
بسم الله الرحمن الرحیم

DRUG THERAPY IN DKD

Dr. Sabbagh
Associate Professor
Mashhad University Of Medical Science

Open Access Commentary

The 2024 American Diabetes Association guidelines on Standards of Medical Care in Diabetes: key takeaways for laboratory

Dipti Tiwari [1], Tar Choon Aw [2,3,4*]

Explor Endocr Metab Dis. 2024;1:158–166 **DOI:** https://doi.org/10.37349/eemd.2024.00013
Received: January 03, 2024 **Accepted:** April 08, 2024 **Published:** July 23, 2024
Academic Editor: Andreas Barthel, University Hospital Carl Gustav Carus of Technische Universität Dresden, Germany

DKD:

- Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in the United States and worldwide.
- About 463 million people worldwide (9.3%) have type 2 diabetes mellitus
- Gold standard for diagnosis : histology of the kidney
  - Majority of patients do not undergo kidney biopsy, as they are presumed to have diabetic kidney disease based upon clinical history and laboratory evaluation.
  - Diabetic kidney disease is now known to be clinically and pathologically heterogeneous
  - DKD does not indicate the specific pathological phenotype of kidney damage due to diabetes
  - DKD underlying pathologic phenotype is unknown in most cases

- Prevalence: ESKD in 20–40% in patients with diabetes
- It may be present at diagnosis of type 2 diabetes
- it typically develops 5–15 years after the diagnosis of type 1 diabetes

HbA1c should not be used for:

I. Screening of cystic-fibrosis-related diabetes
II. Post-transplantation diabetes

Oral glucose tolerance test (OGTT) is preferred

- Plasma glucose levels are preferred in :
  - hemoglobin variants
  - pregnancy
  - glucose-6-phosphate dehydrogenase deficiency
  - other conditions that might potentially interfere with accurate HbA1c measurements

- Diagnosis of diabetes necessitates:
  - two abnormal test results (HbA1c and plasma glucose) either simultaneously or at different time points.

- Alternative biomarkers such as:

  fructosamine and glycated albumin :

  - viable options for monitoring glycemic status.
  - Fructosamine reflects the total pool of glycated serum proteins, mainly albumin, reflecting glycemic trends over a span of 2–4 weeks—a relatively shorter duration compared to A1C.
  - strong correlation and are associated with long-term complications based on epidemiological evidence
  - the empirical support for their application is not as robust as that for HbA1c

"Diabetic kidney disease" :

is a clinical diagnosis based upon the presence of:

- **albuminuria**
- **decreased estimated glomerular filtration rate (eGFR)**
- **or both**

in patients with diabetes

Diabetic kidney disease:

- Spot UACR and eGFR:
  - should be assessed annually in people with type 1 diabetes for ≥ 5 years and in all those with type 2 diabetes regardless of treatment. B

- In established CKD:
  - urinary albumin (e.g., spot UACR) and eGFR should be monitored 1–4 times per year depending on the stage of the kidney disease. B

- Periodically assess :
  - serum creatinine
  - potassium levels when ACE inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists are used. B

3. Prevention or Delay of Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2025;48(Suppl. 1):S50–S58 | https://doi.org/10.2337/dc25-S003

- Balance of risks and benefits of diabetes medications for :
  1. Hypoglycemia (In who have achieved individualized glycemic goals they should deintensify (decrease the dose or stop)
  2. Tolerability
  3. difficulties of administration
  4. impact on education or employment
  5. financial cost

- Hypoglycemia is the major risk to individuals treated with :
  - Insulin
  - Sulfonylureas
  - Meglitinides(nateglinide,repaglinide)

- Switching a high-hypoglycemia-risk medication to lower-hypoglycemia-risk therapy :
  - use of SGLT2 inhibitors in the setting of heart failure diabetic kidney disease
  - use of GLP-1 RAs in the setting of CVD or obesity

11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2025;48(Suppl. 1):S239–S251 | https://doi.org/10.2337/dc25-S011

ADA "Standards of Care in Diabetes"

11.2 Optimize glucose management to reduce the risk or slow the progression of CKD . A

11.3 Optimize blood pressure management (*aim for <130/80 mmHg* and reduce blood pressure variability to reduce the risk or slow the progression of CKD and reduce cardiovascular risk. A

11.4a ***In nonpregnant people with diabetes and hypertension*** :

- either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) B

- and is strongly recommended for those with severely increased albuminuria (UACR≥300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m2 to maximally tolerated dose to prevent the progression of kidney disease and reduce cardiovascular events. A

11.4b Monitor for :

- increased serum creatinine and for increased serum potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists (MRAs) are used,
- or for hypokalemia when diuretics are used
- at routine visits and 7–14 days after initiation or after a dose change. B

11.4c An ACE inhibitor or an ARB *is not recommended for:*

the primary prevention of CKD in people with diabetes who have normal blood pressure, normal UACR (<30 mg/g creatinine), and normal eGFR. A

11.4d *Continue* renin-angiotensin system blockade for:

*mild to moderate increases in serum creatinine (≤30%) i*n individuals who have no signs of extracellular fluid volume depletion. A

11.5a For people with type 2 diabetes and CKD:

use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor with demonstrated benefit is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m2. A

11.5b To reduce cardiovascular risk and kidney disease progression in people with type 2 diabetes and CKD:

- a glucagon-like peptide 1 agonist with demonstrated benefit in this population is recommended. A

11.5c To reduce cardiovascular events and CKD progression in people with CKD and albuminuria:

- a nonsteroidal MRA that has been shown to be effective in *clinical trials* is recommended (if eGFR is ≥25 mL/min/1.73 m2).
- Potassium levels should be monitored. A

- 11.6 Potentially harmful antihypertensive medications in pregnancy should be avoided in:
  - sexually active individuals of childbearing potential who are not using reliable contraception
  - and, if used, should be switched prior to conception to antihypertensive medications considered safer during pregnancy. B

11.7 Aim to reduce urinary albumin by ≥30%:
in people with CKD and albuminuria ≥ 300 mg/g to slow CKD progression. B

11.8

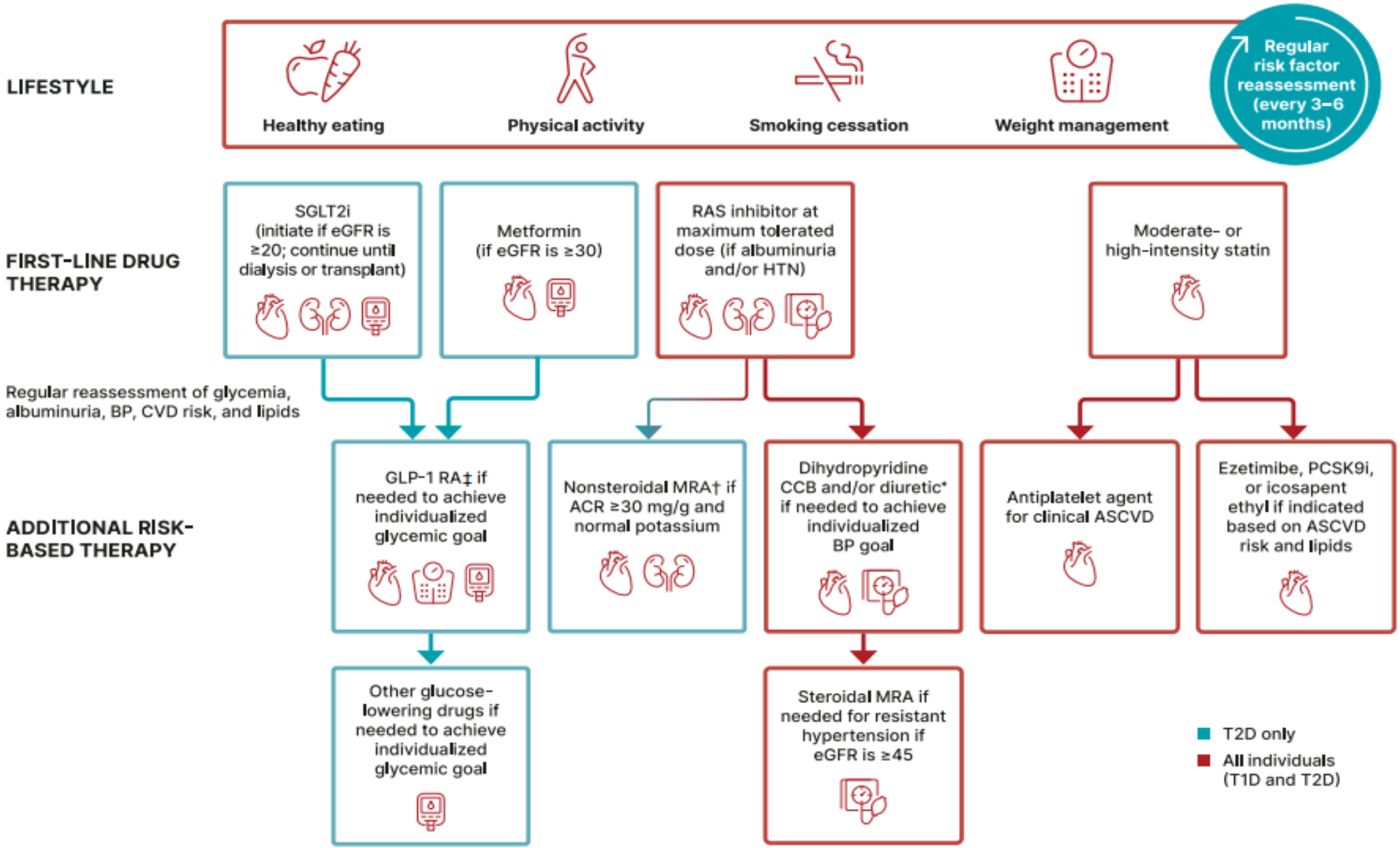
- For people with non–dialysis dependent stage G3 or higher CKD:
  - **protein intake** should be 0.8 g/kg body weight per day, as for the general population. A
- For individuals on dialysis:
  - protein intake of 1.0–1.2 g/kg/day should be considered since protein energy wasting is a major problem for some individuals on dialysis. B

11.9 Individuals ***should be*** referred for evaluation by a nephrologist if :

- they have continuously increasing urinary albumin levels and/
- or continuously decreasing eGFR and/
- or if the eGFR is <30 mL/min/1.73 m2. A

11.10 Refer to a nephrologist for :

- uncertainty about the etiology of kidney disease,
- difficult management issues,
- and rapidly progressing kidney disease. B


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‡ if needed to achieve individualized glycemic goal
Nonsteroidal MRA† 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)

RESEARCH

Comparative effectiveness of second line oral antidiabetic treatments among people with type 2 diabetes mellitus: emulation of a target trial using routinely collected health data

Patrick Bidulka,[1] David G Lugo-Palacios,[2] Orlagh Carroll,[2] Stephen O'Neill,[2] Amanda I Adler,[3] Anirban Basu,[4] Richard J Silverwood,[5] Jonathan W Bartlett,[6] Dorothea Nitsch,[1] Paul Charlton,[7] Andrew H Briggs,[2] Liam Smeeth,[1] Ian J Douglas,[1] Kamlesh Khunti,[8] Richard Grieve[2]

bmj-2023-077097
Accepted: 14 March 2024

- A recent study of second line treatments for people with type 2 diabetes mellitus *across 38 countries* reported that **the most commonly used oral drugs were: (2024)**
  - Dipeptidyl peptidase-4 (DPP- 4) inhibitors (48.3%)
  - Sulfonylureas (40.9%)
  - Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (8.3%)

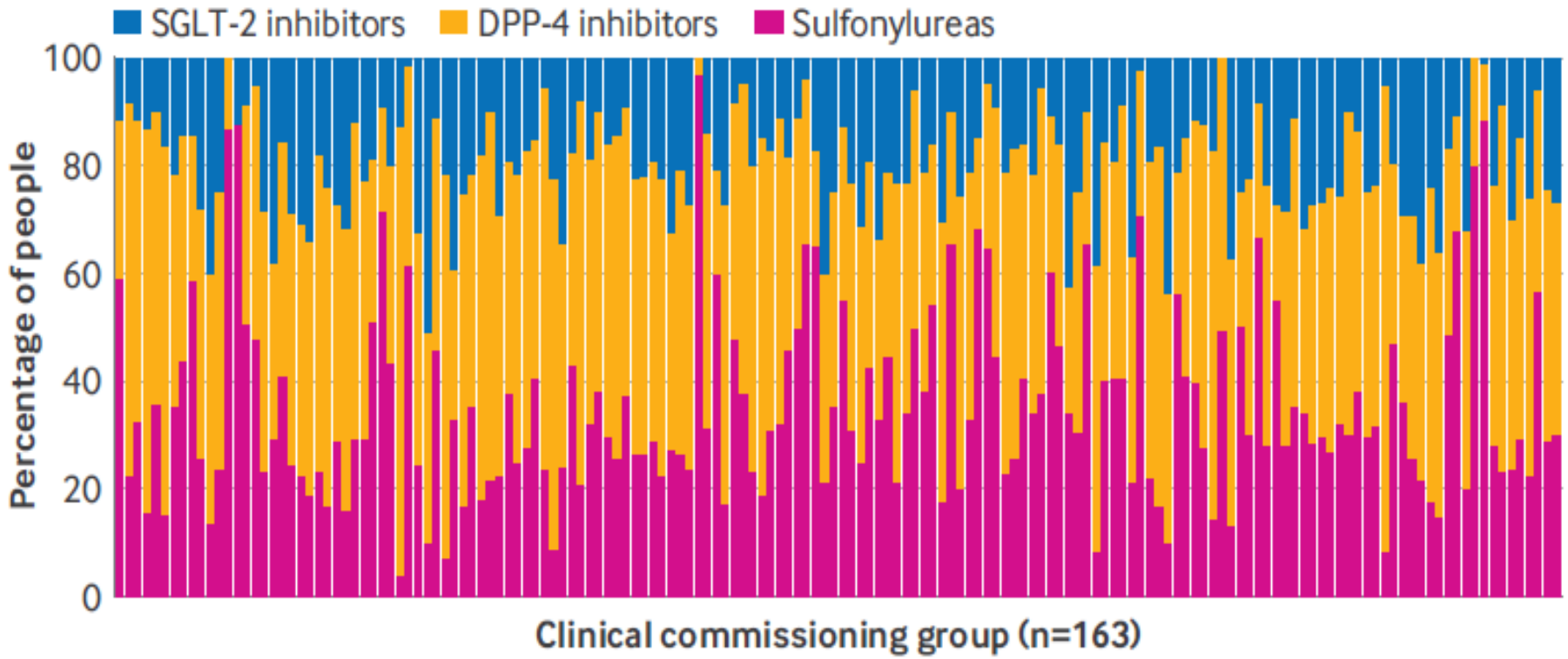


Fig 1 | Stacked bar chart illustrating variation in second line antidiabetic treatment prescribed among people included in the study at the clinical commissioning group level in England, 2014-20. DPP-4=dipeptidyl peptidase-4; SGLT-2= sodium-glucose cotransporter-2

Metformin:

Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
			Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2

Oral/SQ	Cost	Clinical considerations
Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals

Metformin:

- **Metformin remains the preferred initial antihyperglycaemic therapy for most patients with T2D**

- Metformin lowers blood glucose levels:
  - primarily by decreasing the amount of glucose produced by the liver
  - by increasing glucose utilization in the skeletal muscle.

- Metformin is cheap and has proven efficacy with a low risk of hypoglycemia
- Limited data suggest the potential for risk of lactic acidosis in patients with lower eGFR

- For most patients with T2D and DKD, metformin and SGLT2 inhibitors are recommended as the first-line pharmacologic treatment with eGFR is above 30 mL/min/1.73 m2

- Metformin has been shown to:
  - activate muscle AMPK and promote glucose uptake
  - reduce ROS production
  - delay the progression of DKD

SGLT-2 inhibitors:

Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
			Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR

Oral/SQ	Cost	Clinical considerations
Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable

CAUTION in SGLT2I (KDIGO 2024):

I. with the initiation of an SGLT2 inhibitor:

- ✓ it is expected to see an early reversible decline in eGFR (5–8 mL/min/1.7m2) in the first 2 weeks of initiation, which is explained by the hemodynamic effect of this medication in reducing glomerular hyperfiltration

- ✓ In elderly patients with advanced CKD, it is reasonable to check kidney function 2–4 weeks after initiation to establish a new baseline eGFR

- ✓ A more-than-expected decline in eGFR should prompt the discontinuation of SGLT2 inhibitors until further evaluation is completed.

Glucagon-Like Peptide-1 Receptor Agonist:

Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
			Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions

Oral/SQ	Cost	Clinical considerations
SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; 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 patients experiencing GI challenges • Counsel patients about potential for ileus • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected

Practical considerations:

Weight loss:

- Tirazepatide(Mounjaro) :
  - has demonstrated the maximum benefits on weight loss among all weight loss-promoting medications :
    - up to 20.9% mean percentage change in weight at week 72 (18 month) when the maximum dosage of tirazepatide is used
    - benefits on renal and cardiovascular disease are still under investigation
- Semaglutide :
  - 14.9% at week 68 with the maximum dosage of semaglutide
- Liraglutide :
  - 8% at 56 weeks with liraglutide 3 mg

Combination Therapy:

- with insulin:
  - it is crucial to monitor their insulin dosage closely.
  - Increasing the dose of the GLP-1 receptor agonist may require a decrease in insulin dosage and adjustment or discontinuation of insulin secretagogues if hypoglycemia is a concern.
- Combination therapy with other oral medications:
  - NOT with other incretin therapies such as : DPP-4 inhibitors; this combination is unlikely to provide additional benefits on glycemic targets.

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Dual GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions

Oral/SQ	Cost	Clinical considerations
SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; 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 patients experiencing GI challenges • Not recommended for individuals with history of gastroparesis • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin

Oral/SQ	Cost	Clinical considerations
Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention

Oral/SQ	Cost	Clinical considerations
Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia

Oral/SQ	Cost	Clinical considerations
Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia

		Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
					Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Insulin	**Human**	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response
	Analogs							

Oral/SQ	Cost	Clinical considerations
SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
SQ	High	

International Journal of
Molecular Sciences

MDPI

Review

Recent Advances in the Management of Diabetic Kidney Disease: Slowing Progression

Na Wang and Chun Zhang *

Department of Nephrology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China; wnflora_2011@163.com
* Correspondence: drzhangchun@hust.edu.cn

Received: 2 January 2024
Revised: 28 February 2024
Accepted: 5 March 2024
Published: 7 March 2024

V. Endothelin antagonists:

- Endothelins were first discovered in 1985 with the first endothelin aptly named endothelin 1.

- Endothelin 1 has simultaneously been implicated in inflammation, vasoconstriction, and mesangial proliferative effects mediated by endothelin receptor A.

- Endothelin A receptor blockade has multiple effects :
  - a reduction in glomerular vasodilation which can also alter permeability for proteins including albumin leading to a lower tubular load of protein excretion
  - Though sparsentan has been granted accelerated FDA approval for the treatment of IgA nephropathy in adults, ***there are currently no medications approved for treatment of DKD in this class.***

VI. Promising therapeutic options

- New alternative treatment options encompass antifibrotic interventions utilizing:
  - Pirferidone or pentoxifylline
  - Nox1/4 inhibition
  - Chemokine cytokine inhibition
- Other pharmacological options targeting several inflammatory pathways:
  - ❖ Most recently baricitinib, a JAK1/2 inhibitor, was shown to decrease albuminuria in patients with type two diabetes and DKD
  - ❖ Bardoxolone methyl has also been studied since it *activates the Keap1/Nrf2 system* which plays an important role in defense responses against oxidative stress
  - ❖ Other herbal supplements with antioxidant properties have also been investigated such as:
  - ❖ silymarin(عصاره گیاه خار مریم), but more research is needed before adding these agents to our growing list of management options
  - ❖ Preliminary findings suggest that DDP-4 inhibitors such as saxagliptin and linagliptin, may offer potential advantages for patients with DKD
  - ❖ Overall research is **moving toward a more personalized approach** based on the patient's genetic and biomarker profile as the future of DKD management

Other Agents Exhibiting Potential Effectiveness on DKD

PFT(Pentoxifylline):

- The nonspecific phosphodiesterase inhibitor
- Antiproliferative, Anti-inflammatory, Antifibrotic roles
- Smaller decrease in eGFR and a greater decline in residual albuminuria in patients with type 2 diabetes and stages 3–4 CKD under standard administration of RAS blockade (In 2015)
- Slow the progression of DKD through increasing the expression of soluble Klotho, which was associated with anti-inflammatory and antialbuminuric properties
- Further rigorous trails of PTF need to be initiated to consolidate the reno-protective actions

Baricitinib, a JAK1/2 inhibitor:

- Predominately reduced albuminuria and inflammatory factors (including intercellular adhesion molecule-1, plasma TNF receptor-1/2, and serum amyloid A) in patients T2D and DKD
- Baricitinib can effectively prevent the progression of DKD.

  supporting their **potential therapeutic role** in slowing the progression of DKD.
- Further trails need to be performed to investigate

ASK1 inhibitor

- **Selonsartib** (selective ASK1 (apoptosis signal-regulating kinase 1 inhibitor) :
  - Protective effects on kidney injury through reducing inflammation and fibrosis in rodent models of DKD
  - A phase 2 clinical trial of selonsertib, a selective ASK1 (apoptosis signal-regulating kinase 1)inhibitor, suggested selonsertib might be a potential therapeutic agent to prevent the progression of DKD despite the fact that the trail did not achieve the primary endpoint .
  - Data from MOSAIC, NCT04026165 study has yet to be published.