KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE

Dr. Firouzeh Moeinzadeh
Associate professor of Nephrology
Isfahan University of Medical Sciences

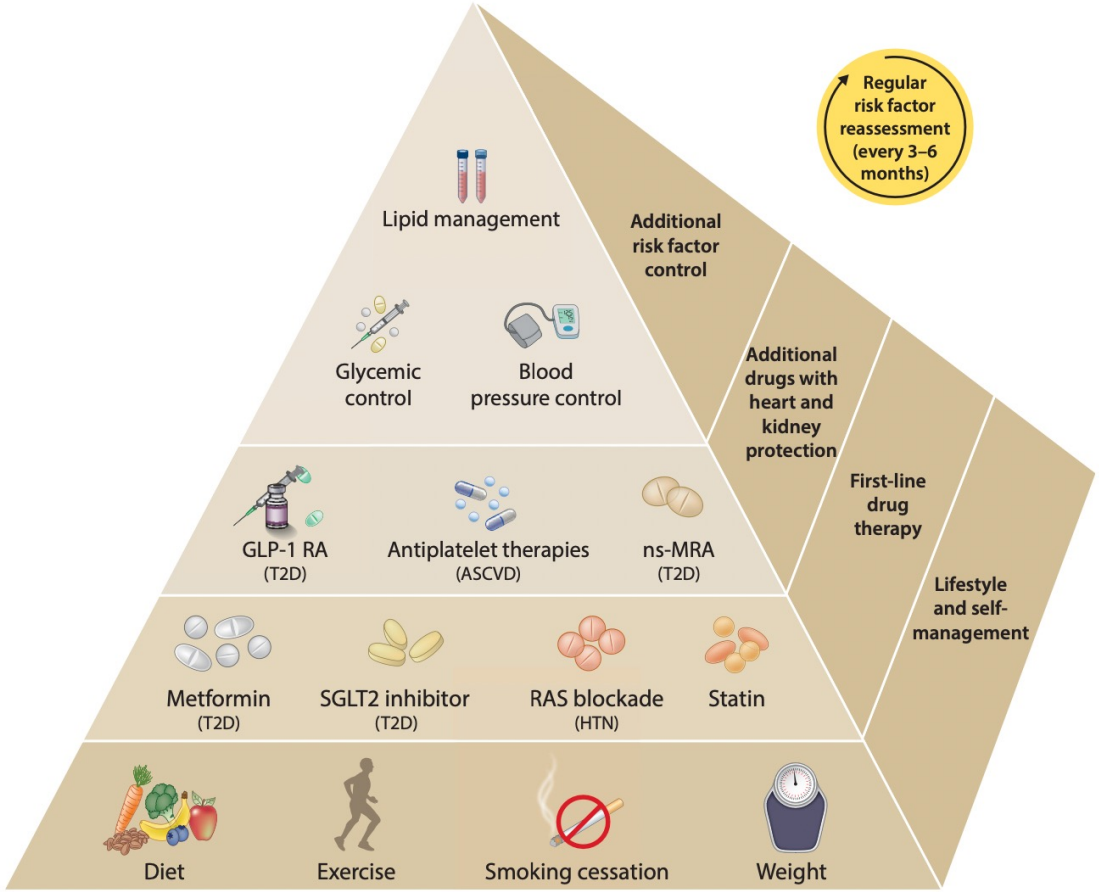
Outlines

- Cardiorenal protection
  - SGLT2Inhibitors
- Mineralocorticoid receptor antagonists (MRA)
- Glycemic control
- Nutrition
- Antihyperglycemic drugs

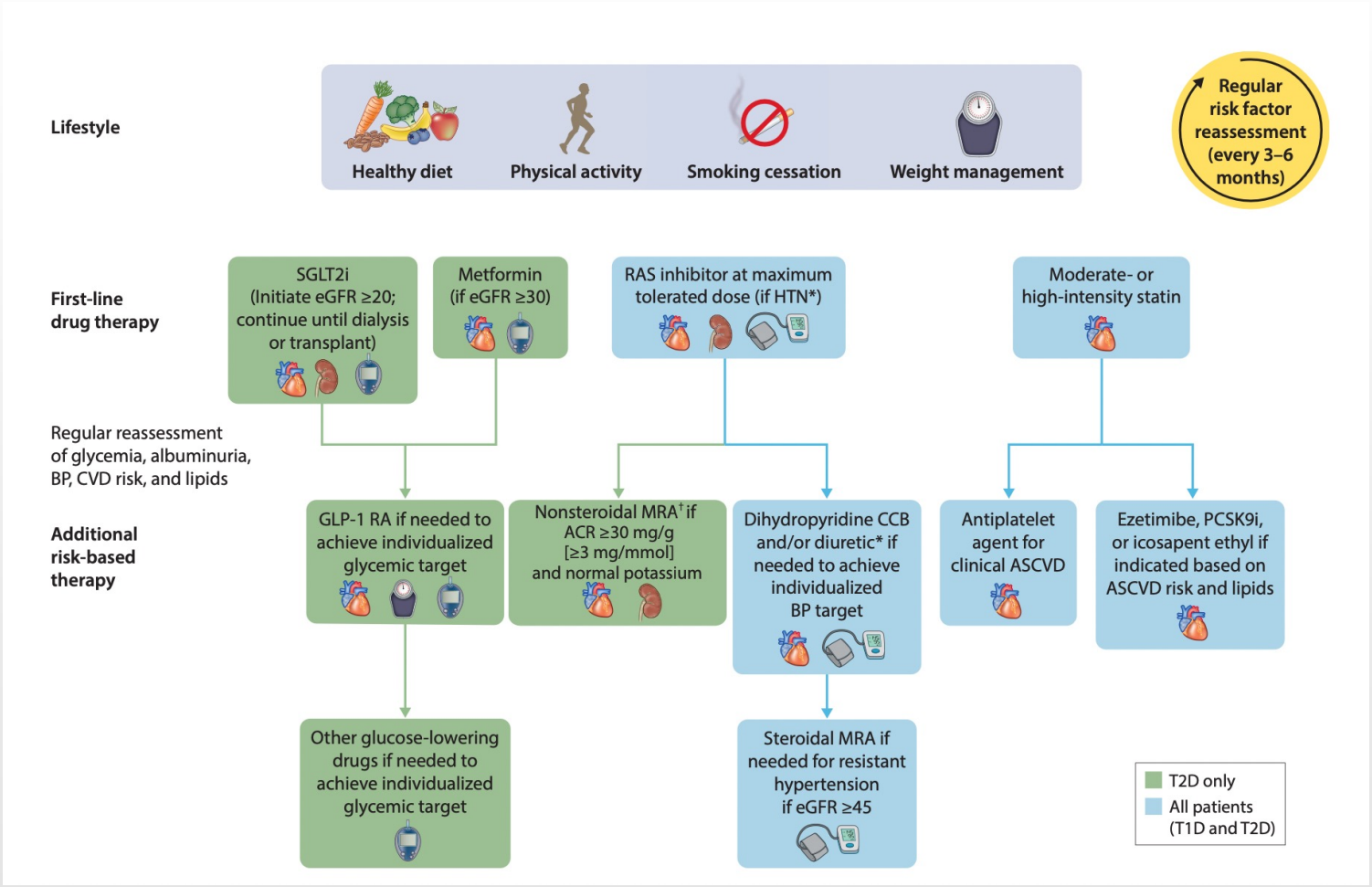
Practice Point 1.1.1:

- Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease

Kidney–heart risk factor management.



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



Recommendation 1.2.1:

- We recommend that treatment with an ACEi or ARB be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated

Drug considerations

Drug	Starting dose	Maximum dose	Kidney impairement
Captopril	12.5 mg to 25 mg 2 to 3 times daily	Usually 50 mg 3 times daily (may go up to 450 mg/day)	Half-life is increased in eGFR: **10–50** ml/min: administer **75% of NL dose q12–18 h.** CrCl **<10** ml/min: administer **50% of NL** dose **q24 h**. HD: administer after dialysis. About 40% of drug is removed by HD
Enalapril	5 mg once daily	40 mg	CrCl ≤**30** ml/min: reduce initial dose to 2.5 mg PO once daily. 2.5 mg PO after HD on dialysis days; dosage on non-dialysis days should be adjusted based on clinical response
Lisinopril	10 mg once daily	40 mg	CrCl **10–30** ml/min: Reduce initial recommended dose by **50%** for adults. Max: 40 mg/day CrCl <**10** ml/min: Reduce initial dosage to 2.5 mg PO once daily. Max: 40 mg/day

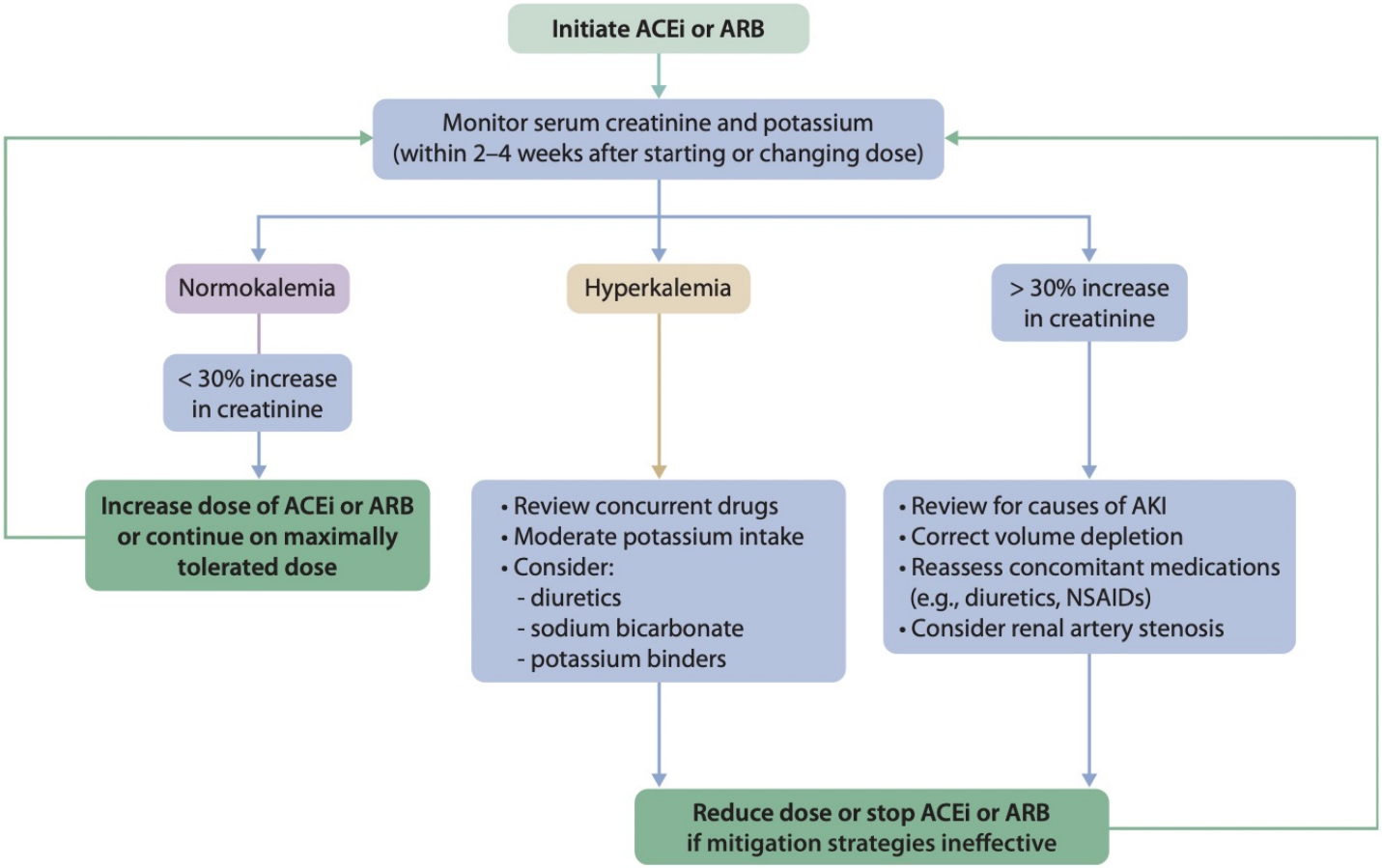
Drug considerations

Drug	Starting dose	Maximum dose	Kidney impairement
Losartan	50 mg once daily	100 mg	No dosage adjustment necessary. Not removed by hemodialysis
Valsartan	80 mg once daily	320 mg	No dosage adjustment available in eGFR<30ml/min . Use with caution. Not removed significantly by hemodialysis

Practice Point 1.2.2:

- Monitor for changes in blood pressure, serum creatinine, and serum potassium **within 2–4 weeks** of initiation or increase in the dose of an ACEi or ARB

Monitoring of serum Cr and K during ACEi or ARB treatment—dose adjustment and monitoring of side effects.



Practice Point 1.2.4:

- Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.

Practice Point 1.2.5:

- Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping the ACEi or ARB immediately

Practice Point 1.2.6:

- Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite the medical treatment outlined in Practice Point 1.2.5, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m2).

Practice Point 1.2.7:

- Use only one agent at a time to block the RAS.
- The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

- Recommendation 1.3.1:
- We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR >20 ml/min per 1.73 m2 with an SGLT2i (1A).

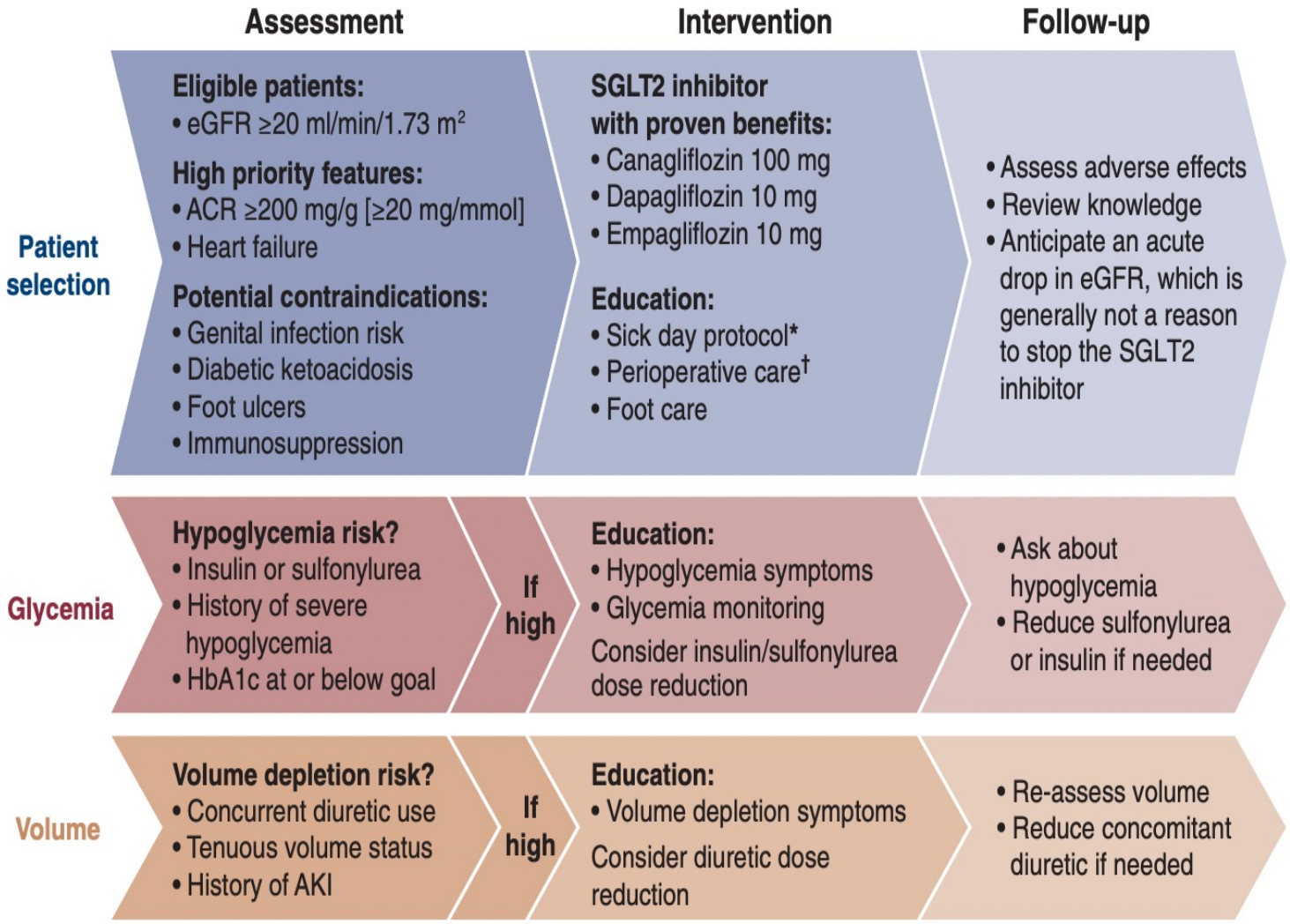
Practice Point 1.3.1:

- The recommendation for SGLT2i is for kidney and cardiovascular protection and SGLT2i have been shown to have safety and benefit in CKD patients, even for those without T2D.
- Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen

Practice Point 1.3.3:

- It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD



Practice Point 1.3.4:

- If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

SGLT2Is

SGLT2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Dapagliflozin	10 mg daily	eGFR ≥25 ml/min per 1.73 m^2 in DAPA-CKD eGFR ≥30 ml/min per 1.73 m^2 in DAPA-HF and DECLARE	eGFR ≥25 ml/min per 1.73 m^2
Empagliflozin	10 mg daily (Can increase to 25 mg daily if needed for glucose control)	eGFR ≥30 ml/min per 1.73 m^2 in EMPA-REG eGFR ≥20 ml/min per 1.73 m^2 in EMPEROR-Reduced and EMPEROR-Preserved	eGFR ≥30 ml/min per 1.73 m^2 for T2D and ASCVD for glucose control eGFR ≥20 ml/min per 1.73m^2 for HF
Canagliflozin	100 mg daily (The higher dose of 300 mg is not recommended for CKD)	eGFR ≥30 ml/min per 1.73 m^2 in CREDENCE	eGFR ≥30 ml/min per 1.73 m^2

Practice Point 1.3.5:

- A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 1.3.6:

- Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m2, unless it is not tolerated or kidney replacement therapy is initiated.

Practice Point 1.3.7:

- SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use **SGLT2i does not apply to kidney transplant recipients** (see Recommendation 1.3.1).

Mineralocorticoid receptor antagonists (MRA)

- Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with **T2D, an eGFR >25 ml/min per 1.73 m2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol])** despite maximum tolerated dose of RAS inhibitor (RASi) (2A).

Practice Point 1.4.1:

- Nonsteroidal MRA are most appropriate for patients with T2D who are **at high risk of CKD progression and cardiovascular events**, as demonstrated by **persistent albuminuria despite other standard-of-care therapies**.

- Practice Point 1.4.2. A nonsteroidal MRA can be added to a RASi and an SGLT2i for treatment of T2D and CKD.

- Practice Point 1.4.3: To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.

Serum K monitoring during treatment with finerenone.

K^+ ≤4.8 mmol/l

- Initiate finerenone
  - 10 mg daily if eGFR 25–59 ml/min per 1.73 m^2
  - 20 mg daily if eGFR ≥60 ml/min per 1.73 m^2
- Monitor K^+ at 1 month after initiation and then every 4 months
- Increase dose to 20 mg daily, if on 10 mg daily
- Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l

K^+ 4.9–5.5 mmol/l

- Continue finerenone 10 mg or 20 mg
- Monitor K^+ every 4 months

K^+ >5.5 mmol/l

- Hold finerenone
- Consider adjustments to diet or concomitant medications to mitigate hyperkalemia
- Recheck K^+
- Consider reinitiation if/when K^+ ≤5.0 mmol/l

Practice Point 1.4.5:

- A **steroidal MRA** should be used for treatment of **heart failure, hyperaldosteronism, or refractory hypertension**, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.

Smoking cessation

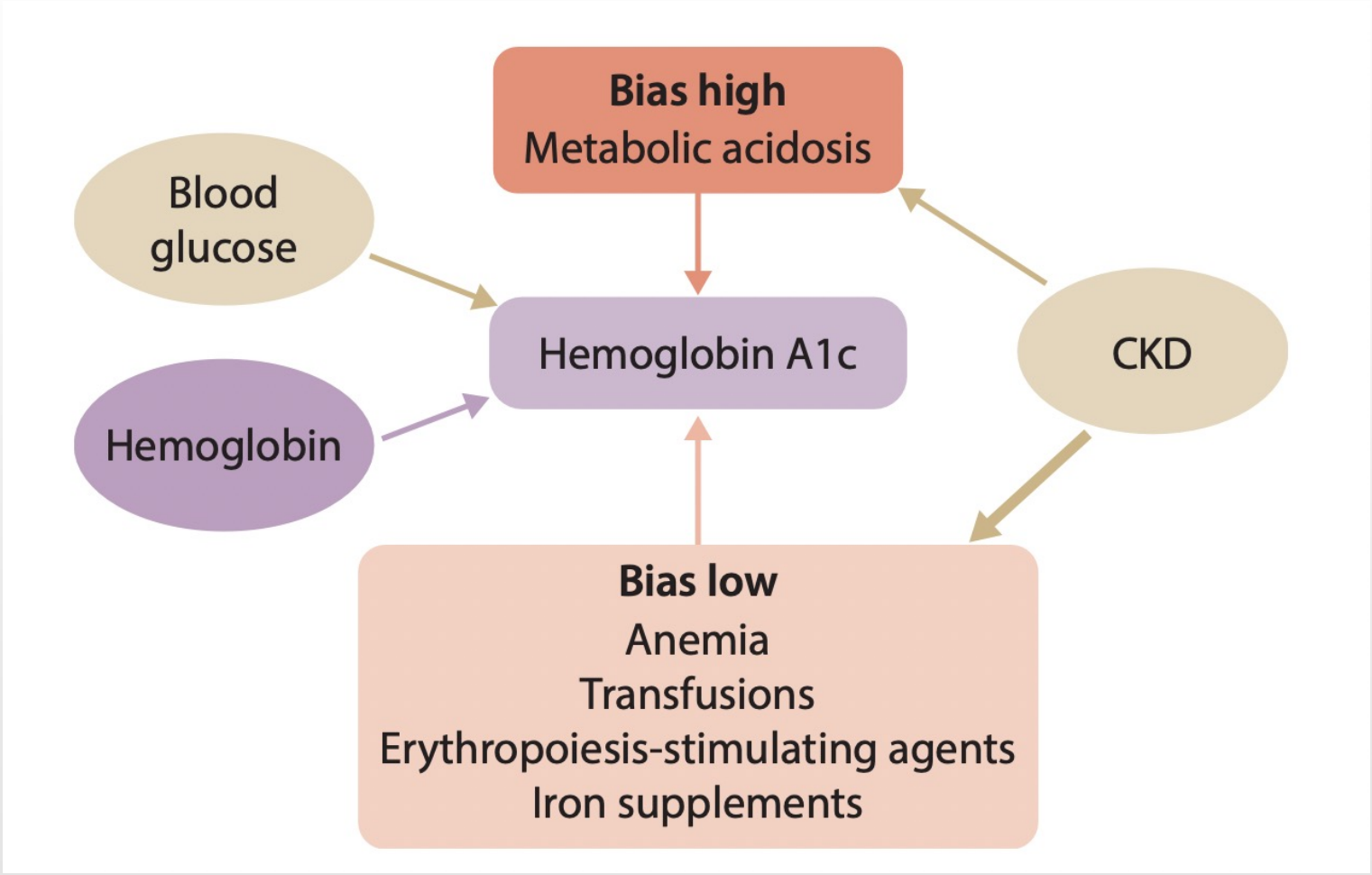
- Recommendation 1.5.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products (1D).

- Practice Point 1.5.1: Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.

Glycemic monitoring

- Recommendation 2.1.1: We recommend using hemoglobin A1c (HbA1c) to monitor glycemic control in patients with diabetes and CKD (1C).

Effects of CKD–related factors on HbA1c



Frequency of HbA1c measurement and use of glucose management indicator (GMI) in CKD

Population	HbA1c			GMI
	Measure	Frequency	Reliability	
CKD G1–G3b	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	High	Occasionally useful
CKD G4–G5 including treatment by dialysis or kidney transplant	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	Low	Likely useful

Recommendations

- **Practice Point 2.1.4:** Daily glycemic monitoring with CGM or self-monitoring of blood glucose (SMBG) may help prevent hypoglycemia and improve glycemic control when glucose-lowering therapies associated with risk of hypoglycemia are used.

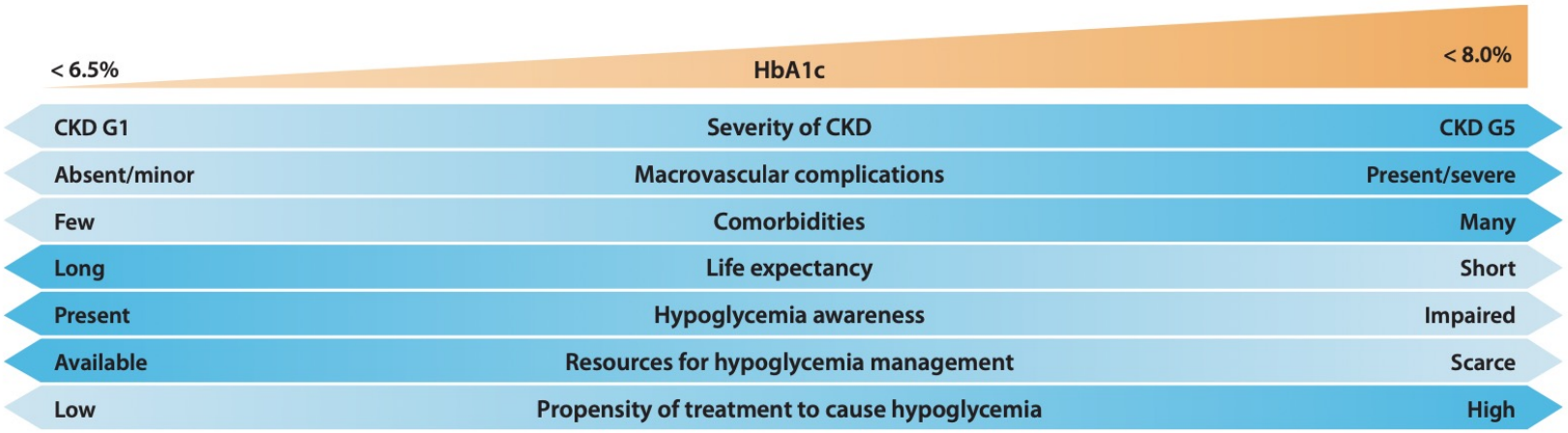
Practice Point 2.1.5:

- For patients with T2D and CKD who choose not to do daily glycemic monitoring by CGM or SMBG, glucose-lowering agents that pose a lower risk of hypoglycemia are preferred and should be administered in doses that are appropriate for the level of eGFR.

Glycemic targets

- Recommendation 2.2.1: We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (1C).

Factors guiding decisions on individual HbA1c targets



Recommendations

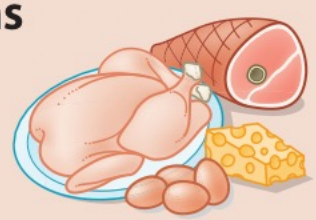
- Practice Point 2.2.1:Safe achievement of lower HbA1c targets (e.g., <6.5% or <7.0%) may be facilitated by CGM or SMBG and by selection of glucose-lowering agents that are not associated with hypoglycemia.

Nutrition intake

- Practice Point 3.1.1: Patients with diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages.
- Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g protein/kg/d for those with diabetes and CKD not treated with dialysis (2C).

Average protein content of foods in grams.

Animal proteins



Meat, poultry, fish, seafood, eggs:
28 g (1 oz) = 6–8 g protein
1 egg = 6–8 g protein

Dairy, milk, yogurt, cheese:
250 ml (8 oz) = 8–10 g protein
28 g (1 oz) cheese = 6–8 g protein

Plant proteins

Legumes, dried beans, nuts, seeds:
100 g (0.5 cup) cooked = 7–10 g protein

Whole grains, cereals:
100 g (0.5 cup) cooked = 3–6 g protein

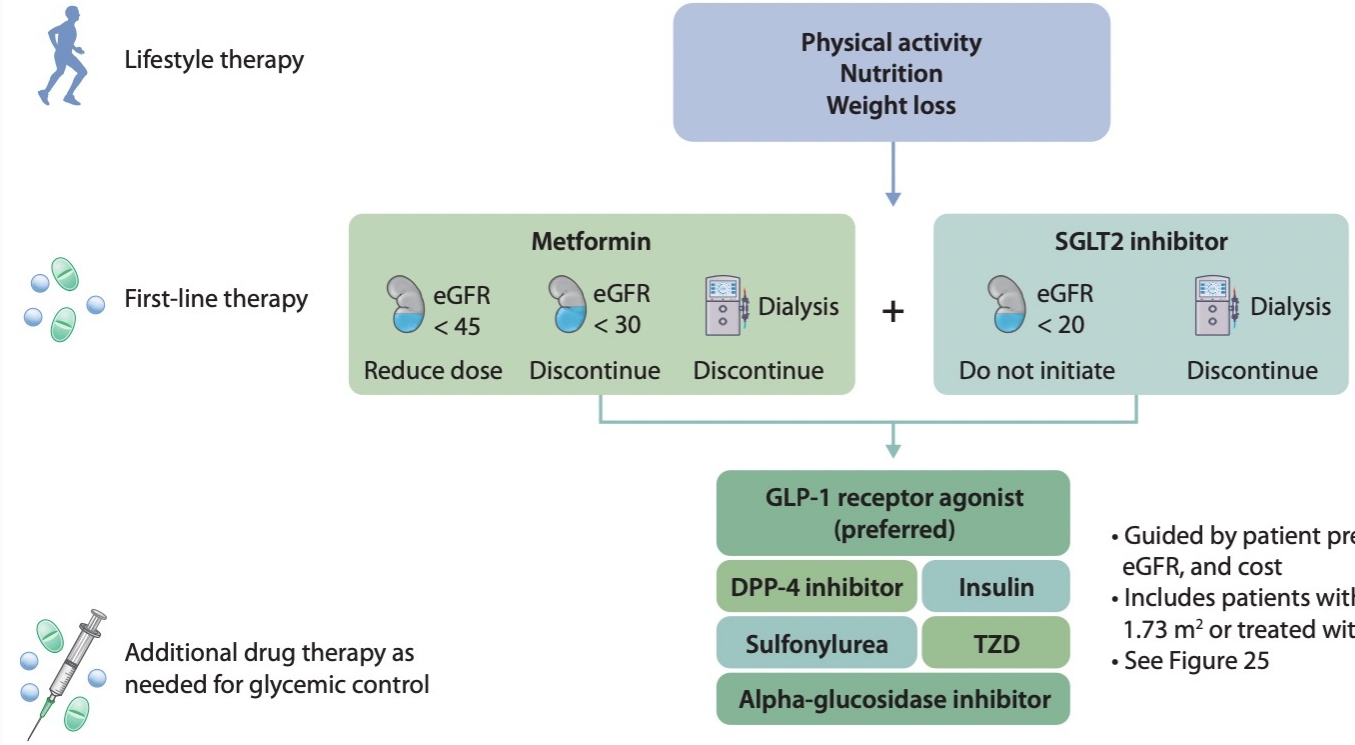
Starchy vegetables, breads:
2–4 g protein

Recommendation 3.1.2:

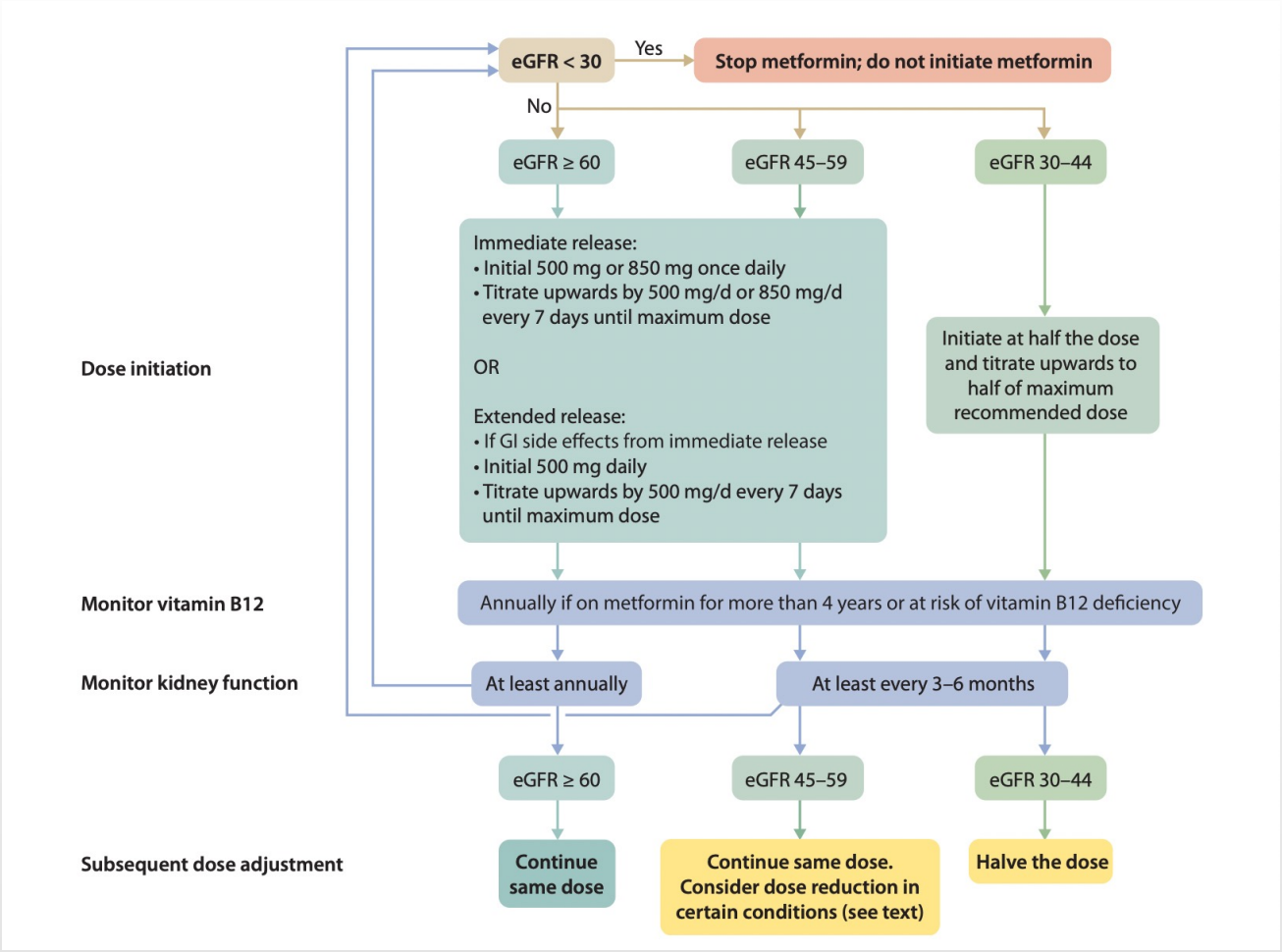
- We suggest that sodium intake be **<2 g of sodium** per day (or <90 mmol of sodium per day, or **<5 g of sodium chloride per day**) in patients with diabetes and CKD (2C).

Ten ways to cut out salt.

Glucose-lowering therapies in patients with T2D and CKD



Suggested approach in dosing metformin based on the level of kidney function



Considerations for selecting glucose-lowering agents in patients with T2D and CKD

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Dose adjustments for eGFR <45 ml/min/1.73 m2

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡	Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

In brief

- Starting SGLT2Is in eGFR>20ml/min/m2.
- Continue using these drugs in decreasing eGFR<20ml/min/m2 until RRT.
- Using MRAs (NS-MRA for renal protection and S-MRA for HTN controling if eGFR>45ml/min/m2).

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

KDIGO executive conclusions

Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence