

# 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. Mozawa et al. Circulation. 2022;146:1636-1664

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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

Mozawa et al. Circulation. 2022;146:1636-1664

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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)

Mozawa et al. Circulation. 2022;146:1636-1664

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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	<ul style="list-style-type: none"> <li>*Must have diabetes with CKD</li> <li>* 300 mg only for eGFR &gt; 60</li> </ul>
Ertugliflozin (Steglatro®)	≥ 45	15 mg daily	**NOT FDA APPROVED for CKD**
Bexagliflozin (Brenzavvy®)	≥ 30	20 mg daily	**NOT FDA APPROVED for CKD**

Farxiga® FI, Jardiance® FI, Invokana® FI, Steglatro® FI, Brenzavvy® FI

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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**

Wheeler GL, et al. Curr Opin Nephrol. 2021;21:19-22.

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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<sup>2</sup>
  - 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<sup>2</sup>
  - Median uACR: 927 mg/g

Perkovic V, et al. N Engl J Med. 2019;381(24):2295-2304.

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## Canagliflozin – CREDENCE Trial (2019) Results

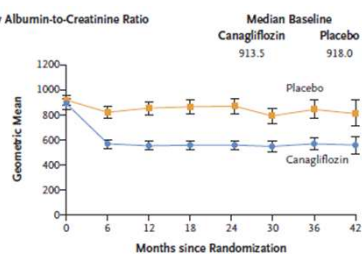
- Primary composite outcome met statistical significance (HR 0.70 (CI 0.59-0.82),  $p=0.00001$ )
- Each individual renal outcome and all related secondary individual outcomes were also statistically significant
  - Composite ESKD, doubling of SCr, or renal death
- uACR average was 31% lower with canagliflozin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

Perkovic V, et al. N Engl J Med. 2019;381(24):2245-2254.

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## Canagliflozin – CREDENCE Trial (2019) Results

A Urinary Albumin-to-Creatinine Ratio



No. of Patients

Placebo 2113  
Canagliflozin 2114

2061  
2070

1986  
2019

1865  
1917

1714  
1819

1158  
1245

685  
730

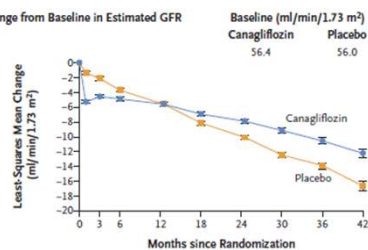
251  
271

Perkovic V, et al. N Engl J Med. 2019;381(24):2245-2254.

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## Canagliflozin – CREDENCE Trial (2019) Results

B Change from Baseline in Estimated GFR



No. of Patients

Placebo 2178  
Canagliflozin 2179

1985  
2005

1882  
1919

1720  
1782

1536  
1648

1006  
1116

583  
652

210  
241

Perkovic V, et al. N Engl J Med. 2019;381(24):2245-2254.

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### Dapagliflozin – DAPA-CKD (2020)

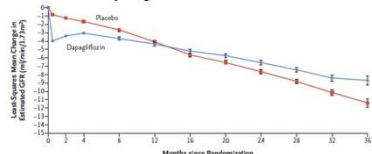
- Primary outcome: first occurrence of a >50% decline in eGFR, onset of ESKD, or death from kidney or CV causes
- Important inclusion criteria:
  - eGFR 25-75 mL/min/1.73m<sup>2</sup>
  - uACR 200-5000 mg/g
  - ACE-I or ARB required
- Groups divided based on presence of diabetes and uACR  $\leq$  1000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

Georgarakis AJL, 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



No. of Participants  
Placebo 2112 2029 1961 1866 1795 1733 1672 1643 1602 1558 1517 1475 1433 1391 1349 1307 1265 1223 1181 1139 1097 1055 1013 971 929 887 845 803 761 719 677 635 593 551 509 467 425 383 341 299 257 215 173 131 89 47 5  
Dapagliflozin 2112 2031 2003 1895 1812 1765 1705 1642 1582 1522 1462 1402 1342 1282 1222 1162 1102 1042 982 922 862 802 742 682 622 562 502 442 382 322 262 202 142 82 22 38 78 118 158 198 238 278 318 358 398 438 478 518 558 598 638 678 718 758 798 838 878 918 958 998 1038 1078 1118 1158 1198 1238 1278 1318 1358 1398 1438 1478 1518 1558 1598 1638 1678 1718 1758 1798 1838 1878 1918 1958 1998 2038 2078 2118 2158 2198 2238 2278 2318 2358 2398 2438 2478 2518 2558 2598 2638 2678 2718 2758 2798 2838 2878 2918 2958 2998 3038 3078 3118 3158 3198 3238 3278 3318 3358 3398 3438 3478 3518 3558 3598 3638 3678 3718 3758 3798 3838 3878 3918 3958 3998 4038 4078 4118 4158 4198 4238 4278 4318 4358 4398 4438 4478 4518 4558 4598 4638 4678 4718 4758 4798 4838 4878 4918 4958 4998 5038 5078 5118 5158 5198 5238 5278 5318 5358 5398 5438 5478 5518 5558 5598 5638 5678 5718 5758 5798 5838 5878 5918 5958 5998 6038 6078 6118 6158 6198 6238 6278 6318 6358 6398 6438 6478 6518 6558 6598 6638 6678 6718 6758 6798 6838 6878 6918 6958 6998 7038 7078 7118 7158 7198 7238 7278 7318 7358 7398 7438 7478 7518 7558 7598 7638 7678 7718 7758 7798 7838 7878 7918 7958 7998 8038 8078 8118 8158 8198 8238 8278 8318 8358 8398 8438 8478 8518 8558 8598 8638 8678 8718 8758 8798 8838 8878 8918 8958 8998 9038 9078 9118 9158 9198 9238 9278 9318 9358 9398 9438 9478 9518 9558 9598 9638 9678 9718 9758 9798 9838 9878 9918 9958 9998 10038 10078 10118 10158 10198 10238 10278 10318 10358 10398 10438 10478 10518 10558 10598 10638 10678 10718 10758 10798 10838 10878 10918 10958 10998 11038 11078 11118 11158 11198 11238 11278 11318 11358 11398 11438 11478 11518 11558 11598 11638 11678 11718 11758 11798 11838 11878 11918 11958 11998 12038 12078 12118 12158 12198 12238 12278 12318 12358 12398 12438 12478 12518 12558 12598 12638 12678 12718 12758 12798 12838 12878 12918 12958 12998 13038 13078 13118 13158 13198 13238 13278 13318 13358 13398 13438 13478 13518 13558 13598 13638 13678 13718 13758 13798 13838 13878 13918 13958 13998 14038 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60558 60598 60638 60678 60718 60758 60798 60838 60878 60918 60958 60998 61038 61078 61118 61158 61198 61238 61278 61318 61358 61398 61438 61478 61518 61558 61598 61638 61678 61718 61758 61798 61838 61878 61918 61958 61998 62038 62078 62118 62158 62198 62238 62278 62318 62358 62398 62438 62478 62518 62558 62598 62638 62678 62718 62758 62798 62838 62878 62918 62958 62998 63038 63078 63118 63158 63198 63238 63278 63318 63358 63398 63438 63478 63518 63558 63598 63638 63678 63718 63758 63798 63838 63878 63918 63958 63998 64038 64078 64118 64158 64198 64238 64278 64318 64358 64398 64438 64478 64518 64558 64598 64638 64678 64718 64758 64798 64838 64878 64918 64958 64998 65038 65078 65118 65158 65198 65238 65278 65318 65358 65398 65438 65478 65518 65558 65598 65638 65678 65718 65758 65798 65838 65878 65918 65958 65998 66038 66078 66118 66158 66198 66238 66278 66318 66358 66398 66438 66478 66518 66558 66598 66638 66678 66718 66758 66798 66838 66878 66918 66958 66998 67038 67078 67118 67158 67198 67238 67278 67318 67358 67398 67438 67478 67518 67558 67598 67638 67678 67718 67758 67798 67838 67878 67918 67958 67998 68038 68078 68118 68158 68198 68238 68278 68318 68358 68398 68438 68478 68518 68558 68598 68638 68678 68718 68758 68798 68838 68878 68918 68958 68998 69038 69078 69118 69158 69198 69238 69278 69318 69358 69398 69438 69478 69518 69558 69598 69638 69678 69718 69758 69798 69838 69878 69918 69958 69998 70038 70078 70118 70158 70198 70238 70278 70318 70358 70398 70438 70478 70518 70558 70598 70638 70678 70718 70758 70798 70838 70878 70918 70958 70998 71038 71078 71118 71158 71198 71238 71278 71318 71358 71398 71438 71478 71518 71558 71598 71638 71678 71718 71758 71798 71838 71878 71918 71958 71998 72038 72078 72118 72158 72198 72238 72278 72318 72358 72398 72438 72478 72518 72558 72598 72638 72678 72718 72758 72798 72838 72878 72918 72958 72998 73038 73078 73118 73158 73198 73238 73278 73318 73358 73398 73438 73478 73518 73558 73598 73638 73678 73718 73758 73798 73838 73878 73918 73958 73998 74038 74078 74118 74158 74198 74238 74278 74318 74358 74398 74438 74478 74518 74558 74598 74638 74678 74718 74758 74798 74838 74878 74918 74958 74998 75038 75078 75118 75158 75198 75238 7

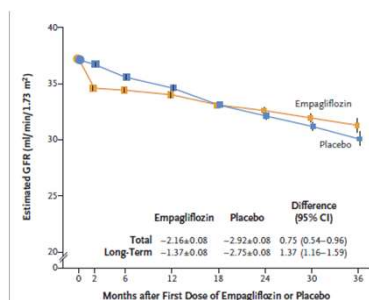
## Empagliflozin – EMPA-KIDNEY (2023) Results

- 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 ( $< 30$ ,  $\geq 30$ – $< 45$ ,  $\geq 45$  mL/min/1.73m<sup>2</sup>)

EMPA-Kidney Collaborative Group. N Engl J Med. 2023;389:117–127.

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## Empagliflozin – EMPA-KIDNEY (2023) Results



EMPA-Kidney Collaborative Group. N Engl J Med. 2023;389:117–127.

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## Guidelines

### KDIGO 2024

- Treat with an SGLT2i (1A):
  - T2D+ CKD + eGFR  $\geq 20$  mL/min/m<sup>2</sup>
  - CKD + uACR  $\geq 200$  mg/g
  - CKD + heart failure
- eGFR  $\geq 20$ – $45$  mL/min/m<sup>2</sup> + uACR  $< 200$  mg/g (2B)

### ADA 2024

- Treat with an SGLT2i (A)
  - T2D and CKD with eGFR  $\geq 20$  mL/min/m<sup>2</sup> and uACR  $\geq 200$  mg/g
- Treat with an SGLT2i (B)
  - T2D and CKD with eGFR  $\geq 20$  mL/min/m<sup>2</sup> and uACR normal to 200 mg/g

Almond D, et al. KDIGO 2024. Kidney International. 2024;105:1017–1014.  
 Eljamel M, et al. Diabetes Care. 2024;47(12):1930–1932.  
 de Zeeuw D, et al. Diabetes Care. 2022;45(12):1970–1980.

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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%

Shao H, et al. *Kidney360*. 2022;3(1):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 <sup>2</sup> )	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	

Benavente D

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## Guidelines

### KDIGO 2024

- **NS-MRA (2A):**
  - T2D+ eGFR ≥25 mL/min/m<sup>2</sup> + 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<sup>2</sup>

Almeid R, et al. *MDIO 2024*. *Kidney International*. 2024;105(1):17-2314.  
Bischoff G, et al. *Endocrine Care*. 2024;14(1):113-122.

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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

Recommendation #1

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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	
Exenatide (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(13):1388-1396.  
Gheorghiade M et al. Lancet. 2019;394(10193):121-130.  
Trulicity® Rx, Victoza® Rx, Ozempic® Rx, Adlyxin® Rx, Byetta® Rx.

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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 ≥ 25 mL/min/m<sup>2</sup>
  - Use agent with proven CV benefit when SGLT2i not tolerated or contraindicated

Almond R, et al. KDIGO 2024. Kidney International. 2024;105(S1):17-6104.  
Wingard RL, et al. Diabetes Care. 2024;47(1):253-262.

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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  $\geq 50\%$  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, Wegovy® PI  
Mounjaro® PI, Zepbound® PI  
Saxenda® PI, Wegovy® PI, Mounjaro® PI, Zepbound® PI  
Tirzepatide PI, Zepbound® PI  
Saxenda® PI, Wegovy® PI, Mounjaro® PI, Zepbound® PI  
Tirzepatide PI, Zepbound® PI  
Saxenda® PI, Wegovy® PI, Mounjaro® PI, Zepbound® PI  
Tirzepatide PI, Zepbound® PI

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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

Wegryn JC, Idorn TG, et al. *Diabetes Care*. 2016;39(2):204-213.  
Bomholt G, et al. *Am J Kidney Dis*. 2012;145(2):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

OMB ESRD PPS Transitional Drug Add-on Payment Adjustment: <https://www.cms.gov/medicare/payment/prospective-payment-systems/esrd-stage-1>  
https://www.cms.gov/medicare/payment/prospective-payment-systems/esrd-stage-1  
OMB ESRD PPS Drug Reimbursement Review: <https://www.cms.gov/medicare/payment/prospective-payment-systems/esrd-stage-1>

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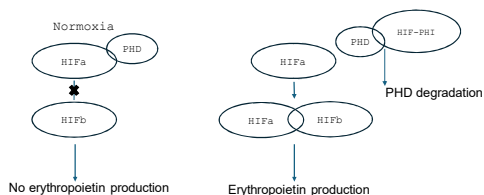
## HIF-PHI Agents

- 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/Regulatory-and-Program-Changes/Rate-Setting/ESRD-PPS-TDAPA>  
 Capparelli M, Haddad L. <https://www.fda.gov/drugs/development-resources/2024/03/27/fda-approves-vadadustat-cabotani>  
 Capparelli M, Haddad L. <https://www.fda.gov/drugs/development-resources/2023/10/01/fda-approves-daprodustat-cabotani>

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## HIF-PHI – Mechanism of Action



Kassam HS, Kidney Int Suppl. 2021;111(1):4-25.

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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):

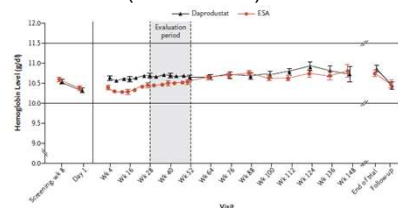
- Mean age 58.5 years, 42.8% female
- Mean hemoglobin:  $10.4 \pm 1.0$  g/dL
- Median TSAT: 32.5%
- Median ferritin: 589 ng/mL daprodustat vs 604 ng/mL ESA
- Mean CV disease: 44.9%
- Mean IV iron dose/month: 138.3 mg
  - ~64% patients receiving IV iron
- Hemodialysis modality: 88.5%

Singh AN, et al., N Engl J Med. 2021;385(25):2225-2235.

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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 (CI 0.81-1.07) met noninferiority



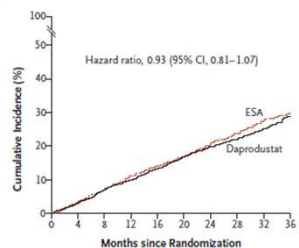
No. of Patients  
ESA 1477 1475 1449 1381 1323 1270 1225 1175 1125 1059 998 838 601 419 230 839 628  
Daprodustat 1487 1485 1453 1403 1336 1274 1241 1195 1138 1080 1009 863 612 432 244 862 639

Singh AN, et al., N Engl J Med. 2021;385(25):2225-2235.

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## Daprodustat – ASCEND-D Trial (2021) Results

A MACE



No. at Risk  
ESA 1477 1427 1348 1271 1217 1170 1108 836 525 245  
Daprodustat 1487 1425 1352 1297 1240 1181 1129 861 559 250

Singh AN, et al., N Engl J Med. 2021;385(25):2225-2235.

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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

Jandornig P1

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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

Jandornig P1

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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

Jandornig P1

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## Vadadustat – INNO<sub>2</sub>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

Kochcharov BS, et al. N Engl J Med. 2021;384(17):1602-1612.

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## Vadadustat – INNO<sub>2</sub>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%

Kochcharov BS, et al. N Engl J Med. 2021;384(17):1602-1612.

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## Vadadustat – INNO<sub>2</sub>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)		

Kochcharov BS, et al. N Engl J Med. 2021;384(17):1602-1612.

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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 PZ

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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
- 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 PZ

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## 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

- **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
- **PROTECT** (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 MK, 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

Khorasani JF. Dept Med Medical Regulation. <https://pubmed.ncbi.nlm.nih.gov/35922222/>. Daprodustat denied approval. 2022;17(17):1600-1607. Fluckiger J, et al. N Engl J Med. 2020;383(13):1221-1232.

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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

Reference 32

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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

Reference 32

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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. 2023	≥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)

Appendix 92

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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

Appendix 92

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## Taurolidine/heparin catheter lock

- Approved 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 thiazolidine 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)

Reference 91

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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, Cline D, Wu H, et al. 2023;18(11):2440-2455.

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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

DRG 8200 PPS. Discontinuing oral-only drugs in DRG 8200 PPS bundle payment. <https://www.cms.gov/1-9c4/drug-drug/medication-management/medication-management-payment.pdf>  
 Update 2: 4/24/2024  
 DRG 8200 PPS bundle payment. CMS will begin DRG 8200 PPS bundle payment for oral-only drugs in January 2025. <https://www.cms.gov/1-9c4/drug-drug/medication-management/medication-management-payment.pdf>

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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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## References

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- A research study to find out how semaglutide works in the kidneys compared to placebo, in people with type 2 diabetes and chronic kidney disease (the REMODEL Trial) (REMODEL ). ClinicalTrials.gov identifier NCT04865770. Updated March 19 2024. Accessed April 4, 2024. <https://clinicaltrials.gov/study/NCT04865770>.
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- Brenzavvy [package insert]. Marlborough, MA: TherascosBio, LLC. 2023.
- Byetta [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2014.

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Abbreviations

• ACE-i: angiotensin converting enzyme inhibitor	• EDW: estimated dry weight	• HIF-PH: hypoxia inducible factor prolyl hydroxylase inhibitor	• OAT: organic anion transporter
• ADA: American diabetes association	• ESA: erythropoietin stimulating agent	• HR: hazard ratio	• PD: peritoneal dialysis
• ADE: adverse drug events	• ESKD: end stage kidney disease	• HTN: hypertension	• PHD: prolyl hydroxylase domain
• ARB: angiotensin receptor blocker	• GI: gastrointestinal	• KDIGO: kidney disease improving global outcomes	• RAAS: renin angiotensin aldosterone system
• ASN: American society of nephrology	• GIP: glucose dependent insulinotropic polypeptide	• MACE: major adverse cardiovascular event	• SCr: serum creatinine
• BCRP: breast cancer resistance protein	• GFR: glomerular filtration rate	• MI: myocardial infarction	• SGLT2: sodium-glucose co-transporter-2 inhibitor
• CI: confidence interval	• GLP-1 RA: glucagon-like peptide-1 receptor agonist	• NKF: national kidney foundation	• T2D: type 2 diabetes
• CKD: chronic kidney disease	• HD: hemodialysis	• No-MRA: non-steroidal mineralocorticoid receptor antagonist	• TDAPA: transitional drug add-on payment adjustment
• CMS: Centers for Medicare and Medicaid Services	• HF: heart failure	• NHYA: New York heart association	• TSAT: transferrin saturation
• CrCl: creatinine clearance	• HFrEF: heart failure with reduced ejection failure		• uACR: urine albumin-creatinine ratio
• CRBSI: catheter related bloodstream infections			• VTE: venous thromboembolism
• CV(D): cardiovascular (disease)			