Diagnosis and Management of Type 2 Diabetic Kidney Disease

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Abstract

Type 2 diabetic kidney disease (DKD) is the most common cause of CKD and ESRD worldwide, and carries with it enormous human and societal costs. The goal of this review is to provide an update on the diagnosis and management of DKD based on a comprehensive review of the medical literature. Topics addressed include the evolving presentation of DKD, clinical differentiation of DKD from non-DKD, a state-of-the-art evaluation of current treatment strategies, and promising emerging treatments. It is expected that the review will help clinicians to diagnose and manage patients with DKD.

Introduction

Type 2 diabetes is the most common cause of CKD and ESRD worldwide (1). In the United States, >40% of the >29 million individuals with type 2 diabetes have diabetic kidney disease (DKD) (2). In 2011, Medicare alone spent $25 billion caring for patients with presumed DKD (3).

In light of its widespread prevalence and massive health and financial toll, the diagnosis and management of DKD are of great clinical and societal relevance. This review is therefore designed to update clinicians on the diagnosis and management of DKD through a comprehensive review of the medical literature. We will focus on the evolving clinical presentation of DKD, strategies for diagnosis, contemporary treatment options, and promising new therapies.

In the management section, we emphasize the existing randomized trial data on preventing the development and/or progression of type 2 DKD. Because of well founded concerns that microalbuminuria may not represent established kidney disease (4), we excluded studies that had microalbuminuria as their only kidney-related outcome.

The Evolving Presentation of DKD

The classic description of DKD involved progressive stages of glomerular hyperfiltration, microalbuminuria, overt proteinuria, and a decline in the GFR, eventually leading to dialysis (5). In recent years, this concept has been increasingly challenged as evidence suggests that DKD in the contemporary era presents in a more heterogeneous manner.

Large cross-sectional studies reveal that a large minority of patients with type 2 diabetes and reduced kidney function present with normal levels of albuminuria (6–9). In the Developing Education on Microalbuminuria for Awareness of Kidney and Cardiovascular Risk in Diabetes Study, 17% of this international cohort of 6072 individuals with type 2 diabetes of mean duration of 8 years and an eGFR<60 ml/min per 1.73 m² had normoalbuminuria (6). In one United States population-based study this number was reported to be as high as 33% (7). These findings are consistent with a recent report in which the prevalence of albuminuria in patients with type 2 diabetes decreased from about 21% in 1988–1994 to 16% in 2009–2014, despite a rise in the prevalence of reduced eGFR (1).

Whether these observations are a result of misdiagnosing DKD in patients who have another kidney disease, the effects of routine use of renin-angiotensin-aldosterone system (RAAS) blockers or other therapies, or other factors remains uncertain. Regardless, a less uniform presentation poses challenges for the clinician in terms of diagnosing DKD, selecting the appropriate treatment regimen, and identifying treatment success.

Differentiating DKD from Non-DKD

Retrospective studies of kidney biopsy specimens in cohorts of patients with type 2 diabetes identify several clinical features (presented in Table 1) that can help differentiate DKD from other kidney diseases (10–12). In patients who have had type 2 diabetes for at least 10 years and who do not present with atypical findings (see Table 1), a tissue diagnosis is not usually necessary (10,13). Such a strategy is supported by findings from the largest such study of kidney biopsy specimens performed in patients with type 2 diabetes (14). In 620 middle-aged patients from the United States with a median time from diagnosis of diabetes of 10 years, 37% of biopsy specimens were consistent with DKD, 36% had non-DKD, and 27% showed coexisting DKD and non-DKD. The most common causes of non-DKD were FSGS (22%), hypertensive nephrosclerosis (18%), acute tubular necrosis (17%), IgA nephropathy (11%), membranous nephropathy (8%), and pauci-immune GN (7%). Duration of diabetes ≥12 years was the best predictor of
DKD alone (sensitivity 58%, specificity 73%, positive predictive value 56%, negative predictive value 75%). These numbers are quite good when considering that the patients probably underwent a biopsy because of their atypical presentation.

Until such time when noninvasive biomarkers for DKD are available, the decision to biopsy a patient will remain a clinical judgment that should take into account, for each individual, the risk of the procedure and the likelihood that if another diagnosis should be uncovered then appropriate treatment will not only be offered but will influence the prognosis.

Current Treatment Strategies

BP Control

The Kidney Disease Improving Global Outcomes clinical practice guidelines recommend that patients with DKD achieve systolic and diastolic targets of ≤130 and ≤80 mmHg, respectively, for patients with urine albumin excretion >30 mg/24 h (grade 2D). This guideline was made purely on the basis of observational data that demonstrate urine albumin levels are predictive of adverse cardiovascular and kidney outcomes and a lower BP is inversely associated with albuminuria or kidney failure, de

A post hoc analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) (discussed below) in 1590 adults with overt DKD found a systolic BP ≤120 (versus >120) mmHg to be associated with an increased risk of cardiovascular and all-cause mortality and congestive heart failure events (19).

Preferred Antihypertensive Agents

The use of RAAS blockers as first-line BP-lowering agents in patients with DKD is based on high quality randomized controlled trials throughout the range of type 2 diabetes and DKD (20–23).

In a study of patients with early DKD (21), the angiotensin receptor blocker (ARB) irbesartan was compared with placebo in 590 patients with type 2 diabetes, hypertension, normal mean creatinine clearance, and microalbuminuria. Over a median of 2 years, irbesartan reduced the likelihood of the development of macroalbuminuria or a rise in microalbuminuria by 30% (primary composite outcome) in a statistically significant and dose-dependent manner (44% reduction with 150 mg/d, 68% reduction with 300 mg/d, after adjustment for baseline albuminuria level and BP).

RAAS inhibition has also been studied in patients with more advanced DKD. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (22) randomized 1513 patients with type 2 diabetes and proteinuric DKD (serum creatinine, 1.3–3.0 mg/dl; urine albumin-to-creatinine ratio [UACR] >300 mg/g creatinine or proteinuria >500 mg/g creatinine) to losartan or placebo for a mean of 3.4 years. Losartan therapy resulted in a 16% reduced risk in the primary composite end point of death, ESRD, or doubling of serum creatinine, with the individual risk of ESRD or doubling of serum creatinine dropping by 25% and 28%, respectively. Losartan reduced the median rate of decline in eGFR by 0.8 ml/min per 1.73 m² per year.

Similarly, the IDNT (23) Study randomized 1715 patients with DKD and hypertension to irbesartan, amlopidine, or placebo and followed them over a mean of 2.6 years. Compared with placebo or amlopidine, use of irbesartan was associated with a 20% and 23% lower risk of developing the primary composite end point, respectively, which included doubling of baseline serum creatinine, ESRD, or death. With regard to individual end points, irbesartan lowered the risk of doubling of serum creatinine by 33% and 37%, respectively, and reduced the risk of ESRD by 23%, although this was of borderline statistical significance. The rate of decline in the eGFR was 5.5, 6.8, and 6.5 ml/min per 1.73 m² per year in the irbesartan, amlopidine, and placebo arms, respectively.

Of note, although the data supporting the use of angiotensin-converting enzyme inhibitors (ACEIs) does not rise to the level of evidence for that of ARBs, these medication

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Non-DKD</th>
<th>DKD</th>
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<tbody>
<tr>
<td>Onset of proteinuria</td>
<td>Rapid</td>
<td>Gradual</td>
</tr>
<tr>
<td>Progression of CKD</td>
<td>Rapid</td>
<td>Gradual</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>&lt;5 yr</td>
<td>&gt;10 yr</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Active sediment (hematuria, pyuria, casts)</td>
<td>Bland sediment</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Absent</td>
<td>Present</td>
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Table 1. Clinical features distinguishing type 2 diabetic kidney disease (DKD) from Other Causes of Kidney Disease
classes have been used interchangeably in general clinical practice and published guidelines.

Combination ACEI/ARB therapy was evaluated as a prespecified secondary end point in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (24), which randomized 25,620 patients with atherosclerotic vascular disease or diabetes and end-organ damage and a mean baseline creatinine of 1.06 mg/dl to ramipril, telmisartan, or both, and followed them over a median of 56 months. Combination therapy was associated with significantly worse outcomes (greater number of events in the primary and secondary renal composite outcomes, which included doubling of serum creatinine, dialysis, or death). The Veterans Affairs Nephropathy in Diabetes Trial similarly assigned 1448 patients with type 2 diabetes, a baseline eGFR between 30 and 89.9 ml/min per 1.73 m², and UACR=300 mg/g to losartan alone or in combination with lisinopril (25). No cardiovascular or mortality benefit was observed with combination therapy, although trends suggesting benefits were observed with respect to the secondary end point (first occurrence of decline in eGFR) (hazard ratio [HR], 0.78; 95% confidence interval [95% CI], 0.58 to 1.05; \( P=0.10 \)) and development of ESRD (HR, 0.66; 95% CI, 0.41 to 1.07; \( P=0.07 \)). However, safety concerns over a higher incidence of hyperkalemia (6.3 versus 2.6 events per 100 person-years with monotherapy; \( P<0.001 \)) and AKI (12.2 versus 6.7 events per 100 person-years; \( P<0.001 \)) in the combination therapy arm led to early termination of the trial. Interestingly, a secondary analysis of this trial showed that participants who developed AKI in the dual therapy arm actually had a lower 30-day mortality (4.7% versus 15.0%; \( P<0.01 \)), lower risk for first occurrence of reduction in eGFR (HR, 0.60; 95% CI, 0.37 to 0.98), and higher rate of kidney function recovery (75.9% versus 66.3%; \( P=0.04 \)) during follow-up than individuals in the monotherapy arm. (26)

Direct renin inhibition as add-on therapy to ACEI/ARB treatment has been examined in two trials. The Aliskiren in the Evaluation of Proteinuria in Diabetes Trial (27) randomized 599 patients with type 2 diabetes, hypertension, and DKD (defined as UACR>300 mg/g, or >200 mg/g if on RAAS blockers) to aliskiren or placebo. Over a 6-month study period, aliskiren reduced the primary outcome of UACR by 20%, although a small effect on BP was also noted. In contrast, the much larger Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTIITUDE) (28) compared aliskiren to placebo in 8561 patients with type 2 diabetes and nephropathy (UACR>200 mg/g; eGFR=30 ml/min per 1.73 m², or eGFR≤60 ml/min per 1.73 m² with 20 mg/g ≥UACR <200 mg/g or cardiovascular disease). ALTIITUDE was terminated prematurely because of lack of effect on kidney-related outcomes, and a higher rate of hyperkalemia in the add-on arm.

Glycemic Control

The putative benefit of glycemic control on DKD has been the focus of several major studies. The previously mentioned UKPDS Study (29) randomized 3867 patients with newly diagnosed type 2 diabetes to intensive versus conventional glycemic control (median achieved hemoglobin A1c [HbA1c], 7.0% versus 7.9%) using oral hypoglycemic agents or insulin, followed them for up to 15 years, and studied a number of clinical end points. The most consistent finding from a kidney standpoint was a reduction in the development of microalbuminuria in the intensive glycemic control group, but macroalbuminuria and doubling of serum creatinine were also significantly lower in that group at 9 and 12 (but not 15) years of follow-up, with events in these two categories being infrequent.

Another trial measuring the effect of tight glycemic control on kidney outcomes was the Veterans Affairs Diabetes Trial (30) which randomized 1791 veterans with mean duration of type 2 diabetes of 11.5 years, mean HbA1c of 9.4%, and serum creatinine ≤1.6 mg/dl to intensive (achieved mean HbA1c of 6.9%) versus standard (achieved mean HbA1c of 8.4%) glucose control. Over a 5–7 year follow-up period the secondary outcome of nephropathy was assessed. The intensive control group had a significantly lower rate of progression to micro- and macroalbuminuria and any increase in albuminuria, but no difference was noted between the groups in terms of decline in GFR.

Two very large studies examined the effect of glycemic control in populations that included patients with mild to moderate DKD. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Trial (31) followed 11,140 patients with type 2 diabetes randomized to intensive versus standard glycemic control (mean achieved HbA1c, 6.5% versus 7.3%) for a median of 5 years. A total of 19% of participants at baseline had an eGFR<60 ml/min per 1.73 m² and 31% had microalbuminuria or greater. Intensive glycemic control was associated with improvements in a variety of kidney outcomes, including a 9% reduction in new microalbuminuria, 30% reduction in new macroalbuminuria, and 65% reduction in ESRD (with relatively few of these events).

Contrasting findings were reported in the ACCORD Study, which randomized 10,251 patients with type 2 diabetes and high cardiovascular risk to intensive versus standard glycemic control (median HbA1c, 6.4% versus 7.5%) and followed them for an average of 3.5 years. At baseline, median eGFR was 90 ml/min per 1.73 m² and 33% of participants had microalbuminuria or greater. Although the trial was terminated early because of higher mortality rates in the intensive glucose control arm, kidney-related outcomes were measured as prespecified secondary end points (32). Intensive glycemic control was significantly associated with a 21% and 31% lower incidence of micro- and macroalbuminuria, respectively, a 7% higher rate of doubling of serum creatinine, or a >20 ml/min per 1.73 m² decrease in eGFR, with no effect found on development of ESRD.

In summary, intensive glycemic control appears to have a beneficial effect on micro- or macroalbuminuria, with conflicting data on whether it protects kidney health in the long term. The higher mortality risk associated with stricter glycemic control reported in the ACCORD Study is also of obvious concern.

Preferred Diabetes Regimen

Growing evidence suggests that certain medication classes offer kidney protection independent of diabetes control. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are the most exciting such class. SGLT-2 is almost exclusively expressed in the proximal kidney tubule and is believed
to be the main mechanism for tubular reclamation of glucose. SGLT-2 inhibition not only lowers HbA1c by inhibiting tubular glucose uptake but also leads to weight loss and lower BP. Because the actions of SGLT-2 inhibitors require filtration through the glomerulus, its beneficial effects may be blunted at lower levels of GFR.

SGLT-2 inhibitors have been shown to influence kidney function and health. For example, they transiently lower GFR presumably by stimulating the tubulo-glomerular feedback mechanism, and also reduce albuminuria (34). The most impressive evidence for renoprotection comes from the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) Trial, which randomized 7020 patients with type 2 diabetes and cardiovascular disease to the SGLT-2 receptor empagliflozin at two doses versus placebo (35). At baseline, 26% of patients had an eGFR<60 ml/min per 1.73 m² and 40% had micro- or macroalbuminuria. After a median of 3.1 years of follow-up, not only was empagliflozin use linked to fewer cardiovascular and death events but it also improved kidney-related outcomes. Specifically, it was associated with a statistically significant lower rate of incident macroalbuminuria (38%), doubling of serum creatinine and eGFR=45 ml/min per 1.73 m² (44%), and initiation of RRT (55%), although the latter end points were few in number (Figure 1). These findings were consistent throughout the range of baseline eGFR and dose of empagliflozin.

Although the early evidence for SGLT-2 inhibition appears promising, it remains to be seen whether these results will be duplicated in several ongoing clinical trials that have primary kidney-related outcomes (Clinicaltrials.gov identifiers: NCT02065791, NCT02065791, and NCT01989754). In addition, the US Food and Drug Administration recently released a warning about the risk of AKI with SGLT-2 inhibitor use (36). Although the EMPA-REG OUTCOME Trial did not report higher rates of AKI, postmarketing surveillance will be important in determining its frequency.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are another class of diabetes drugs with possible kidney protective effects. DPP-4 inhibitors block the degradation of molecules like glucagon-like peptide-1, leading to augmented pancreatic secretion of insulin. A post hoc analysis of 217 patients with type 2 diabetes and micro- or macroalbuminuria on RAAS blockers collected from several phase 3 randomized, placebo-controlled clinical trials found that the use of the DPP-4 inhibitor linagliptin for 24 weeks led to a 32% drop in albuminuria, independent of BP or HbA1c values (37). More recently, a post hoc analysis of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin, which included 14,735 patients with type 2 diabetes and cardiovascular disease randomized to the DPP-4 inhibitor sitagliptin versus placebo as add-on therapy, reported that over the 4-year follow-up period, the sitagliptin group had a marginally lower median UACR (−0.18 mg/g) and lower mean eGFR (−1.34 ml/min per 1.73 m²) (38).

Weight Reduction and Diet

Because the development of type 2 diabetes is strongly linked to dietary habits and excess adiposity, it is reasonable to consider strategies targeting these factors in the management of DKD. Although there are no dietary recommendations tailored specifically for patients with DKD, the Action for Health in Diabetes Trial (39) compared the effect of intensive lifestyle intervention (i.e., decreased caloric intake and increased physical activity) versus standard diabetes support and education on the prespecified secondary end point of DKD. Participants included 5145 overweight or obese patients with type 2 diabetes and baseline mean albuminuria and serum creatinine levels within the normal range. Over 10 years of follow-up, the intensive lifestyle group had a 4 kg reduction in weight compared with the group on standard treatment. They also had a statistically significant 31% lower cumulative incidence of developing very high-risk CKD (40). Although preliminary, these findings suggest that diet and weight can modify the development and progression of DKD.

Whether bariatric surgery, the most effective and sustained of the weight reduction strategies, is effective in treating DKD has recently been comprehensively reviewed (41). An even more recent case-control study of 985 patients who underwent bariatric surgery and matched controls also addressed this question (42). Over a median follow-up of 4 years, bariatric surgery was associated with a 58% lower risk of ≥30% decline in eGFR and a 57% lower risk of doubling of serum creatinine or ESRD. Similar findings were seen in the approximately 40% of individuals with type 2 diabetes who were included in the study. Results should be interpreted cautiously in light of the influential effect large weight reduction has on serum creatinine (and eGFR) through the loss of muscle mass and the relatively small number of individuals who achieved the clinical end points. Nevertheless, in light of the positive results and ongoing advances in surgical weight reduction strategies, bariatric surgery may turn out to be an important addition to the clinical armamentarium for DKD.

Emerging Therapies for DKD

This section reviews several novel therapies for DKD that are being studied in phase 3+ clinical trials.

Endothelin-1 Receptor A Antagonists

Endothelin-1 receptor A activation within the kidney results in increased oxidative stress, podocyte injury, vasoconstriction, fibrosis, and inflammation (43). A phase 2 clinical trial, the Reducing Residual Albuminuria in Subjects with Diabetes and Nephropathy with Atrasentan Trial, showed that the selective endothelin-1 receptor A antagonist atrasentan lowered albuminuria and BP in patients with DKD (44). A post hoc analysis showed decreased renal risk with use of atrasentan and served as the basis for the Study of Diabetic Nephropathy with Atrasentan (SONAR) (Clinicaltrials.gov identifier: NCT01858532) (45). SONAR is expected to enroll 4148 patients with DKD and has a composite end point of ESRD, doubling of serum creatinine, or death. Its expected completion date is late 2018.

Mineralocorticoid Receptor Antagonists

There is growing interest in the protective role of agents that block the RAAS cascade downstream. Steroidal
mineralocorticoid receptor (MR) antagonists like spironolactone and eplerenone have a limited role to play as adjunct therapy to ACEI/ARBs because of hyperkalemia and other adverse effects. It is thought that this is, in part, because of variations in cell-specific effects of steroidal MR antagonists and incomplete antagonism. Identification of nonsteroidal MR antagonists that have a predictable antagonistic response and more tolerable side effect profile is currently underway. Finerenone is one such agent under investigation. The Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy Study showed that addition of finerenone to ACEIs/ARBs resulted in improvement in UACR (46). The Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease Study (Clinicaltrials.gov identifer: NCT02545049) has a planned enrollment of 6400 patients with type 2 diabetes, has kidney outcomes as secondary end points, and an estimated completion date in early 2019. The Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and Diabetic Kidney Disease Study has a planned enrollment of 4800 patients, a kidney end point as the primary end point, and an estimated completion date in mid-2019.

**TGF-β Inhibitors**

Fibrosis is a hallmark of DKD and TGF-β1 is a potent profibrotic molecule. Pirfenidone interferes with the secretion, expression, and action of TGF-β1 by an unknown...
Table 2. Contemporary management of diabetic kidney disease (DKD)

<table>
<thead>
<tr>
<th>Therapeutic Options</th>
<th>Comment</th>
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<tbody>
<tr>
<td>BP control</td>
<td>Guidelines’ goal of &lt;130/&lt;80 mmHg is not supported by data from randomized controlled trials. Ideal BP is not known</td>
</tr>
<tr>
<td>RAAS blockade</td>
<td>Strongest evidence supports ARB use. Combination ACEI/ARB or direct renin inhibitor use are not supported by data</td>
</tr>
<tr>
<td>Glycemic control</td>
<td>Intensive control (HbA1c≤7%) protects against micro- or macroalbuminuria but data are conflicting regarding effects on CKD progression. Also carries risk of serious complications</td>
</tr>
<tr>
<td>SGLT-2 inhibition</td>
<td>Promising evidence for renoprotection from secondary end point in EMPA-REG OUTCOME Trial. Awaiting results of additional confirmatory trials</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Preliminary data suggest a benefit but require confirmation</td>
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RAAS, renin-angiotensin-aldosterone system; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; HbA1c, hemoglobin A1c; SGLT-2, sodium-glucose cotransporter2; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2.

Discussion

The contemporary management of DKD, as seen in Table 2, offers some reasons for optimism, including the proven efficacy of RAAS blockers, the excitement over SGLT-2 inhibitors, and the possibility of novel therapies on the horizon. Yet critical gaps remain in our understanding of DKD. Diagnosis of DKD remains a matter of subjective assessment because a noninvasive biomarker is lacking. This limitation makes it more difficult to design clinical trials to identify effective treatments for DKD. Whether nonproteinuric DKD requires a different treatment strategy than proteinuric DKD is not known. The roles of BP and glycemic control in managing DKD still remain controversial despite decades of study. In addition, the influence of diet and obesity on the development and progression of DKD is also unclear. Insights into these issues will be necessary to further advance clinical management of DKD.

Disclosures

None.

References


Phosphodiesterase Inhibitors

The nonselective phosphodiesterase inhibitor pentoxifylline has demonstrated anti-inflammatory, antifibrotic, and anti-proteinuric effects in several small studies. It is currently being evaluated in a prospective clinical trial (Clinicaltrials.gov identifier: NCT01377285) of 350 patients with advanced DKD versus CKD stages 3 and 4 in nonpatients with diabetes. The study has a primary kidney end point and is expected to be completed in December 2018.

5-Hydroxytryptamine 2a Receptor Antagonists

The selective 5-hydroxytryptamine 2a receptor antagonist sarpogrelate hydrochloride has been shown to have renoprotective effects in a series of diabetic animal studies. The Sarpogrelate on the Nephropathy in Type 2 Diabetes Study (Clinicaltrials.gov identifier: NCT01377285) of 350 patients with advanced DKD versus CKD stages 3 and 4 in nonpatients with diabetes. The status of the study remains unknown as the last Clinicaltrials.gov update was in July of 2014.


40. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 Clinical Practice Guideline for the


Published online ahead of print. Publication date available at www.cjasn.org.