ASN American Society of Nephrology

Diabetes Kidney Disease Special Edition

Kidney News

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HHS Unveils Kidney Initiative with Bold Goals to Increase Home Dialysis, Transplants

By Laura Williamson

Last month, the Trump administration announced ambitious new plans for a kidney health initiative that seeks to improve care for people with kidney diseases by significantly increasing the number of Americans receiving home dialysis, reducing the incidence of kidney failure, and hastening and increasing access to kidney transplants.

Although the details of how the initiative will achieve these goals have not yet been fully revealed, industry leaders say the broad language set forth in the President's July 10, 2019, Executive Order aligns with a growing shift toward providing greater consumer choice in kidney care and the need for a greater focus on prevention.

The Advancing American Kidney Health initiative established by the executive order calls for reducing the number of Americans developing ESKD by 25% by 2030, ensuring that 80% of new ESKD patients in 2025 receive home dialysis or a transplant, and doubling the number of kidneys available for transplant by 2030. It aims to achieve these goals by loosening restrictions and raising incentives for organ donation, launching a public awareness campaign to increase knowledge of CKD and encourage greater use of home dialysis, and instituting a set of five new payment models.

Industry leaders say these plans have the potential to accelerate growth and innovation in kidney care, but the devil will be in the details. The initiative is also expected to jumpstart the work of some of the smaller players in the industry.

"We're in the middle of analyzing what's been released so far," said Frank Maddux, MD, Global Chief Medical Officer for Fresenius Medical Care. "I think it's really a question of how the [Centers for Medicare and Medicaid Services] adjusts the delivery system and care models to achieve such aspirational goals."

"[Starting in 2006], we invested in many different areas that have led to our alignment with the administration's direction with this Executive Order," Maddux said. For example, Fresenius has been investing in monitoring devices that make it safer for patients to receive dialysis at home or other locations outside a dialysis center and has educated more than 45,000 patients and physicians on home therapy modalities and techniques. "Those are really only starting points," he said. "There's much more to be done."

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ASN Announces Diabetic Kidney Disease Collaborative to Ensure Patient Benefit, Increased Coordination across Specialties

Diabetic kidney diseases develop in approximately 40% of patients who have type 2 diabetes and are the leading cause of CKD worldwide. The condition also accounts for more than 40% of kidney failure in the United States.

With more than 100 million U.S. adults living with diabetes or prediabetes, according to a recent Centers for Disease Control and Prevention report, new treatments are urgently needed to stem the tide of diabetic kidney diseases.

Fortunately, "the outlook for people diagnosed with type 2 diabetes and CKD today is more hopeful than it has ever been," says Vlado Perkovic, MBBS, PhD, in this special edition of *Kidney News*. ". . . the last decade has seen an explosion of evidence from high-quality, properly powered, randomized trials that have defined the benefits and risks of many of these treatment options." Perkovic is executive director of the George Institute, Australia, professor of medicine at UNSW Sydney, and a staff specialist in nephrology at the Royal North Shore Hospital.

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KidneyNews

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Likewise, "DaVita's strategy is very much aligned with the aspirational goals of President Trump's Executive Order," said DaVita Chief Medical Officer Allen Nissenson, MD, FACP. Nissenson noted that 12% of DaVita's dialysis patients receive treatments outside a dialysis center. "We have had an intense focus on this for many years. At DaVita, we've been really trying to push the envelope, but we've been constrained because of the way the system is organized," he said.

Reimbursement for kidney care has historically focused on the end stages of disease, ever since Congress extended Medicare coverage to anyone with kidney failure in 1972.

"That was the right thing to do then, because we didn't know a lot about the earlier stages of kidney disease at the time and because it provided life-saving therapy regardless of ability to pay," said Carmen Peralta, MD, a professor of medicine at the University of California, San Francisco, and chief medical officer for Cricket Health, a specialty care provider for patients with CKD and ESRD. "But in trying to do a good thing, it then sort of created a monster. We put a pot of gold at the end of the journey for our patients. If you reached kidney failure, Medicare paid for your dialysis and all your associated care."

"Now the conversation is shifting to prevention," she said, "and clinicians are out there trying to stop the progression of the disease and do the best for patients with no payment infrastructure to support it. Seeing patients every three to six months pays nothing compared to what physicians get when the patients are on dialysis. Allowing for payment to happen when the patient presents earlier on, that's where I see the win."

The push toward preventive care, upstream of the need for kidney replacement therapy, could be a boon for new providers such as Cricket. With just 300 patients nationwide, Cricket approaches kidney care with a multidisciplinary team that aims to treat all of a kidney patient's needs, especially during the earlier stages of disease before dialysis becomes necessary, Peralta said. The preventive approach outlined in the new initiative, she said, "validates the Cricket clinical model, which is based upon the best available evidence."

"This opens up economic opportunities for us," said Peralta. "It's good for the business, because the new financial incentives allow us to expand our clinical model to serve more patients."

She's hopeful the new payment models will remove barriers to better preventive care and encourage other payors to follow the government's lead, especially in providing greater coverage of chronic conditions that lead to kidney failure. "Kidney disease never travels alone," she said. "It travels with heart disease and diabetes. We need to treat the patient as a whole. We can slow the progression of kidney disease by treating all of these other diseases."

CVS Kidney Care, a division of CVS Health launched a year ago, is also positioned to gain from the provisions of the Advancing American Kidney Health initiative.

CVS Kidney Care is devoted to early identification of kidney disease, targeted patient engagement and ongoing education to slow disease progression, and expansion of kidney transplantation and home dialysis. The company has just begun clinical trials of a home dialysis system it hopes to have on the market by 2021.

"With successful completion of the clinical trial and FDA approval, we plan to also provide a comprehensive home dialysis program," said Bruce Culleton, MD, Vice President and Chief Medical Officer for CVS Kidney Care.

Culleton said the home dialysis system was just one of "a series of comprehensive solutions focused on improving health and outcomes for people living with kidney diseases and kidney failure" that CVS Kidney Care is beginning to provide, and that the company's objectives align with the president's goals.

"We have an existing CKD education program available in several markets today. As we expand our CVS Kidney Care programs and services, we will continue to offer all-inclusive education to diagnosed patients, and will soon offer face-to-face, personalized support and therapy education, as well as other proven patient engagement strategies," Culleton said. "This begins with helping patients better understand the treatment options available to them, as well as educating them on critical factors such as kidney health, diet, comorbidities, and prescription management."

Whether the goals of the administration's initiative—particularly getting 80% of new patients transplanted or on home dialysis by 2025—are overly ambitious remains to be seen. Some in the industry are skeptical, but hopeful that the changes will result in at least making progress toward this goal.

"I think this combined transplant/home dialysis goal of 80% is very aspirational," said DaVita's Nissenson, noting that countries with high percentages of patients on home dialysis, such as Hong Kong, require patients to use home therapy unless there is a medical reason not to do so. "I think that's not really practical here. It goes against our core principle of choice. It's great to aspire to and stimulate people to work toward the goal, yet it will take time."

Even if the industry can't reach the 80% goal, Nissenson and others said they believe a substantially greater number of patients can be shifted to home dialysis if both patients and physicians are educated about the value of doing so. When educated early in the progress of their disease, he said, many kidney patients say they would prefer to be treated at home. DaVita's growth rate in home dialysis is four times that of its in-center dialysis growth.

"We need to make sure we partner with our nephrologists, who are really the people who are driving the clinical care of the patient," Nissenson said. "I think nephrologists are ready to step up to the plate, but we need to make sure they get sufficient training."

Fresenius Medical Care's Maddux said greater competition is sure to emerge as a result of the initiative, but it would ultimately result in better patient care. "I am much in favor of many people contributing to this dialogue," he said. "The obligation is not just to demonstrate a novel approach to care, but to build that at scale so that everybody gets a chance to benefit from these therapeutic advances."

"It's all about the patients and the real epidemic of kidney disease in this country that has not gotten the attention from the public or regulators that it needs," said Nissenson, "and now this is happening. Finally, the stars are aligning."

Diabetic Kidney Disease Collaborative

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In response to the recent development of new therapies for people with diabetic kidney diseases, the American Society of Nephrology launched the Diabetic Kidney Disease Collaborative (DKD-C) on July 25, 2019.

"It's time for nephrologists to step up and take the lead in the care of patients with DKD," said Katherine R. Tuttle, MD, FASN, a member of the ASN DKD-C Task Force and Kidney Health Initiative Board of Directors. "It's the most common problem in nephrology and a general health problem as well." Tuttle is Executive Director for Research, Providence Health Care, professor of medicine, University of Washington, and co-principal investigator, Institute of Translational Health Sciences.

The Diabetic Kidney Disease Collaborative will work to increase coordination among primary care physicians, nephrologists, and other specialists to deliver appropriate therapies to people living with diabetic kidney diseases, according to a press release issued by ASN.

"Life with a kidney disease can be extremely challenging, and patients deserve the most advanced and innovative treatment in order to manage their conditions," said ASN Councilor Susan Quaggin, MD, FASN. "We are launching DKD-C to help accelerate the use of new therapies, educate the healthcare community, and address the legislative and regulatory policy issues that can prevent patient access to quality care." Quaggin is chair of the DKD-C and is director of the Feinberg Cardiovascular and Renal Research Institute and chief of nephrology and hypertension in the Department of Medicine at Northwestern University in Chicago.

The goals of the Diabetic Kidney Disease Collaborative are to:

- Determine the role of the nephrologist in diagnosing and treating diabetic kidney diseases, including advocating for people with DKD, having ASN review current and future clinical practice guidelines, and ensuring that nephrologists prescribe the appropriate therapies.
- Encourage nephrologists to interact proactively with primary care physicians, endocrinologists, and other specialists to ensure people with DKD receive the highest-quality care possible.
- Provide educational information to help nephrologists and other health professionals provide high-quality care to people with DKD.
- Address legislative and regulatory policy issues that affect the ability of nephrologists and other health professionals to provide high-quality care to people with DKD.
- Hold multi-stakeholder conference(s) to build on the momentum surrounding DKD.

"With the recently reported results of CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), which demonstrated substantial kidney and cardiovascular benefits in patients with T2D and DKD through the use of SGLT-2 inhibitors on top of standard of care, ASN has prioritized educating the nephrology community and increasing collaboration across specialties on the use of these life-changing therapies," the ASN press release states.

Noted Tuttle: "ASN's DKD-C emphasizes the integral role of nephrologists in providing and overseeing high-quality care for people living with DKD. To ensure new therapies are accessible and utilized appropriately, this initiative will require collaboration, partnership, innovative approaches, and multi-stakeholder engagement."

For more information about the Diabetic Kidney Disease Collaborative, please contact Susan Stark, Project Director, at sstark@asn-online.org.

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FRESENIUS MEDICAL CARE
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Policy Update

The Advancing American Kidney Health Initiative

Payment Models, Public Awareness Initiative, and Incentives for Innovation

By David White

On July 10, 2019, President Donald J. Trump and Health and Human Services (HHS) Secretary Alex M. Azar II unveiled a much-anticipated new HHS-wide kidney care initiative called *Advancing American Kidney Health* (AAKH). The initiative will bring sweeping changes to care for people with kidney diseases, including more focus on upstream treatment to slow the progression of kidney diseases, choices for dialysis modalities, greater access to transplantation, and concerted support for development of innovative therapies, including artificial kidneys.

Executive Order

The initiative was rolled out in a public signing of an Executive Order accompanied by a white paper published by HHS and the release of a proposed rule from the Centers for Medicare and Medicaid Services (CMS) to create the End-Stage Renal Disease (ESRD) Treatment Choices Model (ETC Model)—four additional nephrology payment models will be released this month. The Executive Order established the following three objectives as official U.S. policy:

- Reduce the risk of kidney failure.
- Improve access to and quality of person-centered treatment options.
- Increase access to kidney transplants.

In the Executive Order, the White House and HHS laid out the case for a national focus on kidney diseases and the urgent need to realign policies to achieve greater kidney health. "Kidney disease was the ninth-leading cause of death in the United States in 2017. Approximately 37 million Americans have chronic kidney disease and more than 726,000 have ESRD. More than 100,000 Americans begin dialysis each year to treat ESRD. Twenty percent die within a year; fifty percent die within 5 years. Currently, nearly 100,000 Americans are on the waiting list to receive a kidney transplant" (1).

"Today was a gamechanger for people with kidney disease and for the care of these people. For the entire government and president to show this much interest in kidney disease and kidney failure is unprecedented," said ASN President Mark E. Rosenberg, MD, FASN, following the unveiling. "Having the president sign an Executive Order that increases the recognition of the value, diagnosis, development, and use of alternative dialysis therapies, and increasing the number of transplants signals to the kidney community that they are serious about changing the care of kidney patients."

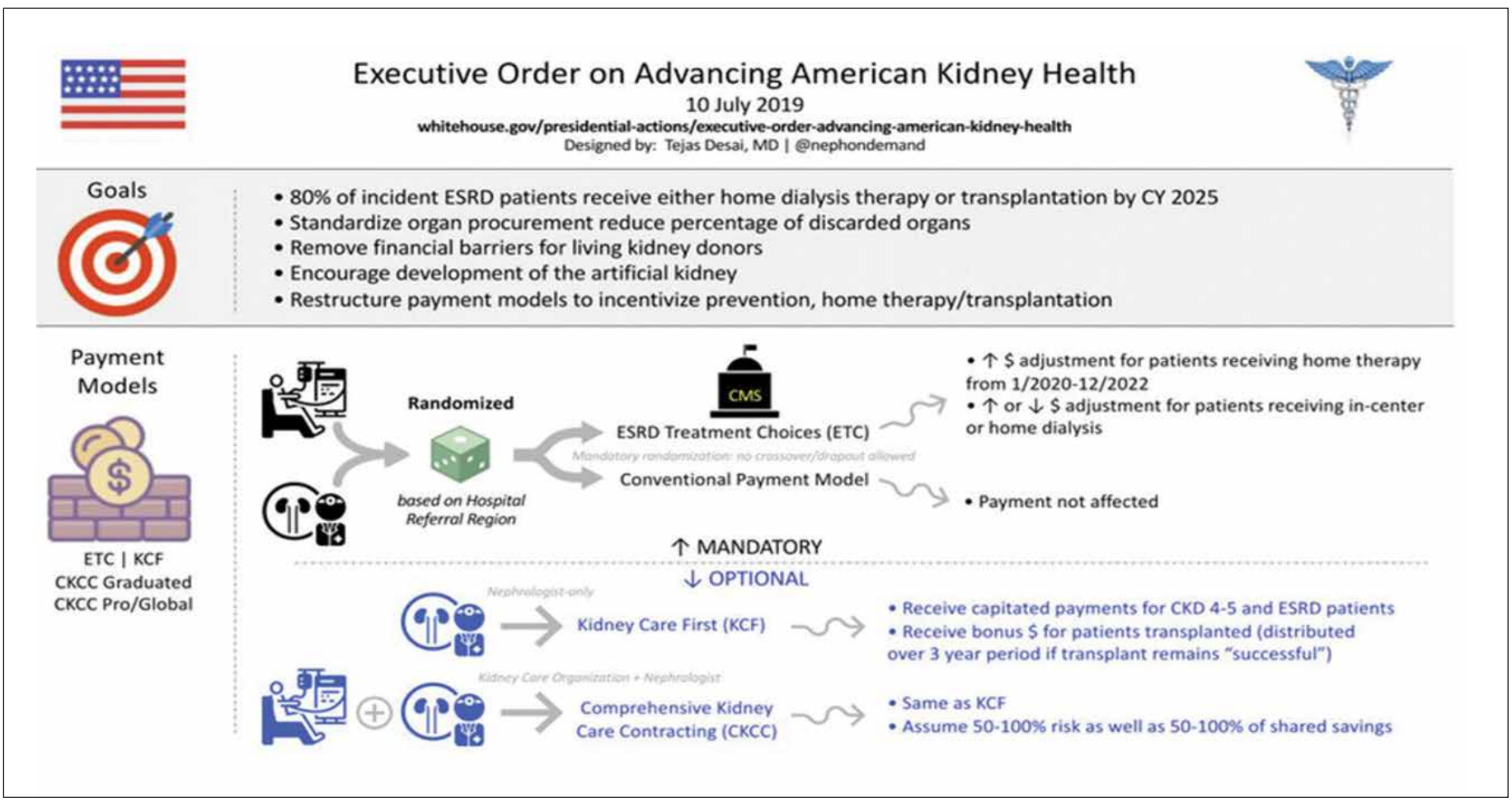
In addition to establishing the three objectives above as official policy, the Executive Order announced several kidney health action items and directs HHS and its various agencies to execute these items. These items closely mirror recommendations ASN has made to HHS over many years and, in development of this initiative, specifically over the last year. To begin, the Order announced an Awareness Initiative on Kidney and Related Diseases and directs HHS to launch a kidney disease awareness campaign within 120 days (by mid-November). Placing kidney diseases in the category of an urgent healthcare priority is a step ASN leadership views as long overdue.

The White House also directed HHS to develop several new payment models for testing by the Innovation Center in CMS (Figure 1). These models include the proposed ETC Model and the four additional models that are discussed in more detail later in this article.

In service of encouraging the development of an artificial kidney, the Order directs HHS to "(a) announce that the Department will consider requests for premarket approval of wearable or implantable artificial kidneys in order to encourage their development and to enhance cooperation between developers and the Food and Drug Administration (FDA); and (b) produce a strategy for encouraging innovation in new therapies through the Kidney Innovation Accelerator (KidneyX), a public-private partnership between the Department and the American Society of Nephrology" (1). These directives will help streamline the process for reviewing and approving innovation in the development of artificial kidneys at FDA and boost the role of KidneyX in developing strategies to foster innovation in kidney health.

In order to increase the utilization of available organs, the Order directs HHS to revise, within 120 days, Organ Procurement Organization (OPO) rules and evaluation metrics to establish more transparent, reliable, and enforceable objective metrics for evaluating an OPO's performance. HHS is also required to streamline and expedite the process of kidney matching and delivery to reduce the discard rate within 180 days. The initiative plans to boost transplantation using several levers, in ad-

Figure 1.



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Policy Update

Advancing American Kidney Health Initiative

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dition to OPO metrics, such as more support for living organ donors.

The White House had already announced in its spring agenda for rulemaking that HHS would be issuing a proposed rule to provide financial assistance for living organ donors. ASN, the American Association of Kidney Patients (AAKP), and others in the kidney community have been advocating for more support for living donors, including coverage of lost wages, with HHS and Congress for many years. The Executive Order specifically directs HHS that new regulation in this area "should expand the definition of allowable costs that can be reimbursed under the Reimbursement of Travel and Subsistence Expenses Incurred Toward Living Organ Donation program, raise the limit on the income of donors eligible for reimbursement under the program, allow reimbursement for lost-wage expenses, and provide for reimbursement of child-care and elder-care expenses."

Payment Models: ETC

The proposed ETC Model, which is a mandatory model, and the four voluntary models that will be unveiled this month are designed to test the effectiveness of increasing home dialysis and transplantation through realigned payment incentives within the five models as well as support more nephrology care upstream before a person reaches kidney failure. The four voluntary models soon to be unveiled are the Kidney Care First (KCF) Model, Graduated Comprehensive Kidney Care Contracting (CKCC) Model, Professional CKCC Model, and Global CKCC Model.

Participants in the proposed ETC model will be "managing clinicians" and ESRD facilities. CMS defines a managing clinician as a healthcare professional who bills the Monthly Capitated Payment (MCP), whether it is a nephrologist, an internist, or even a non-physician practitioner. Across the five models, managing clinicians may participate in the KCF Model or one of the CKCC Models. If assigned to the ETC Model, managing clinicians may still participate in the KCF Model or one of the CKCC Models.

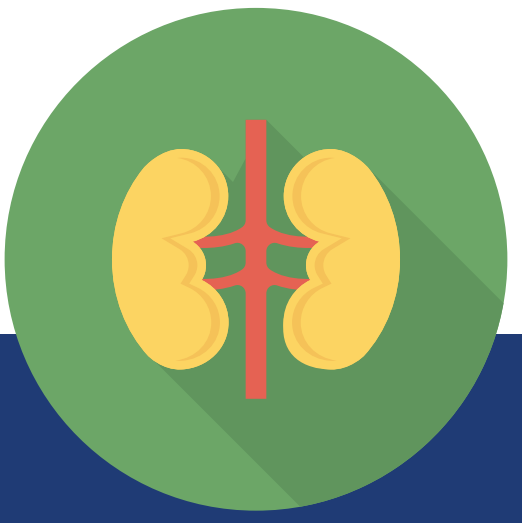
Managing clinicians and ESRD facilities will be assigned to the ETC model if located in randomly "selected geographic area(s)." The "selected geographic area(s)" to be used will be Hospital Referral Regions (HRRs). The use of HRRs in the model is a new approach for the CMS Innovation Center.

CMS explains the use of HRR for the selection of participants in the model in the proposed rule. Primarily, CMS wanted to capture approximately 50% of U.S. adult ESRD beneficiaries, include rural as well as metropolitan areas, and ensure the model has a cross-cutting sample of kidney transplantation. There are 306 HRRs in the U.S., and CMS will randomly select HRRs from all 50 states and the District of Columbia, stratified by region: South, Midwest, West, and Northeast (Maryland will be included under a slightly different approach due to its participation in the Maryland Total Cost of Care [TCOC] Model).

The ETC model payment adjustments will be based on rates of home dialysis utilization and rates of kidney and kidney-pancreas transplantation for both managing clinicians and ESRD facilities. The model would begin January 1, 2020, or April 1, 2020 (CMS is asking for comments on the start date). There are two model payment adjustments: Home Dialysis Payment Adjustment (HDPA) and the Performance Payment Adjustment (PPA).

The HDPA would be a + payment adjustment on home dialysis/home dialysis-related claims during the initial 3 years of the ETC Model. Year one (2020) is a +3% adjustment, year two (2021) is a +2% adjustment, and year three (2022) is a +1% adjustment.

The PPA would be a **+ or -** payment adjustment, increasing over time, on dialysis/dialysis-related claims, both home and in-center, based on the ETC model participant's home dialysis rates and transplant rates during a 12-month measurement year in comparison to achievement and improvement benchmarks. The 12-month measurement year would be in six-month increments with an overlap to create a rolling average approach for calculating PPA. CMS proposes using Medicare claims data, administrative data, and Scientific Registry of Transplant Recipients (SRTR) data to measure these rates. The numerators would be attributed patients on either home dialysis or who received a transplant (including preemptive transplants), and the denominators would be all attributed patients. The magnitude of the positive and negative PPAs would increase over the course of the model while the HDPA's magnitude decreases and ends after year three. The PPAs would begin July 1, 2021, and conclude June 30, 2026.



Placing kidney diseases in the category of an urgent healthcare priority is a step ASN leadership views as long overdue.

The proposed ETC model will also include a low-volume threshold exclusion specifically for the PPA. For managing clinicians, CMS proposes excluding those who fall below the low-volume threshold of the bottom 5% of managing clinicians in terms of the number of beneficiary-years for which the managing clinician billed the MCP during the measurement year. For ESRD Facilities, CMS proposes excluding ESRD facilities that have fewer than 11 attributed beneficiary-years during a given measurement year from the application of the PPA. This means that a facility must have at least 132 total attributed beneficiary months for a measurement year.

As with most CMS payment programs, the ETC model will include risk adjustment. CMS considered using the same risk adjustment for home dialysis patients and transplant patients but decided that the risk factors for both groups is sufficiently different to justify different risk adjustment methodologies. For risk adjusting home dialysis rates, CMS proposes using the CMS-5 HCC (Hierarchical Condition Category) dialysis model approach. For transplant patients, CMS proposes using the methodology of the percentage of Prevalent Patients Waitlisted (PPPW) from the ESRD Quality Incentive Program (QIP) with similar exceptions of not including anyone over 75 years of age, in a skilled nursing facility, or in hospice.

The ETC model also addresses another high priority policy issue of ASN: the kidney disease education (KDE) benefit. CMS proposes waiving the requirement that KDE be performed by a physician, physician assistant, nurse practitioner, or clinical nurse specialist, to allow additional clinical staff such as dietitians and social workers to furnish the service under the direction of a managing clinician. The staff are not required to be Medicare-enrolled as long as the managing clinician is authorized to bill Medicare for KDE services. CMS is also waiving the restriction that KDE services only be provided to CKD stage 4 patients and will allow the services to be provided to stage 5 patients and those in the first six months of an ESRD diagnosis. CMS is also waiving: (1) the requirement that the KDE curriculum cover issues of comorbidities and delaying the need for dialysis be covered, since it will now cover stage 5 patients in the model; and (2) the requirement that an outcomes assessment be performed within a KDE session (CMS maintains that an outcomes assessment should still occur, but it is not required to occur within a session).

Payment Models: Kidney Care First (KCF) and Comprehensive Kidney Care Contracting (CKCC) Models

In August 2019, CMS will send out a Request for Applications for the four voluntary models. The four voluntary models soon to be unveiled are the Kidney Care First (KCF) Model, Graduated Comprehensive Kidney Care Contracting (CKCC) Model, Professional CKCC Model, and Global CKCC Model. The first (the KCF) is a nephrology-specific model with a chronic kidney disease (CKD) MCP added for services provided to stage 4 and 5 CKD patients. The CKCC models provide the opportunity for groups of healthcare providers to jointly provide integrated kidney care. CMS specifically notes that in the CKCC models nephrologists/nephrology practices and transplant providers are required participants, with dialysis facilities and other providers being optional.

The KCF and CKCC models will run from January 1, 2020, through December 31, 2023, with the option for one or two additional performance years at CMS's discretion. Healthcare providers interested in participating will apply to participate in the fall of 2019, and if selected, begin model participation in 2020. However, financial accountability will not begin until 2021. During 2020, or Year 0, model participants will focus on building necessary care relationships and infrastructure.

Payment in the CKCC model will have three options, a one-sided risk model, a model where participants can earn 50% of shared savings or be liable for 50% of shared losses based on the total cost of care for Part A and B services, and a 100% risk/reward model. Participants in the KCF and the Professional and Global risk-bearing CKCC models will qualify as Advanced APMs in 2021; participants on the one-sided CKCC model will not. ■

Kidney News will continue reporting on the *Advancing American Kidney Health* initiative.

1 .https://www.whitehouse.gov/presidential-actions/executive-order-advancing-american-kidney-health/Ibid

Diabetes is the second most common cause of kidney failure in the United States. Diabetic Kidney Disease (DKD) encompasses structural and functional abnormalities involving the kidneys. Clinically, these changes result in hypertension, proteinuria, and progressive decline in kidney function, ultimately leading to ESKD. Diabetic kidney disease accounts for more than 40% of all ESKD In the United States. Therefore, regarding the progression of this particular form of kidney disease holds the key to reducing the incidence of ESKD and meeting one of the goals of the Advancing American Kidney Health initiative. In this issue of *ASN Kidney News*, we gathered a group of experts to address some of our latest understandings of this condition, particularly focusing on advances in treatment. Dr. Anders leads with the evolution of our understanding of the disease and gives an overview of renoprotective agents and their mechanisms to slow disease progression. Dr. Batuman focuses on the important landmark trials that have shaped our current knowledge. Drs. Argyropoulos, Alicic, Maqbool, and Cooper go into a bit of detail regarding novel anti-diabetic agents, namely: SGLT-2 inhibitors, GLP1 agonists, and DPP-4 inhibitors, respectively. Dr. Perkovic addresses ongoing and upcoming trials that will further elucidate safety and efficacy of these novel agents on cardiovascular and renal outcomes. Dr. Diamantidis reminds us that an old drug, metformin, still has an important role in the management of diabetes in this era. Last, Dr. Molitch gives us his perspective on how these novel agents fit with the current guidelines and how they may potentially shape future ones.

—Chrystos Argyropoulos, MD, PhD, FASN, and Edgar Lerma, MD, FASN, Editors

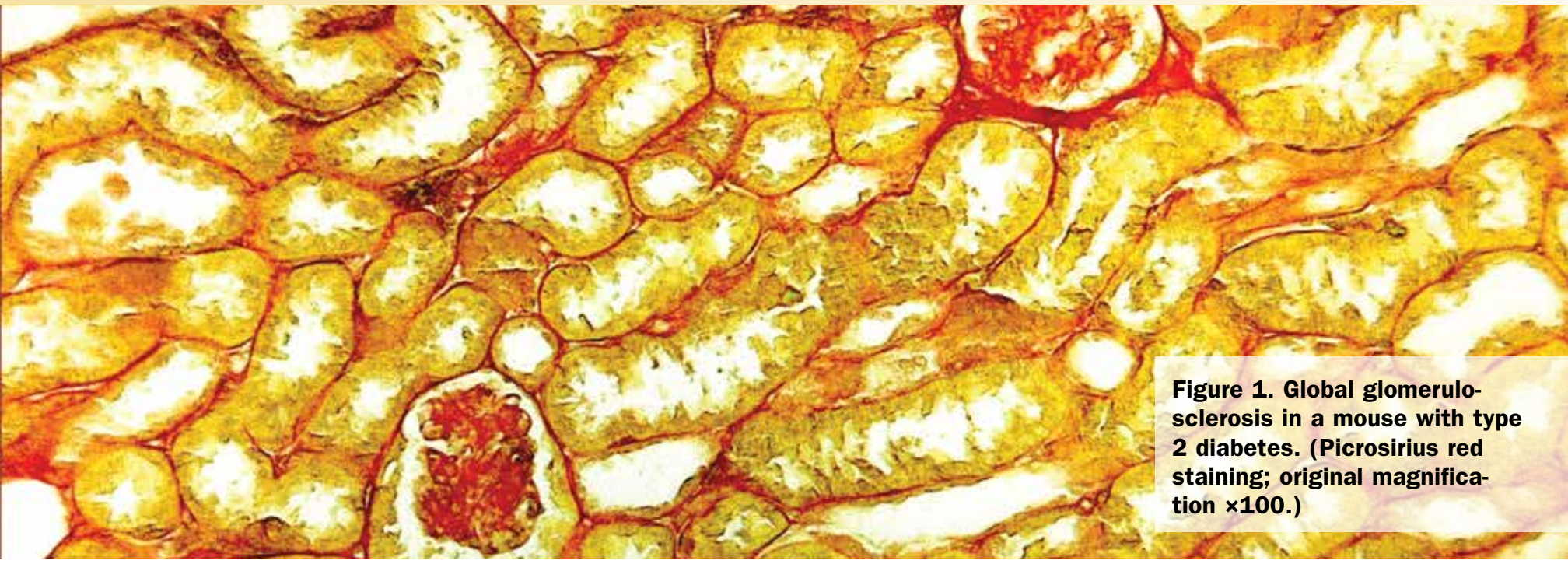


Figure 1. Global glomerulosclerosis in a mouse with type 2 diabetes. (Picrosirius red staining; original magnification ×100.)

Diabetic Kidney Disease

What We Knew, What We Know, and What We Still Do Not Know

By Lidia Anguiano and Hans-Joachim Anders

What we knew

The epidemic increase in the prevalence of diabetes mellitus (DM) has led to an increase in the incidence and prevalence of DM-associated complications, including diabetic kidney disease (DKD). Two major concerns in DKD are progression to ESKD and the high risk for cardiovascular morbidity and mortality. Treatments based on inhibition of the renin angiotensin system (RAS) alone have significant effects on microalbuminuria, an early marker of vascular dysfunction, but not necessarily of progressive DKD (1). Indeed, RAS inhibitors can reduce the rates of cardiovascular morbidity and mortality (2).

Regarding chronic kidney disease (CKD) progression, bardoxolone methyl showed promising results but increased the incidence of heart failure in the phase 3 trial, so the sponsor stopped the DKD program (3). Over the years, preclinical studies in animal models of DKD have predicted numerous targets for therapy outside the renin-angiotensin-aldosterone axis, but most have failed in subsequent randomized clinical trials in humans or have shown only mild effects on urinary albumin excretion (4). Retarding the progression of DKD to ESKD had remained an unsolved, unmet medical need until recently.

What we know

Recently, inhibition of sodium-glucose co-transporter 2 (SGLT-2) showed combined effects on cardiovascular and renal outcomes in DKD patients. The EMPA-REG OUTCOME trial showed unexpected and significant renoprotective effects of a combination of RAS inhibitors with empagliflozin, although the trial was not specifically designed to test kidney endpoints (5). This renoprotective effect was associated with strongly reduced fatal cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke (6). These results were recently replicated in the CREDENCE study for canagliflozin, a trial whose primary composite endpoint was ESKD, doubling of serum creatinine level, or death of renal or cardiovascular causes (7).

Other upcoming compounds include dipeptidyl peptidase 4 inhibitors and glucagon-like peptide-1 agonists, which were shown to improve glycemic control and lower the rates of macroalbuminuria, and also to lower the risk of cardiovascular outcomes (8, 9) but at a lower effect size than SGLT-2 inhibitors. Other agents, such as protein kinase C-β inhibitors, Janus kinase 1 and 2 inhibitors, and endothelin A receptor antagonists are still under study in patients with diabetes, either because there is no available phase 3 clinical trial or because adverse effects were observed.

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Diabetic Kidney Disease

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Recently, the "omics" techniques have become powerful tools for the identification of new potential biomarkers of DKD progression. Genome-wide association studies allow for the identification of genetic variants influencing DKD predisposition, which could help with the characterization of the biologic basis of DKD. Techniques of urinary proteome analysis (proteomics) (10) and metabolites analysis (metabolomics) (11) have taken a systematic approach to the identification and quantification of urinary proteins and metabolites.

What we do not know

The profound renoprotective effects of dual RAS inhibition with SGLT-2 inhibition in DKD raise the question whether these effects can be replicated also in non-DKD, a question currently under study. The prospects of a potentially wider use of SGLT-2 inhibitors raise the question about their safety profile. Genital infections, urinary tract infection, ketoacidosis, pyelonephritis, bone fractures, and lower-limb amputation for gangrene have inconstantly been reported across trials of SGLT-2 inhibitors, but the related concerns affect their implementation into clinical practice (5, 7).

The renoprotective effects of SGLT-2 inhibitors come as a breakthrough not only from a clinical perspective but also because they warrant a new paradigm in the understanding of DKD pathophysiology. The previous "glomerulocentric" view of DKD was largely driven by the idea that RAS inhibitors reduce proteinuria by decreasing glomerular afterload, which was obviously insufficient to significantly affect DKD progression. With SGLT-2 inhibitors, the focus now moves to the proximal tubule as the primary driver of DKD. The SGLT-2–driven reuptake of filtered glucose and sodium in the proximal tubule is massively increased by glucose filtration in DM, which, as a consequence, permanently inhibits the tubuloglomerular feedback and by dilating the afferent arteriole drives persistent glomerular hyperfiltration. Only dual RAS inhibition with SGLT-2 inhibition seems to correct glomerular hemodynamics; hence, GFR initially drops when SGLT-2 inhibitors are started (5). However, other mechanisms of action may apply, such as reducing tubular reabsorption load and hence tubular "stress," a diuretic effect that improves cardiac preload. Furthermore, it has been postulated that the natriuresis that occurs in SGLT-2 inhibition is promoted by the downregulation of Na+/H+ exchanger 3 isoform, which may serve as an additional mechanism to restore whole-body sodium homeostasis and reduce cardiac failure (12). SGLT-2 inhibitors are also known to increase the production of ketone levels, which seems to arise from an effort to raise glucagon levels and through a reduction in ketone body excretion through the kidneys. It has been suggested that ketone bodies are oxidized by the heart in preference to glucose and that this leads to an improvement of cardiac function in the failing heart. Another proposed mechanism of action is that increased ketone levels are associated with inhibition of histone deacetylase, which may prevent prohypertrophic transcription pathways (12).

Another unsolved issue is the potential clinical use of the upcoming "omics" data. Which of these markers could outweigh the current albuminuria/eGFR-driven approach at affordable costs remains to be worked out in the future. Finally, the gap between the design of preclinical studies versus clinical trials has remained a major hurdle for translational research and drug development programs. Overcoming this hurdle with animal models that more closely mimic the characteristics of the target population, comedication, and mirroring the design and endpoints of randomized clinical trials in preclinical animal studies should be possible, but these issues have not yet been rigorously addressed. ■

Lidia Anguiano, PhD, and Hans-Joachim Anders, MD, are in the renal division of the Medizinische Klinik and Poliklinik IV, Klinikum der Universität München, LMU München, Germany.

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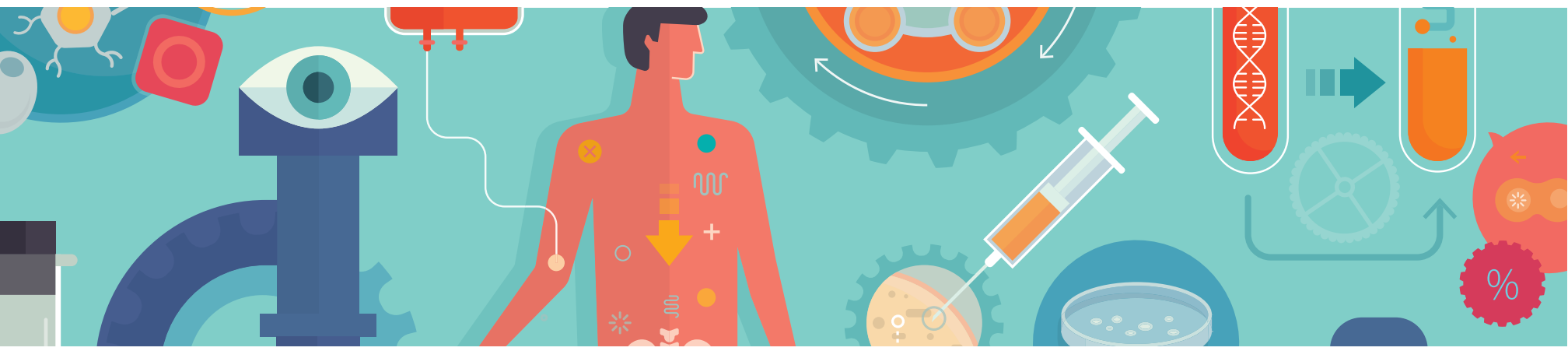

Clinical Trials on Diabetic Kidney Disease:
What Have We Learned from Landmark Trials?

By Vecihi Batuman

In the era of evidence-based medicine, high-quality clinical trials are the key to the development of sound practice guidelines. Many landmark trials have enabled us to make significant progress in our approach to diabetic nephropathy, the leading cause of ESKD worldwide, although we are still short of a cure. The two enduring lessons learned from these trials are that glucose control and BP control by renin-angiotensin-aldosterone system (RAAS) antagonists helps reduce the risk of diabetic kidney disease but do not entirely prevent it. The main trials that constitute the basis of this dual approach are briefly discussed here, along with a table summarizing the key findings extracted from them (Table 1).

Although the pathophysiology of diabetes is complex, the main factor responsible for kidney and eye damage is glucose toxicity. So, intuitively one would expect that glucose control should make a difference.

Both the Diabetes Control and Complications Trial (DCCT), conducted from 1983 to 1993, and the follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), showed that "intensive control" of hyperglycemia (achieving hemoglobin A1c [HbA1c] <7%) is effective in reducing the microvascular complications of diabetes (1). The UK Prospective Diabetes Study (UKPDS), the largest prospective study of patients with newly diagnosed type 2 diabetes, showed similar beneficial effects. A summary review of the major glycemic control trials clearly shows that intensive control achieving an HbA1c level around 6.5% to 7% helps reduce the risk of albuminuria and kidney disease. For example, the ADVANCE trial, which enrolled over 11,000 patients with type 2 diabetes, showed that achieving an HbA1c level of 6.5% led to a reduction of approximately 20% in kidney disease (2, 3). By contrast, ACCORD, a similarly large trial, showed that more aggressive glucose control targeting an HbA1c level of 6% is not beneficial.

The landmark captopril trial published in 1993 (4) was

followed by many others that confirmed the beneficial effects of both the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the course of diabetic nephropathy (Table 1). Thus, based on the lesson learned from these landmark trials the antiangiotensin strategy became the standard of care in patients with both type 1 and type 2 diabetes with kidney disease. It seemed intuitive that by combining angiotensin-converting enzyme inhibitors with angiotensin receptor blockers we might achieve more effective renoprotection, but we learned from the ONTARGET and NEPHRON-D studies that this approach was not viable because of the increased risk of adverse events, including worse renal outcomes (5).

Thus, the combined strategy of intensive glycemic control and blood pressure control by the use of RAAS antagonists offered hope to patients with diabetes and seemed successful—most trials showed a marked decrease in proteinuria and a slower progression of kidney disease. Still, diabetic nephropathy remains the most common cause of ESKD, both in the United States and worldwide. Why? Did we hit a wall with this strategy? Searching for alternative or complementary approaches, other trials using a direct renin antagonist, an antioxidant (bardoxolone), and an endothelin type A receptor antagonist were disappointing and, in fact, yielded adverse outcomes (Table 1).

Medical care has improved much and is organized better since the publication of these landmark trials, and these strategies are now available to larger populations of individuals with diabetes and kidney disease. We are far better at achieving simultaneously better glycemic control and BP

Table 1. Selected landmark clinical trials on diabetic nephropathy

Study, year	Number, diagnosis	Follow-up	Design	Outcome
DCCT, 1993 (2)	1441, T1DM	6.5 years	Intensive vs. standard glycemic control	Intensive glycemic control (HbA1c 7.3% vs. 9.1%) reduced incidence of micro- and macroalbuminuria by 39% and 54%.
EDIC/DCCT, 2014 (3)	1441, T1DM	18 years	Intensive vs. standard glycemic control	Renoprotective effect of intensive control persisted and resulted in 45% reduction in risk of microalbuminuria at 18 years.
UKPDS, 1998 (4)	3867, T2DM	10 years	Intensive vs. standard glycemic control	Intensive glycemic control vs. standard control (HbA1c 7.0% vs. 7.9%) reduced risk of microalbuminuria by 33%.
ADVANCE, 2013 (5)	11,140, T2DM	5 years	Intensive vs. standard glycemic control	Intensive glycemic control (HbA1c 6.5% vs. 7.3%) reduced risk of micro-, macroalbuminuria, and ESKD by 9%, 30%, and 65%; for those with macroalbuminuria, number needed to treat to prevent one ESKD was 41.
ACCORD, 2008 (6)	10,251, T2DM	Terminated at 3.5 years	Intensive vs. standard glycemic control	Targeting HbA1c 6.0 vs. 7.0%–7.9% resulted in excess mortality (HR 1.22; 95% CI 1.01–1.46; p = 0.04).
"Captopril" trial, 1993 (7)	409, IDDM	4 years	Captopril vs. placebo	Captopril slowed down progression of kidney disease in IDDM patients; captopril was more effective than BP control alone.
RENAAL, 2001 (8)	1513, T2DM	3.4 years	Losartan vs. placebo	Every 10 mm Hg systolic BP rise increased risk of ESKD or death by 6.7%; losartan decreased proteinuria by 35% (p < 0.001); serum creatinine doubling risk was reduced by 25% (p = 0.006, and ESKD by 28% (p = 0.002).
IDNT, 2001 (9)	1715, T2DM	2.6 years	Irbesartan vs. amlodipine vs. placebo	Irbesartan was renoprotective with lower risk of serum creatinine doubling (33%; p = 0.003) and ESKD (23%; p = 0.07) compared with amlodipine and placebo.
ROADMAP, 2001 (10)	4447, T2DM	3.2 years	Olmesartan vs. placebo	Olmesartan reduced time to microalbuminuria onset, and BP control was similar in both arms.
ONTARGET, 2008 (11)	25,620, T1DM T2DM	55 months	Telmisartan/ramipril combo vs. telmisartan vs. ramipril	Combination therapy was associated with increased composite outcome of dialysis, serum creatinine doubling, and death (HR 1.09; 95% CI 1.01–1.18; p ≤ 0.037).
VA NEPHRON D, 2013 (12)	1448, T2DM	Terminated at 2.2 years	Losartan/lisinopril combination vs. losartan alone	Combination therapy offered no renal benefit but resulted in excessive risk of hyperkalemia and acute renal failure.
ALTITUDE, 2012 (13)	8561, T2DM	Terminated at 2.7 years	RAS blockade plus aliskiren vs. placebo	Addition of aliskiren to maximal ARB offered no additional benefit; hyperkalemia and hypotension were significantly increased in the aliskiren arm.
BEACON, 2011 (14)	2185, T2DM	Terminated at 9 months	Bardoxolone methyl vs. placebo	Bardoxolone methyl led to a significant increase in cardiovascular morbidity (HR 1.83, p < 0.001).
ASCEND, 2010 (15)	1392, T2DM	Terminated at 4 months	Avosentan vs. placebo	Avosentan reduced proteinuria compared with placebo, but had excess adverse cardiovascular events.
CREDENCE, 2019 (16)	4401, T2DM	Terminated at 2.6 years	Canagliflozin vs. placebo	Relative risk for renal events (doubling of creatinine or ESKD) was significantly lower in canagliflozin group.

Table adapted from Chan GC and Tang SC. Diabetic nephropathy: Landmark clinical trials and tribulations. *Nephrol Dial Transplant* 2016; 31:359–368.

Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ALTITUDE = Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints; ASCEND = A Study of Cardiovascular Events iN Diabetes; BEACON = Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes; CI = confidence interval; CREDENCE = Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; HbA1C = hemoglobin A1c; HR = hazard ratio; IDDM = insulin-dependent diabetes mellitus; IDNT = Irbesartan Diabetic Nephropathy Trial; ONTARGET = ONgoing Telmisartan Alone and in Combination With Ramipril global Endpoint trial; RAS = renin-angiotensin system; RENAAL = Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan; ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention Study; TIDM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; UKPDS = UK Prospective Diabetes Study; VA NEPHRON D = Veterans Affairs Nephropathy in Diabetes

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control with the novel classes of antidiabetic drugs, including dipeptidyl peptidase-4 antagonists, incretins, and most sodium glucose co-transporter 2 (SGLT-2) inhibitors combined with anti-RAAS drugs.

Although these agents are helpful in achieving better glycemic control, we do not yet have robust data on the benefits of the newer antidiabetic drugs on diabetic kidney disease, except for the SGLT-2 inhibitor canagliflozin. The CREDENCE trial, which included 4401 patients with type 2 diabetes, was terminated prematurely because the early data showed a clear benefit of canagliflozin on renal outcomes, including the doubling of serum creatinine or ESKD (6). The response from the medical community to the recently published results of this trial suggests that the use of SGLT-2 inhibitors may well rise to the level of standard of care in the treatment of patients at risk for diabetic nephropathy.

It could be argued that the landmark trials completed since the early 1990s have shown that the efforts to achieve optimal glucose control (i.e., HbA1c level of 6.5% to 7%; and optimal BP control, usually suggested as <130/80 mm Hg) with the use of RAAS antagonists are rewarded by favorable outcomes. Yet, both of these therapy targets remain controversial. The HbA1c levels may not always be accurate in different populations and may not be the best biomarker of glycemic control. More aggressive BP lowering (i.e., systolic pressure <120 mm Hg) may be better. But, to date, we do not have robust clinical trials to resolve these lingering questions.

Nevertheless, after a long and bumpy road, we have accumulated substantial evidence on which to base our current approach: to contain if not to fend off the diabetic nephropathy epidemic completely. Ongoing work suggests that among the newer antidiabetic agents, the SGLT-2 inhibitors may confer additional benefit for patients with diabetes who are at risk for microvascular complications. Clearly, much additional work is needed to curb the diabetic nephropathy epidemic. ■

Vecihi Batuman is with the department of internal medicine and chief, division of nephrology, at Tulane University.

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Rapid Growth in DKD Studies: Research Trends and Hotspots

If it seems like you've been seeing more published papers on diabetic kidney disease in recent years, you're not mistaken. The number of DKD studies has risen rapidly and steadily over the past two decades, according to a review and meta-analysis published in the journal *Medicine*. And this study included a time period prior to the more recent spate of clinical trials.

More than 27,500 DKD papers were published from 2000 to 2017, reports the bibliometric analysis by Lu-Xi Zou, PhD, of Zhejian University and Ling Sun, MD, of' Xuzhou Central Hospital, China. Their open access study provides insights into "structure, hotspots, and evolution trends" in DKD research.

The systematic review identified a total of 27,577 DKD studies published between 2000 and 2017. The number of papers increased over time, with growth accelerating after 2007. Research papers accounted for nearly three-fourths of the total.

The top five journals publishing DKD papers were, in order, *Nephrology Dialysis Transplantation, Kidney International, Diabetes, JASN*, and *Diabetologia*. On analysis of co-citation networks, papers published in journals with higher impact factors had more citations and "greater influence in DKD research," the authors write. Among the nephrology journals identified, *JASN* had the highest 5-year impact factor, followed closely by *Kidney International*.

"Diabetic kidney disease is a very important topic for *JASN*, and we are proud of the quality of research we are publishing on this critical public health issue," said *JASN* Editor-in-Chief Josephine P. Briggs, MD.

The United States was the most productive country for DKD research, with 7100 publications. China was next, followed by Japan, Germany, and Italy. Analysis of country co-authorship showed very active networks of international collaboration in DKD research.

Harvard University was the top institutional producer of DKD research, followed by Steno Diabetes Center and University of Melbourne. Co-citation network analysis highlighted the contributions of H.H. Parving and colleagues during the study period—reflecting their studies establishing the renal and cardiovascular protective effects of renin angiotensin-aldosterone system blockade in patients with diabetes.

Drs. Zou and Sun discuss reasons for the burgeoning growth in DKD research, starting with the rising worldwide prevalence of diabetes. They also cite discoveries in histopathologic diagnosis, new therapeutic agents, and biomarkers, as well as the increasing ability to access and share massive volumes of medical data.

Zou L-X, Sun L. Global diabetic kidney disease research from 2000 to 2017: a bibliometric analysis. *Medicine* 2019; 98: 6(e14394).

Sodium Glucose Co-transporter 2 Inhibitors

By Christos Argyropoulos

Reducing the human and financial burden of progressive diabetic kidney disease (DKD) and ESKD stalled after the landmark trials of renin-angiotensin system inhibitors (RASi) in the early 2000s. The recent introduction of sodium glucose co-transporter 2 inhibitors (SGLT-2i) appears to reverse 20 years of stagnation in this area. This short review summarizes the key findings in this emerging success story of nephrology therapeutics.

Of rodents …

According to the Brenner hypothesis (1), hyperfiltration drives nephrons to glomerulosclerosis and eventually leads to chronic kidney disease (CKD) and ESKD. Reducing hyperfiltration has been the major paradigm for slowing the progression of CKD through RASi. However, the actual mechanisms of hyperfiltration in DKD remained poorly defined until the seminal report that a phlorizin, a naturally occurring SGLT-2i found in the unripe apple, inhibited glomerular hyperfiltration in the diabetic rat (2). The hypothesis was put forward that stimulation of tubular glucose/sodium transport through the SGLT-2 system reduced tubuloglomerular feedback, decreasing hyperfiltration in DKD. Subsequent micropuncture studies provided evidence in support of this hypothesis under long-term SGLT-2i administration and in diabetic mice lacking the SGLT-2 transporter (3, 4). In similar studies, SGLT-2i prevented changes in BP, glomerular size, and markers of inflammation (5).

… and humans

The U.S. Food and Drug Administration (FDA) approved the first SGLT-2i in early 2013, followed by the report of the mandatory cardiovascular outcomes safety trials (Table 1) (6–9). Overall, the trials reported to date show that SGLT-2i do not raise cardiovascular risk. Two of the SGLT-2i (canagliflozin and empagliflozin) are associated with clinically meaningful reductions in major cardiovascular events and cardiovascular death. All-cause mortality was reduced by empagliflozin, and all three SGLT-2i safety trials reported reductions in congestive heart failure (CHF). In these trials, there was an impressive reduction in the risk for hard renal endpoints (ESKD, need for dialysis or doubling of serum creatinine [DSC], or death), with relative risk reductions between 40% and 24%. These reductions, along with the effects of SGLT-2i on cardiac outcomes, are much larger than those obtained with RASi (Table 1). However, renal endpoints were either secondary or exploratory in these cardiovascular safety trials, requiring further confirmation.

The first dedicated renal endpoint, double-blind, randomized trial was recently reported for canagliflozin (CREDENCE) (10). This trial enrolled patients with estimated GFR (eGFR) between 30 and 90 mL/min per 1.73 m^2, on a background of RASi therapy. The composite endpoint of ESKD/DSC or renal death was lowered by 34%, and the relative risk of ESKD was lower by 32%. The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke and CHF (Table 1). Importantly, there were no differences in rates of amputation or fracture, safety signals that had been reported in previous studies.

Examination of the slope of the eGFR over time shows that the SGLT-2i conform to the pattern anticipated from the Brenner hypothesis and verified in the RASi era: An initial decline over the first couple of months of therapy is followed by dramatically reduced loss of eGFR over time (10, 11). Viewed as a class, SGLT-2i also reduce BP by 2.46 mm Hg

(systolic) and 1.46 mm Hg (diastolic) while also reducing body weight by 1.88 kg and waist circumference by 2.89 cm (12).

SGLT-2i in nephrology practice

The American Diabetes Association (ADA) guidelines (13) recommend that SGLT-2i with documented cardiovascular benefit (to date, empagliflozin and canagliflozin) should be the second agent added after metformin in patients with type 2 diabetes (T2D) and CKD or CHF. This recommendation is in alignment with the FDA-approved indications for these two agents (Table 2). Currently four SGLT-2i have been approved in the United States (Tables 2 and 3); they are similar in many regards but also different in others (e.g., status of completed trials, heterogeneity in renal and cardiovascular outcomes, dosing recommendations, intrarenal handling, and an emerging, highly technical literature about off-target effects).

A suggested pragmatic approach to how these agents may be introduced into nephrology practice follows: The ADA guidelines (a live document updated throughout the year) should be consulted for the currently approved indications for SGLT-2i. As nephrologists, we want to reduce cardiorenal risk in our patients, not just lower the hemoglobin A1c, so SGLT-2i with proven benefit should be prescribed, not merely recommended, by our specialty first (Table 2). Nevertheless, the inclusion of drugs in formularies does not always follow the clinical evidence, and the clinician will often have to choose between any SGLT-2i or no SGLT-2i at all. In these situations, one should opt for the SGLT-2i whose more robust evidence the insurance will cover and the patient can afford the copay for. For optimal effect, these agents should be added on the background of RASi therapy (CREDENCE), yet, even RASi-intolerant patients can benefit, as shown in the large subgroup (20%) of the cardiovascular safety trials who

Table 1. Composite renal and cardiovascular safety outcomes of the approved (May 2019) SGLT-2 inhibitors reported in cardiovascular safety (EMPAREG, CANVAS program, DECLARE-TIMI-58) and dedicated renal outcomes trials (CREDENCE) against ACEi and ARBs in patients with diabetes

Angiotensin receptor blockers		SGLT-2 inhibitors		
Composite renal outcome				
Irbesartan (IDNT)	Losartan (RENAAL)	Canagliflozin (CREDENCE CANVAS program)	Dapagliflozin (DECLARE-TIMI-58)[9]	Empagliflozin (EMPA-REG)[7,11]
0.80 (0.66–0.97)	0.84 (0.72–0.98)	0.66 [10] (0.53–0.81) 0.60 [8] (0.47–0.77)	0.76 (0.67–0.87)	0.61 (0.53–0.70)
ESKD / Need for Renal Replacement Therapy (RRT)/DSC				
All ARB	0.78 [14] (0.67–0.91)	0.68 [10] (0.54–0.82)	0.76 (0.67–0.87)	0.45 (0.40–0.75)
All ACEi	0.60 [14] (0.39–0.93)			
MACE 3 outcome (cardiovascular death, myocardial infarction, ischemic stroke)				
All ARB	0.94 [15] (0.85–1.01)	0.80 [10] (0.67–0.95)	0.93 (0.84–1.03)	0.86 (0.74–0.99)
All ACEi	0.86 [15] (0.77–0.95)	0.86 [8] (0.75–0.97)		
Dapagliflozin				
Death of any cause				
All ARB	0.94 [15] (0.82–1.08)	0.83 [10] (0.68–1.02)	0.93 (0.82–1.04)	0.68 (0.57–0.82)
All ACEi	0.87 [15] (0.78–0.98)	0.87 [8] (0.74–1.01)		
Cardiovascular death				
All ARB	1.21 [15] (0.81–1.80)	0.78 [10] (0.61–1.00)	0.98 (0.82–1.17)	0.62 (0.49–0.77)
All ACEi	0.83 [15] (0.70–0.99)	0.87 [8] (0.74–1.01)		
Congestive heart failure				
All ARB	0.70 [15] (0.59–0.82)	0.61 [10] (0.47–0.80)	0.73 (0.61–0.88)	0.65 (0.50–0.85)
All ACEi	0.81 [15] (0.71–0.93)	0.67 [8] (0.52–0.87)		

Outcomes as reported in cardiovascular safety (EMPAREG, CANVAS program, DECLARE-TIMI-58) and dedicated renal outcomes trials (CREDENCE) against ACEi and ARBs in patients with diabetes. The definitions of the composite renal outcomes differed among trials : IDNT and RENAAL (development of ESKD), Doubling of Serum Creatinine (DSC) or death from any cause, CREDENCE (ESKD, DSC, or death from renal or cardiovascular causes), CANVAS (40% reduction in eGFR, need for renal replacement therapy (RRT) or death from renal causes), EMPAREG (progression to macroalbuminuria, DSC, RRT, renal death, and incident albuminuria; this composite outcome was not prespecified in EMPA-REG but need for RRT was), DECLARE-TIMI-58 (40% reduction in eGFR, ESKD, or death from renal or cardiovascular causes). Data on ACEi/ARB from studies in patients with both type 1 and 2 diabetes, whereas all SGLT-2i studies are in patients with diabetes type 2.

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; DSC = doubling of serum creatinine; eGFR = estimated GFR; RRT = renal replacement therapy; SGLT-2i = sodium glucose cotransporter-2 inhibitor.

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were not receiving RASi.

In contrast to the antiglycemic effect, the cardiorenal benefit appears to be dose independent, so the lowest dose of all drugs should be used. Dosing in relation to eGFR is likely to evolve over time, so the prescribing information should be consulted. The guidelines in Table 3 are likely to be modified to allow continuation of drugs even when the eGFR declines after CREDENCE. As with RASi, kidney function should be monitored periodically because these drugs have been associated with acute kidney injury (AKI). However, AKI should be clearly distinguished from the expected initial drop in kidney function, which, as with RASi, may signal a long-term benefit.

Patients should be warned about potential side effects, especially euglycemic ketoacidosis in patients already receiving insulin, and fungal genital infections. Commonsense clinical measures that may reduce the frequency (such as drying the genital area), prevent or reduce severity (instituting "sick-day" rules), or allow the early detection of these complications (e.g., providing urinary ketone strips) should be discussed with our patients. Despite the reassuring follow-up data about amputations, a thorough discussion of the risk-versus-benefit ratio should be undertaken in patients with pre-existing peripheral vascular disease.

Going forward, additional studies will report kidney and cardiac efficacy, dosing, and safety data about rare, yet sensational, side effects (e.g., amputations or Fournier gangrene) about all SGLT-2i. Given the magnitude of benefit seen in the existing trials, waiting for these future studies to conclude before we use these agents in patients with type 2 diabetes and CKD implies that we forego the opportunity to improve the care of our patients today. ■

Christos Argyropoulos, MD, FASN, is assistant professor, and division chief, nephrology, in the department of internal medicine at the University of New Mexico School of Medicine in Albuquerque, NM.

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Table 2. Indications for and pharmacologic properties of the approved (May 2019) SGLT-2 inhibitors

	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Antiglycemic indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Cardiovascular indication	To reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established CVD		To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established CVD	
Bioavailability	65%	72%	78%	~100%
Peak plasma time	1–2 hours	2 hours (fasting) to 3 hours (fatty meal)	1.5 hours	1 hour (fasting) to 2 hours (after meal)
Protein binding	99%	91%	86.2%	93.6%
Volume of distribution	119 L	118 L	73.8 L	85 L
Half-life	10.6 hours (100 mg) to 13 hours (300 mg)	12.9 hours	12.4 hours	16.6 hours
Total body clearance	192 mL/min	207 mL/min	177 mL/min	187 mL/min
Hepatic route	>50%	21%	41.2%	40.9%
GI recovery of parent compound	41.5%	15%	>35%	33.8%
Renal route	~33%	75%	54%	50.2%
Renal recovery of parent drug	<1%	<2%	~20%	1.5%

Hepatic and renal routes of elimination refer to the recovery of radioactive labeled parent drug either as the parent drug or as one of its metabolites. None of the metabolites of the currently approved SGLT-2 inhibitors are pharmacologically active. CYP metabolism of all SGLT-2i is also minimal.

Abbreviations: CVD = cardiovascular disease; GI = gastrointestinal.

Table 3. Renal dosage adjustments for the approved (May 2019) SGLT-2 inhibitors

eGFR range	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
>60 mL/min per 1.73 m^2	100–300 mg/day	5–10 mg/day	10–25 mg/day	5–15 mg/day
45–60 mL/min per 1.73 m^2	Not to exceed 100 mg/day	5–10 mg/day	10–25 mg/day	**Not recommended**
<45 mL/min per 1.73 m^2	**Do not initiate**	**Not recommended**	**Do not initiate**	**Not recommended**
<30 mL/min per 1.73 m^2	**Contraindicated**	**Contraindicated**	**Do not initiate**	**Contraindicated**

Abbreviation: eGFR = estimated GFR.

Emergence of GLP-1 Receptor Agonists as a Therapy for Diabetic Kidney Disease

By Radica Z. Alicic, Emily J. Cox, and Katherine R. Tuttle

A multitude of clinical effects beyond glycemic control have placed glucagon-like peptide-1 (GLP-1) receptor agonists front and center in the fields of diabetology, cardiology, and nephrology. These incretin-based antihyperglycemic agents reduce the risk of new or worsening kidney disease and decrease the risk of cardiovascular death and atherosclerotic events (1–5). In the wake of these findings, the American Diabetes Association Standards of Care for treatment of hyperglycemia in type 2 diabetes now state that GLP-1 receptor agonists with proven cardiovascular benefits (liraglutide > semaglutide > exenatide extended release) should be added to the therapeutic regimen if glycemic targets are not achieved with metformin, particularly in patients with atherosclerotic cardiovascular disease (6). GLP-1 receptor agonists currently approved by the United States Food and Drug Administration are liraglutide (Victoza, Saxenda), semaglutide (Ozempic), lixisenatide (Adlyxin), exenatide (Byetta) and exenatide extended-release (Bydureon, Bydureon, BCise), and dulaglutide (Trulicity). Approved combination therapies are insulin glargine/exanitide (Soliqua 100/33) and insulin degludec/liraglutide (Xultophy 100/3.6).

Evidence supporting the kidney and cardiovascular benefits of the GLP-1 receptor agonists comes from large clinical trials enrolling patients with type 2 diabetes, cardiovascular disease, chronic kidney disease (CKD), or a combination of these conditions (Figure 1).

The dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate to severe CKD (AWARD-7) clinical trial was the first to be conducted in patients with moderate to severe CKD; nearly a third of enrolled patients had stage 4 CKD (4). Dulaglutide outperformed insulin glargine, the active comparator, in achieving glycemic control in patients with type 2 diabetes and a mean estimated GFR (eGFR) of 38 ± 13 mL/min per 1.73 m^2. Over 1 year, the average eGFR decline was –3.3 mL/min per 1.73 m^2 in the insulin-treated group and –0.7 mL/min per 1.73 m^2 in both the higher-dose (1.5 mg weekly) and lower-dose (0.75 mg weekly) dulaglutide-treated groups (4). Among AWARD-7 patients with macroalbuminuria (urine-to-albumin creatinine ratio >300 mg/g) at high risk for progression of kidney disease, attenuation of mean eGFR decline was maintained (–5.5 mL/min per 1.73 m^2 in the insulin glargine group compared with –0.7 mL/min per 1.73 m^2 and 0.5 mL/min per 1.73 m^2 in the dulaglutide 0.75-mg and 1.5-mg groups, respectively). Notably, fewer patients in the higher-dose dulaglutide group reached the composite endpoint of ESRD or >40% eGFR decline in comparison with the insulin glargine group (5.2% vs. 10.8%, p = 0.038) (7).

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) clinical trial and the Semaglutide and Cardiovascular outcomes in patients with type 2 diabetes (SUSTAIN-6) clinical trial, treatment with liraglutide or semaglutide compared with placebo resulted in fewer patients experiencing a composite cardiovascular outcome and decreased risk of CKD development and progression—benefits mainly driven by the reduction in new-onset macroalbuminuria (2, 3, 5). Similarly to AWARD-7, in patients with albuminuria as well as those with eGFR <60 mL/min per 1.73 m^2, the LEADER trial demonstrated reduction of a composite of new-onset macroalbuminuria, doubling of serum creatinine, requirement for kidney replacement therapy, and death due to kidney causes (2). Importantly, the reduction of cardiovascular events and all-cause mortality was greater in LEADER participants with eGFR <60 mL/min per 1.73 m^2 than in those with eGFR ≥60 (8). In patients with type 2 diabetes and a recent acute coronary syndrome, the addition of lixisenatide to usual care moderately reduced albuminuria, even though the rates of cardiovascular events were unaffected (1).

The mechanism by which GLP-1 receptor agonists reduce the risk of macroalbuminuria and slow eGFR decline in patients with type 2 diabetes remains to be fully elucidated. These agents favorably affect major CKD risk factors by improving control of hyperglycemia, hypertension, and excess body weight (9–11). In addition to modifying CKD risk factors, GLP-1 signaling directly promotes antioxidant, anti-inflammatory, and antifibrotic effects in the diabetic kidney (12, 13).

GLP-1 receptor agonists fill longstanding unmet needs: antihyperglycemic agents that can be used safely and effectively in patients with moderate to severe CKD, and agents that will slow eGFR decline in patients with eGFR <30 mL/min per 1.73 m^2. The encouraging results from the AWARD-7 and cardiovascular outcome trials provide hope that the GLP-1 receptor agonists will join a growing menu of agents available to tackle the burgeoning problem of CKD in type 2 diabetes. ■

Radica Z. Alicic, MD, FHM, FACP, is with Providence Health Care and the University of Washington School of Medicine. Emily J. Cox, PhD, is with Providence Health Care. Katherine R. Tuttle, MD, FACP, FASN, FNKF, is with Providence Health Care, the Kidney Research Institute, the Institute of Translational Health Sciences, and the University of Washington School of Medicine.

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Emergence of GLP-1 Receptor Agonists

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Figure 1. Kidney outcomes in four major clinical trials evaluating glucagon-like peptide-1 receptor agonist medications in patients with type 2 diabetes.

	AWARD-7 Dulaglutide 0.75 - 1.5 mg vs. insulin glargine	**LEADER** Liraglutide 0.6 - 1.8 mg vs. placebo	**SUSTAIN-6** Semaglutide 0.5 - 1 mg vs. placebo	**ELIXA** Lixisenatide 10 - 20 µg vs. placebo
	N=577 52% male Mean age: 65	N=9340 64% male Mean age: 64	N=3297 61% male Mean age: 65	N=6068 69% male Mean age: 60
	Mean HbA1c 7.5 - 10.5% CVD NR Mean BP 137/75 mm Hg	Mean HbA1c > 7% Prior CVD: 81% Mean BP 167/77 mm Hg	Mean HbA1c > 7% Prior CVD: 83% Mean BP 136/77 mm Hg	Mean HbA1c 7.7% Acute coronary syndrome Mean systolic BP 130 mm Hg
	Mean BMI 32.5 kg/m^2	Mean BMI 32.5 ± 6.3 kg/m^2	Mean body weight 92.1 kg	Mean BMI 30.2 kg/m^2
	90-94% on ACE/ARB	83% on ACE/ARB	83.5% on ACE/ARB	NR
	Mean eGFR 38 26% eGFR 45 - 60 35% eGFR 30 - 45 31% eGFR < 30 29% UACR > 30 mg/g 46% UACR > 300 mg/g	21% eGFR 30 - 59 2% eGFR < 30	25% eGFR 30-59 3% eGFR ≤ 30	Median UACR 10.4 mg/g Mean eGFR 77
	52-week treatment	Median follow-up: 3.84 years	Median follow-up: 2.1 years	Median follow-up: 2.1 years
	eGFR decline (mL/min) -3.3 insulin glargine - 0.7 dulaglutide 0.75 mg† - 0.7 dulaglutide 1.5 mg† **eGFR decline (mL/min)** in UACR > 300 mg/g group -5.5 insulin glargine - 0.7 dulaglutide 0.75 mg† - 0.5 dulaglutide 1.5 mg† **UACR reduction** -13% insulin glargine - 12.3% dulaglutide 0.75 mg - 29% dulaglutide 1.5 mg†	**Primary kidney composite outcome*** 3.9 placebo 3.4 liraglutide†† **New onset macroalbuminuria**** 6.0 placebo 5.3 liraglutide††	**Nephropathy (new, worsening)** 6.1% placebo 3.8% semaglutide††	**UACR reduction** 24% placebo 34% lixisenatide††

†Significant from insulin glargine ($p < 0.05$).
*Primary composite outcome, new-onset persistent macroalbuminuria, persistent doubling of serum creatinine, and eGFR ≤45 mL/min per 1.73 m^2, requirement for kidney replacement therapy, or kidney disease death in number of patients (rate per 1000 patient-years of observation).
**Rate per 1000 patient-years of observation.
††Significant from placebo ($p < 0.05$).

Abbreviations: ACE/ARB, angiotensin converting enzyme inhibitors or angiotensin receptor blockers; BMI, body mass index; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated GFR in units of mL/min per 1.73 m^2; GLP-1, glucagon-like peptide-1; NR, not reported; UACR, urine albumin-to-creatinine ratio.

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Dipeptidyl Peptidase-4 Inhibitors

By Muhammad Maqbool and Mark E. Cooper

After a long period of very few drug choices for the management of type 2 diabetes, during the past 15 years a range of new drug classes has been developed (1). One of these is the dipeptidyl peptidase 4 (DPP-4) inhibitors, including drugs such as sitagliptin, saxagliptin, vildagliptin, alogliptin, and linagliptin.

These agents inhibit the enzyme DPP-4, which acts to degrade glucagon-like peptide-1 (GLP-1), an incretin hormone. GLP-1 triggers glucose-dependent insulin secretion, reduces glucagon release, and delays gastric emptying (2). The action of GLP-1 depends on the presence of the N-terminal amino acids, which are cleaved by the enzyme DPP-4 (2). Thus, inhibitors that inhibit this enzyme, DPP-4, lead to increased concentrations of active GLP-1, an action that lowers fasting and postprandial glucose concentrations. It needs to be appreciated that DPP-4 inhibits other hormones, including gastric inhibitory peptide, an incretin, along with numerous other peptides. The relevance of the action of DPP-4 on these other hormones has not been fully determined.

Current guidelines from both American and European diabetes organizations recommend that first-line treatment should be with metformin (3). After metformin, DPP-4 inhibitors are considered appropriate as a second choice, particularly if there is no indication for specific cardiovascular (CV) or renoprotection. In terms of glycemic control, they are as potent as most other oral agents, although they are not as effective at glucose lowering as injectables such as insulin or GLP-1 analogs (4). The advantages of these drugs include neutrality on weight in contrast to insulin, sulphonylureas, or thiazolodinediones, which are associated with weight gain. Furthermore, hypoglycemia is not seen with these agents unless they are administered with drugs that are associated with hypoglycemia, such as insulin and sulphonylureas.

A major reason for the widespread use of this class of glucose-lowering drug is the low risk of side effects. In most major trials with these agents, no increase in side effects was seen versus placebo. This contrasts with the common side effects seen with most other classes of antidiabetic drugs. However, a few side effects, albeit rare, have been identified as a result of very large clinical trials including thousands of patients and over a decade of millions of patients with type 2 diabetes receiving long-term treatment with these drugs. Side effects include a less than twofold increase in pancreatitis (5). The issue of an increased risk of pancreatic cancer with these agents has been raised but has not been confirmed in meta-analyses of studies with these drugs. Finally, a rare bullous skin disorder, pemphigoid, has been confirmed to be increased with various DPP-4 inhibitors and is likely to be a class-related side effect (6).

Given that DPP-4 inhibitors are often prescribed as second-line drugs, a common clinical scenario is the combined use of these agents with metformin. This has led to the development of fixed combinations of metformin and DPP-4 inhibitors, which are widely prescribed in clinical practice.

DPP-4 inhibitors are widely used oral antidiabetic drugs with an excellent side effect profile and with documented renal and CV safety.

Most DPP-4 inhibitors are primarily cleared by the kidney (7). Thus, as GFR declines most DPP-4 inhibitors need their dose reduced. With such dose reductions, these drugs are considered safe in patients with renal impairment, including those using dialysis. However, one particular DPP-4 inhibitor, linagliptin, is not cleared by the kidney, and thus no dose reduction is required with increasing renal impairment with this agent (7).

In addition to combinations with metformin, this class of drugs can be added to most other antidiabetic drugs except GLP-1 analogs. This includes use with sulphonylureas and thiazolidinediones. Furthermore, with increasing evidence of a role for sodium glucose co-transporter 2 (SGLT-2) inhibitors in type 2 diabetes, fixed combinations of SGLT-2 and DPP-4 inhibitors are now available, including linagliptin/empagliflozin, saxagliptin/dapagliflozin, and sitagliptin/ertugliflozin. These combinations act in a complementary manner synergistically to reduce HbA1c more than either agent as a monotherapy (8). Finally, clinical trial data indicate that these agents can be used with insulin to afford a further improvement in HbA1c.

As a result of an initiative by the U.S. Food and Drug Administration to confirm the CV safety of new antidiabetic drugs, large clinical trials have been performed with various DPP-4 inhibitors. On the basis of meta-analyses of phase 2 trials of these agents, it was predicted that they may confer CV protection. Unfortunately, no such benefit was identified, but in general these agents were deemed to have CV safety with no increase in CV events, based on the 3P-MACE, a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke (Table 1). However, an increase in hospitalization for heart failure was identified in the SAVOR-TIMI trial with saxagliptin, an adverse event not seen in the TECOS trial with sitagliptin or the CARMELINA trial with linagliptin.

Since kidney disease remains a major complication in type 2 diabetes, the role of this drug class on albuminuria and decline in GFR has been examined. Initial trials, albeit predominantly post hoc analyses of small trials, suggested an anti-albuminuric effect of these agents in that clinical context (9). With linagliptin widely used in patients with reduced GFR because no dose change is required and renal safety had been reported previously, a number of trials with this agent prospectively assessed the renal effects of this agent.

Unfortunately, the MARLINA-2D study failed to show a statistically impressive effect on reducing albuminuria although there was a trend toward reduced progression of renal disease (10). The more recent CARMELINA study, which included renal as well as CV endpoints, showed no benefit of linagliptin on influencing decline in GFR, but there was a modest effect on reducing albuminuria (11). Thus, in contrast to SGLT-2 inhibitors and GLP-1 agonists, these agents are not considered in the latest international guidelines as renoprotective agents (3).

Finally, since these drugs are usually considered second line after metformin, a major unresolved issue is their advantage over other glucose-lowering agents such as the cheaper alternative, including sulphonylureas. The CAROLINA study has compared the DPP-4 inhibitor linagliptin with the widely prescribed sulphonylurea glimepiride (12). CV safety has been reported with linagliptin in that trial, but as yet no renal endpoints have been reported

In summary, DPP-4 inhibitors are widely used oral antidiabetic drugs with an excellent side effect profile and with documented renal and CV safety. They can be used in patients with renal disease, although dose reductions need to be considered with certain but not all DPP-4 inhibitors. ■

Table 1. Major cardiovascular safety DPP-4 inhibitor trials

Trial	Year published	Participants randomized	Median follow-up time (years)	MACE definition
EXAMINE	2013	5380	1.5	3P: Cardiovascular death, nonfatal MI, or stroke
SAVOR TIMI	2013	16,492	2.1	3P: Cardiovascular death, nonfatal MI, or stroke
TECOS	2015	14,671	3.0	4P: Cardiovascular death, nonfatal MI, or stroke, or hosp. unstable angina
CARMELINA	2018	6980	2.2	3P: Cardiovascular death, nonfatal MI, or stroke

Abbreviations: 3P-MACE = three-point major adverse CV event; CARMELINA = Cardiovascular and Renal Microvascular Outcomes with Linagliptin in Patients with Type 2 Diabetes Mellitus; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; MI = myocardial infarction; SAVOR TIMI = The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

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Muhammad Maqbool and Mark E. Cooper are with the Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia.

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New Directions in Diabetic Kidney Disease Trials

By Vlado Perkovic

The outlook for people diagnosed with type 2 diabetes and chronic kidney disease today is more hopeful than it has ever been. A broad array of treatments are available, and the last decade has seen an explosion of evidence from high-quality, properly powered, randomized trials that have defined the benefits and risks of many of these treatment options.

The 2008 decision by the U.S. Food and Drug Administration (FDA) and other regulatory agencies to require the conduct of cardiovascular safety trials for all new diabetes medications (1) has directly led to the generation of evidence that can guide treatment. We now know which agents reduce the risk of cardiovascular disease, kidney disease, or both, as well as lowering glucose levels. These trials have also taught us much about the effects of these agents on both common and uncommon adverse events, and have driven new areas of basic research, as we try to understand the mechanisms underpinning the clinical effects observed. The decision to mandate these trials will allow more effective and efficient use of glucose-lowering treatments, and has directly improved outcomes for people with diabetes.

Over the coming years, a number of additional placebo-controlled outcome trials of novel glucose-lowering therapies will report (Table 1), providing further richness to the available evidence. But a number of factors suggest that the landscape of trials going into the next decade are likely to look quite different from those completed over the past 10 years.

One reason for this is that the proven benefits of existing treatments must be taken into account in designing new trials. Previous trials looking at clinical renal outcomes in diabetes and CKD have required most or all participants to be receiving renin-angiotensin system blockade. Clear benefit for canagliflozin was demonstrated in people with diabetes and very high albuminuria in the CREDENCE trial (2), and there is growing evidence of renal benefits for SGLT-2 inhibitors across the spectrum of diabetes and kidney disease (3). Rapid increases in the use of these agents by nephrologists and other practitioners is therefore appropriate and will need to be taken into account for future trial design. While it would be ideal to test future treatments on top of SGLT inhibitors, many people may not have access to them for financial reasons, or be able to tolerate SGLT-2 inhibitors. So some degree of pragmatism will be required, particularly as uptake is (unfortunately) likely to take some time.

Slower kidney function loss in diabetes with proven new treatments is obviously a great outcome. But it may also make it more difficult to demonstrate benefits on existing renal outcomes. Event rates will be lower in treated participants, so that larger sample sizes will be required to demonstrate realistic effects on these outcomes. In this light, the recent initiatives by the National Kidney Foundation, the U.S. FDA, and the European Medicines

Table 1. Ongoing renal and cardiovascular outcome trials in Type 2 Diabetes

Trial Name	Treatment	Number of participants	Primary Outcome	Planned completion date
VERTIS CV	Ertugliflozin	8000	Cardiovascular	2019
Dapa HF	Dapagliflozin	4744	Heart Failure	2019
FIDELIO-DKD	Finerinone	5734	**Renal**	2020
Dapa_CKD	Dapagliflozin	4000	**Renal**	2020
EMPOROR	Empagliflozin	8850	Heart Failure	2020
DELIVER	Dapagliflozin	4700	Heart Failure	2021
FIGARO	Finerinone	7437	Cardiovascular	2021
SCORED	Sotagliflozin	10,500	Cardiovascular	2022
EMPA-Kidney	Empagliflozin	5000	**Renal**	2022
SOUL	Semaglutide	9642	Cardiovascular	2024
FLOW	Semaglutide	3160	**Renal**	2024

Abbreviations: VERTIS CV = eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial; Dapa HF = Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure; FIDELIO-DKD = Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease; Dapa CKD = Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; EMPOROR = EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; DELIVER = Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; FIGARO = Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; SCORED = Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; EMPA-Kidney = Study of Heart and Kidney Protection With Empagliflozin; SOUL = Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes; FLOW = Semaglutide versus Placebo in People With Type 2 Diabetes and Chronic Kidney Disease.

Agency to explore the role of changes in kidney function (eGFR slope) as an outcome for future trials may be critical (4). Slope-based outcomes are likely to make reliable demonstration of benefit easier, but separate attention to collecting adequate safety data will also be required. Slope-based outcomes may also facilitate the development of more efficient approaches to the conduct of trials, using platform approaches and adaptive methodologies (5), particularly as new targets are identified through modern 'omics' approaches.

Another difference will be a growing need to understand the absolute and relative effects of combinations of therapy. Incomplete uptake of SGLT-2 inhibitors in future trials will allow assessment of effects in people with and without this treatment. As more renoprotective therapies (hopefully) are identified, the assessment of different combinations is likely to become more important.

Perhaps most important, the development of a growing number of proven renoprotective therapies poses a new challenge. Use of RAS blockade among people in whom it is indicated is still likely to be suboptimal, almost two decades after the benefits were proven. Vast numbers of people who could have benefited from this treatment are likely to have reached kidney failure prematurely as a result of implementation failure. The challenge for us going forward will be to make the development and testing of implementation strategies a research focus, so that we can translate research findings much faster, for the benefit of people with kidney disease.

We have achieved much in diabetic kidney disease, and the rich tapestry of ongoing research suggests we are likely to achieve much more over the coming years. But we will need to adapt our questions, our approaches, and our goals if we want to achieve the best possible outcomes for our patients into the future. ■

Vlado Perkovic, MBBS, PhD, is Executive Director of The George Institute, Australia, Professor of Medicine at UNSW Sydney, and a staff specialist in nephrology at the Royal North Shore Hospital.

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Metformin: The Forgotten Agent

By Clarissa Diamantidis

Effective, safe glycemic control is a global priority because uncontrolled diabetes contributes to a substantial burden of morbidity and mortality related to chronic kidney disease (CKD), ESKD, and cardiovascular disease (CVD) (1, 2). However, achieving this goal in patients with advanced kidney disease is complicated by evolving safety recommendations and contraindications to several existing antihyperglycemic medications when kidney function is substantially impaired (2). Amid robust evidence for inhibition of the renin-angiotensin system as the mainstay of managing diabetic kidney disease and growing attention to the significant cardiovascular, kidney, and survival benefits of sodium glucose cotransporter 2 inhibitors, the important role of metformin should not be forgotten (1, 3, 4).

The therapeutic efficacy of metformin, its 60-plus-years history of use, and its relatively strong safety profile, low cost, and weight neutrality render it a first-line antiglycemic agent by European and U.S. guidelines (Figure 1) (5, 6). Metformin is a biguanide recognized for its important role in improving glycemic control through mechanisms distinctly different from those of insulin, sulfonylureas, glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose co-transporter 2 inhibitors. Our understanding of the mechanisms of action of metformin remains incomplete, although its antiglycemic effects occur primarily through enhanced insulin sensitivity and decreased gluconeogenesis by mitochondrial inhibition and increased activation of AMP-kinase (7, 8).

Bolstered by evidence regarding the long-term cardiovascular, diabetes-related, and survival benefits of metformin therapy, the American Diabetes Association (ADA) 2019 guidelines recommend consideration of metformin for the prevention of type 2 diabetes in individuals with prediabetes, especially in those older than 60 years, those with body mass index >35, and women with a history of gestational diabetes (9). Moreover, metformin continues to be the ADA's preferred initial agent for the treatment of type 2 diabetes as long as it is well tolerated and not contraindicated.

When metformin is used as a single agent, the average hemoglobin A1c reduction associated with it ranges from 1% to 1.5%. In addition, important longer-term benefits of metformin in reducing cardiovascular risk date back to compelling data from the UK Prospective Diabetes Study (UKPDS) (8). Metformin significantly reduced the risk for any diabetes-related endpoint, diabetes-related mortality, and all-cause mortality in obese individuals with newly diagnosed type 2 diabetes when it was compared with conventional therapy (with dietary control) alone (8). Although additional studies are needed to 1) understand the effects of metformin in combination with sulfonylureas and 2) better understand the impact of metformin in non-U.S. and European populations, the long-term effects of metformin are robust. For example, the 10-year follow-up of the metformin group in UKPDS showed that significant reductions persisted for diabetes-related endpoints, death of any cause, and myocardial infarction (10). Finally, metformin continues to be studied for its potential pleiotropic benefits, including antineoplastic effects mediated by AMP-kinase–dependent and independent inhibition of mTOR, treatment of polycystic ovary syndrome, attenuated atherosclerosis and vascular senescence as demonstrated in mouse models, and lipid-lowering and anti-inflammatory effects (2, 11).

Before 2016: the legacy of phenformin

Despite abundant evidence regarding its benefits, the U.S. Food and Drug Administration (FDA) regulations before 2016 restricted the use of metformin in several groups because of concerns regarding a relatively uncommon but dreaded complication: metformin-associated lactic acidosis (MALA) (1).

Concerns regarding metformin date back to the use of phenformin, the predecessor of metformin, which was withdrawn in 1977 because of concerns about lactic acidosis (12). Phenformin alters hepatic oxidative phosphorylation and thus leads to increased lactate production. It is distinguished from metformin because of its more lipophilic nature and its slower renal excretion: half-life 7 to 15 hours versus an estimated 6.5 hours for metformin (3, 12). Metformin, unlike phenformin, has been shown to be maintained closer to therapeutic and safe ranges, even in mild to moderate CKD (eGFR >30). In sum, there is no consistent association between metformin and lactic acidosis, and the overall number of cases is small (1 per 23,000 to 30,000 person-years among metformin users compared with approximately 1 per 18,000 to 21,000 person-years among patients with type 2 diabetes using other agents) (12).

A landmark publication in 2014 by Inzucchi et al. (12) suggested expanding the use of metformin to previously ineligible populations (e.g., individuals with mild to moderate CKD). Furthermore, the study suggested that avoiding MALA and its sequelae requires understanding the unique risk factors for MALA, including less common situations in which systemic hypoperfusion and hypoxia result in excess lactic acidosis production (3, 12).

2016: expansion of FDA guidance

These findings are reflected in the revised 2016 FDA guidance, which states that metformin is contraindicated in patients with an eGFR <30, which is in line with the report by Hung et al. (4) suggesting that metformin may be an independent risk factor for death in comparison with propensity-matched non–metformin users among individuals with stage 5 CKD. The FDA guidelines further suggest careful eGFR monitoring in a patient using metformin, reassessment of the risks and benefits when eGFR is <45, avoiding initiation of metformin when eGFR is <45, and temporary discontinuation before and during iodinated contrast imaging procedures in patients with eGFR 30 to 60.

Beyond 2016: metformin use in contraindicated conditions

An important 2017 systematic review and meta-analysis by Crowley et al (1), released after the 2016 FDA labeling changes, evaluated metformin use in individuals with type 2 diabetes and moderate to severe CKD, congestive heart failure (CHF), or chronic liver disease with impaired hepatic function. Four retrospective cohort studies, one prospective cohort study, and one nested case-control study were evaluated, and follow-up in these studies ranged from 1 to 3.9 years. Among these studies, which included 33,442 individuals and examined all-cause mortality, the relative chance of death was 22% lower for individuals using versus not using metformin ($p < 0.001$, $I2 = 89.8\%$).

The authors found associations of metformin use with reduced all-cause mortality in all three groups for which metformin had been previously contraindicated. Metformin use was also noted in two separate studies to be 1) significantly associated with lower risk of CHF readmissions and 2) not significantly associated with a difference in major adverse cardiovascular events among individuals with GFR 40 to <60 compared with those with GFR 30 to <45. Supporting its overall safety profile, metformin was associated with less hypoglycemia than were glyburide and insulin among individuals with GFR <30 and <45. In spite of limitations in this meta-analysis, including the use of observational studies with moderate risk of bias and low strength of evidence overall, the authors suggest that metformin may be associated with important mortality benefits and other benefits in individuals with moderate CKD. They also corroborate the evidence from a similar systematic review suggesting that metformin is associated with reduced mortality in CHF, a condition often comorbid in patients with CKD (13).

Given these findings, additional studies focused on the

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Metformin

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safety and benefits of metformin use in individuals with eGFR 30 to 45 and <30 are warranted to guide nuanced clinical decision-making. In the meantime, nephrologists and other clinicians who care for individuals with mild to moderate CKD should remember metformin as a critical part of the antiglycemic pharmacologic repertoire, using clinical equipoise and FDA guidelines to guide an individualized approach to prescribing and to patient education. ■

Clarissa Jonas Diamantidis, MD, is a nephrologist affiliated with Duke University School of Medicine.

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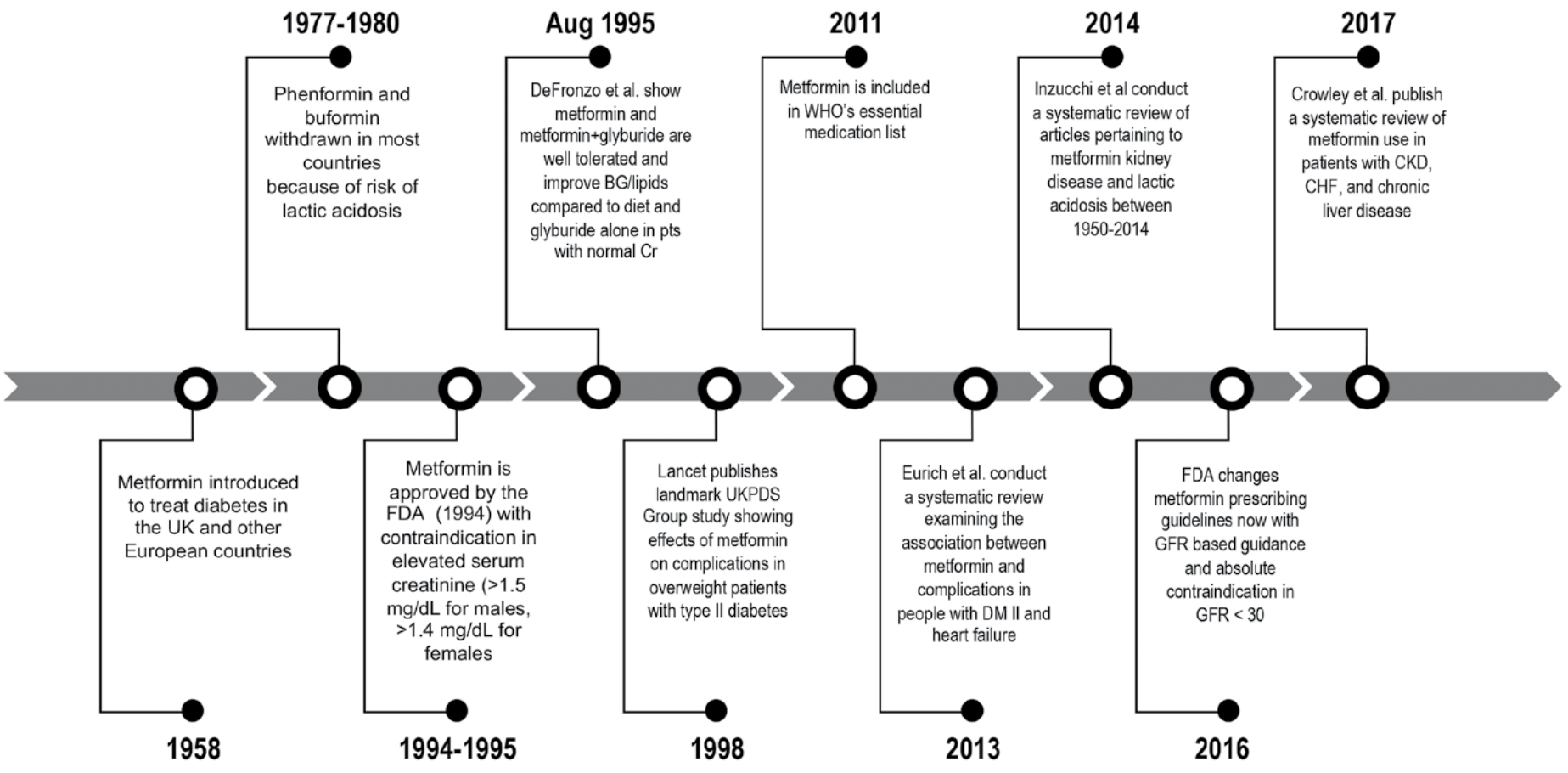
Figure 1. An abbreviated history of metformin. Adapted with permission from Bailey (6).



Diabetes Guidelines: Where Do the Old and New Agents Fit?

By Mark Molitch

The treatment landscape of management of type 2 diabetes has changed substantially over the past few years. Before the various cardiovascular outcome trials (CVOT) for the dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor analogs (GLP-1RA) and the sodium glucose co-transporter 2 (SGLT-2) inhibitors (reviewed in other articles in this issue), it was generally recommended that metformin should be the initial treatment along with lifestyle modifications for people with type 2 diabetes. The choice of second agent was left open, with little apparent benefit of one drug class over another, even in patients with known cardiovascular disease (CVD) or chronic kidney disease (CKD) (1–3).

However, it has now been shown that for patients with preexisting heart disease, there are clear differences between classes of medications. For such patients, DPP-4 inhibitors provide no cardiovascular or kidney benefit over and above their efficacy in improving glycemic control; they also cause no harm and are generally well tolerated, although saxagliptin may increase heart failure risk. In CVOTs, the GLP-1RAs liraglutide, semaglutide, and dulaglutide showed clear CVD benefit, with exenatide showing a borderline positive result. However, with respect to kidney findings, there is a lowering of urinary albumin excretion, but none have shown a reduction in the rate of fall of estimated GFR (eGFR) in these GLP-1RA CVOTs. By contrast, the CVOTs for the SGLT-2 inhibitors empagliflozin, canagliflozin, and dapagliflozin have shown not only CVD benefit but also very significant reductions in albumin excretion and in the rate of fall of eGFR. The CVD benefit was most impressive for patients with heart failure. Interestingly, the CVD and kidney benefits, blood pressure reduction, and weight loss found with the SGLT-2 inhibitors remained even in patients with eGFR levels <60 mL/min per 1.73 m^2, despite minimal blood glucose–lowering effects at that degree of CKD. The details of these studies are outlined in other articles in this issue.

These CVD benefits for GLP-1RA and CVD and CKD benefits for SGLT-2 inhibitors were so robust that the guidelines for the management of type 2 diabetes by various organizations and expert panels were recently revised. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended in 2018 that in patients with type 2 diabetes and known CVD, GLP-RA and SGLT-2 inhibitors should be added to metformin as second-line therapy for patients not at glycemic goals, with a specific preference for SGLT-2 inhibitors for patients with heart failure (4). Because the CVOTs did not show statistically significant similar benefits for patients at high risk for CVD, the ADA/EASD guideline did not make a specific recommendation for such individuals (4). The ADA/EASD guideline also recommended using SGLT-2 inhibitors for patients with type 2 diabetes and CKD with or without CVD (4). These recommendations were then incorporated into the American Diabetes Association 2019 Standards of Medical Care in Diabetes (5).

Guidelines from other groups have similarly been modified. The 2019 diabetes guideline of the American Association of Clinical Endocrinologists has moved the GLP-1RAs and the SGLT-2 inhibitors to the top of the list of drugs to be added if glycemic control is not achieved by metformin and lifestyle changes for all patients with type 2 diabetes (6). Furthermore, they state that "certain GLP-1RAs and SGLT-2s have shown CVD and CKD benefits and are preferred in patients with those complications," implying an equal benefit of the two classes on CKD (6). However, as noted from the discussion above, the SGLT inhibitors have been shown to reduce albuminuria and slow loss of GFR progression, whereas the GLP-1RAs have only been shown to reduce albuminuria.

The American College of Cardiology Task Force on Expert Consensus Decision Pathways recommended both GLP-1RAs and SGLT-2 inhibitors for patients with type 2 diabetes and CVD who are already taking metformin, with a preference for the latter in patients with heart failure (7). This cardiology guideline did not address the issue of progression of CKD.

In its 2018 Clinical Practice Guidelines, the Diabetes Canada Clinical Practice Guidelines Expert Committees have also recommended GLP-RAs and SGLT-2 inhibitors as second line therapy in patients with clinical CVD (8, 9). The Canada guidelines also recommended using SGLT-2 inhibitors to retard the progression of CKD (10).

The Taiwan Society of Cardiology and the Diabetes Association of the Republic of China (Taiwan) came up with different recommendations for patients with type 2 diabetes with known CVD, recommending thiazolidinediones as the best class to add after metformin, with SGLT-2 inhibitors and GLP-1RA coming in third, except for patients with heart failure, for whom SGLT-2 inhibitors were recommended as second-line therapy after metformin (11). They also recommended SGLT-2 inhibitors as second-line therapy for patients with CKD (11).

In the recent Endocrine Society Clinical Practice Guideline for the Treatment of Diabetes in Older Adults, the CVD and CKD benefits of GLP-1RAs and SGLT-2 inhibitors were discussed, but these benefits did not rise to the level of being specific recommendations (12). The same is true of the 2019 standards of medical care for type 2 diabetes in China (13).

Overall, these changes in guidelines are generally consistent with one another (except for the recommendation from Taiwan to start thiazolidinediones) with respect to adding a GLP-1 receptor agonist or an SGLT-2 inhibitor to metformin in patients with type 2 diabetes with established CVD inadequately controlled on metformin plus lifestyle change, with the additional recommendation that SGLT-2 inhibitors would be favored in patients with heart failure. In patients with CKD, SGLT-2 inhibitors also slow down the rate of progression of GFR loss, whereas this was not demonstrated for any other class of drugs. These beneficial CVD and CKD effects of SGLT-2 inhibitors are independent of glucose lowering, and these agents can be used at GFRs below 60 mL/min per 1.73 m^2, where they have little glycemic efficacy. Whether these classes should be used in patients at high risk for CVD and/or CKD but without overt disease is not established from clinical trials, but many clinicians might extrapolate these findings to this larger group of patients as well. ■

Mark Molitch, MD, is the Martha Leland Sherwin Professor of Endocrinology in the division of endocrinology, metabolism, and molecular medicine, department of medicine at Northwestern University Feinberg School of Medicine.

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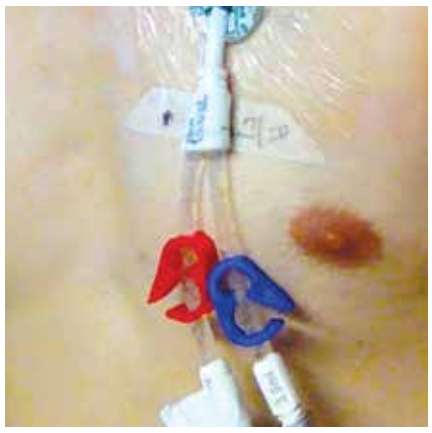
Findings

Too Many CKD Patients Have PICCs



Contrary to current guidelines, peripherally inserted central catheters (PICCs) are used in a high percentage of hospitalized patients with chronic kidney disease (CKD), reports a study in *Annals of Internal Medicine.*

The prospective cohort study analyzed the frequency of PICC use and associated characteristics among patients with stage 3b or higher CKD: estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2. The collaborative quality initiative included data from 52 participating hospitals in the Michigan Hospital Medicine Safety Consortium. Primary analysis included 20,545 (of a total 23,392) PICC placements between 2013 and 2016.

Overall, 23.1% of PICCs were placed in patients with eGFR less than 45 mL/min/1.73 m^2. Of these patients, 56% were on general medical units and 44% in the ICU, while 3.4% were receiving hemodialysis. Patients with eGFR less than 45 mL/min/1.73 m^2 accounted for 30.9% of PICC placements in the ICU versus 19.3% on the wards. Rates of PICC use in CKD patients varied substantially among hospitals, with interquartile ranges of 12.8% to 23.7% on the wards and 23.7% to 37.8% in the ICU. More than one-fourth of CKD patients with PICCs had dwell times of less than 5 days.

The CKD patients were more likely to have multilumen versus single-lumen PICCs. On the wards, the rate of PICC-related complications was 15.3% in patients with advanced CKD and 15.2% in those with an eGFR of 45 mL/min/1.73 m^2. In the ICU, the rates were 22.4% and 23.9%, respectively.

The "Choosing Wisely" guidelines, among others, recommend that PICC placement be avoided in patients with advanced CKD. The new analysis of data from a statewide hospital collaborative suggests that nearly one-fourth of PICC placements are in patients with an eGFR less than 45 mL/min/1.73 m^2.

"Taken together, these data suggest that PICC placement in patients with CKD is common and discordant with guidelines," the researchers write. They discuss possible reasons for the widespread use of PICCs in CKD patients, as well as strategies to improve appropriate PICC use [Paje D, et al. Use of peripherally inserted central catheters in patients with advanced chronic kidney disease: a prospective cohort study. *Ann Intern Med* 2019; 171:10–18].

Patients Starting Peritoneal Dialysis: Where Are They 5 Years Later?

Only 1 out of 7 patients who initiate peritoneal dialysis (PD) in the United States are still on PD at 5 years' follow-up, reports a study in the *American Journal of Kidney Diseases*.

The retrospective study included 25,573 adults who initiated PD from 2008 through 2011, identified via the US Renal Data System (USRDS). Five-year follow-up data were analyzed to assess the proportion of patients transferring to hemodialysis (HD), along with the competing outcomes of death and kidney transplant. The patients' mean age was 58 years: 56% were male, 71% white, and 22% African American. Mean baseline estimated glomerular filtration rate (eGFR) was 12.2 mL/min/1.73 m^2.

During a median follow-up of 21.6 months, 41.2% of patients transferred to HD, 25.9% died, and 17.1% received a kidney transplant. The percentage of patients still on PD fell below 50% at 22.6 months; by 5 years, only 14.2% were still on PD.

Based on Medicare claims, 40.2% of patients developed peritonitis, which was a risk factor for HD transfer: hazard ratio (HR) 1.82. Other significant vari-

ables included African American race, higher body mass index, and diabetic or hypertensive kidney disease.

The investigators developed a tool for predicting patient transition from PD to HD, based on data obtained at enrollment in the USRDS. On the prediction tool, higher quartile scores were associated with a higher risk of HD transfer: HR 1.31 in the 2nd quartile, 1.51 in the 3rd quartile, and 1.78 in the 4th quartile, compared to the 1st quartile.

Peritoneal dialysis is an attractive option for some patients. However, many of those who initiate PD eventually transfer to HD. Early identification of patients likely to transfer from PD to HD might improve their subsequent care.

Based on analysis of nearly 30,000 patients initiating PD, only about 14% are still on this dialysis modality at 5 years' follow-up. More than two-thirds transfer to HD or die by this time.

The report includes a prediction model for PD failure, accounting for the risks of competing outcomes. The researchers conclude, "Transition to HD needs to be considered for all new PD patients with favorable survival prognoses, especially when there is no plan for expedited kidney transplantation" [McGill RL, et al. Transfers to hemodialysis among US patients initiating renal replacement therapy with peritoneal dialysis. *Am J Kidney Dis* 2019; DOI: 10.1053/j.ajkd.2019.05.014].

Dialysis Patients Overestimate Their Survival

Patients undergoing regular dialysis have overly optimistic expectations of their prognosis, according to a study in *JAMA Internal Medicine*.

The cross-sectional survey study included 996 patients receiving regular dialysis at 31 nonprofit facilities in two US metropolitan areas (Seattle and Nashville). The main outcome of interest was response to the question: "How long would you guess people your age with similar health conditions usually live?" Responses were classified as less than 5 years, 5 to 10 years, more than 10 years, or "not sure."

Patients' expectations of survival were compared with those of a cohort of more than 307,000 patients receiving in-center dialysis, drawn from the US Renal Data System. The survey also asked about documented preferences related to end-of-life care.

The survey response rate was 69.5%. The patients' mean age was 62.7 years; 56% were men, 55% were white, 38% were black, and 16% were Hispanic. Sixty percent of patients died within 5 years and 19% within 5 to 10 years, while 21% survived for more than 10 years. Those figures contrasted with the survey, in which the selected prognosis was less than 5 years for 11% of patients, 5 to 10 years for 15%, and more than 10 years for 33%. Forty percent were unsure of expected survival.

On adjusted analysis, patients with expected survival of more than 10 years were less likely to have documentation of a surrogate decision-maker or treatment preferences, and more likely to desire cardiopulmonary resuscitation and mechanical ventilation. Patients who were unsure of their prognosis had a similar pattern of associations.

Patients receiving dialysis have limited life expectancy, but there are few data on their expectations of prognosis. This survey study suggests that a large majority of dialysis patients either have overly optimistic expectations or are unsure of their prognosis. The researchers conclude, "Further studies are needed to determine whether interventions to raise prognostic awareness can shape treatment preferences, values, quality of life, and preparedness for end-of-life care in this population" [O'Hare AM, et al. Assessment of self-reported prognostic expectations of people undergoing dialysis: United States Renal Data System Study of Treatment Preferences (USTATE). *JAMA Intern Med* DOI:10.1001/jamainternmed.2019.2879].

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ASN invites you to take part in the 2019 ASN Career Fair and Digital Recruitment Guide. This event is held in conjunction with Kidney Week.

RECRUITMENT BOOTH PACKAGE

- $3,950 for Industry
- $2,950 for University/Institution/Hospital
- $1,750 for Private Practice

- 10 X 10 carpeted booth, pipe and drape, a 6' skirted table, 2 chairs, and company sign
- (3) 60-day job postings on the ASN Job Board
- 60-day access to the ASN candidate CV/ resume database
- Ad in on-site and digital ASN Recruitment Guide

Add Ons:

- Make your ad stand out! - Make It Color $500
- Bring you ad to life in the digital guide! - Add Embedded Video $500
- Gain Added Visibility by Showing Your Ad on the Inside Front Cover $1500
- Get Maximum Exposure with the Back Cover Ad $2500

ONLINE RECRUITMENT PACKAGE

- $1,275

- Ad in on-site and digital ASN Recruitment Guide
- Single 30-day posting an the ASN Job Board
- 30-day access to the ASN candidate CV/ resume database

Submit ads 5 inches wide by 7.75 inches tall. No bleed. PDF file.

If your company is interested in participating or would like additional information, please contact:
Jim Cook at 727-497-6552 or by email at jim.cook@communitybrands.com.

ASN
American Society of Nephrology

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.

ASN
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CLASSIFIED ADVERTISING WORKS!

contact Rhonda Truitt
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443-512-8899 x. 106

KidneyNews Classified Advertising Information

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Display Advertising Rates

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1/3 Page	**$1,525**	**$1,455**
1/4 Page	$1,275	$1,155
1/6 Page	**$1,095**	**$1,085**

Line Advertising Rates

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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.

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rhonda.truitt@wt-group.com
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- ☐ 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:
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Bob Henkel, 1401 H Street NW, #900, Washington, DC 20005
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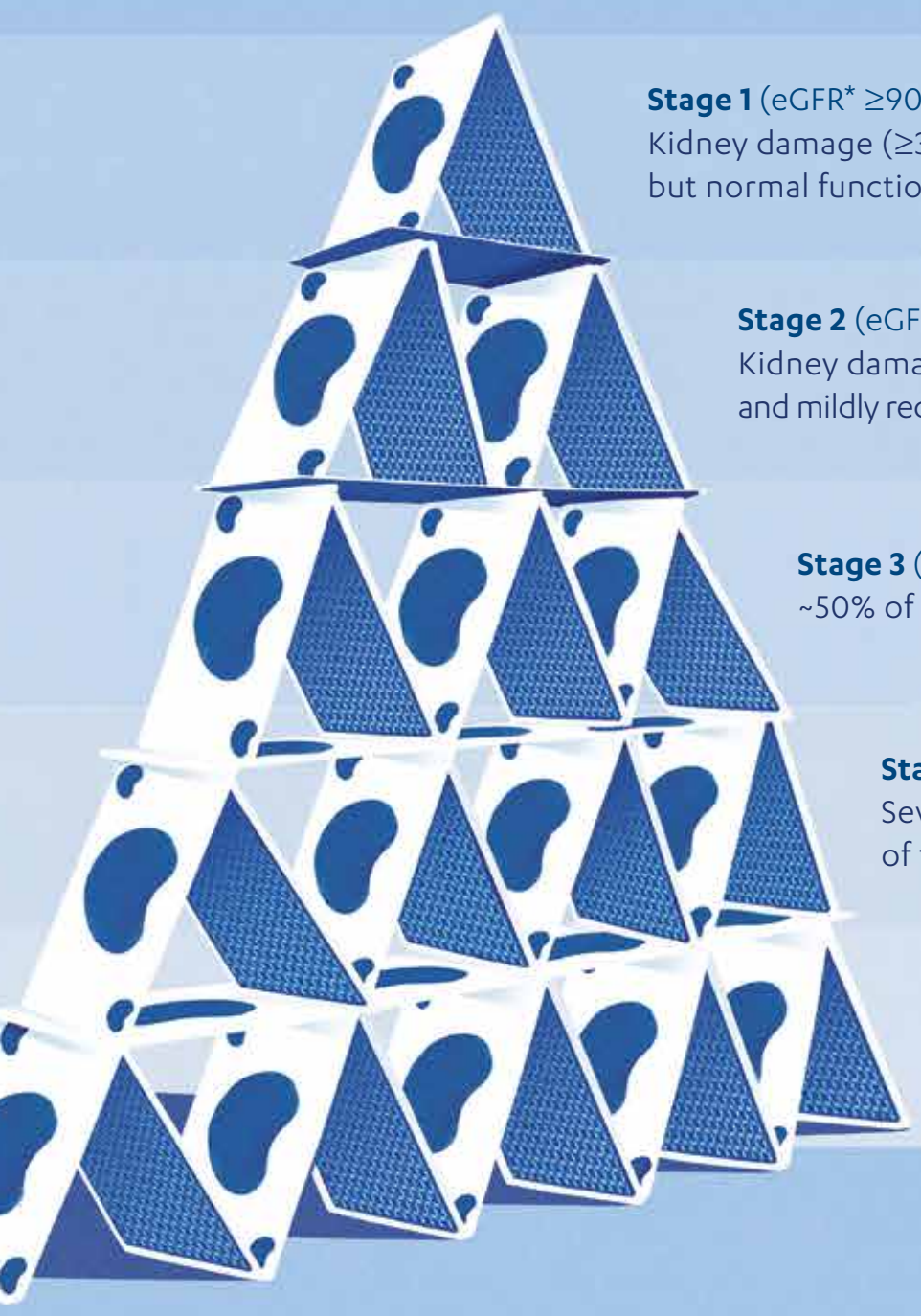
Index to Advertisers

how stable is a future with CKD and T2D?

CKD is progressive, irreversible, and often goes undetected.[1,2] More than 1/3 of patients with T2D also have CKD.[3] CKD multiplies the risk of CV events, such as heart attack, stroke, and CV death, and puts patients on a path toward dialysis or kidney transplant. **This risk grows with every stage.**[2,4,5]

Stages of CKD from the National Institute of Diabetes and Digestive and Kidney Diseases[2]



Stage 1 (eGFR* ≥90)
Kidney damage (≥3 months persistent proteinuria) but normal function

96% of these patients are unaware[5]

Stage 2 (eGFR* 60-89)
Kidney damage (≥3 months persistent proteinuria) and mildly reduced kidney function

Stage 3 (eGFR* 30-59)
~50% of kidney function is lost[6]

Stage 4 (eGFR* 15-29)
Severe kidney damage and loss of function

48% of these patients are unaware[5]

Stage 5 (kidney failure; eGFR* <15)
85%-90% of kidney function is lost[6];
requires a transplant or dialysis for survival

CKD is defined as any condition that causes reduced kidney function over a period of time. CKD may develop over many years and lead to end-stage kidney (or renal) disease (ESKD).
*eGFR measured in mL/min/1.73 m^2.
CKD=chronic kidney disease; CV=cardiovascular; T2D=type 2 diabetes.

Learn more about the chronic connection at **T2DandCKD.com**

References: 1. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. *Phys Ther.* 2008;88(11):1254-1264. **2.** Kidney disease statistics for the United States. National Institute of Diabetes and Digestive and Kidney Diseases website. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease. Accessed May 20, 2019. **3.** Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. *BMC Res Notes.* doi:10.1186/1756-0500-7-415. **4.** Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol.* 2013;24(2):302-308. **5.** National chronic kidney disease fact sheet, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/kidneydisease/pdf/kidney_factsheet.pdf. Accessed May 20, 2019. **6.** Key points: living with stage 4 kidney disease. National Kidney Foundation website. https://www.kidney.org/patients/peers/stage4. Accessed May 20, 2019.

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