Diabetic Kidney Disease

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Disclosure

Dr. Skolnik:

**Consultant and/or Advisory Board** for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; GlaxoSmithKline; Intarcia Therapeutics, Inc.; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; Mylan N.V.; Sanofi-Aventis U.S. LLC; Sanofi Pasteur, and Teva Pharmaceuticals USA, Inc.

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Definition

• 3 or more months of either kidney damage (albuminuria, kidney biopsy findings, or imaging abnormalities) or an estimated GFR <60 mL/min/1.73 m2.

• CKD is classified based on cause, GFR category, and albuminuria category (CGA)

• Diabetic Kidney Disease (DKD) is a clinical diagnosis requiring the presence of albuminuria and/or reduced eGFR in the absence of signs of symptoms of other primary causes of kidney damage.
Epidemiology

- CKD attributed to diabetes (diabetic kidney disease) occurs in 20–40% of patients with diabetes
- DKD markedly increases CV risk
- DKD is the leading cause of ESRD requiring dialysis (45%)

**Etiology of CKD**

- Diabetes: 38%
- Glomerulonephritis: 26%
- High Blood Pressure: 16%
- Other Cause: 15%
- Unknown Cause: 5%

N=726,331 (all ages, 2016)
Source: US Renal Data System
*Includes polycystic kidney disease, among other causes.

2019 Chronic Kidney Disease Fact Sheet  https://nkf.egnyte.com/dl/h2PeqRLmEB/
Classification

In predicting risk for outcome of CKD, identify:
1) Cause of CKD
2) GFR category
3) Albuminuria category
4) Other risk factors and comorbid conditions.

### Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>A3</td>
<td>Severely increased</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high ≥90</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased 60-89</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased 45-59</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased 30-44</td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased 15-29</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure &lt;15</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.
CKD Progression

• Small fluctuations in GFR are common

• A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

Identification of DKD

- At least once a year, assess urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate (eGFR) in patients with type 1 diabetes with duration of >5 years and in all patients with type 2 diabetes regardless of treatment. B

- Normal UACR is defined as <30 mg/g Cr, and high urinary albumin excretion is defined as >30 mg/g Cr (NOTE: high biological variability of >20% between measurements, so 2 of 3 specimens over six months is considered abnormal albuminuria.

- Patients with urinary albumin >30 mg/g creatinine and/or an eGFR <60 mL/min/1.73 m² should be monitored twice annually to guide therapy. C
Management

• Interventions that delay chronic kidney disease progression:
  • Management of hypertension
    • Use of a renin angiotensin aldosterone system (RAAS) blocker, an ACE-I, or ARB for hypertension and albuminuria
  • Control of diabetes
  • Choice of medication for diabetes
  • Dietary protein intake should be of approx. 0.8 g/kg body weight per day
  • Correction of metabolic acidosis

STANDARDS OF CARE, Diabetes Care 2020;43(Supp 1):S135-S151
Hypertension – Target BP

• “Blood pressure levels <140/90 mmHg are generally recommended to reduce CVD mortality and slow CKD progression among all people with diabetes.

• Lower blood pressure targets (<130/80 mmHg) should be considered for patients based on individual anticipated benefits and risks. Patients with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD and therefore may be suitable in some cases for lower blood pressure targets, especially in those with >300 mg/day albuminuria.”
Hypertension – Preferred Agent

• ACE inhibitors or ARBs are the preferred first-line agent for blood pressure treatment among patients with diabetes, hypertension, eGFR <60 mL/min/1.73 m², and UACR ≥300 mg/g Cr because of their proven benefits for prevention of CKD progression
  • Absent kidney disease, ACE inhibitors or ARBs are useful to control blood pressure but have not proven superior to alternative classes of antihypertensive therapy

STANDARDS OF CARE, Diabetes Care 2020;43(Supp 1):S135-S151
Hypertension – Preferred Agent

• Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the drug combination had higher adverse event rates (hyperkalemia and/or AKI). Therefore, the combined use of ACE inhibitors and ARBs should be avoided.

• Follow renal function and potassium (check BMP within a few weeks of starting or increasing dose).

• Expect small decrease in GFR (up to 30% increase in serum creatinine)
  • An analysis of the ACCORD BP trial demonstrated that those randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease

STANDARDS OF CARE, Diabetes Care 2020;43(Supp 1):S135-S151
Diabetes Management - Glucose Control

• A1c Target– Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of albuminuria and reduced eGFR in patients with type 1 diabetes and type 2 diabetes

• BUT.... CKD affects the risks and benefits of intensive glycemic control.
  • In ACCORD - adverse effects of intensive glycemic control (hypoglycemia and mortality) were increased among patients with kidney disease at baseline
  • Given the lag time till benefit (2-10 years) in some patients with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive

STANDARDS OF CARE, Diabetes Care 2020;43(Supp 1):S135-S151
Diet

• Protein intake should be approximately 0.8 g/kg body weight per day. (A)
  • Dietary protein intake less than the recommended daily allowance of 0.8 g/kg/day does not improve outcomes.
  • For patients on dialysis, higher levels of dietary protein intake should be considered, as malnutrition is a major problem in some dialysis patients. (B)

• Restriction of dietary sodium ( <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk

• Restriction of dietary potassium may be help if K increased

• Refer to RD/CDE

STANDARDS OF CARE, Diabetes Care 2020;43(Supp 1):S135-S151
Diabetes Management – Glucose Control: Choice of Agent

- Metformin – FDA revised label (2016)
  - the benefits and risks of continuing treatment should be reassessed when eGFR falls <45 mL/min/1.73 m²; metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m²;
  - metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m²

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR, mL/min per 1.73 m²</th>
<th>Maximal Total Daily Dose, mg</th>
<th>Other Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60 -&lt;90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>45 -&lt;60</td>
<td>2000</td>
<td>Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>3B</td>
<td>30 -&lt;45</td>
<td>1000</td>
<td>Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15 -&lt;30</td>
<td>Do not use</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Do not use</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes Management – Glucose Control: Choice of Agent

- SGLT-2 inhibitors
- GLP-1 Receptor Agonists
SGLT-2 Inhibitors

- **Empaliflozin**
  - reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g Cr, doubling of serum creatinine, ESRD, or death from ESRD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR <45 mL/min/1.73 m² by 44%

- **Canagliflozin**
  - reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40%

- **Dapagliflozin**
  - A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87); We identified a 46% reduction in sustained decline in eGFR by at least 40% to less than 60 mL/min per 1.73 m²
GLP-1 Receptor Agonists

- Liraglutide
- Semaglutide
- Dulaglutide
- Exenatide

- EFFECT – decrease the development of new macroalbuminuria

STANDARDS OF CARE, Diabetes Care 2020;43(Supp 1):S135-S151
Composite Renal Outcomes of SGLT2i and GLP1-RAs

**EMPA-REG OUTCOME** (Empagliflozin)
- Composite renal endpoint: macroalbuminuria, doubling of serum creatinine level, eGFR ≤45 mL/min/1.73 m², initiation of renal-replacement therapy or renal death
- HR: 0.61
- 95% CI (0.53; 0.70)
- P<0.001

**CANVAS program** (Canagliflozin)
- Composite renal endpoint: 40% reduction in eGFR, ESRD, or renal death
- HR: 0.60
- 95% CI (0.47; 0.77)

**LEADER** (Liraglutide)
- Composite renal endpoint: macroalbuminuria, doubling of serum creatinine, and eGFR ≤45 mL/min/1.73 m² per MDRD, ESRD, or renal death
- HR: 0.78
- 95% CI (0.67; 0.92)
- P=0.003

**SUSTAIN 6** (Semaglutide)
- Composite renal endpoint: macroalbuminuria, doubling of serum creatinine, and eGFR ≤45 mL/min/1.73 m² per MDRD or need for continuous renal replacement therapy
- HR: 0.64
- 95% CI (0.46; 0.88)
- P=0.005

Empagliflozin Demonstrated Slower Progression of DKD vs Placebo

Change in eGFR over 192 weeks

Empagliflozin, 25 mg
Empagliflozin, 10 mg
Placebo

Reduced doubling of creatinine (44 %)


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CREDENCE Trial

• Double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo.

• All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m² of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade.

• The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m²), a doubling of the serum creatinine level, or death from renal or cardiovascular causes.

*Choice of Glycemic Lowering Medication*

**INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF**

**CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET**

**ASCVD PREDOMINATES**
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LV/H)

**HF OR CKD PREDOMINATES**
- Particularly HFREF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

**PREFERABLY**
- GLP-1 RA with proven CVD benefit¹
  - OR
  - SGLT2i with proven CVD benefit¹ if eGFR adequate²

**PREFERABLY**
- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³
  - OR
  - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate³ add GLP-1 RA with proven CVD benefit¹

If A1C above target

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Diabetes Care 2020;43(S 1):S98–S110
Mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone)

• Mineralocorticoid receptor antagonists are effective for management of resistant hypertension, have been shown to reduce albuminuria in short-term studies of CKD, and may have additional cardiovascular benefits

• Studies with spironolactone and eplerenone added to single RAS-blockade showed that these agents are associated with greater reductions in urine albumin or protein excretion compared to either placebo or dual RAS blockade, but...hyperkalemia as adverse effect.

• A non-steroidal MRA, finerenone, has decreases albuminuria in diabetic nephropathy with low rates of hyperkalemia

Curr Pharm Des. 2018;24(46):5528-5536
JAMA. 2015;314(9):884-89
Metabolic Acidosis

• Treatment of CKD associated metabolic acidosis to achieve a normal serum bicarbonate level has been shown in observational studies to slow CKD progression.

• When the bicarbonate level < 22 mmol/L, sodium bicarbonate (650 mg) should be prescribed 3 times daily.
Additional Issues

• Hemoglobin – measure annually stating with G3a CKD as decreased erythropoietin production becomes more common with increasing renal impairment

• Monitor for Secondary hyperparathyroidism, hypocalcemia, hyperphosphatemia, decreased vitamin D, periodically measuring intact parathyroid hormone, and total 25-hydroxy vitamin D should be measured at least once to document baseline levels.

Additional Issues – Medicine Safety

• Hypoglycemics – sulfonylureas, insulin, metformin renally excreted
• NSAIDS
• RAAS antagonists – hold during volume depletion
• Opioids - be aware of renal excretion for morphine, hydrocodone, codeine
• Antibiotics – reduce dose macrolides, Fluoroquinolones, Tetracyclines, Trimethoprim
• Iodinated Contrast

When to Refer to Nephrology

• GFR <30 mL/min/1.73 m² (GFR categories G4-G5)
• A >25% drop in eGFR
• A consistent finding of significant albuminuria (Alb/Cr ratio > 300 mg/g (protein excretion > 500 mg/24 hours))
• Persistent unexplained hematuria
• Secondary hyperparathyroidism, persistent anion gap acidosis, non-iron deficiency anemia
• CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
• Persistent abnormalities of serum potassium
• Recurrent or extensive nephrolithiasis
• Hereditary kidney disease or unknown cause of CKD

Conclusion

• Screen at least annually for eGFR and UACR

• Once CKD identified:
  • Hypertension control
  • Glycemic control
  • Choice of Medication for Glycemic Control – SGLT-2 is preferred, if not SGLT-2 then GLP-1 RA
  • Modify Dietary Protein and salt intake
  • Correction of metabolic acidosis
  • Appropriate referral to nephrology