, based on three groups of intact parathyroid hormone levels in accordance with the KDIGO guideline recommendations, followed again by ascertaining serum concentrations of bone-specific alkaline

phosphatase (4). Both reviews also quite pragmatically discussed and considered the potential of bone biopsy in their management schemes. Although these publications obviously reflect the authors' opinions, they appear to provide rather sensible advice about issues for which the data are limited.

Biomarker FGF23

One of the most interesting but challenging issues in CKD-MBD is the role of FGF23 as a diagnostic biomarker or even a therapeutic target. It seems quite evident that this phosphatonin is crucial in the regulation of phosphate and vitamin D homeostasis in progressive CKD, especially in earlier stages, but it might also develop into a cardiovascular threat for patients, owing to possible myocardial toxicity.

A recent article suggested that absolute FGF23 serum levels may be of secondary importance concerning risk prediction, especially in CKD patients not receiving dialysis, in comparison with the dynamics and trends of this biomarker (so-called trajectories) (5). By far, the highest risk prediction was observed when FGF23 levels rapidly rose over time, in contrast to slowly rising or stable FGF23 serum concentrations. This observation might potentially qualify FGF23 as a longitudinal marker of CKD severity and cardiovascular consequences. In this context, further insights about the power of available medications to substantially lower FGF23 blood levels (e.g., calcimimetics, phosphate binders) may thus have an impact on treatment modalities if FGF23 lowering can be proved to associate with improved patient-meaningful outcomes in rand-

omized controlled trials.

Management of vitamin D status

The current recommendations about vitamin D deficiency and insufficiency from the original KDIGO CKD-MBD 2009 guidelines remain oriented toward targets for the normal population as published by most osteoporosis societies and the Institute of Medicine (6). The latter position paper recommended a range of 25-hydroxy-vitamin D levels between 20 and 60 ng/mL as necessary to achieve, and it emphasized the importance of vitamin D for bone health while remaining cautious about the so-called pleiotropic effects on cancer and cardiovascular disease protection, infectious diseases, or autoimmunity.

Nevertheless, this unsolved issue triggered a few new study approaches that demonstrated the potentially beneficial effects of high-dose vitamin D3 supplementation with regard to endothelial function and vascular stiffness (7, 8). As reported at the recent ERA-EDTA Congress 2019 in Budapest, the VITALE study found that high-dose vitamin D3 treatment was associated with a lowered risk of symptomatic fracture (1% vs. 4% in low dose, odds ratio = 0.24, $p = 0.02$) in kidney transplant recipients, although other major study endpoints (cardiovascular events, diabetes incidence, cancer, death) were not reached (9). Further, the results of treatment studies in which extended-release calcifediol was used revealed that levels of 25-hydroxy-vitamin D between 50 and 80 ng/mL—even higher than those recommended by the Institute of Medicine (IOM)—are required to effectively control secondary hyperparathyroidism in CKD patients not using dialysis (10–12).

Recently, however, two large randomized controlled trials (ViDa [$n = 5108$], VITAL [$n = 25,871$]) failed to demonstrate beneficial effects on cardiovascular and cancer endpoints by high-dose vitamin D3 supplementation in the normal population (13–15). Both trials potentially suffered from the fact that most patients were not in a state of vitamin D deficiency at baseline (actually levels at both baseline and the end of study were within the IOM recommended range in the two trials). A recent subgroup analysis of VITAL (VITAL-DKD) in patients with type 2 diabetes mellitus ($n = 1,312$) reported no significant difference in the change of estimated glomerular filtration rate with vitamin D supplementation (16). Nonetheless, follow-up periods of 3 or 5 years may still be too short to enable credible conclusions to be reached. It is hoped that further *post hoc* analyses of subgroups with impaired kidney function may become available from these trials, enabling an informative view on vitamin D supplementation in CKD patients.

Perspective

Guideline publications are always a chance and a challenge. Unanswered questions still need to be pragmatically addressed, and if this is preliminarily done by balanced expert opinion, it will be of great help for the practitioner. When research questions are raised, knowledge gaps may be subsequently closed one by one. In about 3 years from now, the CKD-MBD field will have yet again to be reappraised concerning the accumulated evidence so that

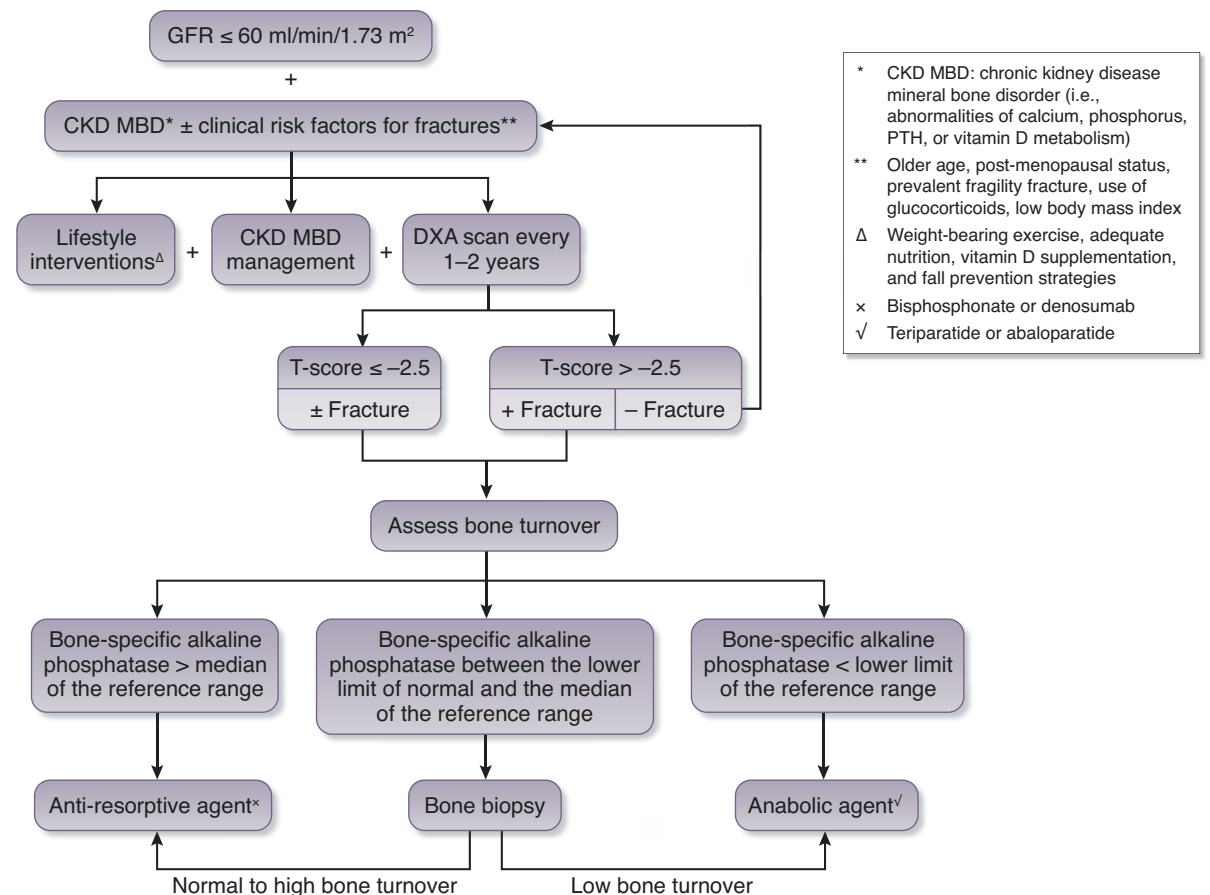
ever more sustainable advice can be generated for clinical decision-making. ■

Markus Ketteler, MD, FERA, is the head of the Department of General Internal Medicine and Nephrology, Robert Bosch Hospital, Stuttgart, Germany.

References

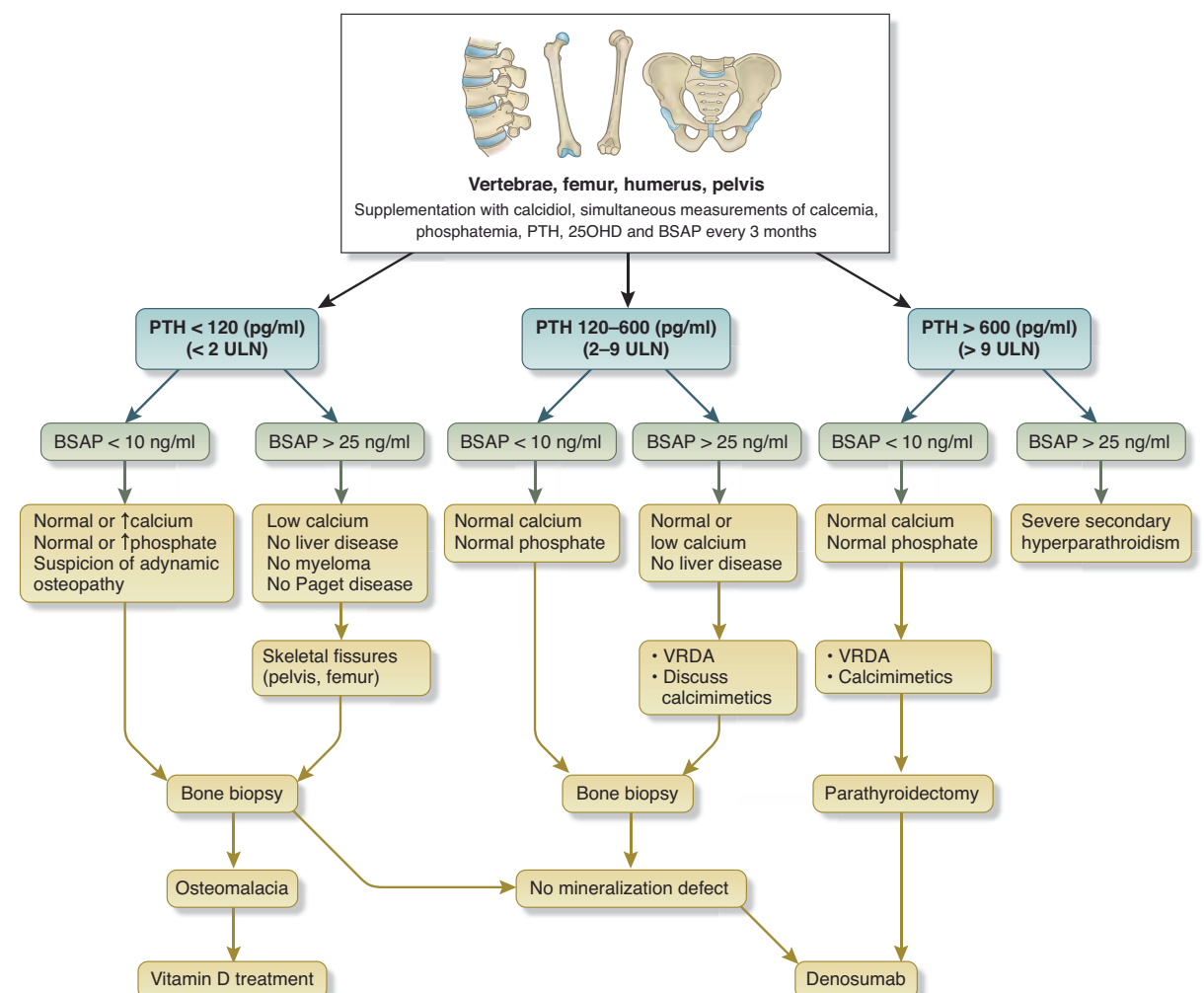
1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2009; 76 (Suppl 113): S1–130.
2. Ketteler M, et al. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD. *Kidney Int Suppl* 2017; 7[Suppl 1]:1–59.
3. Khairallah P, Nickolas TL. Management of osteoporosis in CKD. *Clin J Am Soc Nephrol* 2018; 13:962–969.
4. Pimentel A, et al. Fractures in patients with CKD—diagnosis, treatment, and prevention: A review by members of the European Calcified Tissue Society and the European Renal Association—European Dialysis and Transplant Association. *Kidney Int* 2017; 92:1343–1355.
5. Isakova T, et al. Longitudinal FGF23 trajectories and mortality in patients with CKD. *J Am Soc Nephrol* 2018; 29:579–590.
6. Ross AC, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab* 2011; 96:53–58.
7. Levin A, et al. Randomized controlled trial for the effect of vitamin D supplementation on vascular stiffness in CKD. *Clin J Am Soc Nephrol* 2017; 12:1447–1460.
8. Kumar V, et al. A randomized trial of vitamin D supplementation on vascular function in CKD. *J Am Soc Nephrol* 2017; 28:3100–3108.
9. Courbebaisse M, et al. Non-skeletal and skeletal effects of high doses versus minimum recommended intake of vitamin D3 in renal transplant recipients in a prospective, multicenter, double-blind, randomized study. Late Breaking Clinical Trial Abstract, ERA-EDTA Congress 2019, Budapest.
10. Sprague SM, et al. Use of extended-release calcifediol to treat secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. *Am J Nephrol* 2016; 44:316–325.
11. Strugnelli SA, et al. Rationale for raising current clinical practice guideline target for serum 25-hydroxyvitamin D in chronic kidney disease. *Am J Nephrol* 2019; 49:284–293.
12. Cozzolino M, Ketteler M. Evaluating extended-release calcifediol as a treatment option for chronic kidney disease-mineral and bone disorder (CKD-MBD). *Expert Opin Pharmacother*. 2019; 20: 2081–2093.
13. Scragg R, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study: A randomized clinical trial. *JAMA Cardiol* 2017; 2:608–616.
14. Scragg R, et al. Monthly high-dose vitamin D supplementation and cancer risk: A post hoc analysis of the vitamin D assessment randomized clinical trial. *JAMA Oncol* 2018; 4:e182178.
15. Manson JE, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019; 380:33–44.
16. de Boer IH, Zelnick LR, Ruzinski J, et al. Effect of vitamin D and omega-3 fatty acid supplementation on kidney function in patients with type 2 diabetes: A randomized clinical trial. *JAMA*. 2019; doi: 10.1001/jama.2019.17380.

Figure 1. Suggested algorithm for fracture risk screening and initiation of anti-fracture strategies in patients with CKD



Abbreviations: CKD-MBD, chronic kidney disease-mineral and bone disorder; DXA, dual-energy X-ray absorptiometry; GFR, glomerular filtration rate; PTH, parathyroid hormone. Reprinted from Khairallah P et al. (3) with permission.

Figure 2. Suggested algorithm for management of fractures



Abbreviations: BSAP, bone-specific alkaline phosphatase; PTH, parathyroid hormone; ULN, upper limit of normal; VRDA, vitamin D receptor activators. Reprinted from Pimentel A, et al. (4) with permission.

Living Kidney Donation: Advancing a New Framework for Donor Evaluation

By Krista L. Lentine, Andrew S. Levey,
and Amit X. Garg

Since the advent of the successful practice of living donor kidney transplantation more than 60 years ago, over 150,000 healthy persons in the United States have donated a kidney to help a family member, a friend, or even a stranger. Currently, more than 30,000 living kidney donations are performed worldwide each year. Living donor transplantation is clearly established as the best treatment option for kidney failure, offering patients the best chance of long-term dialysis-free survival, with a better quality of life, at lowest costs to the healthcare system. However, despite the tremendous benefits to recipients and society, the outcomes in and optimal care of donors themselves have been relatively understudied. Fortunately, things are changing, including recent landmark developments in living donor risk assessment, policy, and guidance. One key advance is recognition of the critical importance of perspectives of comparison for drawing inferences about donor health outcomes. General population comparisons can have value as one context. However, because donors are carefully evaluated and selected, methodologies to assemble control groups of healthy nondonors who would otherwise meet donor selection criteria have been a breakthrough in facilitating estimates of the attributable risks of donation. The policy of the U.S. Organ Procurement and Transplantation Network now requires that the small but significant donation-attributable risks of kidney failure and gestational hypertension be disclosed to potential living donors. This is an example of new evidence informing policy to support the optimal care and informed choice of living donors.

The limitations of available data and inconsistent guidance have underscored a critical need to strengthen the rigor, safety, and defensibility of donor selection. Importantly, 2017 also marked the publication of the first Kidney Disease: Improving Global Outcomes (KDIGO) “Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors.” A central goal of the guideline is to advance a framework for evaluating and selecting donor candidates based on the long-term risk of adverse outcomes estimated from simultaneous consideration of a profile of demographic and health characteristics. Prior living kidney donor guidelines described postdonation risk in relation to single predonation characteristics assessed in isolation, and they differed on the recommended specific thresholds for a characteristic that should be used to accept or decline living kidney donor candidates; the inconsistency potentially undermined defensible decision making. For example, before the 2017 KDIGO guideline, most programs excluded donors with a body mass index exceeding a predetermined threshold, usually between 30 and 35 kg/m², without consideration of additional donor characteristics or risk factors. By comparison, the KDIGO guideline endorses individualizing the decision to approve donation by obese candidates based on their predicted long-term risk in relation to the transplantation program’s acceptance threshold. A risk threshold is de-

finied as the upper limit of acceptable risk established by a program for donor candidate selection. Under the KDIGO framework, when a candidate’s estimated risk is above the acceptable threshold, the transplantation program is justified in declining the candidate and can ground its decision in a quantitative framework. When a donor candidate’s estimated risk is below the acceptable risk threshold, the transplantation program should accept a donor candidate, and it should be the candidate’s decision whether to proceed with living kidney donation after being informed of the risks (Figure 1). Once established, acceptable risk thresholds should be applied consistently and transparently for all donor candidates evaluated at a program.

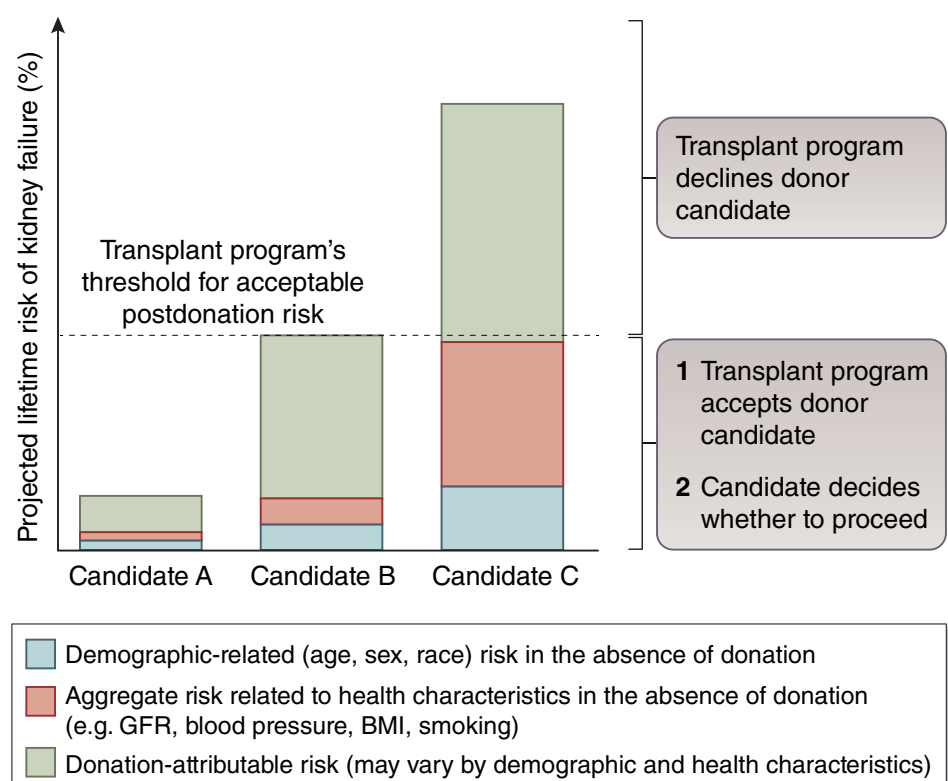
Living donation may have an impact on multiple health outcomes, but the KDIGO framework focuses on the development of kidney failure requiring dialysis or transplantation because it is a central outcome of a donor candidate’s long-term risk and has a biologically plausible link to donation. The KDIGO framework was informed by a systematic evidence review. However, in response to a lack of sufficient data for a quantitative framework, the guideline development methodology also included partnering with the Chronic Kidney Disease Prognosis Consortium to conduct a *de novo* meta-analysis of data on nearly 5 million healthy persons from seven general population cohorts who are similar to kidney donor candidates to develop an online tool for projecting 15-year and lifetime risks of ESKD based on predonation demographic and health factors. Although this work is critically important in establishing a framework, it is only a starting point; ongoing efforts are needed to improve the precision and generalizability of predonation risk estimation, including consideration of additional factors such as genetic and familial traits, and to incorporate tailored prediction of the risk impact of donation.

Extending the theme of personalized risk prediction, the potential relevance of novel genetic risk markers in the evaluation of living donor candidates, such as recently recognized kidney disease risk variants (KDRVs) in the apolipoprotein L1 (*APOL1*) gene, is a subject of intense attention. Beyond implications of the presence of two donor KDRVs for increased risk of allograft loss in the recipient, a donor’s

APOL1 genotype may also have critical implications for the long-term health of the living donor. A recent cohort study of 136 African-American living kidney donors reported that those with *APOL1* high-risk genotypes had lower predonation kidney function and faster rates of decline in postdonation estimated GFR; 11% (2/19) experienced ESKD after an average of 12 years of follow-up. Some transplantation programs now offer *APOL1* genotyping in the evaluation of African-American living kidney donor candidates, but the practice is controversial and varies across transplantation programs because of uncertainty about the implications of genotype for the outcomes in the individual. While recommending that *APOL1* genotyping may be considered in the living donor candidate evaluation, the 2017 KDIGO guideline identified the need to define the role of *APOL1* genotyping in the evaluation of donor candidates with recent African ancestry as a key research priority. Importantly, late-2019 marked the launch of enrollment in the collaborative “*APOL1* Long-Term Kidney Transplantation Outcomes” (APOLLO) Consortium, sponsored by the National Institutes of Health, charged with prospectively assessing the effects of *APOL1* KDRVs on the outcomes in recipients of kidneys from donors with recent African ancestry, and the impact of *APOL1* KDRVs on the health of living kidney donors. An ancillary study specifically focused on and powered for the kidney outcomes in living donors—the “Living Donor Extended Time Outcomes” (LETO) study—is also being launched in 2020. The critical importance of accurately assessing risk among African-American potential donors is highlighted by new data demonstrating growing disparities in access to living donor transplantation among African-American candidates for transplantation.

To strengthen informed choice by prospective living donors, and the safety, protection, and care of all living donors, robust commitment and collaboration across researchers, clinicians, and policy makers is needed to measure and present risks and benefits, and to support donor candidates in informed decision-making. The more we understand risk, and disclose it transparently, the more we can ensure public trust and advance living donation within a defensible system of practice. An additional promising development is the

Figure 1. Applying the KDIGO framework to accept or decline donor candidates based on a transplantation program’s threshold of acceptable projected lifetime risk of kidney failure, quantified as the aggregate of risk related to demographic and health profile and donation-attributable risks. Reproduced with permission from Lentine et al. *Transplantation* 2017; 101(8S Suppl 1):S1-S109.



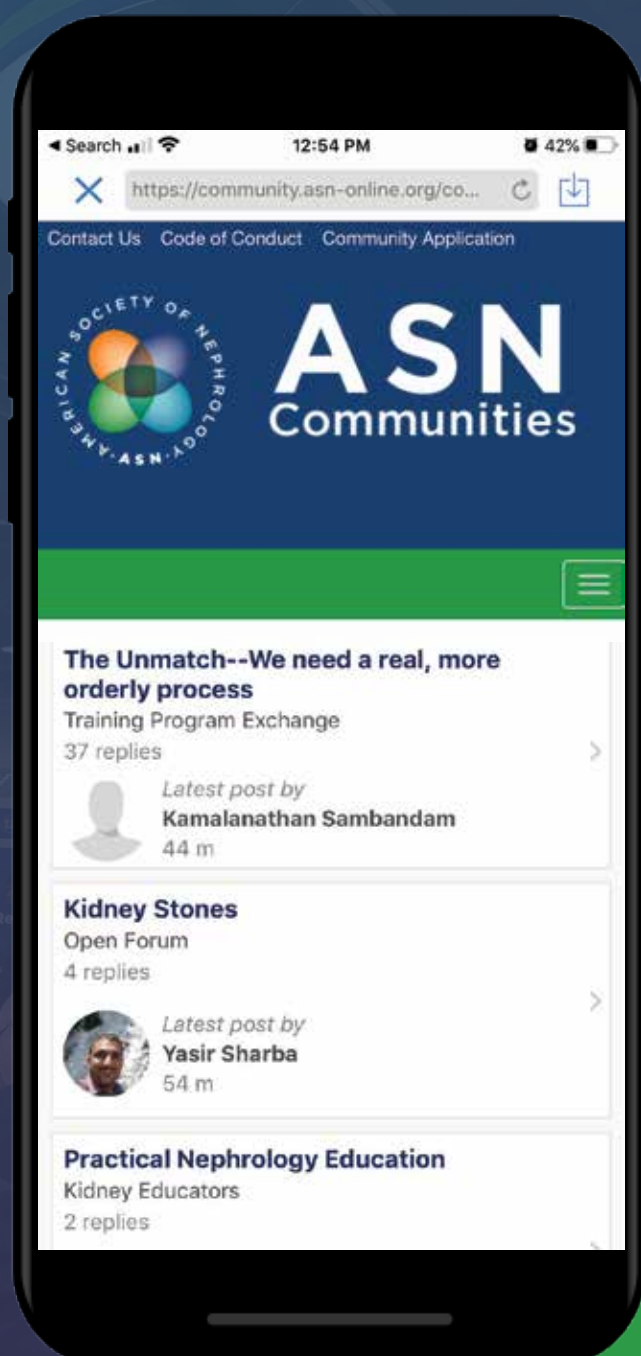
launch of the Living Donor Collective pilot, a scientific registry designed to prospectively follow up donors and donor candidates over their lifetimes. The 2017 KDIGO guideline is a milestone in advancing a new framework for consistent, transparent decision-making in the evaluation and selection of living donor candidates that can and should be updated with evolving evidence. Empiric studies including formal evaluations of education, removal of disincentives, practice efficiency, and risk evaluation and communication are feasi-

ble and necessary to advance the evidence base that grounds the practice of living donation and living donor transplantation. Ongoing efforts to identify and address knowledge gaps related to living donor care are vital in honoring the life-saving gift of living donors and in supporting opportunities for healthy, willing persons to safely give the gift of life to patients in need. ■

Krista L. Lentine, MD, PhD, is Professor of Medicine, Saint

Louis University Center for Transplantation & Department of Medicine/Division of Nephrology, St. Louis, Missouri, USA; Andrew S. Levey, MD is Chief Emeritus, Division of Nephrology; Professor of Medicine, Tufts University School of Medicine; and Dr. Gerald J and Dorothy R. Friedman Professor Emeritus, at Tufts University School of Medicine, Boston USA; Amit X. Garg, MD, PhD is Nephrologist, London Health Sciences Centre and Professor Medicine, Epidemiology & Biostatistics at Western University, London, Canada

ASN Communities is the online place to go for members to collaborate, discuss challenging issues, and network with other kidney professionals.



To access the full power of Communities on the go, many members are using the one-click app to:

- ✓ Receive immediate notification of responses to posts
- ✓ Directly view messages
- ✓ Create one-to-one connections with members around the world

Download the ASN Communities app to get the most from your membership experience!

Get the Free App
www.membercentric.info/ASN

Diabetes and CKD: New Approaches to Managing a Common Condition

By Ian H. de Boer

Diabetes treatment has advanced rapidly over the past decade, with new drugs and technologies developed and translated into clinical care. Many of these treatments affect the kidney, are affected by chronic kidney disease (CKD), or carry both effects. In addition, new data have been published on foundational elements of care for people with diabetes and CKD, including lifestyle, ascertainment of glycemia, glycemic targets, and use of renin-angiotensin system (RAS) inhibitors. Providers and patients rightly ask how to apply the new treatments and integrate them into tailored existing care paradigms.

KDIGO has initiated a new clinical practice guideline to help guide medical management for people with diabetes and CKD. The goal of the new clinical practice guideline is to provide evidence-based recommendations for the care of people with diabetes and CKD. The guideline arose from a KDIGO Controversies Conference held in 2015 that outlined critical areas in need of evidence-based recommendations (1). The scope of the guideline was then refined by the KDIGO diabetes and CKD guideline writing group, with input through open commentary from the broad commu-

nity engaged in managing diabetes and CKD. The new guideline will take a comprehensive approach, covering lifestyle, glycemia assessment and targets, use of medications that target both glycemia and other intermediate targets, self-management, and systems of care (see box). The guideline is designed to apply to people with diabetes and any stage of CKD, from elevated urine albumin excretion and normal estimated GFR (eGFR) to severely reduced eGFR to ESKD treated with dialysis or kidney transplantation, highlighting the aspects of care that are common across the CKD spectrum and also those that should differ by severity of CKD. Similarly, the guideline will address care for people with both type 1 and type 2 diabetes, highlighting common and differential approaches where appropriate. The guideline will be informed by a systematic literature review performed by an expert evidence review team, focusing on high-level evidence from clinical trials.

New drugs will be addressed by this new diabetes and CKD guideline. Three new classes of drugs are revolutionizing diabetes care: sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors (2). All three classes reduce blood glucose, with a low risk of hypoglycemia. In addition, SGLT2 inhibitors and GLP-1 receptor agonists have shown substantial benefits in terms of cardiovascular and kidney outcomes (Table 1). These benefits were first demonstrated in large cardiovascular outcomes trials that were mandated by regulatory agencies to ensure cardiovascular safety of new diabetes drugs. SGLT2 inhibitors and GLP-1 receptor agonists proved to be not only safe but beneficial. In each of these drug classes, several specific drugs reduced cardiovascular events in high-risk populations (2). SGLT2 inhibitors also substantially reduced GFR loss in secondary analyses (3)—an effect confirmed in the recent CREDENCE trial (4). GLP-1 receptor agonists may also have renal benefits (5). However, all of these drugs do have adverse effects, most are restricted below certain eGFR thresholds and in kidney failure, and combinations with other glucose-lowering drugs remain poorly developed (3). Therefore, further guidance is needed on the implementation of these promising new drugs in clinical nephrology practice.

Table 1. Summary of the benefits and harms of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, by class, as observed in large, placebo-controlled clinical outcomes trials

Drug	HbA _{1c} lowering	Cardiovascular effects		Kidney effects		Notable adverse effects
		Major atherosclerotic cardiovascular events	Heart failure	Albuminuria or albuminuria-containing composite outcome	GFR loss*	
SGLT2 inhibitors	↓ 0.6–0.9% (CKD G1–G2) ↓ 0.3–0.5% (CKD G3a) ↔ (CKD G3b–G4) NA (CKD G5)	↓/–	↓↓	↓↓	↓↓	Genital mycotic infections, diabetic ketoacidosis, possibly amputations (canagliflozin)
GLP-1 receptor agonists	↓ 1.0–1.2% (CKD G3a–4)	↓/–	–	↓	↓/–	Gastrointestinal, primarily nausea and vomiting
DPP-4 inhibitors	↓ 0.5–0.7% (CKD G3a–4)	–	–/↑	↓	–	Possibly heart failure (saxagliptin)

Notes: ↓ = significant reduction in risk, with HR estimate > 0.7 and 95% confidence interval not overlapping 1; ↓↓ = significant reduction in risk, with HR estimate ≤ 0.7 and 95% confidence interval not overlapping 1; ↔ = no change; ↑ = increase; – = no significant effect; * = variable composite outcomes that include loss of eGFR, ESKD, and related outcomes.

DPP-4, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide 1; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

Key questions to be addressed by the new KDIGO guideline on diabetes and CKD

- 1 Do lifestyle interventions (exercise/physical activity, and smoking cessation) versus usual care improve clinically relevant outcomes and intermediate outcomes and reduce clinically relevant harms?
- 2 Do dietary interventions (caloric restriction diet, low-potassium diet, low-sodium diet, low-phosphate diet, low-protein diet and whole food diets) versus usual diet improve clinically relevant outcomes and intermediate outcomes and reduce clinically relevant harms?
What is the equivalency of HbA_{1c} compared with frequently measured blood glucose (continuous glucose monitoring or multiple capillary blood glucose measurements)?
- 4 Compared with blood glucose monitoring and/or HbA_{1c} determination, do alternative biomarkers (glycated albumin, fructosamine) improve clinically relevant outcomes and decrease clinically relevant harms?
- 5 Compared with HbA_{1c} determination, does blood glucose monitoring (continuous interstitial glucose monitoring, self-monitoring blood glucose) improve clinically relevant outcomes and decrease harms?
- 6 Does reducing blood glucose to a lower versus higher target improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?
- 7 What are the most effective education, self-management, and healthcare delivery programs to improve clinically relevant and intermediate outcomes, and reduce clinically relevant harms?
- 8 What are the effects of metformin on clinically relevant outcomes, intermediate outcomes, and clinically relevant harms?
- 9 What are the effects of other glucose-lowering medications (sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, insulin) on clinically relevant outcomes, intermediate outcomes, and clinically relevant harms?
- 10 Do renin-angiotensin system (RAS) inhibitors improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?
- 11 Does dual RAS inhibition compared with single RAS inhibition improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?
- 12 Does the addition of a medication blocking the production or action of aldosterone to RAS inhibitors compared with RAS inhibition alone improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?

Technology has also advanced in diabetes care. In particular, continuous glucose monitoring is facilitating more intensive glycemic control, particularly in type 1 diabetes (6). New biomarkers, such as glycated albumin and fructosamine, have also been proposed to assess glycemia in CKD, because hemoglobin A1c may be biased or imprecise when red blood cell turnover increases with low eGFR and the use of erythropoietin-stimulating agents.

Of course, new drugs and technologies cannot treat diabetes and CKD on their own. These new treatments must be added to and integrated with established therapies, including lifestyle interventions and proven therapies, such as metformin and RAS inhibitors. Of lifestyle interventions, dietary sodium, dietary protein, and physical activity have been best studied. All treatments must be applied in a manner that engages and is acceptable to patients and is delivered in care models that acknowledge local patterns of care and local resources. Importantly, diabetes has grown most rapidly in low-income countries. Treatment paradigms must take into account the cultural values and resources of diverse contexts.

The care of people with diabetes and CKD makes large demands on patients and is necessarily multidisciplinary in nature. Effective guidelines must therefore reflect patient priorities and the perspectives of multiple approaches to care. Such guidelines must also acknowledge and account for the large range of care settings across the world. For these reasons, the KDIGO diabetes and CKD guideline writing group includes patients along with members from diverse professional backgrounds (nephrology, endocrinology, primary care, cardiology, pharmacology, nutrition) and from across the globe (United States, United Kingdom, Netherlands, Germany, India, Nigeria, Singapore, Hong Kong, and Brazil). It is anticipated that KDIGO and this writing group will release a draft set of recommendations for public commentary in December 2019, with a final guideline published in early 2020. ■

Ian H. de Boer, MD, MS, is Professor of Medicine in the Division of Nephrology and Associate Director of the Kidney Research Institute at the University of Washington, Seattle, USA.

References

1. Perkovic V, et al. Management of patients with diabetes and CKD: Conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. *Kidney Int* 2016; 90:1175–1183.
2. Davies MJ, et al. Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41:2669–2701.
3. de Boer IH. The expanding resume of SGLT2 inhibitors. *Lancet Diabetes Endocrinol* 2019; 7:585–587.
4. Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380:2295–2306.
5. Tuttle KR. SGLT2 inhibitor and incretin mimetic therapy for type 2 diabetes and chronic kidney disease. *Lancet Diabetes Endocrinol* 2019; 7:414–415.
6. American Diabetes Association. 7. Diabetes Technology: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019; 42[Suppl 1]:S71–S80.

KDIGO Hypertension Guideline

By Johannes F.E. Mann and Alfred K. Cheung

In 2012, KDIGO issued a clinical practice guideline for the management of blood pressure in chronic kidney disease (CKD) which excluded patients receiving maintenance dialysis. This guideline is now being revised on the basis of new clinical trial evidence, particularly from SPRINT, SPS3, and others. A multidisciplinary KDIGO guideline panel of clinical and scientific experts has convened in person and over teleconferences to discuss the excellent work of the Evidence Review Team with the aim to publish an update to the 2012 guideline in 2020. This revision will address several major subjects, such as optimal blood pressure (BP) measurement techniques, BP targets, antihypertensive agents, and the role of lifestyle and dietary interventions in CKD patients, including the special populations of pediatric patients and kidney transplant recipients.

A key issue of this new guideline will be a new chapter on how to measure BP properly. As a rule, casual office BP is 5 to 10 mm Hg higher than both standardized office and automated oscillometric office BP. Still, it is impossible to come up with conversion factors to adjust one measuring technique to another because that difference of 5 to 10 mm Hg refers to population means and those differences may vary vastly in each individual. The variabilities in BP obtained by the use of different techniques of measurements in CKD appear similar to those in the general population, although the available data are more limited. The utility of out-of-office BP is important in CKD because the prevalence of white-coat hypertension, masked hypertension, white-coat effect, and masked uncontrolled hypertension appears to be higher than in individuals without CKD. Nonetheless, there is insufficient literature to support guidelines on how to manage BP based on out-of-office measurements.

When BP targets are discussed, it is of utmost importance that BP measurement be performed in a highly

standardized manner, probably using an automated oscillometric device that incorporates, by default, a five-minute rest period and averaging three measurements several minutes apart. This Work Group panel is considering a target systolic BP of less than 120 mm Hg as determined using standardized office BP measurement, based on the new evidence from the SPRINT and recent meta-analyses. Such a low target would obviate separate recommendations for different risk populations such as individuals with diabetes or variable degrees of proteinuria. The targets are mainly chosen based on their effects on cardiovascular events, which are rampant in CKD, and mortality. The effect of intensive BP lowering on kidney outcomes, GFR decline and end-stage kidney disease, is surprisingly small. In fact, in the intensive BP-lowering arms of the SPRINT, SPS3, and ACCORD studies, the decrease in GFR was consistently, albeit only slightly, greater than in the control arms.

In regard to preferred antihypertensive agents of choice, KDIGO will likely recommend, as before, angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) as first-line agents in those with very heavy albuminuria (>300 mg/g or >300 mg/24 h) and in those with diabetes. One unresolved issue is how best to handle an acute decrease in GFR in the first few weeks after antihypertensive therapy has been started, particularly with an ACEi or an ARB. Randomized intervention trials in this area are lacking, and more recent observational studies cast uncertainties on the predictive value of these acute early changes in GFR for long-term renoprotective effects. There is also no randomized trial to inform whether potassium binders would allow better control of hypertension in hyperkalemia-prone CKD by enabling the use of RAAS blockers and thus reduce cardiovascular and kidney complications.

What about the other special groups with CKD, namely older patients, children, or those with a kidney transplant? There is a large unmet need for studying the effects of antihypertensive therapy on cardiovascular and kidney outcomes in older patients with advanced CKD, given the increasing incidence of ESKD in this population. Because the aggregate benefits of antihypertensive therapy require at least one to two years to materialize, clinical judgment and shared decision-making is essential, and should take into consideration such factors as patient preferences, life expectancy, and potential adverse effects of therapy. We also note that the cardiovascular and apparent cognitive benefits of intensive BP lowering in the SPRINT trial persisted in the predefined subgroup

above age 75 years and it was not associated with a higher risk of injurious falls or other serious adverse event than with standard BP goal.

Providing advice for the management of hypertension in pediatric CKD is a challenge for a number of reasons. Cardiovascular events, even over a 10-year time frame, are rare in this population. Thus, evidence is based primarily on the ESCAPE trial which examined kidney outcomes or surrogate outcomes such as left ventricular mass. Unfortunately, there is no good evidence to support the use of automated oscillometric BP devices in children with CKD, and normative values for ambulatory BP are available largely for Western populations only. Scientific societies do not agree on whether antihypertensive therapy should be initiated when BP is consistently above the 90th or 95th percentile for a child's age, sex, and height, but the target BP is consistently stated as < 50th percentile.

In kidney transplant recipients, there are no randomized trials to inform the optimal BP target with regard to cardiovascular or kidney allograft outcomes. ACEi, alpha-blockers, beta-blockers and mineralocorticoid receptor antagonists were compared with placebo with no differences in cardiovascular and kidney outcomes. ARBs and dihydropyridine calcium channel blockers (CCB) have been shown to reduce graft loss, compared to placebo. There are also several special aspects, such as renal artery stenosis and the use of vasoactive immunosuppressants (e.g., calcineurin inhibitors) that may complicate BP management in transplant recipients.

Finally, is there any role for nonpharmacologic treatment (e.g., dietary interventions, salt restriction, exercise, alcohol use) of hypertension in patients with CKD? There really is no evidence from randomized studies in CKD with patient-relevant outcomes to answer this question. However, most experts would agree that moderate salt restriction, physical activity, weight reduction in the obese, and attention to healthy diet, as recommended for the general population with the exception of high-potassium-containing food in advanced CKD, would likely to be helpful. ■

Johannes F. E. Mann, MD is currently Professor of Medicine, University of Erlangen-Nürnberg, Germany and Director, KfH Kidney Centre Munich, Germany. Alfred K. Cheung, MD is currently Professor of Internal Medicine, Executive Director of Dialysis Program and Vice Chair for Research, Department of Internal Medicine at the University of Utah, Salt Lake City, USA.

KDIGO Quo Vadis: Updating Guidance for the Management and Treatment of Glomerulonephritis

By Jürgen Floege and Brad H. Rovin

In November 2017, KDIGO hosted a Controversies Conference in Singapore on glomerular diseases. The goal was to determine the best practice and evidence gaps in the treatment of glomerular diseases, review the key literature published since the 2012 KDIGO Glomerulonephritis (GN) Guideline, identify topics or issues for future guideline updating, and outline unmet needs in the management of GN (1, 2).

Since the 2012 KDIGO GN guideline, there have been marked advances in our understanding of the pathogenesis, diagnosis, and potential new treatment approaches or therapeutic agents for several glomerular diseases. A few highlights follow.

IgA nephropathy (IgAN) has now been classified by the histology-based MEST and MEST-C scoring system, which has potential to improve outcome prediction in IgAN. Regarding treatment, two major trials, STOP-Ig-

AN and TESTING, have provided conflicting results on the use of corticosteroids in IgAN, but they raised similar safety concerns. The results of the phase 2 NEFIGAN trial suggested that delivering a corticosteroid agent (enteric steroid budesonide) to the gut immune system may be beneficial (Figure 1). Also encouraging is that other novel approaches to the treatment of IgAN are being tested, including inhibition of complement pathway components and tyrosine kinase signaling.

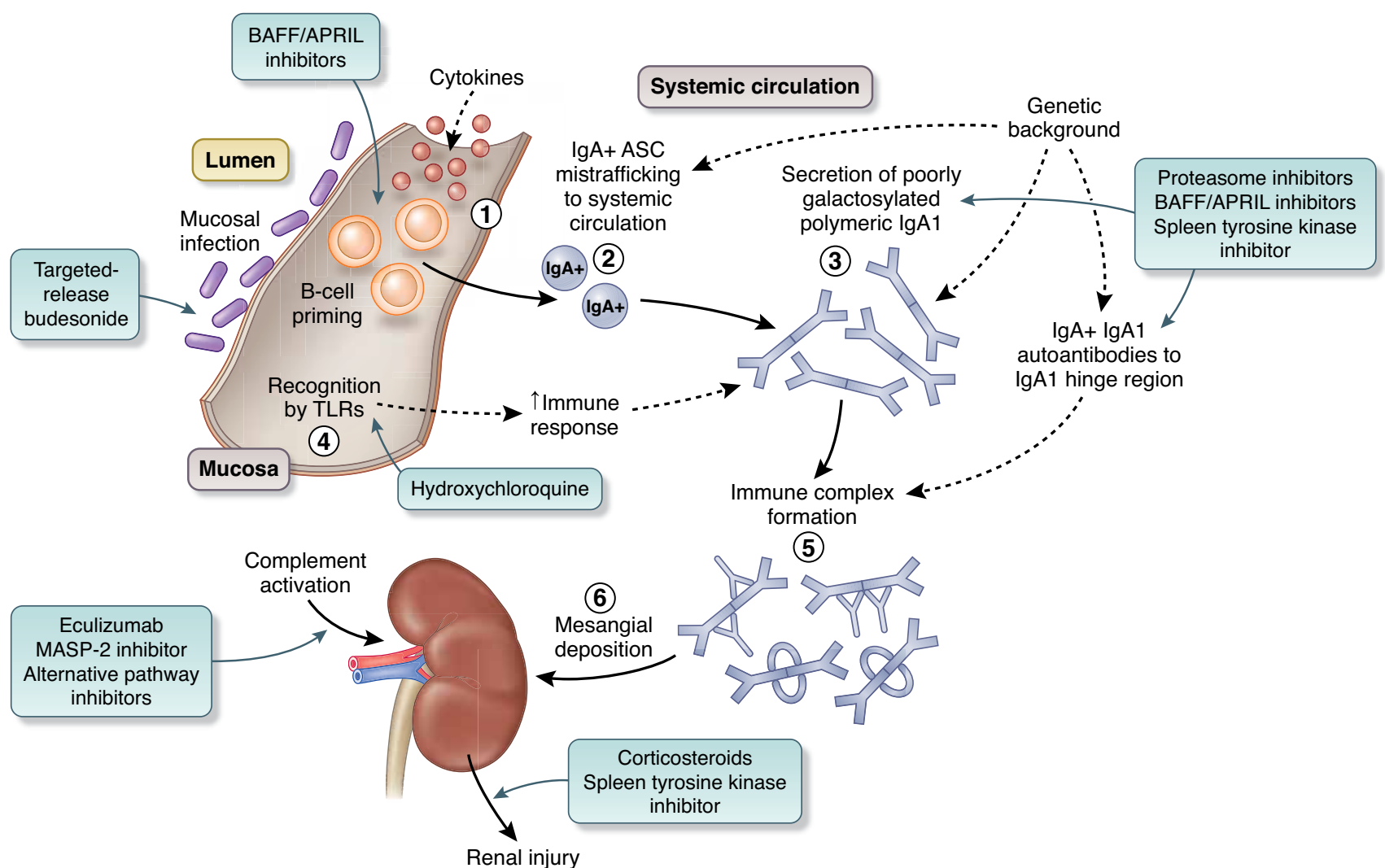
Another remarkable breakthrough since 2012 was the discovery of the podocyte autoantigens PLA2R and THSD7A in membranous glomerulopathy (MN). Anti-PLA2R antibody is present in 50% to 80% of MN cases, whereas the anti-THSD7A can be found in 2% to 4% of such cases. Emerging data now point to the diagnostic, prognostic, and disease-monitoring value in particular of anti-PLA2R. The use of anti-PLA2R to detect im-

munologic remission in MN has been incorporated into recent clinical trials such as GEMRITUX, STARMEN, and MENTOR, which have examined the role of B-cell targeting to induce remission.

The use of a multitargeted approach to the treatment of lupus nephritis (LN) has garnered considerable interest in the nephrology community. Whereas the initial trials suggesting that a regimen of corticosteroid, mycophenolate mofetil, and a calcineurin inhibitor was superior to standard of care were performed in all Asian cohorts, a recent successful international trial recapitulated these results in an ethnically diverse LN population. Several other novel approaches to the treatment of LN are being trialed, including antibodies targeting the interferon- α receptor.

Continued on page 22 ➤

Figure 1. Proposed pathogenesis of IgA nephropathy (IgAN) and potential therapeutic targets.



(1) Mucosal infection primes naive B cells to class switch to become IgA antibody-secreting cells (ASCs) through both T-cell-dependent (cytokine mediated) and T-cell-independent (Toll-like receptor [TLR] ligation) pathways. (2) Some IgA ASCs mis-home to the systemic compartment during lymphocyte trafficking. (3) Displaced IgA⁺ ASCs take up residence in systemic sites and secrete normal “mucosal-type” (poorly galactosylated and polymeric) IgA1 into the systemic circulation. (4) IgA1 secretion by displaced mucosal ASC is augmented by TLR ligation from mucosal-derived pathogen-associated molecular patterns, which have entered the systemic compartment. (5) IgA1 immune complexes form in the systemic circulation. Poorly galactosylated polymeric IgA1 molecules are the substrate for immune complex formation and combine with IgG and IgA autoantibodies reactive to exposed neopeptides in the poorly galactosylated IgA1 hinge region. (6) IgA1 immune complexes deposit in the mesangium through a combination of mesangial trapping and increased affinity of poorly galactosylated IgA1 for extracellular matrix components. Immune complex deposition triggers a series of downstream pathways, including complement activation via the mannose-binding lectin and other pathways, leading to glomerular injury and tubulointerstitial scarring.

APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; MASP-2, mannan-binding lectin-associated serine protease-2. Adapted from Boyd JK, Cheung CK, Molyneux K, et al. An update on the pathogenesis and treatment of IgA nephropathy. *Kidney Int* 2012; 81:833–843, with permission.



Spend less time searching and more time connecting with potential employers using the ASN Career Center.

Whether you're actively seeking new employment, or seeing what opportunities are currently available, ASN provides you the most comprehensive list of positions in kidney medicine and research.

Access the newest jobs available, filter positions to best fit your needs, and create job alerts so you never miss a matching job opportunity.

Find your perfect fit.

careers.asn-online.org



KDIGO Quo Vadis

Continued from page 20

The approach to antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has changed considerably with the approval of rituximab as an alternative to cyclophosphamide as first-line therapy. The use of rituximab alone still remains controversial for patients with severe ANCA-associated nephritis. In addition to induction, rituximab has found utility for the maintenance of remission and may offer an advantage over azathioprine, the standard of care for maintenance. The recently presented PEXIVAS trial did not support the use of plasma exchange to enhance remission but demonstrated its use for reducing corticosteroid exposure in ANCA patients. Similarly, the phase 2 trial of avacopan, a complement component C5a receptor blocker, demonstrated its potential as a corticosteroid sparing agent in the treatment of ANCA.

To incorporate these and other updates to the GN guideline, a meeting was convened in April 2018 with

the guideline co-chairs, Drs. Jürgen Floege and Brad Rovin, Methods chair Marcello Tonelli, and the Evidence Review Team from the Cochrane Kidney and Transplant group. A key component of these discussions was to outline the literature search parameters (i.e., PICOS [Population, Intervention, Comparator, Outcomes, and Study design criteria]) for each of the key questions to be addressed in the guideline. It was clear that patient-reported outcome measures (PROMS) would be important for this guideline update, given the scarcity of clinical trials that examined hard outcomes in kidney patients. Effort has been made to consider such measures during the literature review.

The role of kidney biopsy was a key topic in conference discussions on the general management of GN. Although kidney biopsies are still the foundation of diagnosis and often of prognosis for most glomerular diseases, in some instances other diagnostic tools are now available that may be less invasive but can still aid clinical decision-making. An example may be the use of anti-PLA2R antibodies to diagnose primary MN in the absence of other confounding conditions. Assessment of proteinuria and hematuria still plays a prominent role in GN man-

agement, but the need for more specific biomarkers of disease activity, chronic kidney damage, and disease response was recognized as a priority for a future research agenda.

With an improved understanding of the pathophysiology behind glomerular diseases, there has been a greater appreciation that the classification of GNs should embrace an approach that considers both pathobiology and renal histology (Table 1). This is perhaps best exemplified by the term membranoproliferative glomerulonephritis (MPGN), which is a histologic descriptor of disease patterns caused by diverse origins, ranging from monoclonal gammopathies to alternate pathway of complement activation (3). Other areas where nomenclature needs to be updated include steroid-sensitive and steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis (FSGS). Therefore, an important aspect of the new guidelines will be to provide a uniform definition and classification of GNs.

Logistically, the systematic reviews that will be used to inform the 2020 guideline update have largely been completed and the Work Group panel is now in the process of finalizing guideline recommendations, reviewing the final grading for guideline statements, and formulating the underlying supportive rationale. This guideline update is being developed in a new era for KDIGO, which now includes a new approach that calls for a transparent and closer coupling between the recommendation statements and the underlying evidence base while still providing much-needed guidance to our audience through the use of practice points, particularly in areas where strong conclusive evidence is lacking in the GN population. Additionally, the guideline will be published both in print and in an electronic format, MAGICapp, so as to create a “living guideline” that can be updated in real time as new trial results become available. ■

Jürgen Floege, MD, PhD, is director of the Division of Nephrology, Rheinisch-Westfälische Technische Hochschule Aachen University, Aachen, Germany. Brad H. Rovin, MD, is director of the Division of Nephrology, Wexner Medical Center at Ohio State University, Columbus, USA.

References

1. Floege J, et al. Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; 95:268–280.

2. Rovin BH, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; 95:281–295.

3. Goodship TH, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. *Kidney Int* 2017; 91:539–551.

Table 1. A pathogenesis-based approach to glomerulonephritis

Pathogenic type	Disease examples
Immune complex glomerulonephritis	<ul style="list-style-type: none">• IgA nephropathy• Lupus nephritis• Fibrillary glomerulonephritis (polyclonal/DNAJB9-positive subtype)• Infection-associated glomerulonephritis• Mixed (types II and III) cryoglobulinemic glomerulonephritis
Pauci-immune glomerulonephritis	<ul style="list-style-type: none">• ANCA-associated vasculitis• ANCA-negative pauci-immune glomerulonephritis
Antiglomerular basement membrane glomerulonephritis	<ul style="list-style-type: none">• Antiglomerular basement membrane disease
Monoclonal Ig-associated glomerulonephritis	<ul style="list-style-type: none">• Monoclonal Ig deposition disease (LCDD, HCDD, LHCD)• Proliferative glomerulonephritis with monoclonal Ig deposits• Monoclonal (type I) cryoglobulinemic glomerulonephritis• Immunotactoid glomerulopathy• Fibrillary glomerulonephritis (monoclonal subtype)
Complement-mediated glomerulonephritis	<ul style="list-style-type: none">• C3 glomerulonephritis• Dense deposit disease
Mutation of podocyte proteins	<ul style="list-style-type: none">• FSGS
Unknown circulating permeability factors	<ul style="list-style-type: none">• FSGS• Minimal change disease
Secondary glomerulonephritides	<ul style="list-style-type: none">• Glomerulonephritis due to infections, drugs, malignancy

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; DNAJB9, DNA J homolog subfamily B member 9; FSGS, focal segmental glomerulosclerosis; HCDD, heavy chain deposition disease; LCDD, light chain deposition disease; LHCD, light and heavy chain deposition disease. Adapted from Sethi S, et al. Mayo Clinic/Renal Pathology Society Consensus report on pathologic classification, diagnosis, and reporting of GN. *J Am Soc Nephrol* 2016; 27:1278–1287 with permission.



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

Check out Kidney News Online at www.kidneynews.org

KDIGO Quo Vadis: Anemia

By Iain C. Macdougall

It is now seven years since the KDIGO guideline on anemia management in chronic kidney disease (CKD) was published in August 2012 (1). To accuse KDIGO of being lazy and idle in generating any updates or revisions would be inappropriate on two accounts.

First, and most important, there has really not been enough truly robust scientific data that would dramatically alter the evidence base from the previous version of the anemia guideline, in which the four *NEJM* “biggies” on erythropoiesis stimulating agent (ESA) therapy were reviewed and critiqued by the evidence review team: US Normal Hematocrit Trial (2), CREATE (3), CHOIR (4), and TREAT (5). Within the past few months, however, this deficiency has perhaps been partially corrected with the publication of the PIVOTAL study (6); (please forgive the egotistical plug)—more on that later.

The second reason why KDIGO should be forgiven is that they organized a superb Controversies Conference on iron management in San Francisco in March 2014, with a much-cited conference report published in *Kidney International* in January 2016 (7).

The iron Controversies Conference and PIVOTAL share a common theme: both had the aim of critically examining the risk-to-benefit ratio of intravenous (IV) iron in patients with CKD. The conference highlighted several concerns and potential adverse consequences of using IV iron (Table 1), whereas PIVOTAL was a large randomized controlled trial that compared hard endpoints in patients randomly assigned to a proactive high-dose IV iron regimen with those randomized to a reactive low-dose IV iron regimen. The primary endpoint was a composite of all-cause death, myocardial infarction, stroke, and hospitalization for heart failure; secondary endpoints included the components of the composite primary endpoint and a recurrent event analysis of the primary endpoint, along with some additional safety outcome measures.

The statistical plan prespecified an initial noninferiority analysis, which, if met (which it was; $p < 0.001$), allowed progression to a superiority analysis; this too was met with a p value of 0.04. Thus, the authors concluded that proactive high-dose IV iron reduced the composite hard endpoint of all-cause death and the three nonfatal cardiovascular events. Secondary endpoints included a recurrent event analysis, which again was positive in favor of the

high-dose iron arm ($p = 0.0027$), and also fatal or nonfatal myocardial infarction (31% reduction in favor of the high-dose arm; $p = 0.015$) and hospitalization for heart failure (34% reduction in favor of the high-dose arm; $p = 0.023$). The ESA dose requirements and use of blood transfusions were both reduced by approximately 20%. Contrary to widespread opinion and observational data, no excess of infections was seen in the high-dose iron arm (6). This study therefore generated level A evidence to inform future clinical guidelines, including KDIGO, and will no doubt be scrutinized by the evidence review team in relation to any KDIGO update.

The other huge development in the anemia field has been the extensive global assessment of a new class of agents, which are orally active and act by upregulating erythropoietin gene expression in the kidneys and liver. This new class of drugs is called the hypoxia-inducible factor prolyl hydroxylase domain inhibitors (HIF PHD inhibitors) (8, 9).

The HIF PHD inhibitors inhibit the breakdown of the transcription factor, HIF, thus inducing an increase in endogenous levels of erythropoietin. Phase 2 trials of five such drugs in this class (roxadustat, daprodustat, vadadustat, molidustat, and enarodustat) have confirmed the ability of HIF PHD inhibitors to both correct anemia and maintain hemoglobin in patients already taking an ESA (Table 2).

Furthermore, there are positive effects on iron metabolism, with the upregulation of several iron regulatory genes and a secondary downregulation of hepcidin, all of which seek to improve iron availability and enhance erythropoiesis. Finally, this new class of drugs achieves its biologic effects with the patients exposed to much lower circulating levels of erythropoietin, which could have positive cardiovascular benefits. This is currently being tested in large phase 3 clinical trials in thousands of patients with major adverse cardiovascular events (MACE) endpoints. Preliminary information on the MACE results from the phase 3 roxadustat program has recently become available in a FibroGen press release (10). Further information from the phase 3 trials on the safety of roxadustat, and of the other HIF PHD inhibitors, will be forthcoming, and this is particularly pertinent given that these agents also upregulate several hundred other hypoxia-sensitive genes, including vascular endothelial growth factor, glycolytic enzymes, and others, which could potentially produce hitherto unexpected adverse clinical consequences. Whether or not these theoretic concerns are borne out in clinical practice remains to be seen.

Once we have the phase 3 data to inform us about cardiovascular events and safety, it then seems timely to update the KDIGO anemia guideline. Several scenarios are possible. The studies could meet noninferiority for their primary endpoint in terms of MACE outcomes, with regard to both

active ESA comparator and placebo. MACE outcomes could be reduced with HIF PHD inhibitors in comparison with ESA therapy. MACE events could be increased in comparison with ESA therapy. In addition to the primary endpoint, many other permutations of outcomes are possible with regard to the secondary endpoints. Speculating on all the possible permutations, along with their implications for future clinical use, is beyond the scope of this commentary, but review of the data by the evidence review team and a future working group of KDIGO will be helpful, informative, and vital to ensure that the correct evidence-based guidelines on their use are achieved. ■

Iain C. Macdougall, MD is Consultant Nephrologist and Professor of Clinical Nephrology, Department of Renal Medicine at King's College Hospital, London, United Kingdom.

References

1. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012; 2:292–298.
2. Besarab A, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; 339:584–590.
3. Drüeke TB, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; 355:2071–2084.
4. Singh AK, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355:2085–2098.
5. Pfeffer MA, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; 361:2019–2032.
6. Macdougall IC, et al. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019; 380:447–458.
7. Macdougall IC, et al. Iron management in chronic kidney disease: Conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) controversies conference. *Kidney Int* 2016; 89:28–39.
8. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. *Am J Kidney Dis* 2017; 69:815–826.
9. Locatelli F, et al. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. *Am J Nephrol* 2017; 45:187–199.
10. <https://fibrogen.gcs-web.com/news-releases/news-release-details/fibrogen-announces-positive-phase-3-pooled-roxadustat-safety-and>

Table 1. Previous concerns regarding intravenous iron discussed at the KDIGO iron Controversies Conference

• Increased oxidative stress
• Increased atherogenesis
• Cardiovascular toxicity
• Inflammation
• Immune dysfunction
• Cellular toxicity
• Increased infections

Table 2. Five of the HIF PHD inhibitors currently in clinical development

Company	Molecule	Drug name	Phase of development
FibroGen Astellas AstraZeneca	FG-4592	Roxadustat	Phase 3
GSK	GSK 1278863	Daprodustat	Phase 3
Akebia Mitsubishi Otsuka Vifor Fresenius	AKB-6548	Vadadustat	Phase 3
Bayer	BAY 85-3934	Molidustat	Phase 2/3
Japan Tobacco Inc	JTZ-951	Enarodustat	Phase 2

Abbreviations: HIF PHD = hypoxia-inducible factor prolyl hydroxylase domain.

Cardiovascular Disease in CKD Controversies Conferences

By Charles A. Herzog

My involvement with KDIGO began a decade ago. In December 2009, international co-chairs Bertram Kasiske, MD, and Prof. Dr. Kai-Uwe Eckardt invited me to co-chair a Controversies Conference on cardiovascular disease in chronic kidney disease (CKD) with Professor Eberhard Ritz.

This conference, titled “Cardiovascular disease in CKD: What is it and what can we do about it?” was held in October 2010 in London. It focused on areas of clinical relevance in four breakout groups: 1) coronary artery disease and myocardial infarction; 2) congestive heart failure; 3) cerebrovascular disease, stroke, atrial fibrillation, and peripheral arterial disease; and 4) sudden cardiac death (1). Designed to address the broad area of intersection between cardiology and nephrology, the conference was unique in that the invited international experts included equal numbers of nephrologists and cardiologists (and additional representation by neurologists and other disciplines). Each breakout group was co-chaired by a cardiologist and a nephrologist (a breakout session on stroke and atrial fibrillation also included a neurologist). A main point of feedback I received after the conference related to how unusual and valuable an extended conversation between cardiologists and nephrologists was, inasmuch as this was unique in the experience of conference participants.

The conference report was published in *Kidney International* in July 2011 (1). In my opinion, the conference was a great success because it provided a remarkably prescient roadmap for future research (Table 1). The conference report provided a detailed picture of the areas of uncertainty in cardiovascular disease in patients with CKD. I still find it valuable to consult this roadmap, even a decade later, for perspective. For example, knowledge gaps related to the treatment of ischemic heart disease were identified. A decade later, we await results of the ISCHEMIA-CKD trial. The large knowledge gaps related to the treatment of atrial fibrillation for prevention of cardioembolic stroke occupied one breakout group, and the conference report prefigured a large body of investigation that occurred in the subsequent decade. Also noteworthy was the call for clinical trials involving anticoagulant agents that were novel at the time, now not so novel, for stroke prevention in patients with CKDG4-G5D with atrial fibrillation. Even a decade later, such a trial in this population is yet to be completed.

Half a decade later, I received a new invitation to help organize a series of CKD–cardiovascular Controversies Conferences modeled on the framework of the original London conference, but with a narrower focus. I accepted this invitation in December 2015, and on January 26, 2016, I sat down with KDIGO staff and the international co-chairs, Professors Wolfgang Winkelmayer and David Wheeler, in the Tanglely room of the Hilton Paddington in London. We agreed to plan a series of four or five CKD–cardiovascular Controversies Conferences spanning the next 3 to 5 years. Much of the 2010 conference agenda would be revisited in the light of new knowledge, and some new areas of discussion would be added. We agreed that for all these conferences, broad representation of the international cardiology and nephrology communities would be desirable. The overall conference series was entitled “KDI-

GO Cardiovascular and CKD Conference Series on the Kidney, Heart, and Vasculature.”

The first conference, held in Berlin in October 2016, focused on atrial fibrillation and stroke in kidney disease, stroke prevention with oral anticoagulation, rate vs. rhythm: control of atrial fibrillation, sudden cardiac death, and potassium homeostasis. The overall charge to conference participants was to “identify key issues relevant to the optimal prevention, management, and treatment of arrhythmias and their complications in patients with kidney disease.” The conference co-chairs were Professors Mintu Turakhia and Christoph Wanner.

One notable result was the drafting of a new definition of sudden cardiac death specific to patients receiving hemodialysis. Echoing comments I heard in London six years earlier, many participating cardiologists were impressed by their first opportunity to work with nephrologists in the broad area of arrhythmias in CKD. The conference report was published in the *European Heart Journal* (2). This was a departure from the previous publication of conference reports in *Kidney International*; an international cardiology readership was con-

sidered an appropriate audience for the first in the new kidney, heart, and vasculature conference series. The KDIGO Controversies reports have traditionally enjoyed a very wide audience. Reflecting the interest in the 2010 London conference, the 2011 *Kidney International* conference report has been cited 617 times (as of May 8, 2019).

The second conference, focused on heart failure, occurred in Athens in May 2017 and was co-chaired by Professors Andrew House and Peter McCullough. It included a detailed discussion of the epidemiology, pathophysiology, diagnosis, and treatment of heart failure across the spectrum of CKD, including kidney transplant recipients. The conference report was published in *Kidney International* in June 2019.

The third conference, on ischemic and valvular heart disease, was held in Vienna in June 2018 and was co-chaired by Professors Tom Marwick and Mark Sarnak. Some of the most spirited discussions of all the conferences occurred at the plenary sessions of the Vienna conference. The conference report was divided into two separate publications, both published in 2019 (valvular heart disease in

Table 1. Future directions for cardiovascular disease in chronic kidney disease

Condition	Knowledge gaps	Research needs
CAD, MI	<ul style="list-style-type: none">• Screening may be beneficial, but data are insufficient to advocate screening asymptomatic patients• Evidence lacking regarding primary and secondary treatment of CAD• Cardiovascular trials have frequently excluded CKD patients from enrollment	<ul style="list-style-type: none">• Clarify the interdependence of CKD with MI, and its relation to demographic characteristics such as gender• Clarify the pathophysiological relationship between development of plaque and subsequent rupture of selected plaques• Clarify roles of novel risk factors that are potential therapeutic targets• Broad-based validation of current stress and imaging modalities using coronary angiography with fractional flow reserve• Adequately powered CKD-specific clinical trials of aspirin, statins, novel anti-lipidemic agents, ACEIs, and ARBs• Define the ideal LDL cholesterol level and the role of newer antiplatelet and anticoagulant therapies• Randomized clinical trials comparing early invasive with conservative therapy post-ACS, and PCI with CABG
CHF	<ul style="list-style-type: none">• Understanding development and prevention of LVH, fibrosis, and LV dysfunction (systolic and diastolic)• Benefits of prolonged or quotidian dialysis• Absence of CKD-specific data on CHF treatment• Impact of sodium balance (intake, dialysate sodium concentration)	<ul style="list-style-type: none">• Evaluate asymptomatic LV dysfunction, examine changes in the kidney and cardiac function over time, and incorporate kidney- and cardiac-specific biomarkers• Clinical studies to investigate innovative monitoring and management techniques (serial biomarkers, bioimpedance, chronic <i>in vivo</i> monitoring)• Evaluate effects of CHF-specific risk-modifying and cardio-protective therapies (ACEIs, ARBs, renin and mineralocorticoid hormone inhibitors)• Investigate speculative treatments (vitamin D analogs/calcimimetics, cytokine-modulating drugs, iron-related treatments, endothelin receptor blockers, regenerative therapies)
Stroke	<ul style="list-style-type: none">• High-quality observational data on risk factors, precipitants, etiological subtypes, causes of death, and underlying arteriopathies• Risk of carotid artery stenting is undefined• Few data on treatment of acute stroke	<ul style="list-style-type: none">• Randomized clinical trials testing interventions for secondary prevention of stroke• Determine safety of intravenous thrombolysis of CKD G5D patients with acute ischemic stroke
Atrial fibrillation	<ul style="list-style-type: none">• Risks/benefits of anticoagulation with warfarin for stroke prevention• Efficacy, safety of dabigatran in CKD G4• Uncertainty regarding validity of the 2005 KDOQI guidelines regarding anticoagulation in dialysis patients with atrial fibrillation	<ul style="list-style-type: none">• Randomized clinical trials of warfarin and novel anticoagulants for stroke prevention in CKD G4–G5D patients with atrial fibrillation• Interventions to prevent atrial fibrillation: radiofrequency ablation, percutaneous closure of the left-atrial appendage, surgery
PAD	<ul style="list-style-type: none">• Few high-quality observational data on risk factors• Role of ankle–brachial index vs other diagnostic techniques• Prospective data on non-surgical therapies• Data regarding percutaneous vs surgical revascularization	<ul style="list-style-type: none">• Determine prevalence of preventive foot care• Assess regional differences in practice patterns• Generate management guidelines• Assess amputation frequency in programs that do and do not perform preventive foot care• Study bacteriology of diabetic patient feet
SCD	<ul style="list-style-type: none">• Standard risk factors derived from the general population may not apply• Few autopsy data• Dialysis patients excluded from primary and secondary prevention trials	<ul style="list-style-type: none">• Disease-specific, large-scale prospective cohort studies for risk stratification• Study heterogeneous CKD populations at all stages using all available risk-stratification techniques• Remove barriers preventing data linkage to allow for population-wide cohort and case–control studies• Randomized trials assessing the spectrum of interventions: β-blockers (such as carvedilol), ICDs, sympathetic ablation• Incorporate SCD as specific outcome in registry and clinical trial data. Investigate the potential role of sleep apnea in SCD

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; ICD, implantable cardioverter-defibrillator; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; LV, left ventricular; LVH, LV hypertrophy; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.

Kidney International (3), and ischemic heart disease in *Journal of the American College of Cardiology* (4)).

The final conference of the series will focus on aortic and peripheral arterial disease in CKD. During our planning for the London conference a decade ago, I was struck by the scarcity of knowledge regarding the management of peripheral arterial disease in patients with CKD. A decade later, I am still struck by the same large knowledge gaps. This fourth and last conference, scheduled for February 2020 in Dublin, will be co-chaired by Professors Holger Reinecke, who was a breakout session co-chair at the Berlin conference, and Kirsten Johansen, MD. The planned areas of focus will include aortic disease, peripheral arterial diseases, renovascular disease, and cerebrovascular disease.

It has been my pleasure to work with KDIGO in the

planning of these cardiovascular Controversies Conferences, now spanning an entire decade. Although the fourth conference will be the last of the kidney, heart, and vasculature series, given the importance of cardiovascular disease in the health of CKD patients, it is unlikely to be the last KDIGO conference on cardiovascular disease in CKD. ■

References

1. Herzog CA, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; 80:572–586.
2. Turakhia MP, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies

Conference. *Eur Heart J* 2018; 39:2314–2325.

3. Marwick TH, et al. Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; 96:836–849.
4. Sarnak MJ, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; 74:1823–1838.

Charles A. Herzog, MD, FACC, FAHA, is an Investigator with the Chronic Disease Research Group, Hennepin Healthcare Research Institute, and is a cardiologist and Professor of Medicine, in the Division of Cardiology, Department of Medicine, Hennepin Healthcare and the University of Minnesota, Minneapolis, USA.

KidneyCure

The ASN Foundation CureKidneyDiseases.org

Fund it. Find it.

Funding the cause. Finding the Cure.

Cardiorenal Syndrome

By Peter A. McCullough

The complex interplay between the kidney and the heart where one organ dysfunction can initiate or accelerate the decline of the other was recently addressed at a KDIGO Controversies Conference on the prevention, diagnosis, and management of heart failure in kidney disease (1). Since cardiorenal syndrome (CRS) is often observed in the setting of heart failure, CRS continues to be one of the highest topics of interest among those caring for medical patients in the hospital and for those in ambulatory primary and medical subspecialty care (2, 3). In 2019, Rangaswami et al. (4) published the first American Heart Association (AHA) Scientific Statement on the topic. This well-written document goes a long way in explaining what we know and how much more we don't know about CRS.



For type 1 CRS, which is most commonly acute heart failure (HF), followed by azotemia in response to intravenous diuretics, the important message is that the biomarkers of tubular injury in general are not elevated, which suggests that it is not a form of bona fide acute kidney injury (AKI) (5). Additionally, multiple studies have found that withdrawing renin-angiotensin-aldosterone system inhibitors (RAASi) because of clinical concern for the azotemia is associated with higher rates of readmission and death. Thus, one may take the view that in the absence of superimposed sepsis

or shock, type 1 CRS is a problem of insufficient plasma refill and relative arterial underfilling in the setting of excess venous congestion. Because RAASi lowers cardiac filling pressures acutely and antagonizes the maladaptive effects of angiotensin II in the kidney, it is mechanistically attractive to continue these agents in the setting of acute HF unless there is a compelling indication (hypotension, hyperkalemia, or drug intolerance) to withdraw them. Contextual cessation of RAASi because of azotemia does not appear to be well supported, and nephrologists should reconsider this common approach.

Type 2 CRS is chronic HF contributing to the progression of chronic kidney disease (CKD), and this certainly happens in the setting of type 2 diabetes and macroalbuminuria (6, 7). HF itself may contribute to proteinuria, and the combined effect on peripheral edema leads to escalating doses of diuretics. Whereas the principles of decongestion and a narrow therapeutic window for cardiac volume loading are manifest, observational data suggest that patients with HF who are receiving the highest doses of diuretics have the worst outcomes. Additionally, strategies such as one-size-fits-all high/low-dose loop diuretics in HF or intravenous infusions have failed to shed light on the optimal approach. However, when diuretic management is guided by the use of blood biomarkers such as B-type natriuretic peptide (BNP) in the office or implantable pulmonary pressure monitors, HF outcomes including hospitalization and death can be improved.

Type 3 CRS is AKI that leads to HF (8). This can certainly happen in an elderly hospitalized patient; the AKI usually must be anuric and the patient be predisposed to diastolic or systolic dysfunction. Few data exist on this problem; however, observational studies suggest that inadvertent intravenous fluid administration may make it worse. Thus, our use of intravenous crystalloid must be goal directed, and “maintenance” parenteral fluid approaches should be discouraged.

Type 4 CRS is progressive CKD that leads to left ventricular hypertrophy and dysfunction (9, 10). It is important to realize that 20% of CKD patients carry a diagnosis of HF before they start renal replacement therapy, and there is a wealth of opportunity upstream in CKD to prevent HF and/or decrease the risk for hospitalization or death (11, 12). For patients who are receiving dialysis, the choice of frequent home dialysis 5 or 6 days a week appears to be the most beneficial in preventing the development or worsening of HF (13).

Finally, type 5 CRS is simultaneous heart and kidney failure in the setting of an overwhelming systemic illness such as influenza, sepsis, or multiple trauma (14). The principles here are supportive care to allow the opportunity for organ recovery (15). Avoidance of superimposed ischemic or chemotoxic injury to either organ is a high priority. The data suggest that maintaining mean arterial pressures > 65 mm Hg is essential to organ preservation and survival. In this setting, biomarkers of cardiac injury and failure (troponin, BNP) and also AKI (TIMP2 × IGFBP7, NGAL, L-FABP) can be enormously useful in distinguishing transient hemodynamic effects from acute tubular injury (16). The AKI biomarkers strongly predict the development of stage 2/3 AKI (doubling or more of serum creatinine) over the following 12 to 48 hours (17). This can be enough time to change clinical strategies, including use of hemodynamic monitoring, inotropic agents, and withdrawal of nephrotoxins such as certain antibiotics or the use of iodinated contrast material.

In summary, the work of the AHA Scientific Committee has been extremely valuable in moving this field forward, and to find this piece in a cardiology journal is a welcome sight for cardioneurologists, who are working so hard to care for these patients. To learn more about this topic, please consider attending the annual meeting of the Cardiorenal Society of America, to be held in Phoenix, Arizona, March 6–7, 2020, www.cardiorenalsociety.org. ■

Peter A. McCullough, MD, MPH, is Professor of Medicine

and Vice Chair of Internal Medicine at Baylor University Medical Center, Dallas, Texas.

References

- House AA, Wanner C, Sarnak MJ, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2019; 95:1304–1317.
- McCullough PA. Cardiorenal syndromes: Pathophysiology to prevention. *Int J Nephrol* 2010; 2010:762590.
- McCullough PA, Ahmad A. Cardiorenal syndromes. *World J Cardiol* 2011; 3:1–9.
- Rangaswami J, et al. Cardiorenal syndrome: Classification, pathophysiology, diagnosis and treatment strategies: A scientific statement for healthcare professionals from the American Heart Association. *Circulation* 2019; 139:e840–e878.
- Haase M, et al. Pathogenesis of cardiorenal syndrome type 1 in acute decompensated heart failure: Workgroup Statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol* 2013; 182:99–116.
- McCullough PA, Verrill TA. Cardiorenal interaction: Appropriate treatment of cardiovascular risk factors to improve outcomes in chronic kidney disease. *Postgrad Med* 2010; 122:25–34.
- Cruz DN, et al. Pathophysiology of cardiorenal syndrome type 2 in stable chronic heart failure: Workgroup Statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol* 2013; 182:117–136.
- Bagshaw SM, et al. Cardiorenal syndrome type 3: Pathophysiologic and epidemiologic considerations. *Contrib Nephrol* 2013; 182:137–157.
- Larsen T, et al. Type 4 cardiorenal syndrome: Myocardial dysfunction, fibrosis, and heart failure in patients with chronic kidney disease. *J Clin Exp Cardiol* 2012; 3:4. DOI: 10.4172/2155-9880.1000186
- Tumlin JA, et al. Cardiorenal syndrome type 4: Insights on clinical presentation and pathophysiology from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol* 2013; 182:158–173.
- McCullough PA. Future therapeutic prospects for treatment of cardiorenal syndromes. In: *Cardio-Renal Clinical Challenges*, edited by Goldsmith DA, Covic A, Spaak J., Springer International Publishing AG, 2015, pp. 189–195.
- McCullough PA, et al. Nutritional deficiencies and sarcopenia in heart failure: A therapeutic opportunity to reduce hospitalization and death. *Rev Cardiovasc Med* 2016; 17:S30–S39.
- Rangaswami J, McCullough PA. Heart failure in end-stage kidney disease: Pathophysiology, diagnosis, and therapeutic strategies. *Semin Nephrol* 2018; 38:600–617.
- Larsen T, et al. A lethal case of influenza and type 5 cardiorenal syndrome. *Crit Care Med* 2013; 41:1296.
- Mehta RL, et al. Cardiorenal syndrome type 5: Clinical presentation, pathophysiology and management strategies from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol* 2013; 182:174–194.
- Ostermann M, et al. Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. *Crit Care Med* 2017; 46:375–383.
- Tecson KM, et al. Optimal cut points of plasma and urine neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury among critically ill adults: retrospective determination and clinical validation of a prospective multicentre study. *BMJ Open* 2017; 7:e016028.

KDIGO: One Guideline to Rule Them All?

“Rules are for the guidance of wise men and the obedience of fools.” Group Captain Sir Douglas Bader, 1910–1982

By Swapnil Hiremath

One of the first major guidelines in nephrology was the Dialysis Outcomes Quality Initiatives (DOQI), which later morphed into the KDOQI guidelines that we all know today. Good as they were, they were developed by the National Kidney Foundation, based in the United States, and other countries went their own way. The Canadian Society of Nephrology has had slightly different variations in their guidelines, its last major one from 2011, on the timing of initiation of dialysis (1). One reason for this lull is that producing guidelines is a time-intensive and resource-intensive process. So, 15 years ago, when *Kidney Disease: Improving Global Outcomes (KDIGO)* came into being, there was a collective sigh of relief. The KDIGO Work Groups include experts from all over the world; they undergo a rigorous process and use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework for appraising the evidence and making the recommendations.

So how have the past 11 years of living in the KDIGO era been since its first guideline? It has been a mixed bag, to be sure. Paradoxically, one of the most useful guidelines, which this author has personally referred to the most, has been the one for which the evidence is the thinnest. The glomerulonephritis guideline covers each glomerular disease separately, and the best way to think of them is as excellent review articles covering the existing evidence and giving helpful advice (2).

Some other guidelines veer off strangely in places—perhaps related to the process and timelines. In 2011, the largest trial of N-acetylcysteine in contrast-induced acute kidney injury with a sample size five times larger than in any previous study, was published (3). Despite the clear results of this trial showing no benefits, the 2012 KDIGO acute kidney injury guideline recommended the use of N-acetylcysteine (Grade 2D) (4). There was also a Grade 2B recommendation for the use of citrate over heparin in continuous renal replacement therapy. Given the logistics and cost implications of citrate continuous renal replacement therapy, this does read like ivory tower academia interpreting the evidence narrowly and calling the shots. Similarly, even in the revised mineral bone disease guideline (MBD), a 2017 update calls for routine bone mineral density testing (5). What does one do with those data, given that there is not a single trial with clinically relevant outcomes to guide therapy in this area? The Grade 2B recommendation to avoid or limit the use of calcium-based phosphate binders relies on data that are

not very robust, to say the least (6).

But these are minor quibbles. There has been much progress overall; for example, the 2017 update took away some of the egregiously narrow MBD targets and sensibly allows for analysis of trends before decisions are made. The “research needs” paragraphs at the end of each section have been helpful for researchers to focus their efforts on high-yield topics. From a local perspective, the KDIGO guidelines serve as a baseline starting point, and the Canadian Society of Nephrology is then able to publish their review of the KDIGO guidelines, adding their perspective, points to highlight, and recommendations on which the Canadian guidelines differ, with a detailed supporting rationale (7).

What should come next for KDIGO? There is now a greater focus on patient-reported outcome measures and patient-reported experience measures, and some incorporation of these elements is a natural progression. There is also a greater shift away from experts who may have conflicts of interest in the wider guideline world—and this is decidedly a complex topic but worthy of consideration. Last, do we need more guidelines or fewer guidelines? As has been famously said, perhaps guidelines should be like wars, waged only when there is absolute consensus and overwhelming evidence (8). In the case of nephrology, sadly, we might end with very few guidelines if we follow this advice. Another way of looking at the problem is to view them truly like guidelines—for guidance, not as quality metrics or performance measures. The aforementioned glomerulonephritis guideline represent an obvious example of how this can play out.

Paradoxically, one area in which this clinician is eagerly waiting for the KDIGO guidelines to drop is a guideline for hypertension, for which there is no lack of existing guidelines. The current buffet of blood pressure (BP) guidelines leaves much to be desired and serves to confound and confuse the unwary clinician. Table 1 shows the smorgasbord of available advice on BP management (9–14). The choices range from the 130/80 mm Hg one size fits all to the systolic BP <120 mm Hg because CKD

means high cardiovascular risk, but not if you are diabetic, in which case it's <130/80 mm Hg, but if GFR is <20 then maybe it should be <140/90 mm Hg. The recently released European guidelines also have a floor, with a BP target being <140 mm Hg but not less than 120 mm Hg. In this bewildering Byzantine area, KDIGO can serve as a beacon of clarity. Let's hope the BP Work Group lives up to our hopes and expectations. ■

Swapnil Hiremath, MD, MPH, FASN, is Staff Nephrologist at the Ottawa Hospital, an Associate Professor at the University of Ottawa, and an Associate Scientist at the Ottawa Hospital Research Institute, Ottawa, Canada.

References

1. Nesrallah GE, et al. Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. *CMAJ* 2014; 186:112–117.
2. *Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl* 2012; 2:139–274.
3. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: Main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation* 2011; 124:1250–1259.
4. *Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl.* 2012; 2: 1–138.
5. Ketteler M, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: What's changed and why it matters. *Kidney Int* 2017; 92:26–36.
6. Hiremath S, Akbari A. Calcium-based phosphate binders and chronic kidney disease. *Lancet* 2014;

Continued on page 28 ➤

Table 1. Summary of existing national and international hypertension guidelines, as of June 2019

	ACC/AHA (2017)	KDIGO (2012)	ESH/ESC (2018)	NHF Australia (2016)*	HTN Canada (2018)	ACF/AAFP (2017)
No DM No proteinuria	130/80	140/90	SBP target to 130 but not < 120 DBP 70–79	140/90 120 if tolerated	140/90 SBP < 120 if high CV risk**	
CKD No DM Proteinuria	130/80	130/80	SBP < 140 to < 130 if tolerated DBP 70–79	140/90 120 if tolerated	140/90 SBP < 120 if high CV risk**	
CKD DM No proteinuria	130/80	140/90	SBP < 140 to < 130 if tolerated DBP 70–79	140/90 120 if stroke priority	130/80	
CKD DM Proteinuria	130/80	130/80	SBP < 140 to < 130 if tolerated DBP 70–79	140/90 120 if stroke priority	130/80	
Renal transplant	130/80	130/80	No specific statement	No separate recommendation	140/90 SBP < 120 if high CV risk**	
Elderly	130/80	Individualize	Elderly = 65 years or older SBP target 130–139 if tolerated DBP 70–79	Aim towards 120 if tolerated	140/90 SBP < 120 if high CV risk**	< 150 (strong) < 140 if h/o stroke or high CV risk (weak)*

Notes:

Proteinuria = 30 mg/day for KDIGO; > 300 mg/day for ACC/AHA

*The NHF Australia guidelines specify different strengths and levels of evidence for 140 (usually strong and level 1) vs for 120 (strong to moderate, level 2)

**See details at guidelines.hypertension.ca for definitions/cautionary statements

*AAFP/ACP use their own grades (strong to weak, recommendation, high to low quality of evidence)

AAFP, American Academy of Family Physicians; ACC, American College of Cardiology; ACP, American College of Physicians; AHA, American Heart Association; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; DM, diabetes mellitus; ESC, European Society of Cardiology; ESH, European Society of Hypertension h/o, history of; HTN Canada, Hypertension Canada; KDIGO, Kidney Disease: Improving Global Outcomes; NHF, National Heart Foundation of Australia; SBP, systolic blood pressure.

KDIGO: One Guideline

Continued from page 27

- 383:216.
7. Ruzicka M, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for the management of blood pressure in CKD. *Am J Kidney Dis* 2014; 63:869–887.
8. Husten L. Why health guidelines should be waged like war. *Forbes Magazine* August 2014. <https://www.forbes.com/sites/larryhusten/2014/08/22/why-guidelines-should-be-waged-like-war/>. Accessed November 18, 2019.

9. Nerenberg KA, et al. Hypertension Canada's 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children. *Can J Cardiol* 2018; 34:506–525.
10. Williams B, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39:3021–3104.
11. Whelton PK, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA /PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension* 2018; 71:e13–e115.
12. Qaseem A, et al. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: A clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2017; 166:430–437.
13. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl* 2012; 2: 337–414.
14. Gabb GM, et al. Guideline for the diagnosis and management of hypertension in adults - 2016. *Med J Aust* 2016; 205:85-89.

KDIGO Leadership: Our Vision for KDIGO's Future: A Push Toward More Current Guidelines

By Wolfgang C. Winkelmayer and Michel Jadoul

Over the past decade, Kidney Disease: Improving Global Outcomes (KDIGO) has established as a leading global force in making observations about the practice of kidney health care and in synthesizing recommendations for best practices. This has occurred through staging Controversies Conferences with global experts and practitioners on relevant topics in kidney health, developing Clinical Practice Guidelines, and building a portfolio of Implementation Programs through which the products from the aforementioned two activities are interpreted and discussed in the local or regional context. All these activities are based on the premise articulated in KDIGO's mission statement: to improve the health of patients with kidney diseases.

We see KDIGO continuing to be innovative and creative. We aim to establish a library of 20 to 25 guidelines that cover most aspects of kidney health. These guidelines will provide vital information to clinicians around the world who care for patients with kidney disease. Furthermore, our vision is that KDIGO Guidelines will always be current. As we are doing now, we shall continue to devote efforts and resources to the challenge of updating our guidelines in an ongoing fashion rather than in a discontinuous manner. This requires a paradigm change in the operative approach toward evidence surveillance, appraisal, interpretation, and dissemination.

Our future will involve working with an electronic guideline publishing platform, MAGICApp (Figure 1) where guideline recommendations, their rationale, and the underlying meta-analyzed data are stored in modular form. As such, when new data prompt an update of a single recommendation, the corresponding module can be modified and then reloaded in the system, thus ensuring currency of

the complete guideline. KDIGO will continue to lead nephrology in using novel technology like this. This modular updating process will be faster, cheaper, and less labor intensive than before because it builds on work performed by prior guidelines. This can be achieved while still maintaining the scientific rigor that has served as the foundation of our reputation. The guideline Work Group, an independent Evidence Review Team, and a public commenting phase will remain critically essential in preserving the integrity of our work as we leverage this electronic platform to better streamline and simplify our guideline development efforts.

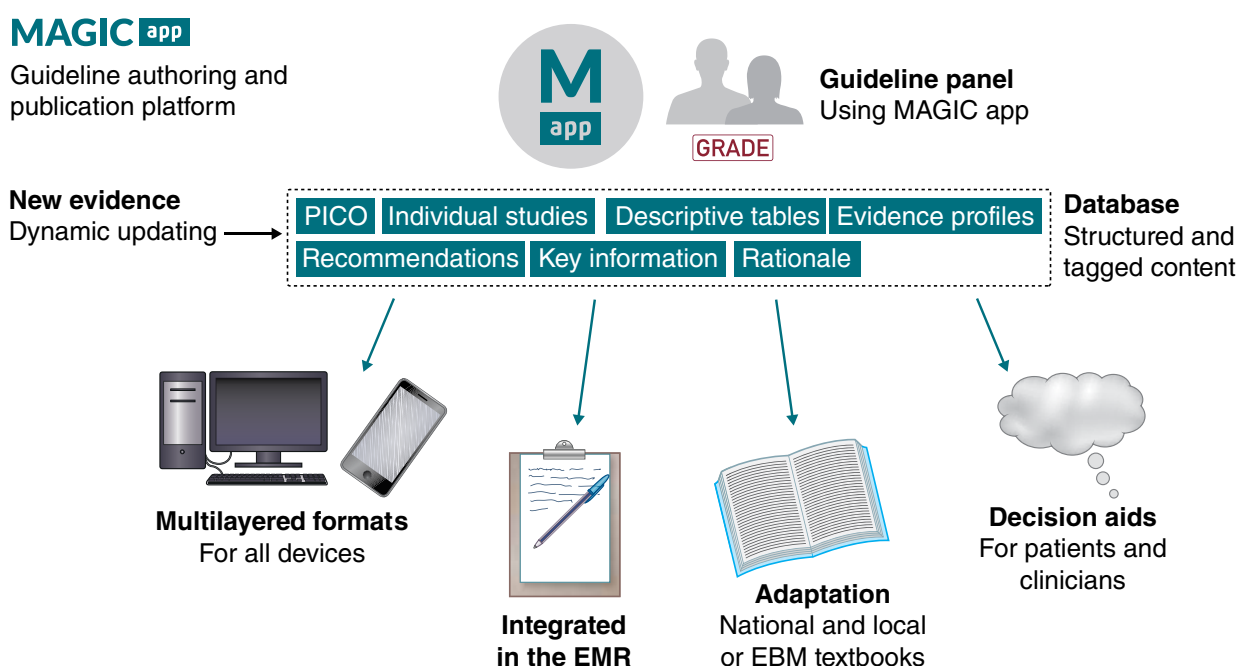
After a guideline is published, a few of the Work Group members will participate in ongoing evidence surveillance efforts (Figure 2). When new studies are found, KDIGO leadership and the appropriate guideline Work Groups will be informed and these Work Group members will determine what the new evidence means in the context of the existing guideline. If it is significant, the KDIGO Executive Committee can authorize the launch of an update process. That process is identical with that of a *de novo* guideline except that it examines only a discrete set of recommendations directly related to the new evidence. Once the updated systematic review has been completed, the new or revised guideline recommendation(s) will be added to MAGICApp and published in conjunction in *Kidney International*. The update is also made available on the KDIGO website so that

the currency of all guidelines can be assured when the reader searches www.MAGICApp.org or www.kdigo.org.

KDIGO also aims to continue to organize four or five Controversies Conferences each year. This signature program of KDIGO has brought together hundreds of globally recognized experts and kidney health practitioners to discuss and make observations on relevant aspects of kidney diseases that are not fully decided. Traditionally, these experts have been nephrologists, but more recently we have specifically sought input from a variety of other disciplines. Indeed, great contributions and valuable insights to the Conferences have been made by cardiologists, oncologists, intensivists, endocrinologists, emergency physicians, and other specialists who participate in the care of patients with kidney disease. The reports from our Controversies Conference are widely read online (Figure 3), downloaded, and cited, and our work is used around the world to help treat patients.

KDIGO also aims to build even more relevance to our constituents into our work by meaningfully involving patients. Our vision is to include patients at Controversies Conferences and even in Guideline Work Groups. We have established a Global Patient Network consisting of patients who told us that they want to volunteer as public reviewers, participate in focus groups, attend Controversies Conferences, and serve on Work Groups. They will

Figure 1. Sample of MAGICApp content and format



be asked for input on all our activities. To further solidify this patient-centered approach, KDIGO will continue its relationship with the innovative Standardizing Outcomes in Nephrology (SONG) initiative, which convenes focus groups for structured input on our work and helps us to better communicate with patients around the world. This effort is very important and builds commitment to our sole constituency: the patients.

We are also thinking creatively about ways to improve and enhance our guideline development process and knowledge translation. In this vein we have appointed a new Methods Committee to work with our esteemed Methods Chair and well-known evidence-base researcher, Marcello Tonelli, in strengthening and formalizing our guideline methodology. We are developing a Methods Manual to provide a formal source of benchmarks and reference support for future Work Groups, Evidence Review Teams, and the KDIGO organization as a whole.

We are also investing in our human resources. This

year we added a new staff consultant, who worked for more than 14 years at the Tufts University and Brown University Evidence Review Centers, with which we had contracted in the past. We have continued the tradition of recruiting a high-quality and active Executive Committee to lead the organization. Its members are working on special projects to broaden their contributions to the organization. This group of 20 people, who meet twice a year, are among the best in the nephrology community. They work with hundreds of volunteers, past and present, to personally support and help advance KDIGO's mission.

The 2019 Executive Committee is an excellent example of how KDIGO is building toward demographic and geographic representation. Our current leadership group has equal numbers of women and men and includes at least one member from every continent. We are also actively reaching out and inviting early-career academicians and non-academic real-world practitioners to participate

in our activities. That kind of diversity will be reflected ever more prominently in future Controversies Conferences and Work Group rosters.

KDIGO's future is very bright. We see an effective, efficient, and inclusive global organization spearheading and partnering in initiatives toward the goal for real improvement in the outcomes in patients with kidney disease worldwide. KDIGO has the resources, talent, and vision to be the vital part of global nephrology that is in keeping with the aspiration of our founders. ■

Wolfgang C. Winkelmayer, MD, FASN, and Michel Jadoul, MD are KDIGO Co-Chairs. Wolfgang C. Winkelmayer is Gordon A. Cain Professor of Medicine; Chief, Section of Nephrology; and Director, Selzman Institute for Kidney Health at Baylor College of Medicine, Houston, Texas, USA. Michel Jadoul is Head of Nephrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

Figure 2. Snapshot of the new KDIGO guideline updating process

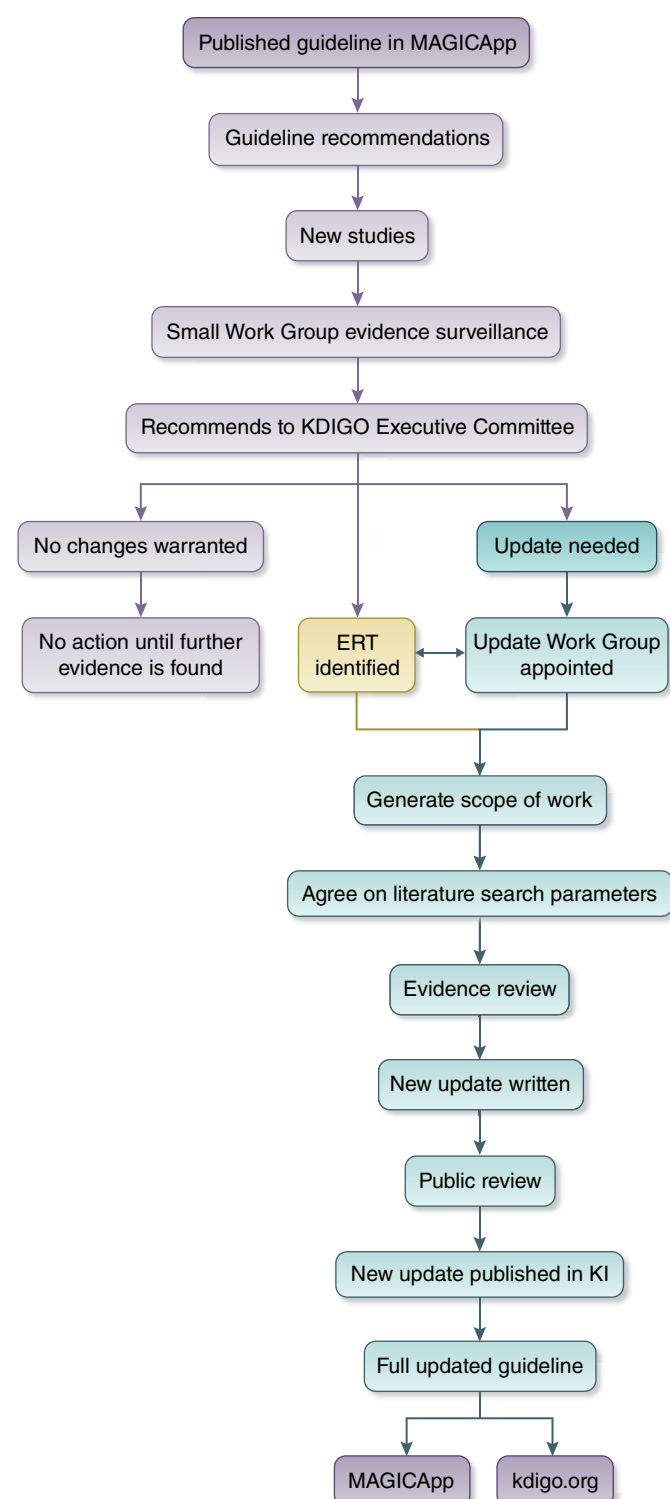
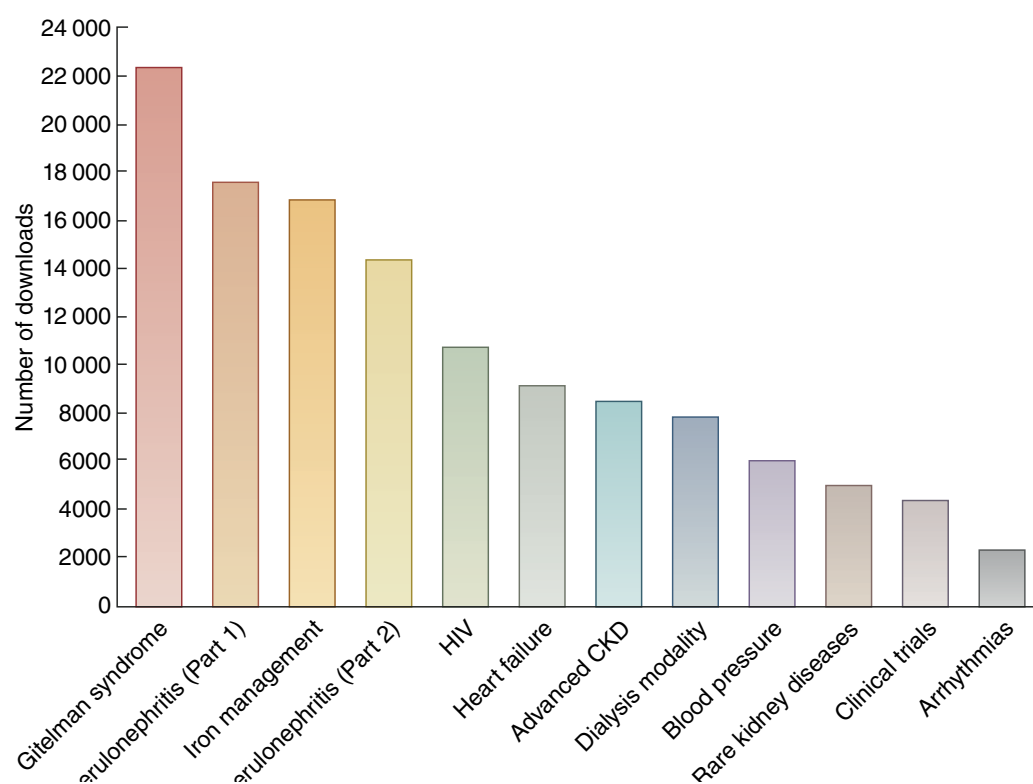


Figure 3. Number of times KDIGO Controversies Conference reports have been accessed online



Can Exercise Training Affect Cardiovascular Morbidity in Patients with CKD?

By Amaryllis H. Van Craenenbroeck

Decreased exercise capacity and cardiovascular risk are integral features of chronic kidney disease (CKD), with a debilitating impact on quality of life and survival.

Exercise capacity (VO₂peak) is an objective assessment of physical functioning, which is the ability to perform physical activity. Physical activity (including exercise) is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure (1). Both reduced physical functioning and physical activity are associated with an increased risk of adverse clinical outcomes in both non-dialysis-dependent (2) and dialysis-dependent people with CKD (3, 4).



Independent of this risk, individuals with CKD must cope with an extremely high cardiovascular risk. The pathophysiology and phenotype of vascular disease in CKD patients is unique: both the intimal and medial layer are concomitantly affected, in part by common mechanisms, resulting in different clinical entities (5): endothelial dysfunction (the harbinger of atherosclerosis) (6) and arterial stiffness (7), respectively.

Given the association of both exercise capacity and cardiovascular disease with mortality in CKD, several trials have been conducted to investigate causality and the effectiveness of physical activity interventions to improve outcomes. The outcomes studied in this context are manifold and vary from molecular mechanistic endpoints to survival.

Besides traditional risk factor modification, exercise improves vascular health through increased nitric oxide bioavailability and generalized anti-oxidative and anti-inflammatory effects both in patients with and without CKD (8, 9). For endothelial function in vivo, there is extensive clinical evidence that regular physical training partially corrects endothelial dysfunction in prehypertensive subjects (10) and in patients with coronary artery disease (11) and chronic heart failure (12). However, evidence in CKD from properly conducted randomized clinical trials (RCT) is scarce and conflicting.

In non-dialysis-dependent patients with CKD, a 12-week aerobic exercise training program improved

microvascular function, possibly as a consequence of improved redox balance (13). Despite a greater increase in VO₂ peak with a similar 12-week aerobic training regimen, another study did not show improvement in flow-mediated dilation, the gold standard of non-invasive endothelial function measurement (14). Neither study observed an effect on pulse wave velocity (PWV), a measurement of arterial stiffness. This finding is in line with findings in dialysis patients, where a 6-month aerobic exercise training program did not affect PWV (15).

In kidney transplant recipients, however, implementation of a regular aerobic or resistance training program for 3 months resulted in a significant improvement of PWV (16). This beneficial effect can be maintained for up to 12 months by self-managed physical activity (17). In line with findings in the general population (18), a recent meta-analysis confirmed the blood pressure-lowering effect of exercise training (combined aerobic and resistance) in hemodialysis patients using data from 1254 patients in 33 trials. The effect in non-dialysis-dependent CKD is less unequivocal, with a significant blood pressure-lowering effect after 24 weeks of aerobic training (19), but no overall effect at 52 weeks (20). Data regarding cardiovascular mortality is derived from only one (retrospective) study, which reported an association of improved cardiovascular outcome after completion of a 3-month rehabilitation program (21).

In conclusion, well-designed large RCTs in CKD with CV primary endpoints are scarce, but clinical evidence on the beneficial effects outweighs data on potential harm. Accordingly, patient counseling to emphasize

the importance of regular physical activity has been incorporated in American and European clinical practice guidelines.

The stage has been set to test and formally establish from which type of exercise training, and at what intensity and dose, patients derive the largest benefit in well-designed RCTs with sufficient power. ■

Amaryllis H. Van Craenenbroeck, MD, PhD, is with the Department of Microbiology, Immunology and Transplantation, KU, and the Department of Nephrology and Renal Transplantation, University Hospitals, Leuven, Belgium.

References

1. Johansen KL, Painter P. Exercise in individuals with CKD. *Am J Kidney Dis* 2012; 59:126–134.
2. MacKinnon HJ, et al. The association of physical function and physical activity with all-cause mortality and adverse clinical outcomes in nondialysis chronic kidney disease: A systematic review. *Ther Adv Chronic Dis* 2018; 9:209–226.
3. Lopes AA, et al. Associations of self-reported physical activity types and levels with quality of life, depression symptoms, and mortality in hemodialysis patients: the DOPPS. *Clin J Am Soc Nephrol* 2014; 9:1702–1712.
4. Kutner NG, et al. Gait speed and mortality, hospitalization, and functional status change among

hemodialysis patients: A US Renal Data System special study. *Am J Kidney Dis* 2015; 66:297–304.

5. London GM, Drueke TB. Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 1997; 51:1678–1695.
6. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999; 340:115–126.
7. Zoungas S, et al. Association of carotid intima-medial thickness and indices of arterial stiffness with cardiovascular disease outcomes in CKD. *Am J Kidney Dis* 2007; 50:622–630.
8. Van Craenenbroeck AH, Van Craenenbroeck EM, Kouidi E, et al. Vascular effects of exercise training in CKD: current evidence and pathophysiological mechanisms. *Clin J Am Soc Nephrol* 2014; 9:1305–1318.
9. Viana JL, et al. Evidence for anti-inflammatory effects of exercise in CKD. *J Am Soc Nephrol* 2014; 25:2121–2130.
10. Beck DT, et al. Exercise training improves endothelial function in young prehypertensives. *Exp Biol Med* (Maywood) 2013; 238:433–441.
11. Hambrecht R, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation* 2003; 107:3152–3158.
12. Hambrecht R, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998; 98:2709–2715.
13. Kirkman DL, et al. The effects of aerobic exercise on vascular function in non-dialysis chronic kidney disease: A randomized controlled trial. *Am J Physiol Renal Physiol* 2019.
14. Van Craenenbroeck AH, Van Craenenbroeck EM, Van Ackeren K, et al. Effect of moderate aerobic exercise training on endothelial function and arterial stiffness in CKD stages 3–4: A randomized controlled trial. *Am J Kidney Dis* 2015; 66:285–296.
15. Koh KP, et al. Effect of intradialytic versus home-based aerobic exercise training on physical function and vascular parameters in hemodialysis patients: A randomized pilot study. *Am J Kidney Dis* 2010; 55:88–99.
16. Greenwood SA, et al. Aerobic or resistance training and pulse wave velocity in kidney transplant recipients: A 12-week pilot randomized controlled trial (the exercise in renal transplant (ExeRT) Trial). *Am J Kidney Dis* 2015; 66:689–698.
17. O'Connor EM, et al. Long-term pulse wave velocity outcomes with aerobic and resistance training in kidney transplant recipients—A pilot randomised controlled trial. *PLoS One* 2017; 12:e0171063.
18. Dickinson HO, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens* 2006; 24:215–233.
19. Thompson S, et al. The effect of exercise on blood pressure in chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2019; 14:e0211032.
20. Vanden Wyngaert K, Van Craenenbroeck AH, Van Biesen W, et al. The effects of aerobic exercise on eGFR, blood pressure and VO₂peak in patients with chronic kidney disease stages 3–4: A systematic review and meta-analysis. *PLoS One* 2018; 13:e0203662.
21. Greenwood SA, Castle E, Lindup H, et al. Mortality and morbidity following exercise-based renal rehabilitation in patients with chronic kidney disease: the effect of programme completion and change in exercise capacity. *Nephrol Dial Transplant* 2019; 34:618–625.

Classified

Nephrologist for Growing Practice

Growing nephrology practice in Mississippi looking for a physician. Great benefit package. Please email for more information, wlong@nephrologyms.com.



CLASSIFIED
ADVERTISING
WORKS!

contact Rhonda Truitt
rhonda.truitt@wt-group.com
443-512-8899 x. 106

KidneyNews
Classified Advertising Information

Classified space is for advertising positions available, open faculty positions, course announcements, seminars, meetings and educational courses.

Display Advertising Rates

Ad Size	1x	3x
Full Page	\$2,675	\$2,485
1/2 Page	\$1,765	\$1,575
1/3 Page	\$1,525	\$1,455
1/4 Page	\$1,275	\$1,155
1/6 Page	\$1,095	\$1,085

Line Advertising Rates

Contact for Rates

Closing Date & Cancellations:

Copy must be received six weeks in advance of the month in which the ad is to appear. Cancellation requests must be made in written form by fax, e-mail or postal mail and will be honored for the earliest applicable issue.

ALL ADS
MUST BE PREPAID

Contact:
Rhonda Truitt
rhonda.truitt@wt-group.com
P: 443-512-8899 x. 106 F: 443-490-4003

KidneyNews Free Subscriber
Service Request Card

☐ I wish to start/renew a FREE* subscription to Kidney News

7-digit number label (Required for change of name/address only)

Name

Address

City State Zip

Telephone Fax

Email Address

Signature Date

Title/Position

- ☐ Physician
- ☐ Researcher
- ☐ RN, CNN, NM, LPN, APN, PA
- ☐ Dialysis Center Director
- ☐ Administration
- ☐ Clinic Manager/Coordinator
- ☐ Social Work
- ☐ Other

Specialty Area

- ☐ General Nephrology
- ☐ Transplantation
- ☐ Dialysis
- ☐ Laboratory
- ☐ Other

Institution

- ☐ Hospital <100 beds
- ☐ Hospital 100-250 beds
- ☐ Hospital 251-500 beds
- ☐ Hospital > 500 beds
- ☐ Dialysis Center
- ☐ Clinical Lab
- ☐ Other

Please Circle Degree:

- MD MD/PhD DO
- PhD MBA RN MS
- BS Other



Return the completed form to:
Bob Henkel, 1401 H Street NW, #900, Washington, DC 20005
or Fax: 202-403-3615 or Email: bhenkel@asn-online.org

Index to Advertisers

AmgenPages 8-10

ReataPages 4-5



“

**I enjoy the #AskASN
Twitter chats where we
cover a wide variety of
topics on Twitter.**

The chats bring experts and
unique topics so that members
can discuss these topics.

Additionally, it's exciting to work
on several educational initiatives
such as Renal Fellow Network.

Matthew A Sparks MD, FASN
Durham, NC