Balancing patients with Diabetes and CKD

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Objectives

- Epidemiology of diabetic kidney disease
- Review of treatment of diabetic kidney disease
- Overlap of benefits with medications for CKD and hyperglycemia
- Advantages and cautions for use of SGLT-2 inhibitors
- Introduction to finerenone, a new MRA

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Epidemiology of Diabetic Kidney Disease (DKD)

- Occurs in 20-40% of patients with diabetes
- DKD is the leading cause of ESRD in the U.S.
- Presence markedly increases cardiovascular risk and healthcare costs
- Typically develops after diabetes duration of 10 years in type 1 diabetes, but may be present at diagnosis of type 2 diabetes

Treatment of Diabetic Kidney Disease

- Optimize glucose control
- Optimize blood pressure control and reduce variability
- Use medications with proven benefits for kidney disease
- Quit smoking/weight loss
- Improve lipids

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CONSENSUS REPORTS | OCTOBER 03 2022

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) FREE

Ian H. de Boer ; Kamlesh Khunti; Tami Sadusky; Katherine R. Tuttle; Joshua J. Neumiller; Connie M. Rhee; Sylvia E. Rosas; Peter Rossing; George Bakris

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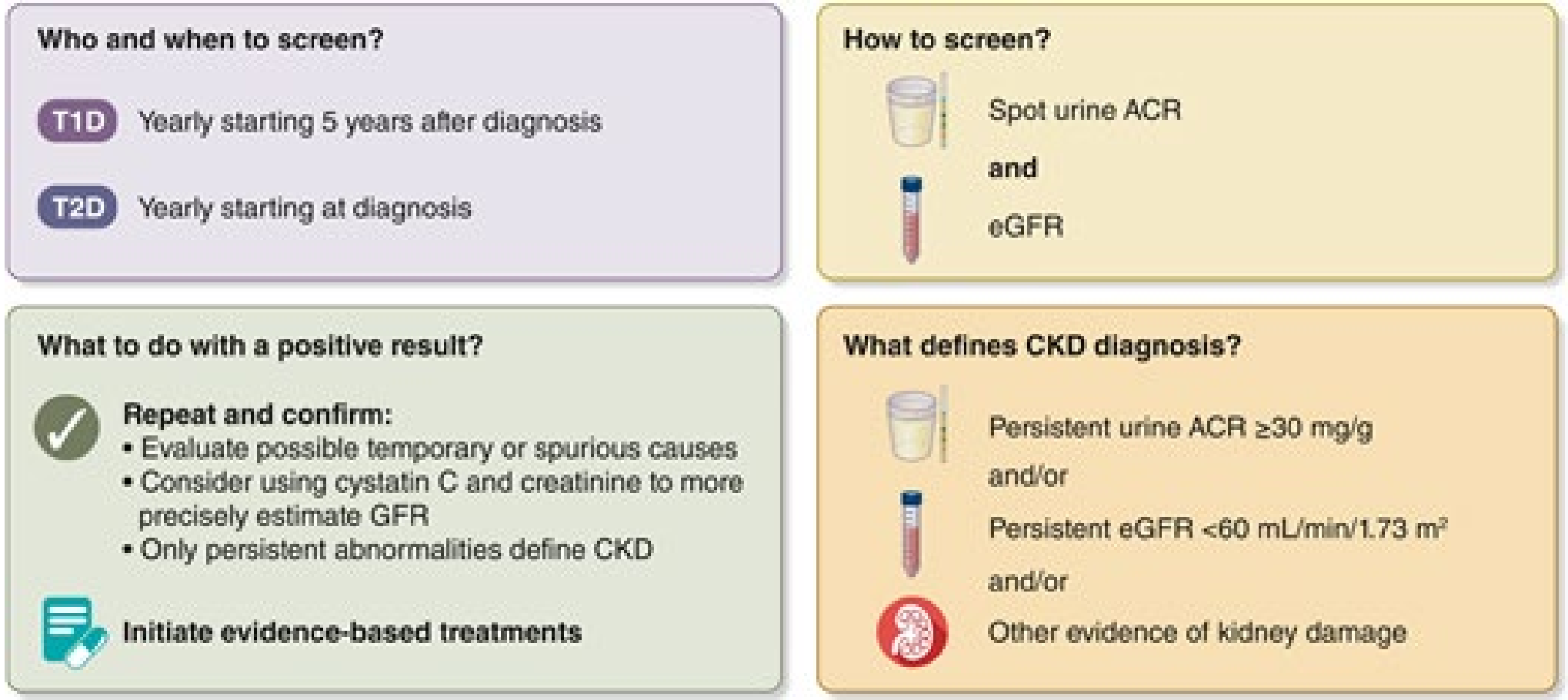
Diabetes Care 2022;45(12):3075–3090

https://doi.org/10.2337/dci22-0027 **Article history**

PubMed:36189689

\+ Kidney Disease Outcomes Quality Initiative (K/DOQI GUIDELINES)

CKD screening and diagnosis for people living with diabetes



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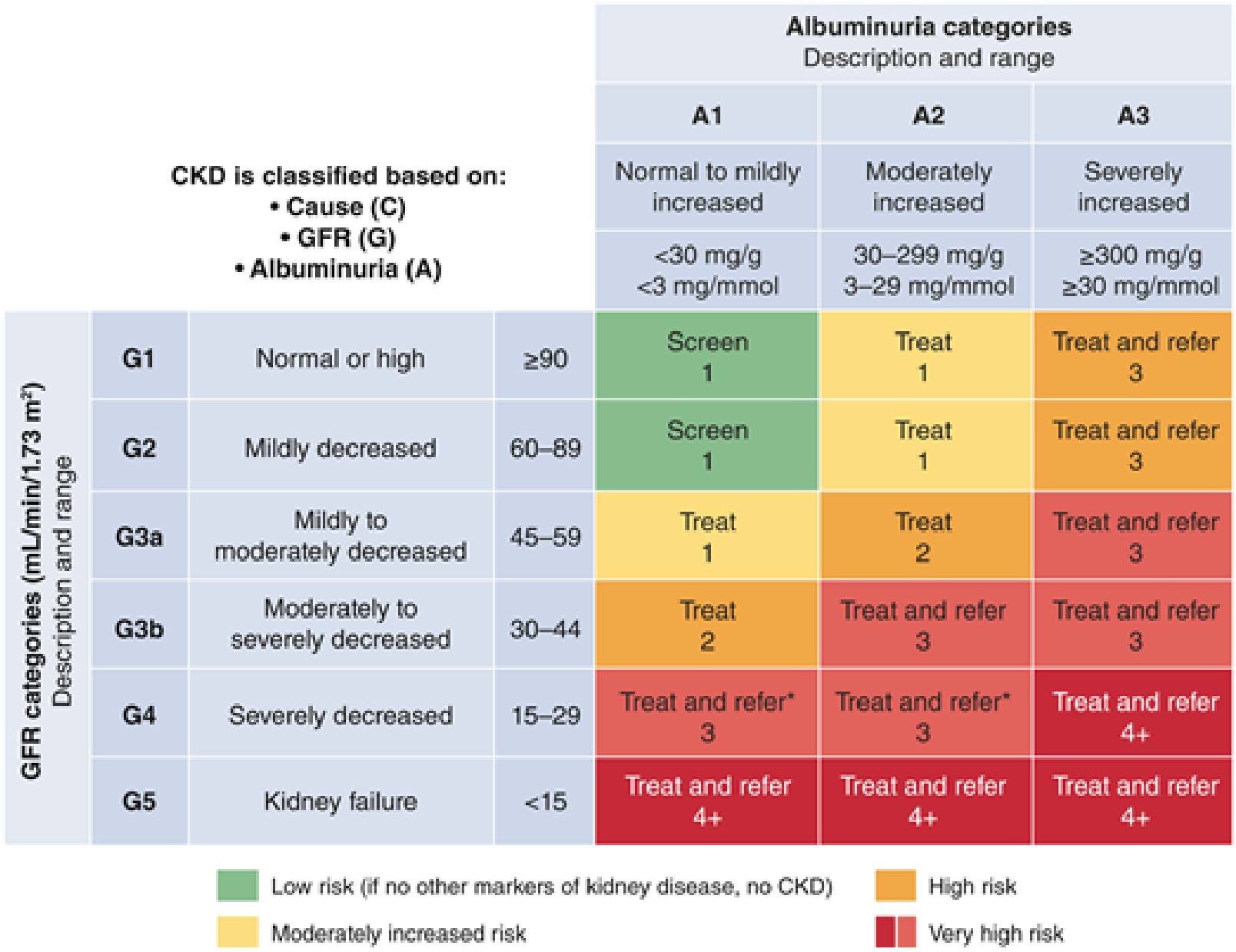

Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria.

The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year).

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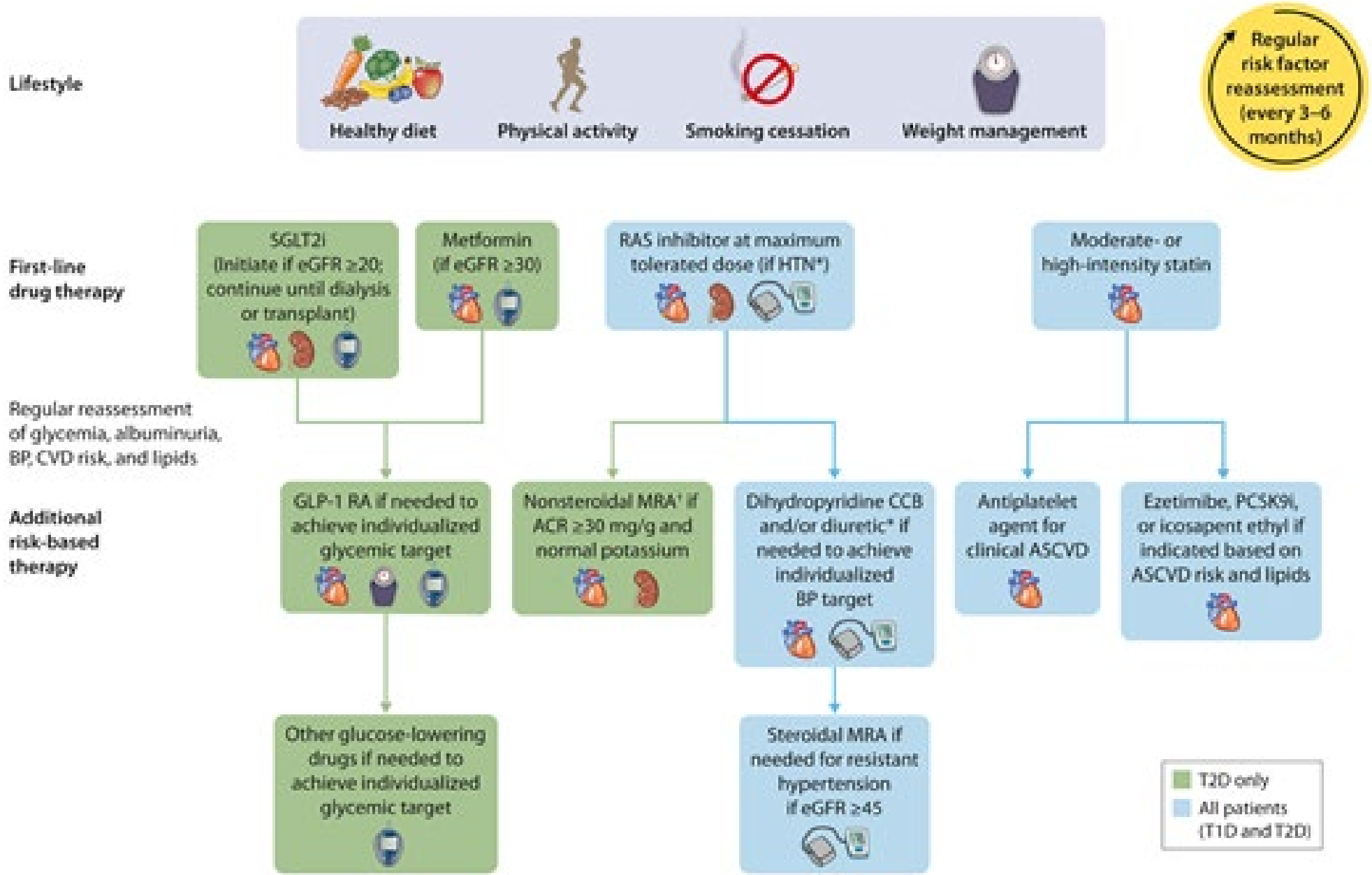

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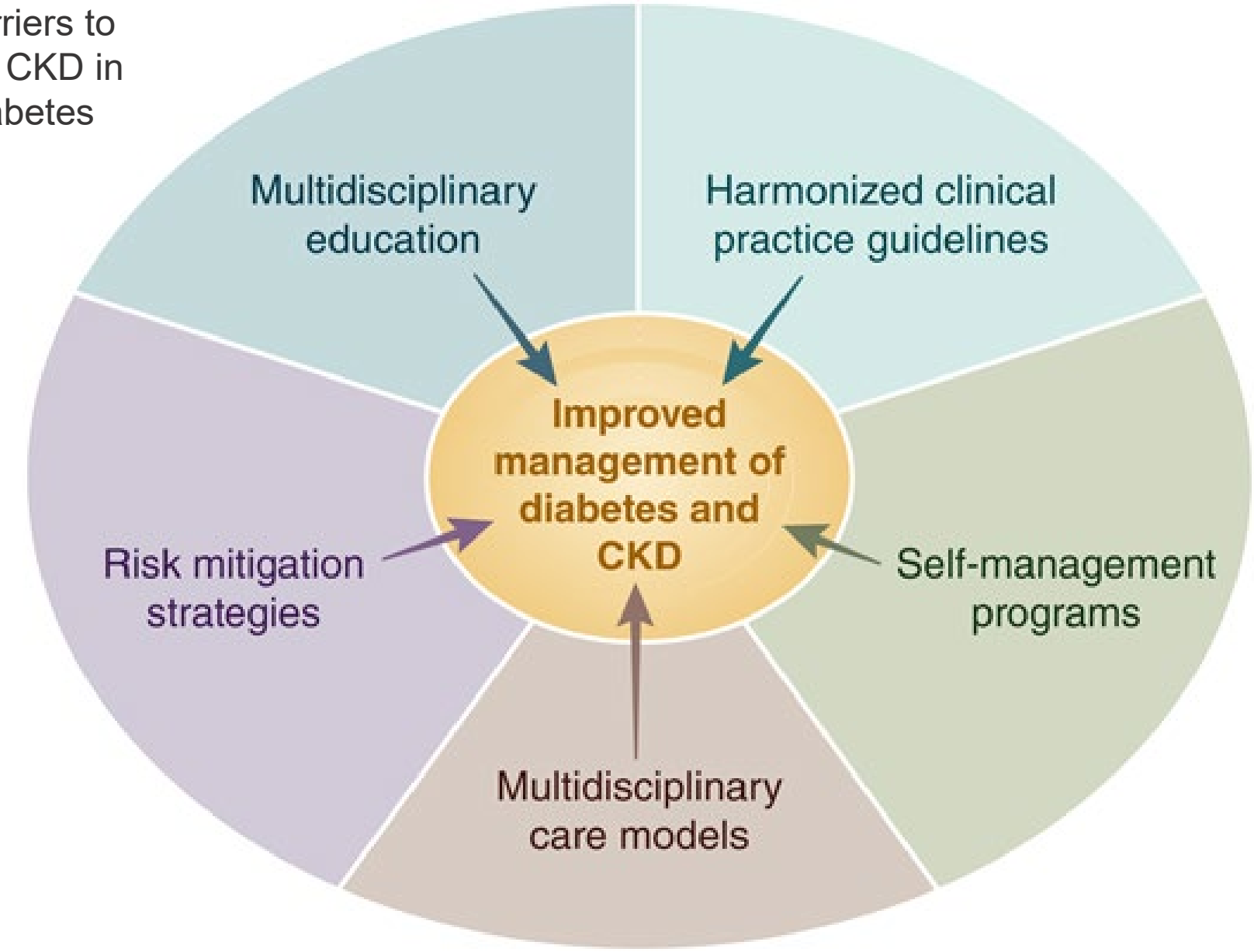
Overcoming barriers to management of CKD in patients with diabetes



Ian H. de Boer, Kamlesh Khunti, Tami Sadusky, Katherine R. Tuttle, Joshua J. Neumiller, Connie M. Rhee, Sylvia E. Rosas, Peter Rossing, George Bakris; Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 1 December 2022; 45 (12): 3075–3090. https://doi.org/10.2337/dci22-0027

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[a]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[b]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

Ian H. de Boer, Kamlesh Khunti, Tami Sadusky, Katherine R. Tuttle, Joshua J. Neumiller, Connie M. Rhee, Sylvia E. Rosas, Peter Rossing, George Bakris; Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 1 December 2022; 45 (12): 3075–3090. https://doi.org/10.2337/dci22-0027

Glucose-lowering efficacy is reduced with SGLT2i as eGFR declines, but kidney and cardiovascular benefits are preserved.

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors[a]			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily[f]	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily[f]	Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists[g]			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

Ian H. de Boer, Kamlesh Khunti, Tami Sadusky, Katherine R. Tuttle, Joshua J. Neumiller, Connie M. Rhee, Sylvia E. Rosas, Peter Rossing, George Bakris; Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 1 December 2022; 45 (12): 3075–3090. https://doi.org/10.2337/dci22-0027

WELL-AHEAD

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2023 ADA Standards of care

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

American Diabetes Association®

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/ renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD;

SGLT2 inhibitors

Clin Diabetes. 2014;32(1):4-11. doi:10.2337/diaclin.32.1.4

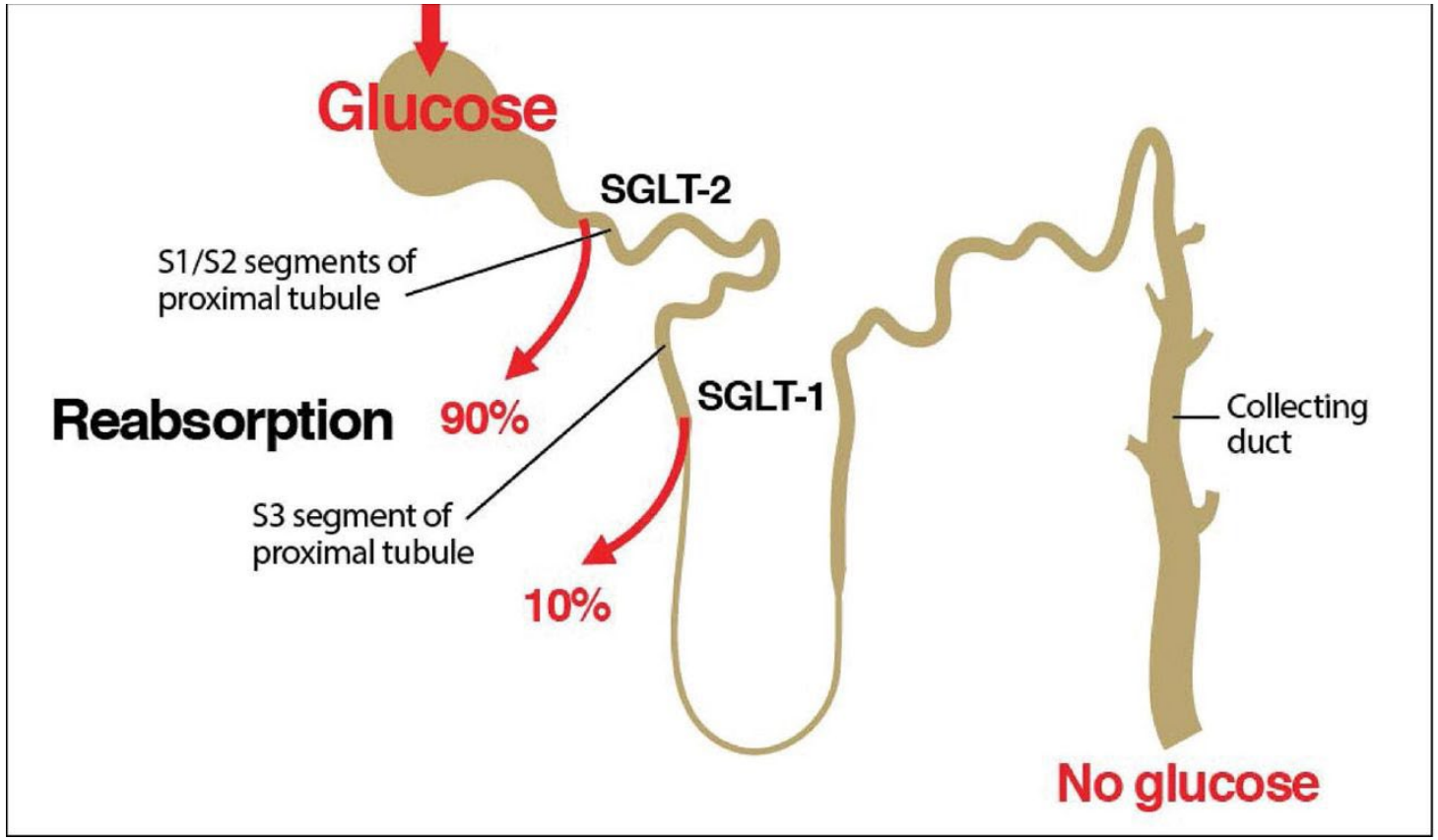


Figure Legend:

Renal glucose handling. In healthy individuals, the vast majority of the glucose filtered by the kidney is reabsorbed by SGLT-2 in the S1 and S2 segments of the proximal convoluted tubule, and the remaining glucose is reabsorbed by SGLT-1 in the S3 segment.[20]

Advantages of SGLT-2 Inhibitors

- Improve hyperglycemia (A1c reduction of 0.5-0.8%)
- Weight loss
  - Loss of glucose in urine and glucose-induced osmotic diuresis
- Reduce blood pressure
- Improve diabetes related co-morbidities
  - ***Delay progression of chronic kidney disease***
  - Reduce cardiovascular events – cardiovascular death, heart failure hospitalization, nonfatal myocardial infarction, or nonfatal stroke

	Delay Progression of DKD	Benefit: ASCVD	Benefit: HF
Empagliflozin	Yes	Yes	Yes
Canagliflozin	Yes	Yes	Yes
Dapagliflozin	Yes	No	Yes
Ertugliflozin	No	No	Yes

Cardiovascular Outcomes Trials (renal effects were secondary outcomes):

- **EMPA-REG** – “empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g Cr, doubling of serum creatinine, ESRD, or death from ESRD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2 by 44%”
- **CANVAS** – “canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40%”

Primary Renal Outcome in patients with CKD:

- **CREDENCE** – Treatment with canagliflozin (vs. placebo) resulted in 32% risk reduction for development of ESRD. 30% reduction in development of chronic dialysis, kidney transplant, or eGFR < 15; as well as doubling of serum creatinine, renal death, or cardiovascular death.
- **DAPA-CKD** – Treatment with dapagliflozin resulted in reduction in time to first occurrence of > 50% sustained decline in eGFR, reaching ESRD, cardiovascular death, or renal death.

Renal Effects of SGLT-2 Inhibitors

- Slow eGFR loss through reduction of…
  - renal tubular glucose reabsorption
  - weight
  - systemic blood pressure
  - intraglomerular pressure
  - albuminuria
- As well as mechanisms that appear independent of glycemia
  - Reduce oxidative stress in the kidney and decrease inflammatory factors in the kidney

SGLT2 inhibitors have less glycemic benefit in patients with more severe kidney disease at initiation

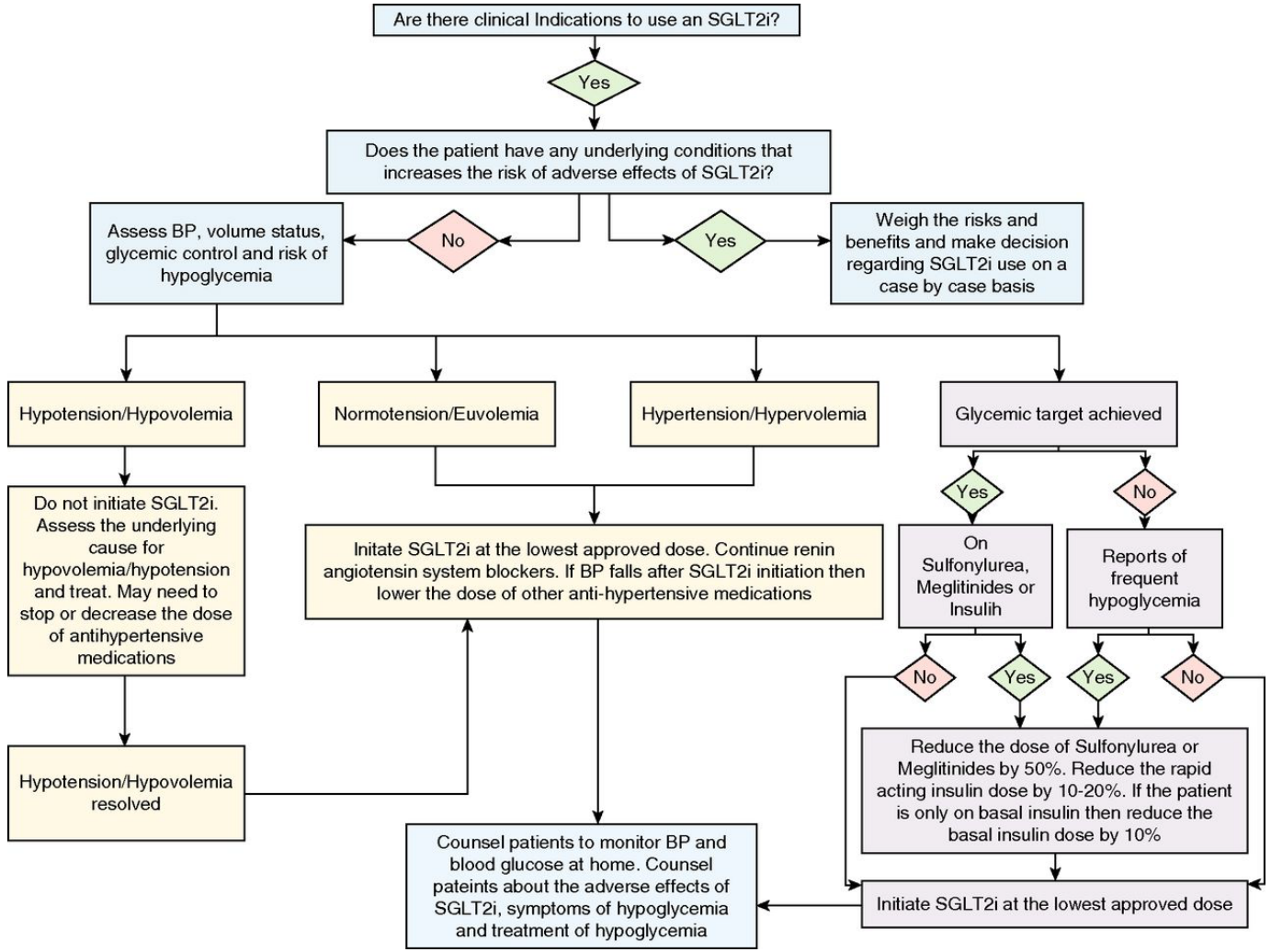
	Available Doses	Adjustment for Renal Function	Hyperglycemia	DKD
Empagliflozin (Jardiance)	10 mg once daily 25 mg once daily	eGFR > 30: No adjustment **eGFR < 30: Do not initiate.** Benefits have been seen in DKD and HF w/ eGFR > 20 no adjustment eGFR < 20 not defined	10 mg once daily -> increase to 25 mg/day if needed to achieve glycemic goals	10 mg once daily
Canagliflozin (Invokana)	100 mg once daily 300 mg once daily	eGFR > 60: No adjustment eGFR **30 to < 60: 100 mg once daily** **eGFR < 25-30: Do not initiate.** Can continue if urinary albumin > 300 and patient already on treatment.	100 mg/day -> increase to 300 mg/day if need to achieve glycemic goals	100 mg once daily
Dapagliflozin (Farxiga)	5 mg once daily 10 mg once daily	eGFR > 45: No adjustment eGFR < 45: Do not initiate for glycemic control; no adjustment for DKD or HF eGFR < 25: Do not initiate for DKD or HF, but can continue if on treatment	5 mg/day -> increase to 10 mg/day if need to achieve glycemic goals	10 mg once daily
Ertugliflozin (Steglatro)	5 mg once daily 15 mg once daily	eGFR > 45: No adjustment eGFR < 45: Use not recommended	5 mg/day -> increase to 15 mg/day if needed to achieve glycemic goals	N/A

While the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits were still seen down to eGFR levels of 25 mL/min/1.73 m^2 with no significant change in glucose

Potential Adverse Effects

- Hypoglycemia
  - Reduce dose of insulin, sulfonylurea, meglitinides
- Volume depletion
  - Encourage Hydration
  - Monitor BP
- Genito-urinary Infections
- Diabetic Ketoacidosis
  - “Euglycemic DKA”
  - Use in T1DM, ketosis-prone T2DM
- Amputations/Fractures
  - Observed with use of Canagliflozin in the CANVAS trial.

Algorithm to assess BP, volume status and glycemic control at the time of sodium-glucose cotransporter-2 inhibitor (SGLT2i) initiation.



David Lam, and Aisha Shaikh Kidney360 2021;2:742-746

Handout for patients when initiating sodium-glucose cotransporter-2 inhibitor therapy

It is recommended that the patients follow the recommendations stated below and must contact their provider if they have any questions or concerns
Increase in urine output
You may notice an increase in your urine output after starting this medication
Monitor your weight at home
BP
Monitor your BP at home because this medicine may lower BP
Inform your doctor if your BP is too low, or if you experience light headedness or dizziness
Blood glucose
Monitor your blood glucose level at home because this medicine may lower blood glucose
Inform your doctor if your blood glucose is low
Follow the "sick-day rule"
Do not take this medicine on days that you are unable to eat because you are feeling sick due to fever, infection, poor appetite, nausea, vomiting, or diarrhea
You can resume the medicine once you are able to eat and drink
If you continue to feel sick, then call your doctor because you may need to have blood tests to rule out diabetic ketoacidosis

Stop the medication 3–4 d before a scheduled surgery that requires you to be "nothing by mouth" (meaning you are instructed to not eat or drink anything for several h before your surgery)
Avoid very low carbohydrate and keto diets because they may increase the risk of diabetic ketoacidosis
Wound on your feet or legs
If you notice a wound, ulcer, or skin breakdown on your feet or legs, then hold this medicine and inform your doctor
Burning or pain during urination
If you experience pain or burning on urination, then inform your doctor because you may need further evaluation
Redness or itching in the genital area, or foul-smelling vaginal or penile discharge
Keep the genital area clean
If you notice redness or itching in the genital area, or foul-smelling vaginal or penile discharge, then inform your doctor; you may need a cream or oral medication to treat an underlying infection

What to expect?

- Decrease in eGFR of 3-6 mL/min per 1.73 m^2 in first 2-4 weeks
  - In some studies, patient had an initial decrease of > 10%
- Partial recover in by week 12
- If decrease in eGFR is > 30%, look for other factors that may be contributing

Monitoring

- Renal Function: Initial decrease in eGFR and increase in serum creatinine

Table 1.

Randomized controlled trials reporting an initial dip of eGFR

Trial Name	Agent Studied	Primary Outcomes	Observed Early Drop in eGFR
CREDENCE (8)	Canagliflozin	Reduction in the composite risk of ESKD, doubling serum creatinine level, or death from renal or cardiovascular causes (HR, 0.70; 95% CI, 0.59 to 0.82), compared with placebo.	5 ml/min per 1.73 m^2
DAPA-CKD (9)	Dapagliflozin	Reduction in the risk of 50% eGFR decline, ESKD, or death from renal or cardiovascular causes (HR, 0.61; 95% CI, 0.51 to 0.72), compared with placebo.	4 ml/min per 1.73 m^2
EMPEROR-Reduced (5)	Empagliflozin	Reduction of the risk of cardiovascular death or hospitalization for worsening heart failure (HR, 0.75; 95% CI, 0.65 to 0.86), compared with placebo.	4 ml/min per 1.73 m^2
EMPA-REG Outcome (11)	Empagliflozin	Canagliflozin decreased the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.86; 95% CI, 0.74 to 0.99), compared with placebo.	3–4 ml/min per 1.73 m^2
CANTATA-SU (12)	Canagliflozin	Canagliflozin slowed the progression of kidney disease compared with glimepiride in patients with type 2 DM ($P<0.01$ for each canagliflozin group versus glimepiride).	3–6 ml/min per 1.73 m^2

CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; HR, hazard ratio; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in CKD; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPA-REG Outcome, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANTATA-SU, Canagliflozin Treatment and Trial Analysis–Sulfonylurea; DM, diabetes mellitus.

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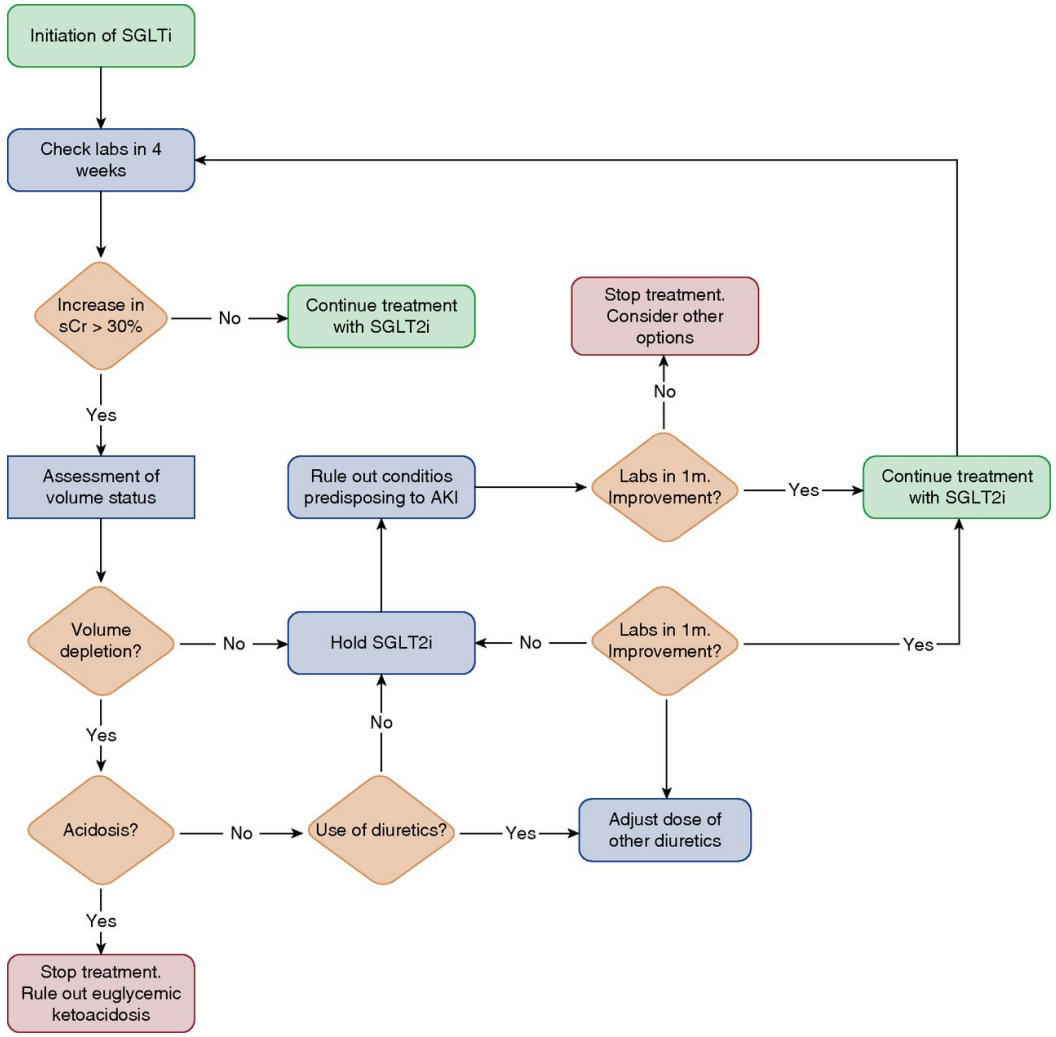
Proposed algorithm for initiation and surveillance of treatment with SGLT2is.

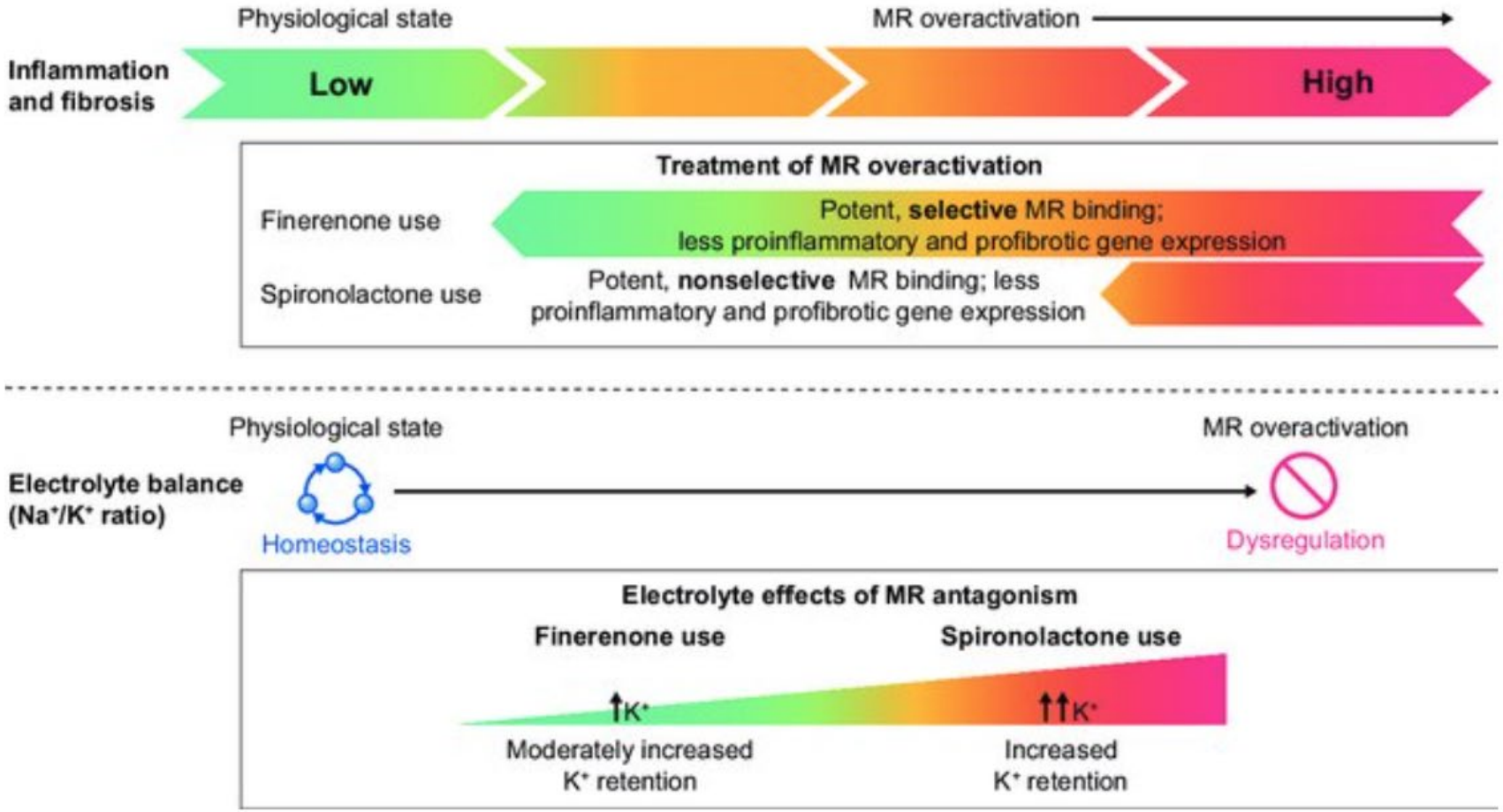


Alejandro Y. Meraz-Muñoz et al. Kidney360 2021;2:1042-1047

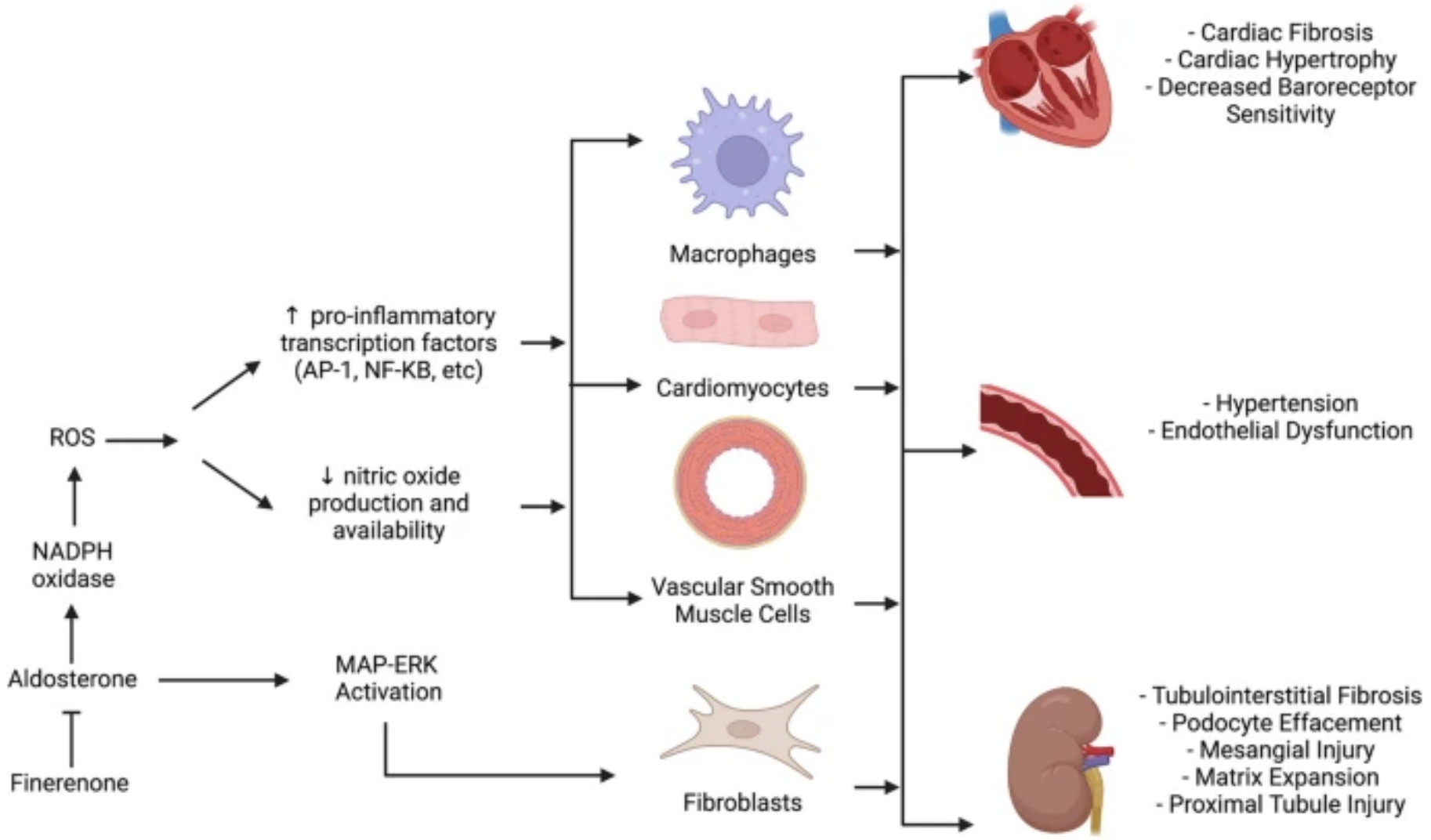
Novel MRA, Finerenone

Finerenone

- is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)



R. Agarwa et al. Nephrology Dialysis Transplantation , 2020



Palanisamy, S., Funes Hernandez, M., Chang, T.I. *et al.* Cardiovascular and Renal Outcomes with Finerenone, a Selective Mineralocorticoid Receptor Antagonist. *Cardiol Ther* **11**, 337–354 (2022). https://doi.org/10.1007/s40119-022-00269-3

11. Chronic Kidney Disease and Risk Management: *Standards of Care in Diabetes—2023*

11.5a For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine. **A**

11.5b For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. **B**

11.5c In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. **A**

11.5d In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. **A**

2024

Summary of Revisions: *Standards of Care in Diabetes—2024*
Section 10. Cardiovascular Disease and Risk Management

Recommendations 10.39a and 10.39b were added to include screening of adults with diabetes for asymptomatic heart failure by measuring a natriuretic peptide level to facilitate the prevention or progression to symptomatic stages of heart failure.

Recommendation 10.40 was modified to include screening for peripheral artery disease with ankle-brachial index testing in asymptomatic people with diabetes aged ≥50 years, microvascular disease in any location, foot complications, or any end-organ damage from diabetes. Peripheral artery disease screening should be considered for individuals with diabetes for ≥10 years or more.

Recommendation 10.42a was updated to recommend either an SGLT2 inhibitor or an SGLT1/2 inhibitor for people with diabetes and established heart failure with preserved or reduced ejection fraction to reduce risk of worsening heart failure and cardiovascular death. Additional text includes a discussion on cardiovascular outcomes trials of the SGLT1/2 inhibitor sotagliflozin.

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WELL-AHEAD

Project ECHO

Thank you!