Use of GLP-1 receptor agonists for kidney disease (and not just diabetes)

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Objectives

- Outline side effects of GLP-1 receptor agonists and provide medication education to patients starting a GLP1 receptor agonist
- Identify patients with chronic kidney disease in whom a GLP1 receptor agonist could be considered based on past medical history

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Abbreviations

ACEi, angiotensin-converting enzyme inhibitor
AKI, acute kidney injury
ARB, angiotensin receptor blocker
CAD, coronary artery disease
CHF, congestive heart failure
CV, cardiovascular
CKD, chronic kidney disease
CrCl, creatinine clearance
DM, diabetes mellitus
DPP4i, dipeptidyl peptidase 4 inhibitor
eGFR, estimated glomerular filtration rate
ESRD, end stage renal disease
GI, gastrointestinal
GIP, gastric inhibitory/glucose dependent insulinotropic polypeptide
GLP-1 RA, glucagon-like peptide-1 receptor agonist
HD, hemodialysis
MACE, major adverse CV event
MRA, mineralocorticoid receptor antagonist
PD, peritoneal dialysis
RASI, Renin-Angiotensin System inhibitors
SCr, serum creatinine
SGLT2i, sodium-glucose cotransporter-2 inhibitors
UACR, urine albumin creatinine ratio

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Incretin hormones

- Elements produced in the gut that control glucose levels by stimulating the release of substances from the pancreas were initially discovered in 1902. Those factors were named incretin (**IN**testine se**CRET**tion **IN**sulin)
- There are two incretin hormones released by gut enteroendocrine cells in response to sugar intake, gastric inhibitory/glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide (GLP-1)
- Both hormones control glucose level by stimulating release of insulin from pancreas in glucose-dependent fashion

Seino Y, et al. J Diabetes Investig . 2010 Apr 22;1(1-2):8–23

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Pancreatic and exopancreatic functions of GLP-1

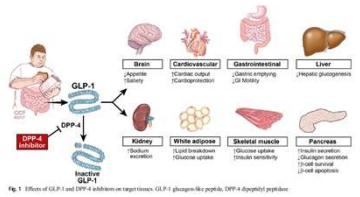

Fig. 1 Effects of GLP-1 and DPP-4 inhibitors on target tissues. GLP-1 glucagon-like peptide, DPP-4 dipeptidyl peptidase

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Lawrence L, et al. Curr Cardiol Rep (2018) 20:65

GLP-1 RA therapeutic agents

- GLP-1 receptor agonist (RA) are synthetic molecules mimicking the action of naturally released incretin hormone
- In 2005 the first GLP-1 RA, exenatide, was approved by Food and Drug Administration (FDA) for the management of diabetes
- Later it was followed by liraglutide (2010), dulaglutide (2014), lixisenatide (2016) and semaglutide (2017) . Liraglutide and semaglutide received weight loss indication in 2014 and 2021, respectively
- Liraglutide and semaglutide were approved for cardiovascular (CV) indications based on their demonstrated benefits in reducing cardiovascular risks in patients with diabetes in 2017 and 2024, respectively. Dulaglutide has also been approved for CV risk reduction in 2020

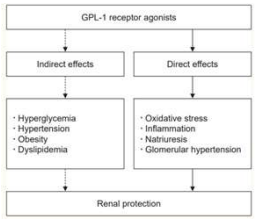
Zeng Z, et al. Signal transduction and target therapy (2024)9:234

GLP-1 RA and GLP-1 RA/GIP therapeutic agents

- Tirzepatide, a combination GIP and GLP-1 RA, approved for DM in 2022, weight loss in 2023 and OSA indications in 2024
- There are also off-label indications associated with GLP-1 RA use including Parkinson's, Alzheimer's , addiction, polycystic ovarian syndrome
- In 01/2025 semaglutide became the first GLP-1 RA approved by FDA to reduce the risk of worsening kidney disease, kidney failure, and death due to CV disease in patients with type 2 diabetes and chronic kidney disease (CKD)
- In 08/2025 FDA granted accelerated approval for semaglutide for the treatment of metabolic-associated steatohepatitis in patients with moderate to advanced fibrosis with no cirrhosis

Zeng Z, et al. Signal transduction and target therapy (2024)9:234

Nephroprotective mechanism of action of GLP-1 RA



Hee Yu, J, et al. Kidney Res Clin Pract. 2022 Mar 25;41(2):136–149

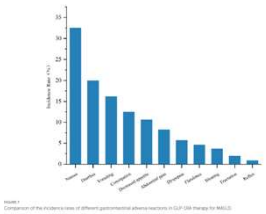
Dramatic increase in GLP-1 use

- The use of GLP-1 RA increased dramatically especially following the addition of weight loss indication
- In 2024 a population-based study showed 700 % increase in the use of GLP-1 RA agents in patients without diabetes between 4-year span (2019-2023)
- Given the widespread use of these drugs, it is essential to review drawbacks and safety concerns associated with the use of GLP-1 RA drug class

Mahase, E. BMJ 2024;386:q1645

Gastrointestinal (GI) side-effects

- The most common GI side-effects are nausea, diarrhea, vomiting and constipation
- Transient, pronounced during dose escalation and subsided after reaching maintenance dose
- Mild to moderate in severity
- Patient education is essential to decrease the risk of GI side



Huang X, et al. Front. Med. 2025 Feb 20:12:1509947
Gorgojo-Martinze, JJ, et al. J Clin Med. 2022 Dec 24;12(1):145

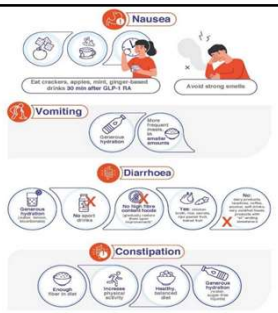
Patient education to minimize GI side-effects

- Start low and go slow
- Ensure patient is following their instructions closely

Gorgojo-Martinze, JJ, et al. J Clin Med. 2022 Dec 24;12(1):145

Management of GI side-effects

- May consider symptomatic treatment
  - Domperidone for nausea and vomiting
  - Probiotics, loperamide for diarrhea
  - Stool softeners along with increase in water and fiber intake, increase in mobility
- Switch to another GLP-1 RA agent



Gorgojo-Martinze, JJ, et al. J Clin Med. 2022 Dec 24;12(1):145

Pancreatitis

- In 2010, the warning about increased risk of acute pancreatitis (AP) has been added to prescribing information of GLP-1 RA agents based on data from the FDA adverse Event Reporting System
- Conflicting results in clinical studies
- Overall, less than 1 % of patients treated with GLP-1 RA experienced AP based on results of several clinical trials
- Patients with history of pancreatitis should not be started on GLP-1 RA unless the cause of pancreatitis has been established and no longer presents a risk
- Risk factors for pancreatitis include elevated triglycerides > 1000 mg/dL, alcohol use, gallstones

Ayoub M, et al. J Clin Med. 2025 Feb 1;14(3):944
Gorgojo-Martinez JJ, et al. J Clin Med. 2022 Dec 24;12(1):145
Marso SP, et al. N Engl J Med. 2016 Nov 10;375(19):1834-1844

Gallbladder and biliary diseases

- Gallbladder and biliary diseases are included as warnings and precautions in US prescribing information of GLP-1 RA agents
- Possible causes include weight loss, decreased gallbladder emptying and motility and suppression of cholecystokinin secretion
- Meta-analysis of 76 randomized clinical trials showed the higher risk cholelithiasis, cholecystitis, biliary disease, cholecystectomy
  - Risk is higher with higher doses (as seen for weight loss indication) and longer duration (>26 weeks)
- Overall absolute risk is 27 cases per 10,000 persons treated per year

Liyun He, et al. JAMA Intern Med. 2022;182(5):513-519

Gastroparesis

- Characterized by delayed gastric emptying with no mechanical obstruction
- Possible causes: DM (25 %), post-surgical complications (7 %) , medications (22%), idiopathic (30-50 %), neurological disorders (Parkinson's)
- The gastric emptying delay associated with GLP-1 RA/GIP may be diminished over time, and might be the most pronounced after the first dose
- In one study 30% of patients with established gastroparesis had worsened gastric emptying after exenatide, while the rest 70% had no to minimal change
- GLP-1 RAs should be held 3-4 weeks before patients undergo a gastric emptying test

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Shankar A, et al. Cardiovasc Endocrinol Metab. 2024 Dec 4;14(1):e00321
Parkman HP, et al. Journal of Nuclear Medicine Technology March 2024, 52 (1) 3-7

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Thyroid cancer

- Thyroid C-cell hyperplasia and tumors have been observed in animal studies. GLP-1 receptors are found on the membrane of parafollicular C-cells and can be stimulated by GLP-1 RA to secrete calcitonin, which can lead to thyroid carcinogenesis (medullary thyroid cancer, MTC) in rodents. The expression of GLP-1 receptors in humans is lower
- More studies are required to investigate the role of incretin system in thyroid cancer in humans
  - While most observational studies showed no increase in thyroid cancer risk, a French case-control analysis showed increased risk in all thyroid carcinomas with GLP-1 RA use from 1 to 3 years
- Speculation if increased risk is seen due to increased vigilance/screening rather than de novo pathogenesis

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Lisco G, et al. Endocr Connect. 2023 Sep 27;12(11):e230257
Bezin J, et al. Diabetes Care 2023;46(2):384–390
Pasternak B, et al. BMJ 2024;385:e078225
Brito JP, et al. JAMA Otolaryngol Head Neck Surg 2025;151;(3);243-252

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Thyroid cancer

- According to the North American Association of Central Cancer Registries, the incidence of MTC was 0.24 per 100,000 person-years before GLP-1 agonists were introduced in the US
- CV and renal outcomes outweigh the risk of thyroid carcinomas
- Per FDA, patients with personal or family history of MTC or patients with multiple endocrine neoplasia syndrome type 2 are contraindicated for GLP-1 RA use

Hale PM, et al. Thyroid. 2020 Oct;30(10):1397-1398
Lisco G, et al. Endocr Connect. 2023 Sep 27;12(11):e230257

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Retinopathy

- GLP-1 RA use linked to worsening diabetic retinopathy (DR) in clinical trials
- Meta-analysis of 6 trials (3.4 year follow-up) showed no significant association, however, significant relationship was seen between HgbA1C reduction and retinopathy outcomes
- Strict diabetes control can reduce DR risk but may temporarily worsen pre-existing DR when intensified control is started (insulin, sulfonylureas)
- Worsening DR may relate to significant HgbA1C reduction; direct link to GLP-1 RA not ruled out
- DR should be screened at the time of type 2 DM diagnosis and annually thereafter
- Providers should evaluate the status of DR prior to GLP-1 RA therapy initiation

Bethel MA, et al. Diabetes Care 2021;44(1):290–296

Nonarteritic anterior ischemic optic neuropathy (NAION)

- NAION is a rare optic-nerve injury with acute vision loss
- 2024 retrospective study at a neuro-ophthalmology clinic
  - Semaglutide vs Non-GLP-1: Risk: 8.9% vs 1.8% (HR, 4.28; 95% CI, 1.62-11.29; P < .001)
  - Overweight/obese risk: 6.7% vs 0.8 % (HR, 7.64; 95% CI, 2.21-26.36; P < .001)
- 2025 retrospective real-world matched cohort study
  - semaglutide vs any GLP-1 RA and non-GLP-1 RA
  - type 2 DM 5 years: 0.065 % risk
  - High BMI 2 years: 0. 038 % risk
- European Medicine Agencies concluded that NAION is a very rare side-effect of semaglutide affecting 1 in 10,000 patients-year

Hathaway JT, et al. JAMA Ophthalmol 2024;142;(8):732-739.
Abbass JT, et al. American Journal of Ophthalmology 2025;Volume 274, 24 - 31

Sarcopenia

- Defined as progressive loss of muscle mass, strength and function. It is associated with higher risk of death, falls, decreased quality of life
- Weight loss (from any interventions) can result in lean body/muscle mass loss
- The goal of weight loss is to maintain or/and to increase muscle mass
  - Physical exercise (endurance and resistance training) is essential to maintain muscle mass. No data about the effect of GLP-1 RA on body composition with or without physical exercise program
  - Diet high in protein intake (1.2 g/kg/daily)

Linge J, et al. Circulation. 2024 Oct 15;150(16):1288-1298

Sarcopenia

- Research on preserving muscle mass during GLP-1 RA therapies was presented at 85th Scientific Sessions of the American Diabetes Association in Chicago in 06/2025
- Bimagrumab is a monoclonal antibody enhances muscle growth via activating activin type II receptors
  - The combination of bimagrumab and semaglutide showed greater reduction in weight, body, visceral fat and markers of inflammation compared to either therapy alone
- Continuous protein sensor monitors phenylalanine level, an amino acid, released during muscle breakdown or after consuming protein

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Linge J, et al. Circulation. 2024 Oct 15;150(16):1288-1298

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Monitoring parameters

- Before initiating GLP-1 RA:
  - Baseline labs (A1C, eGFR, lipid profile)
  - Screen for history of pancreatitis, gallbladder, thyroid cancer (MTC)
  - Reduce insulin and sulfonylureas doses to decrease the risk of hypoglycemia

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Monitoring parameters

- During GLP-1 RA therapy:
  - GI tolerance
  - Renal function especially in patients with CKD for volume depletion
  - Pancreatitis signs (persistent abdominal pain)
  - Gallbladder sings (right upper quadrant pain, nausea, jaundice)
  - Thyroid symptoms (dysphagia, hoarseness, neck mass)
  - Weight and metabolic markers (A1C, lipid panel, blood pressure)

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Conclusion

- GLP-1 RA agents have demonstrated a wide range of benefits. These include not only improved DM management but also positive impacts on CV health, weight loss, kidney function, hepatic steatosis. Research continues to explore new potential applications for these agents
- The use of GLP-1 RA agents has been steadily increasing each year. Proper patient education before initiating GLP-1 RA therapy is crucial to minimize GI side-effects and prevent permanent discontinuation. It is important to discuss potential serious side effects with patients and actively involve them in therapeutic decision-making
- Remember, observational studies show associations rather than causation. Further research is necessary to identify patients who may be at a higher risk for side effects. Despite the rarity of serious side effects, the benefits of GLP-1 RA agents often outweigh the potential risk.

Part 2

- What medications delay CKD progression?
- What does the data tell us re: GLP-1 RA and CKD outcomes?
- What do guidelines recommend re: GLP-1 RA in the CKD population?
- What about special populations, including CKD stage 4/5 and renal transplant?

Question 1

What medications delay CKD progression?

Delaying CKD Progression: Pharmacologic Options

Agent	Examples	Role in CKD	Indication
ACEI & ARBs	Lisinopril,. losartan, etc.	• Decrease macroalbuminuria, eGFR decline, kidney failure • CV benefit (heart failure, CAD)	All patients with CKD with any of the following: • albuminuria • CV indication (CHF, CAD) • DM • HTN
SGLT2-inhibitors	Empagliflozin dapagliflozin, etc.	• Decrease macroalbuminuria, eGFR decline, kidney failure • CV benefit (heart failure, MACE)	All patients with CKD regardless of DM
Non-steroidal MRA	Finerenone	• Decrease eGFR decline 40%, kidney failure, kidney disease death • Decrease MI, stroke, heart failure hospitalization, CV death	Adjunct to ACEI/ARBS in patients with CKD and DM

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KDIGO CKD Work Group. *Kidney Int*.2024;105(4S):S117-S314.
Ammar A, et al. *Pharmacotherapy*. 2025;45(5):291-306.

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Question 2

What does the data tell us re: GLP-1 RA and CKD outcomes?

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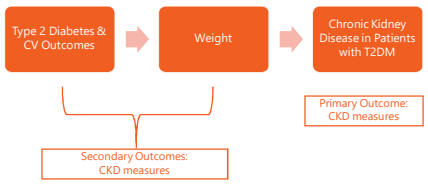
GLP-1 RA Investigational Trial Sequence



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Mann JFE et al. *N Engl J Med*. 2017;377:839-848.
Marso SJ et al. *N Engl J Med*. 2016;375:1834-1844.
Gerstein HC et al. *Lancet*. 2019;13;394(10193):121-130.
Tuttle KR, et al. *Lancet Diabetes Endocrinol*. 2018;6(8):605-617[30]
Frias JP et al. *N Engl J Med*. 2021;385:503-515.

Landmark Trials in T2DM: Secondary renal outcomes

Trial name	LEADER	SUSTAIN	REWIND	AWARD-7	SURPASS
Drug	Liraglutide	Semaglutide inj	Dulaglutide	Dulaglutide	Tirzepatide
% eGFR <60	23%	29%	22%	100%	N/A
Kidney outcome	↓ composite: new severe albuminuria, doubling SCr, kidney failure, death from CKD RRR*: 28%	↓ composite: severe albuminuria, doubling Scr, CrCL <45ml/min, need for KRT* RRR*: 36%	↓ composite: new severe albuminuria, eGFR ↓ 30%, use of KRT* RRR*: 15%	↓ rate of eGFR decline ↔ UACR	↓ composite: eGFR ↓ 40%, ESRD, death from CKD, new macro-albuminuria RRR* 42% ↓ eGFR decline ↓UACR

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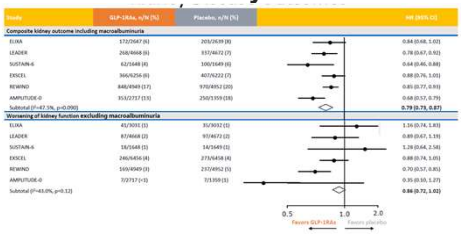
*KRT=kidney replacement therapy
*RRR=relative risk reduction

Mann JFE et al. *N Engl J Med.* 2017;377:839-848.
Marso SJ et al. *N Engl J Med.* 2016;375:1834-1844.
Gerstein HC et al. *Lancet.* 2019;13:394(10193):121-130.
Tuttle KR, et al. *Lancet Diabetes Endocrinol.* 2018;6(8):605-617.
Frias JP, et al. *N Engl J Med.* 2021;385:503-515.

Landmark trial in DM: GLP-1 RA and secondary renal outcomes



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Sattar N et al. *Lancet Diabetes Endocrinol* 2021;9:653–662.

Landmark Trials in Obesity: Secondary renal outcomes

Drug	STEP 1-3	SELECT	SURMOUNT
Drug	Semaglutide inj	Semaglutide inj	Tirzepatide
Mean eGFR (ml/min/1.73m²)	95-96	82	95
Kidney outcome	STEP 2: ↓ UACR -14.8 to 20.6% (vs +18.3%) STEP 1-3: ↔ eGFR trajectory	↓ composite: death from kidney disease, KRT, eGFR <15, new albuminuria, eGFR ↓ 50% RRR 25% - mainly driven by eGFR decrease and UACR endpoints ↓ eGFR decline esp if baseline eGFR <60	↓ UACR -6.2 to -13.9% (vs +0.2%)

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Wilding JP et al. *N Engl J Med.* 2021;384:989-100.
Davies M et al. *Lancet.* 2021;13;397(10278):971-984.
Wadden TA et al. *JAMA.* 2021;13;325(14):1403-1413.
Lincoff AM et al. *N Engl J Med.* 2023;389:2221-2232.
Jastreboff AM et al. *N Engl J Med.* 2022;387:205-216.
Calhoun HM et al. *Nat Med.* 2024;30(7):2058-2066.
Abasheva D et al. *Clin Kidney J.* 2024; 22;17(Suppl 2):19-35.

Landmark FLOW Trial: Primary CKD Outcome in Diabetic Population

Design: DB RCT* (n=3,533)

*Double-blind randomized controlled trial

Inclusion	Intervention	Primary Outcome

• T2DM
• eGFR <75
• UACR >100 (eGFR 25-50)
• UACR>300 (eGFR 50-75)
• RAS inhibitor
	• Semaglutide
	  • 0.25mg x 4 weeks
	  • 0.5mg x 4 weeks
	  • Maintenance=1mg
	• Placebo
		• Major kidney disease event
		  • Kidney failure
		  • ↓ eGFR ≥50%
		  • Death from kidney or CV causes

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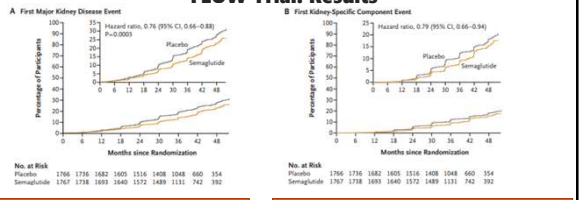
Perkovic V et al. *N Engl J Med.* 2024;11;391(2):109-121. 34

FLOW Trial: Results



1˚ Outcome: 24% RRR (95% CI 12-34%)
Death from CV cause plus kidney outcomes

Kidney only outcome: 21% RRR (95% CI 6-34%)
Kidney failure, eGFR reduction ≥50%, death from kidney causes

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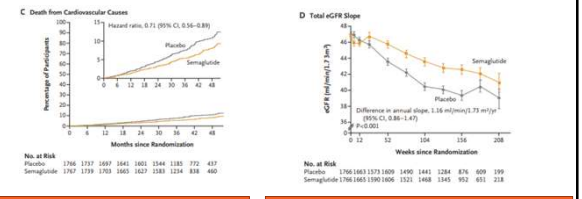
Perkovic V et al. *N Engl J Med.* 2024;11;391(2):109-121. 35

FLOW Trial: Results



CV death: 29% RRR (95% CI 11-44%)

Decline ml/min/1.73m2/yr:
Semaglutide (-2.19) vs Placebo (-3.36), p <0.001

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Perkovic V et al. *N Engl J Med.* 2024;11;391(2):109-121. 36

FLOW Trial: Results

Efficacy
- ↓ UACR 40%
- ↓ 4.1 kg greater weight loss vs placebo
- ↓ A1c 0.81% greater vs placebo
- ↓ SBP* 2.23 mmHg greater vs placebo

Trial stopped prematurely due to positive outcomes with semaglutide!

Safety
- Semaglutide:
  - Fewer serious infections or CV disorders
  - More eye disorders (3 vs 1.7%)
    - Diab retinopathy (22.8 v 22.5%)
  - Discontinuation due to GI disorder (4.5 vs 1.1%)

*Systolic Blood Pressure

Perkovic V et al. *N Engl J Med.* 2024;11;391(2):109-121.

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Question 3

What do guidelines recommend re: GLP-1 RA in the CKD population?

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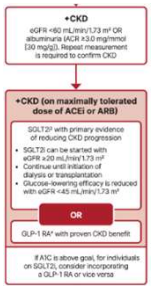
Place In Therapy

American Diabetes Association – 2025
- *In adults with T2DM and CKD, an SGLT2 inhibitor or GLP-1 RA should be used for both glycemic management (irrespective of A1C) and for slowing progression of CKD and reduction in cardiovascular events (A).*



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American Diabetes Association Professional Practice Committee. *Diabetes Care.* 2025; 48: S239-S251.

Place In Therapy

KDIGO – 2022 Clinic Practice Guideline for Diabetes

- *In patients with T2D and CKD who have not achieved individualized glycemic targets **despite use of metformin and SGLT2i treatment**, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).*

- *Practice point: prioritize agents with CV benefits*
  - *Semaglutide (injectable)*
  - *Dulaglutide*
  - *Liraglutide*

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KDIGO Diabetes Workgroup. *Kidney Int*.2022;102(5S):S1-S127.

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Place In Therapy

KDIGO – 2022 Guideline Key Points

- ↓ Major Adverse CV Events (MACE) by 12-27%

- Meta-analysis (8 CV outcome trials) in DM and CKD endpoints
  - **Composite:** new severe albuminuria, eGFR decline, SCr rise, progression to ESRD or death from kidney disease → 21% risk reduction (95% CI, 13-27%)

  - GLP-1 RA association with worsening kidney function → not significant

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KDIGO Diabetes Workgroup. *Kidney Int*.2022;102(5S):S1-S127.

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Conclusions: Place In Therapy

- Semaglutide
  - In a **diabetic** population:
    - Reduces risk of CKD progression and death from kidney and CV causes

- Other GLP-1 RA
  - **Diabetic** and/or **overweight** populations:
    - Albuminuria reduction in most trials
    - Slowing of eGFR decline but not across all trials (likely due to variable enrollment criteria)

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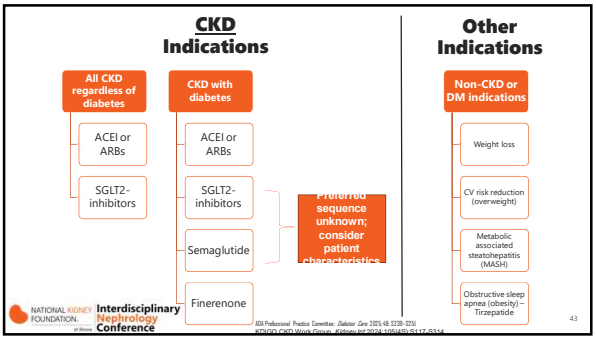

Knowledge Check

When should GLP-1 RA be recommended in patients with CKD?

A. Semaglutide should be used in all CKD patients with or without diabetes.
B. Semaglutide should be considered for CKD with concomitant diabetes given data finding reduced CKD progression and death from cardiovascular and renal causes.
C. Semaglutide oral tablet formulation was used in the FLOW trial and improved composite renal and CV endpoints.
D. Semaglutide should only be used in patients intolerant of ACEI or ARBs.

Knowledge Check

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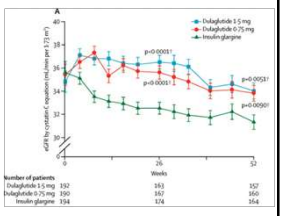
C. Semaglutide oral tablet formulation was used in the FLOW trial and improved composite renal and CV endpoints.
D. Semaglutide should only be used in patients intolerant of ACEI or ARBs.

Question 4
What about special populations, including CKD stage 4/5 and renal transplant?

GLP-1 RA in Special Populations: CKD 4-5

AWARD-7 (dulaglutide)

- Population: DM w/ eGFR 15-30 (29%), eGFR <15 (1%)
  - Efficacy (dulaglutide vs insulin):
    - A1c reduction of 1.1-1.2% (p=NS)
    - Significant more wt loss (-2-3kg vs +1 kg)
    - Slower eGFR decline
  - Serious adverse rate not different vs insulin
    - More nausea (20%) and diarrhea (17%)
    - Less hypoglycemia
  - Dulaglutide treatment discontinuation (10-13%)
  - Side effects similar to general population



Tuttle KR, et al. *Lancet Diabetes Endocrinol.* 2018;6(8):605-617.

GLP-1 RA in Special Populations: Dialysis

*Increased diabetic retinopathy, aHR 1.32, p=0.001
*No difference in pancreatitis, biliary complications, medullary thyroid cancer

Orandi BJ et al. *Clin J Am Soc Nephrol.* 2025;17;20(8):1100-1110.

GLP-1 RA in Special Populations: CKD 4/5

Drug	Semaglutide	Variety GLP-1 RA	Semaglutide PO/SC	Dulaglutide	Variety GLP-1 RA
Design	Prospective cohort	Retrospective GLP-1 RA vs DPP4i	Retrospective cohort	Prospective cohort	Retrospective cohort
Population	• Wt-loss prior to transplant • HD (n=12) • PD (n=1)	• eGFR <15 (n=69) • HD (n=36) • PD (n=12)	• CKD 4 or greater (n=67) • DM (96%)	• HD (n=12) • DM on insulin	• 64 total ESRD (HD=38) • DM
Efficacy	• A1c ↓ 0.3% • Wt ↓ 4.6kg	N/A	• A1c ↓ 0.9% • Wt ↓ 4.9kg	• A1c ↓ 0.4% • Insulin: ↓ 15 units/d • Wt ↓ 1kg	• A1c ↓ 0.8% • Wt ↓ 6kg
Safety	• 1 DC* event after 1st dose (n/v) • Mild GI side effects (n=6)	• 10% DC* for GI effects	• No adverse event (63%) • 37% DC* due to GI effects	N/A	• 10 cases of AKI in non-HD • 2 cases DC* d/t GI side effect

*DC=discontinuation

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Vaněk L et al. *Diabetes Obes Metab.* 2024;26(12):5931-5941.
Sidra F et al. *Diabetes.* 2023; 72(Suppl1).
Long JJ et al. *Endocr Pract.* 2024;30(10):963-969.
Ugamara D et al. 2022;8(26).
Thomas AM et al. J Am Pharm Assoc. 2023;63(5):1612-1616.

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GLP-1 RA in Special Populations: Renal Transplant

- No RCT* data → retrospective/prospective observational studies mostly in diabetic patients
- Most data includes patients >12 mo post transplant
  - Earliest initiation: within 2mo → reduced eGFR decline vs matched controls
- Reduced albuminuria reported
- A1c lowering, weight loss, and GI side effects similar to general population
  - Practice point: ensure GI symptoms from immunosuppression are well controlled prior to initiation
- Impact on post prandial hyperglycemia is beneficial for post transplant diabetes mellitus control

*RCT=randomized controlled trial

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Lawrence SE et al. *Clin Transplant.* 2023;37(3):e14922.
Sato T et al. *J Clin Endocrinol Metab.* 2023; 18;108(10):2597-2603.

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GLP-1 RA in Special Populations: Renal Transplant

- Systematic review and meta-analysis (12 GLP-1RA studies; 3,978 patients)
  - Diker Cohen et al: lower risk of composite graft rejection, start of dialysis, re-transplantation, or all-cause mortality
  - Lin et al: lower risk of all-cause mortality, major adverse CV and kidney events
- Drug Interactions
  - Tacrolimus/Cyclosporine: few studies reported lowering of Tacrolimus/cyclosporine dose required after GLP-1 RA started; most show no significant interaction→ recommend trough within 4 weeks of GLP-1 RA dose adjustments

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Lee S et al.*Transplantation.* 2025; doi: 10.1097/TP0000000000005496. Epub.
Kukla A et al. *Transplant Direct.* 2020 Jan 13;6(2):e524. doi: 10.1097/TXD.0000000000000971
Diker Cohen T et al. *Diabetes Metab.* 2025;51:101624.
Lin LC et al. *Cardiovasc Diabetol.* 2025;24:87.

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Conclusions: Special Populations

- **CKD stage 4-5** (non-dialysis) – reduced macroalbuminuria, eGFR preservation observed; side effect profile appears consistent with general population
- **Dialysis** – safety profile acceptable although data limited; weight loss and glucose lowering effects still observed and meta-analysis found reduced mortality
- **Renal transplant** – favorable for macroalbuminuria reduction, weight loss, A1c reduction and may improve survival as well as reduce cardiovascular and kidney adverse events; well-controlled, prospective trials, ideally RCTs are needed to confirm CV/CKD outcomes

Knowledge Check

AL is 63 year old black male with PMH of hypertension, obesity (BMI 33), T2DM, sleep apnea, gout, and CAD s/p PCI in 9/2024. His current regimen includes insulin glargine 40 units daily and insulin aspart 14 units with meals. Labs today: SCr 2.7 mg/dL (eGFR 25 ml/min), A1c 8.5%, UACR 900 mg/g. He is wondering if semaglutide may be a good option to help with diabetes control, weight loss, and CKD progression. How do you respond?

A. There is no data to support semaglutide use in reducing CKD progression in patients with DM and albuminuria.
B. Semaglutide reduces CKD progression but should only be used in early CKD stages 1-3.
C. Semaglutide decreased kidney failure, eGFR reduction of at least 50%, and death from kidney causes. GLP-1 RA data suggests efficacy in slowing eGFR progression and macroalbuminuria is preserved in CKD stage 4.
D. Weight loss is not expected in patients with diabetes and chronic kidney disease. Only insulin should be used in this population.

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Knowledge Check

MS is a 45 year old female s/p deceased donor kidney transplant in 3/2019 for ESRD due to diabetes. Her endocrinologist contacts you to ask if it is okay to start semaglutide as part of her diabetes management plan. How do you respond?

A. GLP-1 RA should not be used after renal transplant due to the drug interaction with tacrolimus.
B. In a recent meta-analysis, GLP-1 RA were effective in improving some cardiovascular and renal outcomes in renal transplant recipients. A tacrolimus trough should be considered within 4 weeks of initiation.
C. GLP-1 RA should not be trialed after renal transplant because of the unacceptable safety profile observed in prospective trials.
D. GLP-1 RA should be considered for all renal transplant recipients because of large randomized controlled trial data showing improved CKD outcomes.

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Final thoughts

- Semaglutide injection was associated with decreased risk of kidney failure, ↓ eGFR ≥50% and death from kidney or CV causes in patients with CKD and diabetes.
- Analysis of secondary outcomes of other GLP-1 RA in some landmark trials have identified reduction in macroalbuminuria and reduced eGFR decline.
- Patient selection, education, and monitoring are important to prevent adverse effects related to GLP-1 RA medications.

Questions?

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