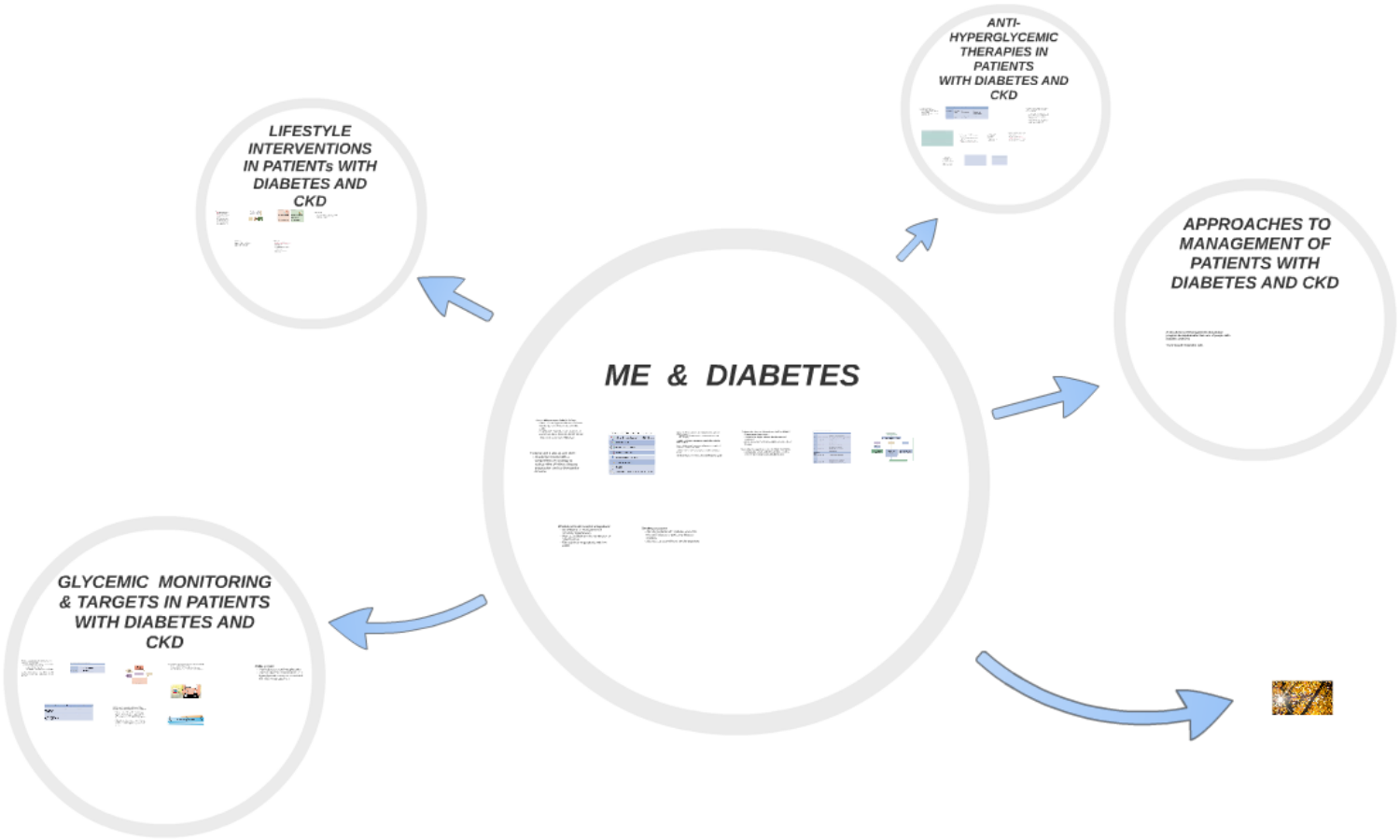
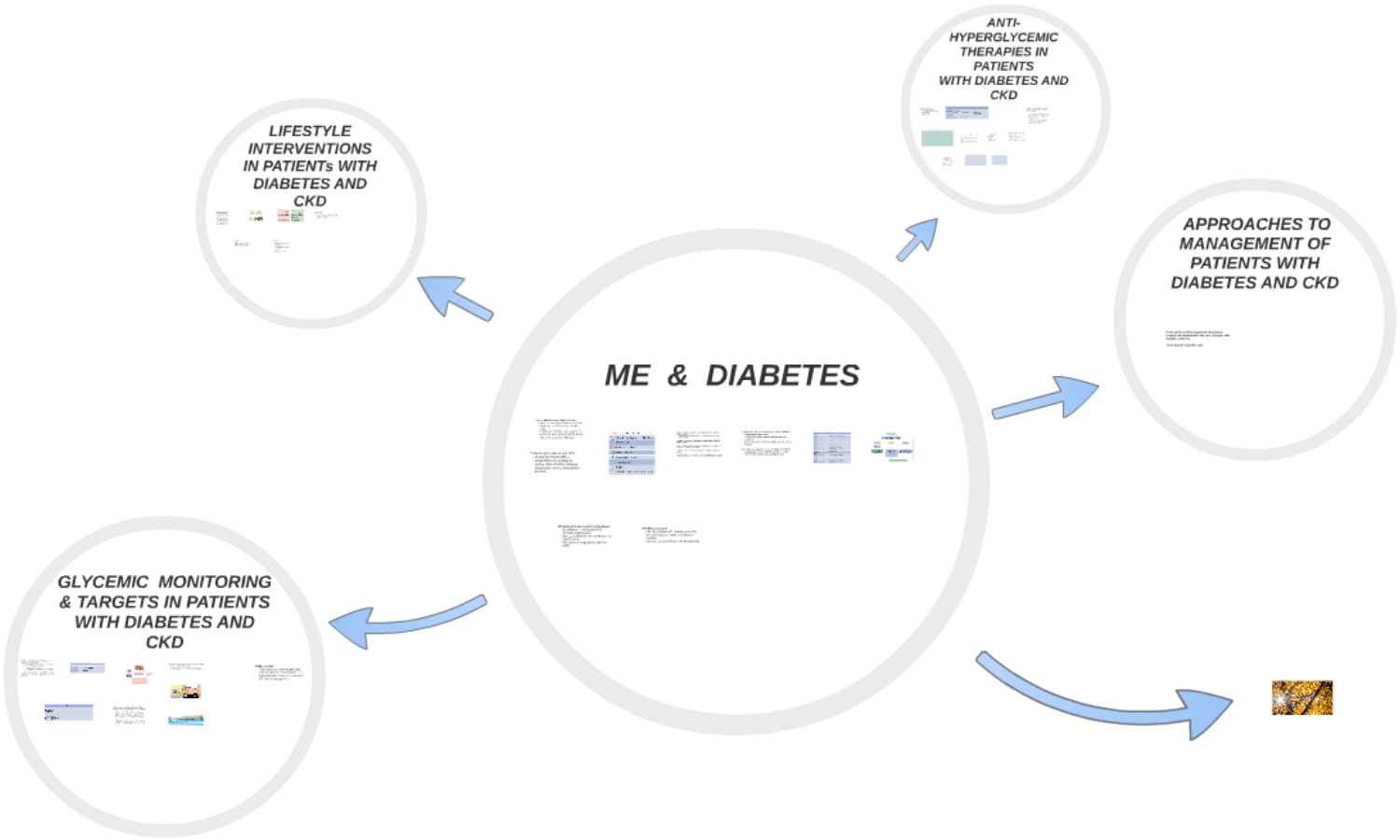


ME,KIDNEY& DIABETES

Dr.M.Matinfar Nephrologist



ME,KIDNEY& DIABETES

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ME & DIABETES

atient attitude about diabet & kidney:
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- Only 59 (28.4%) of the participants had awareness about CKD and its risk factors

nts with diabetes and CKD: hould be treated with a omprehensive strategy to duce risks of kidney disease ogression and cardiovascular sease.

Diabetes with CKD: cardio-kidney treatment

- Glycemic control including SGLT2 inhibitors
- RAAS blockade
- Blood pressure control
- Lipid management
- Lifestyle/physical activity
- Smoking cessation
- Nutrition
- Aspirin for prevalent cardiovascular disease

ACEi or an ARB is recommend be initiated in patients with DM, HTN & albuminuria
- Should be titrated to the highest approved dose that is well tolerated (1B)

Consider ACEi or ARB in patients with DM and albuminuria, but have normal BP

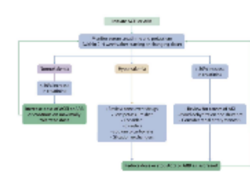
Monitor for BP, serum Cr, potassium within two to four weeks of initiation or increase in the dose

Continue unless serum Cr rises by more than 30% within four weeks

Advise contraception in women & discontinue if become pregnant

Reduce the dose or discontinue ACEi or ARB if:
- Symptomatic hypotension
- Uncontrolled hyperkalemia despite medical treatment
- While preparing for imminent kidney replacement therapy

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



Patient attitude about diabet & kidney:

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Patient Awareness, Prevalence, and Risk Factors of Chronic Kidney Disease . BioMed Research International Volume 2019, Article ID 2383508, 8 pages

Patients with diabetes and CKD:

- Should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.

Diabetes with CKD: cardio-kidney treatment


Glycemic control including SGLT2 inhibitors


RAAS blockade


Blood pressure control


Lipid management


Lifestyle/physical activity


Smoking cessation


Nutrition


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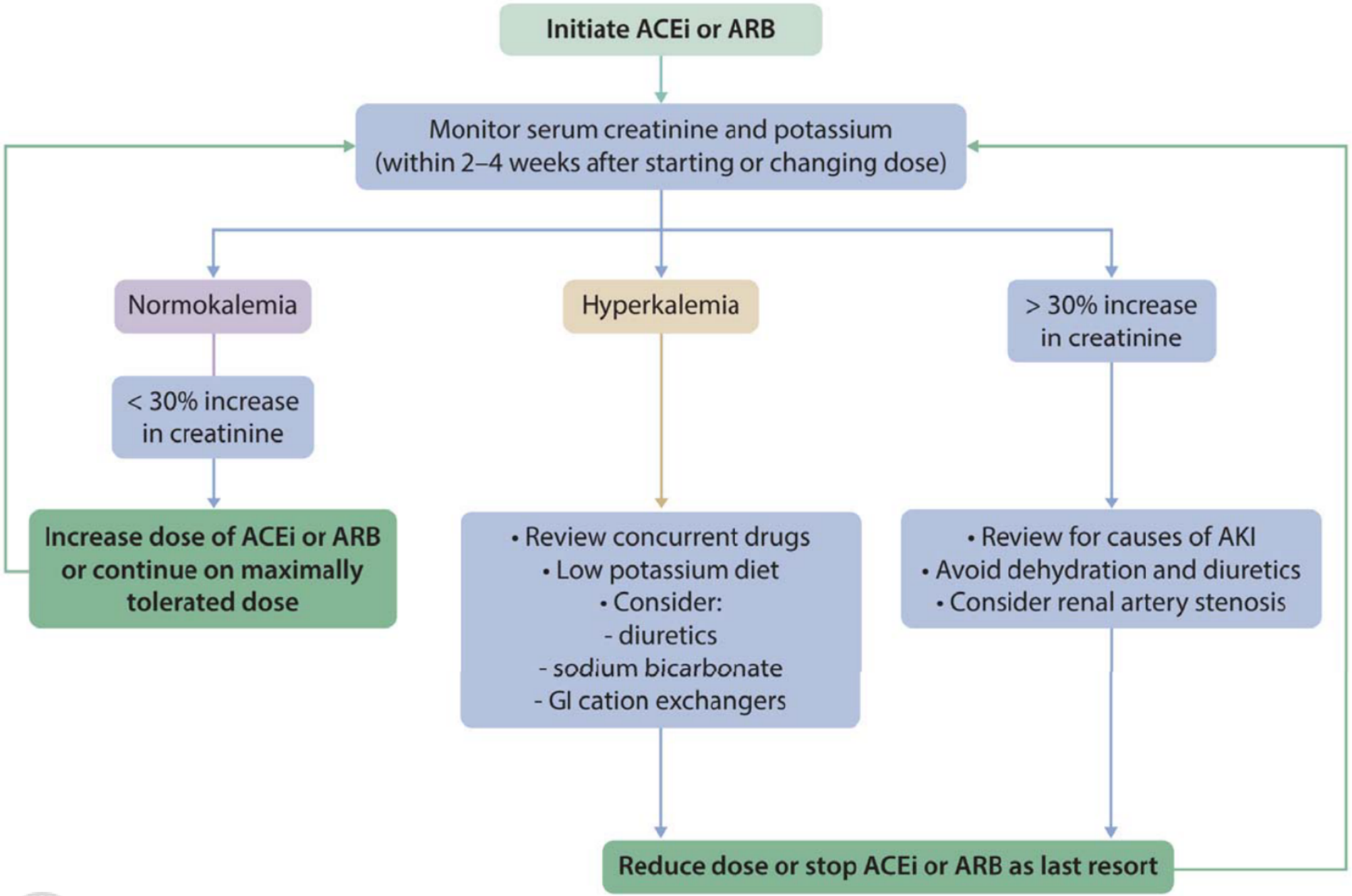
Table 1. Different formulations of ACEi and ARBs

Drug	Starting dose	Maximum daily dose	Kidney impairment
ACE inhibitors			
Benazepril	10 mg once daily	40 mg	Reduce to 25%–50% of usual dose in patients on hemodialysis or peritoneal dialysis. Parent compound not removed by hemodialysis
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 patients with kidney impairment CrCl 10–50 mL/min/1.73m^2: administer 75% of normal dose every 12–18 hours. CrCl < 10 mL/min/1.73m^2: administer 50% of normal dose every 24 hours. Hemodialysis: administer after dialysis. About 40% of drug is removed by hemodialysis
Enalapril	5 mg once daily	40 mg	No dosage adjustment necessary 20% to 50% removed by hemodialysis
Fosinopril	10 mg once daily	80 mg	No dosage adjustment necessary Poorly removed by hemodialysis
Lisinopril	5 mg once daily	40 mg	No dosage adjustment necessary 50% removed by hemodialysis
Perindopril	4 mg once daily	16 mg	Use is not recommended when CrCl < 30 mL/min/1.73m^2 Perindopril and its metabolites are removed by hemodialysis
Quinapril	10 mg once daily	80 mg	No dosage adjustment provided in manufacturer's labelling About 12% of parent compound removed by hemodialysis
Ramipril	2.5 mg once daily	20 mg	Administer 25% of normal dose when CrCl < 40 mL/min/1.73m^2 Minimally removed by hemodialysis
Trandolapril	1 mg once daily	4 mg	Reduce to 50% of usual dose when GFR < 10 mL/min Minimally removed by hemodialysis
Angiotensin receptor blockers			
Azilsartan			
Candesartan	8 mg once daily	32 mg	In patients with CrCl < 30 mL/min/1.73m^2, AUC and Cmax were approximately doubled with repeated dosing. Not removed by hemodialysis
Irbesartan	150 mg once daily	300 mg	No dosage adjustment necessary. Not removed by hemodialysis
Losartan	25 mg once daily	100 mg	No dosage adjustment necessary. Not removed by hemodialysis
Olmesartan	20 mg once daily	40 mg	AUC is increased 3-fold in patients with CrCl < 20 mL/min/1.73m^2, with recommended maximum dose of 20 mg/day. Has not been studied in dialysis patients
Telmisartan	40 mg once daily	80 mg	No dosage adjustment necessary. Not removed by hemodialysis
Valsartan	80 mg once daily	320 mg	No dosage adjustment available for CrCl < 30 mL/min/1.73m^2 – to use with caution. Not removed significantly by hemodialysis


Initiate ACEi or ARB
Monitor serum creatinine and potassium (within 2–4 weeks after starting or changing dose)
Normokalemia
Hyperkalemia
> 30% increase in creatinine
< 30% increase in creatinine
Increase dose of ACEi or ARB or continue on maximally tolerated dose
• Review concurrent drugs
• Low potassium diet
• Consider:
- diuretics
- sodium bicarbonate
- GI cation exchangers
• Review for causes of AKI
• Avoid dehydration and diuretics
• Consider renal artery stenosis
Reduce dose or stop ACEi or ARB as last resort

Mineralocorticoid receptor antagonists:

- Are effective for management of refractory hypertension
- May cause decline in kidney function or hyperkalemia,
- Particularly among patients with low eGFR

Smoking cessation

- Advising patients with diabetes and CKD who use tobacco to quit using tobacco products
- Also reduce second-hand smoke exposure

GLYCEMIC MONITORING & TARGETS IN PATIENTS WITH DIABETES AND CKD

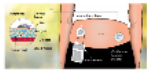
HbA1c is recommended to monitor glycemic control in DM& CKD (1C)

- Monitoring HbA1c twice per year is reasonable
- Measured four times per year if:
  - Glycemic target is not met
  - After change in anti-hyperglycemic therapy

Accuracy and precision of HbA1c will declines with advanced CKD Particularly among patients treated by dialysis

A continuous glucose management indicator (CGM)

- Can be used to index glycemia
- In where HbA1c is not concordant with directly measured blood glucose levels or clinical symptoms



SMBG or CGM

- May help to prevent hypoglycemia
- Improve glycemic control when anti-hyperglycemic therapies associated with risk of hypoglycemia

HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and non-dialysis CKD (3C)

- Safe achievement of lower HbA1c targets (e.g., <6.5% or <7.0%) may be facilitated by SMBG or CGM and by selection of anti-hyperglycemic agents that are not associated with hypoglycemia
- CGM metrics such as time in range and time in hypoglycemia may be considered as alternatives to HbA1c for defining glycemic targets in some patients

HbA1c is recommended to monitor glycemic control in DM& CKD (1C)

- Monitoring HbA1c twice per year is reasonable
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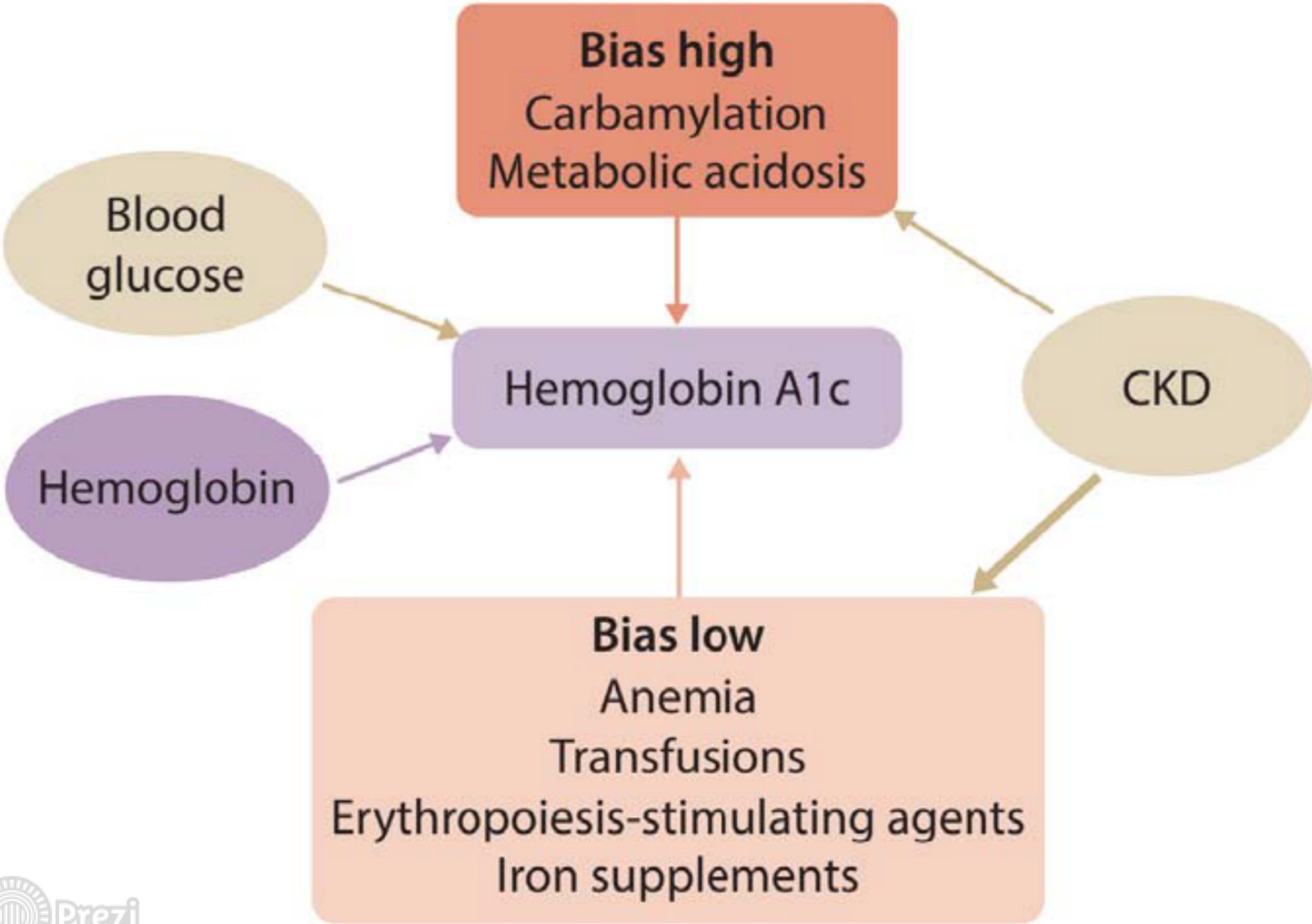
  - After change in anti-hyperglycemic therapy

Accuracy and precision of HbA1c will declines with advanced CKD Particularly among patients treated by dialysis

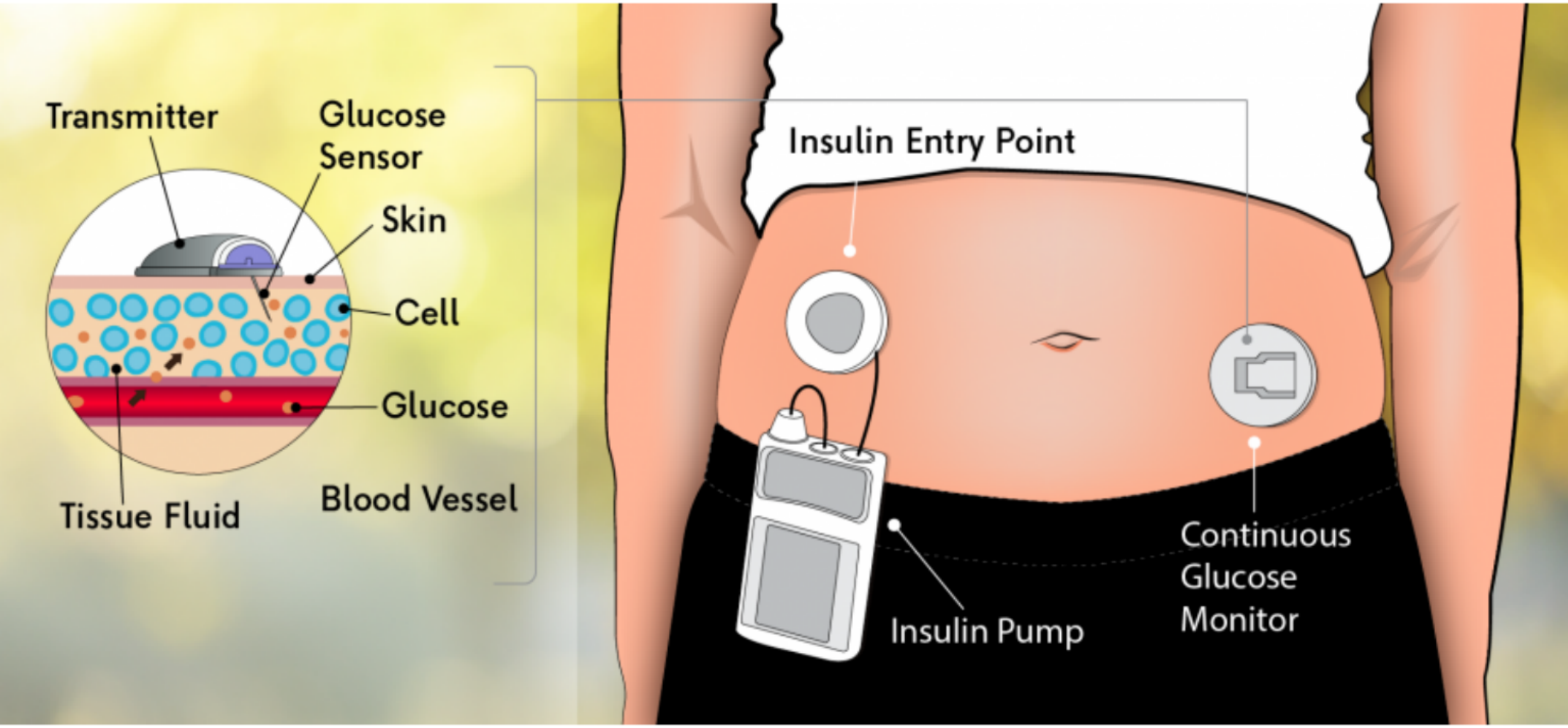
Table 2. Frequency of HbA1c and use of CGMI in CKD

Population	Measure	Frequency of HbA1c	Reliability	CGMI
CKD G1–G3b	Yes	• Twice per year • Up to four 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 four times per year if not achieving target or change in therapy	Low	Commonly useful


Bias high
Carbamylation
Metabolic acidosis
Blood glucose
Hemoglobin A1c
CKD
Hemoglobin
Bias low
Anemia
Transfusions
Erythropoiesis-stimulating agents
Iron supplements

A continuous glucose management indicator (CGMI)

- Can be used to index glycemia
- In whom HbA1c is not concordant with directly measured blood glucose levels or clinical symptoms


Transmitter
Glucose Sensor
Skin
Cell
Glucose
Blood Vessel
Tissue Fluid
Insulin Entry Point
Insulin Pump
Continuous Glucose Monitor

SMBG or CGM

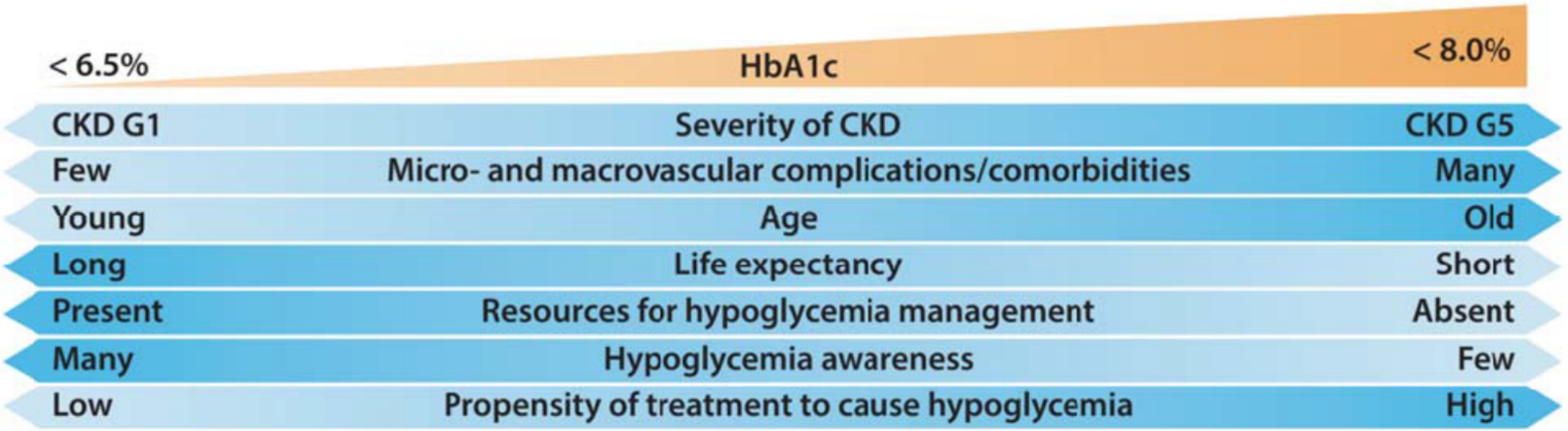
- May help to prevent hypoglycemia
- Improve glycemic control when anti-hyperglycemic therapies associated with risk of hypoglycemia

Anti-hyperglycemic agents	Risk of hypoglycemia	Rationale for SMBG or CGM
• Insulin • Sulfonylureas • Meglitinides	Higher	Higher
• Metformin • SGLT2 inhibitors • GLP-1 receptor agonists • DPP-4 inhibitors	Lower	Lower

H**bA1c target ranging from <6.5% to <8.0% in patients with diabetes and non-dialysis CKD (1C)**

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

- CGM metrics such as time in range and time in hypoglycemia may be considered as alternatives to HbA1c for defining glycemic targets in some patients


< 6.5%
HbA1c
< 8.0%
CKD G1
Severity of CKD
CKD G5
Few
Micro- and macrovascular complications/comorbidities
Many
Young
Age
Old
Long
Life expectancy
Short
Present
Resources for hypoglycemia management
Absent
Many
Hypoglycemia awareness
Few
Low
Propensity of treatment to cause hypoglycemia
High

LIFESTYLE INTERVENTIONS IN PATIENTs WITH DIABETES AND CKD

Diet:

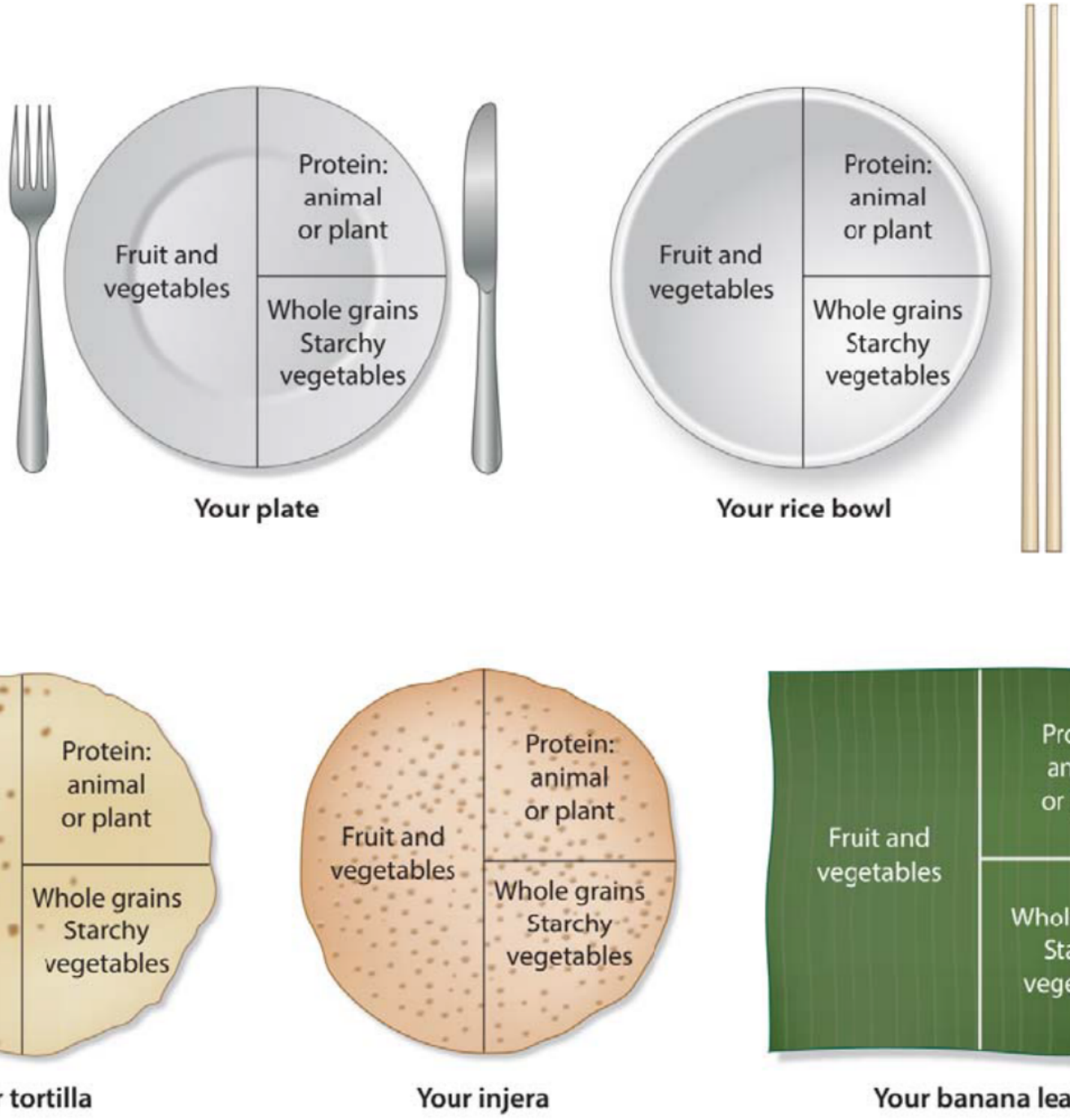
- **High in** vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats,nuts

- **Lower in** processed meats, refined carbohydrates, and sweetened beverages

- Maintaining protein intake of 0.8 g of protein/kg/day for those with DM & non-dialysis CKD (2C)

- Patients treated with hemodialysis, and particularly peritoneal dialysis, should consume between 1.0 and 1.2 gr of protein/kg/day

Figure 5. What does a kidney healthy diet look like?



Animal proteins

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

Dairy, milk, yoghurt, cheese:
250 cc (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

Sodium intake:

- Sodium intake should be <2 g of sodium per day (or <90mmol of sodium per day, or <5 g of sodium chloride per day) (2C)

Nutritional support:

Professional nutritionists, registered dietitians, diabetes educators, community health workers, peer counselors or other health workers should be engaged in the nutritional care of patients with diabetes and CKD

physical activity:

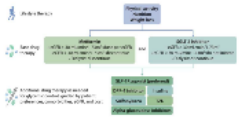
- Moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (1D)
- Cconsider age, ethnic background, presence of other comorbidities, and access to resources
- Avoid sedentary behavior
- Lose the weight, particularly patients with eGFR ≥30 ml/min/1.73 m2

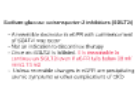
ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

Formulation	Dosage forms	Starting dose	Maximum dose
Metformin Immediate-Release	Tablet, Oral: 500 mg, 850 mg, 1000 mg	500 mg once or twice daily OR 850 mg once daily	Usual maintenance dose: 1 g twice daily OR 850 mg twice daily Maximum 2.55 g/day
Metformin, Extended-Release	Tablet, Oral: 500 mg, 750 mg, 1000 mg	500 mg once daily OR 1 g once daily	2 g/day

Most patients with Type2DM, CKD, and eGFR ≥30 ml/min/1.73 m2 would benefit from both metformin & an SGLT2i.

- Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs
- When needed,GLP-1 receptor agonists generally preferred
- In patients withe(GFR ≥30ml/min/1.73 m2, it's recommended to use metformin as the first-line treatment for hyperglycemia (1B).



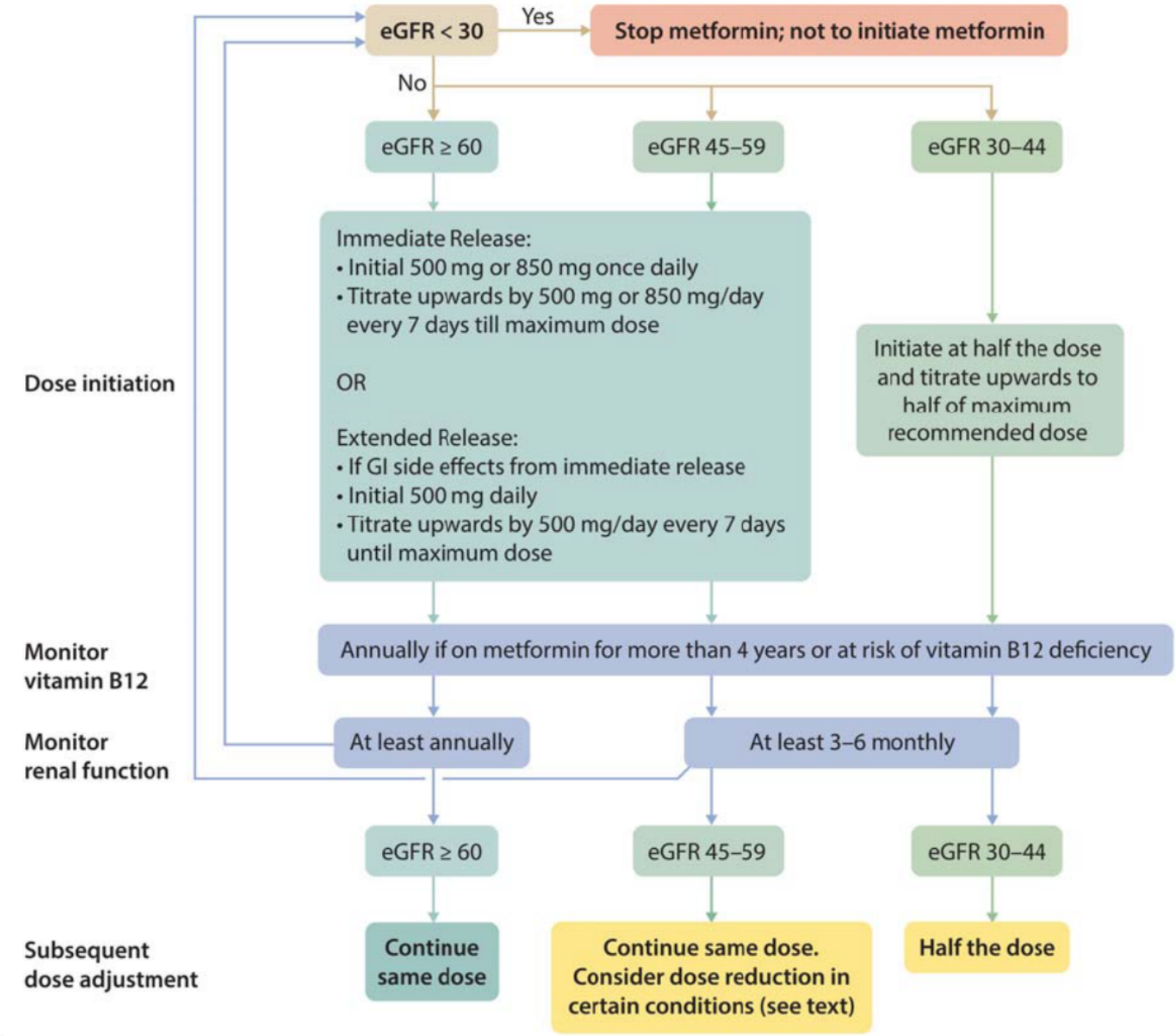


Glycemic management:

- Should include lifestyle therapy
- Base drug therapy with metformin and a SGLT-2 inhibitor
- Additional drug therapy as needed for glycemic control

Formulation	Dosage forms	Starting dose	Maximum dose
Metformin, Immediate Release	Tablet, Oral: 500 mg, 850 mg, 1000 mg	500 mg once or twice daily OR 850 mg once daily	Usual maintenance dose: 1 g twice daily OR 850 mg twice daily Maximum: 2.55 g/day
Metformin, Extended Release	Tablet, Oral: 500 mg, 750 mg, 1000 mg	500 mg once daily OR 1 g once daily	2 g/day

Figure 13. Suggested approach in dosing metformin based on the level of kidney function



eGFR, estimated glomerular filtration rate; GI, gastrointestinal

Most patients with Tyoe2DM, CKD, and eGFR ≥30 ml/min/1.73 m2 would benefit from both metformin & an SGLT2i.

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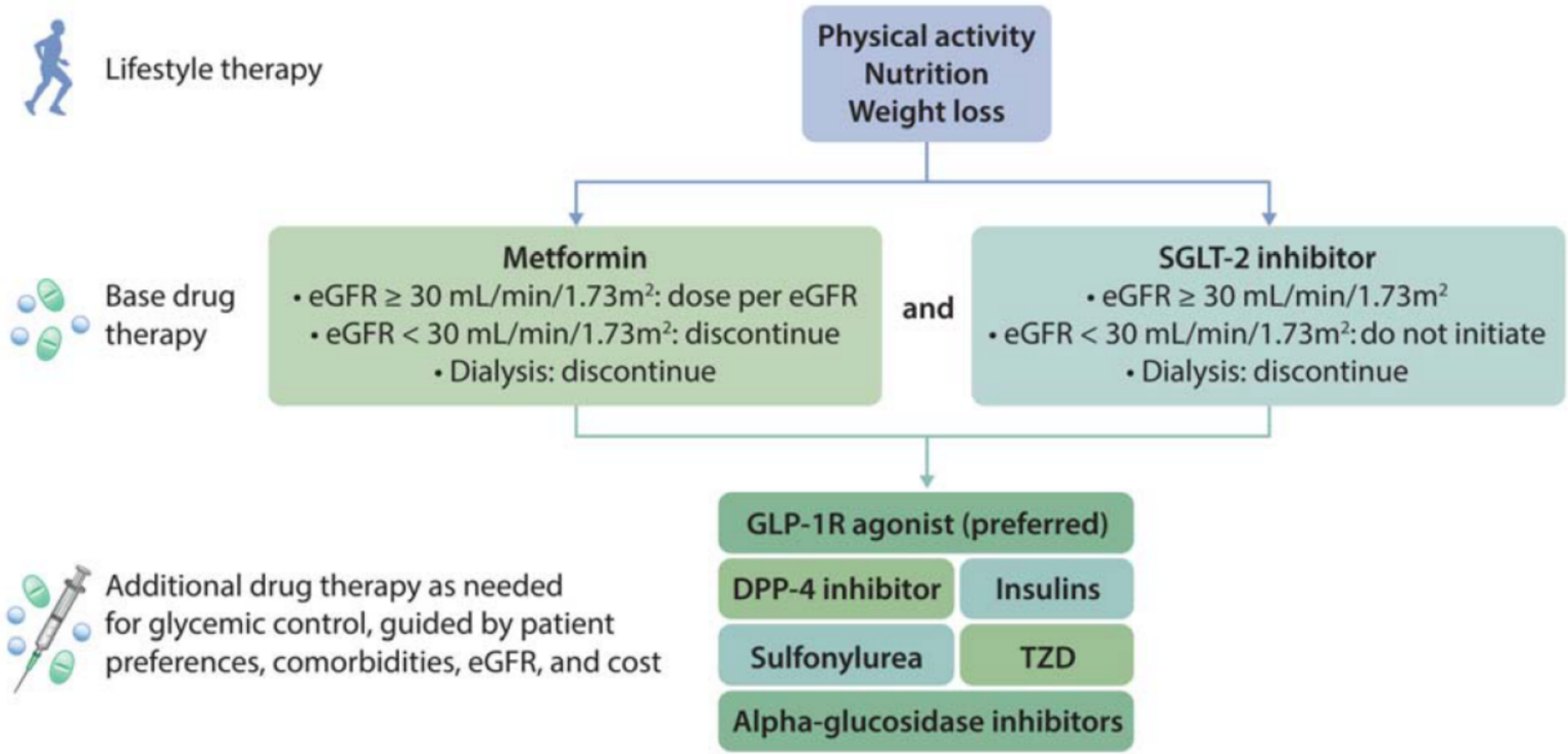

Lifestyle therapy
Physical activity
Nutrition
Weight loss
Base drug therapy
Metformin
• eGFR ≥ 30 mL/min/1.73m²: dose per eGFR
• eGFR < 30 mL/min/1.73m²: discontinue
• Dialysis: discontinue
and
SGLT-2 inhibitor
• eGFR ≥ 30 mL/min/1.73m²
• eGFR < 30 mL/min/1.73m²: do not initiate
• Dialysis: discontinue
GLP-1R agonist (preferred)
DPP-4 inhibitor
Insulins
Sulfonylurea
TZD
Alpha-glucosidase inhibitors
Additional drug therapy as needed for glycemic control, guided by patient preferences, comorbidities, eGFR, and cost

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

- In and eGFR ≥30 ml/min/1.73 m2, it's recommend as an antihyperglycemic treatment regimen (1A).

- Can be added to other antihyperglycemic medications if glycemic targets are not currently met and for patients who are meeting glycemic targets but can safely attain a lower target

- May increase risk for hypoglycemia (in patient who treated with insulin or sulfonylureas and currently meeting glycemic targets)
- It may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

Choice of SGLT2i should prioritize agents with documented kidney or cardiovascular benefits

Reasonable to withhold SGLT2i

- During times of prolonged fasting
- Critical medical illness (when patients may be at greater risk for ketosis)

If a patient is at risk for hypovolemia:

- Consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i
- Advising patients about symptoms of dehydration and low blood pressure
- Follow up volume status after drug initiation

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

- A reversible decrease in eGFR with commencement of SGLT2i may occur
- Not an indication to discontinue therapy
- Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if eGFR falls below 30 ml/min/1.73 m2
- Unless reversible changes in eGFR are precipitating uremic symptoms or other complications of CKD

SGLT-2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials
Dapagliflozin	5–10 mg once daily	No dose adjustment if eGFR ≥ 45 mL/min/1.73m^2 Not recommended with eGFR < 45 mL/min/1.73m^2 Contraindicated with eGFR < 30 mL/min/1.73m^2
Empagliflozin	10–25 mg once daily	No dose adjustment if eGFR ≥ 45 mL/min/1.73m^2 Avoid use, discontinue with eGFR persistently < 45 mL/min/1.73m^2
Canagliflozin	100–300 mg once daily	No dose adjustment if eGFR > 60 mL/min/1.73m^2 100 mg daily if eGFR 30–59 mL/min/1.73m^2 Avoid initiation with eGFR < 30 mL/min/1.73m^2, discontinue dialysis

Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

Is recommended in patients

- **Who have not achieved individualized glycemic targets despite use of metformin SGLT2i,**
- **Who are unable to use those medications**

It's recommend a a long acting GLP-1 RA(1B)

To minimize GI side effects, start with a low dose and titrate up slowly

Should not be used in combination with DPP-4 inhibitors

The risk of hypoglycemia is generally low when used alone
Risk of hypoglycemia is increased with other medications such assulfonylureas or insulin.

The doses of sulfonylurea and/or insulin may need to be reduced

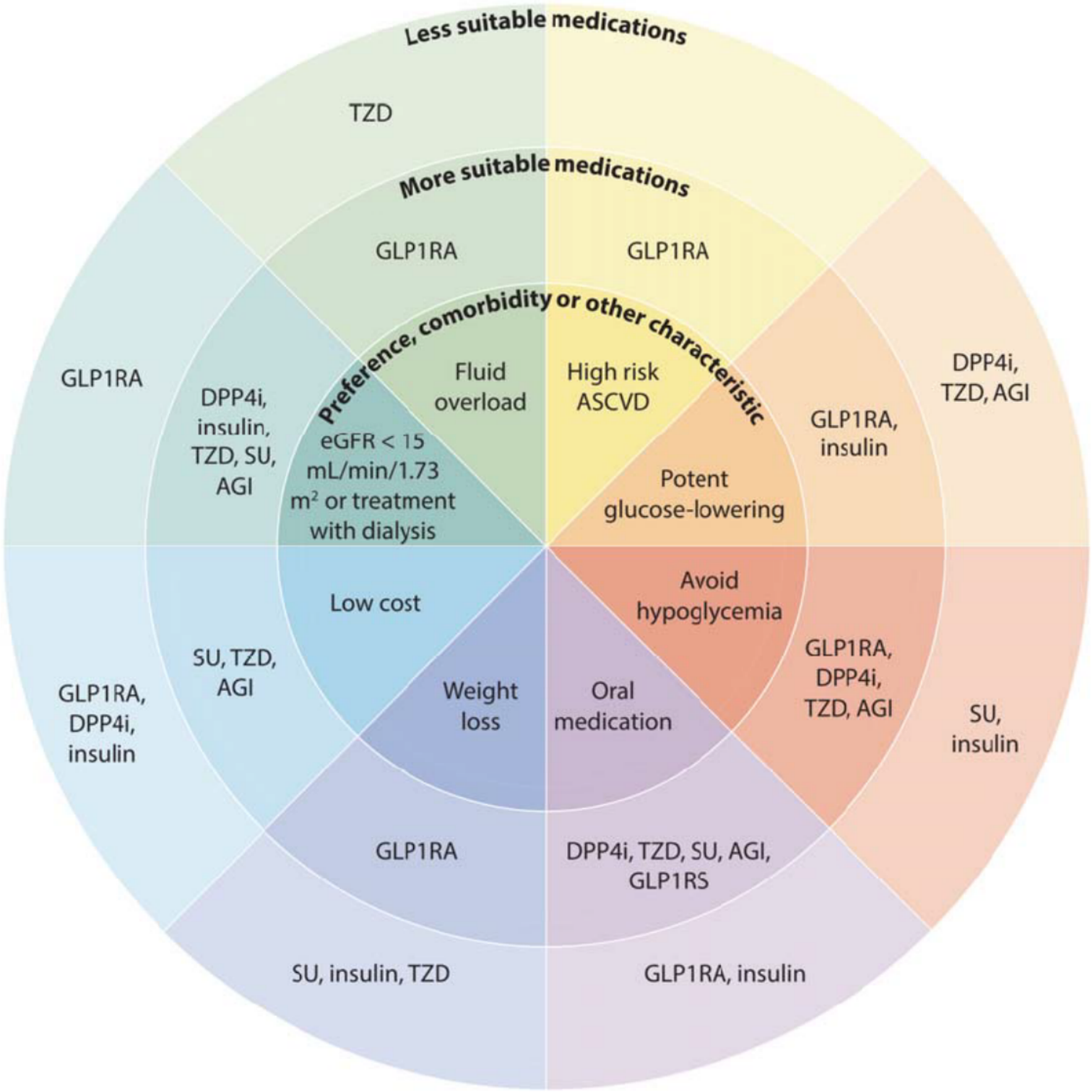
Table 11. Dosing for available GLP-1 RA agents and dose modification for CKD

GLP-1 receptor agonist	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR > 15 mL/min/1.73m^2
Exenatide	10 µg twice daily	Use with CrCl > 30 mL/min
Exenatide Extended-Release	2 mg once weekly	Use with CrCl > 30 mL/min
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

Table 6. Overview of selected large, placebo-controlled clinical outcomes trials assessing the benefits and harms of SGLT2 inhibitors, GLP-receptor agonists, and DPP-4 inhibitors

			Primary outcome		Kidney outcomes		
Drug	**Trial**	**Kidney-related eligibility criteria**	**Primary outcome**	**Effect on primary outcome**	**Effect on albuminuria or albuminuria-containing composite outcome**	**Effect on GFR loss***	**Adverse effects**
SGLT2 inhibitors							
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR > 300 mg/g and eGFR 30–90 ml/min/1.73 m²	Progression of CKD†	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥ 60 ml/min/1.73 m²	MACE composite of HF and cardiovascular death‡	ND/↓	↓	↓↓	Genital mycotic infections, DKA
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	↓	ND	None notable
Liraglutide	LEADER	eGFR ≥ 15 ml/min/1.73 m²	MACE	↓	↓	ND	GI
Semaglutide	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER-6	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	None notable
Albiglutide	HARMONY	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	NA	NA	None notable
Dulaglutide	REWIND	eGFR ≥ 15 ml/min/1.73 m²	MACE	↓	↓	↓	GI
DPP-4 inhibitors							
Saxagliptin	SAVOR-TIMI 53	eGFR ≥ 15 ml/min/1.73 m²	MACE	ND	↓	ND	HF
Alogliptin	EXAMINE	Patients treated with dialysis excluded	MACE	ND	NA	NA	None notable
Sitagliptin	TECOS	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	None notable
Linagliptin	CARMELINA	eGFR ≥ 15 ml/min/1.73 m²	Progression of CKD†	ND	↓	ND	None notable

‡Significant reduction in risk, with HR estimate >0.7 and 95% confidence interval not overlapping 1


Less suitable medications
TZD
More suitable medications
GLP1RA
GLP1RA
Preference, comorbidity or other characteristic
Fluid overload
High risk ASCVD
eGFR < 15 mL/min/1.73 m² or treatment with dialysis
Potent glucose-lowering
Low cost
Avoid hypoglycemia
Weight loss
Oral medication
GLP1RA
DPP4i, TZD, SU, AGI, GLP1RS
SU, insulin, TZD
GLP1RA, insulin
GLP1RA
DPP4i, insulin, TZD, SU, AGI
SU, TZD, AGI
GLP1RA, DPP4i, insulin
GLP1RA, insulin
DPP4i, TZD, AGI
GLP1RA, DPP4i, TZD, AGI
SU, insulin

APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD

A structured self-management educational program be implemented for care of people with diabetes and CKD

Team-based integrated care

A structured self-management educational program be implemented for care of people with diabetes and CKD

Team-based integrated care

Figure 19. Team-based integrated care delivered by physicians and non-physician personnel supported by decision- makers