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Review Article

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A renaissance in the treatment of diabetic kidney disease, hypertension in chronic kidney disease, and beyond

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Abstract: Chronic kidney disease (CKD) affects approximately 15% of the US population and is associated with significant cardiovascular morbidity and mortality. The two leading causes of end stage kidney disease are hypertension and diabetes mellitus, both of which are modifiable risk factors. The cornerstones of CKD care include early detection, management of associated risk factors, modification of cardiovascular disease risk, slowing progression of disease, and management of complications including anemia, acid base disturbance, and mineral and bone disorders. For the last 20 years, renin-angiotensin system inhibitors were the mainstay treatment for proteinuric diabetic and nondiabetic kidney disease. Recently, new therapies such as sodium-glucose linked transporter 2 inhibitors, have emerged as powerful tools in the treatment of CKD with indications in both diabetic and nondiabetic kidney disease. In this article, we define CKD staging, review new hypertension and diabetic guidelines for CKD patients, and discuss major trials for new potential therapies in CKD, particularly diabetic kidney disease. We will provide practical guidance for primary care physicians to diagnose CKD and implement these agents early in the disease course to prevent the progression of disease and reduce the morbidity and mortality of this vulnerable population.

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Chronic kidney disease (CKD) is estimated to affect 14.9% of the US adult population and is associated with significant cardiovascular morbidity and mortality [1]. Less than 2% of those with CKD will progress to end stage kidney or renal disease (ESKD or ESRD) [2]. As of 2018, there were 554,038 adults in the United States on dialysis and an additional 229,887 adults living with a functioning kidney transplant [1]. Those on hemodialysis have a median survival of 47 months [1]. Total expenditures for beneficiaries with ESKD increased to $49.2 billion in 2018, which accounted for 7.2% of the overall Medicare fee-for-service budget [1]. The two leading causes of ESKD are diabetes mellitus (39%) and hypertension (26%), both of which are modifiable risk factors [1]. The goals of CKD management can be separated into different aims including: early detection of CKD and identifying etiology, slowing the progression of CKD, addressing cardiovascular risk factors, managing medical complications of CKD (anemia, metabolic acidosis, and secondary hyperparathyroidism), and preparing patients for transition to dialysis, transplant, or conservative care. Primary care providers (PCPs) are critical in CKD care through recognizing the disease early, managing risk factor modification through patient education, achieving diabetic and blood pressure (BP) targets, and initiating renoprotective treatments early in the disease course. In this article, we will define CKD staging and discuss, review, and compare the new hypertension guidelines from 2021 Kidney Disease Improving Global Outcomes (KDIGO) and 2017 American College of Cardiology/American Heart Association (ACC/AHA). In addition, this article will highlight new therapies for CKD patients, specifically for the treatment of diabetic kidney disease (DKD).

Methods

We performed a search of primary and secondary indexed, peer-reviewed literature through May 2021 utilizing

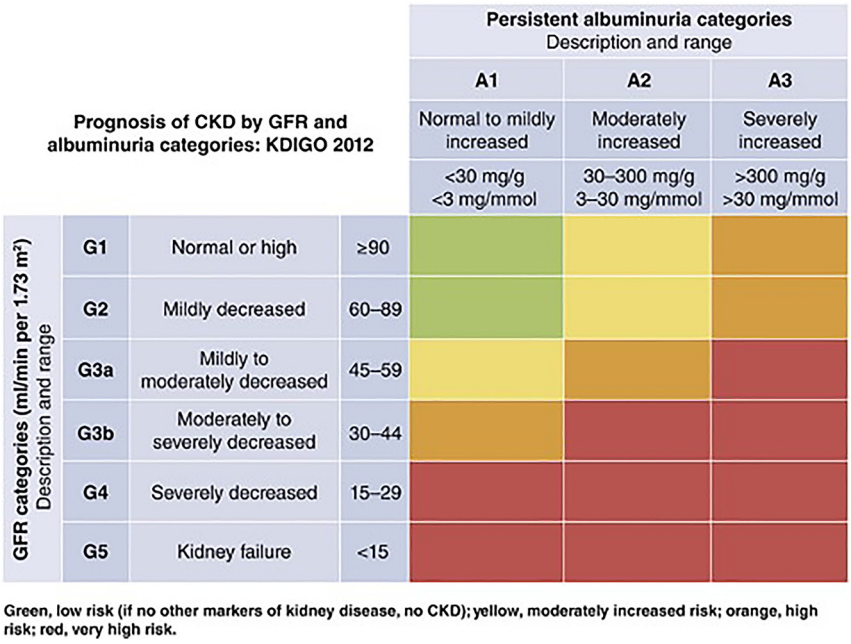

Figure 1: Prognosis of CKD by GFR and albuminuria categories. Reproduced with permission from *Kidney International* [9]. CKD, chronic kidney disease; GFR, glomerular filtration rate.

PubMed and Google Scholar (JT, JY). We utilized a search string to include the words chronic kidney disease, KDIGO, guidelines, American Heart Association, epidemiology, prevalence, risk factors, diabetic kidney disease, proteinuria, albuminuria, treatment, RAS inhibitor, SGLT-2 Inhibitor, GLP-1 receptor agonist, mineralocorticoid receptor antagonist (MRA), and endothelin-A receptor antagonist. The reviewed article types included clinical trials, meta-analyses, systematic reviews, practice guidelines, and pharmaceutical drug information. A total of 50 articles have been included in this review. The authors reviewed all of the results, and disagreements were addressed based on level of expertise (JT).

Discussion

Defining chronic kidney disease

The 2012 KDIGO guidelines defines CKD as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 for 3 months or an eGFR ≥ 60 mL/min/1.73 m^2 with a structural abnormality for >3 months [3]. An abnormality may be defined as albuminuria, abnormalities detected in urine sediment or histology, structural changes seen on imaging, or history of kidney transplant. CKD is classified by the glomerular filtration rate (GFR) category and degree of albuminuria (Figure 1). The 2012 KDIGO heat map differs from the older CKD staging systems by emphasizing the presence and quantity of albuminuria and its impact on CKD progression. It also created a CKD stage 3a (eGFR 45–59 mL/min/1.73 m^2) and 3b (30–44 mL/min/1.73 m^2) to help risk-stratify patients. An independent and graded association of reduced eGFR and risk of death, cardiovascular events, and hospitalization has been shown [4]. KDIGO suggests that patients with an eGFR <30 mL/min/1.73 m^2, urinary albumin-to-creatinine ratio (UACR) > 300 mg/g, or protein-to-creatinine ratio (UPCR) > 500 mg/g should be referred to a nephrologist. However, we suggest early nephrology intervention because studies have shown that earlier referral to a CKD clinic is associated with a decrease in mortality and stabilization of kidney function [5, 6]. The KDIGO heat map provides a powerful visual in assessing the risk of progression to ESKD and highlights the need for disease-altering interventions that can be implemented early on to prevent this progression. Although a complete discussion is out of the scope of this article, readers should be aware that most equations for eGFR use race as a variable such as CKD MDRD (Modification of Diet in Renal Disease) equation and the 2009 CKD EPI equation (Epidemiology Collaboration) [7]. The National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) developed a task force in August 2020 on reassessing the inclusion of race in diagnosing kidney disease. The final report was released on September 23, 2021 which recommends using the eGFR 2021 CKD EPI creatinine equation

that estimates kidney function without a race variable with the goal of providing health equity [8]. Based on these recommendations, many laboratories are starting to implement changes on how they report eGFR. Online calculators for the eGFR 2021 CKD EPI equation may be found by visiting https://www.kidney.org/professionals/kdoqi/gfr_calculator.

Blood pressure targets in patients with CKD

Hypertension is both an etiology and complication of CKD [10, 11]. In a large cross-sectional study of 3,612 patients with CKD, hypertension was seen in up to 85.7% of participants, and only 46.1% were controlled below a systolic blood pressure (SBP)/diastolic blood pressure (DBP) <130/80 mmHg [12]. The mechanism of hypertension in CKD patients includes increased salt and volume retention, upregulated renin-angiotensin system (RAS), endothelial dysfunction, and increased sympathetic activity [13]. Kidney parenchymal disease is a strong risk factor for resistant hypertension [14]. Resistant hypertension is defined as BP that remains above goal despite the use of three antihypertensive medications at optimal doses, one of which is a diuretic or when goal BP is achieved but requires four medications [15, 16]. Additionally, in one study of 1,075 adults with CKD, 30.9% were shown to have masked hypertension (defined as normal office BPs but elevated home pressures) [17]. Elevated BP has been shown to be an independent risk factor for the progression of CKD and the development of ESKD, thus management of hypertension is a crucial component of CKD care [18].

Prior to the 2015 Systolic Blood Pressure Intervention Trial (SPRINT), many guidelines supported a BP goal <140/90 mmHg and a goal <130/80 mmHg for proteinuric kidney disease (defined as urine albumin excretion ≥30 mg in 24 h) [3, 19]. SPRINT, which enrolled 9,361 non-diabetic patients, was stopped early after a median follow-up of 3.26 years after demonstrating lower all-cause mortality (hazard ratio, [HR] 0.73; 95% confidence interval [CI], 0.60 to 0.90; p=0.003) and composite outcome (HR 0.75; 95% CI, 0.64 to 0.89; p<0.001) with more intensive BP lowering (SBP < 120 mmHg) vs. standard BP control (SBP < 140 mmHg) [20]. The primary composite outcome was myocardial infarction (MI), acute coronary syndrome, stroke, heart failure, or death from cardiovascular cause. In a prespecified subgroup analysis of CKD patients, SPRINT Investigators identified that the intensive BP group had a slightly higher rate of decline in eGFR (0.47 vs. 0.32 mL/min/1.73 m^2 per year; p<0.03) and that the overall rate of serious adverse events did not differ between treatment groups. The authors concluded that targeting a SBP < 120 mmHg in patients with CKD would reduce major cardiovascular events and all-cause death without adversely impacting clinical kidney events [21]. As a result, the 2017 ACC/AHA revised their hypertension staging and target guidelines to incorporate these results and suggested targeting SBP < 130 mmHg and DBP < 80 mmHg for patients with CKD (Level 1 Evidence) [22]. (Table 1)

Table 1: Comparison of blood pressure target guidelines.

Population	James et al. (2014 JNC 8) [19]	Whelton et al. (2017 ACC/AHA) [22]	Cheung et al. (2021 KDIGO) [15]
General	<140/90	<130/80	No recommendation
Diabetes	<140/90	<130/80	No recommendation
CKD	<140/90	<130/80	<120[b]
Elderly	<150/90 (≥60 years)	<130/80[a] (≥80 years)	No recommendation[c]

CKD, chronic kidney disease. [a]Randomized controlled trials have proven beneficial for blood pressure goals <130/80 mmHg in functional elderly patients [20]. [b]2021 KDIGO guidelines provide recommendations for systolic blood pressure only. [c]May be reasonable to have less intensive BP-lowering therapy in patients with very limited life expectancy or symptomatic postural hypotension.

In March 2021, KDIGO published new hypertension management guidelines for adult patients with CKD. They suggest a more intensive SBP target of <120 mmHg for adults with CKD with or without diabetes and make no statement of DBP or differentiation between patients with or without albuminuria [15]. These guidelines are clearly influenced from the previously discussed SPRINT trial, but it should be noted that the achieved SBP/DBP of the intensive BP group was 121.4 mmHg/68.7 mmHg compared to standard treatment 136.2 mmHg/76.3 mmHg. These new recommendations are driven by the cardiovascular and mortality benefits and not necessarily kidney protection. For patients with reduced life expectancy or symptomatic postural hypotension, a less intensive BP target should be considered. There were no BP recommendations in the guidelines for the general population, diabetics without CKD, and the functional elderly.

Review of the guidelines: blood pressure treatment in patients with CKD

Physicians should educate patients on lifestyle modification to achieve BP targets. The cornerstone of all therapy includes restricting sodium to <2 g per day, physical activity (moderate intensity, 150 min per week), weight loss if needed, and limiting alcohol intake (men and women ≤2 and ≤1 drinks per day respectively) [15]. First-line antihypertensive agents should be optimized and should include a

thiazide diuretic (preferably chlorthalidone), a dihydropyridine calcium channel blocker (preferably amlodipine or long-acting nifedipine), or either an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) [22]. Beta-blockers should be first-line therapy only if patients have a compelling indication such as heart disease or heart failure [22]. Other comorbidities, like diabetes status, should be taken into account when choosing a first-line agent. Chlorthalidone (12.5–25 mg/day) has re-emerged as the diuretic of choice due to a longer half-life and effectiveness in lower eGFR (~25 mL/min/1.73 m^2) compared to hydrochlorothiazide [22]. If eGFR ≤ 30 mL/min/1.73 m^2 and hypertension is not controlled, the diuretic should be switched to a loop [22]. Mineralocorticoid receptor antagonists (MRAs) are recommended as fourth-line agents in resistant hypertension [15]. Providers should be aware of the increased risk of hyperkalemia associated with this class of medication [15]. Patients with an average SBP/DBP >20/10 mmHg above their target should be initiated on two first-line agents [22].

RAS inhibition in CKD

The renoprotective and cardioprotective benefits of RAS inhibitors, including ACEis and ARBs, have been well demonstrated in multiple subgroups of CKD including those with and without diabetes [23]. It has been over 25 years since the Collaborative Study Group (The Captopril Trial) demonstrated the renoprotective benefits of RAS inhibition in proteinuric type 1 diabetes mellitus [24]. In 2001, the Irbesartan Diabetic Nephropathy Trial (IDNT) studied 1,715 type 2 diabetes mellitus (T2DM) subjects with proteinuria ≥900 mg/day and demonstrated a 20% risk reduction in composite endpoint of doubling of serum creatinine, ESKD, or death from any cause in the irbesartan treatment group compared to placebo (95% CI, 0.66–0.97; p=0.02), and 23% risk reduction compared to amlodipine groups (95% CI, 0.63–0.93; p=0.006) [25]. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial studied 1,513 subjects with T2DM with a UACR ≥ 300 mg/g and showed a 16% risk reduction in the primary composite endpoint of doubling of serum creatinine, ESKD, or death from any cause in the losartan treatment group compared to the placebo group (43.5 vs. 47.1%, p=0.02) [26]. The renoprotective effects of ACEis and ARBs result from the vasodilatory properties that they have on the renal efferent arteriole, which lowers intraglomerular hypertension and reduces GFR [27]. An acute fall in eGFR has been correlated with improved kidney outcomes [27]. The ACC/AHA guidelines recommend treatment with ACEi or ARB in patients with CKD ≥ stage 3 regardless of albuminuria AND in all patients with albuminuria ≥300 mg/day or UACR ≥ 300 mg/g [22].

It is important for physicians to be aware of risks of ACEis and ARBs including acute kidney injury (AKI) and hyperkalemia. A decrease in eGFR may be seen upon initiating an ACEi or ARB due to a reduction in intraglomerular pressures [27]. Current KDIGO 2021 guidelines recommend that a rise in serum creatinine up to 30% is acceptable, as long as it is not associated with other complications such as hyperkalemia. A drop in eGFR >30% may suggest bilateral renal artery stenosis or patients with volume depletion [15]. Renal function and electrolytes should be checked within 2–4 weeks of initiation or increasing the dose of RAS inhibitors. Patients should continue maximal ACEi or ARB therapy unless they experience hyperkalemia not amendable to medical therapy. Medical therapy includes reducing potassium intake to 2,000–3,000 mg per day (50–75 meq per day), discontinuation of potassium-sparing diuretics, and initiating oral potassium-binding agents (patiromer or sodium zirconium cyclosilicate) if needed. The benefits of ACEi or ARB therapy should be prioritized, and the previously mentioned measures should be considered prior to dose reduction or discontinuation of therapy. ACEi and ARB are not recommended to be utilized concomitantly because of an increased risk of acute kidney injury and hyperkalemia [15]. In certain patients, it may be necessary to discontinue ACEis or ARBs for refractory hyperkalemia, particularly in the population transitioning to kidney replacement therapy (KRT).

Major advances in diabetic kidney disease

SGLT-2 inhibitors

Since the landmark trials of RAS inhibition, there has been a paucity of treatment options for patients with CKD. The sodium-glucose cotransporter-2 (SGLT-2) inhibitors have opened the door to a new era as add-on therapy proven to slow the progression of CKD. SGLT-2 inhibitors are rapidly changing practice patterns. The 2020 KDIGO Practice Guidelines for Diabetic Management in CKD goes beyond the 2020 American Diabetic Association and American Association of Clinical Endocrinology recommending SGLT-2 inhibitors *AND* metformin as first-line drugs for DKD [9]. The recommendation to add SGLT-2 inhibitors in combination with metformin is primarily for the beneficial

effects of slowing the progression of kidney and cardiovascular disease. The KDIGO guideline specifically references data from Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD), Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trials that showed benefits in cardiovascular outcomes in both those with and without diabetes, suggesting that the mechanism of benefit was not purely due to glucose control [28–30]. The recommendation goes as far as to recommend decreasing the dose of other antihyperglycemic agents for patients who have met their glycemic goal if they are on agents that put them at risk for hypoglycemia in order to add on an SGLT-2 inhibitor.

The Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes, a prespecified secondary analysis of the Empagliflozin, Cardiovascular Outcomes, and Mortality in T2DM (EMPA-REG Outcomes) trial, showed a reduction in kidney composite outcomes (doubling of serum creatinine, initiation of KRT, death from kidney disease) in those with T2DM (HR 0.54; 95% CI, 0.4–0.75; p<0.001) [31, 32]. The first major randomized placebo-controlled multicenter study to evaluate primary kidney composite outcomes (doubling of baseline serum creatinine, development of ESKD, or death from a renal or cardiovascular cause) with SGLT-2 inhibitors vs. placebo was the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [33]. Approximately 4,400 T2DM patients with eGFR 30–90 mL/min/1.73 m^2 and albuminuria (UACR > 300–5,000 mg/g) treated with optimal doses of RAS blockade were randomized to canagliflozin 100 mg daily or placebo. After a planned interim analysis, the trial was stopped early after a median follow-up of 2.62 years due to the overwhelming beneficial kidney protection. The canagliflozin group experienced a 30% lower risk of kidney events (HR 0.70; 95% CI, 0.59 to 0.82; p=0.00001) compared to placebo. This astonishing outcome was seen in patients who were already taking maximally tolerated ACEis or ARBs. Comparing the previously discussed IDNT and RENAAL trials, the relative risk of doubling of serum creatinine was 40% lower in the CREDENCE trial (HR 0.6; 95% CI, 0.48 to 0.76; p<0.001), compared to the other two studies respectively 29% (HR 0.71; 95% CI, 0.54 to 0.92; p=0.009) and 25% (HR 0.75; 95% CI, 8 to 39; p=0.006). Postulated mechanisms for the renoprotective effects of SGLT-2 inhibitors include a decrease in intraglomerular pressure via indirect vasoconstriction of afferent arteriole via tubuloglomerular feedback, anti-inflammatory, and antioxidant by inducing a starvation state via ketonemia [34, 35].

The CREDENCE trial proved the benefit of SGLT-2 inhibitors for DKD, and the DAPA-CKD trial expanded the indication to proteinuric CKD patients without DKD [30]. The DAPA-CKD trial enrolled 4,304 CKD subjects on maximal RAS blockade with lower eGFRs (25–75 mL/min/1.73 m^2), lesser degree of proteinuria, UACR (≥200–5,000 mg/g), with or without T2DM. Patients received dapagliflozin (10 mg daily) or placebo, and the primary kidney outcome was sustained decline in eGFR of at least 50%, ESKD, or death from kidney or cardiovascular disease [30]. The study was stopped early after 2.4 years because there was a 39% reduction in the primary composite outcome in the dapagliflozin group (HR 0.61; 95% CI, 0.51 to 0.72; p<0.001). The results were similar in T2DM and non-diabetics, which comprised 67 and 33% of the subjects, respectively. A prespecified analysis of a subgroup of DAPA-CKD patients who had concomitant IgA nephropathy (n=270), had a 71% reduction in primary outcomes (HR 0.29; 95% CI, 0.12 to 0.73; p<0.005) suggesting that SGLT-2 inhibitors could be utilized in non-diabetic proteinuric kidney disease [36]. These results led to a new FDA-prescribing indication for dapagliflozin on April 30, 2021, for use in the management of CKD with or without T2DM. The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trial is evaluating 6,000 CKD patients (eGFR ≥ 20–89 mL/min/1.73 m^2) with or without T2DM and is planned to be completed by October 2022 [37].

Providers should be aware that SGLT-2 inhibitors may cause a 5–8 ml/min/1.73 m^2 drop in eGFR in the first 2 weeks of therapy due to the hemodynamic effects similar to those seen in ACEis and ARBs [38]. Prescribers should discuss the risk and benefits of urinary tract infections, diabetic ketoacidosis, and the propensity for volume depletion on "sick days" or in patients who are on concomitant diuretic therapy [39].

GLP-1 receptor agonists

In addition to SGLT-2 inhibitors, other antihyperglycemic agents have shown positive data in the treatment of DKD. Glucagon like peptide-1 (GLP-1) receptor agonists are antihyperglycemics that have been shown to reduce the risk of cardiovascular events in patients with T2DM [40]. GLP-1 receptor agonists work by mimicking the body's natural response to consuming calories, including insulin secretion, appetite suppression, slowing gastric emptying, and utilization of insulin in peripheral tissues [41]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial enrolled 9,340 patients with T2DM and evaluated a secondary

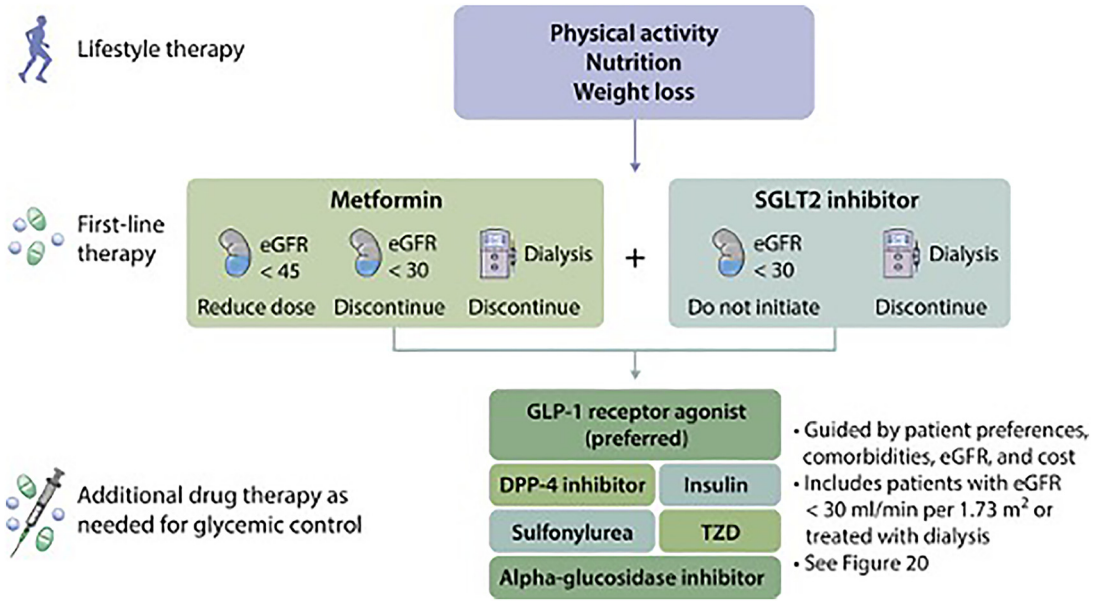

Figure 2: Treatment algorithm for selecting antihyperglycemic drugs for patients with T2D and CKD. Reproduced with permission from *Kidney International* [9]. Kidney icon indicates eGFR (expressed in mL/min per 1.73 m^2); dialysis machine icon indicates dialysis. CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1 (GLP-1); SGLT-2, sodium-glucose cotransporter-2; T2D, type 2 diabetes; TZD, thiazolidinedione.

microvascular, retinal, and kidney composite outcome (defined as new-onset UACR > 300 mg/g, doubling of serum creatinine, and eGFR ≤ 45 mL/min/1.73 m^2, ESKD, or death from renal cause) and retinopathy (defined by the need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or the onset of diabetes-related blindness). The rate of nephropathy events was reduced in the liraglutide group vs. placebo (1.5 vs. 1.9 events per 100 patient-years of observation) (HR 0.78; 95% CI, 0.67 to 0.92, p=0.003) [42]. Renoprotective data was also seen in the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) trial, which enrolled 3,297 T2DM patients. The semaglutide group vs. placebo had a reduction in nephropathy (HR 0.64; 95% CI, 0.46–0.88; p=0.005), but the outcome was primarily driven by the reduction in new-onset UACR >300 mg/g [43]. New or worsening nephropathy was defined as new-onset UACR >300 mg/g, doubling of serum creatinine, and eGFR ≤ 45 mL/min/1.73 m^2, ESKD, or death from a renal cause. In a 2019 meta-analysis, GLP-1 receptor agonists were shown to reduce a primary composite outcome (doubling of serum creatinine, ≥40% decline in eGFR, ESKD, or kidney-related death) by 17% (HR 0.83; 95% CI, 0.78 to 0.89; p<0.001) [44].

Furthermore, the Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND) trial showed a decrease in kidney outcomes (defined as development of a UACR >33.9 mg/mmol, a sustained ≥30% decline in eGFR, or KRT) in the dulaglutide group vs. placebo (HR 0.85; 95% CI, 0.77–0.93; p=0.004) [45]. While SGLT-2 inhibitors and metformin are recommended as first-line therapy for T2DM with CKD, given this data, the 2020 KDIGO Diabetes guidelines recommend GLP-1 receptor agonists as the preferred additional agent for patients with T2DM and CKD whose hemoglobin A1c goals are not met with metformin and an SGLT-2 inhibitor [9]. (Figure 2) Providers should counsel patients on the side effects of GLP-1 receptor agonists, including gastrointestinal distress, which is the most common. Pancreatitis has been associated with GLP-1 agonists and is included in the package insert; however, the LEADER trial demonstrated no association in the liraglutide group compared to placebo [42].

Mineralocorticoid receptor antagonists (MRAs)

Adding MRAs (spironolactone and eplerenone) to ACEi or ARBs has been shown to reduce albuminuria by approximately 25–30%, but with an increased risk of hyperkalemia (2.6-fold increase) and without much efficacy in reducing CKD progression [46, 47]. Finerenone is a nonsteroidal MRA that has a greater receptor selectivity and affinity than the former two aforementioned MRAs. The effect of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial

enrolled 5,734 patients with T2DM and CKD with UACR of 300–5,000 mg/g and an eGFR 25–74 mL/min/1.73 m^2 on maximally tolerated RAS inhibition and randomized them to receive finerenone 10 mg or 20 mg daily or placebo [48]. The primary composite endpoint included ESKD, sustained decrease in eGFR ≥ 40%, or death from a kidney cause. The secondary composite outcome was death from a cardiovascular cause, nonfatal MI, nonfatal stroke, or heart failure hospitalization. After 2.6 years of median follow-up, the finerenone group had an 18% lower incidence of the primary kidney outcome (HR 0.82; 95% CI, 0.73 to 0.93; p=0.001) and a lower secondary composite outcome (HR 0.86; 95% CI, 0.75 to 0.99; p=0.03). Incidences of potassium >5.5 mmol/L (21.7 vs. 9.8%) and >6.0 mmol/L (4.5 vs. 1.4%) were higher in the finerenone group compared to placebo. This led to a higher discontinuation rate in the finerenone group vs. placebo (2.3 vs. 0.9%). It should be mentioned that only 4.6% of all participants were treated with an SGLT-2 inhibitor and 6.9% with a GLP-1 receptor agonist [48]. Therefore, it is unknown whether the beneficial effects of finerenone may be blunted in combination with the former therapies. On July 9, 2021, finerenone was approved by the FDA for use in adults with CKD and T2DM [49].

Endothelin a receptor antagonist

Endothelin A is a vasoactive peptide that constricts blood vessels that result in systemic and pulmonary hypertension. Endothelin A receptor antagonists are an FDA-approved treatment for pulmonary arterial hypertension and have been studied in resistant hypertension [50]. Endothelin A is a mediator for kidney injury via inflammation, endothelial injury, podocyte disruption, and fibrosis. Endothelin A is a profound vasoconstrictor of the afferent and efferent arterioles, which leads to decreases in GFR [51]. Endothelin A receptor antagonists have been shown to reduce BP and albuminuria in patients with T2DM, but they have been associated with fluid overload and heart failure exacerbation [52]. The Study of Diabetic Retinopathy with Atrasentan (SONAR) trial studied T2DM patients with an eGFR of 25–75 mL/min/1.73 m^2, UACR of 300–5,000 mg/g, on maximally tolerated RAS blockade for a minimum of 4 weeks [53]. All patients were initially treated with atrasentan 0.75 mg daily. Only those patients who responded with ≥30% reduction in UACR and showed "no substantial fluid retention" were then randomized to treatment vs. control. The atrasentan treatment group showed a 35% reduction (HR 0.65; 95% CI, 0.49–0.88; p=0.0047) in composite kidney outcomes (doubling of serum creatinine, eGFR < 15, ESKD, kidney transplant, or death from kidney cause), a 52% reduction in UACR, and a lowering of SBP of 1.6 mmHg. There were no differences between the two groups for serious adverse events, but patients taking atrasentan had a higher rate of hypervolemia (36.6 vs. 32.3%, p=0.022) and anemia (18.5 vs. 10.3%, p=0.0001). The trial stopped early after 2.2 years because the primary outcome was lower than expected. Clinical application of this adaptive study design may be more challenging because only study participants who had a ≥30% reduction in albuminuria and no signs of volume retention were studied. Therefore, the actual adverse events due to treatment may be much higher, and the risk of this class of medication may outweigh the benefits.

Conclusions

All osteopathic physicians who provide primary care have a critical role in the early diagnosis and management of CKD. Guidelines recommend referral to a nephrologist with an eGFR < 30 mL/min/1.73 m^2, UACR > 300 mg/g, or UPCR > 500 mg/g. We advocate for earlier referral with an eGFR ≤ 45 mL/min/1.73 m^2 or if the etiology of CKD is unknown. In addition to lifestyle modification, strict BP control and diabetic control are the cornerstones of therapy. For the last 25 years, the medical community only had ACEi and ARBs to slow disease progression. SGLT-2 inhibitors have provided a renaissance in the treatment of proteinuric CKD. GLP-1 receptor agonists, MRAs, and endothelin A receptor antagonists may provide physicians with a potential armamentarium of targeted kidney disease therapies. PCPs should be the initial prescribers of these therapies early in the course of the disease to maximize their benefits and to reduce the prevalence and progression of CKD. The information presented in this narrative review is based on a review of the literature and clinical expertise, but further research in systematic reviews, meta-analyses, and ongoing randomized controlled trials are indicated.

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Competing interests: Jonathan Taliercio DO, is an EMPA KIDNEY and SONAR Co-investigator.

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