Pharmacotherapeutic Updates in CKD

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UI Health

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Objectives

Discuss

Discuss updates in pharmacotherapy in the CKD population

Review

Review updates to clinical guidelines applicable to the CKD population

Apply

Apply pharmacotherapy concepts to a CKD patient case

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Meet the patient

AM is 45 y/o female with PMH HTN and obesity.

Weight: 286 lbs Height: 5'1"
Medications: lisinopril 40 mg daily
Electrolytes: within normal limits
SCr: 1.8 mg/dL
uACR: 472 mg/g
BP: 128/76 HR: 74

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Question 1

What equation would be best to calculate AM's renal function?

A. Cockgroft-Gault
B. CKD-EPI (2012)
C. MDRD
D. CKD-EPIcr-cys (2021)

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Question 2

What treatment would be most appropriate for AM's CKD?

A. Liraglutide
B. Semaglutide
C. Canagliflozin
D. Dapagliflozin

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Question 3

What would be the appropriate agent for treating AM's obesity?

A. Dulaglutide (Trulicity®)
B. Liraglutide (Victoza®)
C. Semaglutide (Wegovy®)
D. Exenatide (Byetta®)

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Evaluating Kidney Function

- Several equations of assessing the kidney
  - CrCl – Cockcroft Gault equation
  - eGFR – MDRD equation
  - eGFR – CKD-EPI equation
- GFR considered "best overall index of kidney function"
- All use serum creatinine as base measurement
  - Can be easily measured and available with all patients
  - Poses problems with validity especially in extremes

Inker LA, Titan S. Am J Kidney Dis. 2021;78(5):736-749.

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Evaluating Kidney Function

<u>CrCl – Cockcroft-Gault</u>

- Oldest equation (1976)
- Small and homogenous population studied
- Overestimates GFR by 10-20%
- Adjustor for females
- Primary reference used in drug dosing

<u>eGFR – MDRD</u>

- Derived in 2006
- Slightly more diverse population studied
- More accurate than CrCl *but* underestimates GFR in high-normal GFR
- Adjustor for race
- Used by majority of U.S. labs

Cockcroft DW, Gault MH. Nephron.1976;16:31-41.
Levey AS, et al. Ann Intern Med. 2006;145:247-254.
CAS Survey. 2020-A Kidney Biomarkers. Available at: https://www.cap.org/search?q=2020-A%20Kidney%20Biomarkers.

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Cystatin C

- Protein produced by all nucleated cells
- Meets ideal criteria
- Not dependent on muscle mass
- Can be affected by:
  - Changes in glucocorticoid levels, inflammation, obesity, smoking, thyroid disease
- Only CKD-EPI equation has incorporated its use
- Limited use and availability

Inker LA, Titan S. Am J Kidney Dis. 2021;78(5):736-749.
Delgado C, et al. Am J Kidney Dis. 2021;79(2):268-88.

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CKD-EPI Equation

- Adjustor for race → overestimated eGFR in black population
- 2021: Race removed from all CKD-EPI equations per recommendation by NKF and ASN
  - Increase in earlier CKD diagnosis in black population
    - Reclassification of current CKD status
    - →Earlier referrals to nephrologist and kidney care
  - Medication changes
    - Earlier starting of medications which can reduce CKD progression (e.g. SGLT2i)
    - Need to adjust dosing or stop medications (e.g. metformin, thiazide diuretics, chemotherapy)

Inker LA, et al. N Engl J Med. 2012;367:20-29.
Delgado C, et al. Am J Kidney Dis. 2021;79(2):268-288.

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CKD-EPI Equation

- Available as CKD-EPIcr, CKD-EPIcys, and CKD-EPIcr-cys
- CKD-EPIcr (2021) has the least amount of bias between black and non-black population
- CKD-EPIcr-cys (2021) considered the **most accurate equation overall**
  - KDIGO 2024 recommends its use to stage CKD if cystatin C available (1B)
- Documentation for medication dosing is limited
  - However more medications are providing adjustments based off eGFR

Inker LA, et al. N Engl J Med. 2012;367:20-29.
Delgado C, et al. Am J Kidney Dis. 2021;79(2):268-88.
Ahmed S, et al. Kidney Int. 2024;105(4S): S117-S314.

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Cardiovascular-kidney-metabolic (CKM) Syndrome

- CKM syndrome established to re-evaluate relationship between obesity, diabetes, kidney disease and CVD
- Aim to help PCPs identify, diagnose, and treat these conditions more holistically – interdisciplinary collaboration
- Staging 0-4
  - 0: no CKM risk factors (**no evidence of CKD**)
  - 1: excess or dysfunctional adiposity w/o other metabolic risk factors OR **CKD**
  - 2: metabolic risk factors OR **moderate-high risk CKD**
  - 3: subclinical CVD in CKM syndrome or risk equivalents (ex. **very high-risk CKD [stage G4-G5]**)
  - 4: clinical CVD in CKM syndrome
    - 4a: **no kidney failure**
    - 4b: **kidney failure present**

Ndumele et al. Circulation; 2023;148:1636–1664

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CKM Syndrome

- eGFR has been historical marker for diagnosis for CKD
  - CKD can be diagnosed based off other criteria – uACR
  - Adding kidney parameters to CKD screening will help in identifying and preventing clinical patient outcomes
- Albuminuria is an important marker for CKD prognosis, diabetes screening, and an independent factor for CVD events
- Pharmacotherapeutic recommendations align with current guidelines (ADA, KDIGO)

Ndumele et al. Circulation; 2023;148:1636–1664.

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Monitoring Parameters

- Significant under ordering of uACR

Claims Data from 1/4/07-9/30/18			
Within 1 year: prevalent + newly diagnosed T2D	uACR	1 test: 43%	2 tests: 13%
	SCr	1 test: 85%	2 tests: 62%
	uACR + SCr	1 test each: 42%	
CKD + T2D	2nd confirmatory eGFR test completed in avg 195 +/- 79.1 days		
	2nd confirmatory uACR test completed in avg 219 +/- 84.7 days		

Folkerts K et al. Mayo Clinic Proceedings 2021;96 (4):975-986.

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SGLT2i

- Several SGLT2i medications have been shown to delay progression of CKD and reduce albuminuria
  - Also have benefit in heart failure patients and reducing CV death

Medication	Minimum eGFR start	Dose	Notes
Dapagliflozin (Farxiga®) ★	≥ 25	10 mg daily	
Empagliflozin (Jardiance®) ★	≥ 20	10 mg daily	Increase to 25 mg daily for glucose control
Canagliflozin (Invokana®	≥ 30	100 mg daily	• *Must have diabetes with CKD • 300 mg only for eGFR > 60
Ertugliflozin (Steglatro®)	≥ 45	15 mg daily	**NOT FDA APPROVED for CKD**
Bexagliflozin (Brenzavvy®)	≥ 30	20 mg daily	**NOT FDA APPROVED for CKD**

Farxiga PI, Jardiance PI, Invokana PI, Steglatro PI, Brenzavvy PI

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SGLT2i Renal Mechanism of Action

- Initial decrease in eGFR (~5 mL/min)→ short-term!
  - Lowest point ~1-2 weeks then recovers to baseline over 3-9 months
  - As Na and glucose reabsorption is decreased in proximal tubule, there is increased Na delivery to distal tubule leading to afferent arteriole vasoconstriction
- Decreased RAAS activity
- Decreased inflammation/fibrosis
- Decreased renal hypoxemia

Lower blood pressure
+
Reduced glomerular and tubular damage
+
Reduced albuminuria
+
Reduced renal ischemia
=
GFR preservation

Bailey CJ, et al. Curr Diab Rep. 2022;22:39-52.

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Canagliflozin – CREDENCE Trial (2019)

- Primary outcome: Composite of kidney failure, doubling of SCr, or death from kidney or CV causes
- Important inclusion criteria:
  - Type 2 diabetes
  - eGFR 30-90 mL/min/1.73m^2
  - uACR 300-5000 mg/g
  - ACE-I or ARB required
- Baseline characteristics (n=4401):
  - Mean age 63$\pm$ 9.2 years, 33.9% female
  - Mean eGFR: 56.2$\pm$ 18.2 mL/min/1.73m^2
  - Median uACR: 927 mg/g

Perkovic V, et al. N Engl J Med. 380(24):2295-2306.

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Canagliflozin – CREDENCE Trial (2019) Results

- Primary composite outcome met statistical significance (HR 0.70 (0.59-0.82), p=0.00001)
- Each individual renal outcome and all related secondary individual outcomes were also statistically significant
  - Composite ESKD, doubling of SCr, or renal death
- uACR average was 31% lower with canagliflozin
- eGFR decline was less with canagliflozin than with placebo (-1.85$\pm$0.13 vs -4.59$\pm$0.14 mL/min/1.73m^2) 95%CI (2.37-3.11)

Perkovic V, et al. N Engl J Med. 380(24):2295-2306.

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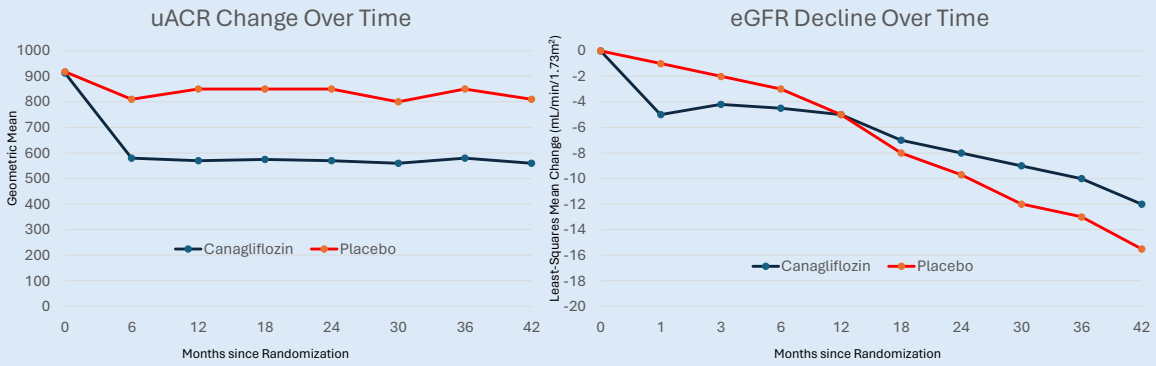
Canagliflozin – CREDENCE Trial (2019) Results



Perkovic V, et al. N Engl J Med. 380(24):2295-2306.

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Dapagliflozin – DAPA-CKD (2020)

- Primary outcome: first occurrence of a ≥50% decline in eGFR, onset of ESKD, or death from kidney or CV causes
- Important inclusion criteria:
  - eGFR 25-75 mL/min/1.73m^2
  - uACR 200-5000 mg/g
  - ACE-I or ARB required
- Groups divided based on presence of diabetes and uACR ≤ 1000 or ≥ 1000 mg/g
- Baseline characteristics (n=4304):
  - Age 61.8±12.1 years, 33.1% female
  - Mean eGFR: 43.1 ±12.4 mL/min/1.73m^2
  - Median uACR: 949 mg/g
  - ACE-I or ARB: 98%

Heerspink HJL, et al. N Engl J Med. 2020;383(15):1436–1446.

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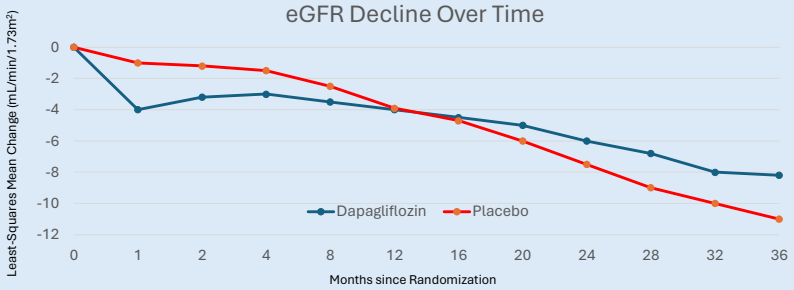
Dapagliflozin – DAPA-CKD (2020) Results

- Primary composite outcome met statistical significance (HR 0.61 (0.51-0.72), p<0.001)
  - Each individual renal outcome was statistically significant
  - All secondary composite and individual outcomes also statistically significant



Heerspink HJL, et al. N Engl J Med. 2020;383(15):1436–1446.

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Empagliflozin – EMPA-KIDNEY (2023)

- Primary outcome: first occurrence of kidney disease progression or death from CV causes
- Important inclusion criteria:
  - eGFR 20-45 mL/min/1.73m^2 (no minimum albuminuria) or
  - eGFR 45-90 mL/min/1.73m^2 with uACR $\geq$ 200 mg/g
  - ACE-I or ARB required
- Baseline characteristics (n=6609):
  - Age 63.8$\pm$13.9 years, 33.2% female
  - Mean eGFR: 37.3$\pm$ 14.5 mL/min/1.73m^2
  - Median uACR: 329 mg/g
  - ACE-I or ARB: 85.2%

EMPA-Kidney Collaborative Group. N Engl J Med. 2023;388:117-127.

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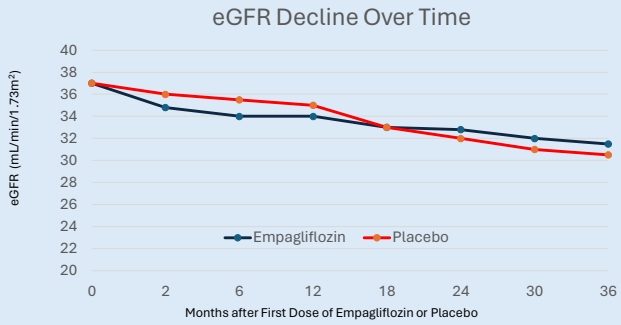
Empagliflozin – EMPA-KIDNEY (2023) Results

- Primary composite outcome met statistical significant (HR 0.72 (0.64-0.82), p<0.001)
  - All renal related secondary outcomes also statistically significant
- Empagliflozin was significantly better than placebo in uACR >300 and across all eGFR groups (< 30, ≥ 30--< 45, ≥ 45 mL/min/1.73m^2)



EMPA-Kidney Collaborative Group. N Engl J Med. 2023;388:117-127.

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Guidelines

KDIGO 2024

- Treat with an SGLT2i (1A):
  - T2D+ CKD + eGFR ≥20 mL/min/m^2
  - CKD + uACR ≥ 200 mg/g
  - CKD + heart failure
  - eGFR ≥ 20-45 ml/min/m^2 + uACR <200 mg/g (2B)

ADA 2024

- Treat with an SGLT2i (A)
  - T2D and CKD with eGFR ≥20 mL/min/m^2 and uACR ≥200 mg/g
- Treat with an SGLT2i (B)
  - T2D and CKD with eGFR ≥20 mL/min/m^2 and uACR normal to 200 mg/g

Ahmed S, et al. KDIGO 2024. Kidney International. 2024;105:S117-S314.
ElSayed NA, et al. Diabetes Care. 2024;47:S219-S230.
De Boer IH, et al. Diabetes Care. 2022;45(12):3075-3090.

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SGLT2i Tips To Consider

- Per KDIGO, SGLT2i may be continued until anuric, initiation of kidney replacement therapy, or intolerance
  - Discontinue once on dialysis
- ADE: genital mycotic infections, volume depletion, euglycemic diabetic ketoacidosis (hold 3-4 days prior to surgery)
- Should be on ACE-I or ARB in addition to SGLT2i
- Do **not** use in the following populations:
  - Type 1 diabetes
  - Kidney cystic disease
  - On immunosuppressive agents for kidney disease
- Are under-prescribed
  - CKD + T2D: 6% CKD alone: 0.3%

Zhuo M, et al. Kidney360. 2022;3(3):455-464.

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Finerenone

- A ns-MRA that blocks activation of aldosterone
  - Inhibits Na reabsorption in distal tubule and MR over-activation in the kidney, heart, blood vessels reducing inflammation and fibrosis
- ADE: hyperkalemia and hypotension
  - Monitor K within 4 weeks of start

eGFR ($mL/min/m^2$)	Starting Dose	K Adjustment
> 60	20 mg po daily	K >5.5: STOP medicine Restart at 10 mg po daily when K ≤ 5
25-60	10 mg po daily	≤ K 4.8: may titrate to 20 mg po daily K 4.8-5.5: continue current dose 10 mg or 20 mg po daily K >5.5: STOP medicine
<25	Do NOT start	

Kerendia PI

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Guidelines

KDIGO 2024

- Ns-MRA (2A):
  - T2D+ eGFR ≥25 mL/min/m^2 + normal K level + albuminuria (≥30 mg/g) + max tolerated RAAS inhibitor
  - "Can be added to a RAAS inhibitor +SGLT2i for treatment of T2D and CKD"

ADA 2024

- Ns-MRA (A):
  - Use if have T2D + CKD + albuminuria to reduce CV events and CKD progression if eGFR ≥ 25 mL/min/m^2

Ahmed S, et al. KDIGO 2024. Kidney International. 2024;105:S117-S314.
ElSayed NA, et al. Diabetes Care. 2024;47:S219-S230.

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Finerenone Tips To Consider

- Should be added on to RAAS inhibitor + SGLT2i
- Must have diabetes to consider its use
  - Not studied in advanced heart failure (HFrEF NYHA II-IV)
- Hyperkalemia may limit its use
- Contraindicated with strong CYP 3A4 inhibitors
  - E.g. ketoconazole, clarithromycin, itraconazole, ritonavir
  - Has major interactions with other CYP 3A4 inhibitors and inducers
- Prior authorization may be necessary

Kerendia PI

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GLP-1 RA

- Use for CKD not FDA approved – no trials showing primary outcome benefits
  - Liraglutide (LEADER trial), semaglutide (SUSTAIN-6 trial), and dulaglutide (REWIND trial) showed positive secondary outcomes in worsening nephropathy

GLP-1 RA	CKD Adjustment	
Dulaglutide (Trulicity®)	None	Showed benefit in CVD
Liraglutide (Victoza®)	None*	
Semaglutide (Ozempic®)	None*	
Lixisenatide (Adlyxin®)	Do not use in eGFR < 15	
Exentanide (Byetta®)	Do not use in eGFR <30	

*Limited severe CKD data

Marso SP et al. N Engl J Med. 2016.375(4):311-322.
Marso SP et al. N Engl J Med. 2016:375(19):1834-1844.
Gerstein HC et al. Lancet. 2019;394(10193):121-130.
Trulicity PI, Victoza PI, Ozempic PI, Adlyxin PI, Byetta Pi.

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Guidelines

KDIGO 2024

- Treat with GLP-1 RA (1B)
  - T2D + CKD if glycemic goals not achieved with use of metformin + SGLT2i **or** unable to use those medications

ADA 2024

- Consider treatment with GLP-1 RA (A)
  - T2D + CKD + eGFR $\geq$ 25 mL/min/m^2
  - Use agent with proven CV benefit when SGLT2i not tolerated or contraindicated

Ahmed S, et al. KDIGO 2024. Kidney International. 2024;105:S117-S314.
ElSayed NA, et al. Diabetes Care. 2024;47:S219-S230.

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GLP-1 RA Future Renal Considerations

- Trials are being done for primary renal outcomes
- ClinicalTrials.gov ID: NCT03819153
  - Semaglutide vs placebo
  - Primary outcome: time to first occurrence of composite eGFR decline of ≥50% from baseline, reaching ESKD, death from renal or CV disease
- ClinicalTrials.gov ID: NCT04865770
  - Semaglutide vs placebo
  - Primary outcome: change in kidney oxygenation, global perfusion, inflammation

Clinicaltrials.gov ID: NCT03819153
Clinicaltrials.gov ID: NCT04865770

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GLP-1 RA

- Also have approved indication for obesity
  - Liraglutide (Saxenda®), semaglutide (Wegovy®)
  - Tirzepatide (Mounjaro®) is a GLP-1 RA/GIP
  - Dosing may be different than for diabetes
- Study being done with GLP-1 RA and SGLT2i in obese patients with CKD
  - ClinicalTrials.gov ID: NCT06344247
    - Primary outcome: change in 24 hour urine protein quantification
    - RAAS inhibitor vs
      - RAAS inhibitor + dapagliflozin
      - RAAS inhibitor + semaglutide
      - RAAS inhibitor + dapagliflozin + semaglutide

Saxenda PI, Wegovy PI, Mounjaro PI
Clinicaltrials.gov ID: NCT06344247

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GLP-1 RA – Can They Be Safely Used In Obese ESKD Patients?

- Semaglutide
  - Per the prescribing information, no clinically relevant changes in pharmacokinetics were observed
  - Studies and case reports have shown favorable results
  - Potential for increased ADEs
- Tirzepatide
  - Per the prescribing information, no change in pharmacokinetics were observed

Saxenda PI, Mounjaro PI
Saito S et al. Ther Apher Dial. 2022;26(1):242-243.
Touzot M, et al. Clin Kidney J. 2022;15(9):1782-1784.
Long JJ, et al. Am J Transplant. 2022; 22 (suppl 3).
Clemens KK, et al. Nutr Metab Cardiovasc Dis. 2023;33(6):1111-1120.

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GLP-1 RA – Can They Be Safely Used In Obese ESKD Patients?

Liraglutide

- Per the prescribing information, caution should be used in this patient population
- Idorn et al showed a 49% increase in plasma trough concentration in ESKD
  - Resulted in increased ADE (nausea, vomiting)
  - Decreasing dose and extending titration schedule recommended
- Bomholt et al showed increased hypoglycemia in diabetic, obese patients on dialysis

Wegovy PI
Idhorn T, et al. Diabetes Care. 2016;39(2):206-213.
Bomholt T, et al. Nephron 2021;145:27-34.

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GLP-1 RA

- Overall would be considered safe to use
- Studies showed favorable responses to weight loss
  - For those with concomitant diabetes, glycemic indexes were also improved
- Extending interval of titration may help with ADE
- Currently there are still shortages across the United States
  - Only approved formulations of GLP-1 RA for obesity should be used!
  - Caution in using compounded GLP-1 RA products as they are not FDA approved/regulated formulations

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Medicare Prospective Payment System

- Also known as the "bundle" allows for certain medications to be covered under the Medicare entity
- Injectable, intravenous, or biological medications covered
  - Regulation revised to include that oral-only drugs are those with no injectable functional equivalent
- New renal drugs or biologics that treat ESKD conditions are placed under TDAPA
  - Injectable, intravenous, oral, or other forms
  - A 2 year program that allows for facilities to incorporate new products while providing additional payments for their use
  - Once TDAPA ends, a post-TDAPA add-on payment applies for 3 years

CMS ESRD PPS Transitional Drug Add-on Payment Adjustment https://www.cms.gov/medicare/payment/prospective-payment-systems/end-stage-renal-disease-esrd/esrd-pps-transitional-drug-add-payment-adjustment
HHS CMS Final Rule. https://public-inspection.federalregister.gov/2023-23915.pdf.

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HIF-PHI Agents

- Currently daprodustat and vadadustat are the only approved HIF-PHI in the United States
- Approval is strictly for dialysis patients
- Daprodustat was the first in class medication HIF-PHI approved in 2023
  - Approved under CMS TDAPA 10/1/23-9/30/25
    - Current payment amount for 1 mg $3.910 (4/1/24-6/30/24)
- Vadadustat recently approved on 3/27/2024
  - Was previously rejected by the FDA due to unfavorable risk-benefit assessment in both non-dialysis and dialysis patients
  - Commercial launch expected in second half of 2024

Payment Amounts for ESRD PPS TDAPA https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ESRDpayment/Downloads/Drugs-and-Biologicals-Eligible-for-TDAPA.pdf
Carrasco M. Akebia. https://ir.akebia.com/news-releases/news-release-details/akebia-receives-fda-approval-vafseor-vadadustat-tablets

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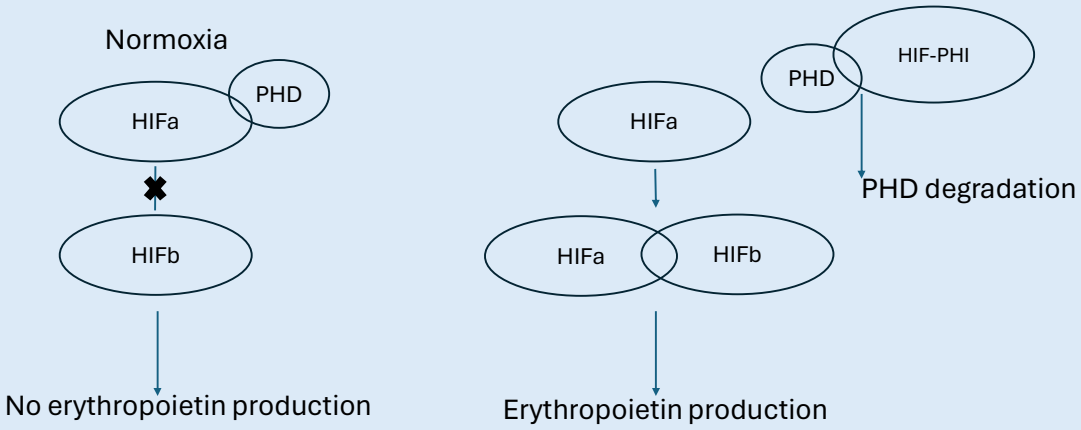
HIF-PHI – Mechanism of Action



Haase VH. Kidney Int Suppl. 2021;11(1):8-25.

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Daprodustat – ASCEND-D Trial (2021)

- Primary non-inferiority outcomes: mean change in hemoglobin level from baseline and first occurrence of MACE, a composite of death from any cause, nonfatal MI, or nonfatal stroke
- Daprodustat vs epoetin alfa IV (hemodialysis) or darbepoetin alfa (peritoneal dialysis)
- Target hemoglobin level: 10-11 g/dL
- Important inclusion criteria:
  - Received an ESA for at least 6 weeks
  - Hemoglobin level between 8-12 g/dL, ferritin >100 ng/mL, and TSAT >20%
- Important exclusion criteria:
  - Anemia from non-CKD causes
  - Recent cardiovascular event
  - Current or recent cancer

Singh AK, et al. N Engl J Med. 2021;385(25):2325-2335.

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Daprodustat – ASCEND-D Trial (2021)

- Baseline characteristics (n=2964):
  - Mean age 58.5 years, 42.8% female
  - Mean hemoglobin: 10.4 ± 1.0 g/dL
  - Median TSAT: 32.5%
  - Median ferritin: 589 ng/mL daprodustat vs 604 ng/mL ESA
  - Mean CV disease: 44.9%
  - Mean IV iron dose/month: 138.3 mg
    - ~64% patients receiving IV iron
  - Hemodialysis modality: 88.5%

Singh AK, et al. N Engl J Med. 2021;385(25):2325-2335.

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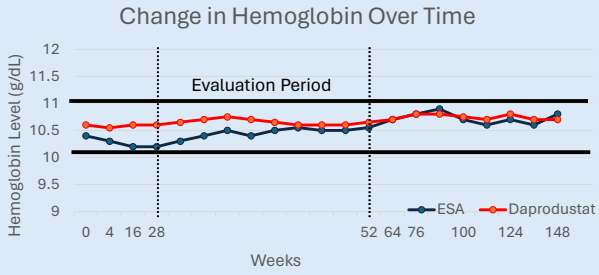
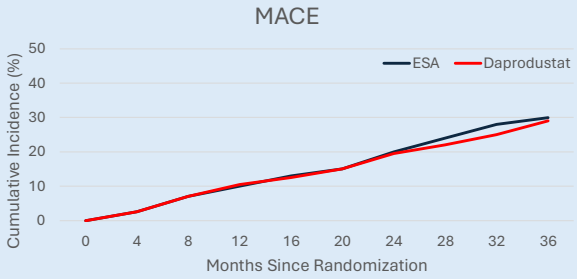
Daprodustat – ASCEND-D Trial (2021) Results

- Primary outcome non-inferiority achieved
  - Mean adjusted difference 0.18 (0.12-0.24)
- MACE: HR 0.93 (0.81-1.07) met noninferiority





Singh AK, et al. N Engl J Med. 2021;385(25):2325-2335.

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Daprodustat – Dosing

- Available in 1 mg, 2 mg, 4 mg, 6 mg, 8 mg tablets
- Daily doses: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, 24 mg

Current ESA Dose			Dose (daily)
Epoetin Alfa (units/wk)	Darbepoetin Alfa (mcg/4weeks)	Methoxy polyethylene glycol beta (mcg/month)	
<2000	20 to 30	30 to 40	4 mg
2000-10,000	> 30 to 150	> 40 to 180	6 mg
10,000-20,000	> 150 to 300	> 180 to 360	8 mg
>20,000	>300	>360	12 mg
Hemoglobin ESA Naïve			**Dose (daily)**
<9			4 mg
≥ 9 to ≤ 10			2 mg
>10			1 mg
Liver Impairment Child-Pugh class B: cut starting doses by half unless starting with 1 mg Do not use in Child-Pugh class C			

Jesduvroq PI

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Daprodustat – Consideration Points

- Must be on dialysis for 4 months before able to start
- Black Box Warning
  - Increased risk of death, MI, stroke, VTE, vascular access thrombosis
- Target hemoglobin levels <11 g/dL and use lowest dose to decrease transfusion
- Ensure iron parameters are within goal
- Dose Adjustments:
  - Hemoglobin monitored q 2 weeks, once stable q month
  - Do not increase dose more frequently than q 4 weeks
  - Increase dose at next increment level

Jesduvroq PI

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Daprodustat – Consideration Points

- Contraindications:
  - Use of strong CYP 2C8 inhibitors (gemfibrozil)
  - Uncontrolled HTN
- Precaution
  - Heart failure
  - HTN
  - GI erosion
  - Malignancy – not recommended to use with active malignancy
- Drug interactions:
  - Increases in daprodustat seen with trimethoprim and clopidogrel
  - Decreases in daprodustat seen with rifampin
- Can be taken with or without food; dialysis timing negligible

Jesduvroq PI

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Vadadustat – INNO$_2$VATE Trial (2021)

- Primary non-inferiority outcomes: mean change in hemoglobin from baseline and first occurrence of an adjudicated MACE (pooled from 2 trials)
- Vadadustat vs darbepoetin IV/SC
  - Stratified by NYHA HF Class 0-1 vs 2-3 and entry hemoglobin <9.5 or ≥ 9.5 g/dL
- Target hemoglobin level: 10-11 g/dL
- Important inclusion criteria:
  - Hemoglobin level between 8-11 g/dL, ferritin >100 ng/mL, and TSAT >20%
- Important exclusion criteria:
  - Anemia from non-CKD causes
  - Use of ESA within 8 weeks prior to screening
  - Active cancer within 2 years

Eckhardt KU, et al. N Engl J Med. 2021;384(17):1601-1612.

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Vadadustat – INNO$_2$VATE Trial (2021)

Baseline Characteristics (n = 3923)

Incident Dialysis

- Mean age 56.1 years, 40.4% female
- Mean hemoglobin: 9.3± 1.1 g/dL
- Mean TSAT and ferritin in vadadustat vs darbepoetin: 31.3% vs 34.2%; 469.7 vs 527.8
- Mean CV disease: 38.1% vs 38.8% vadadustat vs darbepoetin
- IV iron use: 50.8% vs 58.5% vadadustat vs darbepoetin
- Hemodialysis modality: 89.1%

Prevalent Dialysis

- Mean age 58.2 years, 43.9% female
- Mean hemoglobin: 10.4 ± 0.8 g/dL
- Mean TSAT and ferritin in vadadustat vs darbepoetin: 38.3% vs 37.6%; 846.8 vs 840.7
- Mean CV disease: 48.8% vs 52.4% vadadustat vs darbepoetin
- IV iron use: 51.3% vs 48% vadadustat vs darbepoetin
- Hemodialysis modality: 92.4%

Eckhardt KU, et al. N Engl J Med. 2021;384(17):1601-1612.

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Vadadustat – INNO$_2$VATE Trial (2021)Results

- Evaluation between weeks 24-36 and 40-52

Primary Outcome		
Weeks	Incident	Prevalent
24-36	-0.31±0.11 (95% CI, -0.53 to -0.10)	-0.17±0.03 (95% CI, -0.25 to -0.1)
40-52	-0.07±0.13 (95% CI, -0.4 to 0.19)	-0.18±0.04 (95% CI, -0.25 to -0.12)
MACE (pooled)		
18.2% vadadustat vs 19.3% darbepoetin (HR 0.96, 95%, 0.81-1.11)		
MACE (pooled)		
21.6% vadadustat vs 23% darbepoetin (HR 0.96, 95%, 0.814-1.10)		

Eckhardt KU, et al. N Engl J Med. 2021;384(17):1601-1612.

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Vadadustat – Dosing

- Available in 150 mg, 300 mg, 450 mg tablets
- Dose: 300 mg po daily
  - Do not increase more than every 4 weeks
  - Titrate in increments of 150 mg (max 600 mg)
  - With or without food; negligible with dialysis
- Switching from ESA
  - Epoetin: 2 days after stopping
  - Darbepoetin alfa: 7 days after stopping
  - Methoxy-polyethylene glycol epoetin-beta: 14 days after stopping
  - Start at 300 mg dose

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Vadadustat – Consideration Points

- Must have been on dialysis for 3 months prior to starting
- Target hemoglobin levels <11 g/dL and use lowest dose to decrease transfusion
- Ensure iron parameters are within goal
- Black Box Warning
  - Increased risk of death, MI, stroke, VTE, vascular access thrombosis

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Vadadustat – Consideration Points

- Warnings and Precautions:
  - HTN, seizures, GI erosion
  - Malignancy—not recommended to use with active malignancy
  - Hepatotoxicity: baseline ALT/AST, bilirubin should be measured and monthly for first 6 months
    - Do not use in patients with cirrhosis, or active/acute liver disease
- ADEs: HTN and diarrhea
- Drug interactions:
  - Are considerable and warrant close monitoring for both vadadustat and other drugs depending on interaction

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Vadadustat – Drug Interactions

Class	Vadadustat Affecting Other Drugs	Recommendation	Class	Other Drugs Affecting Vadadustat	Recommendation
Statins • Simvastatin • Rosuvastatin	Increase statin ADEs	Simvastatin: start at 5 mg/day, max 20 mg/day Rosuvastatin: max 5 mg/day	Phosphorus binders (non-iron based)	Lowers vadadustat's effectiveness	Give 1 hour prior or 2 hours after binders
OAT 3 substrates (cefaclor, ceftizoxime, famotidine, furosemide, oseltamivir carboxylate, penicillin G, sitagliptin)	Increase substrate's ADEs	Monitor closely for ADEs and adjust substrate's dosage accordingly	Phosphorus binders (iron based)		Give 1 hour prior to binders
BCRP substrate (sulfasalazine)	Increase in substrate's ADEs	Monitor closely for ADEs and adjust substrate's dosage accordingly	Iron supplements		Give 1 hour prior to iron supplements
			OAT 1/OAT 3 inhibitors (probenecid, rifampicin, gemfibrozil, teriflunomide)	May increase hemoglobin too quickly or in large increments	Monitor hemoglobin closely

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HIF-PHI Use In Non-Dialysis Patients

Are approved in Europe and Asia in this population

- Daprodustat denied approval by FDA in non-dialysis patients
- ASCEND-ND (2021): daprodustat vs darbepoetin alfa
  - Showed noninferiority with mean in change in hemoglobin
  - On-treatment MACE analysis showed daprodustat had a **higher incidence of first MACE** compared to darbepoetin 14.1% vs 10.5% (HR 1.4, 1.17-1.68) which was **significant**
- Vadadustat denied approval by FDA in non-dialysis patients
- PRO_2TECT (2021): vadadustat vs darbepoetin alfa
  - Showed noninferiority with mean in change in hemoglobin
  - MACE: **higher incidence of first MACE** 22% in vadadustat vs 19.9% darbepoetin (HR 1.17, 95% CI, 1.01 to 1.36) compared to darbepoetin 14.1% vs 10.5% (HR 1.4, 1.17-1.68) which was **significant**

Singh AK, et al. N Engl J Med. 2021;385(25):2313-2324.
Chertow GM, et al. N Engl J Med. 2021; 384 (17):1589-1600.

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Difelikefalin

- Was approved under CMS TDAPA 4/1/22-3/31/24
  - Post-TDAPA add-on payment will be $0.2493
- Indicated for moderate-severe pruritis associated with CKD in hemodialysis patients only
- Mechanism of action
  - Is a kappa opioid receptor agonist – peripheral nerves carry kappa and mu receptors
  - Will increase activity at the kappa receptor → turns off signal of pruritus
- May perform a Worst Itching Intensity Numerical Rating Scale
  - In studies, mean baseline scores were 7.1 ± 1.5 and 7.2 ±1.4 out of 10
  - Itch reduction by 3-4 points seen at week 4 and maintained through week 12 which was significant
  - Studies allowed concomitant use of antihistamines, glucocorticoids, opioids, gabapentin, and pregabalin

Korsuva PI
Dept HHS Federal Register https://public-inspection.federalregister.gov/2023-23915.pdf
Kim BS, et al. Exp Dermatol. 2022;31(2):1900-1907.
Fishbane S, et al. N Engl J Med. 2020;382(3):222-232.

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Difelikefalin – Dosing & Administration

- Should be on dialysis for 3 months
- Comes as 65 mcg/1.3 mL vial
- Weight based dosing: 0.5 mcg/kg (EDW)
  - Prescribing information has a table of volume to be injected based off EDW ranges
- Must be given at the end of dialysis or during the rinseback
- Line should be flushed with normal saline
- If receiving etelcalcetide, would recommend giving etelcalcetide first, flush the line then given difelikefalin
- Should be stored in the refrigerator and used within 60 minutes of mixing

Korsuva PI

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Difelikefalin – Consideration Points

- ADEs: dizziness, somnolence, mental status changes, gait disturbances
  - Somnolence more prevalent in elderly > 65 years old (7% vs 2.8% placebo)
  - Recommended to avoid driving until effects of drug are known in patient
- Avoid use of medications that may have additive ADEs
  - Anti-histamines or opioid analgesics
- Avoid in severe liver impairment

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Difelikefalin – In the Pipeline

- ClinicalTrials.gov NCT05342623 and NCT05356403
  - Primary outcome: Proportion of subjects achieving a 4 point improvement from baseline to the weekly mean of the daily 24-hour Worst Itching Rating Scale score
  - Includes CKD G4-5D
  - Oral 1 mg tablet vs placebo

ClinicalTrials.gov ID: NCT05342623
ClinicalTrials.gov ID: NCT05356403

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Tenapanor

- Approved in fall 2023 – reimbursed through prescription insurance
- Mechanism of action:
  - Inhibits the sodium/hydrogen exchanger 3 on the epithelial surface of the small intestine and colon leading to a reduction in sodium and phosphate absorption (via reduced phosphate permeability through the paracellular pathway)
- Studies showed a decrease in phosphorus

Trial	Baseline Phosphorus	Decrease in Phosphorus
Block GA, et al. 2019	≥6 to >10 mg/dL	-1.19 ± -1.82 mg/dL
Block GA, et al. 2021	≥6 to >10 mg/dL	-1.4 ± -1.8 mg/dL
Pergola PE, et al. 2021	≥5.5 to 10 mg/dL	-0.84 (-1.21, -0.58) mg/dL

Xphozah PI Block GA, et al. J Am Soc Nephrol. 2019;30(4):641-652.
Block GA, et al. Kidney360. 2021;2(10):1600-1610. Pergola PE, et al. J Am Soc Nephrol. 2021;32(6):1465-1473.

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Tenapanor – Dosing & Administration

- Comes as 30 mg, 20 mg 10 mg tablets
- Starting dose 30 mg po bid
  - If diarrhea is bothersome, may go down in dose to 20 mg or 10 mg po bid
  - If diarrhea is severe, discontinue
- ADE: diarrhea (43-53%)
- Discontinue medications that can induce diarrhea or loose stool
  - Stool softeners (docusate sodium)
  - Laxatives (senna, polyethylene glycol, bisacodyl, etc.)
- Assess current GI effects from binder
  - Avoid use if patient already with looser stool (e.g. iron-based binders)

Xphozah PI

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Tenapanor – Consideration Points

- Should be taken with food: first and last meals of day
  - Increased 24 hour phosphorus excretion compared to empty stomach
  - Important—days of dialysis, do not take dosage prior to dialysis
  - E.g.: skip morning dose for those on the am/mid shifts
- Do not give in those with GI obstruction
- Drug Interactions
  - Enalapril: exposure may be decreased (monitor BP)
  - Sodium polystyrene sulfonate needs to be separated by 3 hours
- Must send prescription to an approved specialty pharmacy
  - Do not send to a local pharmacy
- Prior authorization may be required
  - Important to note in documentation tenapanor has a different mechanism of action and is used with current phosphorus binder

Xphozah PI

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Reassessing the patient

AM is 45 y/o female with PMH HTN and obesity.

Weight: 286 lbs Height: 5'1"

Medications: lisinopril 40 mg daily

Electrolytes: within normal limits

SCr: 1.8 mg/dL

uACR: 472 mg/g

BP: 128/76 HR: 74

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Question 1

What equation would be best to calculate AM's renal function?

A. Cockgroft-Gault
B. CKD-EPI (2012)
C. MDRD
D. CKD-EPIcr-cys (2021)

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Question 2

What treatment would be most appropriate for AM's CKD?

A. Liraglutide
B. Semaglutide
C. Canagliflozin
D. Dapagliflozin

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Question 3

What would be the appropriate agent for treating AM's obesity?

A. Dulaglutide (Trulicity®)
B. Liraglutide (Victoza®)
C. Semaglutide (Wegovy®)
D. Exenatide (Byetta®)

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Discussion

- Important to utilize most accurate equation to assess for renal function
- Look at guidelines and studies to know which agents would be most appropriate for your patient for CKD progression
- SGLT2i are becoming a cornerstone therapy for CKD progression however still under prescribed
- ESKD has seen a boost in new therapies which highlights importance of knowing nuances of medications to choose the appropriate patient that would benefit from such

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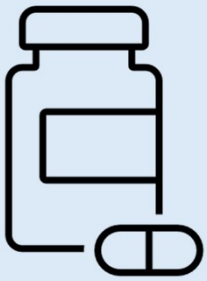
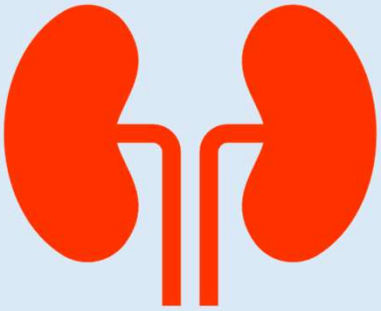
Questions?





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Abbreviations

- ACE-i: angiotensin converting enzyme inhibitor
- ADA: American diabetes association
- ADE: adverse drug events
- ARB: angiotensin receptor blocker
- ASN: American society of nephrology
- BCRP: breast cancer resistance protein
- CI: confidence interval
- CKD: chronic kidney disease
- CKD-EPI: chronic kidney disease epidemiology collaboration
- CMS: Centers for Medicare and Medicaid Services
- CrCl: creatinine clearance
- CV(D): cardiovascular (disease)
- CV(D): cardiovascular (disease)
- EDW: estimated dry weight
- ESA: erythropoietin stimulating agent
- ESKD: end stage kidney disease
- GI: gastrointestinal
- GIP: glucose dependent insulinotropic polypeptide
- GFR: glomerular filtration rate
- GLP-1 RA: glucagon-like peptide-1 receptor agonist
- HIF-PHI: hypoxia inducible factor prolyl hydroxylase inhibitor
- HfrEF: heart failure with reduced ejection failure
- HR: hazard ratio
- HTN: hypertension
- KDIGO: kidney disease improving global outcomes
- MACE: major adverse cardiovascular event
- MDRD: modification of diet in renal disease
- MI: myocardial infarction
- NKF: national kidney foundation
- Ns-MRA: non-steroidal mineralocorticoid receptor antagonist
- NHYA: New York heart association
- OAT: organic anion transporter
- PHD: prolyl hydroxylase domain
- RAAS: renin angiotensin aldosterone system
- SCr: serum creatinine
- SGTL2i: sodium-glucose co-transporter-2 inhibitor
- T2D: type 2 diabetes
- TDAPA: transitional drug add-on payment adjustment
- TSAT: transferrin saturation
- uACR: urine albumin-creatinine ratio
- VTE: venous thromboembolism

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