What's New In Medication Treatment for CKD?

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Disclosure

I have no current or potential conflict of interest to disclose.

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Objectives

Discuss

Describe updates in pharmacotherapy in the chronic kidney disease (CKD) and end stage kidney disease (ESKD) population

Review

Review updates to clinical guidelines applicable to the CKD population

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CKD's Effects

- CKD is not just a disease affecting the kidney
  - Other organs (i.e. heart) are impacted by decline in kidney function
- Often when treating CKD, will need to consider treatments for cardiovascular disease or metabolic disease
  - Cardiorenal syndrome or metabolic syndrome
  - One in three U.S. adults have 3 (+) risk factors that promote these diseases
- New way of thinking of these diseases together → 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

American Heart Association. Heart and stroke statistics.
Ndumele et al. Circulation; 2023;148:1636-1664

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CKM Syndrome Staging

- Stage 0: no CKM risk factors (**no evidence of CKD**)
- Stage 1: excess or dysfunctional adiposity w/o other metabolic risk factors OR **CKD**
- Stage 2: metabolic risk factors OR **moderate-high risk CKD**
  - *Start ACE-I/ARB, SGLT2i, ns-MRA, GLP-1 RA*
- Stage 3: subclinical CVD in CKM syndrome or risk equivalents (ex. **very high-risk CKD [stage G4-G5]**)
- Stage 4: clinical CVD in CKM syndrome
  - 4a: **no kidney failure**
  - 4b: **kidney failure present**
    - *Assess dialyzability of medications (ACE-I, beta-blockers) in HD*
    - *If HF present, PD may be preferable over HD*

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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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± 9.2 years, 33.9% female
  - Mean eGFR: 56.2± 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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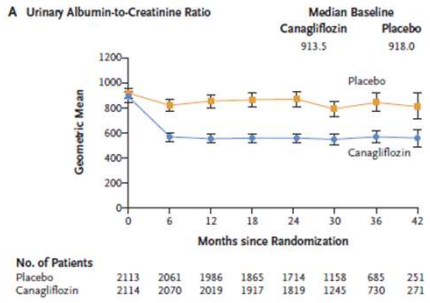
Canagliflozin – CREDENCE Trial (2019) Results

- Primary composite outcome met statistical significance (HR 0.70 (CI 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±0.13 vs -4.59±0.14 mL/min/1.73m^2) [CI 2.37-3.11]

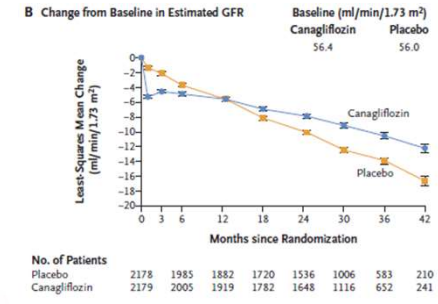
Perkovic V, et al. N Engl J Med. 380(24):2295-2306. 10

Canagliflozin – CREDENCE Trial (2019) Results



Perkovic V, et al. N Engl J Med. 380(24):2295-2306. 11

Canagliflozin – CREDENCE Trial (2019) Results



Perkovic V, et al. N Engl J Med. 380(24):2295-2306. 12

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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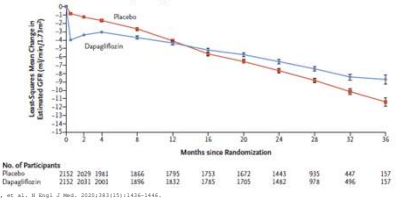
Dapagliflozin – DAPA-CKD (2020) Results

- Primary composite outcome met statistical significance (HR 0.61 (CI 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 ≥ 200 mg/g
  - ACE-I or ARB required
- Baseline characteristics (n=6609):
  - Age 63.8±13.9 years, 33.2% female
  - Mean eGFR: 37.3± 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 (CI 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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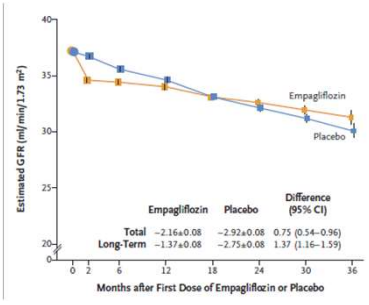
Empagliflozin – EMPA-KIDNEY (2023) Results



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(S1):S231-S233.
De Boer IA, 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

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.

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 ≥ 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.

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®, Zepbound®) 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, Zepbound 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.
Troost M, et al. Clin Kidney J. 2022;15(9):1782-1784.
Long JJ, et al. Am J Transplant. 2022; 22 (suppl 3).
Clemens RK, 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
Idborn 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 Tips To Consider

- 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
  - Goes into effect January 1, 2025
- 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
CMS ESRD PPS Drug Designation Process. https://www.cms.gov/medicare/payment/prospective-payment-systems/end-stage-renal-disease-esrd/esrd-pps-drug-designation-process

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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 (7/1/24-8/30/24)
- 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
  - TDAPA application submitted in June 2024 with expected approval January 2025

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
Carrasco M. Akebia. https://www.morningstar.com/news/pr-newswire/20240711ne59219/akebia-therapeutics-provides-update-on-continued-

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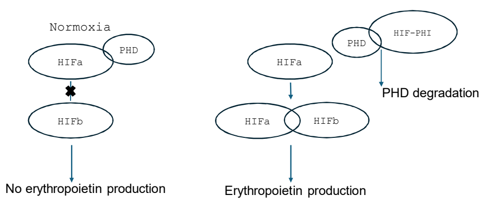
HIF-PHI – Mechanism of Action



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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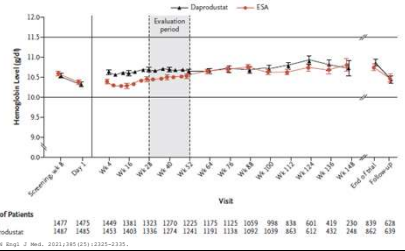
Daprodustat – ASCEND-D Trial (2021)

Baseline characteristics (n=2964):

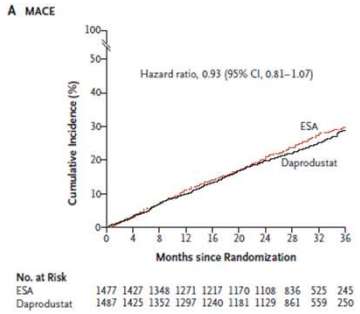
- Mean age 58.5 years, 42.8% female
- Mean hemoglobin: 10.4 ± 1.0 g/dL
- Median TSAT: 32.5%
- Median ferritin: 589 ng/mL daprodustat vs 604 ng/mL ESA
- Mean CV disease: 44.9%
- Mean IV iron dose/month: 138.3 mg
  - ~64% patients receiving IV iron
- Hemodialysis modality: 88.5%

Daprodustat – ASCEND-D Trial (2021) Results

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



Daprodustat – ASCEND-D Trial (2021) Results



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			

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

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

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 (CI, -0.53 to -0.10)	-0.17±0.03 (CI, -0.25 to -0.1)
40-52	-0.07±0.13 (CI, -0.4 to 0.19)	-0.18±0.04 (CI, -0.25 to -0.12)
First MACE (pooled)		
18.2% vadadustat vs 19.3% darbepoetin (HR 0.96, CI 0.81-1.11)		
First expanded MACE (pooled)		
21.6% vadadustat vs 23% darbepoetin (HR 0.96, CI 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

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
- 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

Vadadustat – Drug Interactions

Class	Vadadustat Affecting Other Drugs	Recommendation
Statins • Simvastatin • Rosuvastatin	Increase statin ADEs	Simvastatin: start at 5 mg/day, max 20 mg/day Rosuvastatin: max 5 mg/day
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
BCRP substrate (sulfasalazine)	Increase in substrate's ADEs	Monitor closely for ADEs and adjust substrate's dosage accordingly

Vadadustat – Drug Interactions

Class	Other Drugs Affecting Vadadustat	Recommendation
Phosphorus binders (non-iron based)	Lowers vadadustat's effectiveness	Give 1 hour prior or 2 hours after binders
Phosphorus binders (iron based)		Give 1 hour prior to binders
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

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, CI 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, CI 1.01 to 1.36) compared to darbepoetin 14.1% vs 10.5% (HR 1.4, CI 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/2021-23915.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

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

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

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

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
  - 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)

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

Taurolidine/heparin catheter lock

- Approved under under CMS TDAPA 7/1/24 – 6/30/26
  - Current payment amount for 1.35 mg $8.33 (7/1/24-8/30/24)
- Indicated as a catheter lock solution for patients with central venous catheters in hemodialysis to reduce catheter-related bloodstream infections (CRBSI)
- Taurolidine is a thiadiazinane antimicrobial
- Available as 2 different strengths:
  - 3 mL catheter lock solution with taurolidine 40.5 mg/3 mL + 3,000 units heparin
  - 5 mL catheter lock solution with taurolidine 67.5 mg/5 mL + 5,000 units heparin
- Stored at room temperature
- Contraindications: heparin induced thrombocytopenia, hypersensitivity to product ingredients (taurolidine, heparin, citrate)

Defencath PI

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Taurolidine/heparin catheter lock

LOCK IT-100 trial demonstrated reduction in CRBSI

- Patients randomized to either taurolidine/heparin catheter lock solution or heparin catheter lock solution (1,000 units/mL)
- Primary end-point: time to CRBSI
- Secondary end-point: catheter removal for any reason, loss of catheter patency
- Results:
  - CRBSI: Taurolidine/heparin 9/397 (2%) vs heparin 32/398 (8%)
    - Event rates per 1000 catheter days: 0.13 vs 0.46, p<0.001, HR 0.29 (CI 0.14-0.62) leading to 71% reduction in CRBSI risk
  - Catheter removal: Taurolidine/heparin median time 197 days vs heparin 225 days HR 1.08 (CI 0.9-1.29)
- Study ended early as showed efficacy with no safety concerns

Agarwal A. Clin J Am Soc Nephrol. 2023;18(11);144401455.

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Coming soon 2025…

- As of January 1, 2025, all phosphorus binders and tenapanor will be part of the “bundle”
- CMS modified the definition to include renal dialysis drugs and biologicals with an oral only form
- Will be under TDAPA and payment to be based on 100% of the average sales price
- According to reports however, Ardelyx has not filed for TDAPA and has filed suit against CMS to not be included in the bundle

CMS ESRD PPS. Including oral-only drugs in ESRD PPS Bundle Payment. https://www.cms.gov/files/document/including-oral-only-drugs-esrd-pps-bundled-payment.pdf
Lowie C. Adrelyx. https://ir.ardelyx.com/news-releases/news-release-details/preserve-patient-access-aphosahc-ardelyx-chooses-not-file-tdapa

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Discussion

- 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
- CMS: Centers for Medicare and Medicaid Services
- CrCl: creatinine clearance
- CRBSI: catheter related bloodstream infections
- 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
- HD: hemodialysis
- HF: heart failure
- HfrEF: heart failure with reduced ejection failure
- HIF-PHI: hypoxia inducible factor prolyl hydroxylase inhibitor
- HR: hazard ratio
- HTN: hypertension
- KDIGO: kidney disease improving global outcomes
- MACE: major adverse cardiovascular event
- MI: myocardial infarction
- NKF: national kidney foundation
- Ns-MRA: non-steroidal mineralocorticoid receptor antagonist
- NHYA: New York heart association
- OAT: organic anion transporter
- PD: peritoneal dialysis
- 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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