

بنام خداوند جان و خرد

Diabetes Mellitus and chronic kidney disease

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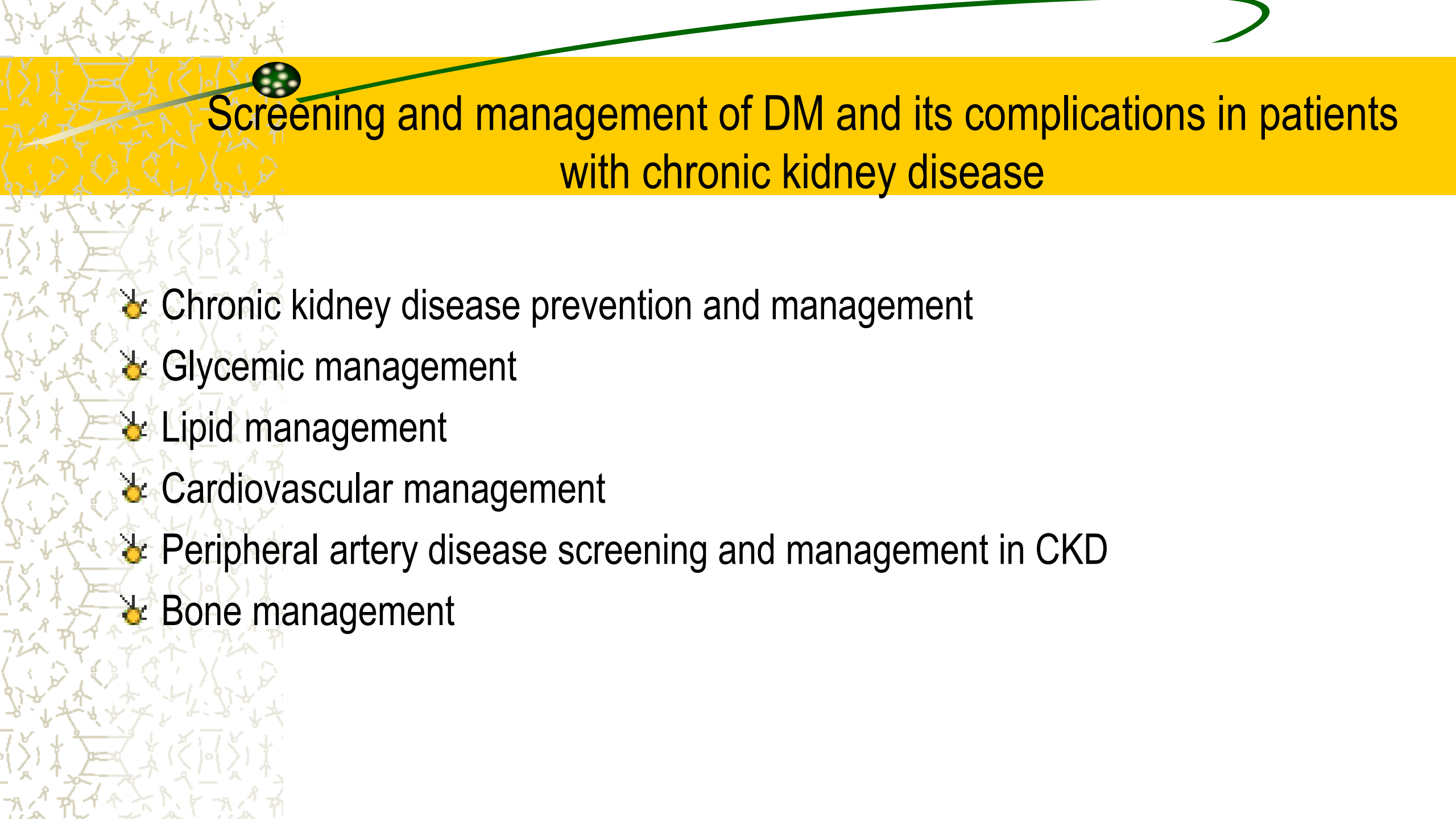
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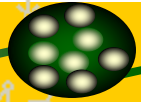
Introduction

- ✱ Chronic kidney disease (CKD), defined by persistent albuminuria, reduced estimated glomerular filtration rate (eGFR), or other markers of kidney damage, develops in 20–40% of individuals with diabetes and represents the leading cause of end-stage kidney disease (ESKD) in the United States.
- ✱ In type 1 diabetes, diabetic CKD typically manifests 5–15 years after diagnosis, whereas in type 2 diabetes it may already be present at the time of diagnosis.
- ✱ Progression to kidney failure necessitates dialysis or transplantation.
- ✱ Beyond kidney-specific outcomes, the presence of CKD in patients with type 1 or type 2 diabetes substantially amplifies cardiovascular risk and healthcare costs.



Screening and management of DM and its complications in patients with chronic kidney disease

- ✱ Chronic kidney disease prevention and management
- ✱ Glycemic management
- ✱ Lipid management
- ✱ Cardiovascular management
- ✱ Peripheral artery disease screening and management in CKD
- ✱ Bone management



Chronic kidney disease prevention and management



Assessment of Albuminuria and Estimated Glomerular Filtration Rate

- ✦ Accurate detection of diabetic kidney disease relies on proper assessment of albuminuria and estimated glomerular filtration rate (eGFR). Screening for albuminuria should be performed using the urine albumin-to-creatinine ratio (UACR) measured in a random spot urine sample, as this is more reliable and practical than timed collections or albumin measurement alone.
- ✦ Normal UACR is <30 mg/g, moderately increased 30–300 mg/g, and severely increased ≥ 300 mg/g; however, UACR is a continuous risk factor, and due to high biological variability ($>20\%$), at least two of three samples collected over 3–6 months should be abnormal to confirm persistent albuminuria.
- ✦ Transient elevations may occur with exercise, infection, fever, heart failure, marked hyperglycemia, or hypertension.
- ✦ eGFR should be calculated using validated creatinine-based equations, preferably the 2021 race-free CKD-EPI creatinine equation (or better, the 2021 CKD-EPI creatinine–cystatin C combination equation) for greater accuracy across all populations.
- ✦ An eGFR persistently <60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g confirms CKD. Laboratories now routinely report eGFR, and combined use of creatinine and cystatin C is increasingly recommended to improve diagnostic precision and guide clinical decisions in adults with diabetes.

Risk of CKD progression, cardiovascular disease risk, and mortality; frequency of visits; and referral to nephrology according to GFR and albuminuria.

The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year.

For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, and hyperparathyroidism).

These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as should the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Adapted from de Boer et al.

CKD is classified based on:

- 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 m ²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 2
	G2	Mildly decreased	60-89	Screen 1	Treat 1	Treat and refer 2
	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



Table 11.1—Reasons to consider nondiabetic kidney diseases in a person with chronic kidney disease and diabetes

-
- Type 1 diabetes duration <5 years
 - Active urine sediment (e.g., containing red blood cells or cellular casts)
 - Chronically well-managed blood glucose
 - Rapidly declining eGFR
 - Rapidly increasing or very high UACR or urine protein/creatinine level
 - No retinopathy in a person with type 1 diabetes
-

Information adapted from Liang et al. (129). eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.



Table 11.3—Interventions that lower albuminuria

- Blood glucose management
- Blood pressure management
- Treatment with ACE inhibitors or ARBs
- Smoking cessation
- Weight loss
- Changes in eating patterns (decreased salt intake and/or protein intake)
- Treatment with SGLT2 inhibitors, MRAs, or GLP-1 RAs

ARB, angiotensin receptor blocker; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MRA, mineralocorticoid receptor antagonist.

LIFESTYLE



Healthy eating



Physical activity



Smoking cessation



Weight management

Regular risk factor reassessment (every 3–6 months)

FIRST-LINE DRUG THERAPY

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



Metformin
(if eGFR is ≥ 30)



RAS inhibitor at maximum tolerated dose (if albuminuria and/or HTN)



Moderate- or high-intensity statin



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

ADDITIONAL RISK-BASED THERAPY

GLP-1 RA \pm if needed to achieve individualized glycemic goal



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



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



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 goal



Steroidal MRA if needed for resistant hypertension if eGFR is ≥ 45

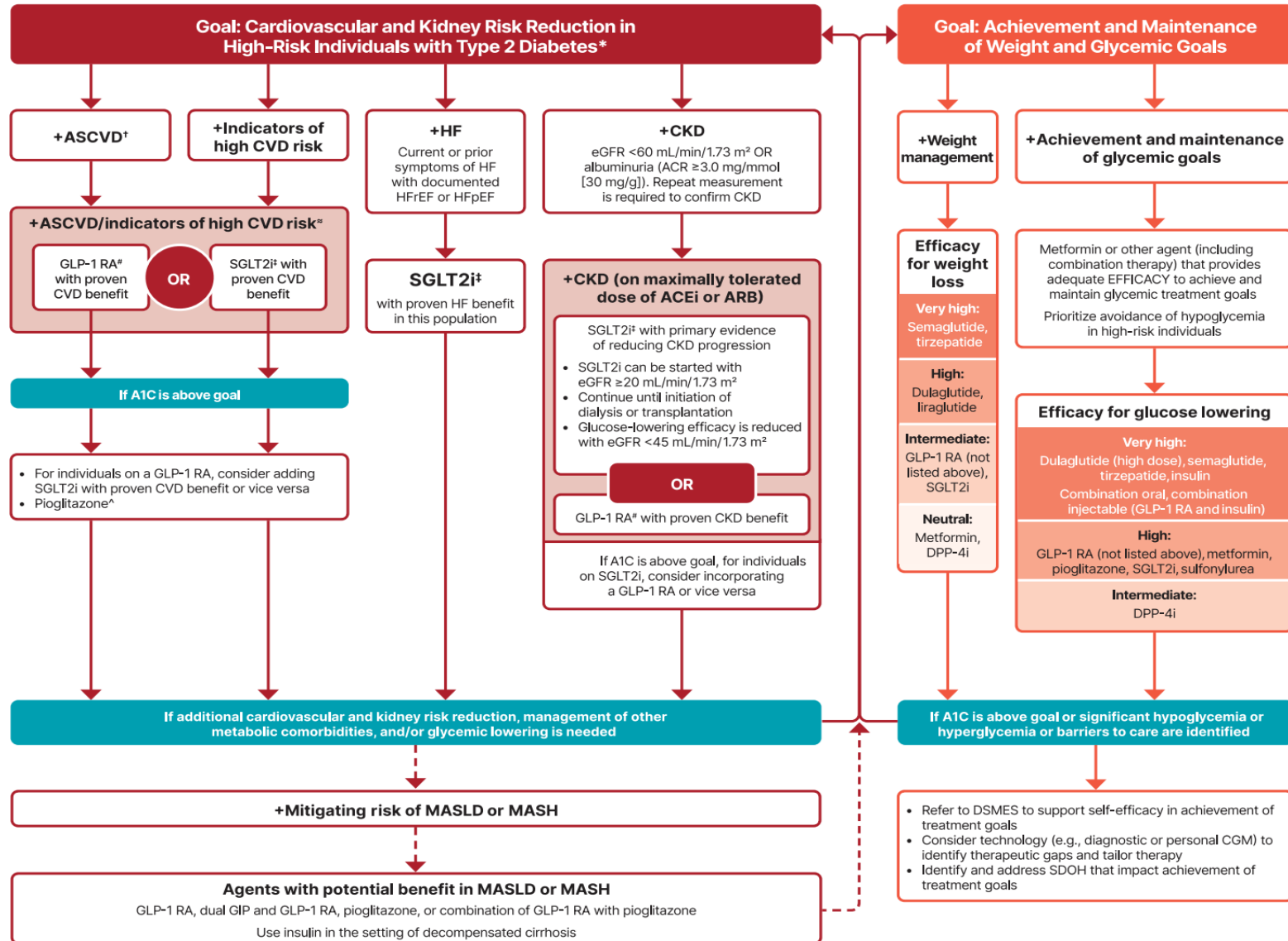


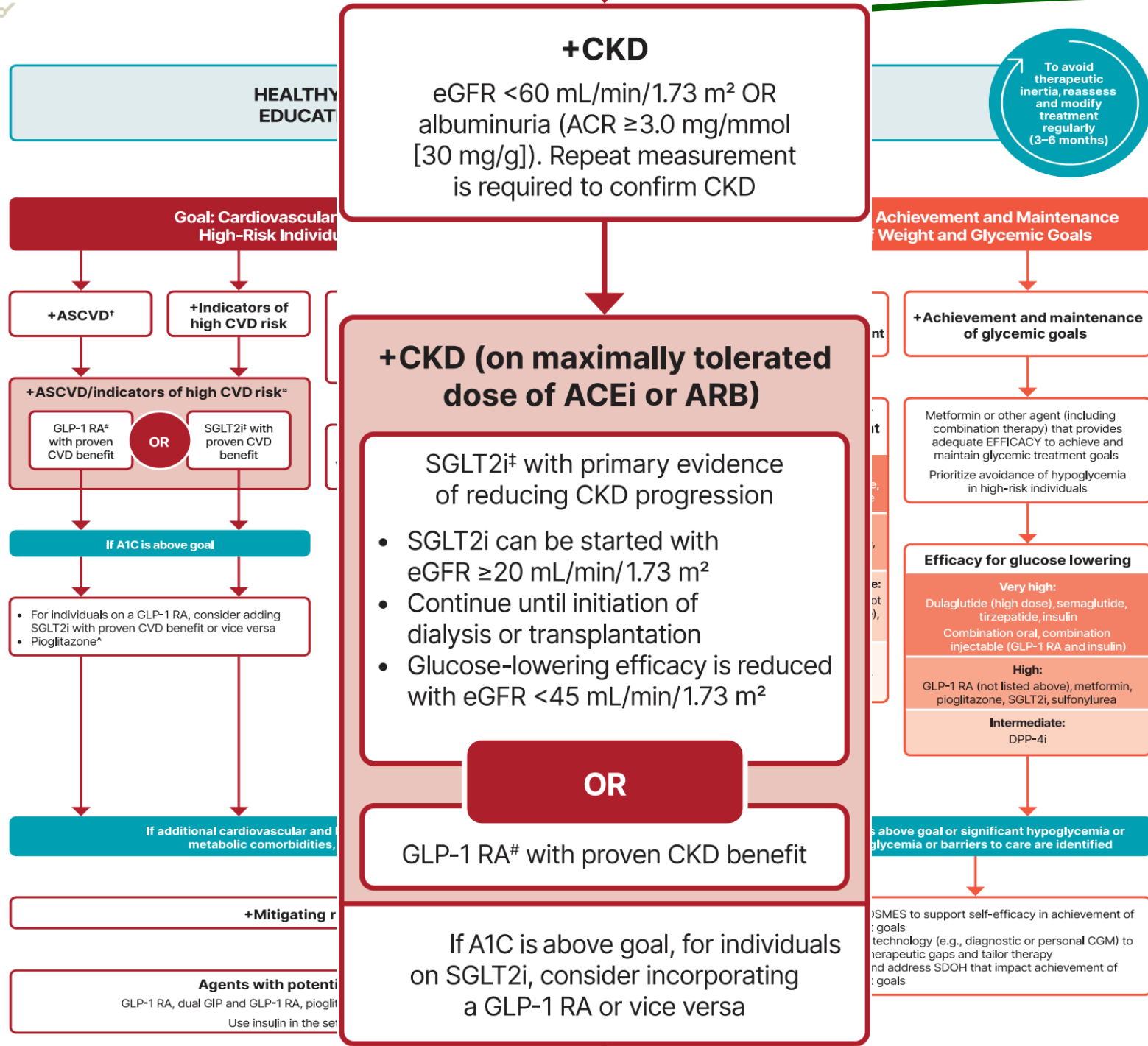
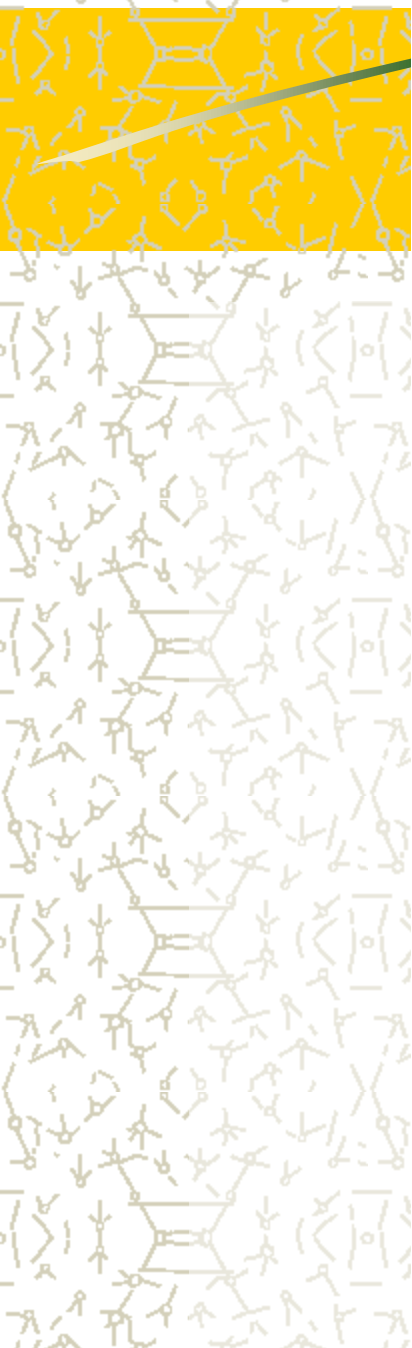
■ T2D only

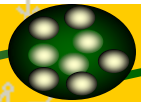
■ All individuals (T1D and T2D)

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH

To avoid
therapeutic
inertia, reassess
and modify
treatment
regularly
(3–6 months)







Glycemic management

Glycemic goals and hypoglycemia

- ⚠️ Glycemic target: Slightly more relaxed than in general population
 - A1c 7.0–8.0% (KDIGO 2022, ADA 2024)
 - Avoid tight control (<7%) → high risk of severe hypoglycemia (especially on dialysis)
 - Individualize: avoid <6.5–7% in frail/elderly patients
- ⚠️ Hypoglycemia risk is dramatically increased due to:
 - Reduced insulin clearance (↓ renal degradation)
 - Decreased gluconeogenesis in kidney
 - Malnutrition, variable appetite on dialysis days – Erythropoietin use, spontaneous resolution of uremic anorexia
- ⚠️ Hemodialysis patients
 - Insulin requirements often decrease on dialysis days (glucose-free dialysate removes glucose)
 - Higher needs on non-dialysis days
 - Frequent SMBG (self-monitoring of blood glucose) or CGM highly recommended



Glycemic goals and hypoglycemia

✦ Peritoneal dialysis patients

- Glucose load from icodextrin/dialysate
- higher insulin requirements, risk of weight gain and hyperglycemia

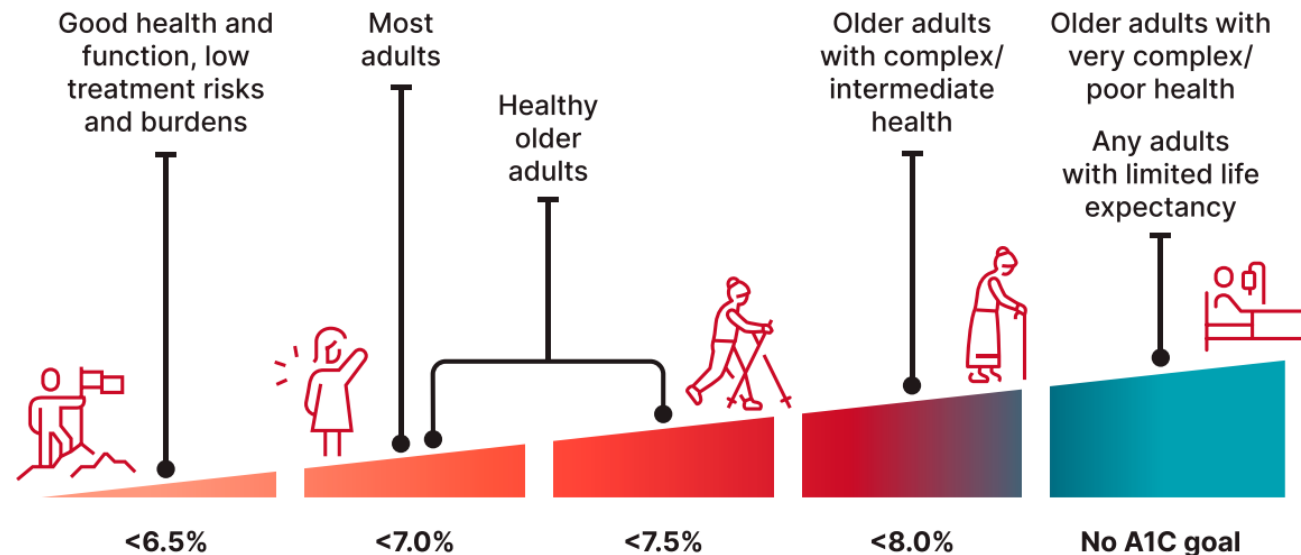
✦ Kidney transplant recipients

- High-dose steroids → marked insulin resistance early post-transplant
- Often need very high insulin doses initially, then taper

✦ Monitoring Recommendations

- A1c limitations in advanced CKD (shorter RBC lifespan, ESA use, acidosis) → consider glycated albumin or fructosamine in dialysis patients
- CGM (continuous glucose monitoring) or flash GM increasingly used → better detection of asymptomatic hypoglycemia

Glycemic goals and hypoglycemia



Modifying Factors

Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

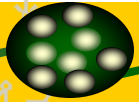
Anti hyperglycemic medications

Medication (route of administration)	Glucose-lowering efficacy ¹	Hypoglycemia risk	Weight effects ²	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
Metformin (oral)	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	<ul style="list-style-type: none"> Contraindicated with eGFR <30 mL/min/1.73 m² 	Neutral	<ul style="list-style-type: none"> GI side effects: mitigate with slow dose titration, extended-release formulations, and administration with food. Potential for vitamin B12 deficiency: monitor and replete as appropriate.
SGLT2 inhibitors (oral)	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	<ul style="list-style-type: none"> See labels of individual agents for dosage considerations for kidney function Glucose-lowering effect is minimal at eGFR <45 mL/min/1.73 m² and lower; continue for cardiovascular and kidney benefit until dialysis or transplantation 	Unknown	<ul style="list-style-type: none"> DKA risk in individuals with insulin deficiency (rare in T2D): discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentations (including euglycemic DKA); mitigate risk with sick-day planning; discontinue before scheduled surgery (e.g., 3-4 days), during critical illness, or during prolonged fasting. Genital mycotic infections: mitigate risk with genital hygiene and avoid use in high-risk individuals. Necrotizing fasciitis of the perineum (Fournier gangrene): rare; prompt treatment if suspected. Intravascular volume depletion: attention to volume status and blood pressure, particularly when ill or fasting; adjust other volume-contracting agents as applicable; monitor kidney function upon initiation.

Anti hyperglycemic medications

Medication (route of administration)	Glucose-lowering efficacy ¹	Hypoglycemia risk	Weight effects ²	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
GLP-1 RAs (SQ; semaglutide also available in oral formulation)	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ) Demonstrated benefit for progression of CKD for semaglutide (SQ)	<ul style="list-style-type: none"> See labels of individual agents for dosage considerations for kidney function No dose adjustment for dulaglutide, liraglutide, or semaglutide Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions 	Potential benefit	<ul style="list-style-type: none"> Thyroid C-cell tumors identified in rodents; human relevance not determined. Ileus: risk level is not well established; provide guidance on discontinuation prior to surgical procedures. Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected. Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals. Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]).
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	<ul style="list-style-type: none"> See labels of individual agents for dosage considerations for kidney function No dose adjustment Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions 	Potential benefit	<ul style="list-style-type: none"> Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including of oral contraceptives). GI side effects: counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g. stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.

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Lipid management



Lipid Management in Patients with Diabetes and Chronic Kidney Disease

- ✶ Lipid abnormalities in diabetic kidney disease (DKD) are characterized by hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and variable low-density lipoprotein cholesterol (LDL-C) levels, driven by insulin resistance, nephrotic-range proteinuria, and uremic dyslipidemia.
- ✶ These contribute to accelerated atherosclerosis and progression to end-stage kidney disease (ESKD).
- ✶ In advanced CKD (stages 4–5, eGFR <30 mL/min/1.73 m², including dialysis), the cardiovascular (CV) risk is markedly elevated (10-year event rate >30%), necessitating aggressive, guideline-directed therapy.

Lipid Management in Patients with Diabetes and Chronic Kidney Disease

- ✱ Risk Stratification: All patients with diabetes and CKD (especially eGFR <60 mL/min/1.73 m²) are high-risk for atherosclerotic CV disease (ASCVD); treat as secondary prevention equivalents.
- ✱ Targets (no strict LDL-C thresholds per KDIGO/ADA; focus on relative risk reduction):
- ✱ LDL-C: Aim for ≥50% reduction from baseline; <70 mg/dL (or <55 mg/dL in very high-risk).
- ✱ Non-HDL-C: <100 mg/dL (or <85 mg/dL in very high-risk).
- ✱ Triglycerides (TG): <150 mg/dL via lifestyle; pharmacotherapy if 150–499 mg/dL on statin.
- ✱ Lifestyle Foundation: Mediterranean or DASH diet, weight loss (5–10% if obese), <7% saturated fat, increased n-3 fatty acids, viscous fiber (oats, legumes), and plant stanols/sterols; ≥150 min/week aerobic exercise. Optimize glycemia to reduce TG/HDL-C discordance.

Anti hyperlipidemic medications

Agent/Class	Recommendation in Advanced CKD (eGFR <30 or Dialysis) + Diabetes	Dosing/Adjustments	Key Evidence/Notes
Statins (atorvastatin, rosuvastatin preferred)	High-intensity for all ≥50 years or ASCVD (Class 1, Level A). Continue if already on; initiate if not.	Atorvastatin 40–80 mg; rosuvastatin ≤10 mg. No adjustment for atorvastatin; limit simvastatin ≤20 mg, pravastatin ≤40 mg.	KDIGO 2024: 20–30% MACE reduction; safe in dialysis. AACE 2025: Use for primary/secondary prevention. Myopathy risk ↑ but manageable with monitoring.
Ezetimibe	Add to statin in all (even if LDL-C <100 mg/dL).	10 mg daily; no adjustment.	IMPROVE-IT/REACT subgroups: ↑ benefit in CKD; no renal excretion. ABCD-UKKA 2024: Improves DKD outcomes.
PCSK9 Inhibitors (evolocumab, alirocumab) or Inclisiran	Add if LDL-C ≥70 mg/dL (or ≥55 mg/dL very high-risk) despite max statin + ezetimibe.	Standard dosing; no adjustment (eGFR ≥15).	FOURIER/ODYSSEY CKD subgroups: 20–25% further MACE reduction; anti-inflammatory effects in DKD. AACE 2025: Preferred non-statin.
Bempedoic Acid	Alternative if statin-intolerant.	180 mg daily; no adjustment.	CLEAR Outcomes: CV benefits in CKD; uricosuric effect may benefit hyperuricemia in DKD.



Management of Hypertriglyceridemia (TG 150–499 mg/dL)

- ✚ First: Optimize statin ± ezetimibe and lifestyle.
- ✚ If persistent: Add fibrate or icosapent ethyl (EPA); avoid niacin (worsens glycemia).
- ✚ Fibrates (Fenofibrate, Gemfibrozil, Pemaifibrate)
- ✚ Fibrates activate PPAR- α , reducing TG (20–50%), raising HDL-C (5–15%), and modestly lowering LDL-C.
- ✚ Beneficial in early DKD (reduce albuminuria, slow eGFR decline via anti-inflammatory/fibrotic effects), but use cautiously in advanced CKD due to reversible creatinine rise (5–10%, not true GFR drop) and rhabdomyolysis risk with statins.

Management of Hypertriglyceridemia (TG 150–499 mg/dL)

- ⚡ Contraindications: eGFR <15 (except pemafibrate), active liver disease, gallbladder disease.
- ⚡ Monitoring: LFTs, CK, creatinine at baseline/1–3 months; hold if TG <200 mg/dL post-therapy.
- ⚡ Icosapent Ethyl (Pure EPA, 4 g/day)
- ⚡ Highly purified EPA ethyl ester; reduces TG (18–25%) without raising LDL-C. Pleiotropic effects: anti-inflammatory, plaque stabilization, membrane incorporation. No renal adjustment; safe/effective across eGFR spectrum.
- ⚡ Recommendation: Add to statin if TG 135–499 mg/dL + ASCVD/diabetes + ≥1 risk factor (Class 1, ADA/AACE 2025). Benefits persist in advanced CKD.
- ⚡ Evidence in Advanced CKD:
- ⚡ REDUCE-IT (n=8179; 23% eGFR <60): Consistent 25% relative MACE reduction (HR 0.75 overall; HR 0.71 in eGFR <60); largest absolute risk reduction (21.8% vs. 28.9% events). ↓ CV death (HR 0.70 in low eGFR). No eGFR change; benefits after 18 months.
- ⚡ Subgroups: ↑ EPA levels correlate with outcomes; no interaction by eGFR (P=0.92 for bleeding/AF). ASN 2020: Significant CV reduction in compromised renal function.
- ⚡ Safety: ↑ bleeding/AF (HR 1.4 in low eGFR, but similar across categories); use PPI if GI risk. No pancreatitis signal.

Management of Hypertriglyceridemia (TG 150–499 mg/dL)

Fibrate	Use in Advanced CKD + Diabetes	Dosing/Adjustments	Evidence/Safety
Fenofibrate	Consider if TG >200 mg/dL and no statin (or low-dose). Avoid gemfibrozil (↑ statin myopathy).	≤48 mg micronized daily if eGFR 15–29; avoid if <15 or dialysis.	ACCORD/FIELD: ↓ micro/macroalbuminuria (HR 0.56–0.72), slower eGFR decline (–0.28 vs. –1.25 mL/min/year); no ↑ CKD/ESKD. Systematic review: CV event prevention, albuminuria reduction. Caution: ↑ creatinine reversible; monitor q3 months.
Pemafibrate	Preferred in advanced CKD; safer renal profile.	0.2–0.4 mg BID; no adjustment (minimal renal excretion).	PROMINENT (2022): No overall CV benefit, but CKD subgroup: ↓ MACE (OR 0.73–0.84), especially current/recent use. Real-world: ↑ eGFR vs. conventional fibrates; ↓ CV events in CKD3 hyperTG (no other lipids). ABCD-UKKA 2024: May delay dialysis.



Special Considerations in Dialysis/Transplant

- ✦ Dialysis: Statin + ezetimibe; EPA if eligible (TG criteria).
 - Avoid fibrates unless TG >500 mg/dL (rhabdomyolysis risk with heparin).
- ✦ Transplant: Same as non-transplant;
 - monitor interactions with immunosuppressants (e.g., cyclosporine ↑ statin levels).
- ✦ Monitoring: Annual lipid panel;
 - more frequent if TG >500 mg/dL or recent changes.
 - Track trending UACR/eGFR for DKD progression.

Thank you and hope for a good rain

