Chronic Kidney Disease in Diabetes

Dr. A Atapour.

Associate prof.

Nephrology department

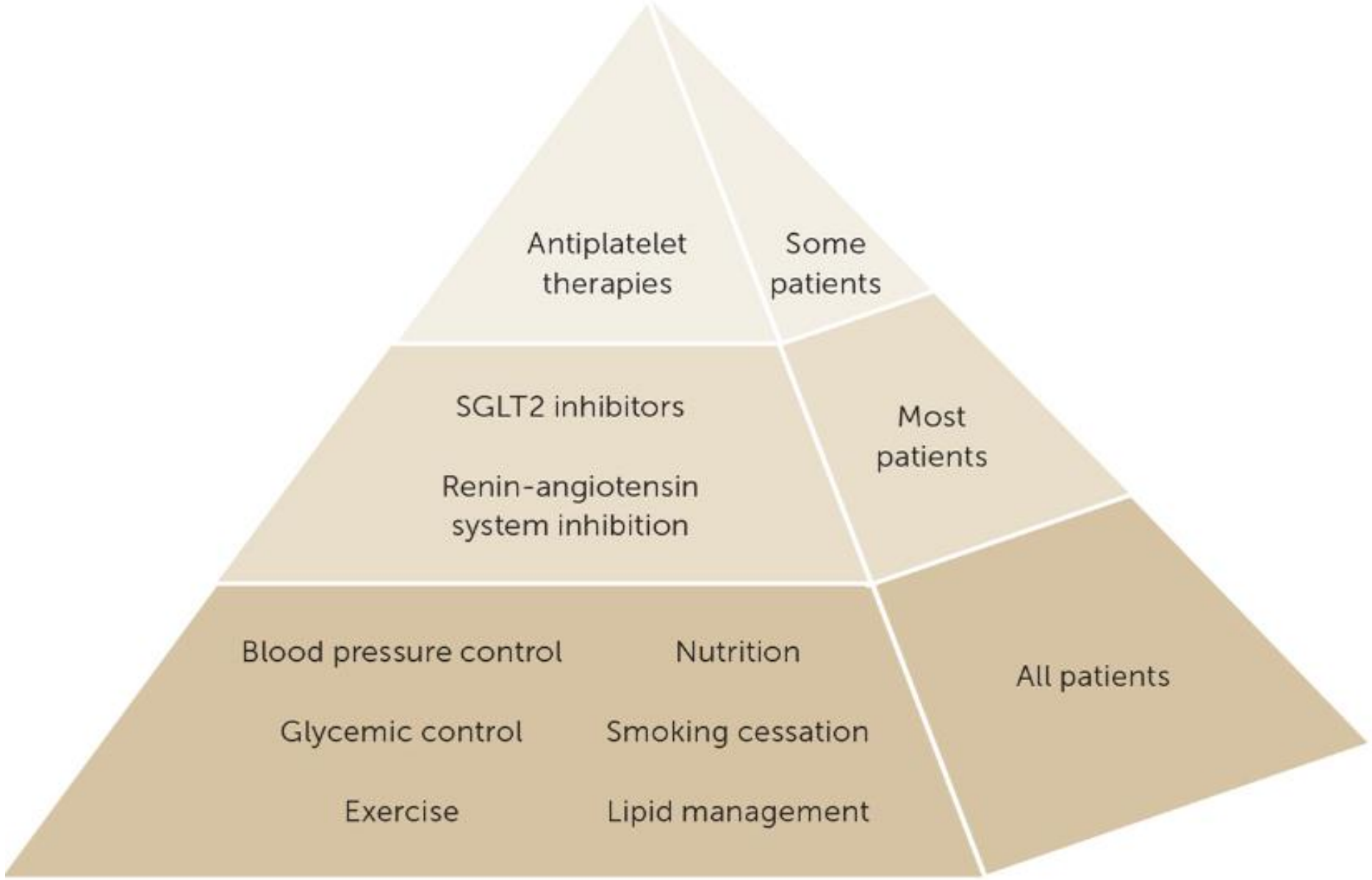
Isfahan University of medicalsciences

Guidelines from KDIGO (2022)

Introduction

- Diabetes mellitus affects more than 450 million people globally
- Up to 40% of cases of diabetes are complicated by chronic kidney disease (CKD)
- People with diabetes and CKD have high risks of
  - CKD progression
  - Cardiovascular disease (CVD)
  - Mortality

Multifactorial kidney-heart risk factor management



Team-Based Care

- Optimal care includes
  - Primary care
  - Cardiology
  - Nephrology
  - Endocrinology
  - Psychology
  - Nutrition
  - Nursing support

Self-Management Education

- Structured education in diabetes self-management is recommended
- Group-based education programs improve
  - A1C level
  - Fasting blood glucose level
  - Body weight
  - Self-efficacy
  - Patient satisfaction.

Dietary and Lifestyle Management

- Healthy diet that is high in vegetables, fruits, whole grains, ……
- Nutritional recommendations may have to be adjusted
  - Hyperkalemia
  - Personality
  - Culture
  - Protein
  - Sodium
- Physical activity

Lifestyle

Healthy diet

Physical activity

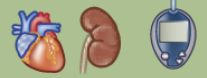
Smoking cessation

Weight management

Regular risk factor reassessment (every 3–6 months)

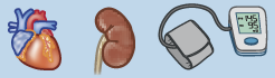
First-line drug therapy

SGLT2i (Initiate if eGFR ≥20; continue until dialysis or transplant)



Metformin (if eGFR ≥30)

RAS inhibitor at maximum tolerated dose (if HTN*)



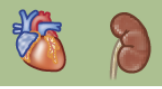
Moderate- or high-intensity statin

Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids

Additional risk-based therapy

GLP-1 RA if needed to achieve individualized glycemic target

Nonsteroidal MRA† if ACR ≥30 mg/g and normal potassium



Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target

Antiplatelet agent for clinical ASCVD

Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids

Other glucose-lowering drugs if needed to achieve individualized glycemic target

Steroidal MRA if needed for resistant hypertension if eGFR ≥45

T2D only

All patients (T1D and T2D)

Glycemic Treatment

- For people with type 2 diabetes
  - Metformin and sodium-glucose co-transporter 2 (SGLT2) inhibitors
  - Metformin limits weight gain and reduces cardiovascular events
  - GLT2 inhibitor improves cardiovascular outcomes and limits kidney disease progression

Glycemic Treatment

- SGLT2 inhibitor use can cause a reversible decline in eGFR (stop or continue?)
  - Genital mycotic infections
  - Diabetic ketoacidosis
  - Limb amputations were increased in one trial.

- Long -acting glucagon-like peptide-1 (GLP-1) receptor agonist

Renin-Angiotensin System Inhibition

- ARBs are recommended to slow kidney disease progression in people with albuminuria and hypertension.
  - Maximal tolerated dosage
  - Monitoring of blood pressure
  - Serum potassium
  - Serum creatinine
- Monitoring within two to four weeks of dosing changes

Antiplatelet Therapy

- Aspirin is recommended for secondary prevention of CVD.
- Primary prevention of CVD with aspirin is not recommended for routine use.

Guideline source:

- Kidney Disease: Improving Global Outcomes (KDIGO)
- KDIGO guidelines are a well-respected international resource for the treatment of CKD.
- This guideline summary was written by guideline authors
- The evidence to support the primary use of SGLT2 inhibitors is strong
  - Reductions in cardiovascular events
  - Progression of CKD
  - Mortality

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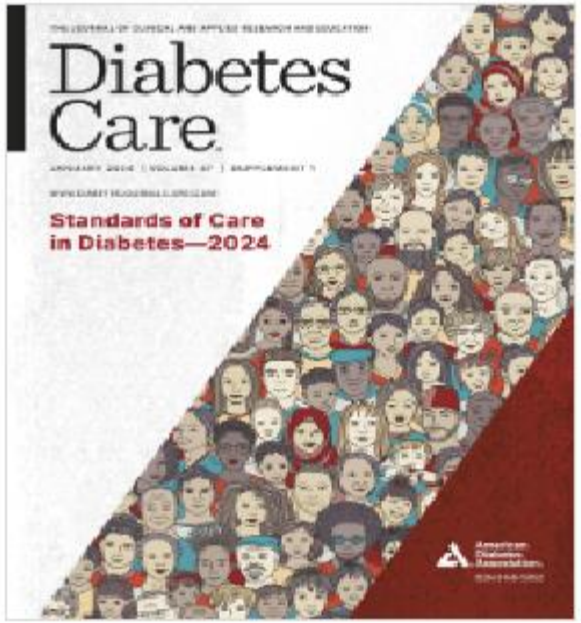

- *Diabetes Care* 2024;47(Supplement_1):S219–S230

Epidemiology of Diabetes and Chronic Kidney Disease

- CKD
  - Persistent albuminuria
  - Low estimated glomerular filtration rate (eGFR),
  - Other manifestations of kidney damage
- CKD attributed to diabetes (diabetic kidney disease) in adults
  - Occurs in 20–40% of people with diabetes

Diagnosis of Diabetic Kidney Disease

- Presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Surveillance

- Both albuminuria and eGFR should be monitored annually
- Diagnosis of CKD
- Monitor progression of CKD
- Detect superimposed kidney diseases
- Assess risk of CKD complications
- Dose medications appropriately

The prevalence of CKD complications

- When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated

Screening for selected complications of CKD

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight, BMI
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron, iron saturation, ferritin testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Prevention

- Blood glucose (A1C goal of 7%)
- Blood pressure control (blood pressure <130/80 mmHg)
- Dose Renin -angiotensin-aldosterone system inhibitors or any other interventions prevent the development of diabetic kidney disease ??
- Does American Diabetes Association recommend any medication for the purpose of prevention of the development of diabetic kidney disease.??

Interventions

- **Nutrition**
- **Glycemic Goals (** Diabetes Control and Complications Trial (DCCT))
  - Multicenter , randomized, clinical study
  - Cohort of 278 subjects}
    - Conclusion that lowering blood glucose itself helps prevent CKD and its progression.
- **Blood Pressure**
  - A blood pressure level
  - ACE inhibitors and ARBs
- **Direct Renal Effects of Glucose-Lowering Medications**
  - SGLT2 inhibitors reduce renal tubular glucose reabsorption

Interventions

- **Direct Renal Effects of Glucose-Lowering Medications**
  - SGLT2 inhibitors (Mechanisms ?)
    - Reduce renal tubular glucose reabsorption
    - Weight
    - Systemic blood pressure
    - Intraglomerular pressure
    - Albuminuria
    - Slow GFR loss

Direct Renal Effects of Glucose-Lowering Medications

- Mechanisms of SGLT2 inhibitors
  - Reduce oxidative stress in the kidney by >50%
  - Blunt increases in angiotensinogen
  - Reduce NLRP3 inflammasome activity
    - (The NLRP3 inflammasome is a critical component of the innate immune system)

Direct Renal Effects of Glucose-Lowering Medications

- Glucagon-like peptide 1 receptor agonists
  - Have direct effects on the kidney
  - Increasing natriuresis and diuresis
  - Decreasing oxidative stress and inflammation
  - Possible glomerular hemodynamic effects.

Cardiovascular outcomes trials examined kidney effects as secondary outcomes

- REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients]
- CANVAS (Canagliflozin Cardiovascular Assessment Study)
- LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
- SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes)

Results

- REG OUTCOME
  - Empagliflozin reduced the risk of incident or worsening nephropathy
  - Progression to UACR >300 mg/g creatinine
  - Doubling of serum creatinine
  - ESKD
  - Death from ESKD by 39%
  - Risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2 by 44%;

Results

- CANVAS
  - Canagliflozin reduced the risk of progression of albuminuria by 27%
  - The risk of reduction in eGFR
  - ESKD
  - Death from ESKD by 40%

Results

- LEADER
  - Liraglutide reduced the risk of new or worsening nephropathy
  - Composite of persistent macroalbuminuria
  - Doubling of serum creatinine
  - ESKD
  - Death from ESKD by 22%;
  - semaglutide reduced the risk of new or worsening nephropathy

DAPA-CKD study

- Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
- Participants had type 2 diabetes and CKD
- The primary outcome
  - Time to the first occurrence ≥50% sustained decline in eGFR
  - Reaching ESKD
  - Cardiovascular death
  - Renal death
- Secondary outcome
  - Cardiovascular death or hospitalization for heart failure
  - Death from any cause.
- Finally, all-cause mortality was decreased in the dapagliflozin group compared with the placebo group ($P < 0.004$).

The most recently published clinical trial was EMPA-KIDNEY

- Participants
  - $20 < eGFR < 45$
  - $45 < eGFR < 90$ mL/min/1.73 m^2 with a UACR of at least 200 mg/g creatinine.
- Approximately one-half of the 6,609 participants had diabetes.
- The empagliflozin-treated participants had lower risk of progression of kidney disease and lower risk of death from cardiovascular causes (HR 0.72 [95% CI 0.64–0.82]; $P < 0.001$).

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

- MRAs have not been well studied in diabetic kidney disease
- Late in 2020, the results of the first of two trials
  - Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial
  - Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial

Recommendations

- Optimize glucose management to reduce the risk or slow the progression of CKD
- Optimize blood pressure control
- In non-pregnant people with diabetes and hypertension, either an ACE or ARB
- Periodically monitor for increased serum creatinine and potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists are used, or for hypokalemia when diuretics are used.

Recommendations

- An ACE inhibitor or an ARB is not recommended for the primary prevention of CKD in people with diabetes who have
  - normal blood pressure
  - normal UACR (<30 mg/g creatinine), and normal eGFR.

- For people with type 2 diabetes and CKD
  - Use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine.

Recommendations

For cardiovascular risk reduction in people with type 2 diabetes

- Consider use of an SGLT2 inhibitor, a glucagon-like peptide 1 agonist, or a non SMRA (if eGFR is ≥25 mL/min/1.73 m^2).

- # Recommendations

  For people with non–dialysis-dependent stage G3 or higher CKD

  - Dietary protein 0.8 g/kg body weight per day.
  - individuas on dialysis, 1.0–1.2 g/kg/day

Recommendations

- Individuals should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing eGFR and/or if the eGFR is <30 mL/min/1.73 m^2.

- Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.

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