Stay in the Loop:
Preventing Progression of Chronic Kidney Disease (CKD) in Type 2 Diabetes Mellitus (T2DM)

UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

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Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Dr. Guadalupe Chavez**
    - None
  - **CE mentor, Dr. Elizabeth Bald**
    - None
- Off-Label uses of the following medications will be discussed:
  - Empagliflozin, dulaglutide, liraglutide, and semaglutide (SUBQ)

Learning Objectives for Technicians

- **At the end of this presentation, you will be able to:**
  - Examine the prevalence of CKD in patients with T2DM
  - Recognize common side effects associated with medications used for the prevention of CKD progression in T2DM
  - Discuss strategies for ensuring patients with T2DM can access and afford medications used for the prevention of CKD progression

Learning Objectives for Pharmacists

- **At the end of this presentation, you will be able to:**
  - Describe the pathophysiology of CKD associated with T2DM
  - Interpret primary literature surrounding the medications used for the prevention of CKD progression in T2DM
  - Design an effective therapy regimen for a patient with T2DM to prevent progression of CKD

CKD Diagnostic Criteria

Abnormalities of kidney structure **or** function ≥ 3 months

Structure: Markers of kidney damage (≥1)

- Urinary Albumin Creatine Ratio (UACR) >30 mg/g (albuminuria)
- Urine sediment abnormalities
- Electrolyte and other abnormalities
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplant

Function: Decreased Estimated Glomerular Filtration Rate (eGFR)

- eGFR <60 ml/min/1.73m²

KDIGO 2012 clinical practice guideline for the evaluation.https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Accessed February 6, 2022.
American Diabetes Association Professional Practice Committee. 11. chronic kidney disease and risk management: Standards of medical care in diabetes-2022. American Diabetes Association. https://diabetesjournals.org/care/article/45/Supplement_1/S175/138914/11-Chronic-Kidney-Disease-and-Risk-Management. Published December 16, 2021. Accessed February 8, 2022.

Staging CKD

1) CAUSE

i.e., glomerular disease due to diabetes, renal artery stenosis, renal tubular cystinuria, etc.

2) GFR CATEGORIES

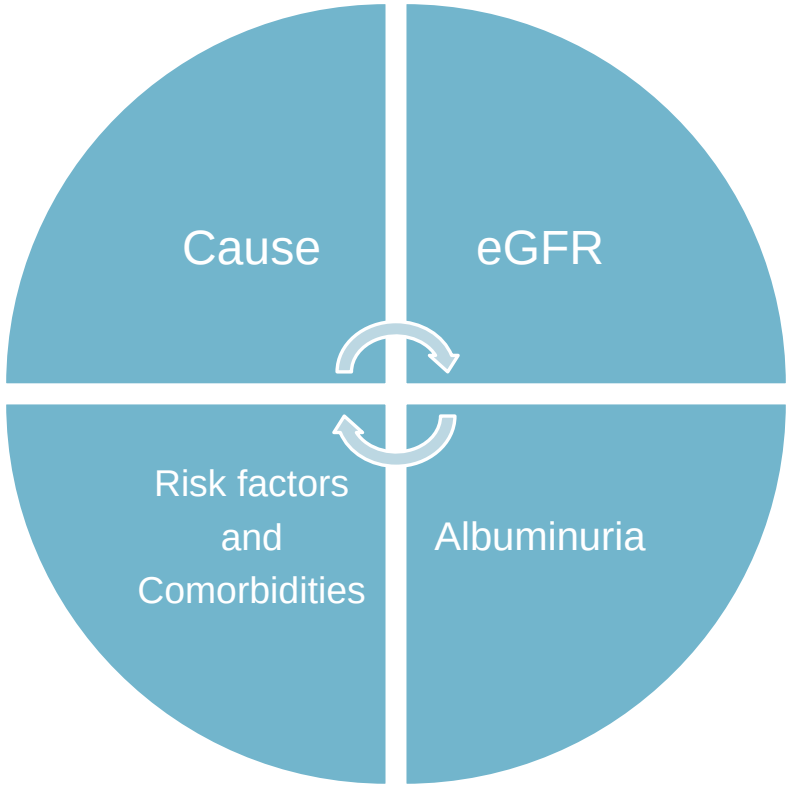
Category	GFR (ml/min/1.73m²)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney Failure

3) ALBUMINURIA CATEGORIES

Category	UACR (mg/g)	Terms
A1	<30	Normal to mildly increased **Normalalbuminuria**
A2	30-300	Moderately increased **Microalbuminuria**
A3	>300	Severely increased **Macroalbuminuria**

KDIGO 2012 clinical practice guideline for the evaluation.https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Accessed February 6, 2022.

Prognosis & Monitoring of CKD



Prognosis of CKD

				Persistent albuminuria categories (mg/g)		
				A1	A2	A3
				Normal to Mildly Increased	Moderately Increased	Severely Increased
				< 30	30-300	>300
GFR categories (ml/min/1.73 m²)	G1	Normal or high	≥ 90	1	1	2
	G2	Mildly decreased	60-89	1	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	≥ 4
	G5	Kidney Failure	<15	≥ 4	≥ 4	≥ 4

Low risk (if not other markers, no CKD)

Moderately increased risk

High Risk

Very high risk

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KDIGO 2012 clinical practice guideline for the evaluation.https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Accessed February 6, 2022.

Epidemiology

37 million or ~ 1 in 7 adults have CKD in the US

- DM is the leading cause of CKD and end stage renal disease (ESRD)

34.2 million or ~ 1 in 10 adults have DM (90-95% T2DM)

- ~ 20-40% of patients with DM develop CKD
- Every 24 hours, 170 people with DM begin dialysis

Demographic Risk Factors for CKD associated with T2DM

- Older adults
- Non-Hispanic Black, Hispanics, and Native American

FAQs. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/data/statistics/faqs.html. Published August 11, 2021. Accessed February 6, 2022.
Diabetes and chronic kidney disease. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/managing/diabetes-kidney-disease.html. Published May 7, 2021. Accessed February 6, 2022.
Chronic kidney disease in the United States, 2021. Centers for Disease Control and Prevention. https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html. Published March 4, 2021. Accessed February 6, 2022.

USHP

Cardiovascular Risk in CKD

2-4x Patients with T2DM more likely to experience cardiovascular (CV) events and have worse outcomes

- 50% of diabetes-related deaths are due to CV causes

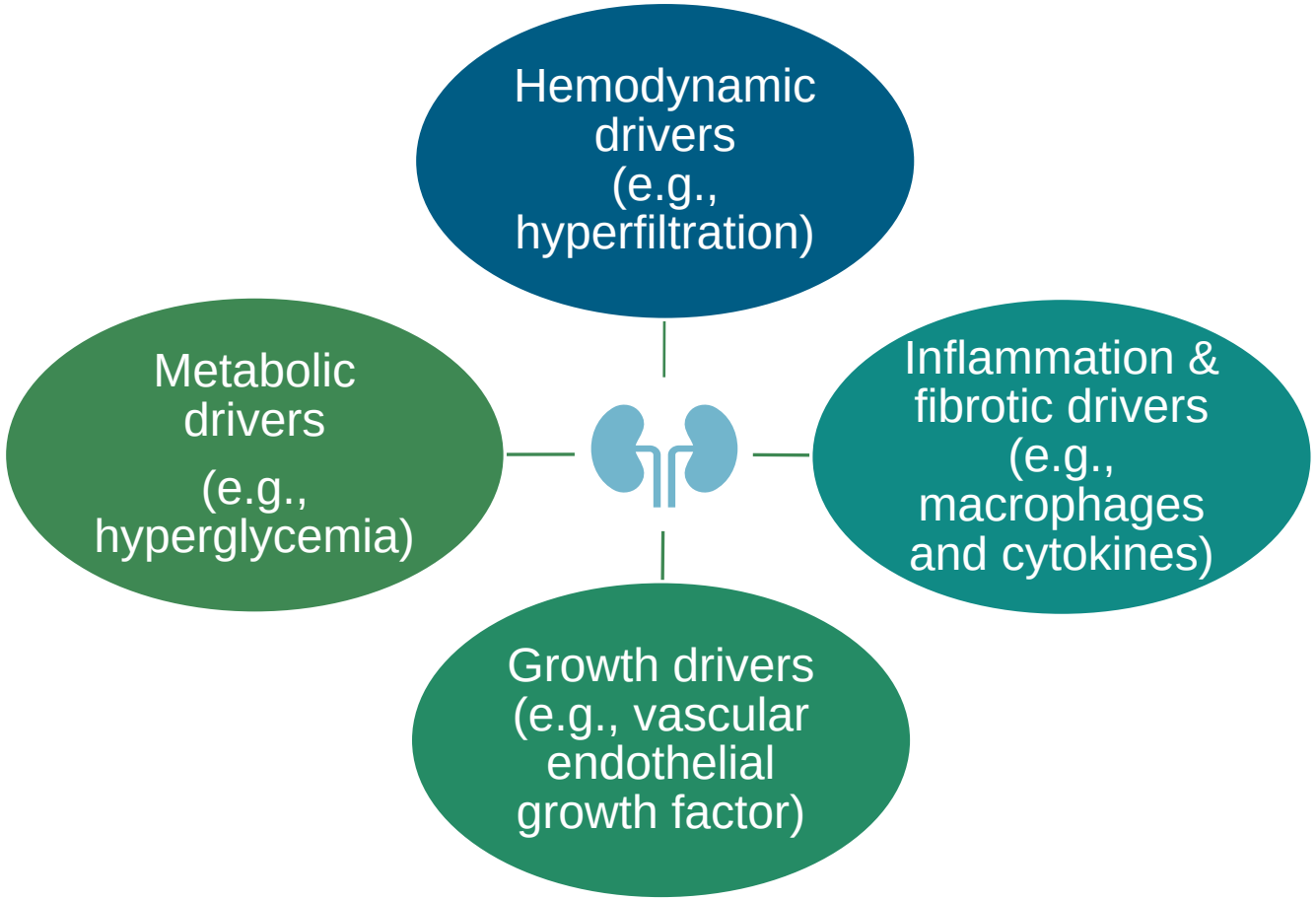
10-20x Patients with CKD more likely to die of CV causes

- CKD is an independent risk factor for cardiovascular disease (CVD)

Chronic kidney disease and type 2 diabetes. https://professional.diabetes.org/sites/professional.diabetes.org/files/media/ckd_compendium_fin_2_web.pdf. Accessed February 6, 2022.

Pathogenesis of Diabetic Kidney Disease

- Diabetic kidney disease is a microvascular complication of diabetes



Chronic kidney disease and type 2 diabetes. https://professional.diabetes.org/sites/professional.diabetes.org/files/media/ckd_compendium_fin_2_web.pdf. Accessed February 6, 2022.

Terminology CKD vs DKD

- For the remainder of this presentation CKD will be used to define CKD associated with T2DM, sometimes referred to as DKD
- Kidney Disease: Improving Global Outcomes (KDIGO) guidelines:
  - We avoid the term “diabetic kidney disease” to avoid the connotation that CKD is caused by traditional diabetes pathophysiology in all cases, although this term is entirely appropriate when this limitation is recognized

Complications of CKD

It’s important to detect CKD as early as possible

- CKD can often be silent in early stages
- Long standing duration of DM, retinopathy, albuminuria, and gradually progressive loss of eGFR is a typical presentation

Symptoms

- Diabetic peripheral neuropathy, peripheral edema, less need for insulin or antidiabetic medications, fatigue, cramps, pruritis, or nausea

Advanced complications

- Elevated blood pressure (BP)
- Volume overload
- Electrolyte abnormalities
- Metabolic acidosis
- Anemia
- Metabolic bone disease

Yee J. Diabetic kidney disease: Chronic kidney disease and diabetes. American Diabetes Association. https://diabetesjournals.org/spectrum/article/21/1/8/2166/Diabetic-Kidney-Disease-Chronic-Kidney-Disease-and. Published January 1, 2008. Accessed February 7, 2022.

CKD Progression Factors

Non-Modifiable	Modifiable
• Older Age/Sex/Race/Ethnicity • History of CVD • Duration of DM • Genetic Factors	• Smoking • Overweight or Obesity • Hyperglycemia • Hypertension • Dyslipidemia • Nephrotoxic agents

Executive summary of the 2020 KDIGO diabetes management in chronic kidney disease. https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-in-CKD-GL-Exec-Summary.pdf. Accessed February 7, 2022.

KDIGO Recommendations

Practice Point 1.1.1: Patients with DM and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease

All patients

- Glycemic control
- BP control
- Lipid management
- Exercise: Moderate-intensity physical activity 150 min/week
- Nutrition: Limit protein intake ~0.8 g/kg/day; limit sodium intake <2 g/day
- Smoking cessation

Most patients

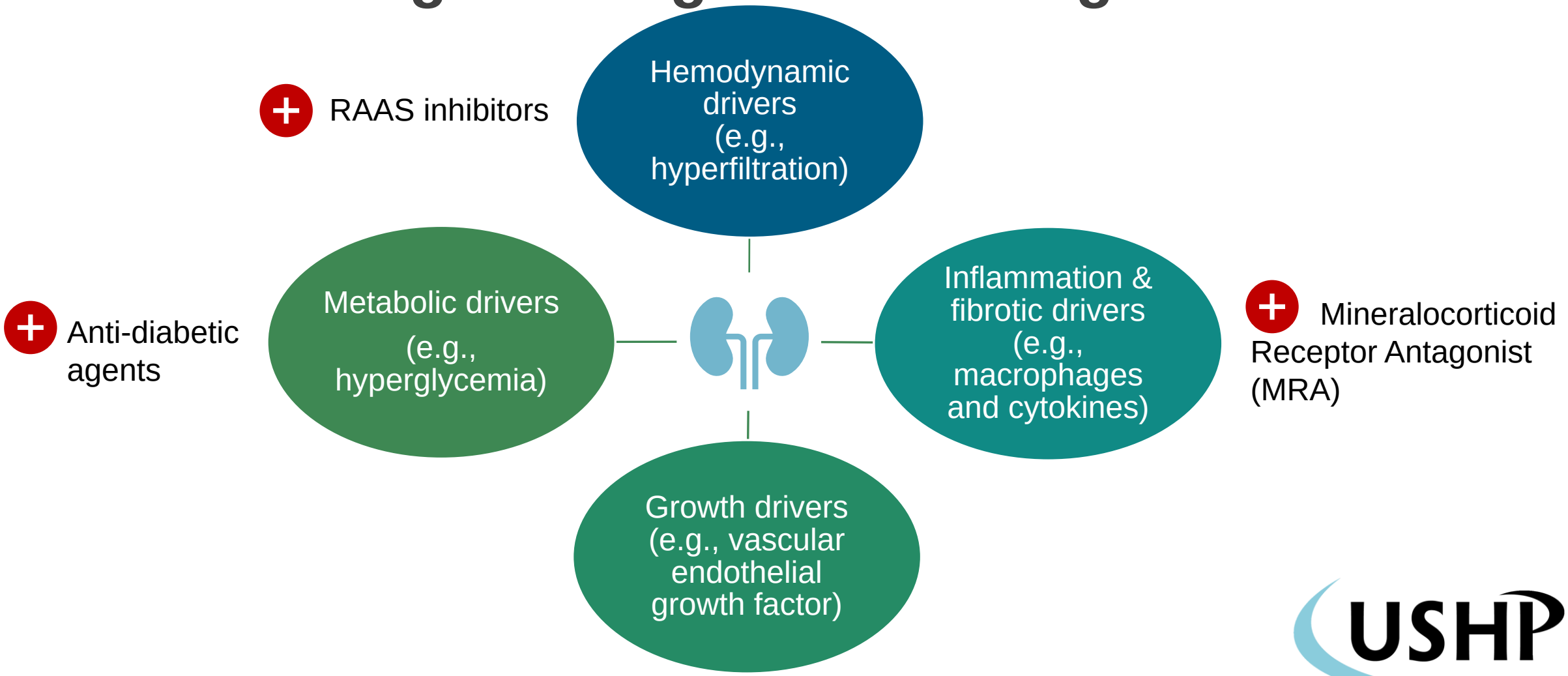
- Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i), renin angiotensin aldosterone system inhibitors (RAASi)

Some patients

- Antiplatelet therapies

Executive summary of the 2020 KDIGO diabetes management in chronic kidney disease. https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-in-CKD-GL-Exec-Summary.pdf. Accessed February 7, 2022.

Pharmacologic Management Strategies



Chronic kidney disease and type 2 diabetes. https://professional.diabetes.org/sites/professional.diabetes.org/files/media/ckd_compendium_fin_2_web.pdf. Accessed February 6, 2022.

Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i)

SGLT2i US Food and Drug Administration (FDA) Approval Dates

Padda IS. Sodium-glucose transport protein 2 (SGLT2) inhibitors. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK576405/. Published January 6, 2022. Accessed February 10, 2022.

Guidelines

KDIGO DKD 2020

Recommend treating patients with T2DM, CKD, and an eGFR ≥ 30 ml/min/1.73 m² with an SGLT2i

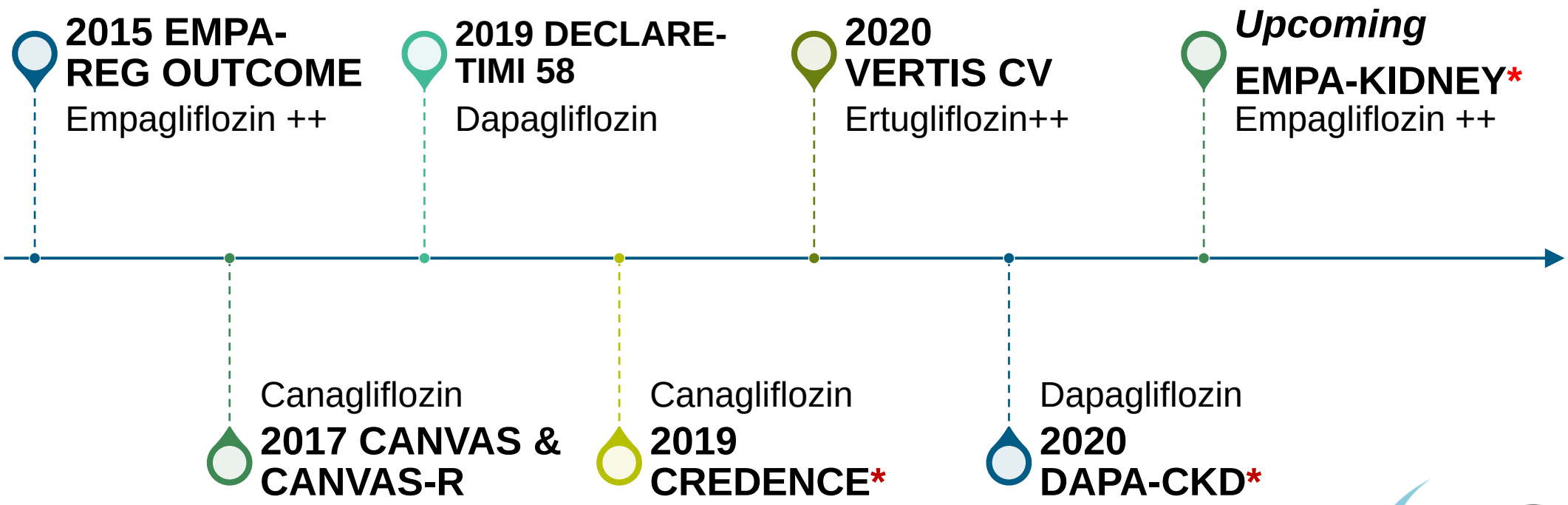
ADA 2022

For patients with **T2DM, DKD**, and an eGFR ≥25 ml/min/1.73 m² **AND** UACR ≥300 mg/g, an SGLT2i is recommended to ↓ **CKD progression and CV events**

In patients with **T2DM, CKD,** and eGFR ≥25 ml/min/1.73 m² **OR** UACR ≥300 mg/g, consider an SGLT2i for **CV risk** ↓

Executive summary of the 2020 KDIGO diabetes management in chronic kidney disease. https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-in-CKD-GL-Exec-Summary.pdf. Accessed February 7, 2022.
American Diabetes Association Professional Practice Committee. 11. chronic kidney disease and risk management: Standards of medical care in diabetes-2022. American Diabetes Association. https://diabetesjournals.org/care/article/45/Supplement_1/S175/138914/11-Chronic-Kidney-Disease-and-Risk-Management. Published December 16, 2021. Accessed February 8, 2022.

Primary Literature



*Designed with primary renal outcomes
++ Off label use in CKD

EMPA-REG OUTCOME

Renal outcomes

- Progression to macroalbuminuria
- Doubling of serum creatinine with an eGFR ≤ 45 ml/min/1.73m²
- Renal Replacement Therapy (RRT)
- Renal death

Baseline Characteristics

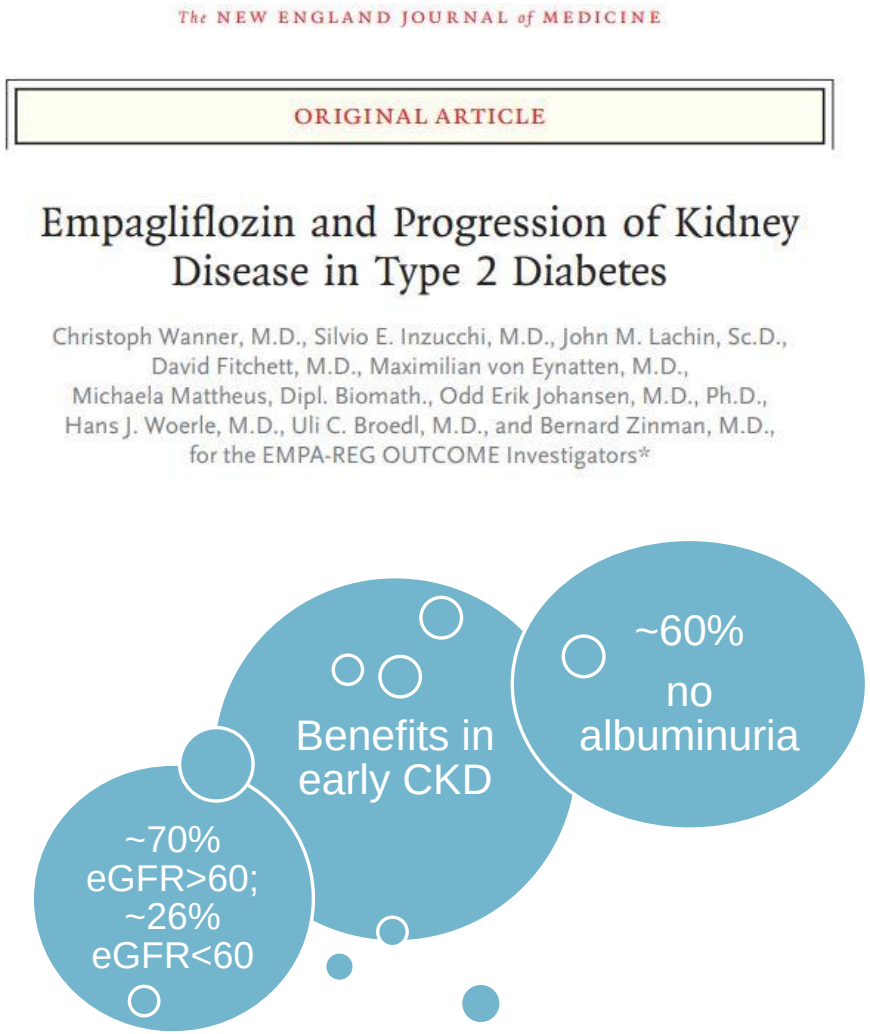
- 99% established CVD
- **17.8% eGFR 45-59 ml/min/1.73m²; 7.7% eGFR 30-44 ml/min/1.73m²**
- **28.7% microalbuminuria; 11% macroalbuminuria**

Results

- 38% relative risk reduction (RRR) in progression of macroalbuminuria
- 44% RRR in doubling of serum creatinine with an eGFR ≤ 45 ml/min/1.73m²
- 55% RRR in renal replacement therapy
- 3 renal related deaths in empagliflozin group and 0 in placebo

Additional Trials

- EMPA-KIDNEY Study (expected completion December 2022)
- Empagliflozin vs Placebo, composite primary renal outcome, in non-diabetes related moderate-severe CKD



Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med. Jul 28 2016;375(4):323-34. doi:10.1056/NEJMoa1515920*
Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med. Nov 26 2015;373(22):2117-28. doi:10.1056/NEJMoa1504720*.

Empagliflozin FDA Indications

Current FDA approved indications

- Adjunct to diet and exercise to improve glycemic control in adults with T2DM
- ↓ the risk of CV death in adults with T2DM and established CVD
- ↓ the risk of CV death plus hospitalization for heart failure (HHF) in adults with heart failure reduced ejection fraction (HFrEF)

Currently **NOT** FDA approved for prevention of CKD progression

Empagliflozin {package insert] ep. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2014.

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CREDENCE Trial

Primary renal composite outcome

- End stage renal disease (ESRD)
- Doubling of creatinine level
- Renal death
- CV death

Baseline characteristics

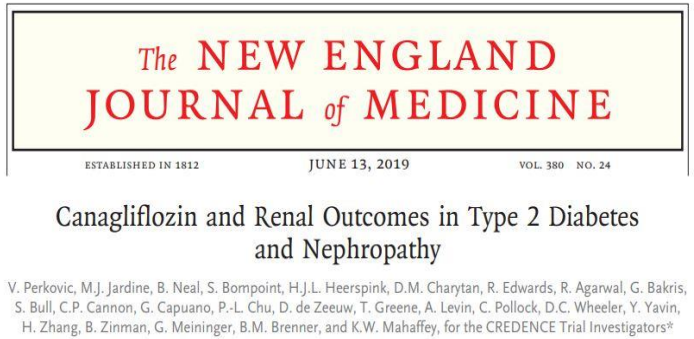
- ~ 50% established CVD
- **~ 59% of participants had eGFR <60 ml/min/1.73 m²**
- **~100% of participants had UACR >300 mg/g**

Results

- NNT=22 for primary renal composite outcome
- Primary renal outcome drivers
  - 40% ↓ in doubling of Scr
  - 32% ↓ in development of ESRD

Additional Trials

- CANVAS-Cardiovascular Outcome Trial (CVOT)
- CANVAS-R



30%

↓ relative risk reduction in the primary renal composite outcome

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Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med. Jun 13 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744*.

Canagliflozin FDA Indications

Current FDA approved indications

- As an adjunct to diet and exercise to improve glycemic control in adults with T2DM
- ↓ the risk of major adverse CV events in adults with T2DM and established CVD
- **↓ the risk of <u>ESRD, doubling of serum creatinine</u>, CV death, and hospitalization for heart failure (HHF) in adults with T2DM and diabetic nephropathy with albuminuria**

Canagliflozin [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2019.

DAPA-CKD Trial

Primary renal compositive outcome

- ESRD
- Sustained decline in eGFR by 50% or more
- Renal death
- CV death

Baseline characteristics

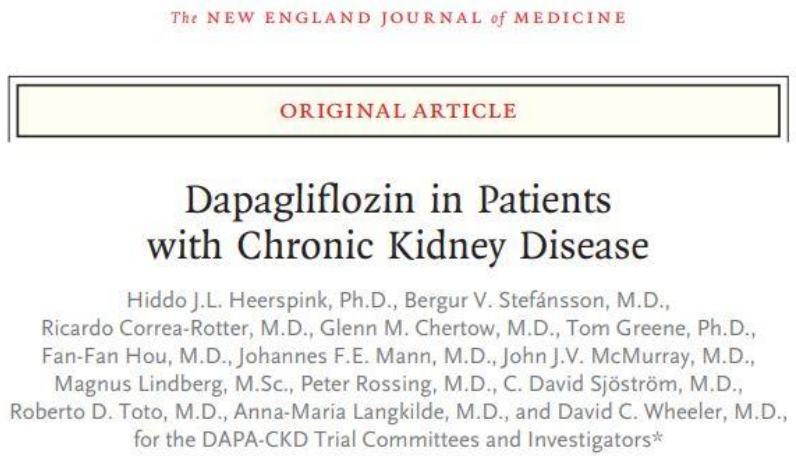
- ~ 37% established CVD
- **~ 90% eGFR <60 ml/min/1.73m²**
- **~ 50% of participants had UACR>1000 mg/g**

Results

- NNT=19 for primary renal composite outcome
- 44% relative risk reduction in renal-specific composite

Additional Trials

- DECLARE-TIMI Trial-CVOT



39%

↓ relative risk reduction in primary renal composite outcome with or w/o T2DM

USHP

Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med. Oct 8 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816*

Dapagliflozin FDA Indications

Current FDA approved indications

- Adjunct to diet and exercise to improve glycemic control in adults with T2DM
- ↓ the risk of HHF in adults with T2DM and either established CVD or multiple CV risk factors
- ↓ the risk of CV death and HHF in adults with HFrEF (NYHA class II-IV)
- **↓ the risk of sustained eGFR decline, ESRD, CV death, and HHF in adults with CKD at risk of progression**

Dapagliflozin [package insert] dp. Washington, DE: AztraZeneca Pharmaceuticals LP; 2014.

VERTIS CV Trial

Exploratory renal composite endpoint

- Sustained eGFR 40% reduction
- Renal replacement therapy (RRT)
- Renal death

Baseline characteristics

- ~100% established ASCVD
- **~ 22% eGFR <60 ml/min/1.73m²**
- **~ 31% UACR 30-299 mg/g; ~ 9.4% UACR ≥ 300 mg/g**

Results

- 34% RRR exploratory renal composite endpoint

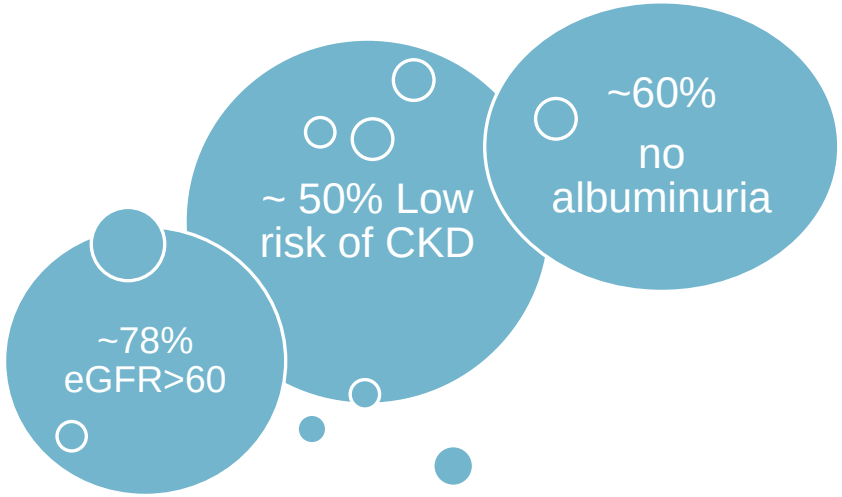
Diabetologia (2021) 64:1256–1267
https://doi.org/10.1007/s00125-021-05407-5

ARTICLE

Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial

David Z. I. Cherney[1] · Bernard Charbonnel[2] · Francesco Cosentino[3] · Samuel Dagogo-Jack[4] · Darren K. McGuire[5,6] · Richard Pratley[7] · Weichung J. Shih[8,9] · Robert Frederich[10] · Mario Maldonado[11] · Annpey Pong[12] · Christopher P. Cannon[13] · on behalf of the VERTIS CV Investigators

Received: 25 August 2020 / Accepted: 11 December 2020 / Published online: 4 March 2021



Cherney DZI, Charbonnel B, Cosentino F, et al. Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. *Diabetologia. Jun 2021;64(6):1256-1267. doi:10.1007/s00125-021-05407-5*

Ertugliflozin FDA Indication

Current FDA approved indications

- Adjunct to diet and exercise to improve glycemic control in adults with T2DM

Currently **NOT** FDA approved for prevention of CKD progression

Ertugliflozin [package insert] ep. Whitehouse Station, NJ: Merck & Co., INC.,; 2014.

Meta-analysis

Composite Kidney Outcome

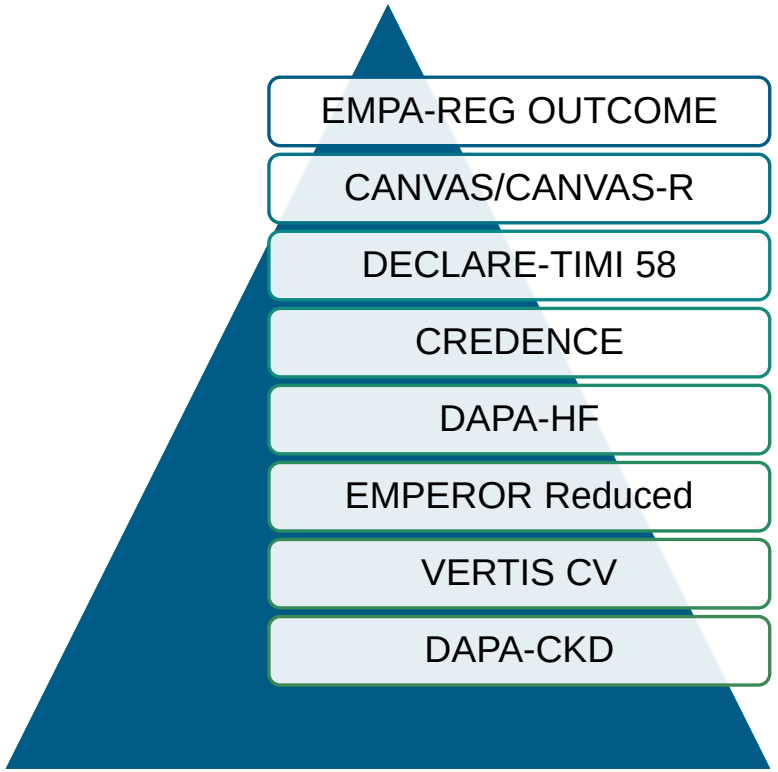
- ESRD
- Doubling serum creatine
- Kidney related mortality

Primary Analysis

- Composite kidney outcome regardless of T2DM, HF, or CKD
- 38% risk reduction

Sub-analysis

- Composite kidney outcome w/CKD (eGFR <60 ml/min/1.73m²)
  - 32% risk reduction
- **Composite kidney outcome in patients w/T2DM**
  - **48% risk reduction**



Salah HM, Al'Aref SJ, Khan MS, et al. Effect of sodium-glucose cotransporter 2 inhibitors on cardiovascular and kidney outcomes-Systematic review and meta-analysis of randomized placebo-controlled trials. *Am Heart J*. Feb 2021;232:10-22. doi:10.1016/j.ahj.2020.10.064

Summary of SGLT2i Kidney Outcomes

			Primary Outcomes		Kidney Outcomes	
SGLT2i	Trials	Kidney-related eligibility criteria	Primary Outcome	Effect on primary outcome	Effect on albuminuria containing composite outcome	Effect on GFR Loss
Empagliflozin N=7,020	EMPA-REG OUTCOME	eGFR ≥30 ml/min/1.73m²	MACE	↓	↓↓	↓↓
Canagliflozin N= 10,142	CANVAS Trials	eGFR ≥30 ml/min/1.73m²	MACE	↓	↓↓	↓↓
N=4,401	CREDENCE	UACR 300-5000 mg/g eGFR 30-90 ml//min/1.73m²	Progression of CKD	↓↓	↓↓	↓↓
Dapagliflozin N=17,160	DECLARE-TIMI	CrCl ≥60 ml/min 45% eGFR 60-90 ml//min/1.73m²	MACE & composite of HHF or CV death	↔/↓	↓	↓↓
N=4,304	DAPA-CKD	UACR 200-5000 mg/g GFR 25-75 ml/min/1.73m²	Progression of CKD	↓↓	↓↓	↓↓
Ertugliflozin N =8,246	VERTIS CV	eGFR ≥30 ml/min/1.73m²	MACE	↔	↔	↓↓

↔ no significant difference

↓ significant reduction in risk, with hazard ratio (HR) estimate >0.7 and 95% confidence interval (CI) not overlapping

↓↓ significant reduction in risk, with HR estimate ≤0.7 and 95% CI not overlapping

Executive summary of the 2020 KDIGO diabetes management in chronic kidney disease. https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-in-CKD-GL-Exec-Summary.pdf. Accessed February 7, 2022

How do SGLT2 inhibitors work?

Glycemic efficacy in eGFR >60 ml/min/1.73 m²

- SGLT-2i ↓ glucose in the proximal tubule, efficacy wanes as eGFR ↓
- Osmotic diuresis, natriuresis, and intraglomerular pressure reduction ↓ eGFR during first weeks of treatment, and ↑ towards baseline and stabilization after ~4 weeks
- ↓ in eGFR not seen in eGFR <40 ml/min/1.73 m², yet renal/CV benefits are seen

Renal and CV benefits (proposed)

- BP ↓ independent of blood glucose and eGFR (BP↓ seen in eGFR 25-80 ml/min/1.73 m²)
- ↓ in body weight (i.e. visceral fat)
- ↓ in albuminuria, serum uric acid, inflammation, etc.

USHP

Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. *Curr Opin Nephrol Hypertens. Mar 2020;29(2):190-198. doi:10.1097/mnh.0000000000000584*

SGLT2i Side Effect Monitoring

Genital mycotic infections and urinary tract infections	• Assess preexisting factors: History of vaginal yeast infections, UTIs, Uncontrolled hyperglycemia, older adults, prior history, uncircumcised males
Ketoacidosis	• Hold SGLT2i in prolonged fasting, critical illness or upcoming surgery to minimize risk
Hypotension/syncope/ dehydration	• Reduce dose of concomitant diuretic medications
Acute kidney injury	• Assess preexisting factors: hypovolemia, chronic kidney insufficiency, heart failure, diuretics/RAASi/NSAIDs
Bone fractures (canagliflozin only)	• Assess fracture history
↑ LDL cholesterol	• Monitor labs
Fournier's gangrene	• Monitor pain, tenderness, redness, or swelling in genital area

Padda IS. Sodium-glucose transport protein 2 (SGLT2) inhibitors. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK576405/. Published January 6, 2022. Accessed February 10, 2022.

CKD SGLT2i Dosing Recommendations

eGFR (ml/min/1.73m²)	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
>60	10 mg daily	100 mg daily	10 mg daily	15 mg
45-60				
30-45	Initiation not recommended			Use not recommended
<30	Contraindicated (CI)	Initiation not recommended Continue in UACR>300 mg/g	Initiation not recommended (<25ml/min/1.73m²)	
On Dialysis	CI	CI	CI	CI

Canagliflozin [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2019.
Dapagliflozin [package insert] dp. Washington, DE: AztraZeneca Pharmaceuticals LP; 2014
Ertugliflozin [package insert] ep. Whitehouse Station, NJ: Merck & Co., INC.,; 2014
Empagliflozin {package insert] ep. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2014

Key Take Aways for SGLT2i

CKD WITH ALBUMINURIA

- SGLT2i w/primary evidence of ↓ CKD progression
  - Canagliflozin
    Dapagliflozin
- SGLT2i w/evidence of ↓ CKD progression in CVOTs
  - Empagliflozin (off-label)
- GLP-1 RA w/CVD labeled indication if SGLT2i not tolerated or CI
  - ?

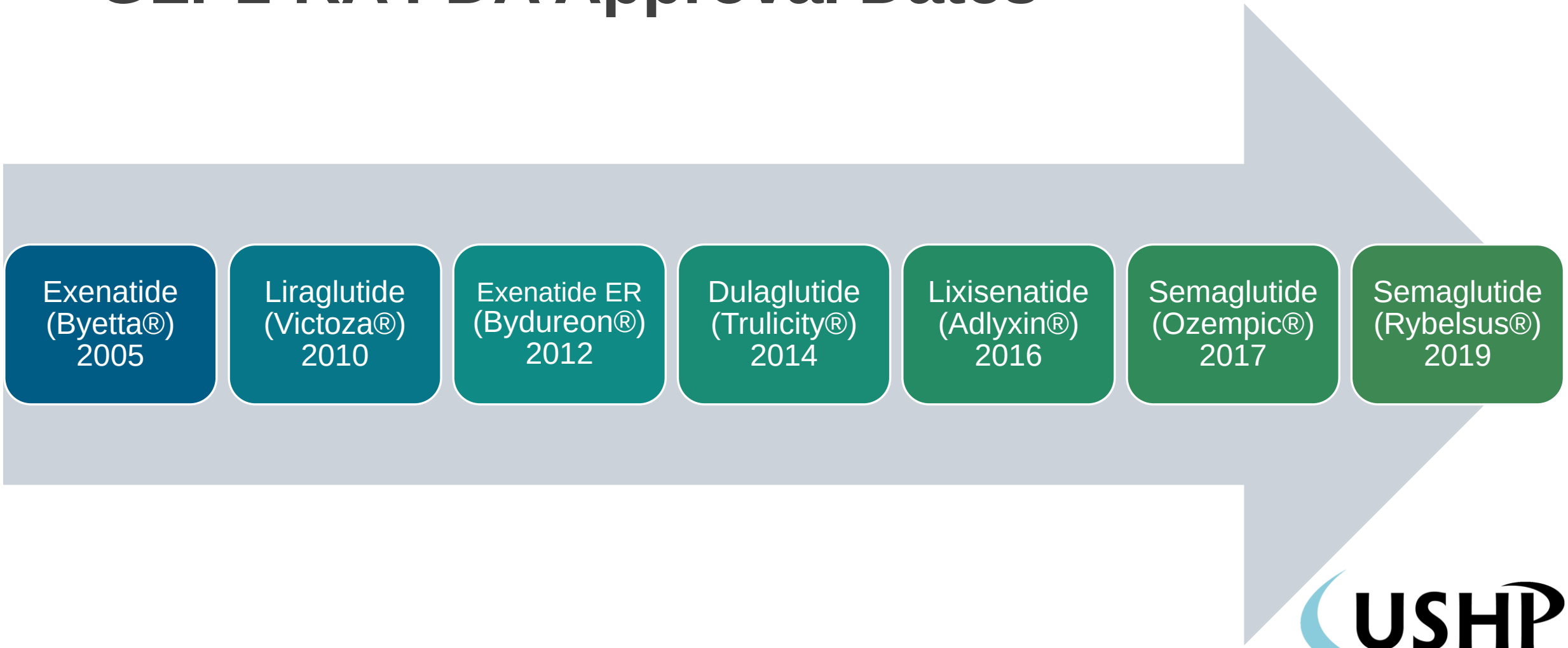
CKD WITHOUT ALBUMINURIA

- SGLT2i w/CVD labeled indication
  - Empagliflozin
    Canagliflozin
- GLP-1 RA w/CVD labeled indication
  - ?

Diabetes care. American Diabetes Association.https://diabetesjournals.org/care/issue/45/Supplement_1. Published January 1, 2022. Accessed February 8, 2022. .

Glucagon-like peptide receptor agonists (GLP-1 RAs)

GLP1-RA FDA Approval Dates



Guidelines

KDIGO 2020

- In patients with T2DM and CKD who have not achieved glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, we **recommend a long-acting GLP-1 RA**

ADA 2022

- GLP-1 RAs are suggested for CV risk ↓ if such risk is a predominant problem, as they ↓ risks of CVD events and **appear to possibly slow CKD progression**

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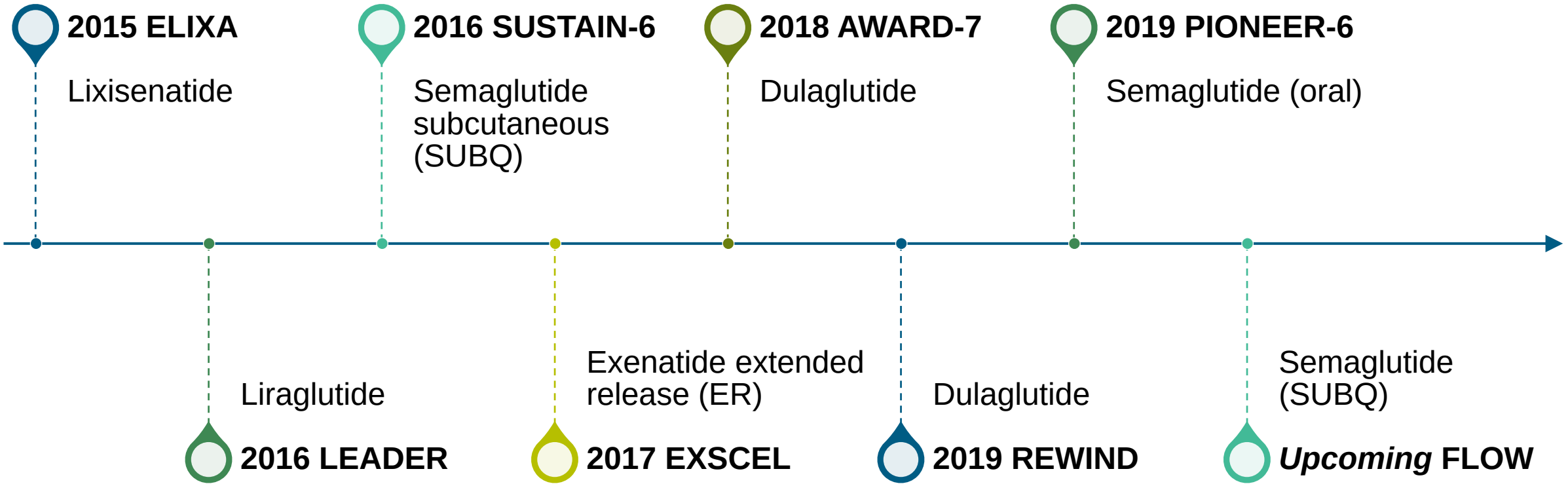
American Diabetes Association Professional Practice Committee. 11. chronic kidney disease and risk management: Standards of medical care in diabetes-2022. American Diabetes Association. https://diabetesjournals.org/care/article/45/Supplement_1/S175/138914/11-Chronic-Kidney-Disease-and-Risk-Management. Published December 16, 2021. Accessed February 8, 2022.

Primary Literature



Review of GLP-1 Kidney Outcomes

			Primary Outcomes		Kidney Outcomes	
GLP-1 RA	Trials	Kidney-related eligibility criteria	Primary Outcome	Effect on primary outcome	Effect on albuminuria containing composite outcome	Effect on GFR Loss
Lixisenatide	ELIXA	eGFR ≥ 30 ml/min/1.73m²	MACE	↔	↓	↔
Liraglutide	LEADER	eGFR ≥ 15 ml/min/1.73m²	MACE	↓	↓	↔
Semaglutide (SUBQ)	SUSTAIN-6	Dialysis patients excluded	MACE	↓	↓↓	N/A
Semaglutide (oral)	PIONEER-6	eGFR ≥ 30 ml/min/1.73m²	MACE	↔	N/A	N/A
Exenatide ER	EXSCEL	eGFR ≥ 30 ml/min/1.73m²	MACE	↔	↔	↔
Dulaglutide	REWIND	eGFR ≥ 15 ml/min/1.73m²	MACE	↓	↓	↓

↔ no significant difference

↓ significant reduction in risk, with hazard ratio (HR) estimate >0.7 and 95% confidence interval (CI) not overlapping

↓↓ significant reduction in risk, with HR estimate ≤0.7 and 95% CI not overlapping

Executive summary of the 2020 KDIGO diabetes management in chronic kidney disease. https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-in-CKD-GL-Exec-Summary.pdf. Accessed February 7, 2022

Summary of GLP-1 Kidney Outcomes

Trial	LEADER	SUSTAIN-6	REWIND	EXSCEL	AWARD-7
Drug	Liraglutide	Semaglutide (SUBQ)	Dulaglutide	Exenatide ER	Dulaglutide vs insulin
N	9340	3297	9901	14,752	577
Criteria	≥30 ml/min/1.73m²	n/a	≥15 ml/min/1.73m²	≥30 ml/min/1.73m²	n/a
eGFR<60	20.7%	28.5%	22.2%	22.9%	100% G3a-G4
UACR	n/a	n/a	7.9% severe	3.5% severe	44% severe
F/u time	3.8 yr	2.1 yr	5.4 yr	3.2 yr	52 wk
CV Outcomes	CV death, Nonfatal MI, Nonfatal stroke	CV death, Nonfatal MI, Nonfatal stroke	CV death, Nonfatal MI, Nonfatal Stroke	CV death, Nonfatal MI Nonfatal stroke	n/a
Results	13% RRR	26% RRR	12% RRR	9% RRR	n/a
Kidney Outcomes	Severe UACR Doubling of Scr ESRD Renal death	Severe UACR Doubling Scr CrCl <45 RRT	Severe UACR 30% eGFR decline RRT	1) 40% eGFR decline, RRT, renal death 2) 40% eGFR decline, RRT, renal death, severe albuminuria	1) eGFR 2) UACR
Results	22% RRR	36% RRR	15% RRR	1) 13% RRR ‘ 2) 15% RRR	1) Less decline 2) No difference

Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: An updated review of head-to-head clinical studies. Therapeutic advances in endocrinology and metabolism. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7953228/. Published March 9, 2021. Accessed February 10, 2022.
Executive summary of the 2020 KDIGO diabetes management in chronic kidney disease. https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-in-CKD-GL-Exec-Summary.pdf. Accessed February 7, 2022

Primary Literature

Renal benefits remain uncertain

- CV outcome trials and metanalysis suggest a renal protective effect of GLP-1RA
- eGFR <60 ml/min/1.73m² ranged from 17-28% in most trials
- Findings driven by macroalbuminuria ↓ and lack of statistical power for other outcomes

Ongoing Trials

- FLOW Semaglutide (SUBQ) trial (Anticipated completion 2024)
  - Purpose: Semaglutide vs Placebo, primary renal outcomes, in T2DM and w/o T2DM
- EMPA-SEMA (Status unknown-anticipated completion was 2019)
  - Synergistic with SGLT2i to optimize renal outcomes?
  - Purpose: Empagliflozin alone vs combination w/semaglutide (SUBQ), change in albuminuria, in T2DM and albuminuria

Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: An updated review of head-to-head clinical studies. Therapeutic advances in endocrinology and metabolism. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7953228/. Published March 9, 2021. Accessed February 10, 2022.

How do GLP-1 RA Work?

Glycemic efficacy

- Stimulate glucose-dependent insulin secretion
- Inhibit glucagon secretion
- Reduce gastric emptying
- Reduce appetite
- Promote satiety

Proposed CV and renal benefits

- Natriuretic and diuretic properties
- ↓ in systolic BP
- ↓ oxidative stress
- ↓ weight
- Improves lipid profiles

Dose adjustments

- Dulaglutide
  - eGFR >15 ml/min/1.73m²
- Exenatide ER
  - CrCl >30 ml/min/1.73m²
- All others: No dose adjustments
- Limited evidence in severe CKD

Rojano Toimil A, Ciudin A. GLP-1 Receptor Agonists in Diabetic Kidney Disease: From Physiology to Clinical Outcomes. *J Clin Med. Aug 31 2021;10(17)doi:10.3390/jcm10173955*

Key Take Aways for GLP-1RA

CKD + ALBUMINURIA

- SGLT2i w/primary evidence of ↓ CKD progression
  - Canagliflozin
  - Dapagliflozin
- SGLT2i w/evidence of ↓ CKD progression in CVOTs
  - Empagliflozin (off-label)
- GLP-1 RA with CVD labeled indication if SGLT2i not tolerated or CI
  - Dulaglutide
  - Liraglutide
  - Semaglutide

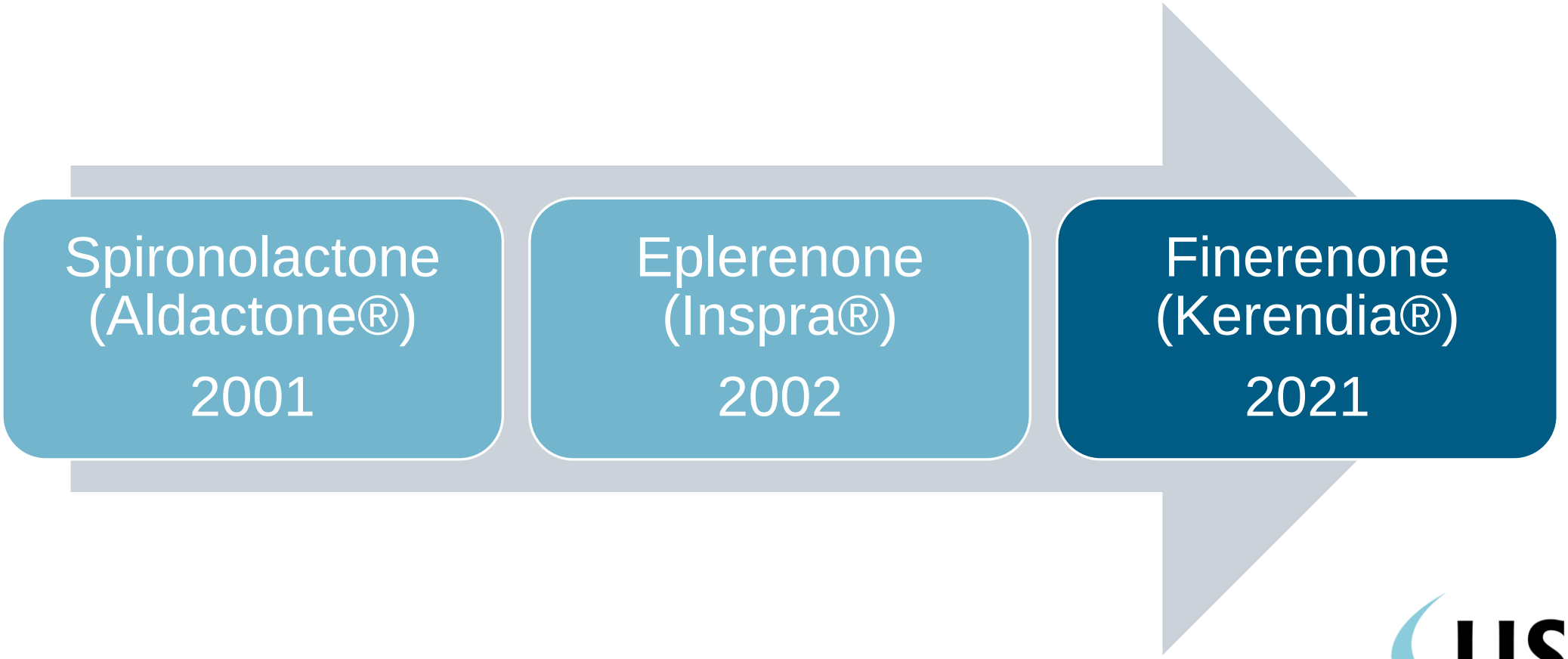
CKD WITHOUT ALBUMINURIA

- SGLT2i w/CVD labeled indication
  - Empagliflozin
  - Canagliflozin
- GLP-1 RA w/CVD labeled indication
  - Dulaglutide
  - Liraglutide
  - Semaglutide

Diabetes care. American Diabetes Association.https://diabetesjournals.org/care/issue/45/Supplement_1. Published January 1, 2022. Accessed February 8, 2022. .

Mineralocorticoid Receptor Antagonists (MRA)

MRA FDA Approval Dates



What is finerenone?

Highly selective non-steroidal mineralocorticoid receptor (MR) antagonist

- Higher selectivity and higher affinity to MR compared to spironolactone and eplerenone (steroidal MRAs)
- Equal tendency to heart and kidney compared to steroidal MRAs

Mechanism of action

- By inhibiting activation of the MR receptor, finerenone inhibits pro-inflammatory and pro-fibrotic factors that halt progression of renal tissue damage

Eplerenone and Spironolactone have limited use in CKD associated w/T2DM

- Hyperkalemia, gynecomastia, etc.

Finerenone [package insert] fp. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2021.

Guidelines

KDIGO 2020

- Guideline published prior to FDA approval of Finerenone

ADA 2022

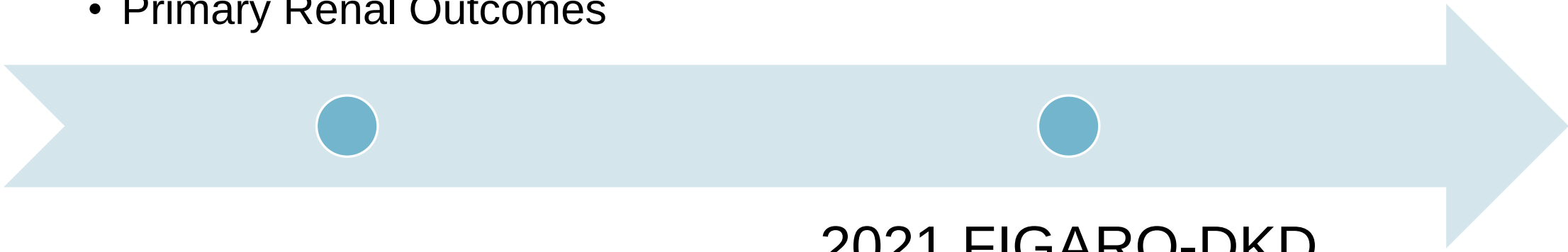
- In patients with CKD who are at ↑ risk for CV events or CKD progression or are unable to use an SGLT2i, **a nonsteroidal MRA (finerenone) is recommended to reduce CKD progression** and CV events

American Diabetes Association Professional Practice Committee. 11. chronic kidney disease and risk management: Standards of medical care in diabetes-2022. American Diabetes Association. https://diabetesjournals.org/care/article/45/Supplement_1/S175/138914/11-Chronic-Kidney-Disease-and-Risk-Management. Published December 16, 2021. Accessed February 8, 2022.

Primary Literature

2020 FIDELIO-DKD

- Finerenone vs Placebo
- Primary Renal Outcomes



2021 FIGARO-DKD

- Finerenone vs Placebo
- CVOT

FIDELIO-DKD

Primary renal composite outcome

- ESRD
- Sustained eGFR decrease of at least 40% (primary driver)
- Renal death

Baseline Characteristics (n = ~5,700)

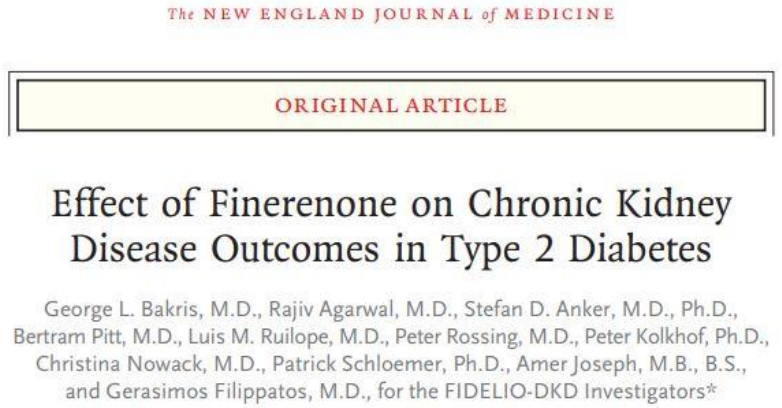
- ~ 99.9% on ACEi/ARB; ~ 7% on SGLT2i
- **~ 52.5% eGFR 25-45 ml/min/1.73m**
- **~ 87.5% UACR >300 mg/g**

Results

- Median duration, 2.6 years
- A 31% greater reduction in UACR from baseline to month 4 was sustained throughout the study
- Hyperkalemia incidence 18.3% vs 9%
- Hyperkalemia leading to discontinuation 2.3% vs 0.9%

Additional Trials

- FIGARO-DKD: Positive cardiovascular outcomes
- Upcoming: Finerenone and Empagliflozin vs Finerenone only in CKD + T2DM



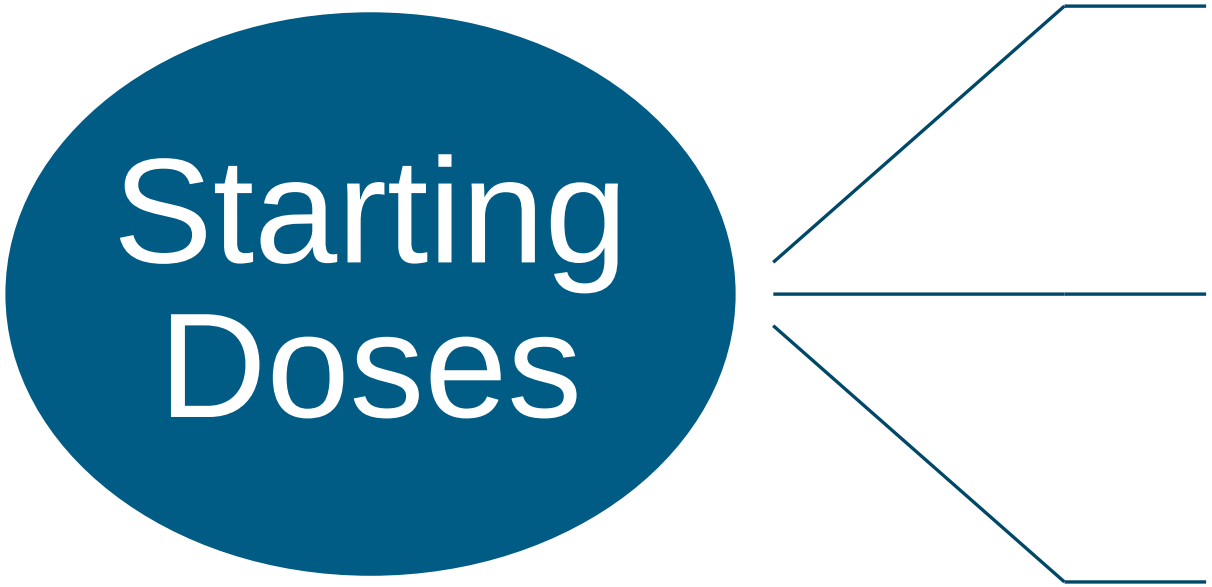
↓

18% RRR in primary renal composite outcome

USHP

Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med. Dec 3 2020;383(23):2219-2229. doi:10.1056/NEJMoa2025845*

Finerenone Dose Adjustments



eGFR ≥60 ml/min/1.73 m^2

20 mg once daily

eGFR ≥25 to <60 ml/min/1.73 m^2

10 mg once daily

eGFR <25 ml/min/1.73 m^2

Not recommended

Finerenone [package insert] fp. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2021.

Potassium Monitoring

K+	If K+ is >5 mEq/L, do NOT start
	Check K+ 4 weeks after staring or sooner if K+ 4.8-5.0 mEq/L
	Monitor throughout treatment and adjust the dose as needed
eGFR	If eGFR ↓ >30%, maintain 10 mg dose

		Current finerenone dose	
		10 mg daily	**20 mg daily**
Current Serum Potassium (mEq/L)	≤ 4.8	Increase 20 mg	Maintain
	> 4.8 – 5.5	Maintain	Maintain
	> 5.5	HOLD Restart ≤ 5.0 mEq/L	HOLD Restart ≤ 5.0 mEq/L

Finerenone [package insert] fp. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2021.

Key Take Aways on Finerenone

When to use Finerenone

- Option for CKD and T2DM patients who cannot tolerate RAASi/SGLT-2i or as an add on in patients with increased risk of CKD progression or CVD

Monitor Potassium (K+)

- Do not a start if K+ is >5 mEq/L
- Adherence to monitoring labs is important, including patients on RAASi and diuretics

Prognosis of CKD				Persistent albuminuria categories (mg/g)		
				A1	A2	A3
				Normal to Mildly Increased	Moderately Increased	Severely Increased
				< 30	30-300	>300
GFR categories (ml/min/1.73 m^2)	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney Failure	<15			

Finerenone [package insert] fp. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2021.

Co-Pay Cards

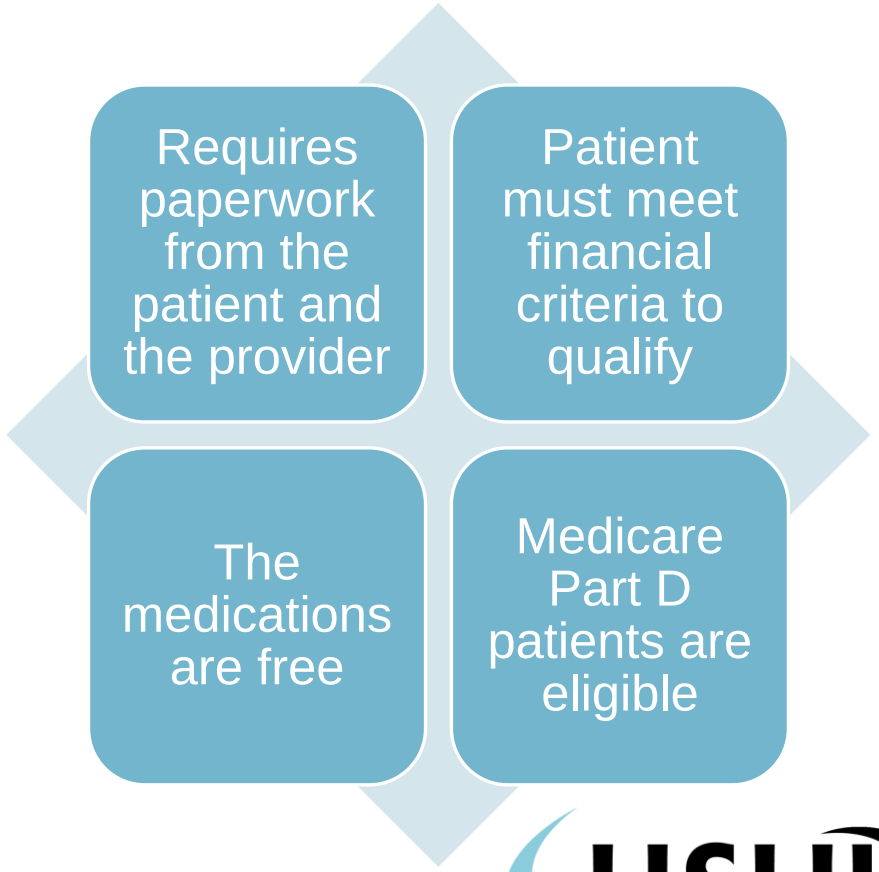
Government insurance beneficiaries are not eligible

Product	Per Month	Max coverage
Canagliflozin (Invokana®)	$0	No limit first month; $200/month; $3,000/year
Dapagliflozin (Farxiga®)	$0	$175/month; $150/month without insurance
Empagliflozin (Jardiance®)	$10	$175/month
Ertugliflozin (Steglatro ®)	$0	$583/month
Dulaglutide (Trulicity®)	$25	$150/month; $1,800/year
Exenatide ER (Bydureon®)	$0	$300/month
Liraglutide (Victoza ®)	Discontinued	
Semaglutide (Ozempic®)	$25	$150/month
Finerenone (Kerendia®)	$10	$3,000/year

Current as of 02/2022

Patient Assistance Programs (PAP)

Invokana®	Johnson & Johnson Patient Assistance Foundation
Farxiga®	AstraZeneca Prescription Savings Program
Jardiance®	Boehringer Ingelheim Cares PAP
Steglatro®	Merck Patient Assistance Program, Inc.
Trulicity®	Lilly Cares Foundation PAP
Victoza®	Novo Nordisk PAP
Rybelsus®	Novo Nordisk PAP
Kerendia®	Bayer US Patient Assistance Foundation



When to Refer to Nephrologist

Indications to refer to nephrologist

- Clinical findings inconsistent with typical diabetic nephropathy
- Massive proteinuria
- Hematuria, casts, and/or active urinary sediment
- AKI or rapidly declining eGFR
- Anemia of CKD
- Complex comorbidities (e.g., hyperparathyroidism or bone disease)
- Advanced CKD (i.e., eGFR <30 ml/min/1.73 m²)

Prognosis of CKD

				Persistent albuminuria categories (mg/g)		
				A1	A2	A3
				Normal to Mildly Increased	Moderately Increased	Severely Increased
				< 30	30-300	>300
GFR categories (ml/min/1.73 m²)	G1	Normal or high	≥ 90		Treat	Refer
	G2	Mildly decreased	60-89		Treat	Refer
	G3a	Mildly to moderately decreased	45-59	Treat	Treat	Refer
	G3b	Moderately to severely decreased	30-44	Treat	Treat	Refer
	G4	Severely decreased	15-29	Refer	Refer	Refer
	G5	Kidney Failure	<15	Refer	Refer	Refer

KDIGO 2012 clinical practice guideline for the evaluation.https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Accessed February 6, 2022.

Conclusion

CKD carries a heavy burden economically and in quality of life

- 5% of Medicare patients have CKD associated with T2DM, yet expenditures account for 11%
- CKD associated with diabetes is the leading cause of ESRD
- Coordinated, multidisciplinary care with attention to appropriate, timely screening and preventative management is crucial to reducing morbidly and mortality

SGLTi

- Data suggests a class effect on ↓ of CKD progression, in addition to CV benefits

GLP1-RA

- Data limited in severe CKD prevention compared to CVD benefits, use in significant CVD

Finerenone

- Monotherapy effects are unknown, use as alternative or add on therapy in high-risk CKD and CVD patients

Jain K, Mottl AK. Comprehensive care for people with diabetic kidney disease. American Diabetes Association. https://diabetesjournals.org/spectrum/article/28/3/187/32196/Comprehensive-Care-for-People-With-Diabetic-Kidney. Published August 1, 2015. Accessed February 14, 2022.