What's New in the Treatment of Diabetic Kidney Disease

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Disclosure

Consultant: AstraZeneca; Bayer; Boehringer Ingelheim; Corcept; CSL Vifor; Mineralys; Novo Nordisk; Vera

Salary Support: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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Overview

- Evidence-based approaches to diabetic kidney disease
  - Blood Pressure
  - RAAS blockade
  - Glucose control
- Pathophysiology of diabetic kidney disease
  - Glomerular capillary hypertension
  - Inflammation
- Albuminuria Suppression
- Newer opportunities

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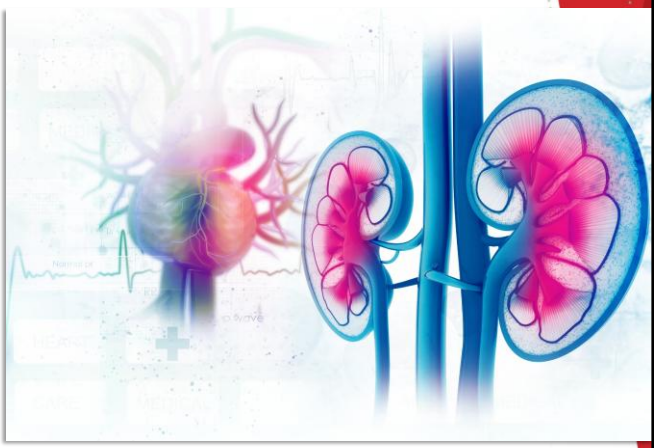
Definition of CKM Syndrome Simplified

Cardiovascular-kidney-metabolic (CKM) syndrome
is a health disorder due to connections among heart disease, kidney disease, diabetes, and obesity leading to poor health outcomes.



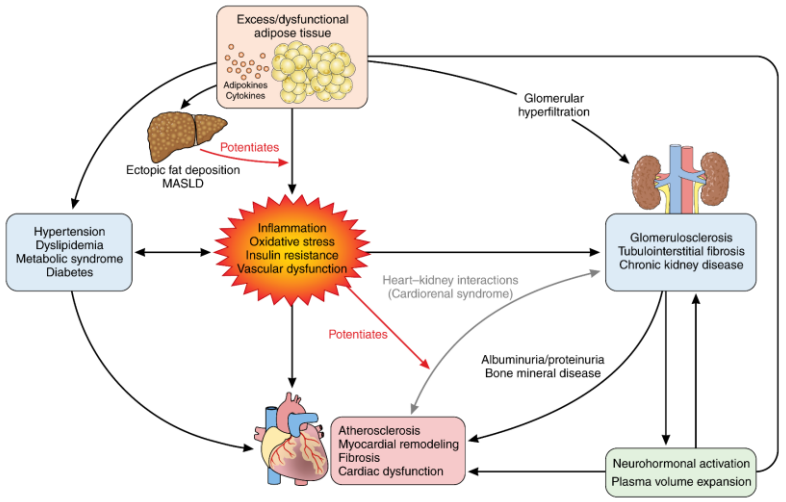
Abbreviations: CKM indicates Cardiovascular-Kidney-Metabolic.

Ndumele, C.E. et al., A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic Syndrome: A Scientific Statement From the American Heart Association. 2023. *Circulation.*

American Heart Association.

4

Conceptual Diagram of the CKM Syndrome



Abbreviations: CKM indicates Cardiovascular-Kidney-Metabolic; and MASLD, metabolic dysfunction-associated steatotic liver disease.

American Heart Association.

Ndumele, C.E. et al., A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic Syndrome: A Scientific Statement From the American Heart Association. 2023. *Circulation.*

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Prevention requires timely evaluation and education of those at risk for kidney and heart disease:

- Hypertension
- Diabetes
- African heritage
- Obesity

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Case Study

JD is a 48-year-old male with hypertension and type 2 DM. BP is 138/82 mmHg. His A1C is 7.7%. His serum creatinine is 1.6 mg/dL and his UACR is 370. He currently takes amlodipine 10 mg, losartan 50 mg / HCTZ 12.5 mg, metformin 500 mg x 1, sitagliptin 50 mg and atorvastatin 40 mg.

All of the Following Are True Except:

A. He is more likely to die from CKD than he is to reach ESRD
B. His goal BP should be less than 120/80 mmHg
C. His goal A1C should be less than 7.0%
D. A statin should almost always be part of a CVD risk-reducing regimen in patients with DM and CKD

SCREENING AND EDUCATION

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*Estimate GFR
*Quantitate albuminuria/proteinuria
*Measure longitudinal changes over time

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Treatment

- Evidence-based approaches to slow chronic kidney disease
  - Blood Pressure
  - RAAS blockade
  - Glucose control
- Correction of acidosis
- Albuminuria Suppression
- Pathophysiology of kidney disease progression
  - Glomerular capillary hypertension
  - Inflammation
- Newer opportunities

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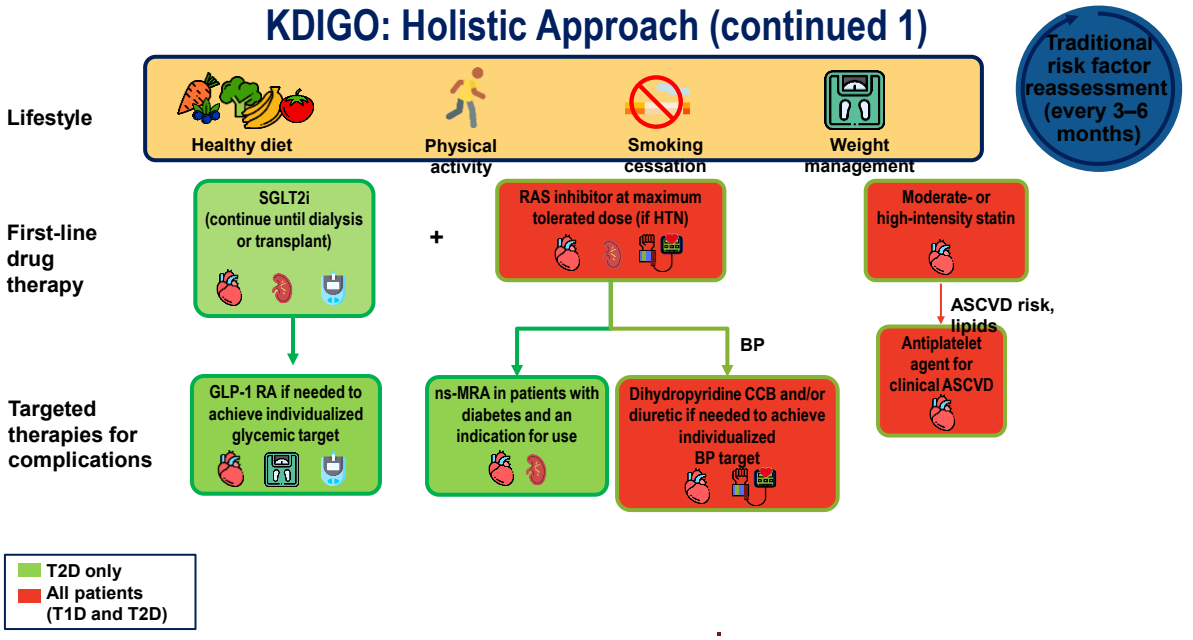
KDIGO: Holistic Approach (continued 1)



Modified from KDIGO CKD Work Group. *Kidney Int.* 2024;105:S117-S314.

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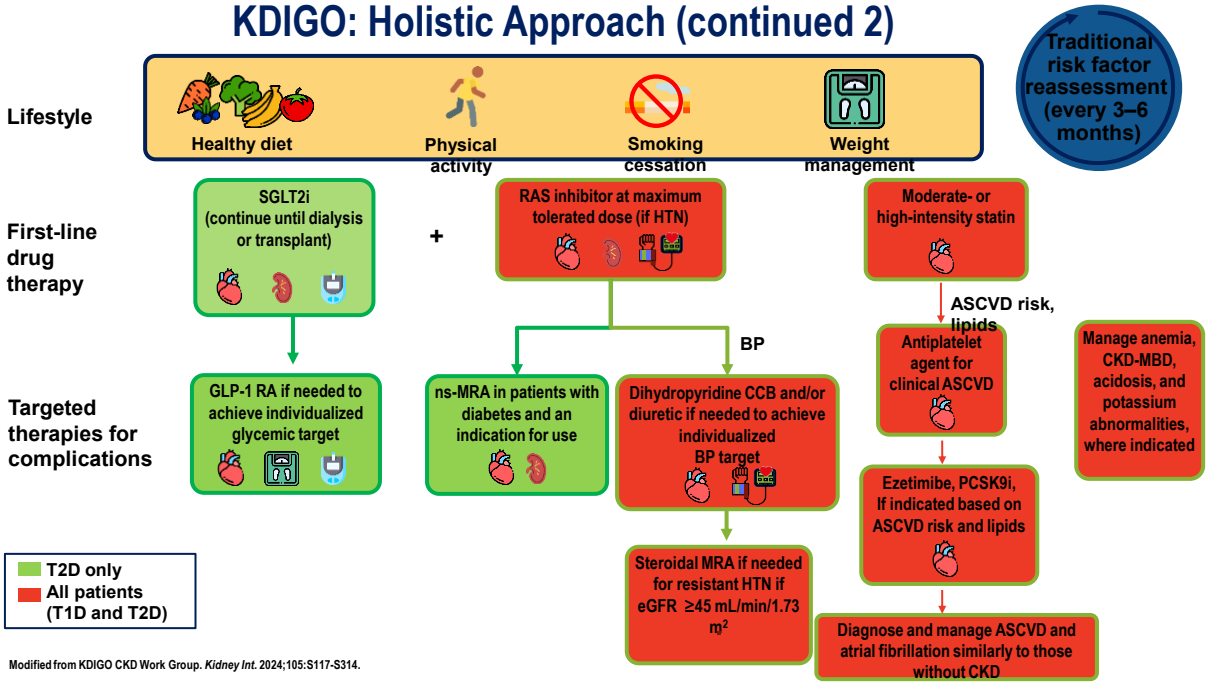
KDIGO: Holistic Approach (continued 2)



Modified from KDIGO CKD Work Group. *Kidney Int.* 2024;105:S117-S314.

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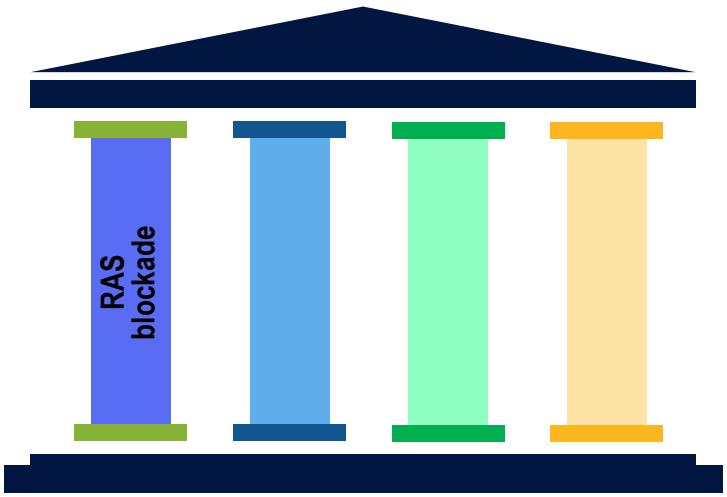
Pillars of Therapy to Reduce Cardiorenal Risk



Slowing DKD progression and Reducing CV risk

DKD = diabetic kidney disease; RAS = renin-angiotensin system.

Modified from Blazek O, Bakris GL. *Am Heart J Plus.* 2022;19:100187 (www.sciencedirect.com/science/article/pii/S2666602222001045). Accessed 7/1/24.

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RAAS Blockade:
Provides on Average a 20% Relative Risk Reduction!

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Try Not to Stop ACEi or ARB: Hyperkalemia

- Dietary potassium counseling
  - Review dietary habits (high potassium foods)
  - Make sure patient not on salt substitute
  - Make sure patient not taking herbals or NSAIDS
- Diuretic dose adjustment
  - Increase dose if
    - BP not low
    - Creatinine not increasing

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RAASIS Are Recommended By Multiple Organizations for the Prevention of Heart Failure and Kidney Function Decline

Class IA recommendation

- ACEi is recommended, in addition to a BB, for symptomatic patients with HF[1–3]*
- ACEi/ARB is recommended for treatment of hypertension[4,5]† and ACEi/MRA for HF in patients with DM[4]
- ARB is recommended when ACEi is not tolerated[1,2]
- MRA is recommended for patients with HF*, who remain symptomatic despite treatment with an ACEi, and a BB[2]

Highest tolerated targeted doses recommended[1,2]

Slow the progression of kidney disease[4]

- Reduce proteinuria[6,7]
- Valuable in CKD and indicated in proteinuria[6–8]
- More effective at reducing kidney function decline than other BP-lowering drugs[6]

* With reduced ejection fraction; † Class A level of evidence.

1. Yancy CW *et al. Circulation* 2017;136:e137–61; 2. Ponikowski P *et al. Eur J Heart Fail* 2016;18:891–975; 3. Lindenfeld J *et al. J Card Fail* 2010;16:475–539; 4. Cosentino F, *et al. Eur Heart J* 2020;41:255–323; 5. American Diabetes Association. *Diabetes Care* 2020;43:S111–34; 6. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;3:1–150; 7. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. 2004. Available at: kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/index.htm (accessed July 2020); 8. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. 2014 (updated 2015). Available at: nice.org.uk/CG182 (accessed July 2020).

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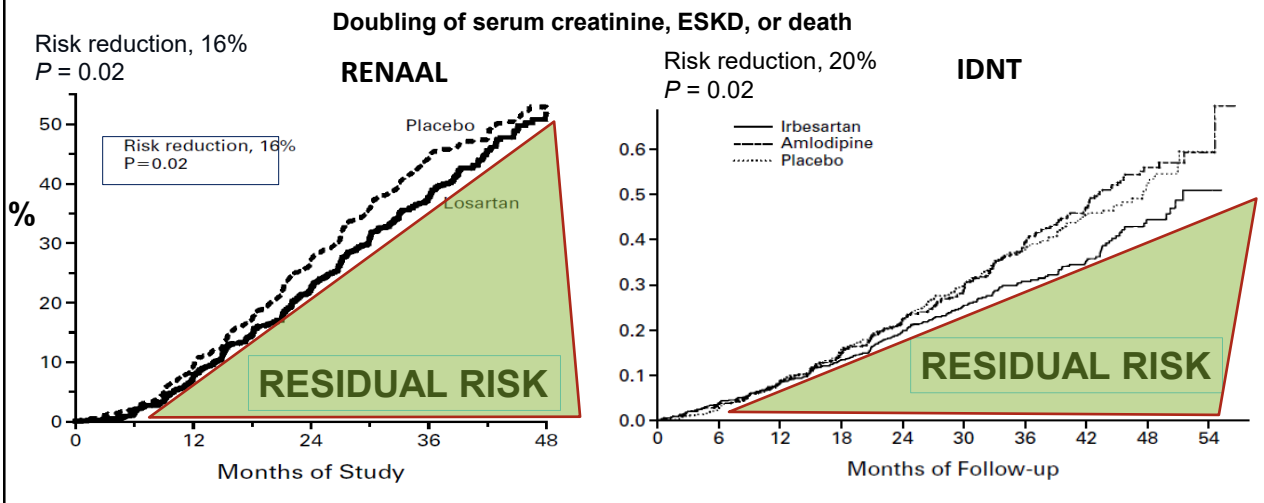
The Only Proven Treatment for Renoprotection in T2DM: RENAAL & IDNT



Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

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His PCP Would Like to Improve His BP Control Below 130/80 mmhg. Next Steps to Facilitate This Could Be All the Following Except:

A. Add ramipril 10 mg
B. Increase losartan HCTZ to 100/25
C. Add doxazosin 1 mg
D. Add metoprolol XL 25 mg

His PCP Would Like to Improve His Glycemic Control By Reducing A1C Below 7%. All of the Following Are Reasonable Considerations Except:

A. Switch sitagliptin to GLP-1RA
B. Add SGLT2 inhibitor
C. Increase metformin 500 x 2
D. Add glyburide 5 mg

Since RENAAL and IDNT, New Therapeutic Strategies for Patients with T2DM and CKD Have Failed

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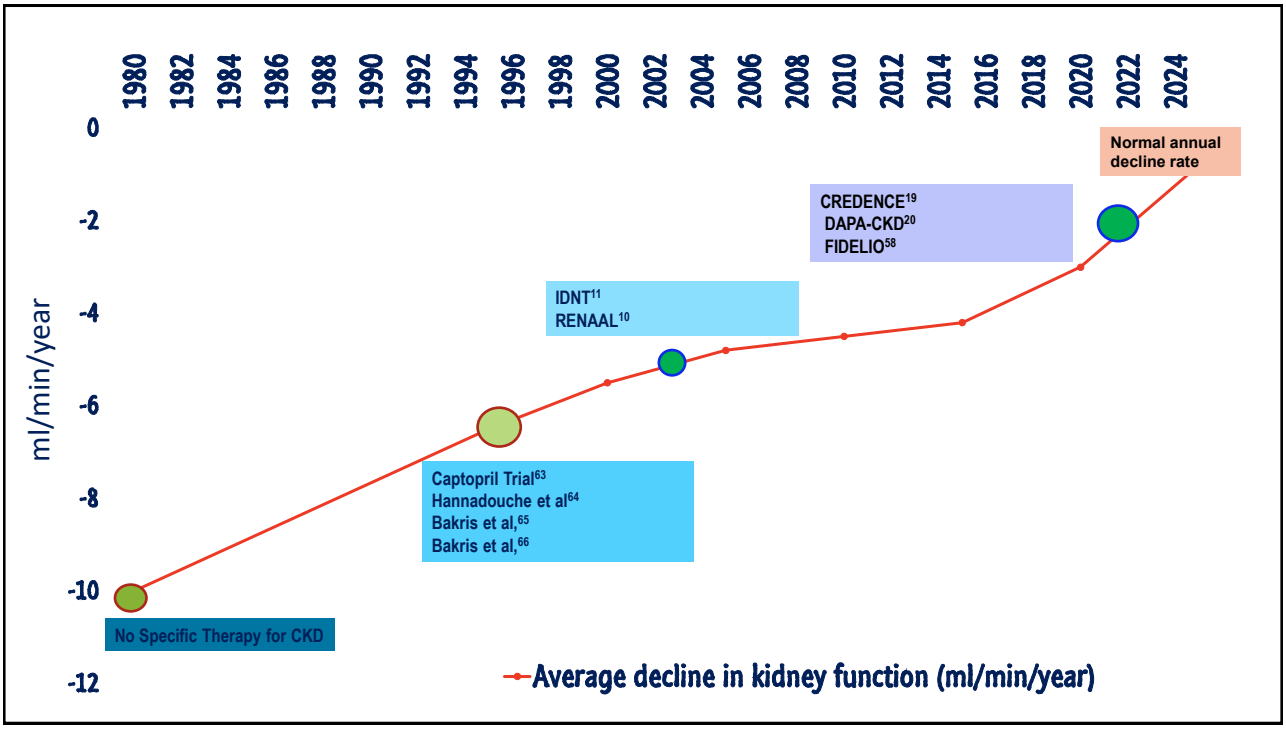

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Some of the Newer Therapies for Diabetic Kidney Disease

- CCR 2 inhibition (CCX 140-B)
- Endothelin receptor antagonist (atrasentan)
- Pentoxifylline
- JAK 2 inhibitor (baricitinib)
- GLP-1 agonists
- SGLT 2 inhibitors
- Finerenone, MRA

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Considerations about Newer Therapies Besides Safety and Efficacy

- Complementary with interstitial BP, glucose and lipid goals
- Complementary with RAAS blockers?
- Tolerability and safety
- Cost

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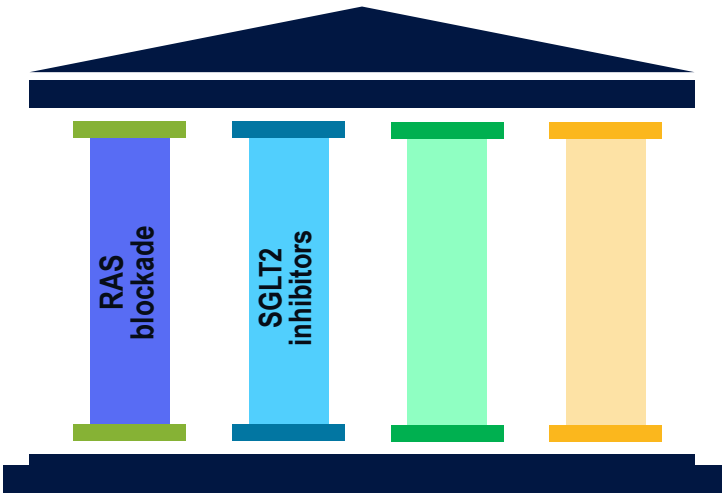
The Patient Has Increased Risk for Both CVD and ESRD Based on His Reduced GFR and Increased UACR. Reducing UACR by 50% or More Has Been Associated with Reduced Risk for Both Incident CHF and ESRD in Patients with T2DM and CKD.

A. True
B. False

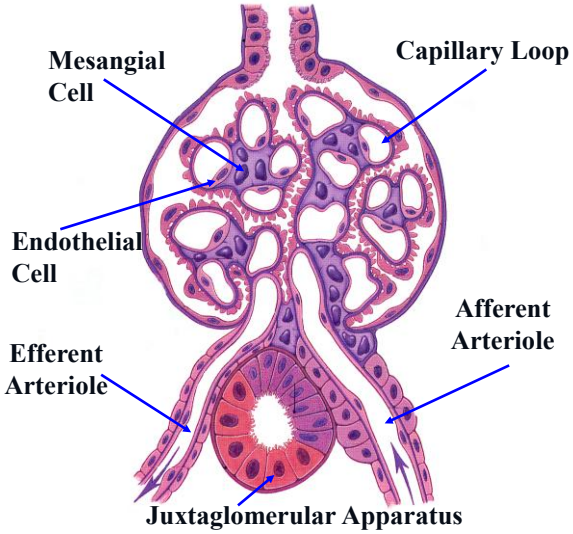
Pillars of Therapy to Reduce Cardiorenal Risk



Slowing DKD progression and reducing CV risk

Modified from Blazek O, Bakris GL. *Am Heart J Plus.* 2022;19:100187 (www.sciencedirect.com/science/article/pii/S2666602222001045). Accessed 7/1/24.

Glomerular Structure



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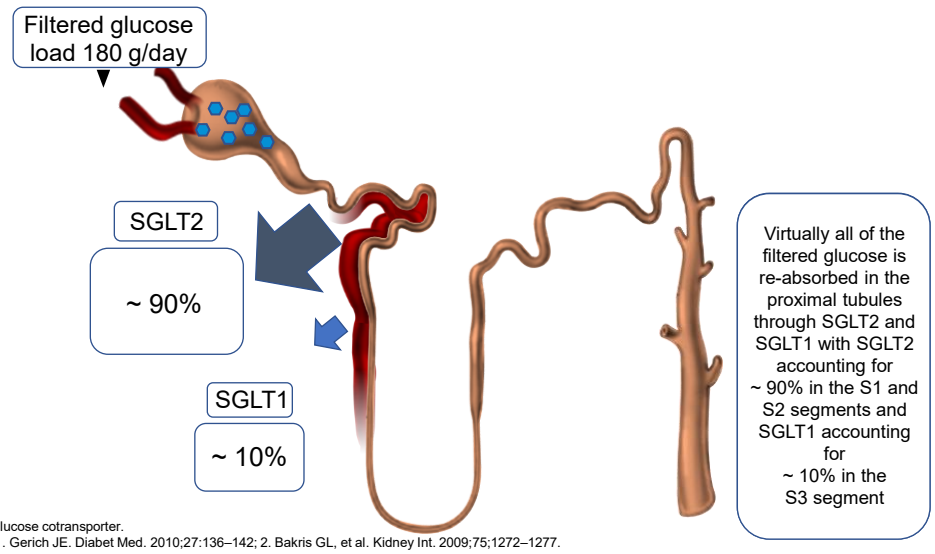
Renal Glucose Re-absorption Under Healthy Conditions[1,2]



SGLT, sodium glucose cotransporter.
Adapted from: 1. Gerich JE. Diabet Med. 2010;27:136–142; 2. Bakris GL, et al. Kidney Int. 2009;75;1272–1277.

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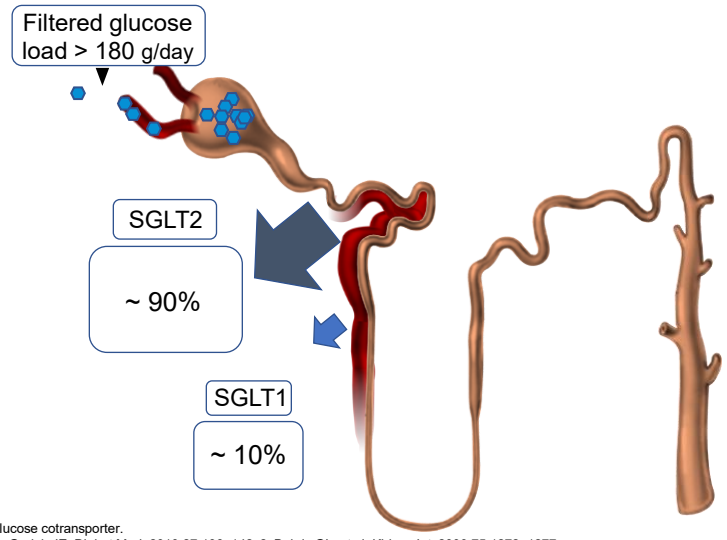
Renal Glucose Re-absorption In Patients with Diabetes[1,2]



SGLT, sodium glucose cotransporter.
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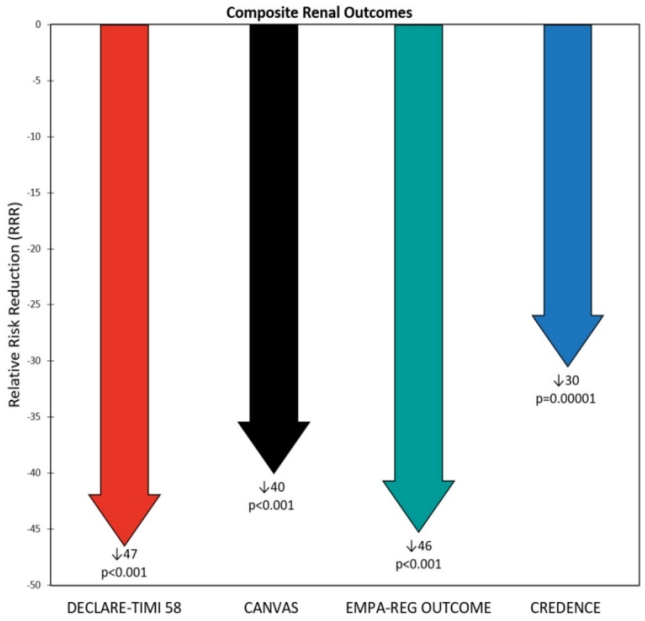
Composite renal outcome relative risk reductions (RRRs) in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials.



Kluger et al. Cardiovasc Diabetol (2019) 18:99

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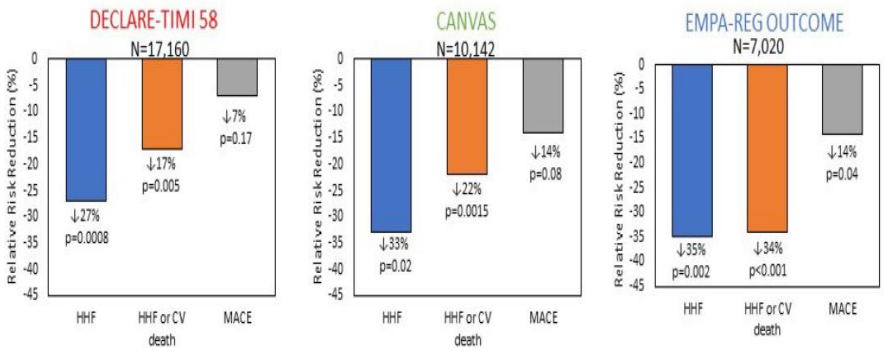
Cardiovascular Outcomes in SGLT2 Inhibitors



Neal B, et al. N Engl J Med. 2017;377:644–657.
Zinman B, et al. N Engl J Med. 2015;373:2117–2128.
Wiviott SD, et al. N Engl J Med. 2019;380:347–357.

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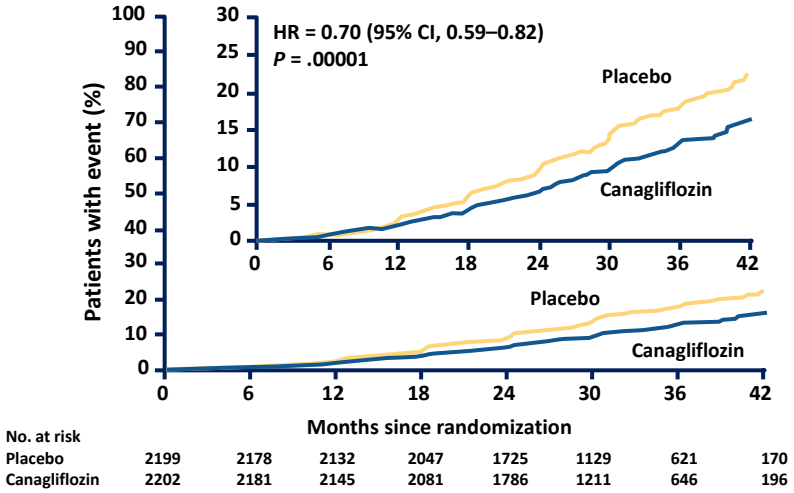
Canagliflozin: CREDENCE Trial Primary Outcome

Composite of ESKD, Doubling of Serum Creatinine, and Renal or CV death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

HR = hazard ratio.

Perkovic V, et al. *N Engl J Med.* 2019;380:2295-2306.

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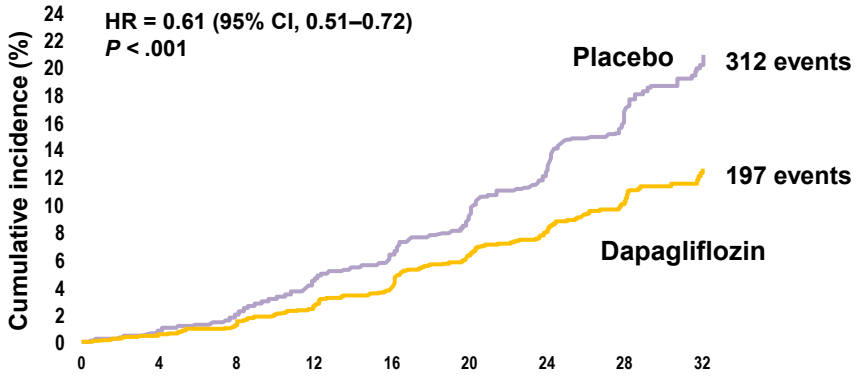
Dapagliflozin: DAPA-CKD Trial Primary Outcome

Composite of ≥50% eGFR Decline, ESKD, Kidney or CV Death



No. at risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

Heerspink HJL, et al. *N Engl J Med.* 2020;383:1436-1446.

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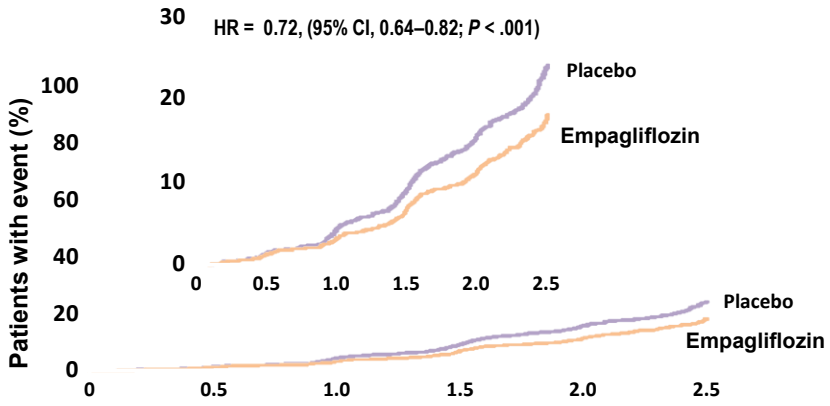
Empagliflozin: EMPA-KIDNEY Trial Primary Outcome

Composite of Progression of Kidney Disease* or Death From CV Causes



No. at risk						
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

*Progression of kidney disease = ESKD, sustained decrease in eGFR to <10 mL/min/1.73 m^2, sustained decrease in eGFR of ≥40% from baseline, or death from renal causes.

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

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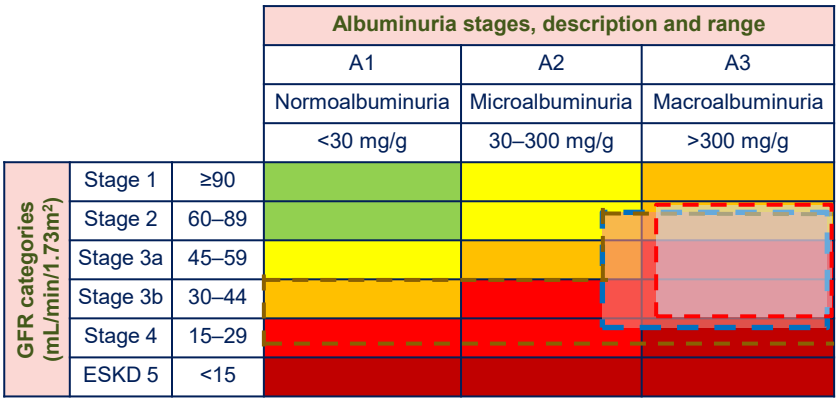
Role of SGLT2 Inhibitors on Kidney Health from 3 Major Large-Scale Clinical Trials, N = 15,314



CREDENCE (DKD only) N = 4401
eGFR ≥30 to <90 mL/min/1.73 m^2
and UACR ≥300 mg/g

DAPA-CKD (CKD) N = 4304
eGFR ≥25 to <75 mL/min/1.73 m^2
and UACR ≥200 mg/g

EMPA-KIDNEY (CKD) N = 6609
eGFR ≥45 to <75 mL/min/1.73 m^2
and UACR ≥200 mg/g
OR
eGFR ≥20 to <45 mL/min/1.73 m^2

Heerspink HJL, et.al. *Nephrol Dial Transplant* 2020;35:274-282.

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Summary of Safety and Tolerability of SGLT2 Inhibitors

- Safe and well-tolerated
- Low risk of UTI, easily treated
- Low risk of genital fungal infections, most are easily treated
- Low risk of ketoacidosis
  - Discontinue therapy, seek medical attention
- Protects against AKI
- Modest reduction of BP by 3–5 mmHg
- Reversible decline in eGFR

AKI = acute kidney injury; UTI = urinary tract infection.

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. KDIGO CKD Work Group. *Kidney Int*. 2024;105(4 suppl):S117-S314. Shubrook JH, et al. *Postgrad Med*. 2022;134;376-387. Xu B, et al. *Cardiovasc Diabetol*. 2022;21:83.

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- Multiple theories about renal and CV benefits with SGLT2 Inhibitors
- Is it more than simply pressure/volume reduction?

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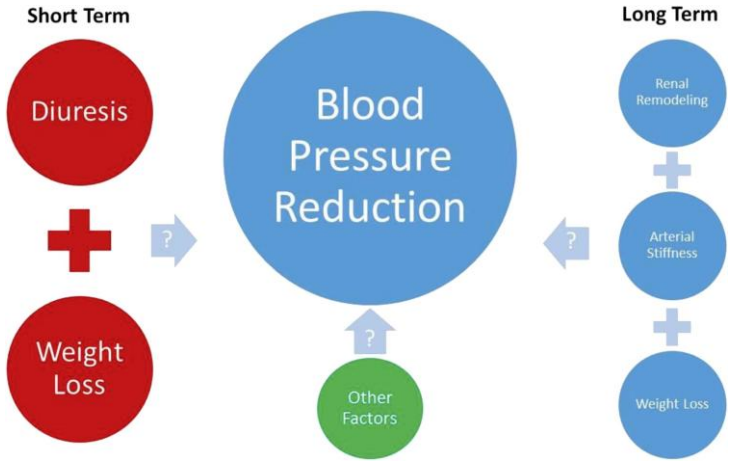
Possible Mechanisms of Blood Pressure Reduction with Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors



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If Hyperfiltration Correction or BP Reduction Cannot Explain the Renoprotection Benefit: What Is the Effect?

- Limitation of oxidative stress by reduction of uric acid reabsorption
- Sympathetic nervous system inhibition
- Increased activity of NHE3
- Increased proximal tubule hydrostatic pressure
- Enhanced sirtuin-1 and HIF-2alpha signaling

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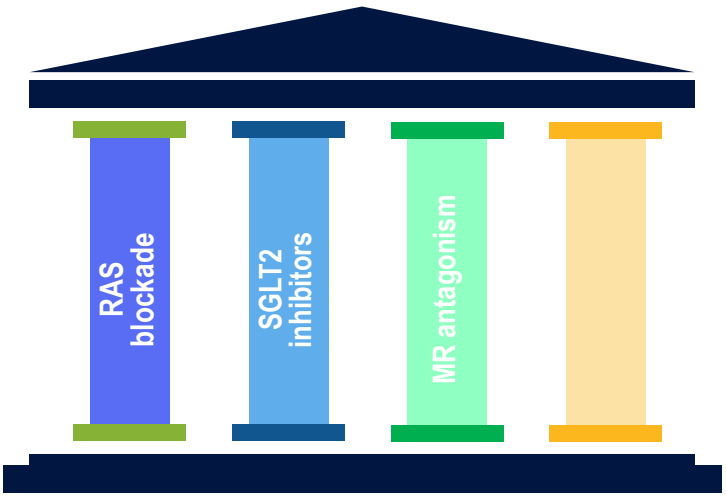
Pillars of Therapy to Reduce Cardiorenal Risk



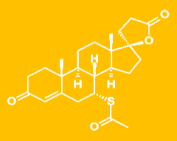
Slowing DKD progression and reducing CV risk

MR = mineralocorticoid receptor.

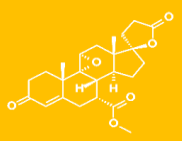
Modified from Blazek O, Bakris GL. *Am Heart J Plus.* 2022;19:100187 (www.sciencedirect.com/science/article/pii/S2666602222001045). Accessed 7/1/24.

40

Different Classes of Agents That Inhibit Mineralocorticoid Receptor (MR)



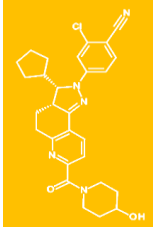
Spironolactone



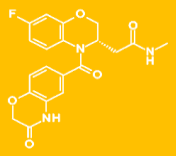
Eplerenone

Steroidal MRAs (aldosterone antagonists)

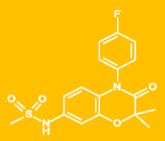
Nonsteroidal MRAs



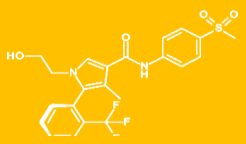
KBP-5074* (Phase 2)
Ocedurenone



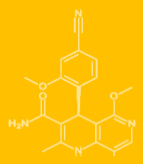
AZD9977* (Phase 2)



Apararenone MT-3995* (Phase 2)



Esaxerenone CS-3150* (launched in Japan)



Finerenone BAY 94-8862 (launched in US)

*This agent is currently under investigation.

Kintscher U, et al. *Br J Pharmacol.* 2022;179:3220-3234.

US = United States.

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Comparison of MRA Inhibitors: Steroidal and Nonsteroidal

	Steroidal MRAs		Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	—
Sexual side effects	++	(+)	—
Half-life	>20 hours	4–6 hours	2–3 hours
Active metabolites	++	—	—
Effect on BP	+++	++	+

CNS = central nervous system.

Kintscher U, et al. *Br J Pharmacol.* 2022;179:3220-3234.

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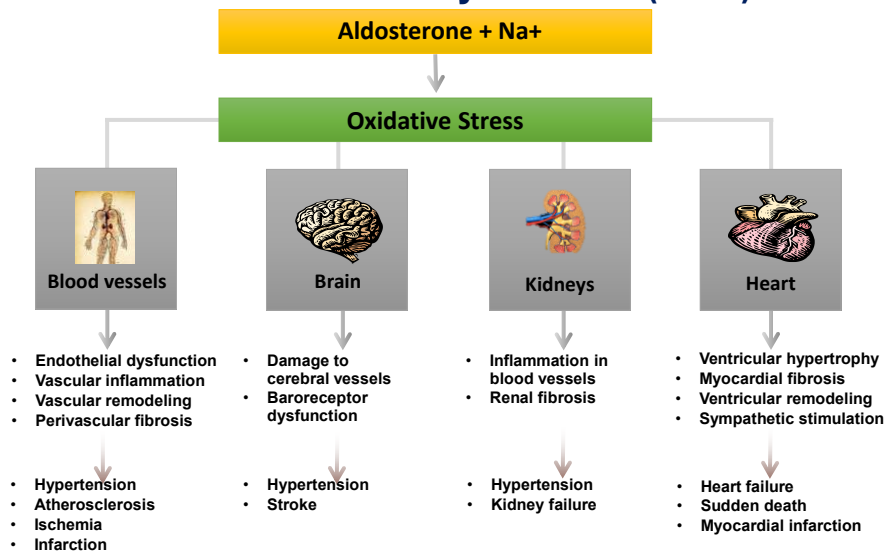
Aldosterone Plays a Critical Role in Cardiovascular Disease and Chronic Kidney Disease (CKD)



Rentoukas EI, Lazaros GA, Zirogiannis PN. *Hellenic J Cardiol.* 2005;46(6):408-419.

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MRA NOT WELL STUDIED IN CKD

- Clinical studies show an important anti-proteinuric effect not always associated with blood pressure reduction
- Experimental studies show attenuation of fibrosis and scarring

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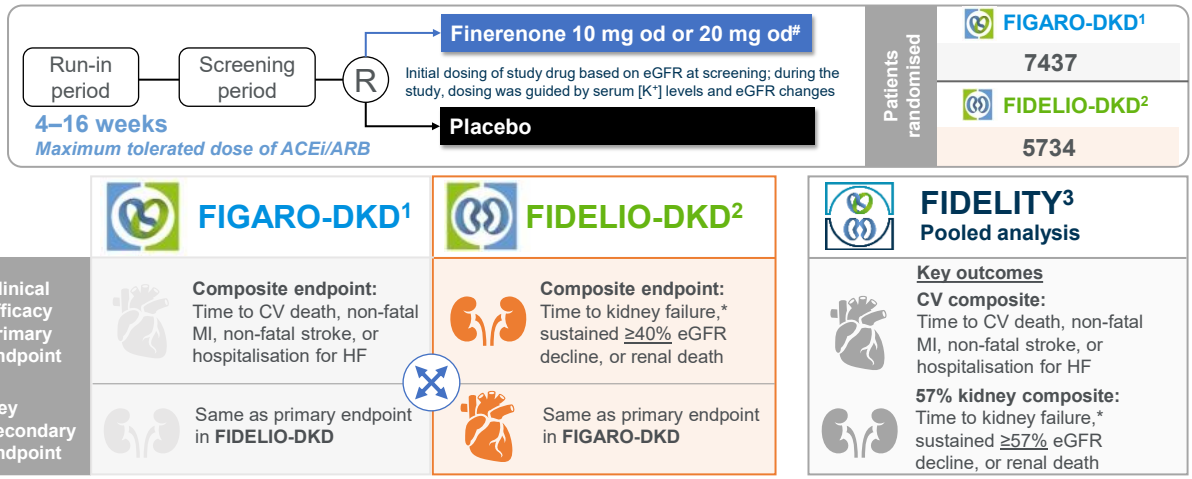
FIGARO-DKD and FIDELIO-DKD Investigated the Effects of Finerenone on Kidney and CV Outcomes in Over 13,000 Patients with CKD and T2D



*Kidney failure defined as initiation of chronic dialysis for ≥90 days or kidney transplantation or sustained eGFR <15 ml/min/1.73 m^2[2,3]; #patients received an initial dose of finerenone of 10 mg od or 20 od based on an eGFR at the screening visit of 25–<60 or ≥60 ml/min/1.73 m^2, respectively.[1,2] Up-titration to finerenone 20 mg od was permitted at any time after visit 2 (month 1); down-titration to finerenone 10 mg od was permitted at any time after start of treatment. Dose titrations were initiated in response to changes in potassium and eGFR[1,2]
CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; od, once daily; T2D, type 2 diabetes
1. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 3. Filippatos G. Abstract 7161 presented at the European Society of Cardiology 2021 (ESC 2021)

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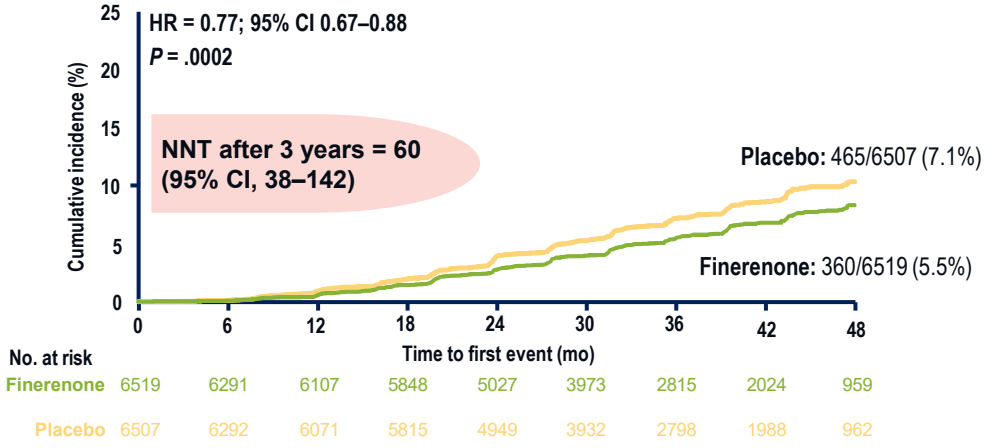
FIDELITY Pooled Analysis

Effect of Finerenone on ≥57% eGFR Kidney Composite Outcome

Time to kidney failure, sustained ≥57% decrease in eGFR from BL, or renal death



NNT = number needed to treat.

Agarwal R, et al. *Eur Heart J.* 2022;43:474-484.

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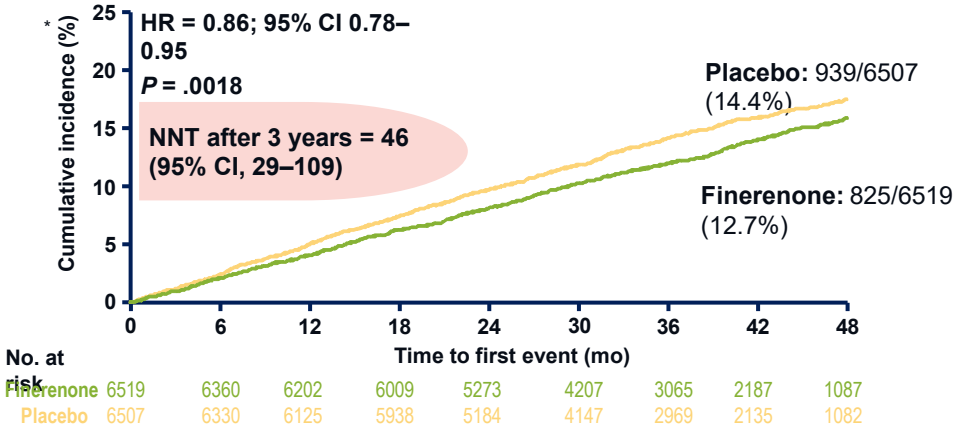
FIDELITY Pooled Analysis

Finerenone Significantly Reduced Risk of CV Composite Outcome by 14%

Time to CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF



Agarwal R, et al. *Eur Heart J.* 2022;43:474-484.

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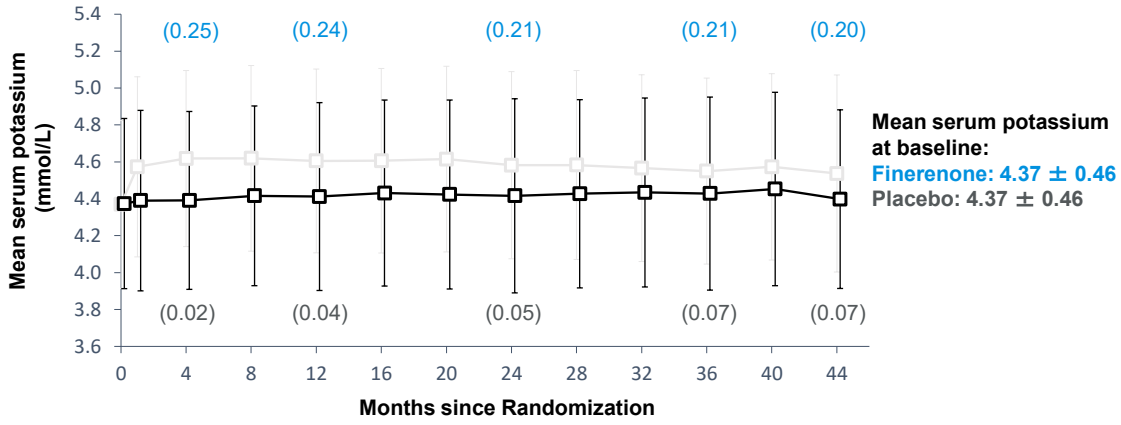
Change in Serum Potassium Over Time



Maximum mean difference in serum potassium between groups = 0.23 mmol/L at month 4

Data in parenthesis are mean change from baseline

Bakris GL et.al. N Engl J Med 2020;383:2219-2229

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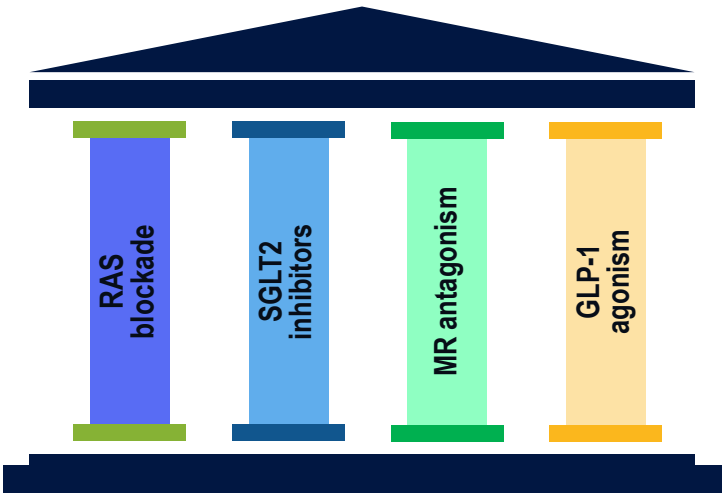
Considerations to Facilitate More Reduction in UACR Include All the Following Except:

A. Low salt diet
B. Add SGLT2 inhibitor
C. Add finerenone
D. Increase dose of atorvastatin 80 mg daily

Pillars of Therapy to Reduce Cardiorenal Risk

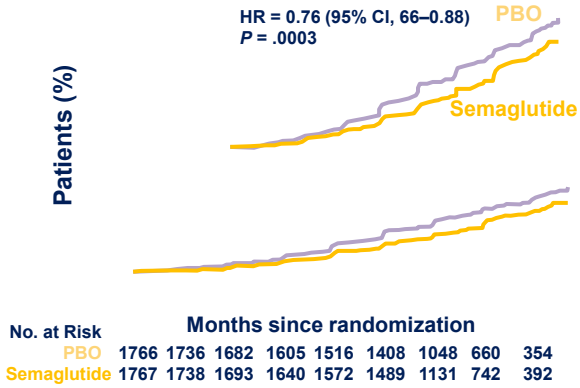


Slowing DKD progression and reducing CV risk

Modified from Blazek O, Bakris GL. *Am Heart J Plus.* 2022;19:100187 (www.sciencedirect.com/science/article/pii/S2666602222001045). Accessed 7/1/24.

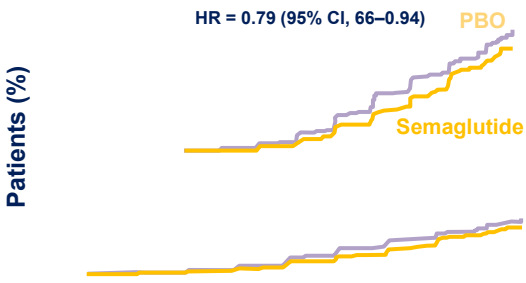
Semaglutide: FLOW Study
First Major Kidney Disease and Kidney-Specific Component Events

First major kidney disease event



No. at Risk	Months since randomization								
PBO	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

First kidney-specific component event



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Perkovic V, et al. *N Engl J Med.* 2024;May 24:Epub ahead of print.

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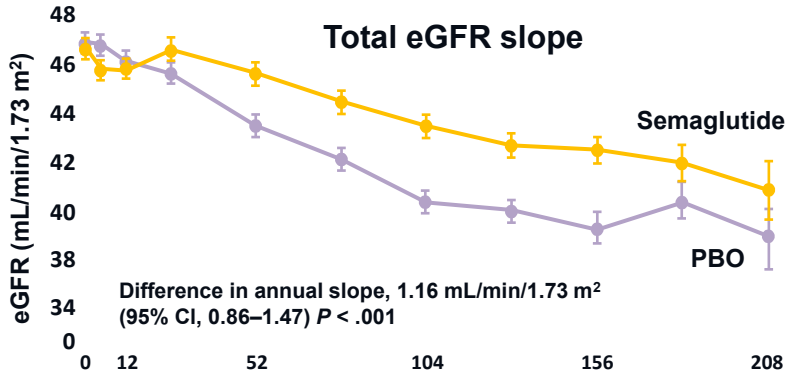
Semaglutide: FLOW Study
Total eGFR Slope



No. at Risk										
PBO	1766	1663	1573	1609	1490	1441	1284	876	609	199
Semaglutide	1766	1665	1590	1606	1521	1468	1345	952	651	218

Perkovic V, et al. *N Engl J Med.* 2024;May 24:Epub ahead of print.

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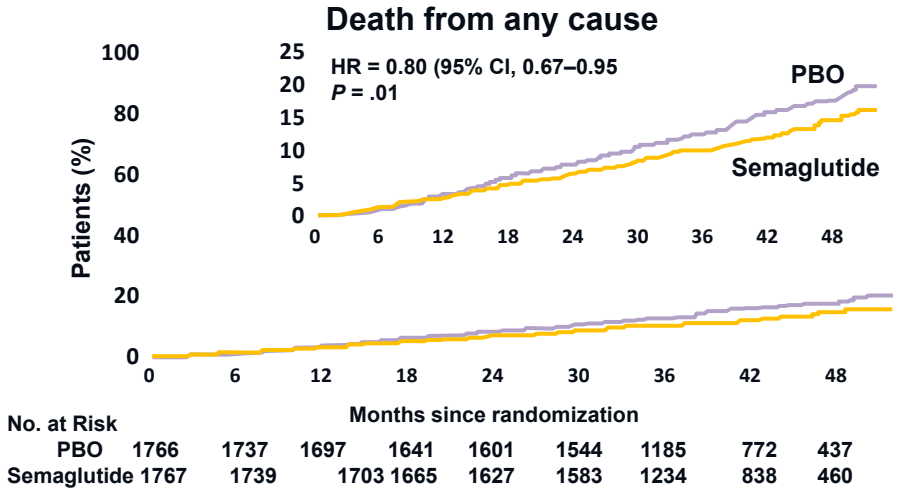
Semaglutide: FLOW Study
Death from Any Cause



Perkovic V, et al. *N Engl J Med*. 2024;May 24:Epub ahead of print.

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Putative Renoprotective Actions and Effects of GLP-1R Agonists on Kidneys

Direct Effects	Indirect Effects
Proximal tubular natriuresis stimulation	Improved glycemic control
Modulation of cAMP/PKA signaling	Improved blood pressure control
Inhibition of renin angiotensin system	Weight loss
↓ Renal hypoxia	↑ Insulin sensitivity
↓ Glomerular atherosclerosis?	↓ Postprandial glucagon
Renal endothelial dependent vasodilation	↓ Intestinal lipid uptake
↑ Tubuloglomerular feedback (through ↓ NHE3 activity)	↑ Brown adipose tissue activation
↑ ANP?	Effects on microbioma?

Abbreviations— GLP-1R: glucagon like peptide-1 receptor; cAMP: cyclic adenosine monophosphate; PKA:protein kinase A; NHE3:sodium–hydrogen exchanger 3; ANP:atrial natriuretic peptide.

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GLP-1 RA: Summary of Pros and Cons

- Clinical effects demonstrated on kidney, cardiovascular, and survival outcomes among high-risk patients
  - Reduced risk of major kidney disease events
  - Reduced risk of major cardiovascular events
  - Reduced risk of death from any cause
- Improves glycemic control in patients with reduced kidney function
- Leads to weight loss
- 20–30% rate of GI side effects (eg, nausea, vomiting, diarrhea)

Perkovic V, et al. *N Engl J Med*. 2024;May 24:Epub ahead of print.

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Current Consideration for Treatment

- ACEI or ARB (preferably in highest possible tolerated dose with potassium mitigation if needed)
- Should we use all 4 drug classes?
- Do we still need them if we use the other drugs?
- A good prescription plan!

We need to evaluate the benefit: risk ratio for all therapies, both traditional and non-traditional

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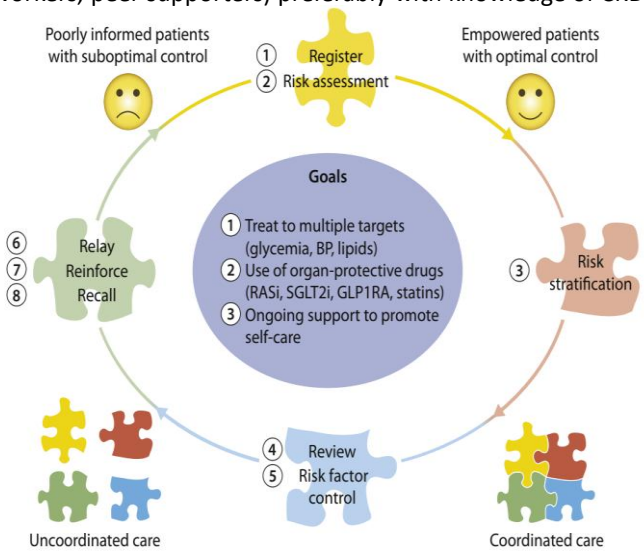
Approaches to Management of Patients with Diabetes and CKD

Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (e.g., trained nurses and dieticians, pharmacists, health care assistants, community workers, peer supporters) preferably with knowledge of CKD (Figure 33).



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