Diabetic CKD

GP Symposium 2020
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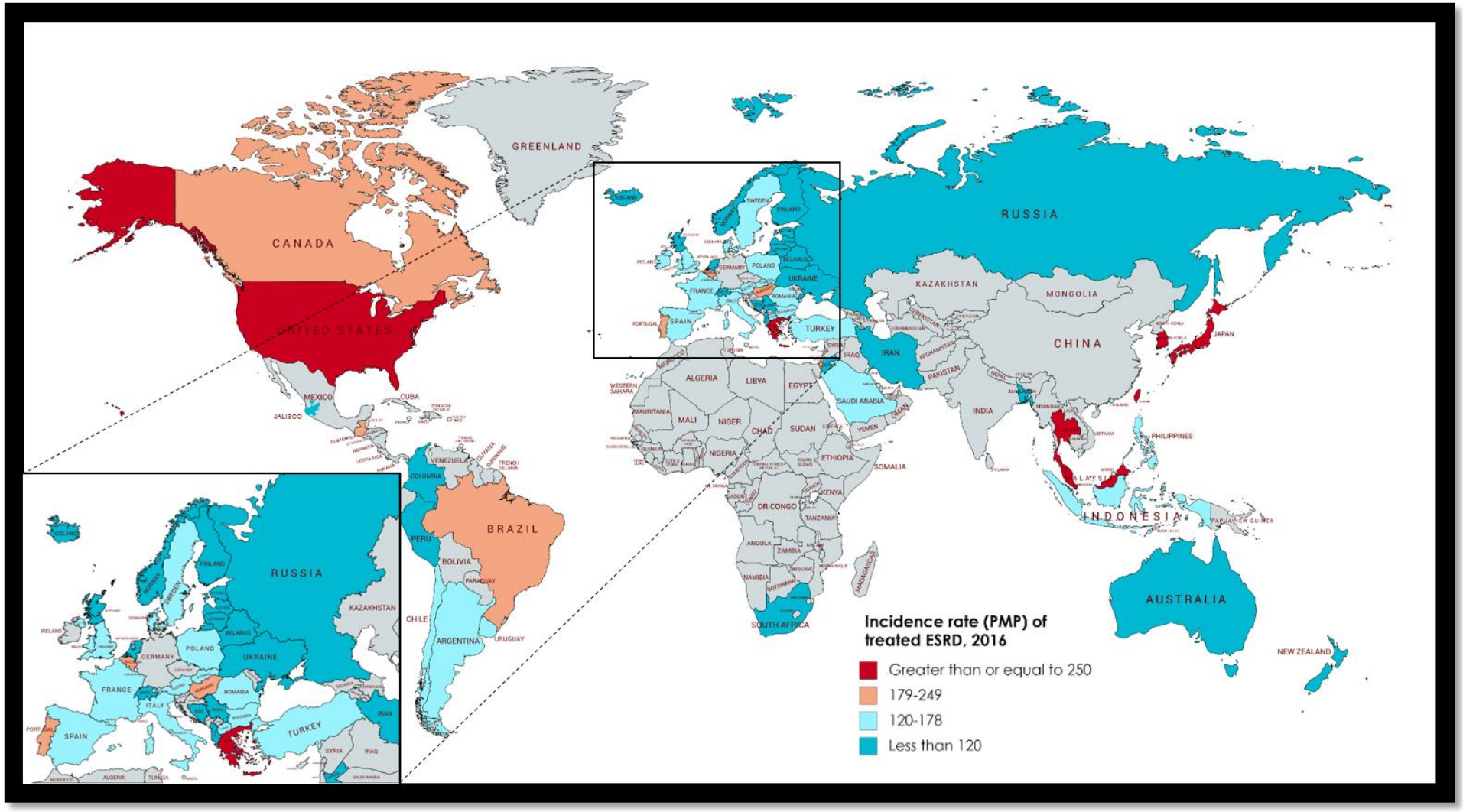
Renal Physician

Introduction

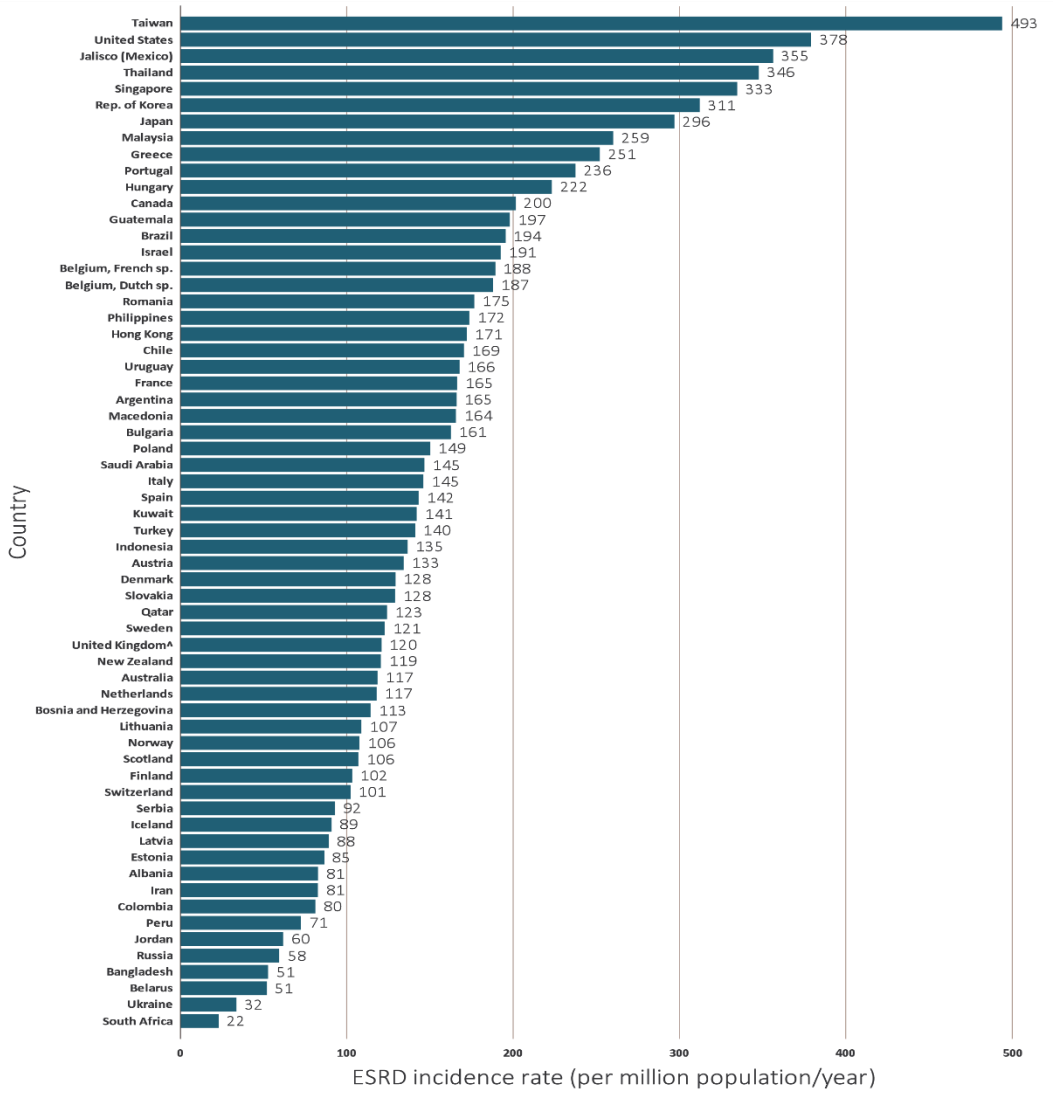
- CKD is global health problem
- Diabetes has reached epidemic proportion, >8% (350 millions)
- Expected to grow 550 millions by 2035
- >40% will likely to develop CKD with significant number will develop ESRD
- Many new agents targeting variety of mechanistic approaches to improve outcomes

vol 2 Figure 11.1 Geographic variation in the incidence rate of treated ESRD (per million population), by country, 2016



Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information was available. Data unavailable for countries pictured above in gray. All rates are unadjusted. Data for Belarus from 43 of 51 RRT centers. Data for Canada exclude Quebec. Data for France exclude Martinique. Data for Guatemala exclude pediatric ESRD patients and patients receiving non-institutional RRT. Data for Indonesia represent the West Java region. Data for Italy representative of 35% (7 out of 19 regions) of ESRD patient population. Japan includes dialysis patients only. Data from Latvia representative of 80% of ESRD patient population. Data for Serbia approx. 30% less than reported in 2015 due to incomplete reporting. United Kingdom: England, Wales, Northern Ireland (Scotland data reported separately). Abbreviation: ESRD, end-stage renal disease. NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.

vol 2 Figure11.2 Incidence rate of treated ESRD (per million population), by country, 2016



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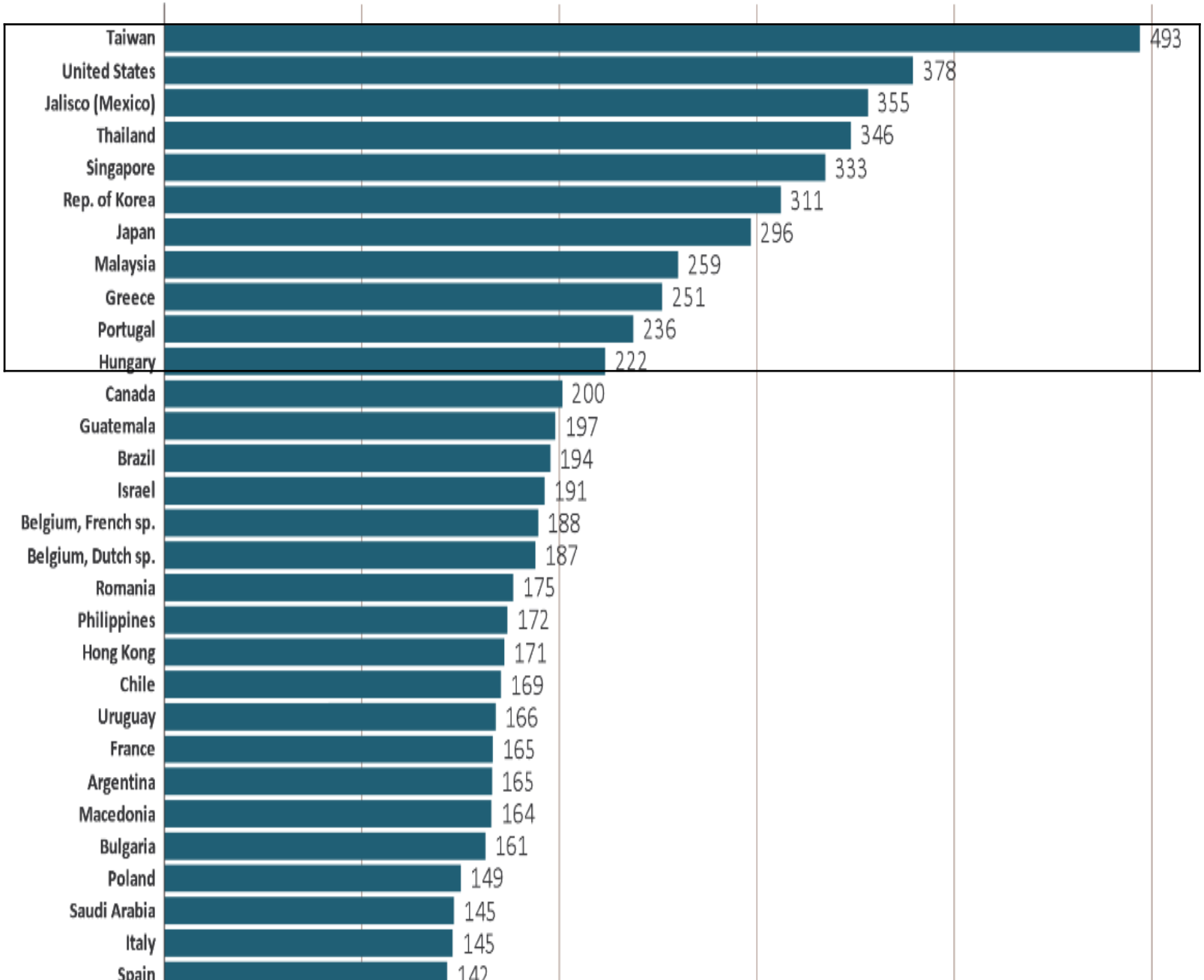
Taiwan 493
United States 378
Jalisco (Mexico) 355
Thailand 346
Singapore 333
Rep. of Korea 311
Japan 296
Malaysia 259
Greece 251
Portugal 236
Hungary 222
Canada 200
Guatemala 197
Brazil 194
Israel 191
Belgium, French sp. 188
Belgium, Dutch sp. 187
Romania 175
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CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is <u>defined</u> as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is <u>classified</u> based on <u>C</u>ause, <u>G</u>FR category (G1-G5), and <u>A</u>lbuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
	G1	Normal or high	□ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	< 15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Comprehensive diabetes and CKD management

- Complex, multidisciplinary, cross functional team effort
- General Practice, diabetology to nephrology
- Multi-morbidity is common, care usually involves many other speciality
- ***Structured education*** is critical for self-management (monitored, individualized and evaluated)
- At risk of acute diabetes related complication as well as long-term complications (micro/macrovascular)
- Cardiovascular risk factors hypertension, dyslipidemia, obesity, life style factors diet, smoking and physical activity
- Studies demonstrated benefit of multifactorial intervention on micro/macrovascular complications and mortality

Diabetes with CKD: cardio-kidney treatment


Glycemic control including SGLT2 inhibitors


RAAS blockade


Blood pressure control


Lipid management


Lifestyle/physical activity

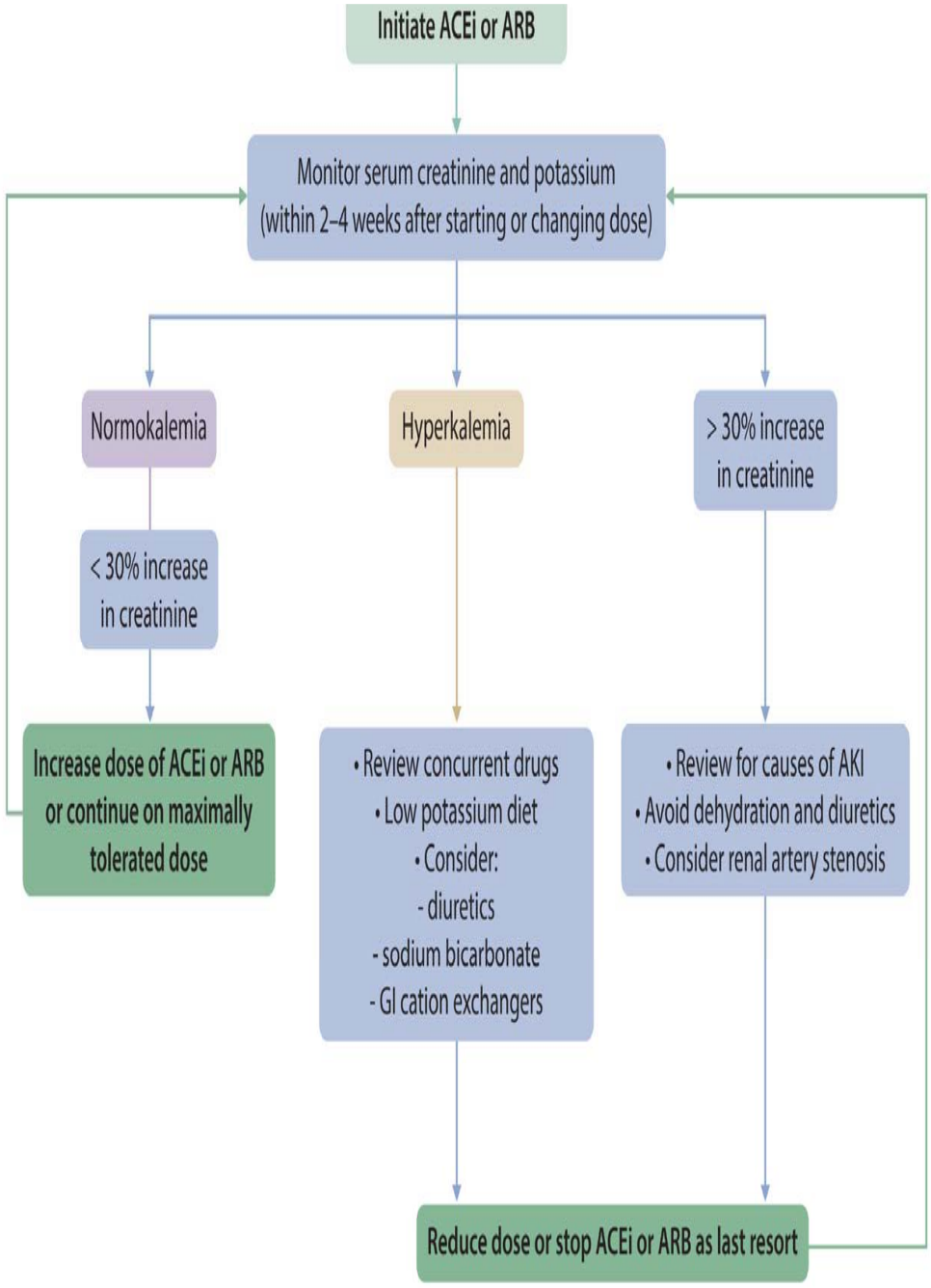

Smoking cessation


Nutrition


Aspirin for prevalent cardiovascular disease

RAAS Blockage

- ACEi or ARB be initiated in patients with diabetes, hypertension and albuminuria
- Monitor BP, serum Cr, K+ (2 weeks)
- Continue unless Cr rises by 30%
- Advise contraception in women
- Hyperkalemia – managed by measure to reduce K+
- Reduce or discontinue - symptomatic hypotension, uncontrolled hyperkalemia
- Combination of ACEi, ARB or direct renin inhibitor is potentially harmful
- Mineralocorticoid recepptor antagonists – effective for refractory hypertension but may cause decline in eGFR or hyperlalemia



Abbreviations: ACEi = angiotensin-converting enzyme inhibitor, AKI = acute kidney injury, ARB = angiotensin II receptor blockade, GI = gastrointestinal

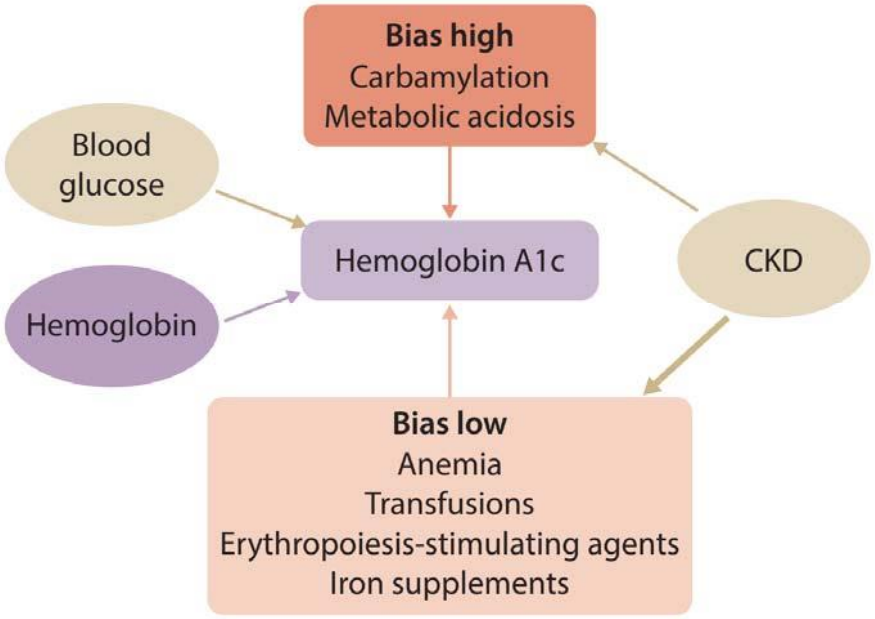
Smoking cessation

- Remains leading cause of death and known risk factor for development of CKD
- No RCTs, observational studies have highlighted harmful cardiovascular effects
- Electronic Nicotine Delivery System (e-cigarettes) have been reported to increase risk of lung and CVD
- Also reduce exposure to second hand smoke

Glycemic Monitoring

- HbA1c standard of care for long-term glycemic monitoring in T1 and T2 D, 2 – 4 times per year
- Accuracy and precision of HbA1c declines with advanced CKD, particularly patients on dialysis
- Continuous glucose management Indicator can be used when HbA1c is not concordant
- Self-monitoring of blood glucose (SMBG) or Continuous glucose monitoring (CMG) may help to prevent hypoglycemia
- CMG devices are rapidly evolving

Figure 3. Effects of CKD-related factors on advanced glycation end-products and glycemic biomarkers



CKD = chronic kidney disease

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

CGMI = continuous glucose management indicator, HbA1c = hemoglobin A1c

Table 3. Relationship of anti-hyperglycemic drug choice to risk of hypoglycemia and rationale for SMBG or CGM

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

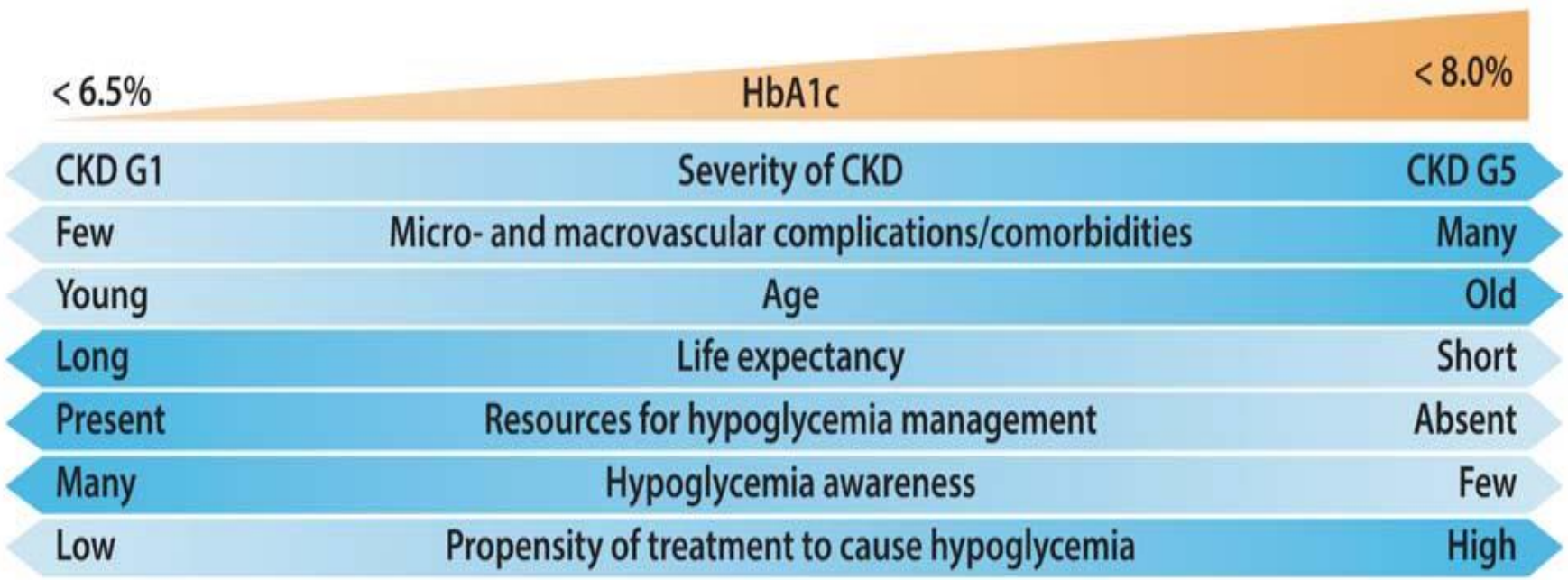
Glycemic Targets

- Main harm associated with lower HbA1c – hypoglycemia
- ACCORD (T2 D) mortality was also higher among patients with lower HbA1c
- Diabetic CKD – U-shaped association of HbA1c with adverse outcome has been observed (studies with anti-hyperglycemic agents)
- RCTs- individualized HbA1c <6.5% to <8% for patients with diabetes and non-dialysis dependent CKD (48 – 64 mmol/mol)

Glycemic Targets

- Safe achievement of lower HbA1c <6.5% may be facilitated by SMBG or CGM and selection of anti-hyperglycemic agents that are not associated with hypoglycemia
- CGM metric (time in range and time in hypoglycemia) may be considered as alternatives to HbA1c in some patients

Figure 4. Factors potentially guiding decisions on individual HbA1c targets



HbA1c CONVERSION CHART

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
5.0	31	6.0	42	**7.0**	**53**	8.0	64	9.0	75
5.1	32	6.1	43	7.1	54	8.1	65	9.1	76
5.2	33	6.2	44	7.2	55	8.2	66	9.2	77
5.3	34	6.3	45	7.3	56	8.3	67	9.3	78
5.4	36	6.4	46	7.4	57	8.4	68	9.4	79
5.5	37	**6.5**	**48**	**7.5**	**58**	8.5	69	9.5	80
5.6	38	6.6	49	7.6	60	8.6	70	9.6	81
5.7	39	6.7	50	7.7	61	8.7	72	9.7	83
5.8	40	6.8	51	7.8	62	8.8	73	9.8	84
5.9	41	6.9	52	7.9	63	8.9	74	9.9	85

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
10.0	86	11.0	97	12.0	108	13.0	119	14.0	130
10.1	87	11.1	98	12.1	109	13.1	120	14.1	131
10.2	88	11.2	99	12.2	110	13.2	121	14.2	132
10.3	89	11.3	100	12.3	111	13.3	122	14.3	133
10.4	90	11.4	101	12.4	112	13.4	123	14.4	134
10.5	91	11.5	102	12.5	113	13.5	124	14.5	135
10.6	92	11.6	103	12.6	114	13.6	125	14.6	136
10.7	93	11.7	104	12.7	115	13.7	126	14.7	137
10.8	95	11.8	105	12.8	116	13.8	127	14.8	138
10.9	96	11.9	107	12.9	117	13.9	128	14.9	139

IFCC-HbA_{1c} (mmol/mol) = [DCCT-HbA_{1c} (%)−2.15] × 10.929

Abbreviations: DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.

Source: Diabetes UK, www.diabetes.org.uk.

LIFE STYLE INTERVENTION

Nutritional Intake

- RCTs few and small number of patients for nutritional intake
- Should consume diet in high in vegetables, fruits, whole grains, fibers, legumes, plant based proteins, unsaturated fats and nuts
- Lower in processed meat, refined carbohydrate, and sweetened beverages
- Protein intake of 0.8g per kg/day for diabetic non-dialysis CKD
- Protein intake of 1 to 1.2 g/kg/day for patients on dialysis particularly on PD

Nutritional Intake

- Sodium <2 g/day or Sodium Chloride <5 g/day
- Shared decision making is corner stone
- Dietitian, diabetic educator, counselor, other healthcare providers
- Should consider cultural differences, food resources, cooking skills, intolerances, *cost*

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

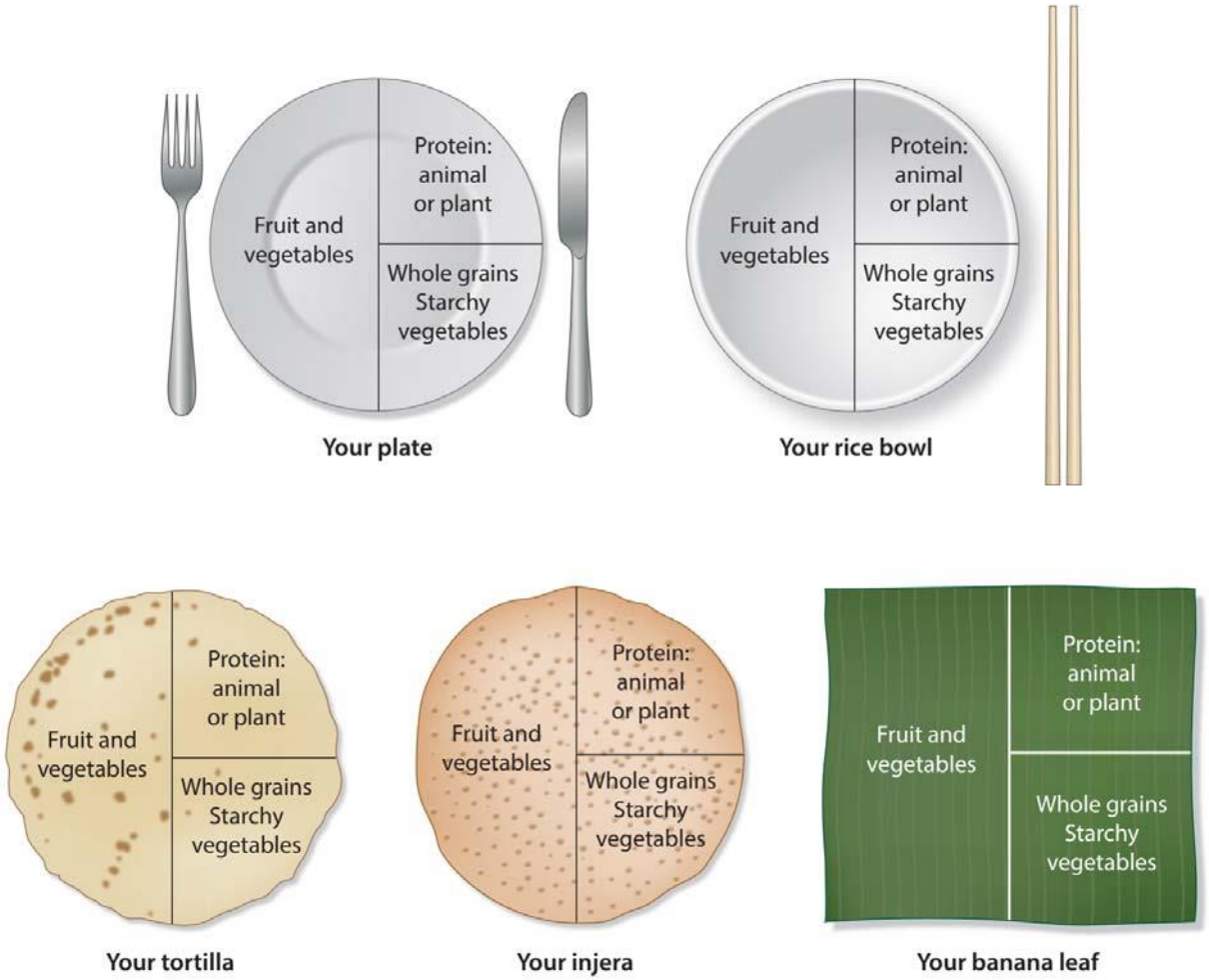


Table 4. Protein guideline for adults with diabetes and non-dialysis CKD

Weight (kg)	35	40	50	55	60	65	70	75	80	85	90	95	100
Grams of protein per day (wt × 0.8 g/kg)	28	32	40	44	48	52	56	60	64	68	72	76	80

Figure 6. Average protein content of foods in grams

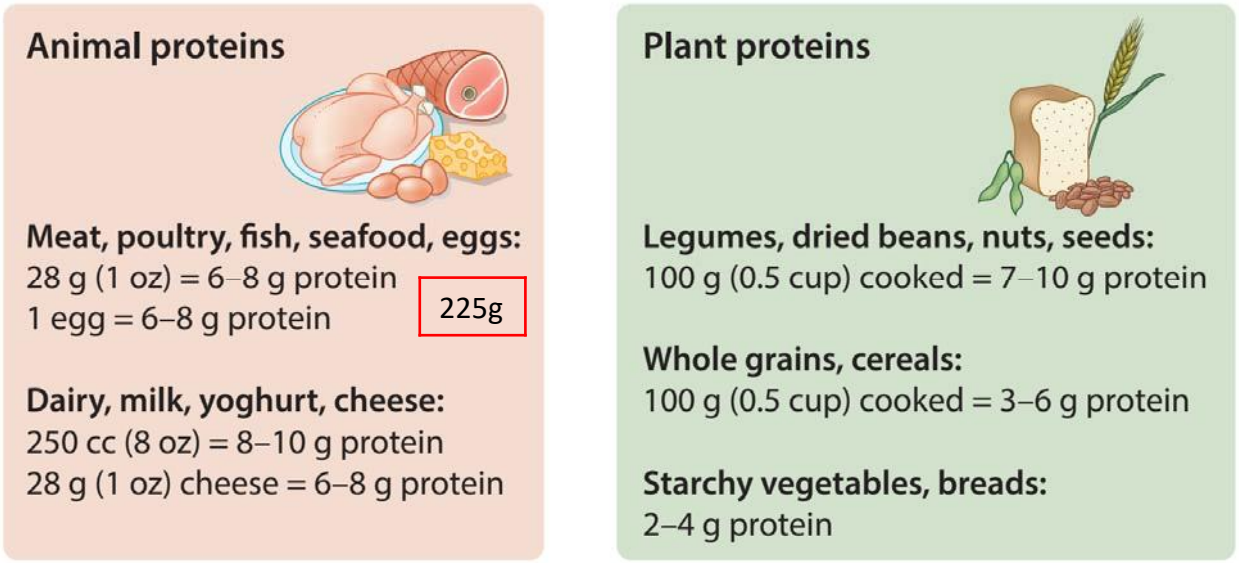


Figure 7. Effects of decreased sodium intake on various outcomes and accompanying quality of evidence[185]

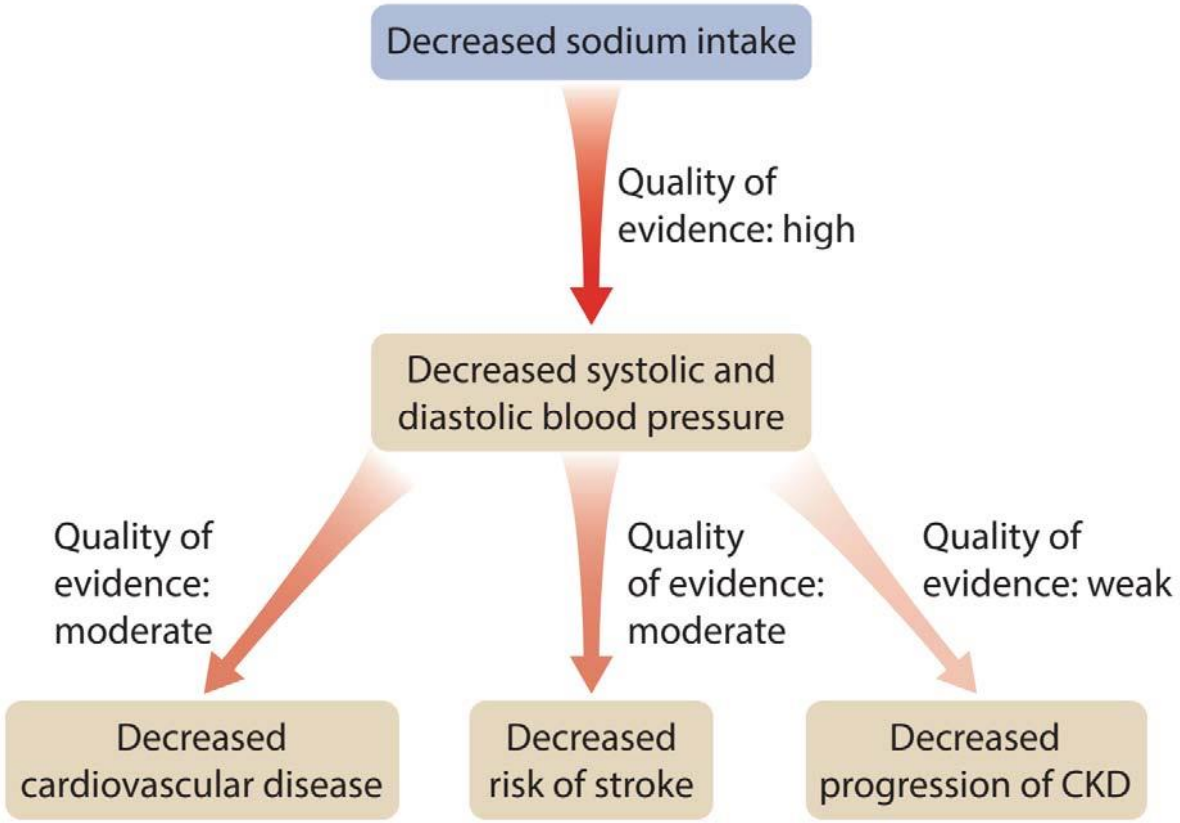
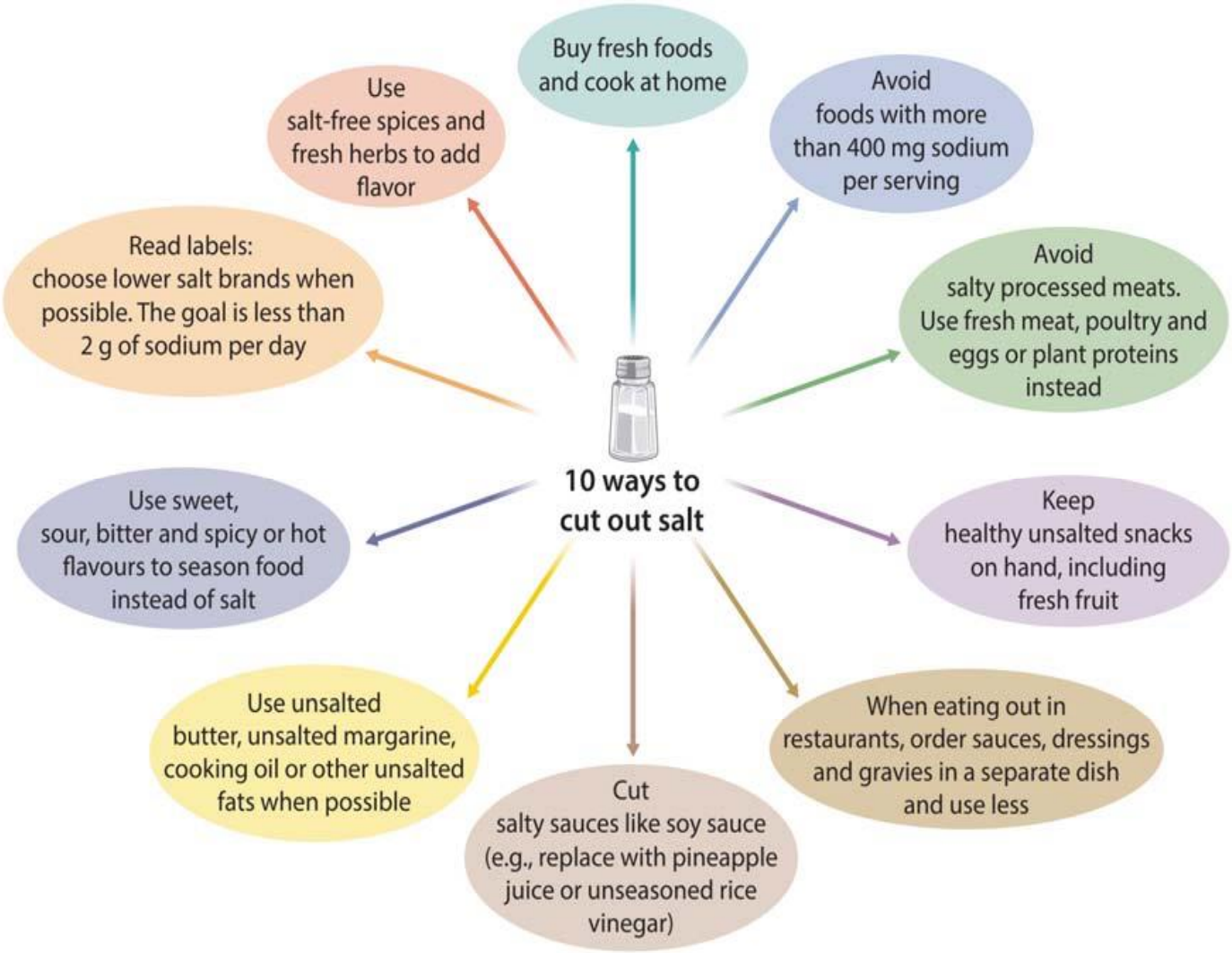


Figure 8. Ten ways to cut out salt



Physical Activity

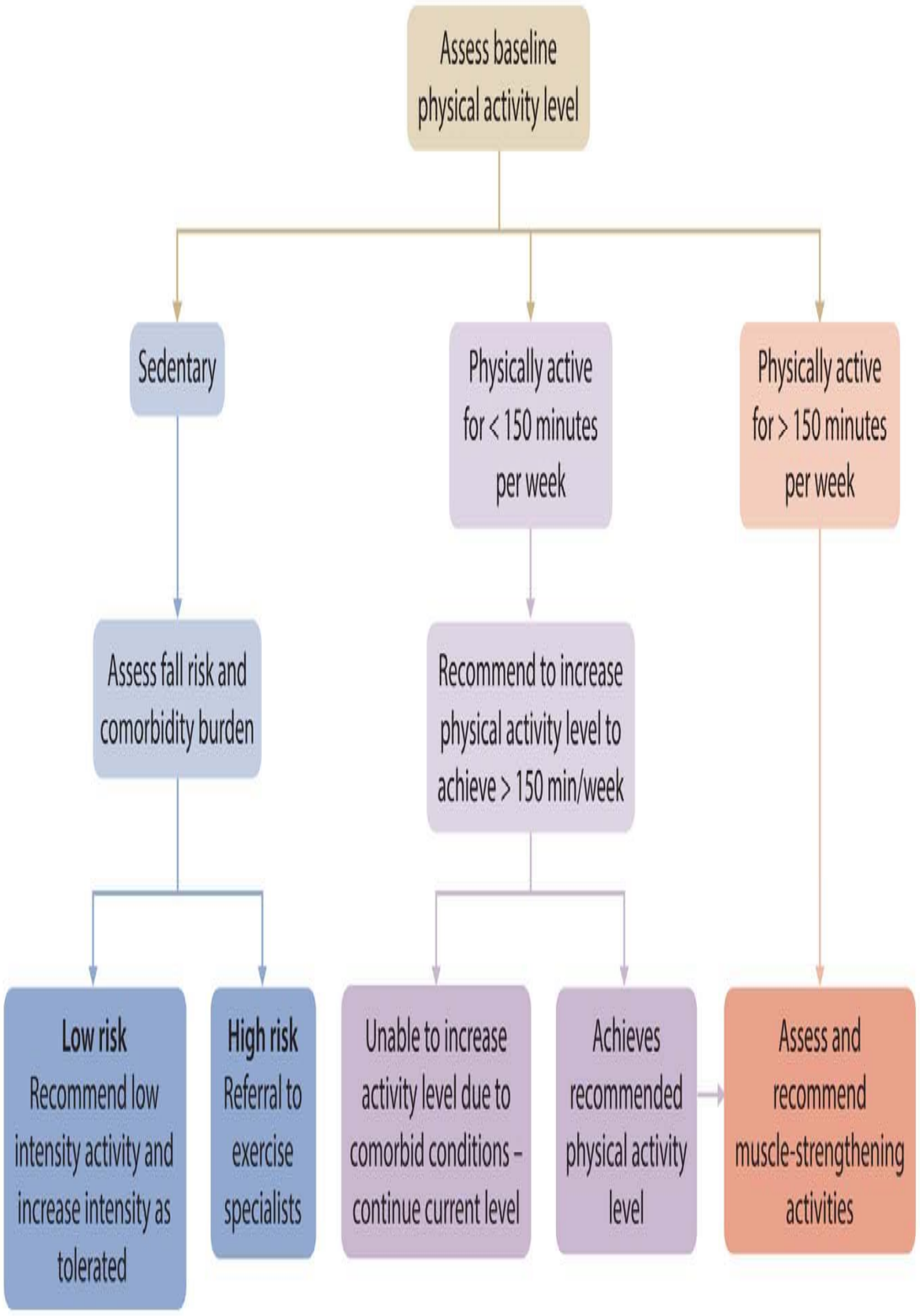
- Improves insulin sensitivity, lowers inflammatory markers and improves endothelial function
- Moderate-intensity physical activity at least 150 minutes per week or to a level compatible with their cardiovascular and physical tolerance
- Consider age, ethnic background, comorbidities, access to resources
- Avoid sedentary behavior
- Patients with hgih risk for fall may need special advice
- Weight loss particularly patients with eGFR>30 ml/min/1.73m2

Table 5. Examples of various levels of physical activity and their associated metabolic equivalent (MET)

Intensity of physical activity	METS	Examples
Sedentary	< 1.5	Sitting, watching television, reclining
Light	1.6 – 2.9	Slow walking, household work such as cooking, cleaning
Moderate	3.0 – 5.9	Brisk walking, biking, yoga, swimming
Vigorous	> 6	Running, biking, swimming, lifting heavy weights

* A metabolic equivalent, or MET, is a unit useful for describing the energy expenditure of a specific activity. MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest.

Figure 10. Suggested approach to address physical inactivity and sedentary behavior in CKD

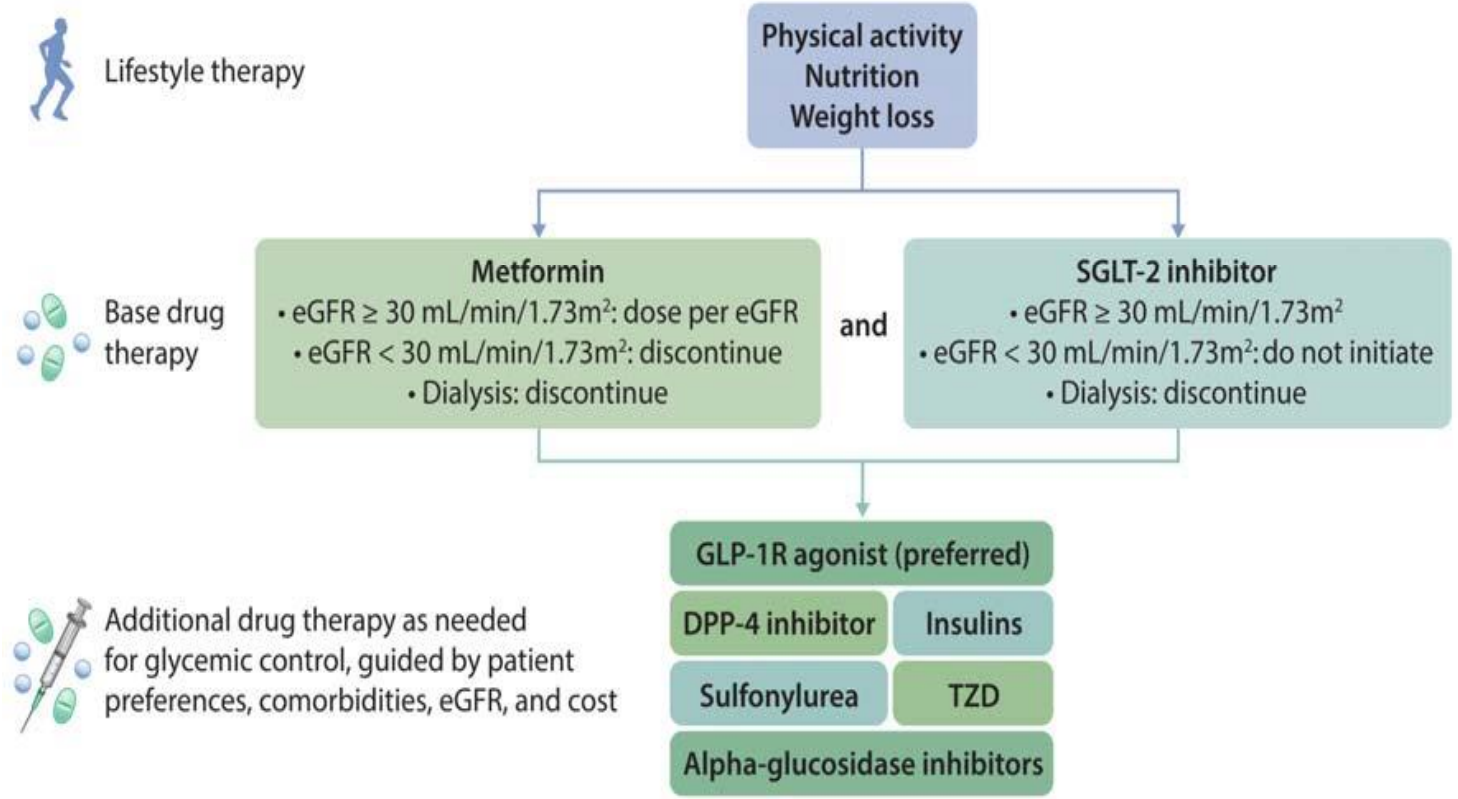


CKD = chronic kidney disease

Anti-Glycemic Therapies

- Should include life style therapy, base drug therapy with metformin & SGLT-2i and additional drug therapy as needed for glycemic control

Figure 11. Glycemic treatment algorithm for patients with T2D and CKD



CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1R = glucagon-like peptide-1 receptor; SGLT2 = sodium–glucose cotransporter 2; T2D = type 2 diabetes; TZD = thiazolidinedione

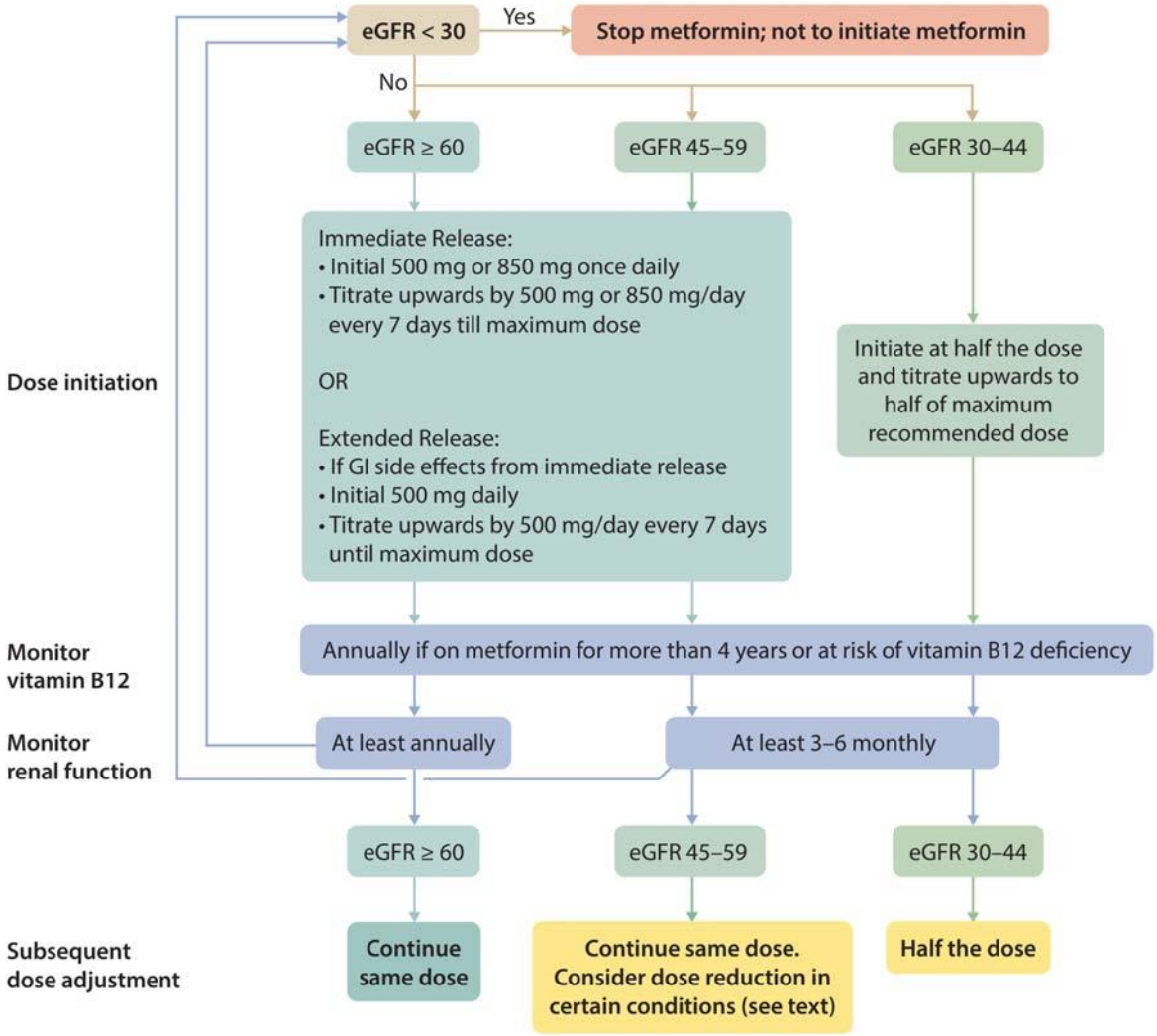
Metformin

- Metformin – effective anti-glycemic agent, shown to be effective in reducing HbA1c in T2D with low risk of hypoglycemia (UKPDS)
- Comparable with thiazolinediones and sulfonylurea, more effective than DDP-4i
- Effective in preventing weight gain
- May be associated with protective effects against cardiovascular events
- Risk of lactic acidosis with metformin is inconsistent in CKD (30 to 60ml/min)

Metformin

- Less robust data with renal transplant patients with T2D – same approach with CKD recommended
- Monitor eGFR and increase frequency when eGFR <60 ml/min
- Adjust dose when eGFR <60 ml/min and stop <30 ml/min
- Monitor B12 deficiency in patients treated with Metformin for > 4 years

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



eGFR, estimated glomerular filtration rate; GI, gastrointestinal

SGLT-2 inhibitors

- Lower blood sugar by inhibiting tubular reabsorption of glucose
- Diuretic effect by osmotic diuresis from glycosuria
- In RCTs SGLT-2i confer modest lowering of HbA1c(0.3-0.6%), sys BP (3-4 mmHg), Dia BP (1-2 mmHg) and weight loss 08-2 kg)
- Substantial reductions in both composite cardiac and renal outcomes
- Appear independent of glucose lowering
- Safety and efficacy – eGFR <30 not yet demonstrated

SGLT-2inhibitors

- SGLT-2i beneficial in T2D, eGFR >30ml/min
- RCTs include patients eGFR 30 ml/min
- Both cardiac and renal outcomes, large patient groups, reasonable follow up time
- Efficacy and safety are consistent across eGFR down to this threshold
- Meaningful kidney outcomes beyond proteinuria
- Updated meta-analysis from 4 major RCTs (39,000 with T2D), reduced risk of dialysis, transplant or kidney death by 30% [RR 0.67 (95% CI 0.53-0.86)]

Table 8. Cardiovascular and kidney outcome trials for SGLT2 inhibitors

	EMPA-REG	CANVAS	DECLARE	CREDENCE	DAPA-HF
Drug	Empagliflozin 10mg, 25 mg once daily	Canagliflozin 100 mg, 300 mg once daily	Dapagliflozin 10 mg once daily	Canagliflozin 100 mg once daily	Dapagliflozin 10 mg once day versus placebo
Total of participants	7,020	10,142	17,160	4,401	4,474
N (%) with T2D	7,020 (100%)	10,142 (100%)	17,160 (100%)	4,401 (100%)	2,139 (45%)
N (%) with CVD	7,020 (100%)	6,656 (66%)	6,974 (41%)	2220 (50%)	4,474 (100%) with HFrEF
eGFR criteria for enrollment	≥ 30 mL/min/1.73m^2	≥ 30 mL/min/1.73m^2	CrCl ≥ 60 mL/min, 45% had eGFR 60–90	30–90 mL/min/1.73m^2, ACR <300–5000 mg/g	≥ 30 mL/min/1.73m^2
Mean eGFR at enrollment (mL/min/1.73m^2)	74	76	85	56	66
N (%) with eGFR < 60	1,819 (26%)	2,039 (20%)	1,265 (7.4%)	40%	1926 (41%)
ACR	No criteria. ACR <30 mg/g in 60%; 30-300 mg/g in 30%; >300 mg/g in 10%	No criteria. Median ACR 12.3 mg/g	No criteria	Median ACR 927 mg/g	
Follow-up (median, yrs)	3.1	2.4	4.2		1.5
Primary outcome	MACE	MACE	MACE	Composite kidney	CV death, HF hospitalization, urgent HF
CV outcome results	MACE: [HR 0.86 (0.74, 0.99)]; hospitalization for HF [HR 0.65 (0.50, 0.85)]	MACE: [HR 0.86 (0.75, 0.97); hospitalizations for HF [HR 0.67 (0.52, 0.87)	MACE [0.93; 0.84, 1.03)]; CV death or hospitalization fo HF [HR 0.83 (0.73, 0.95)]	CV death, MI, stroke: [HR 0.80 (0.67, 0.95)]; Hospitalization for HF: [HR 0.61 (0.47, 0.80)]	Primary: HR 0.74 (95% CI 0.65, 0.85)]
Kidney outcome	Incident or worsening nephropathy (progression to severely increased albuminuria, doubling of SCr, initiation of KRT, or kidney death) and incident albuminuria	Composite doubling in SCr, ESKD, or death from kidney causes	Composite of ≥ 40% decrease in eGFR to < 60, ESKD, CV or kidney death	Composite of ESKD, doubling SCr, or death from kidney or CV causes	Worsening kidney function (defined as ≥ 50% reduction in eGFR, ESKD, or kidney death)
Kidney outcome results	Incident/worsening nephropathy: 12.7% vs. 18.8% in canagliflozin vs. placebo. [HR 0.61 (0.53, 0.70)] Incident albuminuria: NS	Composite kidney: 1.5 vs. 2.8 1000 patient-years in the canagliflozin vs. placebo; [HR 0.53 (0.33, 0.84)]	Composite kidney [HR 0.76 (0.67, 0.87)	Primary kidney: HR 0.70 (0.59, 0.82)	HR 0.71 (0.44, 1.16), p=0.17

Table 6. Overview of selected large, placebo-controlled clinical outcomes trials assessing the benefits and harms of SGLT2 inhibitors, GLP-1 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 m^2	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥ 30 ml/min/1.73 m^2	MACE	↓	↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR > 300 mg/g and eGFR 30–90 ml/min/1.73 m^2	Progression of CKD†	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥ 60 ml/min/1.73 m^2	MACE composite of HF and cardiovascular death‡	ND/↓	↓	↓↓	Genital mycotic infections, DKA
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥ 30 ml/min/1.73 m^2	MACE	ND	↓	ND	None notable
Liraglutide	LEADER	eGFR ≥ 15 ml/min/1.73 m^2	MACE	↓	↓	ND	GI
Semaglutide	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER-6	eGFR ≥ 30 ml/min/1.73 m^2	MACE	ND	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥ 30 ml/min/1.73 m^2	MACE	ND	NA	NA	None notable
Albiglutide	HARMONY	eGFR ≥ 30 ml/min/1.73 m^2	MACE	↓	NA	NA	None notable
Dulaglutide	REWIND	eGFR ≥ 15 ml/min/1.73 m^2	MACE	↓	↓	↓	GI
DPP-4 inhibitors							
Saxagliptin	SAVOR-TIMI 53	eGFR ≥ 15 ml/min/1.73 m^2	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 m^2	MACE	ND	NA	NA	None notable
Linagliptin	CARMELINA	eGFR ≥ 15 ml/min/1.73 m^2	Progression of CKD†	ND	↓	ND	None notable

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

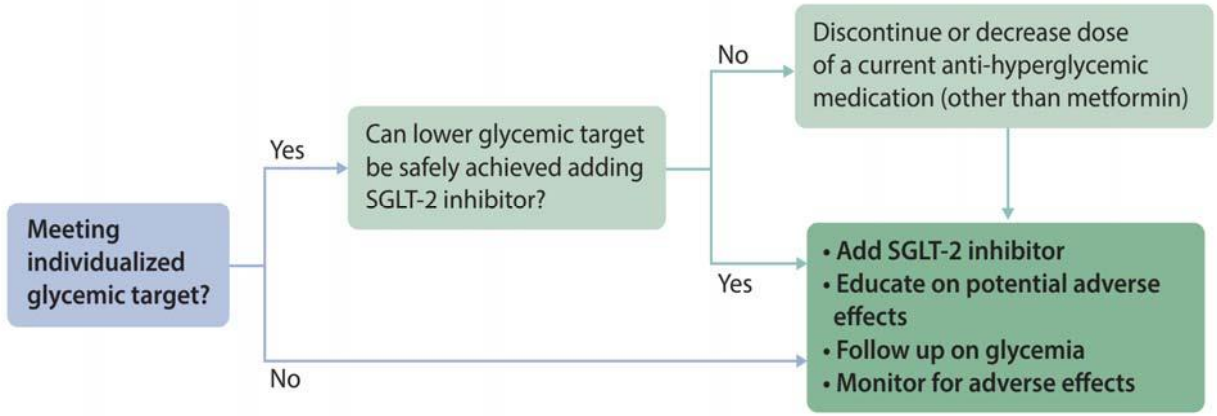
SGLT-2i

- T2D, CKD and eGFR >30 ml/min – include SGLT-2i in anti-glycemic treatment regime
- Can be added to other anti-hyperglycemic medications – glycemic targets are not met or to safely attain lower target
- May increase risk of hypoglycemia (insulin, sulfonylurea), may reduce dose to facilitate addition of SGLT-2i
- Choice of SGLT-2i – kidney or cardiovascular benefits + eGFR

SGLT-2i

- Withhold SGLT-2i during prolonged fasting or critical medical illness
- Consider decreasing diuretic before commencing SGLT-2i (risk of hypovolemia)
- Reversible decrease in eGFR may occur (not an indication to stop)
- Once initiated, can continue SGLT-2i even if eGFR falls below 30ml/min
- No enough data in kidney transplant patients

Figure 14. Algorithm for initiation of SGLT2i therapy for patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2, who are already treated with anti-hyperglycemic medications



CKD = chronic kidney disease, DPP-4i = dipeptidyl peptidase inhibitor, eGFR = estimated glomerular filtration rate, GLP-1 RA = glucagon-like peptide-1 receptor agonist, SGLT2 = sodium–glucose cotransporter 2, T2D = type 2 diabetes.

Table 9. SGLT2i with established kidney and cardiovascular benefits and doses adjustments as approved by FDA (be aware of country-to-country variation)

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

eGFR = estimated glomerular filtration rate, FDA = Food and Drug Administration, SGLT2 = sodium–glucose cotransporter 2

GLP-1 RA

- T2D & CKD, who do not achieve glycemic targets despite use of Metformin and SGLT-2i, long acting GLP-1 RA can be used
- Choice should prioritize agents with CV benefits
- Should not be used in combination with DDP-4 inhibitors
- Risk of hypoglycemia is low (increase with sulfonylurea, insulin)
- Start with low dose to minimize GI side effects

Self-Management Educational Programs

- Learning and behavioral changes
- Tailored to personal needs
- Take into account ethnic, cultural, literacy, cognitive and geographical factors
- Objectives – empower and enable individuals to develop self-management knowledge and skills
- Reducing long-term complications, hypoglycemia
- Improve individual well being, improve quality of life and achieve treatment satisfaction

Table 12. Key objectives of effective diabetes self-management education programs[299]

Key objectives are to:
Improve diabetes-related knowledge, beliefs, and skills
Improve self-management and self-motivation
Encourage adoption and maintenance of healthy lifestyles
Improve vascular risk factors
Increase engagement with medication, glucose monitoring, and complication screening programs
Reduce risk to prevent (or better manage) diabetes-related complications
Improve emotional wellbeing, treatment satisfaction and quality of life

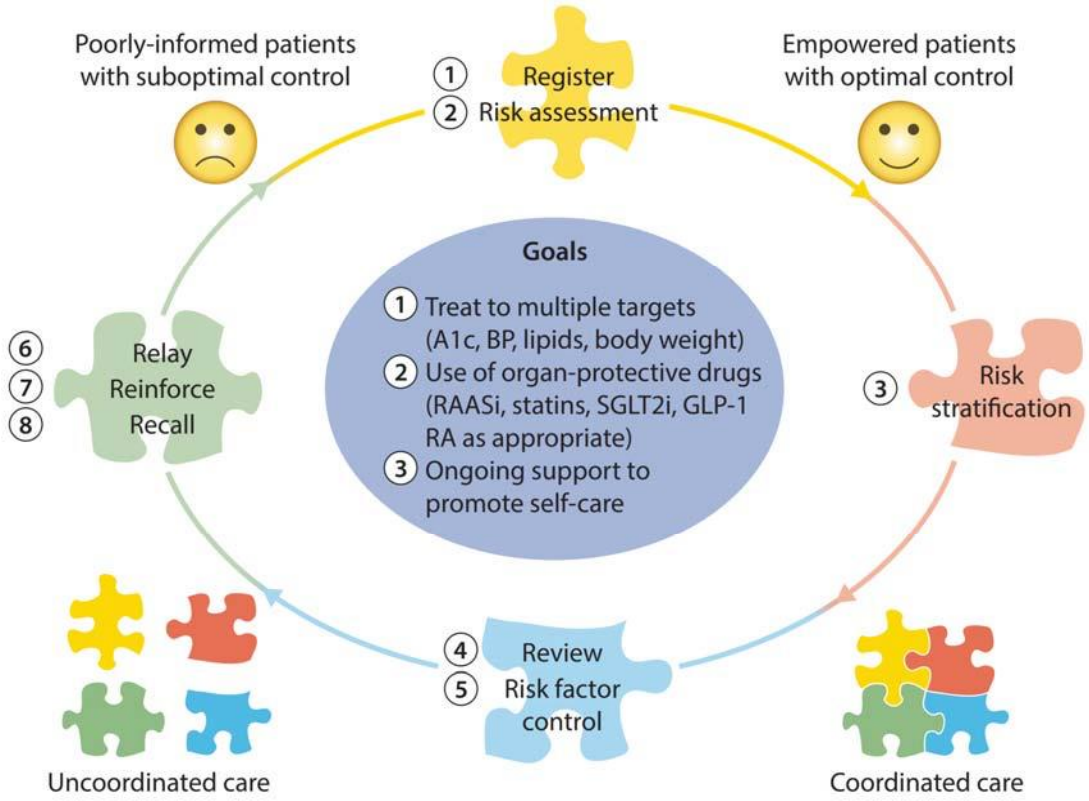
Self-Management Educational Programs

- 21 Studies – improvement in clinical (HbA1c, fasting glucose), body weight, psychosocial (knowledge, self-efficacy, patient satisfaction) outcomes
- Best approach – tailored to individual preferences an learning styles
- Can promote medication adherence, healthy eating, physical activity and increase self efficacy
- Systemic review – cost-effective or superior to usual care

Team-based integrated care

- Healthcare system should implement structured programs
- Risk evaluation and patient empowerment
- Delivered by physician and non-physician personnels (nurse, Healthcare assistant, community worker, peer supporter)

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



HbA1c = glycated hemoglobin, BP = blood pressure, GLP-1 RA = glucagon-like peptide-1 receptor agonist, RAASi = renin-angiotensin-aldosterone system inhibitor, SGLT2i = sodium-glucose cotransporter 2 inhibitor.

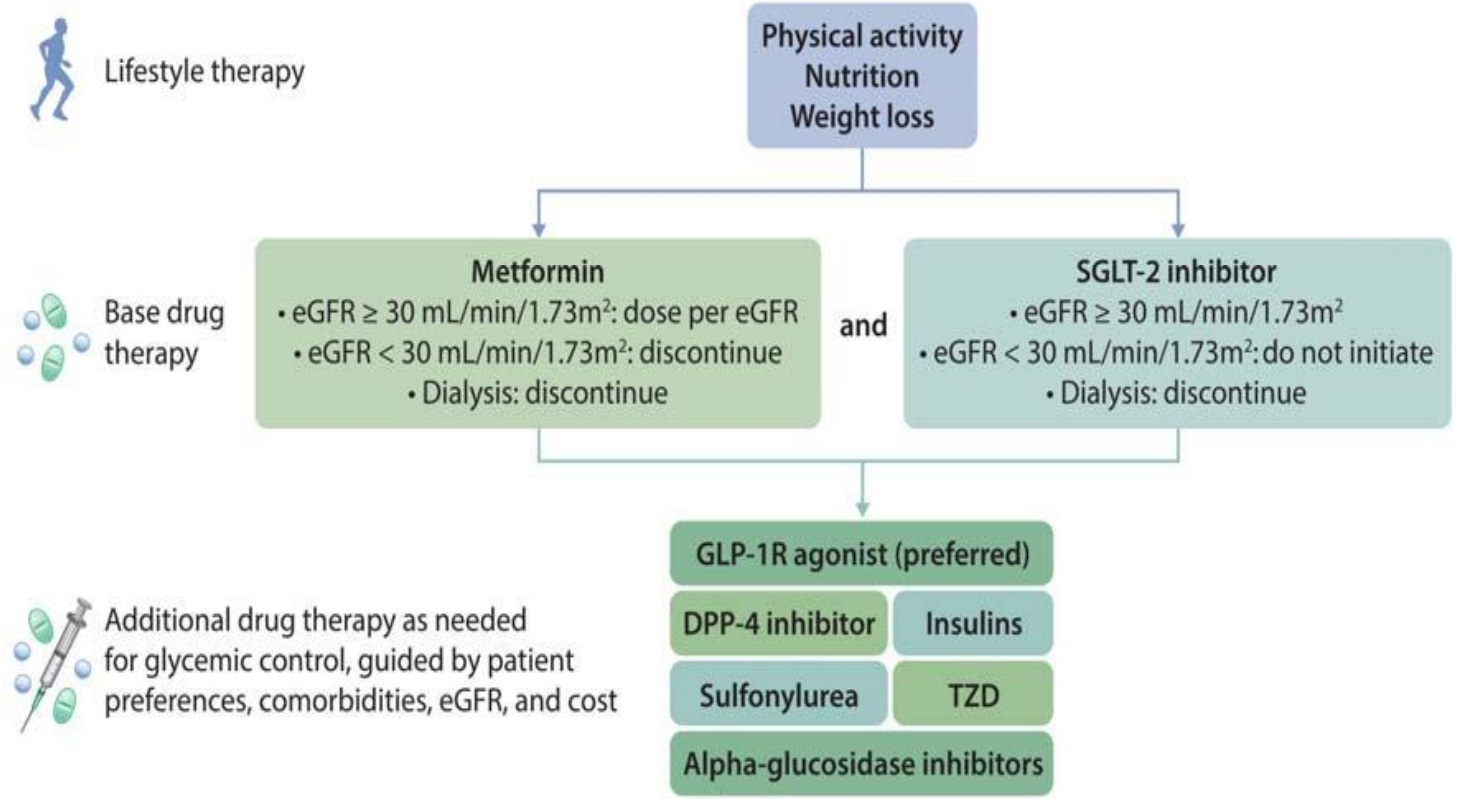
Anti-Glycemic Therapies

- Metformin and SGLT-2 inhibitors are preferred
- Reduce risk diabetic complications
- Low risk of hypoglycemia
- Metformin is inexpensive with modest long term benefits of diabetic complications
- SGLT-2i has larger effect on CKD progression and CVD
- Can be used safely in patients with eGFR >30ml/min
- Combination is logical

Anti-Glycemic Therapies

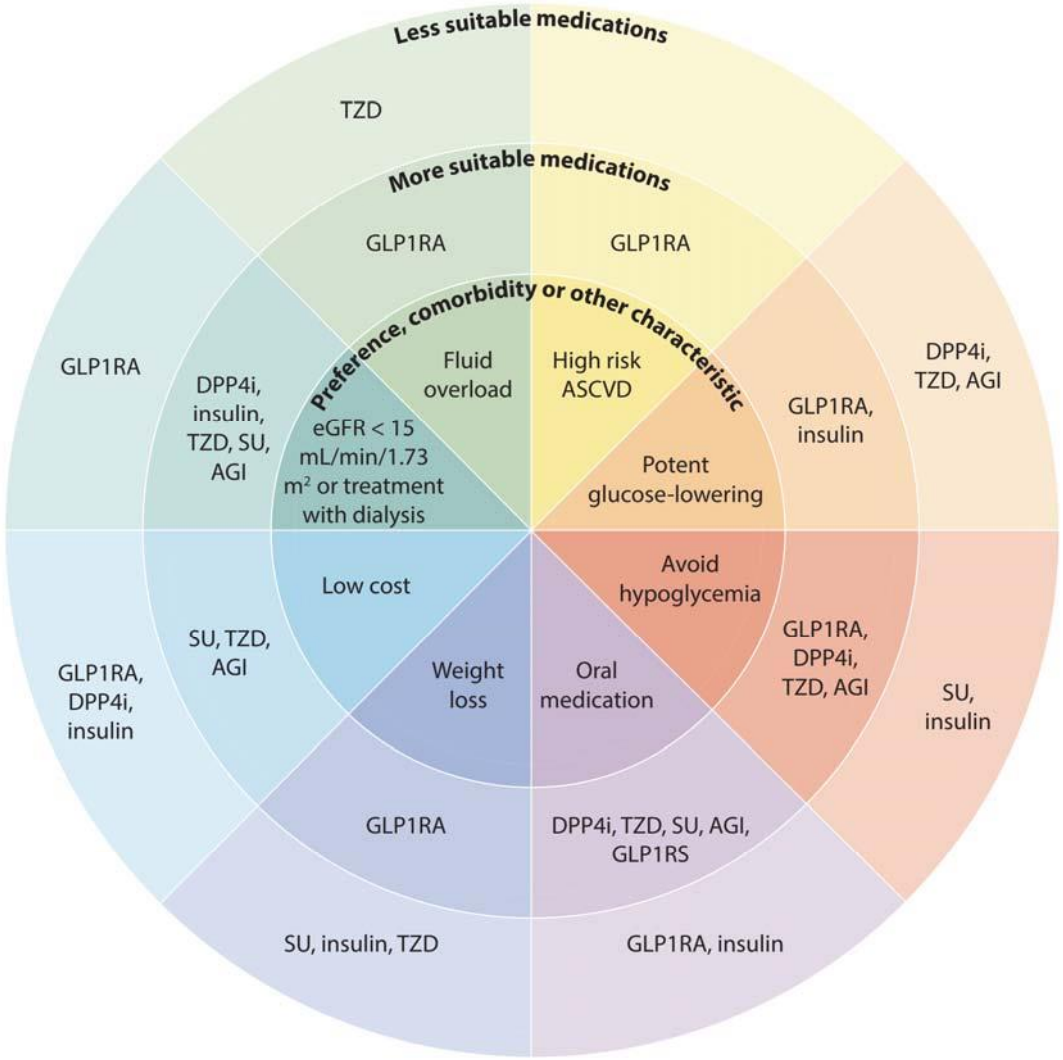
- Life style therapy is cornerstone
- Metformin and SGLT-2 inhibitors as base drug in nearly all patients with eGFR >30ml/min
- GLP-1 RA is preferred

Figure 11. Glycemic treatment algorithm for patients with T2D and CKD

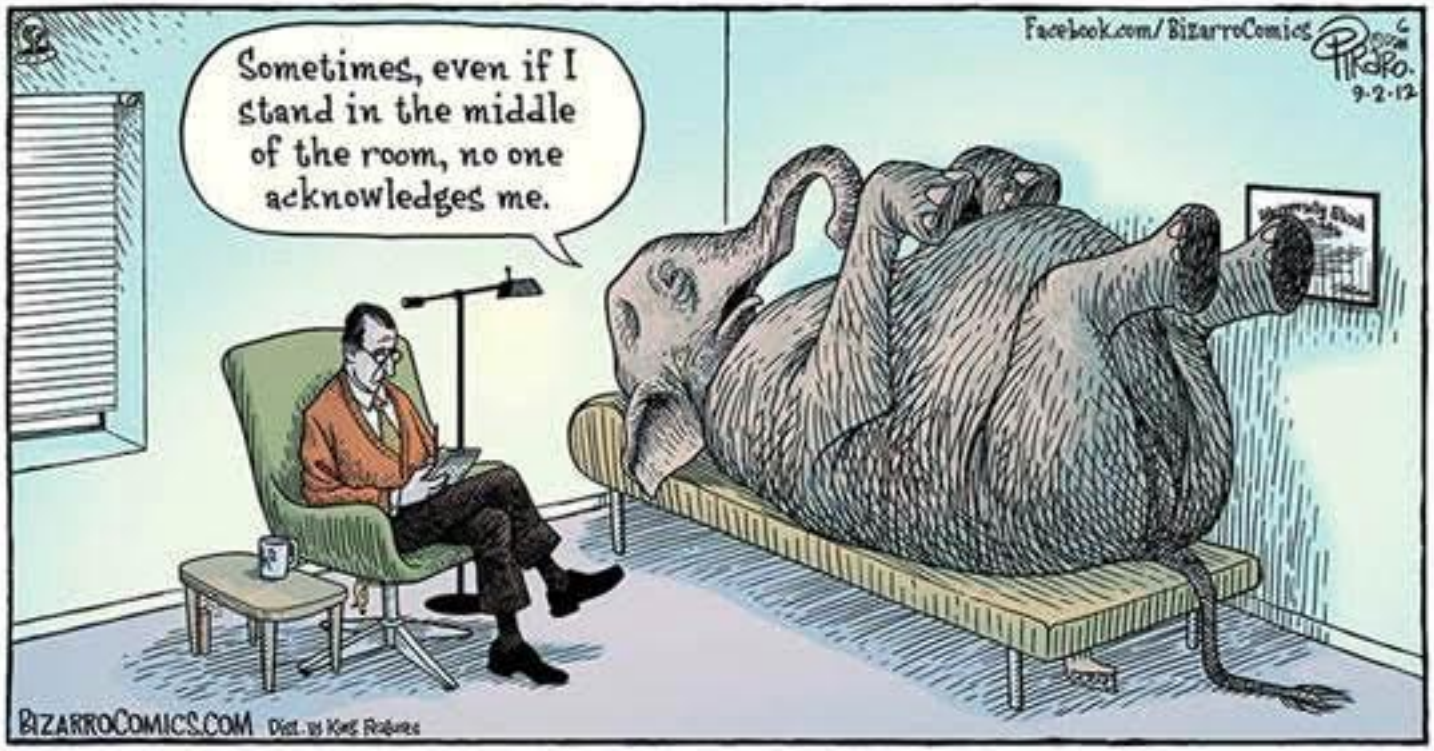


CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1R = glucagon-like peptide-1 receptor; SGLT2 = sodium–glucose cotransporter 2; T2D = type 2 diabetes; TZD = thiazolidinedione

Figure 12. Patient factors influencing selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD



ASCVD = atherosclerotic cardiovascular disease, AGI = alpha glucosidase inhibitor, CKD = chronic kidney disease, DPP-4i = dipeptidyl peptidase 4 inhibitor, eGFR = estimated glomerular filtration rate, GLP-1RA = glucagon-like peptide-1 receptor agonist, SU = sulfonylurea, T2D = type 2 diabetes, TZD = thiazolidinedione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