
بسم الله الرحمن الرحيم

DM & KIDNEY

(DKD)

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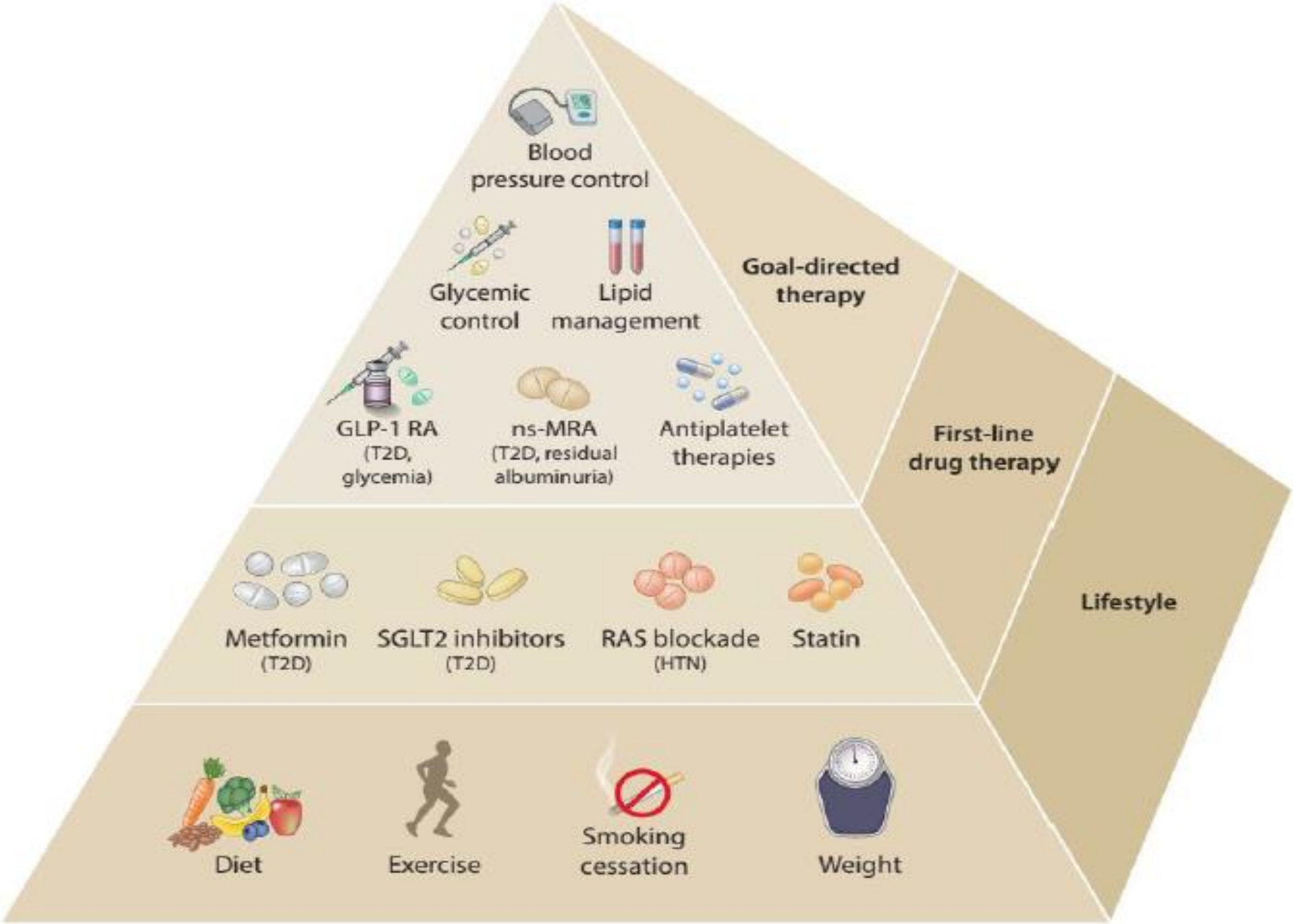

Blood pressure control
Glycemic control
Lipid management
GLP-1 RA (T2D, glycemia)
ns-MRA (T2D, residual albuminuria)
Antiplatelet therapies
Goal-directed therapy
Metformin (T2D)
SGLT2 inhibitors (T2D)
RAS blockade (HTN)
Statin
First-line drug therapy
Diet
Exercise
Smoking cessation
Weight
Lifestyle
Diabetes with CKD

EPIDEMIOLOGY

- CKD: persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage.

- 20–40% of patients with diabetes.

- Diabetic kidney disease typically develops after diabetes duration of 10 years in type 1 diabetes but may be present at diagnosis of type 2 diabetes

- the presence of CKD markedly increases cardiovascular risk and health care costs.

ASSESSMENT

- urinary albumin-to creatinine ratio (UACR) in a random spot urine collection
- Timed or 24-h collections are more burdensome and add little to prediction or accuracy
- Measurement of a spot urine sample for albumin alone!!!

- Normal UACR : <30 mg/g Cr, and mod urinary albumin excretion : ≥30 mg/g Cr.
- two of three specimens of UACR collected within a 3- to 6-month period .
- Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension ???

GFR

- The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is generally preferred.

- *available online at : nkdep.nih.gov*

- An eGFR persistently<60 mL/min/1.73 m2 is considered abnormal

PRESENTATION

- The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR.

- signs of diabetic kidney disease may be present at diagnosis or without retinopathy in type 2.

……..

- Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 and is becoming more common over time.

- An active urinary sediment (RBC or WBC casts), rapidly increasing albuminuria or nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1) !!!!!!!.

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 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

ACUTE KIDNEY INJURY

- higher risk of AKI
- ACE inhibitors, and ARB????????

(Small elevations in serum creatinine up to 30% from baseline)

- sodium–glucose co-transporter 2 (SGLT2) inhibitors.

- in all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the *maximally tolerated doses* were used—not very low doses that do not provide benefit

SURVEILLANCE

- Both albuminuria and eGFR should be monitored annually.
- Serum potassium should also be monitored in patients treated with diuretics.

- For patients with eGFR <60 mL/min/1.73 m2, those receiving ACE inhibitors, ARBs, or MRAs should have serum potassium measured periodically.

Recommendations

11.1a At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be assessed in patients with type 1 diabetes with duration of ≥5 years and in all patients with type 2 diabetes regardless of treatment. B

11.1b Patients with diabetes and urinary albumin ≥300 mg/g creatinine and/or an estimated glomerular filtration rate 30–60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy. B

Table 11.1—Selected complications of chronic kidney disease

Complication	Medical and laboratory evaluation
Elevated blood pressure >140/90 mmHg	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolyte
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

INTERVENTIONS(nutrition)

- dietary protein intake should be 0.8 g/kg body weight per day.
- Restriction of dietary sodium (to <2,300 mg/day).
- For patients on dialysis, **higher levels** of dietary protein intake should be considered.

Glycemic Targets

- **Intensive glycemic control** with the goal of achieving near-normoglycemia has been shown to delay the onset and progression of albuminuria and reduced eGFR in patients with type 1 and type 2.

- In the (ACCORD) trial of type 2, adverse effects of intensive glycemic control (hypoglycemia and mortality) were increased among patients with kidney disease at baseline.

- **Therefore, in some patients** with prevalent CKD and substantial comorbidity, target A1C levels **may be less intensive**

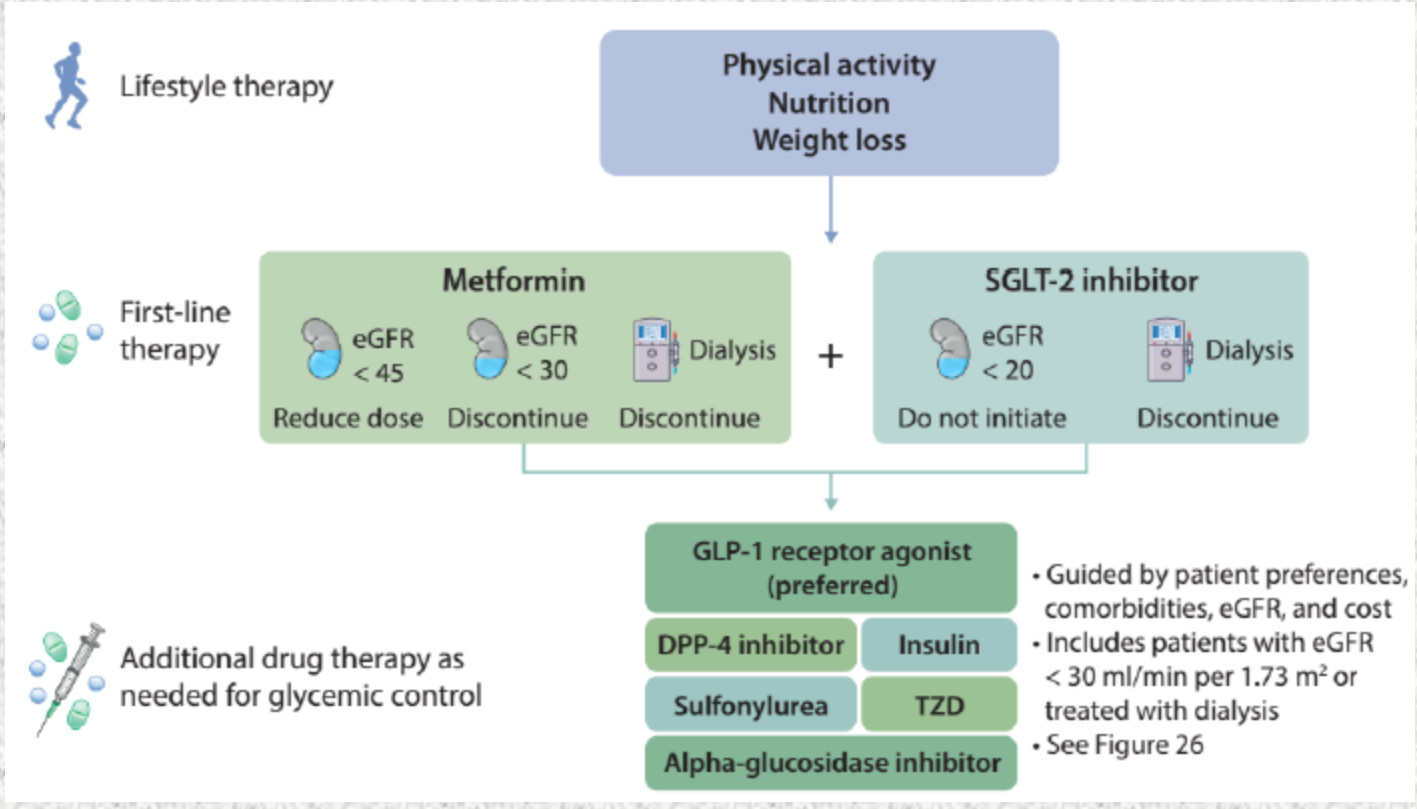
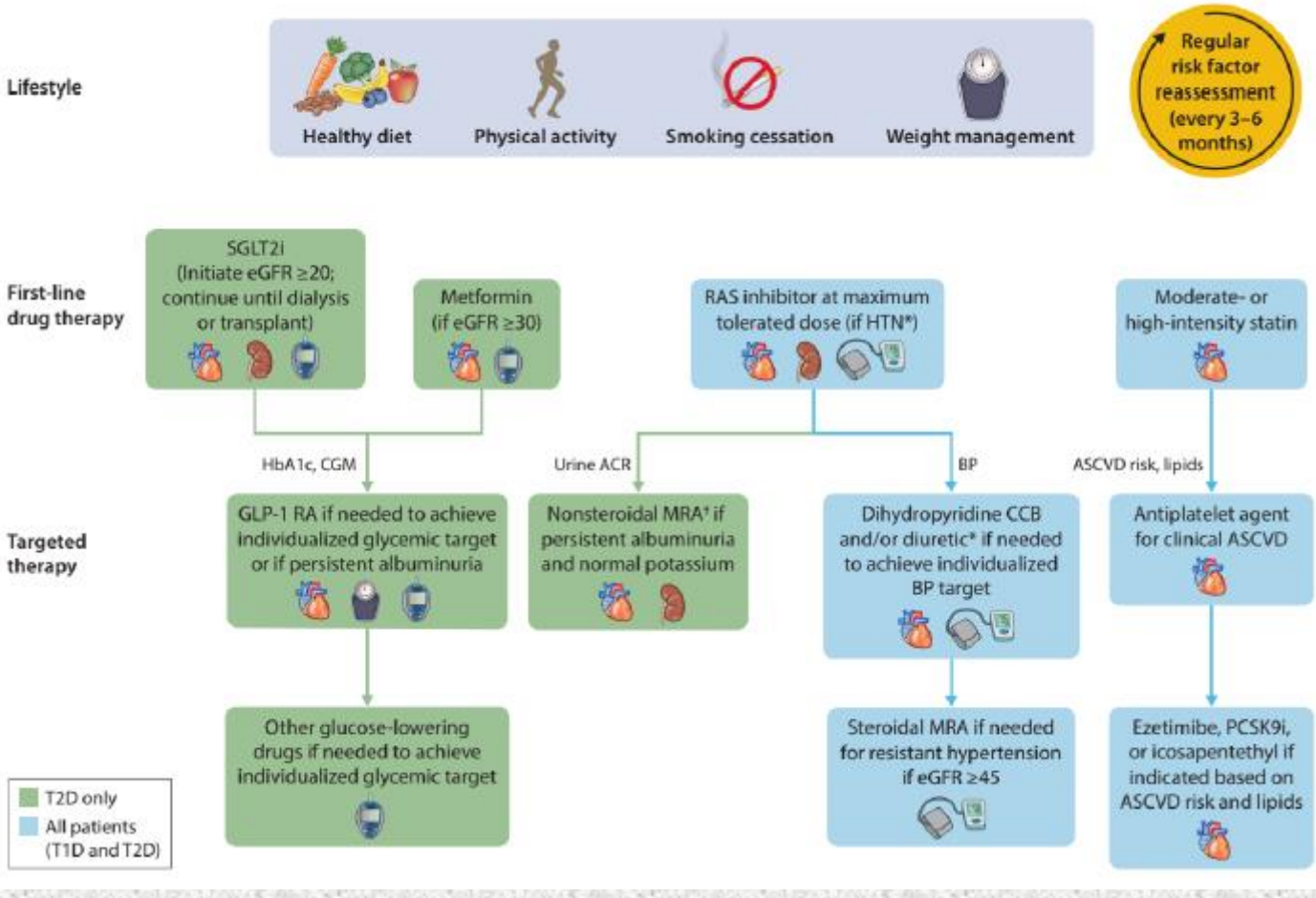
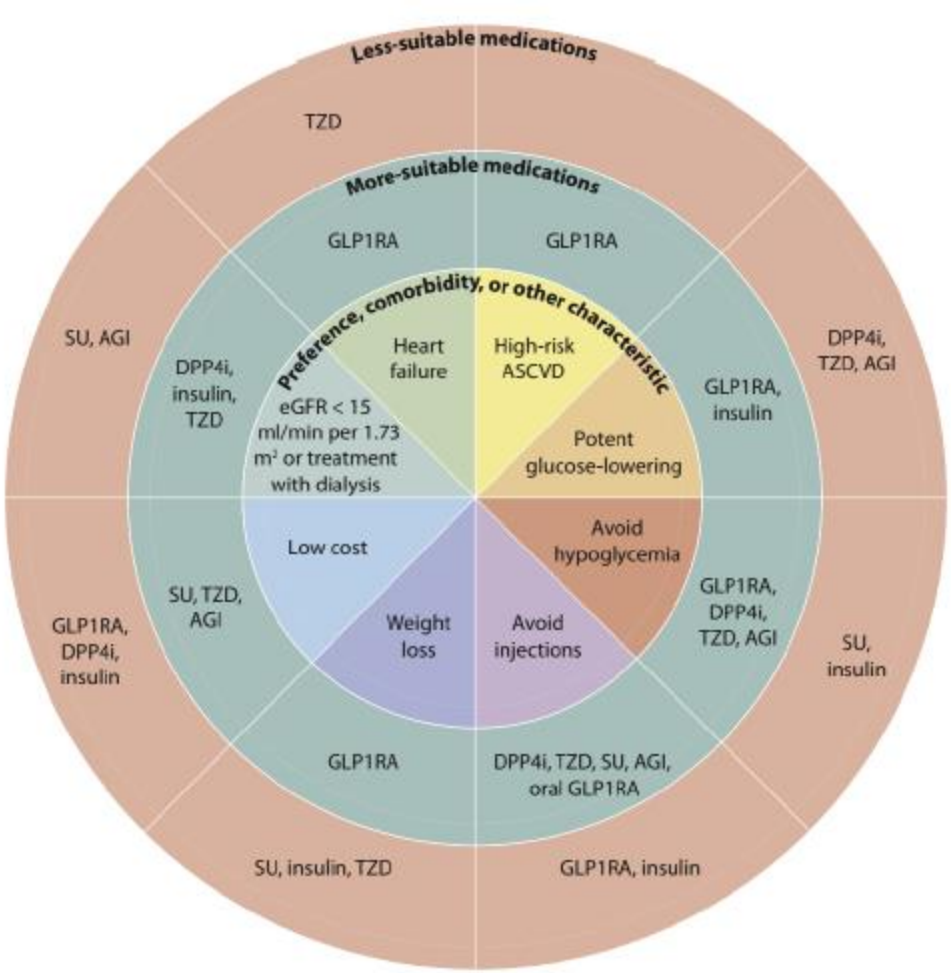
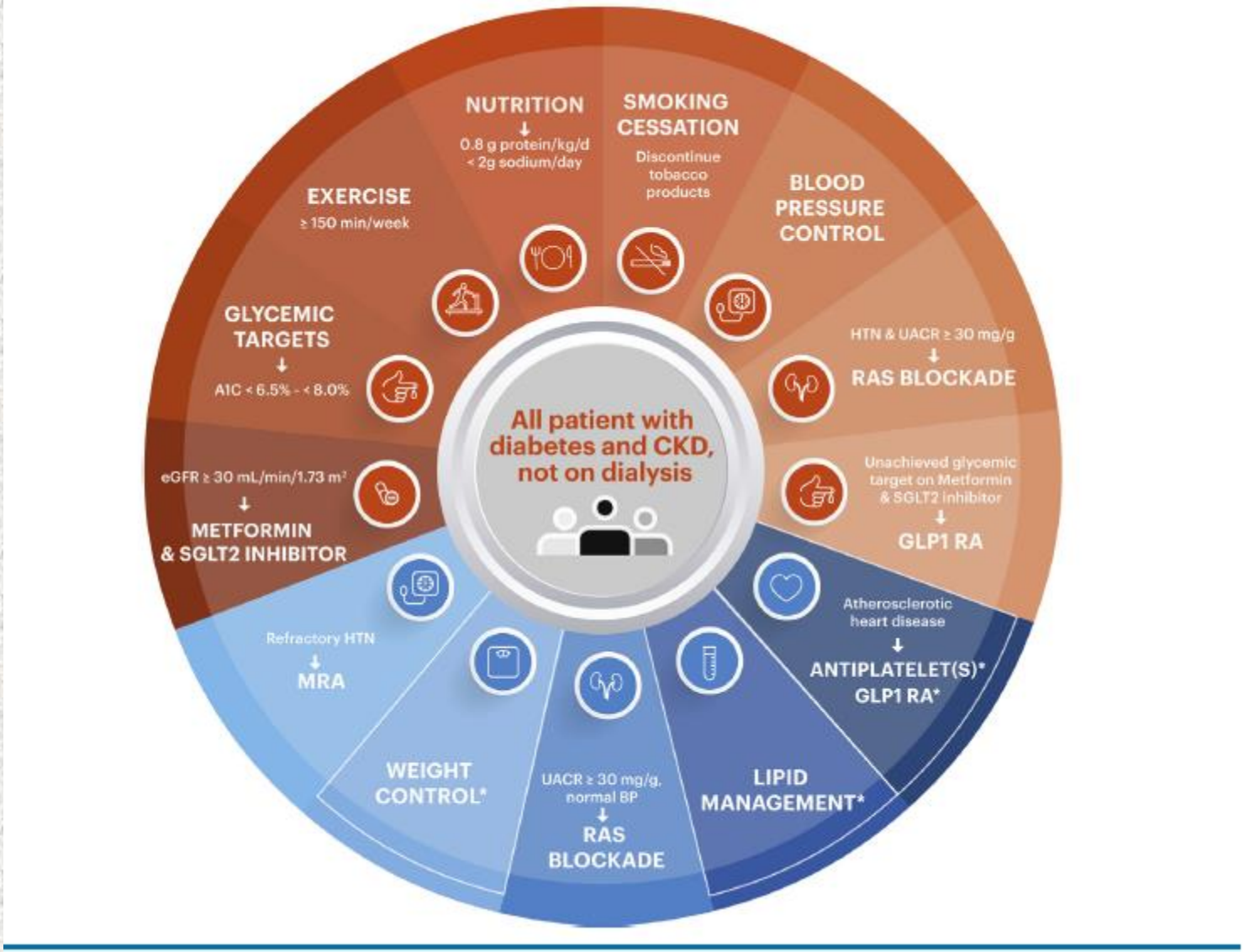

Lifestyle therapy
Physical activity
Nutrition
Weight loss
First-line therapy
Metformin
eGFR < 45
Reduce dose
eGFR < 30
Discontinue
Dialysis
Discontinue
+
SGLT-2 inhibitor
eGFR < 20
Do not initiate
Dialysis
Discontinue
Additional drug therapy as needed for glycemic control
GLP-1 receptor agonist (preferred)
DPP-4 inhibitor
Insulin
Sulfonylurea
TZD
Alpha-glucosidase inhibitor
• Guided by patient preferences, comorbidities, eGFR, and cost
• Includes patients with eGFR < 30 ml/min per 1.73 m² or treated with dialysis
• See Figure 26

*Figure 2. Holistic approach for improving outcomes in patients with diabetes and CKD**




Less-suitable medications
More-suitable medications
Preference, comorbidity, or other characteristic
TZD
GLP1RA
GLP1RA
SU, AGI
DPP4i, TZD, AGI
DPP4i, insulin, TZD
GLP1RA, insulin
Heart failure
High-risk ASCVD
eGFR < 15 ml/min per 1.73 m² or treatment with dialysis
Potent glucose-lowering
Low cost
Avoid hypoglycemia
SU, TZD, AGI
GLP1RA, DPP4i, TZD, AGI
GLP1RA, DPP4i, insulin
Weight loss
Avoid injections
SU, insulin
GLP1RA
DPP4i, TZD, SU, AGI, oral GLP1RA
SU, insulin, TZD
GLP1RA, insulin


All patient with diabetes and CKD, not on dialysis
NUTRITION
0.8 g protein/kg/d
< 2g sodium/day
SMOKING CESSATION
Discontinue tobacco products
BLOOD PRESSURE CONTROL
HTN & UACR ≥ 30 mg/g
RAS BLOCKADE
Unachieved glycemic target on Metformin & SGLT2 inhibitor
GLP1 RA
Atherosclerotic heart disease
ANTIPLATELET(S)*
GLP1 RA*
LIPID MANAGEMENT*
UACR ≥ 30 mg/g, normal BP
RAS BLOCKADE
WEIGHT CONTROL*
Refractory HTN
MRA
eGFR ≥ 30 mL/min/1.73 m²
METFORMIN & SGLT2 INHIBITOR
GLYCEMIC TARGETS
A1C < 6.5% - < 8.0%
EXERCISE
≥ 150 min/week

Direct Renal Effects of Glucose-Lowering Medications

- SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic BP, intra-glomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia.

…… .. ..SGLT2 inhibitors …….

- ***SGLT2*** inhibitors should be given to all patients with stage 3 CKD or higher and type 2 , regardless of glycemic Control.

- **GLP-1 RAs** ….cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression

…… SGLT2 inhibitors ……

- The SGLT2 inhibitors ***empagliflozin and dapagliflozin*** are approved by the FDA for use with eGFR 25–45 mL/min/1.73 m2 for kidney/heart failure outcomes.

- Some GLP-1 Ras require dose adjustment for reduced eGFR (the majority—liraglutide, dulaglutide, semaglutide—do not require it).

Mineralocorticoid Receptor Antagonist

- Hyperkalemia!!!!!
- benefit on albuminuria reduction

- two different classes of MRAs, steroidal and non-steroidal.
- finerenone, a novel nonsteroidal MRA

Cardiovascular Disease and BP

- Antihypertensive therapy reduces the risk of albuminuria.

- Among patients with type 1 or 2 with established CKD (eGFR <60 mL/min/1.73 m2 and UACR ≥300 mg/g Cr), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD

- BP <140/90 are generally recommended to reduce CVD mortality and slow CKD progression among all people with diabetes.

- Lower BP targets (e.g., <130/80 mmHg) should be considered for patients based on individual anticipated **benefits and risk**(especially in those with ≥300 mg/g Cr albuminuria).

ACE inhibitors or ARBs

- Preferred first-line agent for BP 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 .

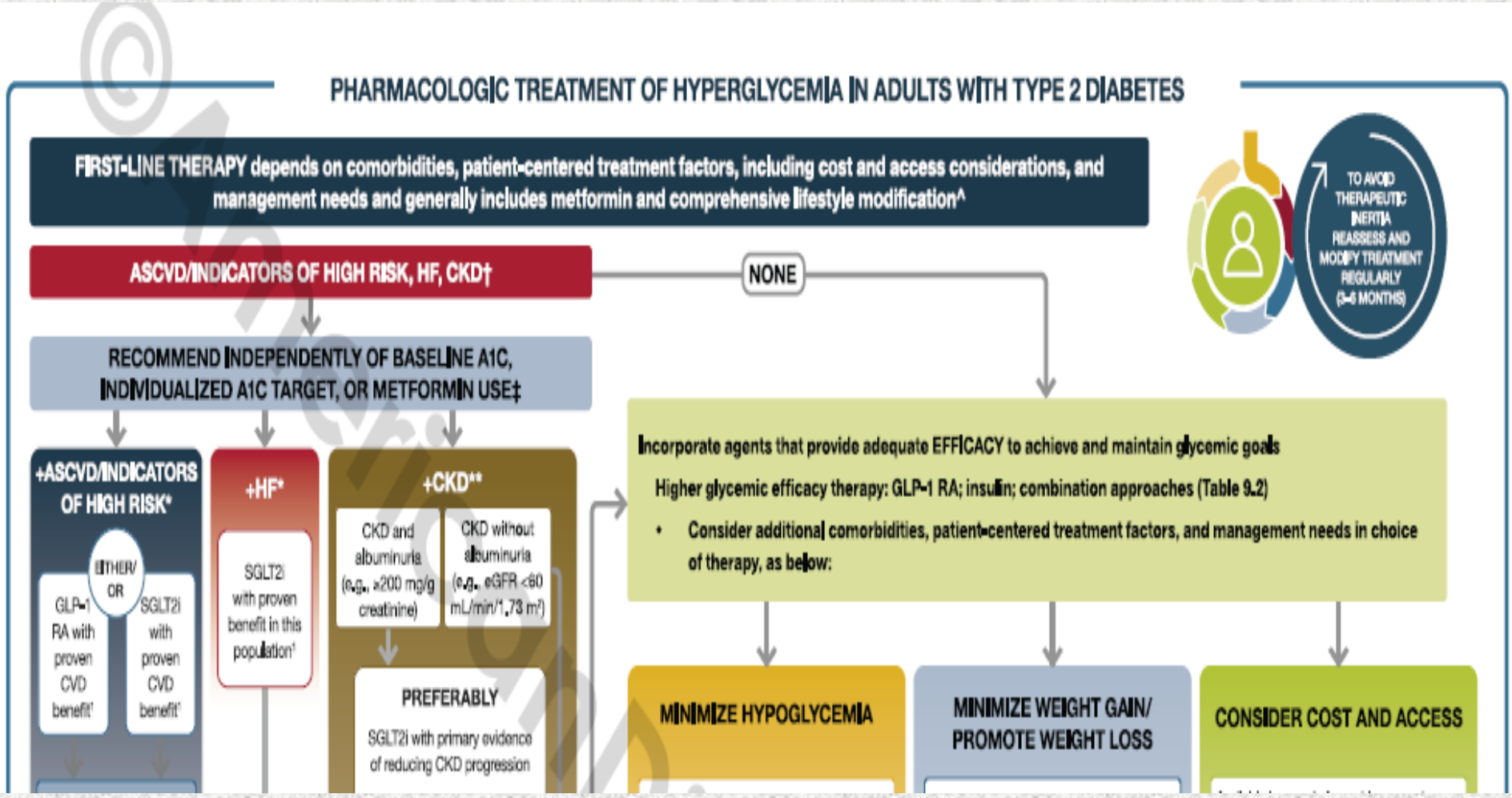
- ACE inhibitors and ARBs are considered to have similar benefits

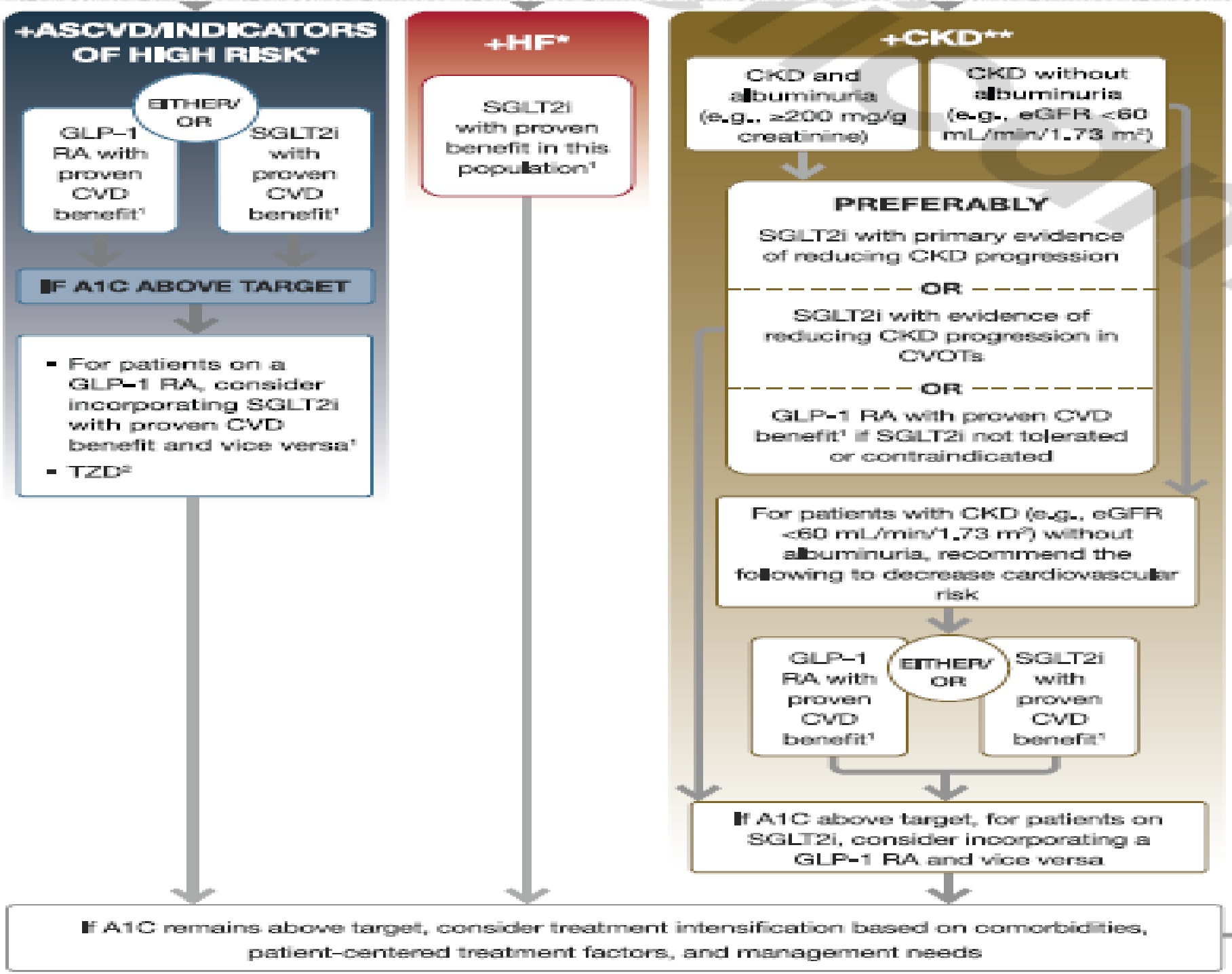
- Absent kidney disease, ACE inhibitors or ARBs are useful to control BP but have not proven superior to alternative classes.

- ACE inhibitors or ARBs are not recommended for patients without hypertension to prevent the development of CKD.
- the combined use of ACE inhibitors and ARBs should be avoided.

Referral to a Nephrologist

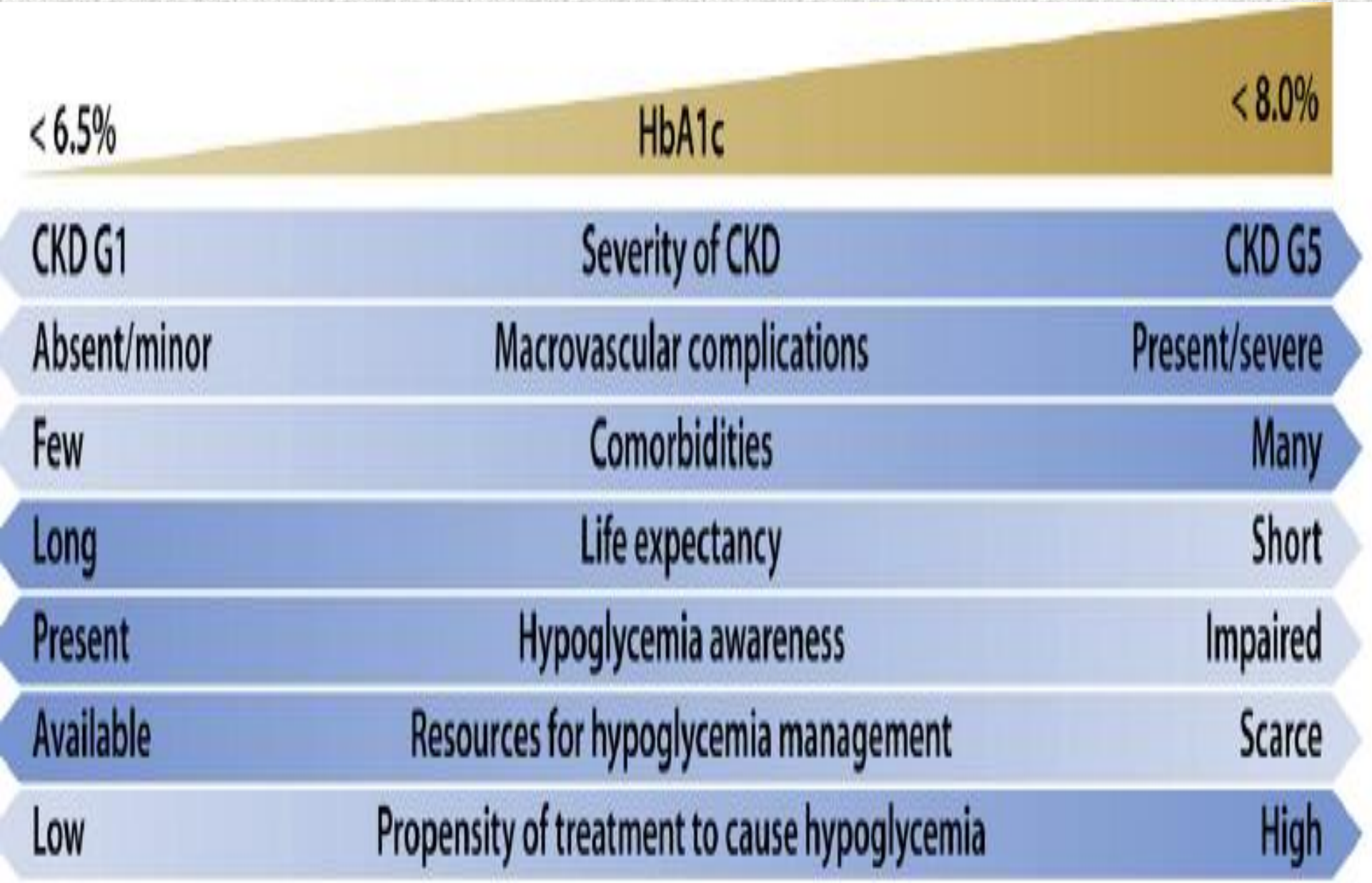
- uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria in spite of good BP control, metabolic bone disease, resistant HTN, or electrolyte disturbances)
- advanced kidney disease (eGFR <30)


PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ASCVD/INDICATORS OF HIGH RISK, HF, CKD†
NONE
RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡
+ASCVD/INDICATORS OF HIGH RISK*
EITHER/ OR
GLP-1 RA with proven CVD benefit†
SGLT2i with proven CVD benefit†
+HF*
SGLT2i with proven benefit in this population†
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals
Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)
• Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:
MINIMIZE HYPOGLYCEMIA
MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS
CONSIDER COST AND ACCESS


+ASCVD/INDICATORS OF HIGH RISK*
EITHER/ OR
GLP–1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
IF A1C ABOVE TARGET
For patients on a GLP–1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa[1]
TZD[2]
+HF*
SGLT2i with proven benefit in this population[1]
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk
EITHER/ OR
GLP–1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA and vice versa
If A1C remains above target, consider treatment intensification based on comorbidities, patient–centered treatment factors, and management needs

HbA1c

Glycemic control has been shown to slow the development of CVD and CKD. The recommended target HbA_{1c} in nonpregnant adults by the American Diabetes Association (ADA) is ≤7%. The ADA supports higher targets (<8%) for select patients, such as those with shorter life expectancies, a history of severe hypoglycemia, extensive comorbidities, and advanced complications. An HbA_{1c} goal of <6.5% may be appropriate for certain populations. A goal HbA_{1c} of ≤6.5% in healthy patients who are at low risk for hypoglycemia has been recommended by the American Association of Clinical Endocrinologists (AACE), but they also acknowledge that these goals need to be individualized.


< 6.5%
HbA1c
< 8.0%
CKD G1
Severity of CKD
CKD G5
Absent/minor
Macrovascular complications
Present/severe
Few
Comorbidities
Many
Long
Life expectancy
Short
Present
Hypoglycemia awareness
Impaired
Available
Resources for hypoglycemia management
Scarce
Low
Propensity of treatment to cause hypoglycemia
High

METFORMIN

- should not be used in patients with an eGFR < 30 .
- should not be started for eGFR of 30- 45 .
- if the eGFR drops <45 , risks and benefits of reviewed.
- dose should be reduced 1,000 mg/d with an eGFR < 45.
- hold metformin : hypoxic, hypotensive, or septic state.

Table 1. Dose Adjustment for Medications for Diabetes in CKD

Medication Class	CKD Stages 3-5[a]
Insulins	No advised dose adjustment[b]
Sulfonylureas	
Glipizide	No dose adjustment
Glimepiride	Start conservatively at 1 mg daily
Glyburide	Avoid use
Gliclazide	Avoid use when eGFR <40 mL/min/1.73 m^2
Glinides	
Repaglinide	No dose adjustment
Nateglinide	Start with 60 mg with meals; do not use if eGFR < 60 mL/min/1.73 m^2 (can be used if on dialysis)
Biguanides	
Metformin	eGFR < 45 mL/min/1.73 m^2, maximum dose is 1,000 mg/d; discontinue for eGFR < 30 mL/min/1.73 m^2

Thiazolidinediones	
Pioglitazone	No dose adjustment
Rosiglitazone	No dose adjustment
α-glucosidase inhibitors	
Acarbose	Avoid if GFR < 26 mL/min/1.73 m^2
Miglitol	Avoid use
DPP-4 inhibitor	
Sitagliptin	GFR >50 mL/min/1.73 m^2: 100 mg daily GFR 30-50 mL/min/1.73 m^2: 50 mg daily GFR <30 mL/min/1.73 m^2: 25 mg daily
Saxagliptin	GFR >50 mL/min/1.73 m^2: 5 mg daily GFR ≤50 mL/min/1.73 m^2: 2.5 mg daily
Alogliptin	GFR >50 mL/min/1.73 m^2; 25 mg daily GFR 30-50 mL/min/1.73m^2; 12.5 mg daily GFR < 30 mL/min/1.73 m^2; 6.25 mg daily
Linagliptin	No restrictions

GLP-1 agonists	
Exenatide	Not recommended if GFR < 30 mL/min/1.73 m^2
Liraglutide	No dose adjustment
Semaglutide	No dose adjustment
Dulaglutide	No dose adjustment
Lixisenatide	Not recommended if eGFR < 15 mL/min/1.73 m^2
SGLT2 inhibitors	
Canagliflozin	eGFR 45-< 60 mL/min/1.73 m^2: max dose 100 mg once daily eGFR < 30 mL/min/1.73 m^2: avoid use
Dapagliflozin	eGFR < 30 mL/min/1.73 m^2: avoid use[c]
Empagliflozin	eGFR < 30 mL/min/1.73 m^2: avoid use[c]
Ertugliflozin	eGFR < 60 mL/min/1.73 m^2: avoid use

GLP-1 agonists	
Exenatide	Not recommended if GFR < 30 mL/min/1.73 m^2
Liraglutide	No dose adjustment
Semaglutide	No dose adjustment
Dulaglutide	No dose adjustment
Lixisenatide	Not recommended if eGFR < 15 mL/min/1.73 m^2
SGLT2 inhibitors	
Canagliflozin	eGFR 45-< 60 mL/min/1.73 m^2: max dose 100 mg once daily eGFR < 30 mL/min/1.73 m^2: avoid use
Dapagliflozin	eGFR < 30 mL/min/1.73 m^2: avoid use[c]
Empagliflozin	eGFR < 30 mL/min/1.73 m^2: avoid use[c]
Ertugliflozin	eGFR < 60 mL/min/1.73 m^2: avoid use