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Raising the Index of Suspicion in Primary Care: The Role of the Nurse Practitioner in Recognizing and Managing Diabetic Kidney Disease

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Learning Objectives

- List recommended screening strategies to ensure early diagnosis of chronic kidney disease (CKD) in patients with diabetes, including the use of urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR)
- Discuss how diabetic kidney disease (DKD) confers a high risk of cardiovascular disease (CVD), renal events, and associated mortality, and DKD's implications for patient management
- Describe the role of inflammation, fibrosis, and the mineralocorticoid receptor in the progression of DKD
- Describe how to incorporate current treatment approaches, and discuss novel treatment approaches based on current and emerging data, to optimize the care of patients with type 2 diabetes and decrease the risk of progression of DKD

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Overview of DKD
Prevalence and Pathophysiology

Prevalence and Multidimensional Burden of DKD

Diabetes is the leading cause of CKD/diabetic nephropathy (DKD)

Association With Diabetes

- Diabetes is the most common cause of kidney failure
- DKD affects patients with both type 1 and 2 diabetes.

Prevalence

- 30-40% of patients with diabetes have concomitant DKD, evidenced by ↑ albuminuria and/or reduced eGFR
- ≥50% of patients with type 1 diabetes will develop kidney damage
  - 1/3 of these will develop severe kidney disease and kidney failure

Associated Risks

- ↑ risk of all-cause mortality, esp with diabetic microvascular complications (eg, diabetic retinopathy)
- ↑ risk of macrovascular complications
- In US, leading cause of ESRD
- Gradual ↓ of QOL with DKD progression

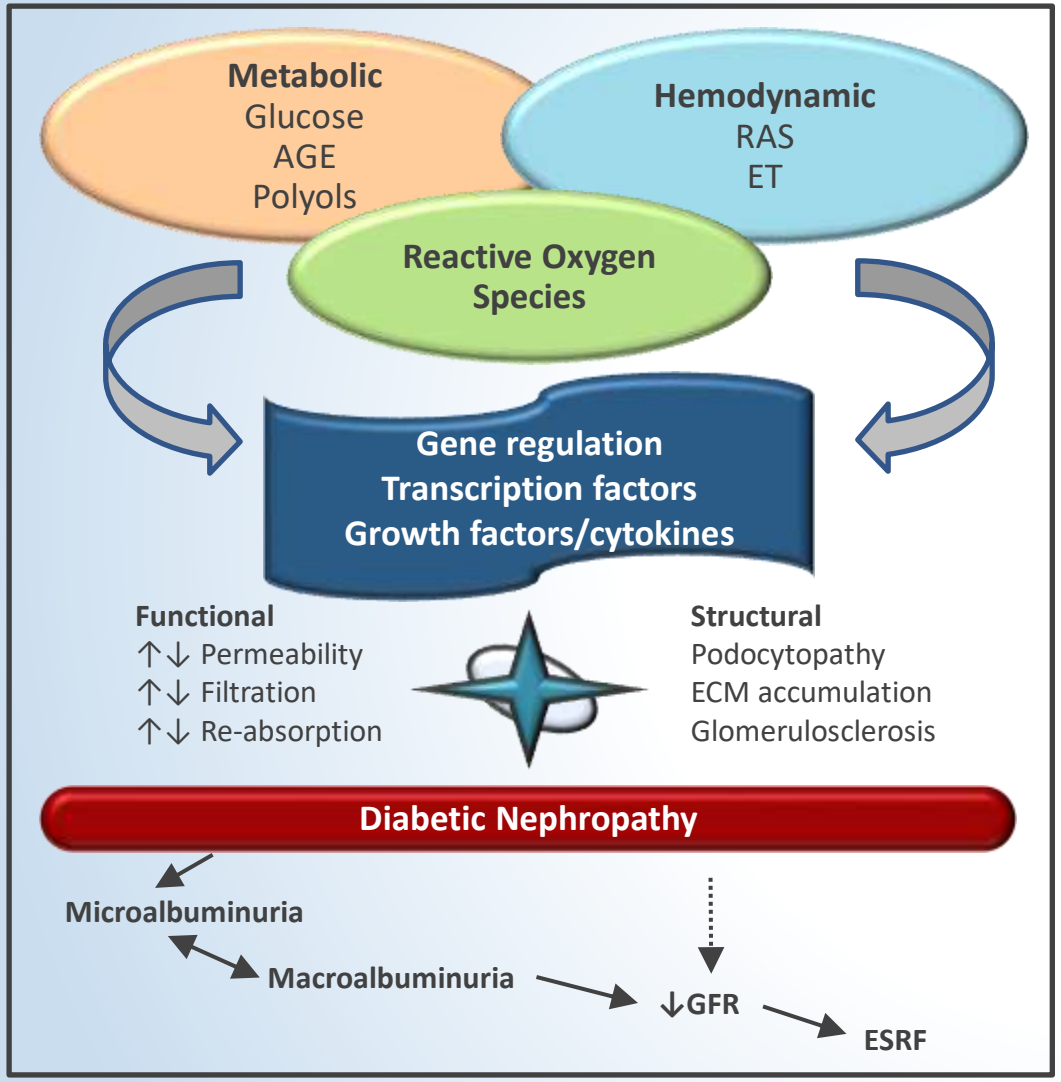
Increased Risk for Certain Populations

- Some population groups (eg, African American, Hispanic, American Indian) with T2 diabetes have ↑ risk of developing kidney failure

esp, especially; ESRD, end stage renal disease; T2, type 2.

American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S135–S151; Centers for Disease Control. National Diabetes Statistic Report 2017. Available at: https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf; Deem M, et al. *Nurse Pract.* 2020;45(4):34-41; Rossing P, et al. *Diabetes.* 2021;70(1):39-50; Sabanayagam C, et al. *JAMA Netw Open.* 2019;2(3):e191540; Zimbudzi E, et al. *BMJ Open.* 2017;7(10):e017695.

Pathophysiology of DKD: Multifactorial Interaction Between Metabolic and Hemodynamic Factors



Pathogenesis of DKD

- Metabolic and hemodynamic abnormalities interact with each other and reactive oxygen species-dependent pathways, influencing gene regulation and activation of transcription factors
- Molecular activation or inhibition results in functional/structural changes leading to signs/symptoms

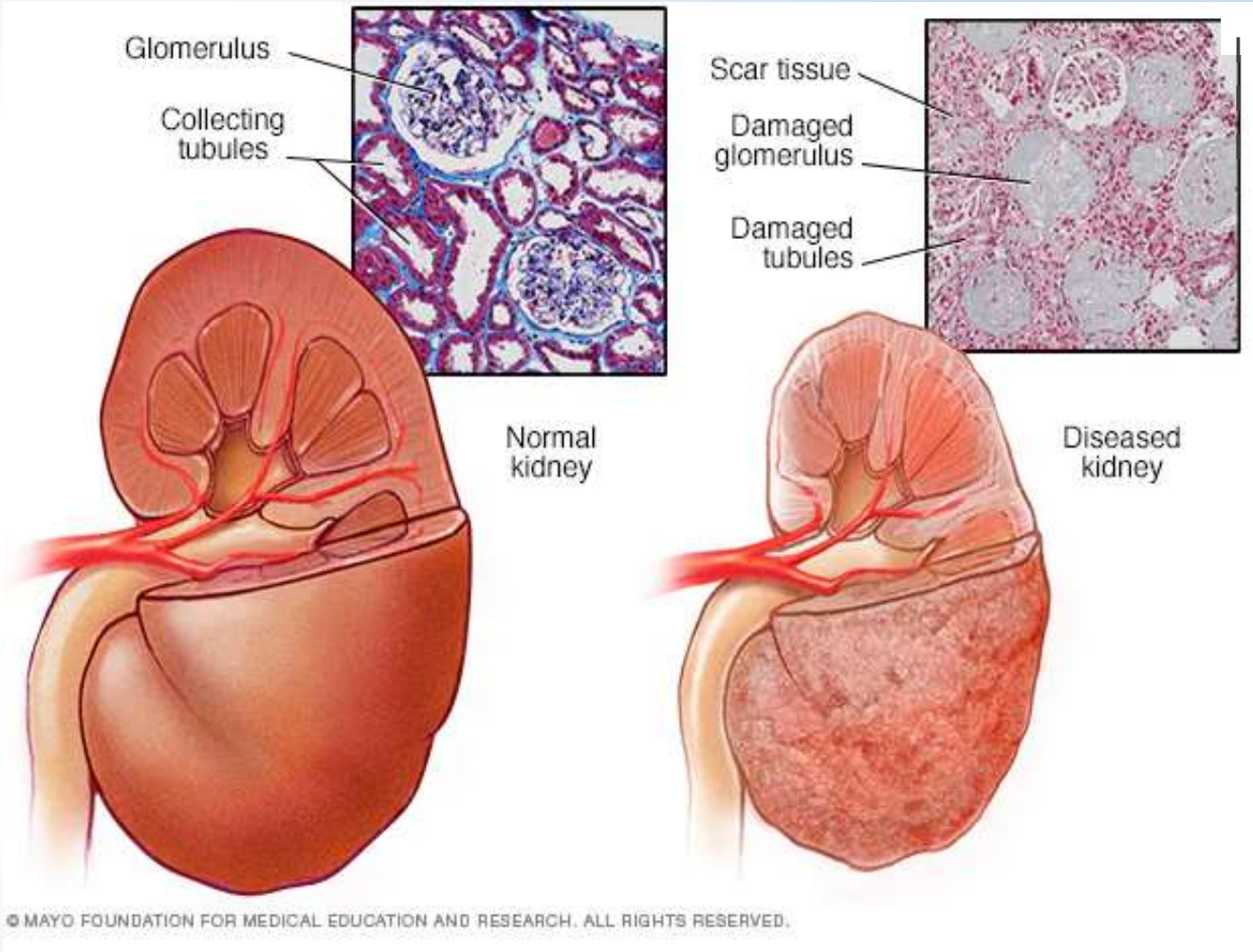
AGE, advanced glycation end-products; ECM, extracellular protein production; ESRF, end-stage renal failure; ET, endothelin; RAS, renin–angiotensin system.

Cao Z, Cooper ME. *J Diabetes Investig*. 2011;2(4):243-247.

Pathophysiology of DKD: Key Roles of MR, Blood Pressure, and Aldosterone

Kidney Dysfunction

- Mineralocorticoid agonism or elevated aldosterone levels damage organ systems and cells relevant to cardiometabolic diseases
  - Results in kidney: ↑ glomerulosclerosis and proteinuria
- High blood pressure and diabetes damage filtering glomerulus and collecting tubules, causing scarring
- Binding of aldosterone causes inflammation and fibrosis

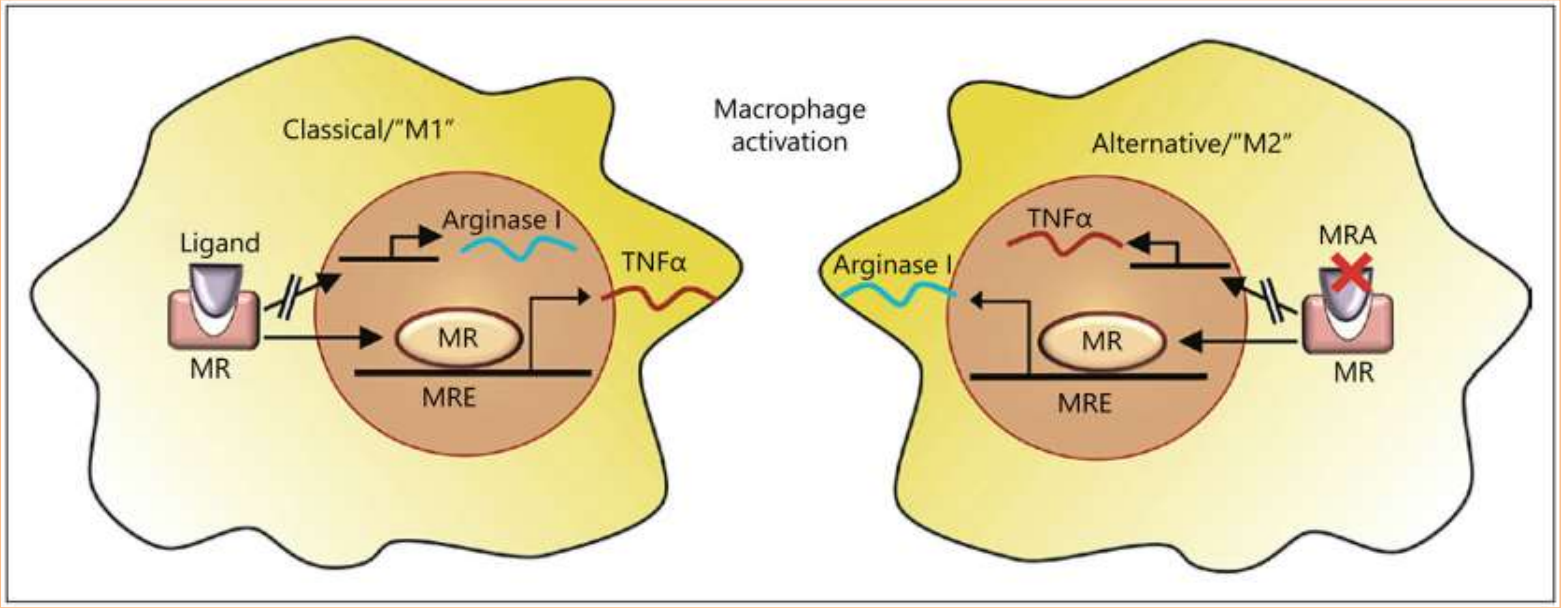


MR, mineralocorticoid receptor.

Artunc F, Lang F. *Nephron Physiol*. 2014;128:35–39; Belden Z, et al. *Am J Nephrol*. 2017;46(4):298-314; Pearce D, et al. *Clin J Am Soc Nephrol*. 2015; 10:135–146.
Image: Mayo Clinic. Diabetic nephropathy (kidney disease). Available at: https://www.mayoclinic.org/diseases-conditions/diabetic-nephropathy/symptoms-causes/syc-20354556

The Central Role of MR and Macrophage in CKD and Target Organ Damage

MR agonism increases classical activation of macrophages, while antagonism MRA promotes alternative activation



- Activation of MR may result in complex effects on macrophages and T cells
- Macrophage infiltration in kidney is common feature of CKD
- Correlation between degree of macrophage infiltration and severity of renal injury

CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist; MRE, mineralocorticoid receptor response element; TNF, tumor necrosis factor.

Belden Z, et al. *Am J Nephrol*. 2017;46(4):298-314; Guiteras R, et al. *Clin Kidney J*. 2016;9(6):765-771. doi:10.1093/ckj/sfw096

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Recognizing Diabetic Kidney Disease

Identifying Kidney Disease: Benefits of Early Screening and Treatment

Benefits of Early Screening	• Screen for microalbuminuria to identify kidney complications at early stages to reduce disease progression and morbidity
Current Recommendations	• ADA recommends screening patients with T2DM for microalbuminuria at time of diagnosis and each year thereafter
Current Lack of Timely Screening and Treatment	• In US, <50% of patients with T2DM are screened for albuminuria within 1 year from diagnosis • ~6-month delay in treatment following lab-diagnosed DKD • 47% of patients with T2DM have serum creatinine tests ordered within 2 weeks of diagnosis • 43% of patients with T2DM receive UACR test during follow up

ADA, American Diabetes Association.

Folkerts K, et al. *Mayo Clin Proc*. 2021;96(4):975-986; Rodriguez F, et al. *Adv Ther*. 2021;38(8):4425-4441.

Guideline-Based Screening/Monitoring Strategies for DKD

The ADA Standards of Medical Care in Diabetes, 2021, provides these screening recommendations for DKD:

Frequency	Type of Screening	Recommendation Strength
≥1× year	Assess urinary albumin (spot UACR) and eGFR in patients with type 1 diabetes with duration of ≥5 years and in all patients with T2DM regardless of treatment	B
2× year	Monitor patients with diabetes and urinary albumin >300 mg/g creatinine and/or eGFR 30 to 60 mL/min/1.73 m^2 to guide treatment decisions	B
Periodically	Monitor serum creatinine and K+ levels for development of increased creatinine or changes in K+ when ACE inhibitors, angiotensin receptor blockers, or diuretics are used	B

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American Diabetes Association. *Diabetes Care*. 2021;44(suppl 1):S1– S232.

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Complex Association Between DKD and Risk of Cardiovascular and Renal Events

Traditional and Nontraditional Risk Factors for DKD and CVD

DKD commonly associated with increased risk for CVD

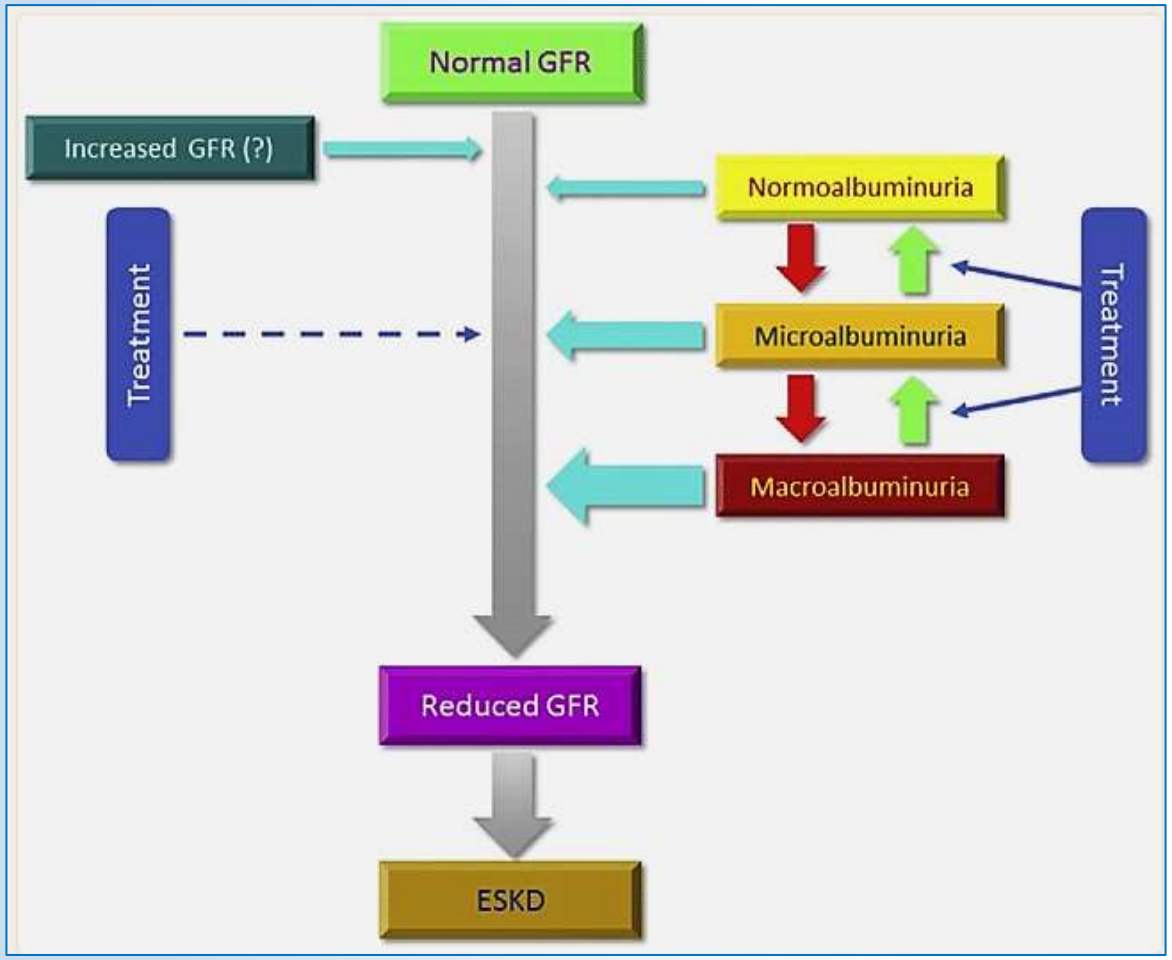
Traditional Risk Factors for DKD and CVD	Nontraditional Uremia-Related CVD Risk Factors
Diabetes	Inflammation
Obesity	Oxidative stress
Hypertension	Abnormal calcium-phosphorus metabolism
Poor glycemic control	Endothelial dysfunction
Dyslipidemia	

"It is likely that there are other pathophysiological mechanisms that explain the clinical phenomenon of increased cardiovascular disease in diabetic patients with chronic kidney and vice versa" **- Maqbool et al**

Leon BM, et al. *World J Diabetes*. 2015;6(13):1246-1258; Maqbool M, et al. *Semin Nephrol.* 2018;38(3):217-232; Penno G, et al. *BMC Med.* 2021;19(1):66; Sarnak MJ, et al. *J Am Coll Cardiol*. 2019;74(14):1823-1838.

Albuminuria and DKD/CVD Progression

Albuminuric and nonalbuminuric pathways of DKD progression



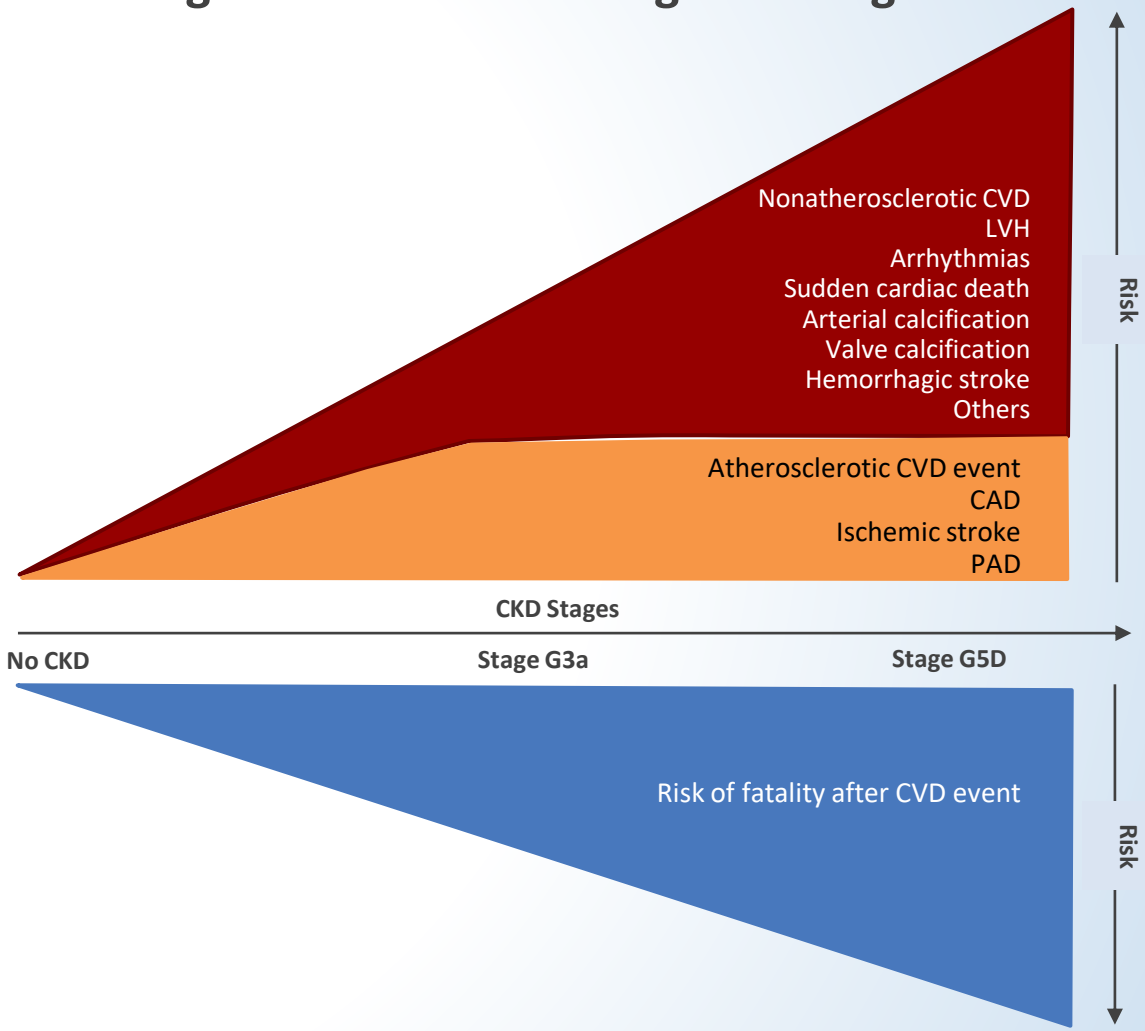
- **Two possible main pathways for onset/progression of DKD:**
  - Albuminuric
  - Nonalbuminuric
- **Complementary manifestations of DKD** (occurring/proceeding together or separately):
  - Albuminuria
  - Reduced eGFR

Pugliese G, et al. *J Nephrol.* 2020;33(1):9–35.

Clinical Course of DKD to CVD and Renal Events

- CV risk factors are common in patients with DM, causing ↑ risk of cardiac events
- CKD and ESKD ↑ risk of CAD and modify its clinical presentation and cardinal symptoms
- Management of CAD is complicated in patients with CKD due to likelihood of comorbid conditions and potential for side effects during intervention
- Evidence demonstrates 60% ↑ rate of CV death among patients with T2DM and DKD vs patients with T2DM alone

Changes in CVD Risk During CKD Progression



CAD, coronary artery disease; LVH, left ventricular hypertrophy; PAD, peripheral artery disease.

Gonzalez-Peres A, et al. *BMJ Open Diab Res Care*. 2021;9:e002146; Sarnak MJ, et al. *J Am Coll Cardiol*. 2019;74(14):1823-1838.

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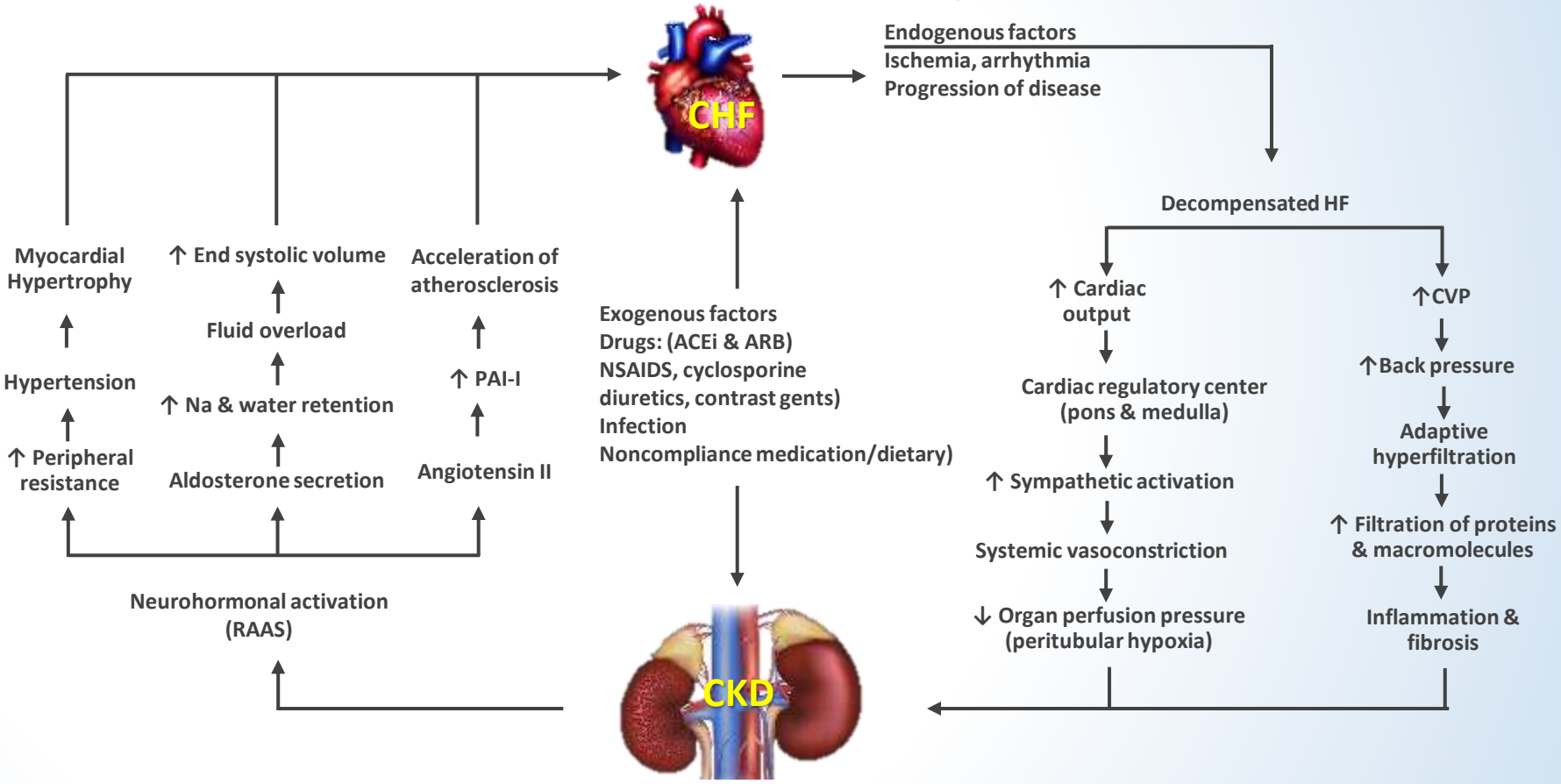
Inflammation, Fibrosis, and Mineralocorticoid Receptor in DKD Progression

Role of the RAAS in Heart Failure and Renal Dysfunction

- RAAS regulates renal vasomotor activity, maintains optimal salt/water homeostasis, controls tissue growth in kidney
- Overactivity of this cascade involves it in pathophysiology of kidney disease
- Activated RAAS promotes systemic and glomerular capillary hypertension; can induce hemodynamic injury to vascular endothelium and glomerulus

Pathophysiologic pathways of RAAS interaction between HF and renal dysfunction.



ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CVP, central venous pressure; HF, heart failure; NSAID, nonsteroidal anti-inflammatory drug; PAI-1, plasminogen activator inhibitor-1; RAAS, renin-angiotensin-aldosterone system.

Brewster UC, Perazella MA. *Am J Med*. 2004;116(4):263-272. doi:10.1016/j.amjmed.2003.09.034; Muneer K, Nair A. *Indian Heart J*. 2017;69(3):371-374.

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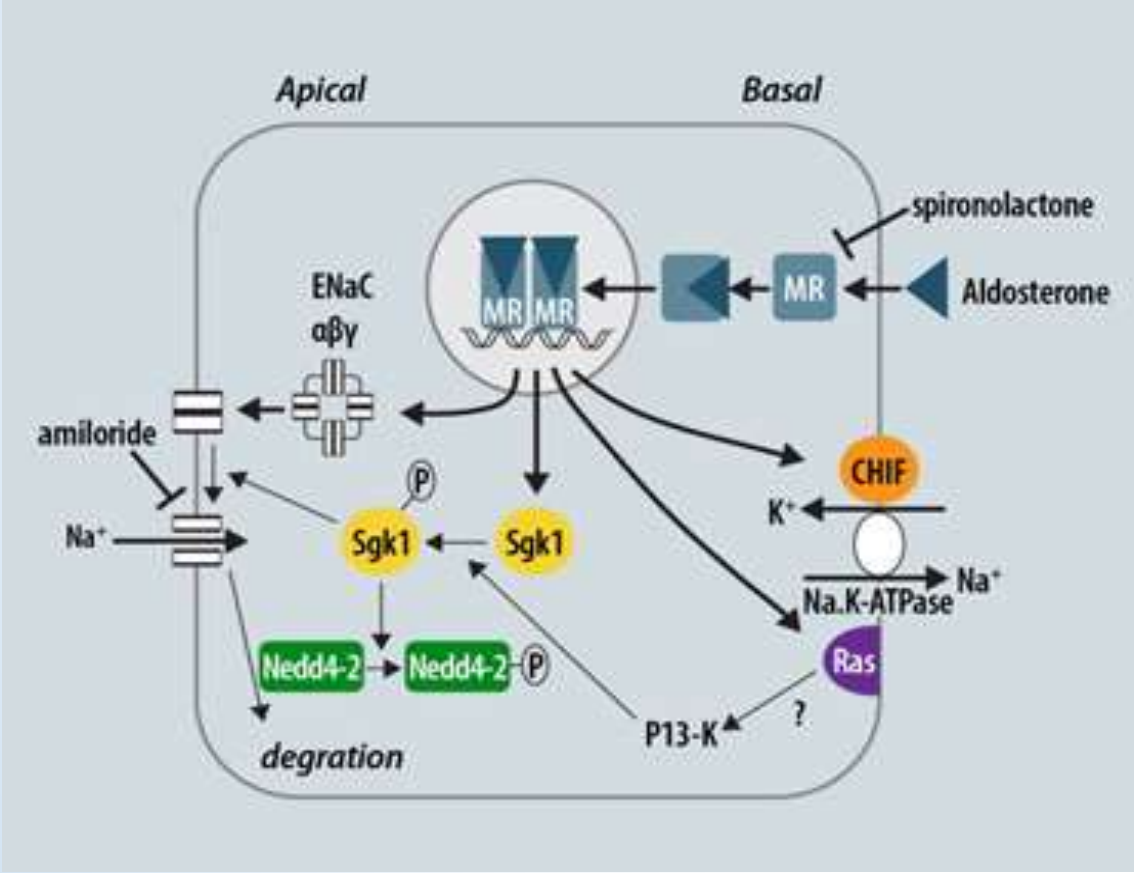
Role of Aldosterone in the Development and Progression of DKD

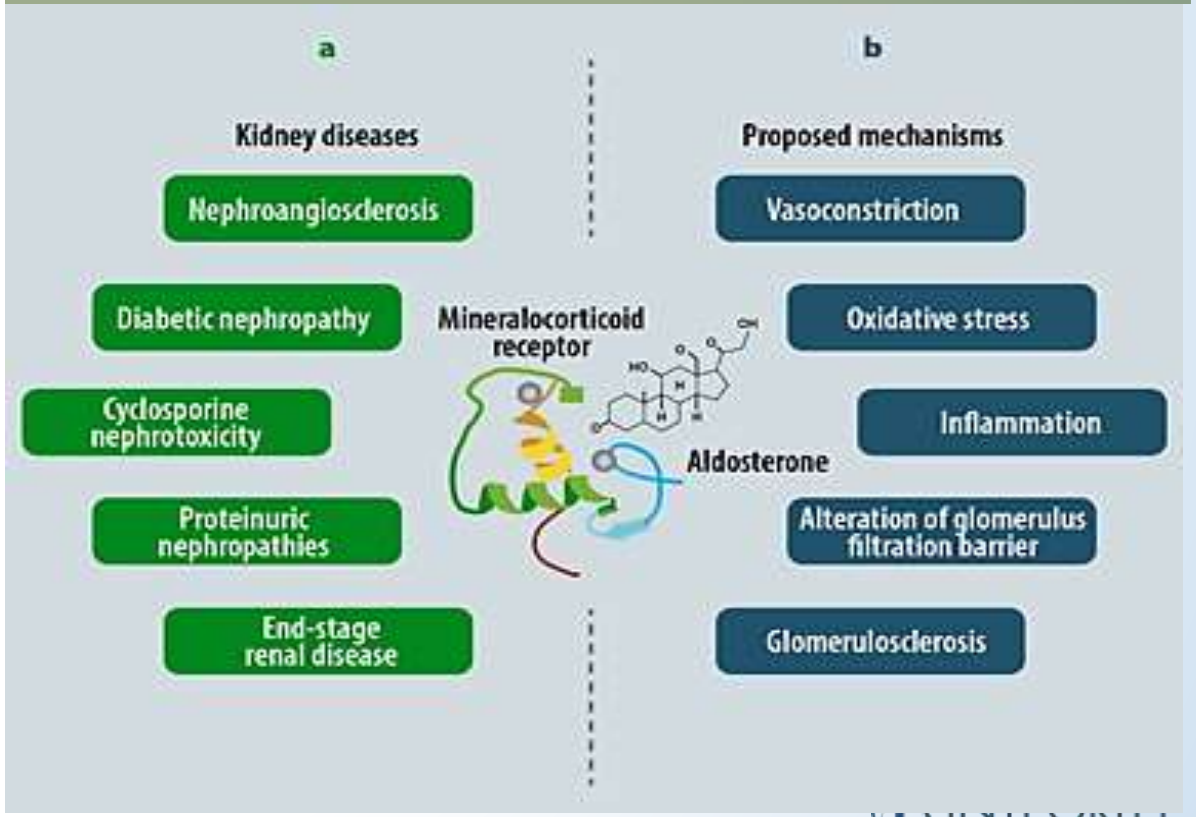
Aldosterone-Responsive Epithelial Cell

Proteins encoded by aldosterone-induced genes: ENAC a, B, and y, CHIF, sgk, and ras are indicated as are known or putative functions



Implication of Aldosterone & MR in Renal Pathophysiology

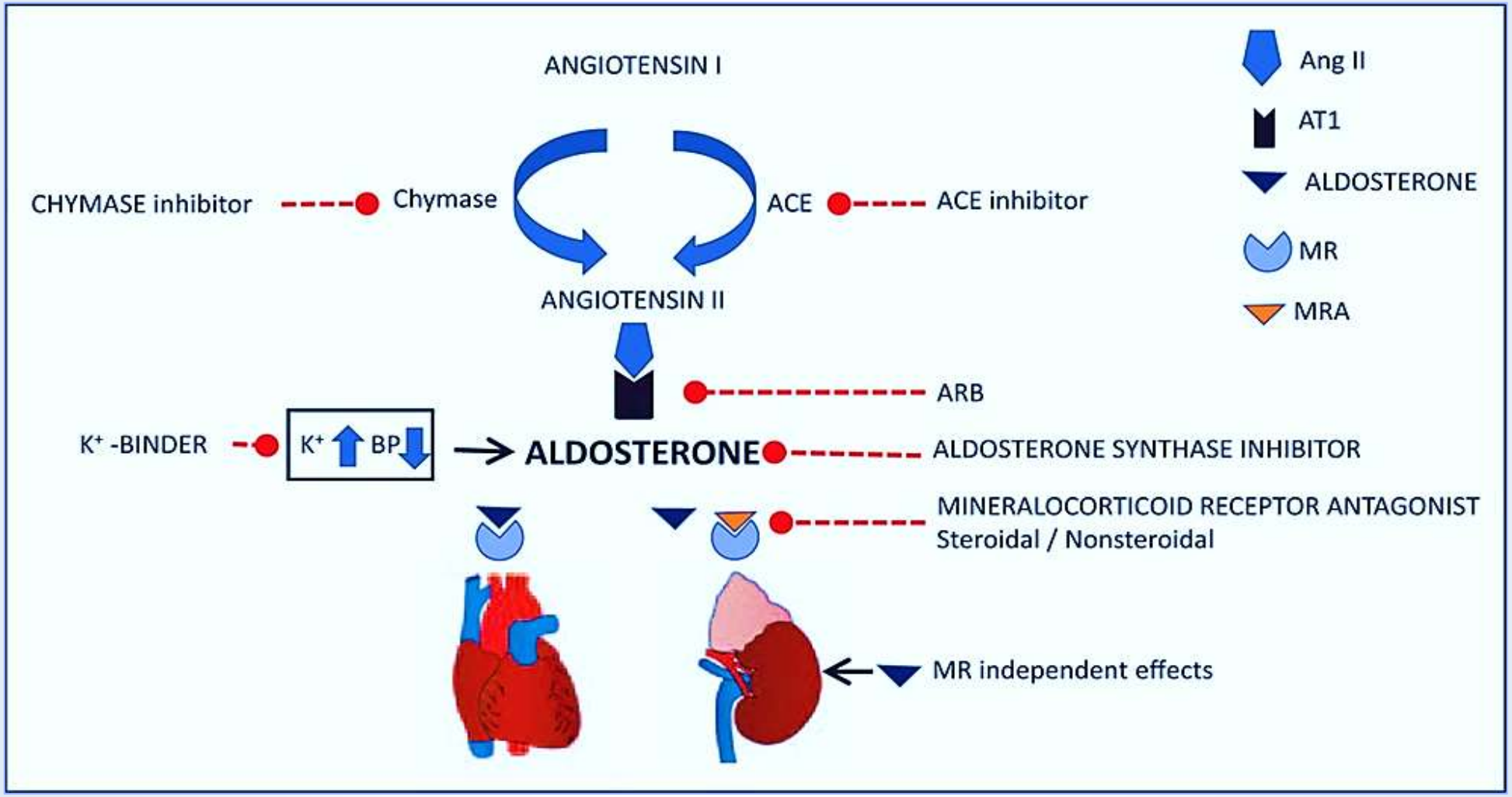
(a) Aldosterone and/or MR involved in various kidney diseases
(b) Proposed pathophysiological mechanism involved in renal lesions linked to aldosterone/MR activation



CHIF, channel inducing factor; EPAC, epithelial sodium channel; Na.K-ATPase, sodium-potassium pump; Ras, rat sarcoma virus.

Bertocchio JP, et al. *J Nephrol.* 2020;33:37-48; Fuller PJ, Young MJ. *Hypertension.* 2005;46:1227-1235.

Opportunities to Mitigate the Effect of Aldosterone



Ang II, angiotensin II; AT1, angiotensin II type 1 receptor; BP, blood pressure.

Frimodt-Møller M, et al. *Curr Opin Nephrol Hypertens*. 2020;29(1):145-151.

Various Strategies to Reduce Effects of Aldosterone in DKD

Target	Intervention and Effects	Results	Challenges	Potential Solutions
Angiotensin-converting enzyme	• ACE inhibition • ↓Angiotensin II and its effects	• ↓BP and proteinuria • Long-term benefit on outcomes in DKD demonstrated	• Alternative Ang II formation • Aldosterone breakthrough • Hyperkalemia	• Combine with Chymase inhibitor • Aldosterone-specific intervention (MRA/ASi) • Diet, loop diuretics • New potassium binders
Angiotensin II receptor 1	• ARB • Block effect mediated from AngIIR stimulation	• ↓BP and proteinuria • Long-term benefit on outcomes in DKD demonstrated	• Aldosterone breakthrough • Hyperkalemia	• Combine with Aldosterone-specific intervention (MRA/ASi) • Diet, loop diuretics • New potassium binders
Mineralocorticoid receptor	• Mineralocorticoid receptor antagonist • Blocks MR-mediated effects of aldosterone	• ↓Proteinuria and BP/resistant hypertension • Only surrogate renal outcome data on DKD • ↓Mortality in heart failure with systolic dysfunction	• Spironolactone: hormonal side effects (gynecomastia) • Hyperkalemia	• Increase selectivity (eplerenone or nonsteroidal MRA) • Diet, loop diuretics • New potassium binders • Nonsteroidal MRA • Aldosterone synthase inhibition
Mineralocorticoid receptor	• Nonsteroidal mineralocorticoid receptor antagonist • Blocks MR-mediated effects of aldosterone	• ↓Proteinuria • ↓NTproBNP in heart failure with systolic dysfunction and CKD • Only surrogate renal outcome data on DKD	• Hyperkalemia (less frequent than for steroidal MRA)	• Diet, loop diuretics • New potassium binders • Nonsteroidal MRA • Aldosterone synthase inhibition • Tested in ongoing phase III trials FIGARO and FIDELIO
Aldosterone synthase	• Aldosterone synthase inhibition • ↓Aldosterone (MR and non-MR) mediated effects affected)	• Lowers aldosterone and blood pressure • Limited clinical data	• Difficult to develop (selectivity, duration of action) • Not clinically available	• Needs further development (ongoing preclinical studies)

ADI, aldosterone synthase inhibition; ASi, aldosterone synthase inhibitor; NT-proBNP, N terminal pro-brain natriuretic peptide.

Frimodt-Møller M, et al. *Curr Opin Nephrol Hypertens*. 2020;29(1):145-151.

The Effect of MRAs on Inflammation/Fibrotic Remodeling

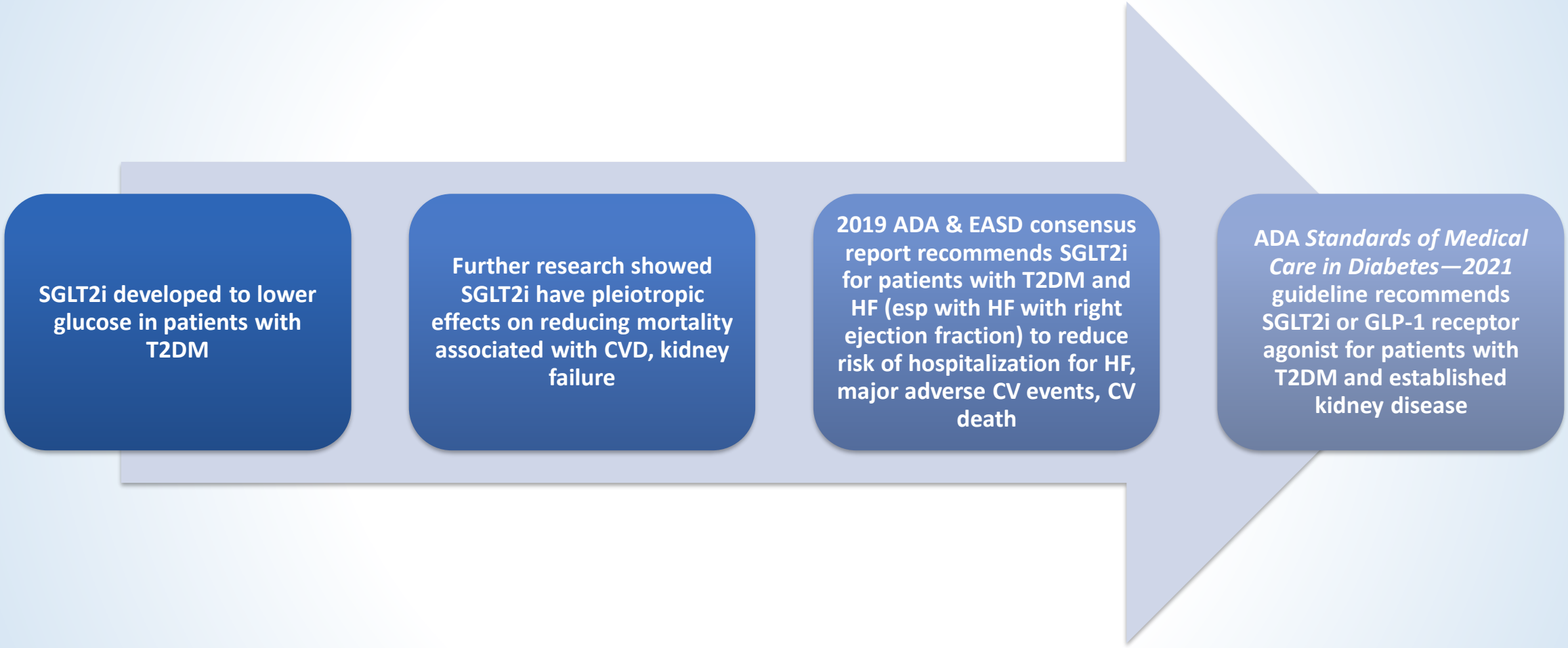
Ligand (aldosterone, cortisol, or corticosterone) binds to receptor, then receptor interacts with a variety of cofactors (eg, those that affect gene transcription)

> 300 different cofactors interact with MR superfamily; different physiologic responses depending on ligand and cell type

MRAs block binding of ligand to receptor to inhibit downstream effects

Agarwal R, et al. *Eur Heart J*. 2021;42(2):152-161.

Role of SGLT2 Inhibitors in Treatment of T2DM, HF, and Kidney Disease



EASD, European Association for the Study of Diabetes; GLP-1, glucagon-like peptide 1; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

American Diabetes Association. *Diabetes Care*. 2021;44(suppl 1):S1– S232; Buse JB, et al. [published correction appears in *Diabetologia*. 2020 Aug;63(8):1667]. *Diabetologia*. 2020;63(2):221-228; Neal B, et al. *N Engl J Med*. 2017;377(7):644-657; Perkovic V, et al. *N Engl J Med*. 2019;380(24):2295-2306.

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New Therapies in the Treatment of DKD

Overview of Finerenone (Nonsteroidal MRA)

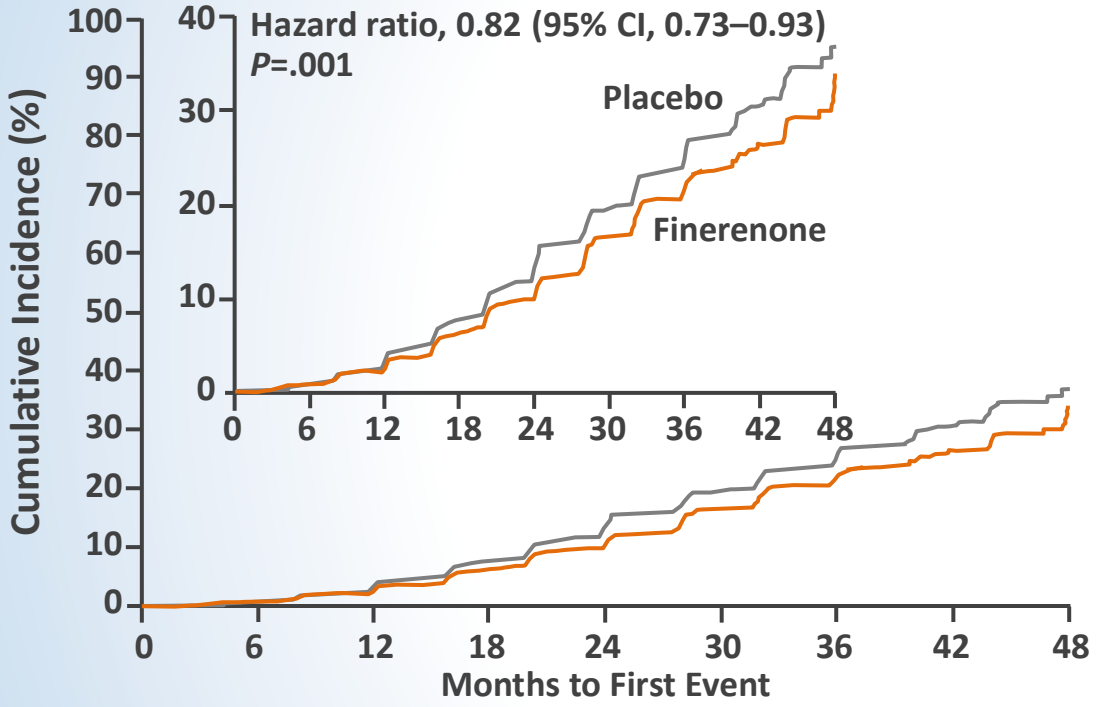
FDA Approval	Indication	Formulation & Dosing	Safety
July 2021	Reduce risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks, and hospitalization for HF in adults with CKD associated with T2DM	• Tablets • **Recommended starting dose:** – 10 or 20 mg QD* – Can increase after 4 weeks to target dose of 20 mg QD* • Taken with or without food **Determined by eGFR and serum K+ thresholds*	• Profile appears favorable

QD, once daily.

Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229; Finerenone Prescribing Information. Accessed August 7, 2021.

FIDELIO-DKD Trial: Efficacy and Safety of Finerenone

Primary Composite Outcome: Kidney failure, sustained decrease of at least 40% in eGFR from baseline, or death from renal causes



No. at Risk									
Placebo	2841	2724	2586	2379	1758	1248	792	453	82
Finerenone	2833	2705	2607	2397	1808	1274	787	441	83

Percent of patients who experienced event from primary composite endpoint during median 2.6-year follow-up:

- Finerenone: 17.8% of 2833 patients
- PBO: 21.1% of 2841 patients

Events included:

- Kidney failure*
- Sustained reduction of ≥40% in eGFR from baseline*
- Death from renal causes*

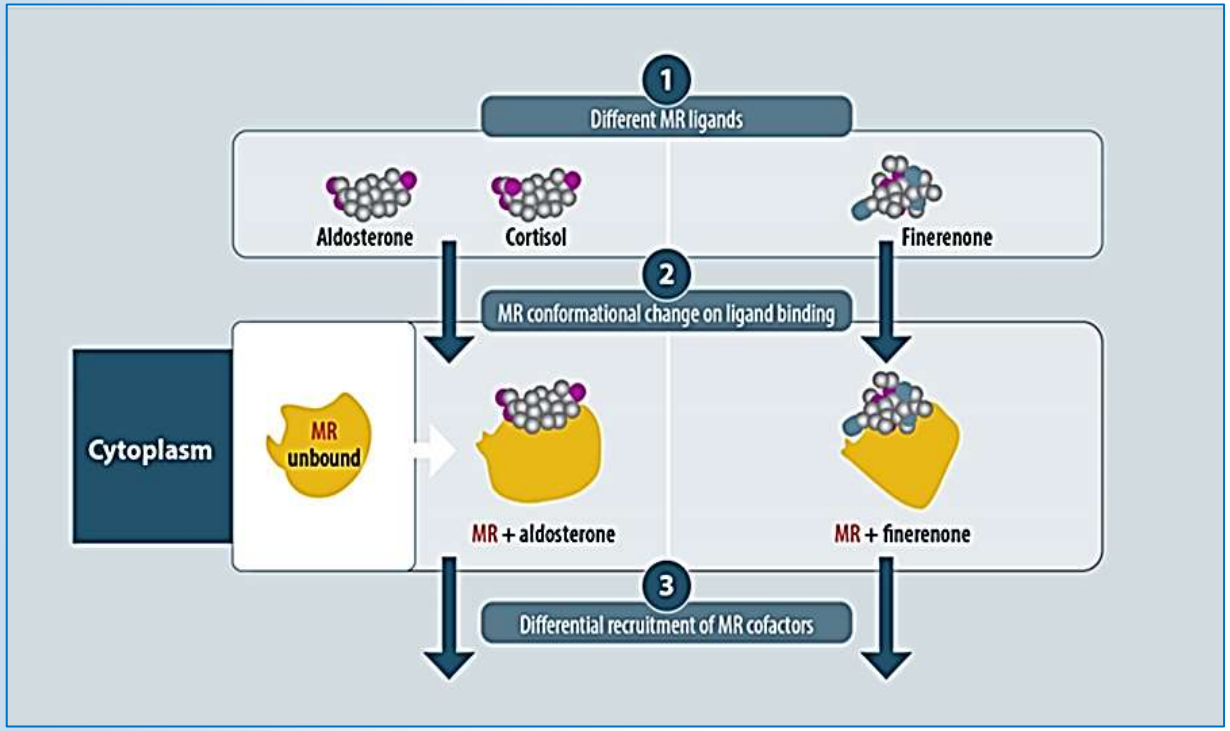
** HR, 0.82; 95% CI, 0.73-0.93; P=.001*

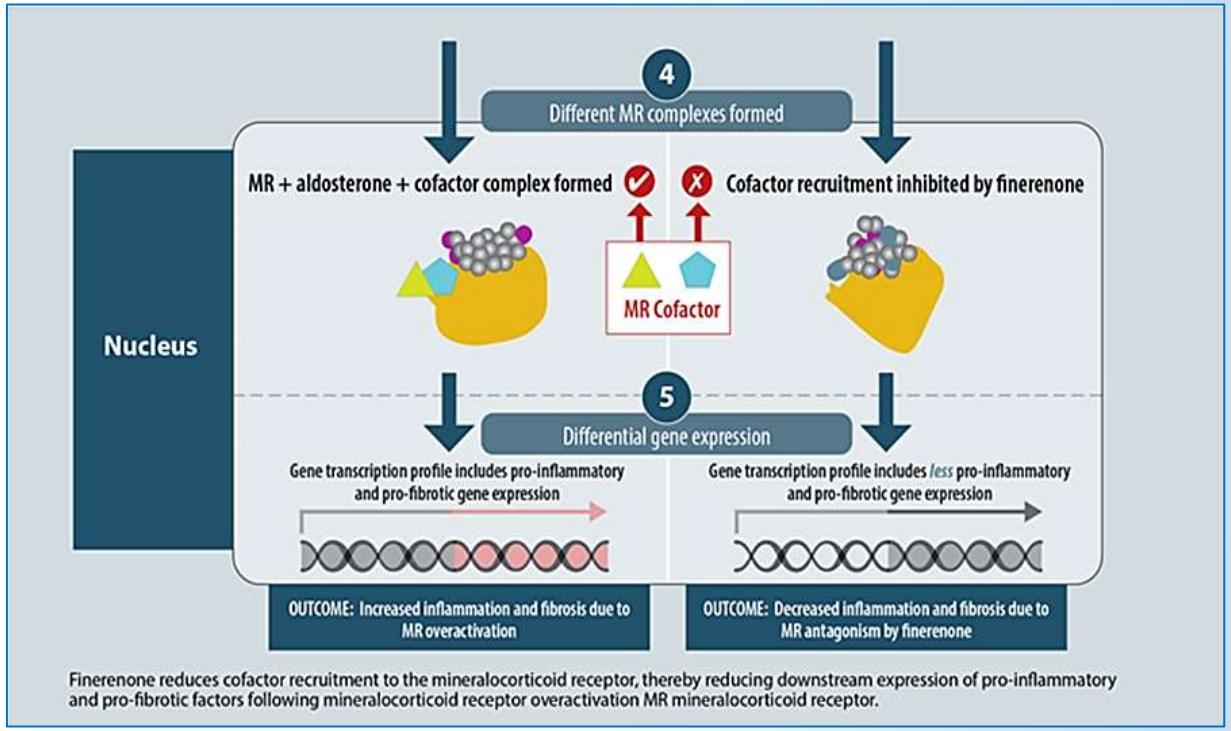
CI, confidence interval; HR, hazard ratio; PBO, placebo.

Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229. Slomski A. *JAMA*. 2021;325(8):713.

MOA of Finerenone

MR antagonists block the binding of aldosterone to the MR to inhibitor





MOA, mechanism of action.

Agarwal R, et al. *Eur Heart J*. 2021;42:152-61.

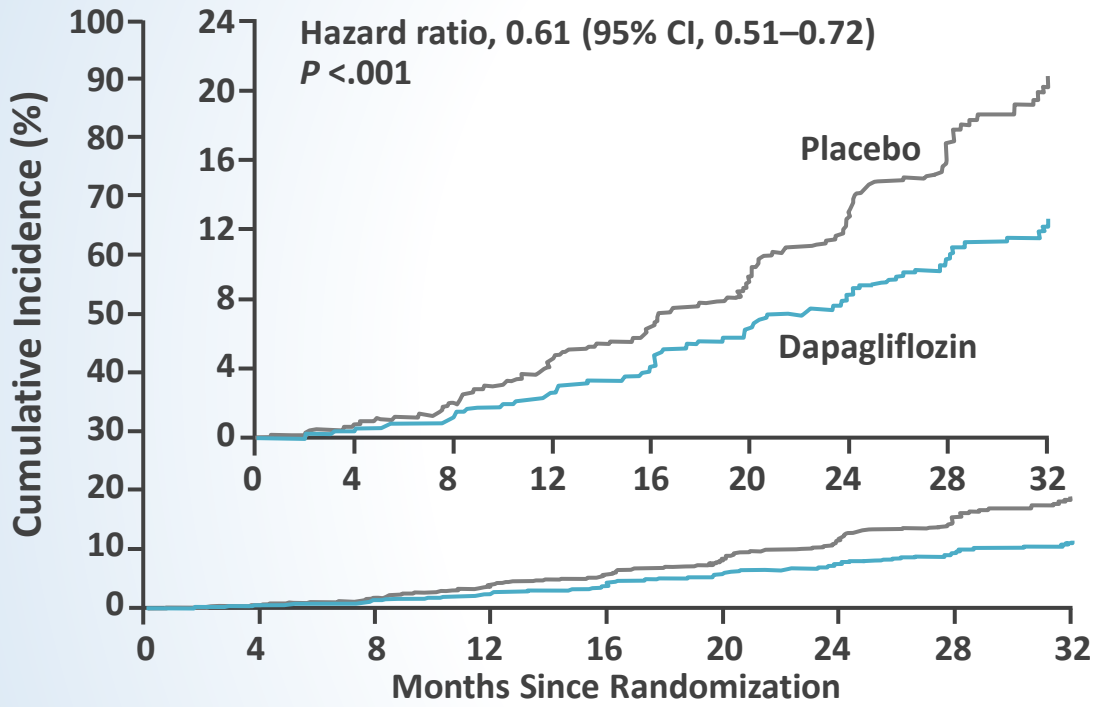
Overview of Dapagliflozin (SGLT2 inhibitor)

FDA Approval	Indication	Formulation & Dosing	Safety
April 2021	Treatment of CKD in adult patients with and without T2DM at risk eGFR decline, ESKD, CV death, and hospitalization for HF	• Tablets • **To improve glycemic control:** – Recommended starting dose 5 mg QD – Can increase to 10 mg QD for additional glycemic control • **For all other indications:** – Recommended dose, 10 mg orally QD	• Profile appears favorable • No major AEs • Incidence of discontinuation due to AEs, serious AEs, and AEs of interest was similar between both study arms

AE, adverse event.

DAPA-CKD Trial: Efficacy and Safety of Dapagliflozin

Primary Composite Outcome



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

- Increased prevention of primary composite outcome of worsening of kidney function or risk of CV or kidney death vs PBO (HR, 0.61; 95% CI, 0.51–0.72; *P* <.001).
- Reduced worsening of kidney function or kidney death by 44% (*P* <.001)
- Fewer patients died during treatment (4.7% vs 6.8%; 0.69; 95% CI, 0.53-0.88; *P*=.004)
- Benefits occurred equally among patients with/without diabetes
- No major AEs associated with dapagliflozin

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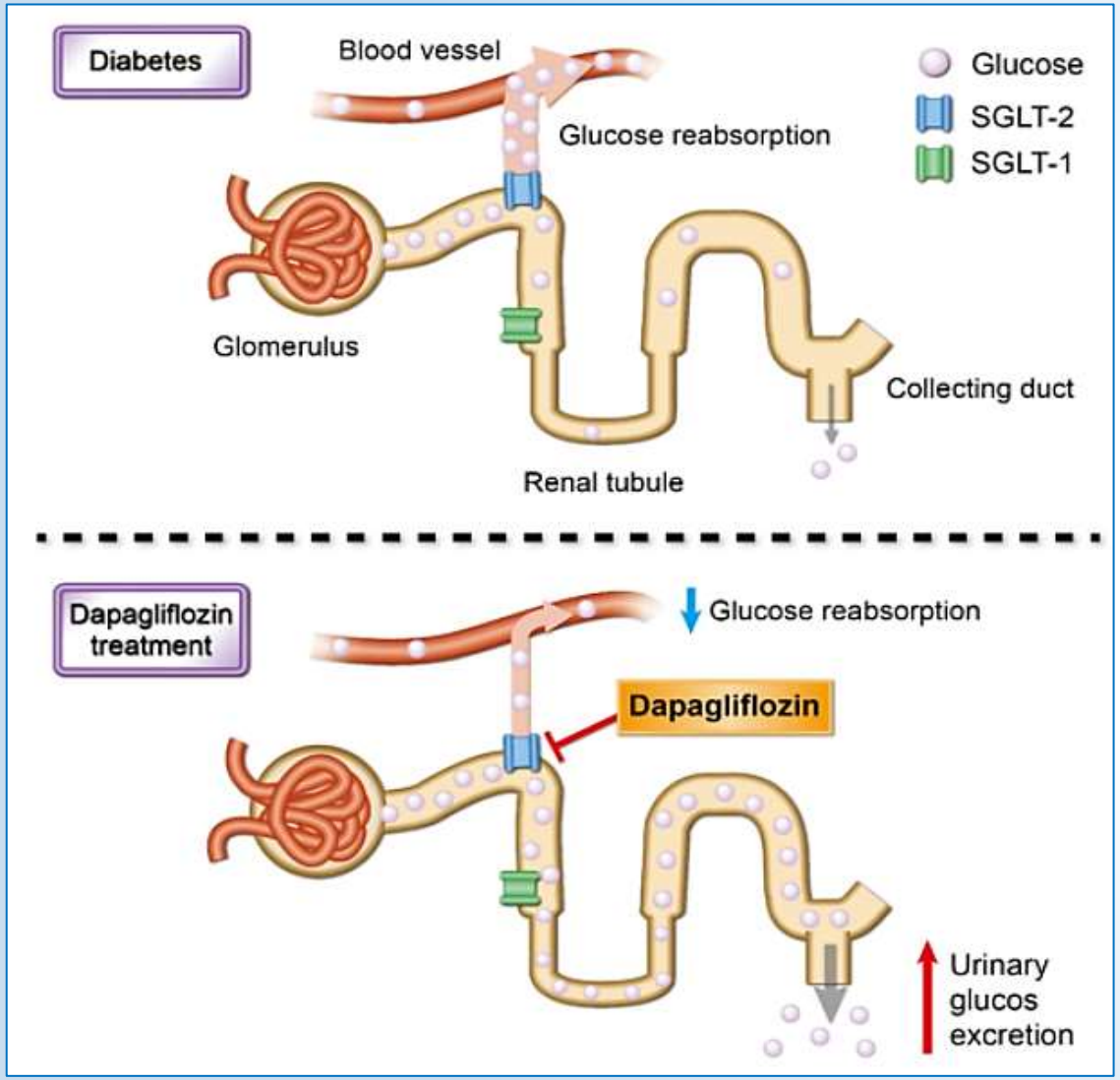
Heerspink HJL, et al. *N Engl J Med*. 2020;383(15):1436-1446.

MOA of Dapagliflozin



- Inhibition of glucose transporter (SGLT2) in the renal tubule, thus reducing resorption of glucose by this transporter
- Consequent reduced blood glucose

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Bailey CJ, et al. *Lancet*. 2010;375(9733):2223-2233; S Melmed. In: *Williams Textbook of Endocrinology*. 2020; [dapagliflozin] Summary of Product Characteristics.

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Emerging Therapies in the Treatment of DKD

Pipeline: Agents in Phase 3 for the Treatment of DKD

Ongoing Phase 3 Trials of Agents for Diabetic Nephropathy in Patients With T2DM

Drug	Age	Planned Completion	NCT
PDE-4 Inhibitor			
Roflumilast	18-65 years	July 2021	NCT04755946
GLP-1 Receptor Agonists			
Semaglutide	≥18 years	July 2023	NCT04865770
	≥18 years	Aug 2024	NCT03819153
Triterpenoid			
Bardoxolone methyl	20-79 years	March 2022	NCT03550443
Fibrate			
Fenofibrate	21-100 years	April 2021	NCT03869931
Small molecule anti-inflammatory			
SER150	18-85 years	April 2023	NCT04881123

US National Library of Medicine. National Institutes of Health. ClinicalTrials.gov.

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Interactive Patient Case Study: Adult With T2DM

Case Study: Meet Jake, 38 Years Old

Jake presents to your office to assess progress after 6 months of treatment with canagliflozin:

Patient Medical History	• 12-year history of T2DM; diagnosed at 26 years old • Pre-existing CVD • 10-year history of hypertension
Current Therapies	• Multidisciplinary treatments: • Blood pressure & lipid control • Blood glucose control • Weight management • Guidance for diet • Guidance for smoking cessation

ACR, ; CVD, cardiovascular disease; eGFR, ; T2DM, type 2 diabetes mellitus

Case Study: Jake, 38 Years Old—Physical Exam and Test History

Physical Exam Results	• BMI: 29 percentile • Feet: thermal and algesic sensitivity
Laboratory Results	• eGFR of 52 mL/min/1.73 m^2 • Albuminuria of 39 mg/24 hours • Creatinine: 5.8 grams/24 hours • UACR: 150

BMI, body mass index.

Case Study: Jake, 38 Years Old—Current Symptoms

Current Presentation	• Ongoing fatigue • Frequent headaches • Diabetic complications continue after normalization of blood glucose
Impact to QOL	• Less productive at work • No longer participating in weekend sport activities

Patient continues to show decreased renal and CV function.

Although Jake indicates that he feels somewhat better on the current regimen, he is concerned about the impact of fatigue on work performance and social activities.

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Patient Case Study Polling Questions

Polling Question #1

Based on Jake's medical history and presentation, is the current therapeutic regimen producing adequate results?

A. Yes
B. No
C. Undecided, require additional information
D. Allow patient to determine adequacy of results

Polling Question #2

Would you recommend a change to Jake's treatment?

A. No, continue SGLT2i and reassess in 6 months
B. Yes, consider switch to a different SGLT2i
C. Yes, add a nonsteroidal MRA
D. Unsure, additional testing needed

Case Patient: Audience Discussion

Discussion Points

- What are your primary concerns for this patient?
  - (eg, cardiovascular disease progression)
- Would you prescribe an MRA for this patient?
  - Why or why not?
- What are your primary concerns with regard to safety?

Case Study: Jake, 38 Years Old—Switching Therapy

Based on Jake's profile, the addition of a nonsteroidal MRA is a good option.

Treatment Adjustment:

- Add on finerenone (MRA)
- Continue canagliflozin
- Continue multidisciplinary treatments

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Patient Case Study Polling Question

Polling Question #3

After adding the MRA to Jake's therapy, how long will you wait to assess response?

A. 2 months
B. 4 months
C. 6 months
D. 8 months

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Case Study: Jake, 38 Years Old—Conclusion of Patient Story

Patient Update

- At 6-month follow-up, after adding on MRA, Jake states that he is experiencing less fatigue and fewer headaches. He is happy with current therapy and worries less about impact of DKD on work and social life
- Lab results show improvement of cardiovascular disease

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Program Summary

Program Summary

- DM is a common cause of CKD and a major risk factor for development of ESRD/ESKD
- DKD may reflect cumulative vascular damage caused by DM and may be causally linked to development of CVD through blood pressure dysregulation, uremic toxin retention, anemia, and mineral metabolism alterations
- DKD is associated with significantly greater risk of all-cause mortality, especially alongside other diabetic microvascular complications
- Current treatment for DKD includes SGLT-2i and GLP-1 receptor agonists
- Two recent FDA approvals:
  - Finerenone: First-in-class nonsteroidal MRA that significantly reduced serious kidney and CV complications in adults with CKD in FIDELIO-DKD trial
  - Dapagliflozin: SGLT2i for the treatment of CKD in patients with and without T2DM at risk of progression
- Emerging treatments in Phase 3 development have potential to further reduce CVD risk and DKD progression

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Thank You!