Relationship of Type 2 Diabetes and Chronic Kidney Disease: Opportunities for Prevention, Intervention, and Mitigation

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View faculty bio at https://www.ashpadvantage.com/t2d/ckd/

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Relationship of Type 2 Diabetes and Chronic Kidney Disease: Opportunities for Prevention, Intervention, and Mitigation

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Learning Objectives

At the conclusion of this educational activity, participants should be able to

• Describe the progressive nature of chronic kidney disease (CKD)
• Summarize recommended guidelines for routine screening for CKD in patients with cardiorenal-metabolic disease
• Discuss indirect and direct approaches for managing CKD

Overview

Burden of CKD
in the U.S.

Progressive
Nature of CKD

Diabetes as a
Driver of CKD

Importance of Screening
and Monitoring

Current Approaches
to Management

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Burden of Chronic Kidney Disease in the U.S.

- Approximately 1 in 7 adults are estimated to have CKD*
- In 2016, all-cause mortality rate for CKD was about 103 per 1,000 patient-years in Medicare patients²
- CKD expenditure represents 25% of overall spending for Medicare patients³,†

*Prevalence of CKD in U.S. adults using NHANES 2013-2016 data. CKD may be overestimated as persistence of albuminuria or creatinine was not accounted for based on KDIGO recommendations; †based on 2017 data.

CKD = chronic kidney disease, KDIGO = Kidney Disease Improving Global Outcomes, NHANES = National Health and Nutrition Examination Survey

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Increases in Prevalence of CKD Risk Factors Anticipated to Increase Burden of ESRD

ESRD Incidence and Prevalence per Million Population^2

<table>
<thead>
<tr>
<th>Year</th>
<th>Simulated Incidence</th>
<th>Projected Incidence</th>
<th>Simulated Prevalence</th>
<th>Projected Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1990</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>2000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2020</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2030</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hypertension  Diabetes  Family History

ASCVD  Diabetic Kidney Disease  Race and Ethnicity

CKD Risk Factors^1

ESRD Incidence per Million

ESRD Prevalence per Million

500  1000  1500  2000  2500  3000  3500


Simulated Prevalence

Projected Prevalence

Projected Incidence

Simulated Incidence

--

CKD Significantly Shortens Life Span

Reference†

Early CKD: 5.7 years shorter^ vs. reference^1

Early DKD: 14.8 years shorter^ vs. reference^1

Early CKD: 6.7 years shorter^ vs. reference^1

Early DKD: 16.9 years shorter^ vs. reference^1

Men

Women

Overall life expectancy was shortened by 6 years with early CKD and by 16 years with comorbid T2D

*At 30 years of age; †Reference group consisted of participants with neither diabetes nor CKD; ^Early CKD was defined as CKD stage 1-3 without diabetes; ^Diabetes was defined as diabetes without CKD; |Early DKD was defined as diabetes with early CKD stages 1-3.

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; ESRD = end-stage renal disease


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Progressive Nature of Chronic Kidney Disease

Progressive Decline in Renal Function in CKD

Common Symptoms

- Asymptomatic in early stages
- Advanced CKD symptoms can include
  - Fatigue
  - Poor appetite
  - Nausea/vomiting
  - Metallic taste
  - Pruritus
  - Peripheral edema
  - Pallor
  - Altered mental status

CKD = chronic kidney disease; GFR = glomerular filtration rate

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Progression of CKD Increases the Risk for Adverse Outcomes

CV Death Is More Likely than Progression to ESRD in Patients with CKD

Leading causes of death in CKD:
- CV events
- non-CV causes (e.g. cancer, infection)
Which of the following is a symptom of uremia? Select all that apply.

a. Altered mental status
b. Fatigue
c. Nausea/vomiting or poor appetite
d. Peripheral edema
e. Fever
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Diabetes as a Driver of Chronic Kidney Disease

Diabetes Is the Leading Cause of CKD

Age-standardized U.S. prevalence of CKD by cause in 2016

Diabetes 53.8%
Glomerulonephritis 18.3%
Hypertension 13.2%
Other 14.7%

CKD = chronic kidney disease
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In Patients with T2D, Early Stages of CKD Are Most Prevalent

Prevalence of CKD in patients with T2D
NHANES, 2007–2012

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90 *</td>
<td>9.1</td>
</tr>
<tr>
<td>60-89 †</td>
<td>9.4</td>
</tr>
<tr>
<td>45-59</td>
<td>11.2</td>
</tr>
<tr>
<td>30-44</td>
<td>5.5</td>
</tr>
<tr>
<td>15-29</td>
<td>2.4</td>
</tr>
<tr>
<td>&lt;15</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*In addition, UACR ≥30 mg/g; †In addition, UACR ≥30 mg/g.

CKD = chronic kidney disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey; T2D = type 2 diabetes; UACR = urine albumin-to-creatinine ratio


Most Patients with T2D Do Not Yet Have Significantly Reduced Renal Function or Proteinuria

Distribution of markers of CKD* in NHANES participants with diabetes 2013–2016

- eGFR 10.2%
- UACR 18.7%
- None 62.6%
- Both eGFR and UACR 8.5%

*CKD defined as UACR ≥30 mg/g or eGFR <60 mL/min/1.73 m²

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey; UACR = urine albumin-to-creatinine ratio

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Long-term Progression of Kidney Disease in Patients with T2D

United Kingdom Prospective Diabetes Study (UKPDS)†
5,102 patients with T2D

15 years after diagnosis‡

Developed albuminuria§
38%

Developed eGFR < 60 mL/min/1.73 m² (CKD stage 3–5)
28%

A substantial proportion of patients with T2D will develop albuminuria and renal impairment

*The UKPDS enrolled patients with newly diagnosed T2D; †Defined as a urinary albumin concentration 50–299 mg/L; ‡Defined as a urinary albumin concentration ≥ 300 mg/L; §Defined as urinary albumin concentration ≥ 50 mg/L.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes


Progression of CKD in Diabetes

GFR = glomerular filtration rate

Mild

Precalculic

Incipient diabetic nephropathy

Moderate

GFR

Overt diabetic nephropathy

Severe

ESRD

Urinary protein excretion (g/d)

Years

0

5

10

15

20

25

5000

1000

200

20

25

150

100

50

0

GFR↑

Microalbuminuria

Hypertension

Proteinuria

GFR↓

Proteinuria, nephrotic syndrome, GFR↓

CV risk

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Diabetes Is the Leading Cause of ESRD

![Graph showing the primary cause of ESRD in the U.S. population in 2017](image)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>47%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7%</td>
</tr>
<tr>
<td>Cystic kidney</td>
<td>3%</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>14%</td>
</tr>
</tbody>
</table>

*Data from the International Dialysis Outcomes and Practice Patterns Study (n=2,855); †Data from the Medical Outcomes Study Short Form-36 manual (n=2,474);‡Physical and mental component scales consist of physical functioning, physical role, physical pain, general health, vitality, social functioning, emotional role, and mental health.


Declining Renal Function Predicts CV Mortality in Patients with CKD, A Pattern that Is Worse in Patients with Comorbid T2D

![Graph showing cardiovascular mortality according to eGFR and UACR](image)

<table>
<thead>
<tr>
<th>Graph 1: Cardiovascular mortality according to eGFR in participants with and without diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graph 2: Cardiovascular mortality according to UACR in participants with and without diabetes</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urine albumin-to-creatinine ratio


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ESRD Risk Appears Stable Despite Improvements in Other Diabetes Complications

Rates of myocardial infarction, stroke, and leg amputation numerators are from the National Hospital Discharge Survey; rates of end-stage renal disease numerators are from the US Renal Data System; and rates of death from hyperglycemic crisis numerators are from the National Vital Statistics System. Denominators are from the National Health Interview Survey.

Note: Circle size is proportional to the absolute number of cases.

ESRD = end stage renal disease

Importance of Screening and Monitoring
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Assessment of Kidney Function and Damage

- **Decreased eGFR**
  - Calculate from the serum creatinine concentration
  - eGFR < 60 mL/min/1.73 m² (Stage 3a–5)

- **Albuminuria**
  - AER ≥ 30 mg/24 hr
  - UACR ≥ 30 mg/g [≥ 3 mg/mmol]

- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

**Kidney damage**

Diagnosis of CKD requires two abnormal measurements at least 3 months apart

AER = albumin excretion rate; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urine albumin-to-creatinine ratio


**Categories of Kidney Function and Damage**

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Kidney function</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1*</td>
<td>≥ 90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2*</td>
<td>60–89</td>
<td>Mildly decreased¹</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt; 15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria category</th>
<th>AER (mg/24 hr)</th>
<th>ACR¹ (mg/mmol)</th>
<th>ACR¹ (mg/g)</th>
<th>Albumin in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt; 30</td>
<td>&lt; 3</td>
<td>&lt; 30</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>30–300</td>
<td>3–30</td>
<td>30–300</td>
<td>Moderately increased¹</td>
</tr>
<tr>
<td>A3</td>
<td>&gt; 300</td>
<td>&gt; 30</td>
<td>&gt; 300</td>
<td>Severely increased⁰</td>
</tr>
</tbody>
</table>

CKD is classified based on cause, GFR category, and albuminuria category

*Does not fulfill the criteria for CKD in the absence of evidence of kidney damage; Relative to young adult level; ¹Approximate equivalent; ²Including nephrotic syndrome (albumin excretion usually > 2200 mg/24 hr [UACR > 2220 mg/g, > 220 mg/mmol])


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Which of the following patients are at risk for progression and should be referred to nephrologist? Select all that apply.

a. 75yo with eGFR 29 mL/min/1.72m² in 2019 & 27 mL/min/1.72m² in 2020
b. 56yo with diabetes, A1C 7.2%, eGFR above 60 mL/min/1.72m², and UACR 486 mg/g
c. 63yo with eGFR 55 mL/min/1.72m² at initial visit, 3 months later with eGFR 56 mL/min/1.72m² and UACR below 30 mg/g

eGFR = estimated glomerular filtration rate
UACR = urine albumin creatinine ratio

Monitoring of CKD Should Intensify as Renal Function Declines

<table>
<thead>
<tr>
<th>GFR Category (mL/min/1.73 m²)</th>
<th>Persistent albuminuria categories</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 Normal or high</td>
<td>Normal to mildly increased</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>G2 Mildly decreased</td>
<td>Mildly increased</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased</td>
<td>30-44 mg/mmol</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>G3b Severely decreased</td>
<td>Severely decreased</td>
<td>3</td>
<td>3</td>
<td>4+</td>
</tr>
<tr>
<td>G5 Kidney failure</td>
<td>≥150 mg/mmol</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
</tr>
</tbody>
</table>

Green = low risk (if no other markers of kidney disease, no CKD)
Yellow = moderately increased risk
Orange = high risk
Red = very high risk

KDIGO recommends referral to a nephrologist for advanced CKD

CKD = chronic kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; UACR = urine albumin-to-creatinine ratio
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Diagnosis of CKD in T2D Patients Is Deficient

CKD Diagnosis Among Patients with T2D and Renal Impairment

- Diagnosed CKD: 12%
- Undiagnosed CKD: 88%

Primary care setting
9,307 patients with T2D
15-month review period

- 52.9% were not tested for urine ACR
- 15.2% were not tested for eGFR

Screening for CKD using GFR and UACR testing should be carried out annually in patients with T2D

Guidelines Recommend Routine Screening for CKD in Patients with Cardiorenal-metabolic Disease

KDIGO
- Regular testing of high-risk groups (including those with diabetes, hypertension, and CVD) can give an early indication of kidney damage
- Public health policies should include screening of these high-risk populations

NICE
- Test for CKD using eGFR creatinine and ACR in people with:
  - Diabetes
  - Hypertension
  - Acute kidney injury
  - CVD (ischemic heart disease, chronic HF, peripheral or cerebral vascular disease)
  - Structural renal tract disease, recurrent renal calculi, or prostatic hypertrophy
  - Multisystem disease with possible kidney involvement (e.g., systemic lupus erythematosus)
  - Family history of ESRD or hereditary kidney disease
  - Opportunistic detection of hematuria

American Diabetes Association
- At least once yearly, assess urinary albumin (spot urinary ACR) and eGFR in patients with:
  - T1D with duration of ≥5 years
  - T2D

ACR = albumin-to-creatinine ratio; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes
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Current Approaches to Management

Effective Treatment of CKD Includes Both Direct and Indirect Approaches

*This is not an exhaustive list of treatable risk factors. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

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### ADA Approach to Selection of Glycemic Target

<table>
<thead>
<tr>
<th>Risks potentially associated with hypoglycemia and other drug adverse events</th>
<th>more stringent</th>
<th>less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td>high</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease duration</th>
<th>newly diagnosed</th>
<th>long-standing</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Life expectancy</th>
<th>long</th>
<th>short</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Important comorbidities</th>
<th>absent</th>
<th>few / mild</th>
<th>severe</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Established vascular complications</th>
<th>absent</th>
<th>few / mild</th>
<th>severe</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient preference</th>
<th>highly motivated, excellent self-care capacities</th>
<th>Preference for less burdensome therapy</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Resources, support system</th>
<th>readily available</th>
<th>limited</th>
</tr>
</thead>
</table>


### 2020 ADA Standards of Medical Care Antihyperglycemic Medication in Type 2 Diabetes: Overall Approach

First-Line Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

If A1C Above Individualized Target, Proceed as Below

<table>
<thead>
<tr>
<th>Indicators of High-Risk or Established ASCVD, CKD, or HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD Predominates</td>
</tr>
<tr>
<td>GLP-1 RA with proven CVD benefit*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>SGLT-2i with proven CVD benefit*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>GIP-1 RA with proven CVD benefit*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>with proven CVD benefit* if eGFR is less than adequate (if SGLT-2i not tolerated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart Failure or CKD Predominates</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>GLP-1 RA with proven CVD benefit*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>with evidence of reducing HF and/or CKD progression in CVOTs if eGFR is less than adequate (if SGLT-2i not tolerated)</td>
</tr>
</tbody>
</table>

Choose an agent with indication to reduce CVD events

Choose an agent with proven HF or CKD benefit for appropriate patients

Recommendations include a treatment approach to T2D that begins with an assessment of ASCVD, HF, and CKD status

*Label indication of reducing CVD events

ADA = American Diabetes Association; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HF = heart failure

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Evolution of the Definition of Hypertension

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>JNC-I</td>
</tr>
<tr>
<td></td>
<td>Diastolic ≥ 105</td>
</tr>
<tr>
<td>1980</td>
<td>JNC-II</td>
</tr>
<tr>
<td></td>
<td>≥ 160/90</td>
</tr>
<tr>
<td>1990</td>
<td>JNC-V</td>
</tr>
<tr>
<td></td>
<td>≥ 140/90</td>
</tr>
<tr>
<td>2000</td>
<td>SPRINT</td>
</tr>
<tr>
<td></td>
<td>ACC/AHA</td>
</tr>
<tr>
<td></td>
<td>≥ 130/80</td>
</tr>
</tbody>
</table>


Renin Secretion:
- Macula densa signal
- Renal artery pressure/blood flow
- Sympathetic stimulation

Angiotensinogen → Angiotensin I → Angiotensin II

Review of Hypertension Treatment
- ACE inhibitors “-pril”
- ARB “-sartan”
- β-blockers “-olol”
- calcium channel blockers
- diuretics
- aldosterone antagonists
- direct renin inhibitor


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Which of the following medication classes has NOT been associated with reduction in albuminuria?

a. Angiotensin-converting enzyme inhibitors
b. Mineralocorticoid/aldosterone antagonists
c. Alpha blockers
d. Angiotensin receptor blockers
e. Sodium-glucose cotransporter 2 inhibitors

Potential Impact of Early Intervention to Prevent Progression of Albuminuria

*Data acquired from the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, a Dutch population prospective cohort study with sequential follow-up over a period of 6.2 years.

eGFR = estimated glomerular filtration rate

Optimal Risk Factor Management Does Not Eliminate Risk of Diabetic Nephropathy*

*Diabetic nephropathy was defined as a urinary albumin excretion of more than 300 mg/24 hr in two of three consecutive sterile urine specimens.²

CI = confidence interval; RR = relative risk


Targets for Therapeutic Intervention in CKD

Reduce Kidney Damage¹⁻³

Proteinuria
Intraglomerular hypertension
Hypoxia
Volume excess
Tubulointerstitial injury

Address CKD Complications⁴

Anemia
Metabolic acidosis
Electrolyte imbalance
Volume status
Bone disorders


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Addressing Glomerular Hypertension in Managing the Risk of Progressive Kidney Damage in CKD

Clinical Implications
- Decreased glomerular pressure
- Reduction in albuminuria
- Less eGFR decline

Afferent arteriole vasoconstriction
Efferent arteriole vasodilation

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

Summary
The Burden of CKD is Significant Despite Current Approaches to Diagnosis and Treatment

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<th>Intervene early</th>
<th>Preserve renal function</th>
<th>Protect against CV risk, morbidity, and mortality</th>
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<td><strong>In patients with T2D, earlier stages (1-3) of CKD are more common than late stages</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>KDIGO recommends routine CKD monitoring with increasing frequency as renal function declines</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td><strong>Lower eGFR and higher albuminuria are independently associated with increased adverse CV outcomes and premature death, which is worse in patients with diabetes</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
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<td><strong>Roughly 10% of patients with CKD and T2D receive a diagnosis</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td><strong>Engage patients in risk factor reduction and use multifactorial interventions to tailor treatment regimens to the individual</strong></td>
<td><strong>CV mortality is more likely than progression to ESRD,</strong> however, protecting against renal decline decreases CV risk&lt;sup&gt;10,11&lt;/sup&gt;</td>
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<td><strong>Progressive deteriorations in renal function increase the risk of adverse outcomes, such as risk of hospitalizations, CV events, mortality, and healthcare costs</strong>&lt;sup&gt;3,4&lt;/sup&gt;</td>
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<td><strong>Several guidelines recommend to regularly screen patients at increased risk</strong>&lt;sup&gt;5,6,7&lt;/sup&gt;</td>
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