

Helping Your Patients with Diabetes Slowing the Progression of Diabetic Kidney Disease in T2D Part 2 -Treatment

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Carol Greenlee MD MACP

Objectives – Part 2

Overarching objective - Improve health outcomes for your patients with T2D and diabetic kidney disease (DKD)

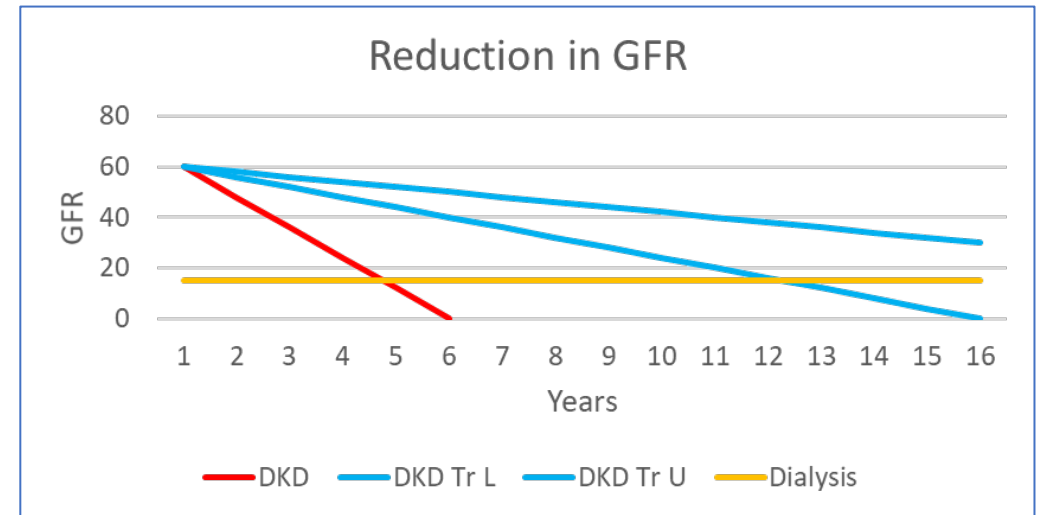
1. Examine the current recommendations and treatment options to help slow the progression of DKD.
2. Identify factors that can contribute to or reduce the progression of DKD.
3. Confidently administer SGLT2i medications to patients with diabetic kidney disease.



Background – Diabetic Kidney Disease (DKD)

Chronic Kidney Disease in Diabetes

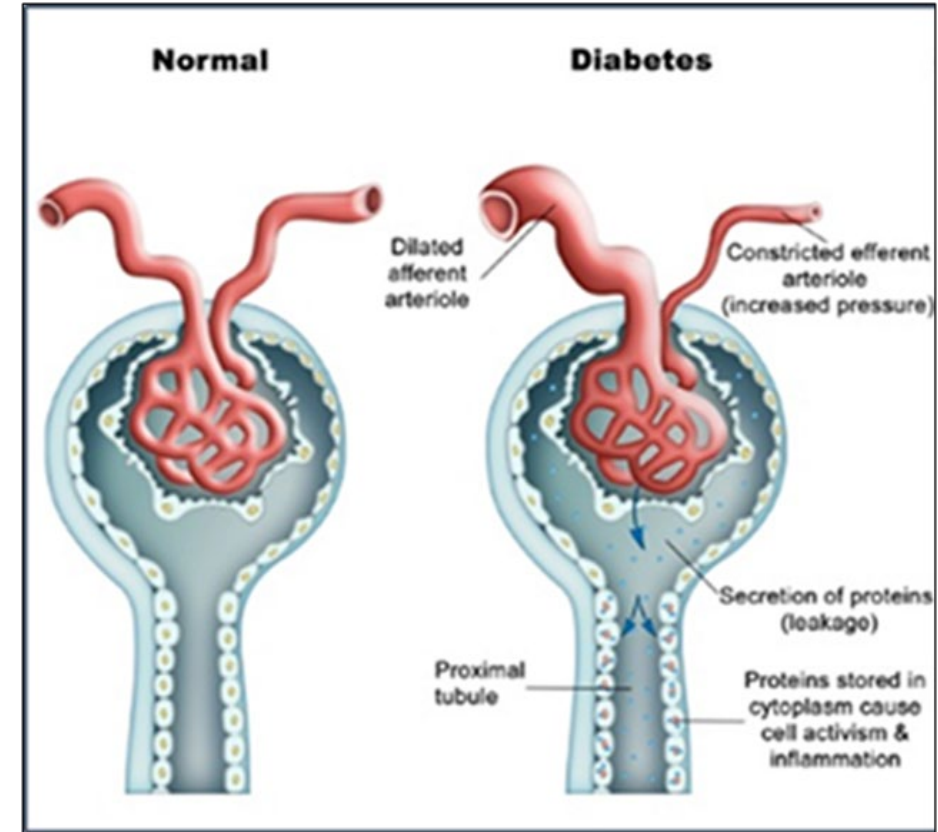
- Occurs in 20-40% of patients with diabetes
 - defined by albuminuria (increased uACR ≥ 30 mg/g) and/or reduced eGFR < 60 ml/min/1.73 M² (for > 3 months) in the setting of diabetes and the absence of signs or symptoms of other primary causes of kidney damage
- Can lead to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation
 - Is the leading cause of ESRD (ESKD) in the US (HTN is second leading cause)
- Markedly increases cardiovascular risk
- Rate of decline of GFR in Diabetic Kidney Disease (DKD) – average 12 ml/min/year
- Decline in GFR associated with structural & functional changes in the kidney → complications of CKD (anemia, bone, electrolytes, volume overload, etc.)
 - At GFR < 15 – require renal replacement
- **Treatment of DKD** can slow decline in GFR from average of **12 ml/min/year** to an average of **2-4 ml/min/year** – thus delaying or avoiding ESRD (ESKD) – and at same time help reduce CVD/HF risk



Hemodynamic Derangements

glomerular hypertension and hyperfiltration

- Auto-regulation of renal blood flow is *impaired* (*faulty tubuloglomerular feedback & RAAS activation*) in CKD in diabetes:
 - abnormal dilation of afferent arteriole &
 - inappropriate constriction of efferent arteriole
 - leads to increased glomerular filtration & perfusion pressure (*glomerular hypertension*)
- This increase in filtration & glomerular hypertension can lead to *glomerular sclerosis* in long term
 - Perpetuated injury: After development of sclerosis blood flow in remaining intact glomeruli increases causing a rise in glomerular pressure and further sclerosis
 - Leads to albuminuria & decline in GFR



Both *albuminuria* & *eGFR* must be quantified to guide treatment decisions

- eGFR levels are essential to modify drug dosages or restrictions of use
 - Risk for complications/management issues (CVD, low BG, anemia, bone disease, volume overload, etc.)
- At any eGFR, the degree of **albuminuria** is associated with risk of
 - Cardiovascular disease (CVD)
 - CKD progression
 - Mortality

At any eGFR, the Degree of Albuminuria is associated with Risk of Cardiovascular Disease (CVD)

Risk of CKD Progression, Morbidity & Mortality

				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Stages	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60-90	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45-59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30-44	Orange	Red	Red
	G4	Severely decreased	15-29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

Key to Figure:
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst.
 Green: Low Risk (if no other markers of kidney disease, no CKD)
 Yellow: Moderately Increased Risk
 Orange: High Risk
 Red: Very High Risk
 Deep Red: Highest Risk

Table 2. Risk Assessment for CVD in CKD

CKD Stages	GFR	10-29	30-299	>300
1	90+	Green	Yellow	Red
2	89-60	Green	Yellow	Red
3A	59-45	Yellow	Orange	Red
3B	44-30	Orange	Red	Red
4	29-15	Red	Red	Red
5	< 15	Red	Red	Red

CVD, cardiovascular disease; CKD, chronic kidney disease; GFR, glomerular filtration rate.
 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group⁹

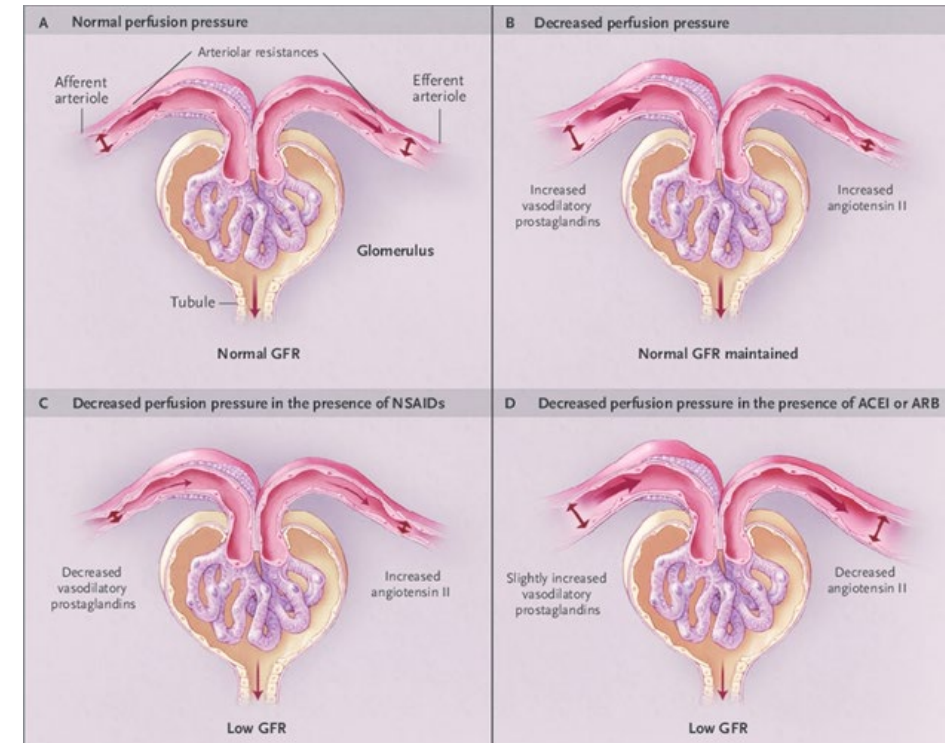
New ADA Standard regarding Treatment Goal for Albuminuria

- 11.1b Patients with diabetes and urinary albumin >300 mg/g Cr and/or an estimated GFR 30-60 ml/min/1.73 m², urinary albumin (e.g., spot urinary albumin-to-creatinine ratio (**UACR**)) and estimated glomerular filtration rate (**eGFR**) should be monitored at least ***twice annually*** to **guide therapy**. B
- 11.3d In patients with chronic kidney disease who have $\geq$ 300 mg/g urinary albumin, a ***reduction of 30% or greater in mg/g urinary albumin*** is recommended to slow chronic kidney disease progression B
 - Monitor for reduction over 6-12 months

*“In clinical trials of ACEI or ARB therapy in T2D, reducing albuminuria to levels <300 mg/g Cr or by >30% from their baseline has been associated with **improved renal & cardiovascular outcomes**”*

On lookout for **Acute Kidney Injury (AKI)** – diagnosed by a 50% or greater increase in serum creatinine (reflected as a rapid decrease in eGFR) over a short period of time (ADA)

- **AKI is associated with increased risk of new CKD and accelerated progression of existing CKD & poor health outcomes – *timely identification & treatment is critical***
- Risk factors for AKI
 - Diabetes
 - Preexisting CKD
 - Medications that cause kidney injury &/or alter renal blood flow & intrarenal hemodynamics (especially if already reduced intrarenal perfusion pressure such as from bilateral renal artery stenosis or congestive heart failure or volume depletion (*intraglomerular hypotension*)
 - e.g., **non-steroidal anti-inflammatory drugs (NSAIDs)**, **iodinated contrast agents**, **diuretics**, **ACE inhibitors**, **ARBs**
 - increased risk with the combination of ACEI/ARB, diuretic & NSAID (“Triple whammy”)
 - caution -avoid diuretics for edema from CCBs (vascular dilation, not volume overload)
 - studies show **SGLT2i meds protect against**, not cause AKI



KDIGO: AKI is diagnosed if serum Cr increases by 0.3 mg/dl or more in 48 h or rises to at least 1.5-fold from baseline within 7 days

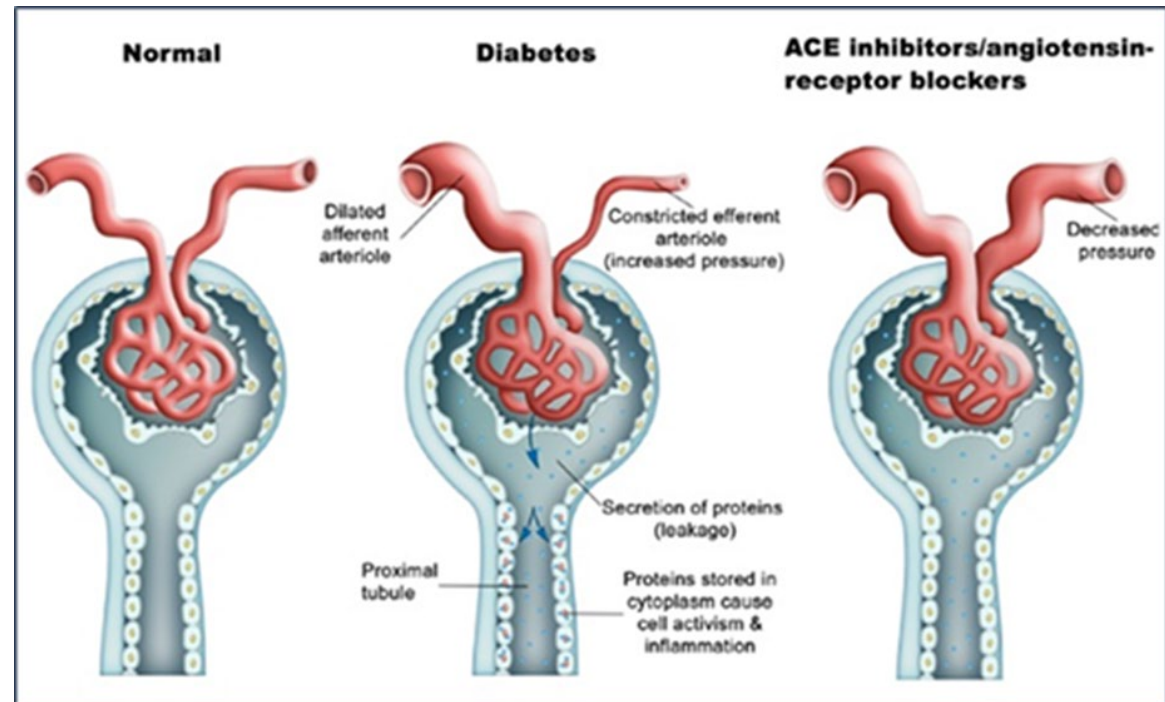
ADA Standards of Care – additional comments

- **Small elevations of serum Cr (*up to 30%* from baseline) with RAAS blockers (ACEIs & ARBs) must *not be confused with AKI* –**
 - usually begins 3-5 days after start of ACEI or ARB therapy
 - Studies found a strong association between acute increases in serum creatinine of up to 30% that stabilize within the first two months of ACE-inhibitor therapy and ***long-term preservation*** of renal function (*reduce intraglomerular hypertension*)

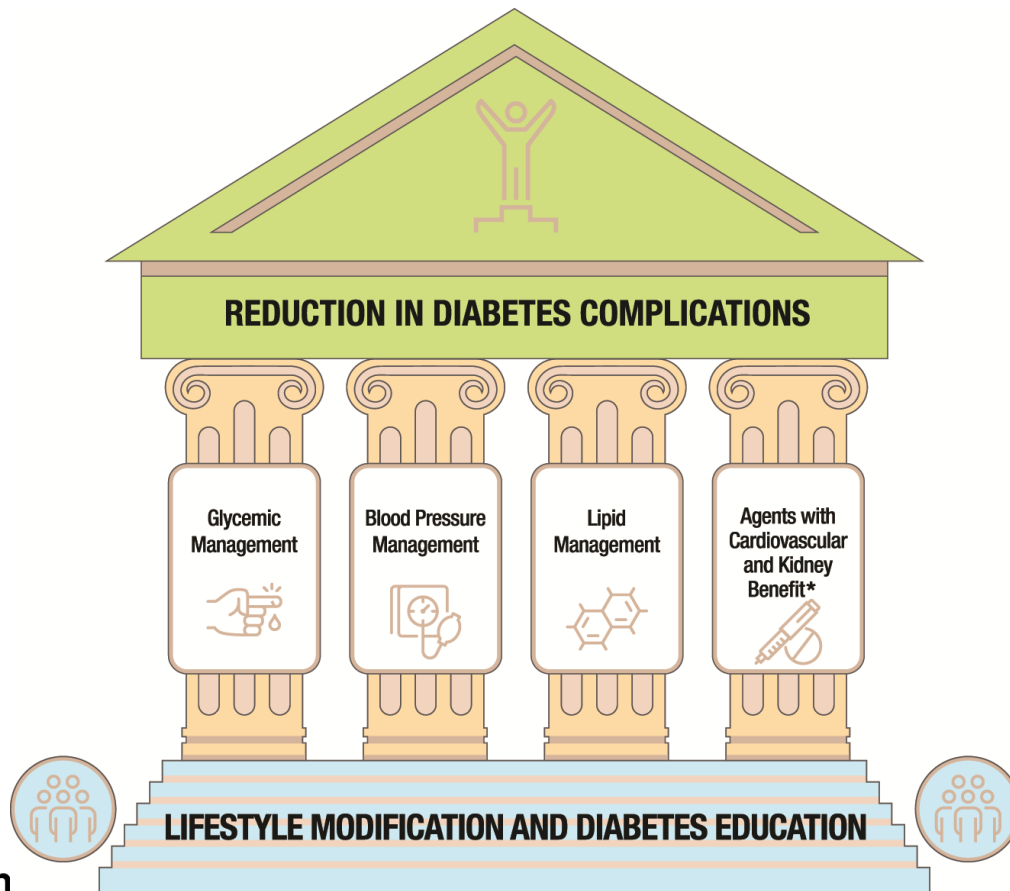
11.5 Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine ($\leq 30\%$) in the absence of volume depletion. A

Also applies with

- SGLT2i therapy
- MRA therapy



Treatment to Slow the Progression of Diabetic Kidney Disease



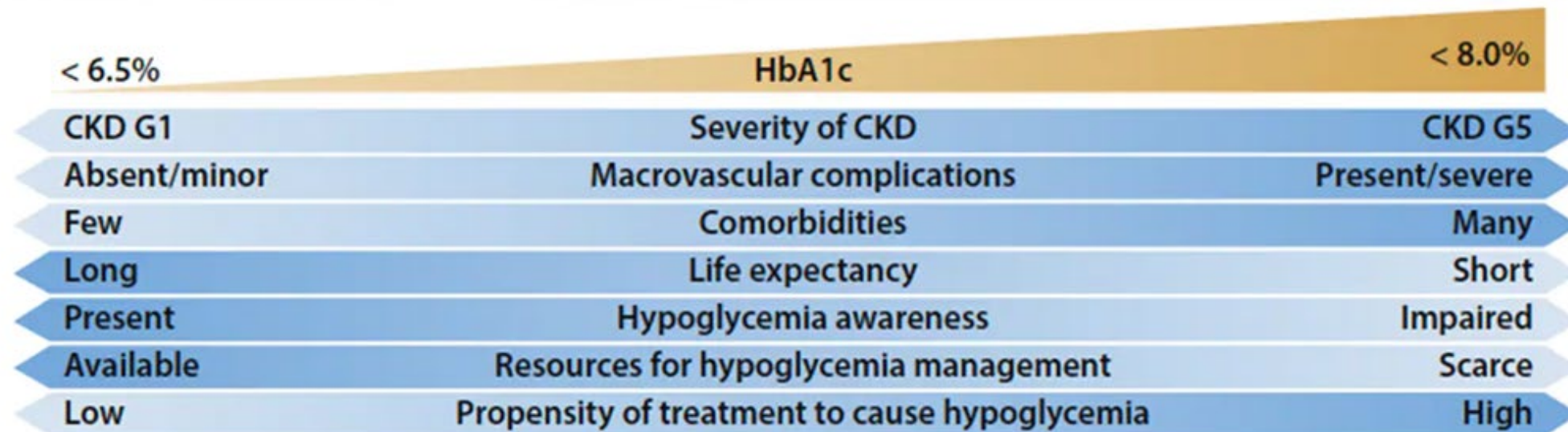
Messaging from NKF:

- treat the underlying disorder(s)
 - glycemia, BP, obesity, etc.
- treat the albuminuria

When possible, select meds that do
“double (or more) duty”

Treatment (ADA Standards of Care)

- 11.2 Optimize **glucose control** to reduce the risk or slow the progression of chronic kidney disease. A
- KDIGO (guidelines for clinicians caring for patients with diabetes and CKD)
 - Glycemic control in patients with diabetes and CKD not receiving dialysis should be monitored with an ***individualized HbA1c target*** ranging from less than 6.5% to less than 8.0% *depending on hypoglycemia risk*.

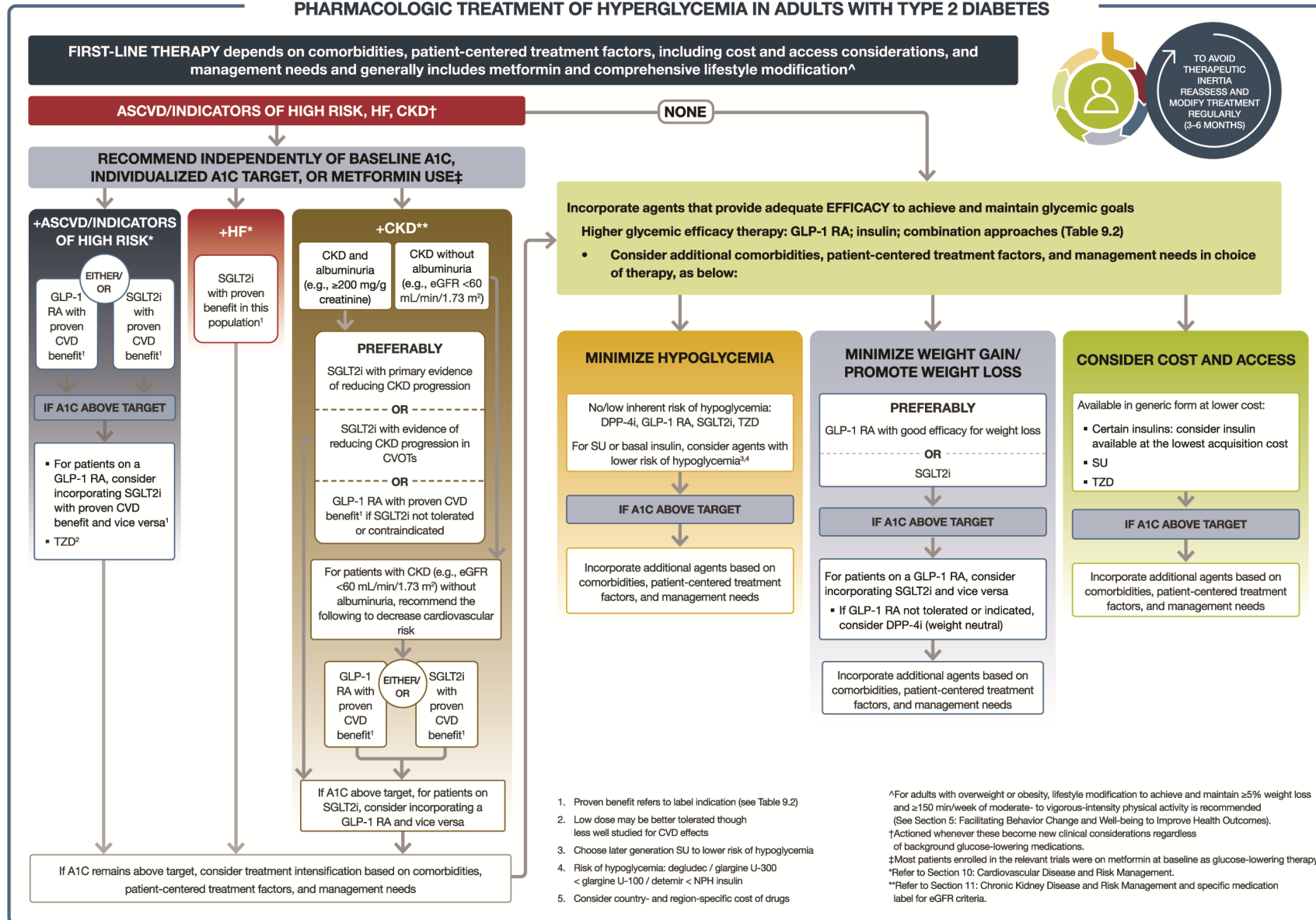


ADA: within the constraints of renal dosing *“metformin should be considered the first-line treatment for all patients with T2D, including those with CKD.”* [survival benefit seen with metformin]

- The renal dosing recommendations from the FDA based on eGFR:
 - Patients with an **eGFR ≥ 60** require *no dose adjustments* and can safely use metformin with *annual* monitoring.
 - Patients with an **eGFR between 45 and 60** may continue treatment but require *more frequent renal function monitoring* every 3 to 6 months.
 - Patients with *moderate chronic kidney disease* (**eGFR between 30 and 45**) aren't candidates for initiation of metformin, but patients currently maintained on the medication *may continue cautiously*.
 - The FDA suggests assessing the appropriateness of continuing metformin in this patient population and **considering a 50% dose reduction** with renal function monitoring every 3 months.
 - The FDA still recommends a **contraindication** in advanced kidney disease (eGFR < 30 mL/min/1.73m²).

Metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30-60 mL/min/1.73 m²

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES



ADA Standards of Care – additional comments re treatment

- Effects of glucose-lowering medications
 - **Glycemic effects** on renal outcomes
 - Intensive glucose control (near-normoglycemia) can delay onset & progression of DKD
 - Lag time of >2-10 years for intensive glucose control to manifest as improved eGFR outcomes
 - ACCORD trial – adverse effects of intensive control (hypoglycemia & mortality) increased in people with diabetes & kidney disease
 - Direct renal effects (not mediated through glycemia – “**non-glycemic** benefits”)
 - SGLT2 inhibitors
 - GLP1 RA agents

Multiple mechanisms, including

 - improved renal hemodynamics & tubuloglomerular feedback
 - reduced fibrosis, inflammation & oxidative stress

Treatment (ADA Standards of Care) Adding SGLT2i for *Non-glycemic* Benefit

- 11.3a For patients with type 2 diabetes and diabetic kidney disease, use of a **sodium-glucose cotransporter 2 inhibitor (SGLT2i)** in patients with an eGFR ≥ 20 ml/min/1.73 m² and urinary albumin >200 mg/g Cr is recommended to ***reduce Chronic Kidney Disease progression & Cardiovascular events***. B
- 11.3b For, patients with type 2 diabetes and chronic kidney disease, use of a **SGLT2i** is recommended to reduce CKD progression and CV events in patients with an eGFR ≥ 20 ***and urine albumin ranging from normal to 200 mg/g***. B

“SGLT2i should be given to all patients with stage 3 CKD or higher regardless of glycemic control, as they slow CKD progression and reduce heart failure risk independent of glycemic control” ADA Standards

Also consider in patients with stage 2 CKD (UACR >30 and eGFR <90) based on study outcomes

What dose of SGLT2i is needed for renal benefit?

- SGLT2i therapy must be initiated at the lowest recommended daily dose (10 mg empagliflozin, 100 mg canagliflozin, 10 mg dapagliflozin, or 5 mg ertugliflozin).
 - SGLT2i titration to a *higher dose is not necessary* for maximal *cardiorenal benefits*
 - A *higher dose* of SGLT2i can be used to *improve glycemic control*
 - the glucose-lowering effect of SGLT2i declines at lower eGFR
- Based on the evidence from CREDENCE and DAPA-CKD trials, once the SGLT2i therapy is initiated at the recommended level of eGFR, *it can be continued until the patient initiates dialysis therapy* (currently not recommended to start at eGFR <20)

Real-Life Prescribing of SGLT2 Inhibitors: How to Handle the Other Medications, Including Glucose-Lowering Drugs and Diuretics David Lam and Aisha Shaikh *Kidney360* April 2021, 2 (4) 742-746;
<https://kidney360.asnjournals.org/content/2/4/742>

SGLT2 inhibitor medications

Benefits

- Glycemic benefits
 - reduced with eGFR <45
- Lower BP
- Weight loss (NAFLD benefit)
- Cardiac protection
 - Heart Failure reduction
 - Reduced MACE/ CVD events
- Renal protection
 - **Slow progression of CKD**
 - Diuresis without risk of AKI
 - Do not increase uric acid
 - Work with diuretics when needed (HF)
 - Potassium moderating

Risks

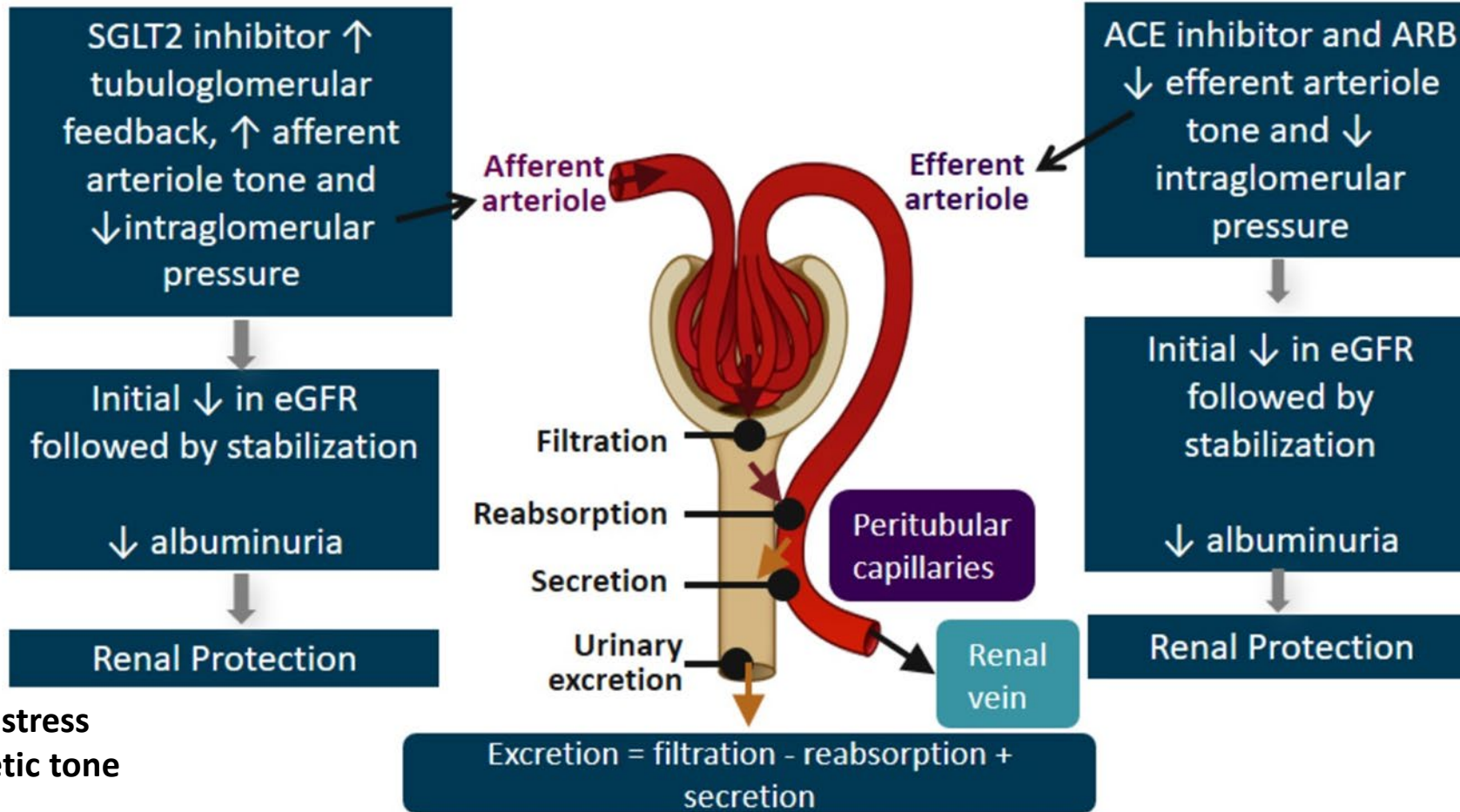
- Mycotic Genital Infections
- Fournier gangrene
- Euglycemic Diabetic Ketoacidosis (euDKA)
- Urinary Tract Infections (UTI)?
- Amputations ?
- Osteoporosis/fractures?

SGLT2i effectiveness in people with CKD

- ***Glycemic efficacy* of SGLT2 inhibitors is dependent on kidney function.**
 - SGLT2 inhibitors have been shown to be very effective in reducing glycated hemoglobin (HbA1c), with an ***average reduction of HbA1c by 0.6 - 1.2*** depending on the baseline level in people with preserved renal function
 - The ***glucose-lowering efficacy*** of SGLT2i in the patients with an **eGFR <45 mL/min/1.73 m²** is ***diminished*** because of their *reduced glucose filtration*
 - The glucose-lowering effect of SGLT2 inhibitors is attenuated in patients with eGFR <60 ml/min per 1.73 m² and minimal when eGFR is <30 ml/min per 1.73 m².¹³
- ***Non-glycemic benefits* are not diminished**
 - In patients with T2D and CKD with low eGFR, despite only modest reductions in A1c, SGLT2 inhibitors **reduce the risk of cardiovascular and renal outcomes**, without clear evidence of additional safety concerns.

SGLT2 Inhibition and ACE Inhibition/ARBs Reduce Intraglomerular Pressure

Newer data suggests minimal vasoconstriction of afferent arteriole & increased vasodilatation of efferent arteriole via TGF



Multiple additional renal protective effects, including:

- Reduced fibrosis
- Reduced oxidative stress
- Reduced sympathetic tone
- Diuretic sparing

Effects of Canagliflozin on eGFR

Change from Baseline in Estimated GFR

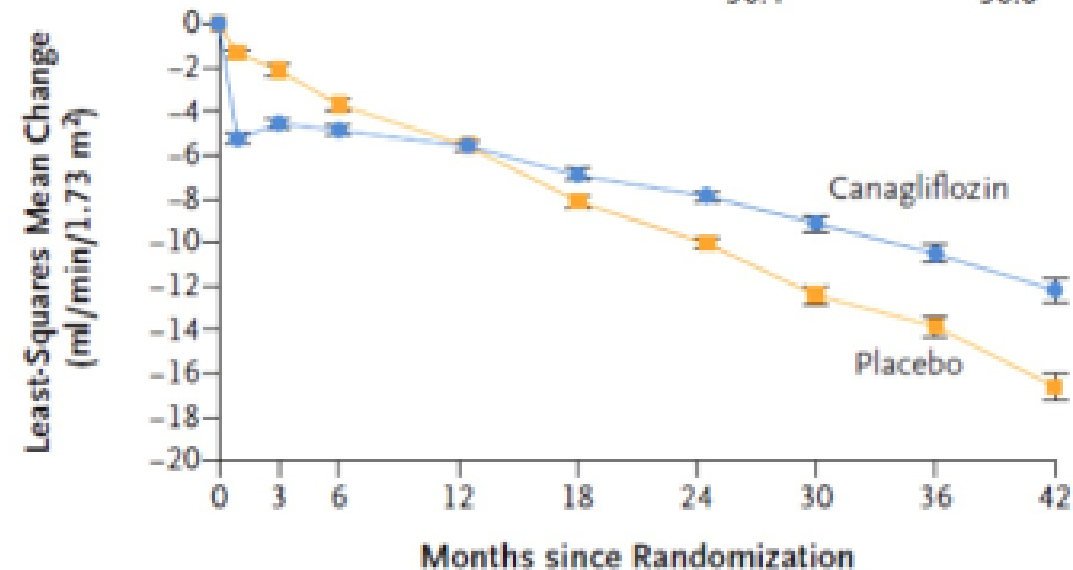
Baseline (ml/min/1.73 m²)

Canagliflozin

Placebo

56.4

56.0



No. of Patients

Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

Acute eGFR slope (3 weeks)

Difference: -3.17 (95% CI: -3.87, -2.47)

Chronic eGFR slope

Difference: 2.74/year (95% CI: 2.37-3.11)

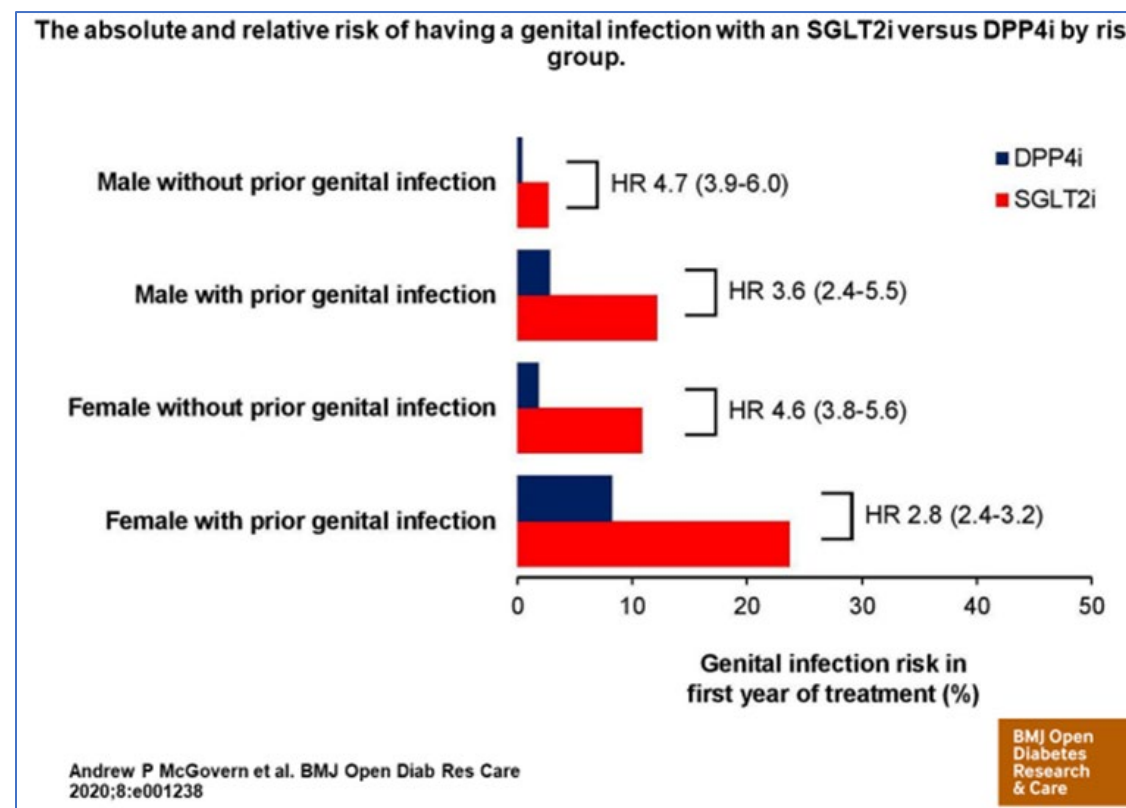
Additional Benefits – Gout, Edema, Hyperkalemia, AKI

- Reduction in uric acid levels and in incidence of gout
 - In several studies, SGLT2 inhibitor medications consistently **lowered blood urate levels**
 - A 2020 study published in Annals of Internal Medicine found ~ **30% reduced incidence of gout with SGLT2i** therapy compared to *GLP1 RA* therapy in patients with T2D
 - A 2021 Taiwanese study found that use of SGLT2 inhibitors is associated with ~**15% lower gout incidence** in patients with T2D compared with *DPP4 inhibitors* (DPP4i meds also reduce gout)
- ***Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials*** Katherine R. Tuttle et al Diabetes Care 2022;45(6):1445–1452
 - **Edema** was *less common* in patients receiving empagliflozin versus placebo
 - *No increase* in **acute renal failure / AKI** or volume depletion
 - Studies show **additive or synergistic natriuretic effects** of SGLT1i with loop diuretics when needed
 - *Lower risks* were observed with empagliflozin for **hyperkalemia**
 - Patients with advanced CKD, especially those receiving renin-angiotensin system blockers, are prone to hyperkalemia.
 - This favorable effect of SGLT2 inhibitors on serum potassium in patients with type 2 diabetes and CKD **might permit the broader use of drugs** associated with hyperkalemia, such as mineralocorticoid receptor antagonists

Increased Risk of Genital Mycotic Infections

- SGLT2i treatment is associated with a 3 to 6-fold increased risk of genital mycotic infections
 - Highest risk association
 - Females
 - History of prior infection
 - Especially within past year
 - No higher risk seen with higher A1c
 - Glucosuria threshold ?
 - Lower incidence rates in advanced CKD

“If those at highest risk elect to start an SGLT2i, then practitioners should pay particular attention to counseling regarding genital hygiene and when to start antifungal treatments.”



Prevention and management of genital mycotic infections in the setting of sodium-glucose cotransporter 2 inhibitors

Annals of Pharmacotherapy 2020

- The 3- to 4-fold increased incidence of GMIs is considered a class wide effect of SGLT2 inhibitors
 - female sex and a prior history of GMIs are factors associated with the highest risk, whereas
 - circumcised males are at the lowest risk of SGLT2 inhibitor–induced GMI
- Personal hygiene advice/education can reduce the infection risk in patients taking SGLT2 inhibitors
 - i.e., **rinse genital area with water after voiding and before bed**; wear cotton underwear
- When candidiasis occurs, it is often mild and responsive to treatment and often *does not require discontinuation of the medication*.
 - management strategies may include the use of
 - oral antifungals (i.e., single dose of oral fluconazole)
 - topical antifungal creams (i.e., miconazole or clotrimazole for 1-3 days)
 - over-the-counter topical antifungals in milder cases
- “Strong consideration should be given to avoid SGLT2 inhibitors in female patients with a history of severe, recurrent infections.”

Fournier Gangrene Associated With Sodium–Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases

Susan J. Bersoff-Matcha, MD; et al

Results: The FDA identified 55 unique cases of FG in patients receiving SGLT2 inhibitors between 1 March 2013 and 31 January 2019 (**55 cases in ~6 years**)

- For comparison, the FDA identified 19 FG cases associated with other anti-glycemic agents between 1984 and 31 January 2019 (**19 cases in 35 years**)

Fournier Gangrene = A type of necrotizing fasciitis or gangrene affecting the external genitalia or perineum (usually **bacterial** etiology)

- Symptoms
 - Fever
 - Pain and swelling in the genitals or anal area
 - Unpleasant odor coming from the affected skin tissue
 - Crackling sound when touching the affected area

Need for Education & Awareness

Causes of Fournier's Gangrene

Fournier's gangrene usually happens because of an **infection near the genitals** including:

- Urinary tract infections/ Bladder infections
- Hysterectomies
- Abscesses
- Piercings

• **Conditions and medications that make it more likely to get this disease, include:**

- Diabetes
- Alcohol abuse
- Trauma to the genital area
- Steroids
- Chemotherapy
- HIV
- Obesity
- Cirrhosis (liver disease)
- Sodium-glucose cotransporter-2 (SGLT2) inhibitor medication use



If patient has multiple risk factors need to be all that more aware of risk

Ketosis vs DKA - Defining

- **Ketosis** results from ***restriction of carbohydrate usage*** with increased reliance on fat oxidation for energy production
 - Fasting (urine ketones usually only 1+, no ketones in blood)
 - Low Carb intake (“ketogenic diet”, the Atkins diet, etc.)
 - SGLT-2 inhibitors (Urinary glucose loss, lowered insulin levels, raised glucagon level)
- **Diabetic Ketoacidosis (DKA)** results when ***absolute insulin deficiency*** occurs in both T1D and T2D,
 - DKA presents with
 - ***marked hyperglycemia*** (>250 mg/dL, typically 350–800 mg/dL),
 - ***profuse glycosuria***
 - ***elevated blood ketones*** as well urinary ketones

Euglycemic DKA (euDKA) with SGLT-2 inhibitors

- **euDKA** due to SGLT2i is similar to DKA except—
 - SGLT2i-induced glycosuria “*artificially*” lowers plasma glucose levels so you get DKA with **glucose <250 mg%**
 - SGLT2i predisposes to ***increased ketogenesis***
- ***SGLT-2 inhibition***
 - ***Induces a rapid increase in urinary glucose excretion***
 - SGLT2-induced glucose loss (ranging 50–100 g/day - a substantial fraction of daily carbohydrate availability)
 - ***As glucose is the chief stimulus for insulin release, plasma insulin levels fall***
 - And/or exogenous insulin dose is reduced or stopped
 - ***In contrast, plasma glucagon concentrations increase significantly***
 - Stimulates production ketones

Euglycemic DKA (euDKA) with SGLT-2 inhibitors

- The risk of bona fide euDKA, vs simple ketosis, in **T2D** related to the use of SGLT2 inhibitors is generally **low**
 - keto-acidosis has not been observed in patients without diabetes in the large SGLT2i trials
- Risk may be increased in people with diabetes if
 - **insulin deficiency is more profound**—as can happen in
 - T1D patients
 - In the CANVAS study, 6 out of the 12 cases of euDKA had evidence of latent autoimmune diabetes in adults (LADA) or T1D or tested **positive for GAD65 antibodies**
 - long-standing T2D patients with marked β -cell insufficiency
 - **carbohydrate availability has been drastically restricted**
 - during prolonged starvation (carb restriction), keto diet, after surgery, alcohol excess, or during intercurrent illness (and colonoscopy prep)

Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study

Chintan V. Dave, PharmD, PhD et al

- Objective: To assess whether patients initiating use of SGLT-2 inhibitors were at increased risk for severe UTI events compared with those initiating use of dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor (GLP-1) agonists
 - SGLT-2 inhibitors **were not associated with increased risk for outpatient UTIs**
- Conclusion: In a large cohort of patients seen in routine clinical practice, **risk for severe and non-severe UTI events among those initiating SGLT-2 inhibitor therapy was similar to that among patients initiating treatment with other second-line antidiabetic medications.**

“SGLT2is do not increase the risk of UTIs; however, their use in patients at high risk for UTIs, such as those with an indwelling Foley catheter, recurrent UTIs, or neurogenic bladder, has not been studied.” Kidney 360 April 2021

Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials

Katherine R. Tuttle et al Diabetes Care 2022;45(6):1445–1452

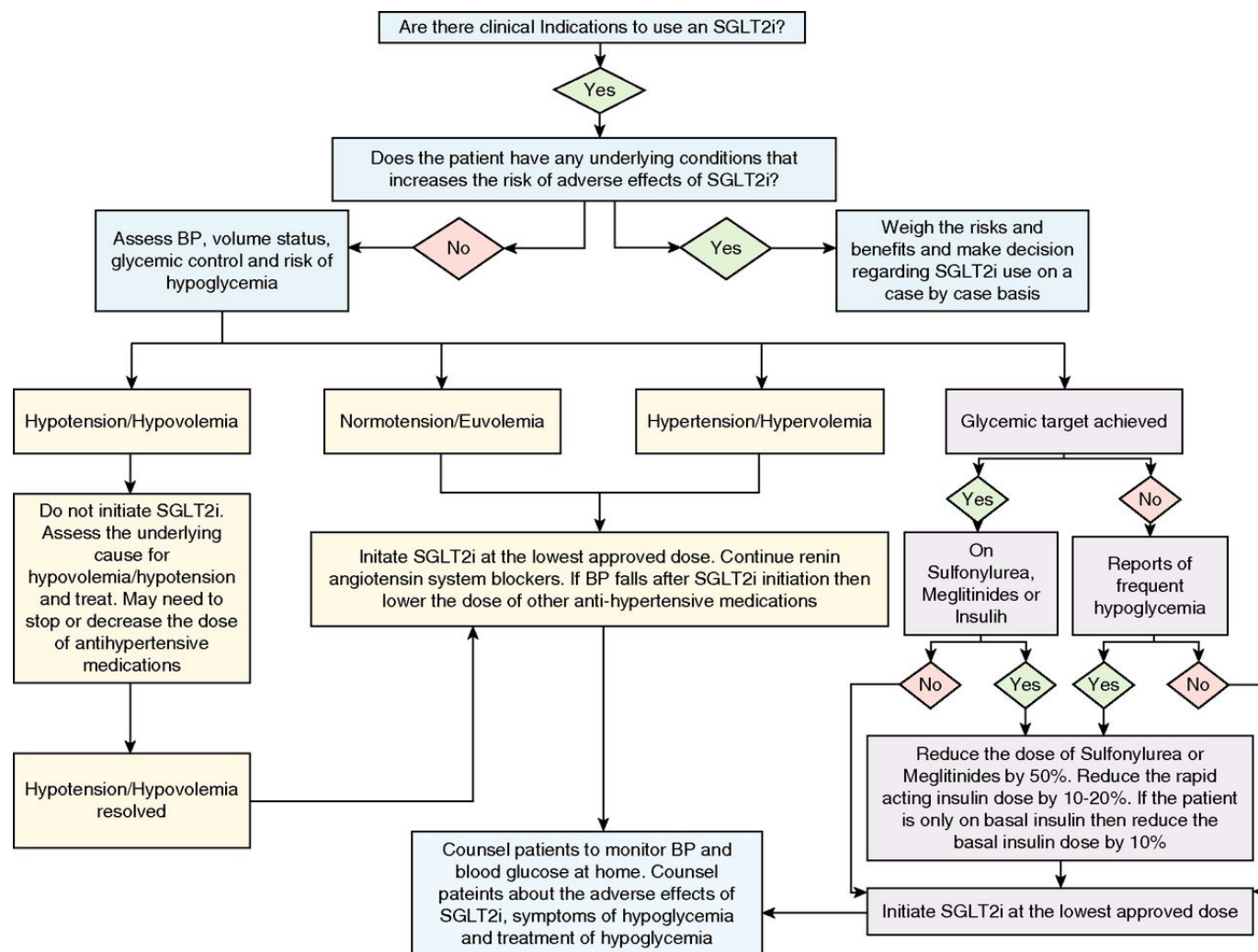
OBJECTIVE: To assess the safety of empagliflozin in patients with type 2 diabetes and moderate to severe chronic kidney disease (CKD) (category G3–4) enrolled in clinical trials

- no significant differences between treatment groups for
 - **ARF (AKI)**
 - **volume depletion**
 - **bone fracture**
 - **lower limb amputations**
 - Consider some caution since patients at high risk of lower extremity amputation (LEA) excluded were from some trials following findings in CANVAS (higher incidence of LEA in those on canagliflozin – not seen in trials with dapagliflozin or empagliflozin)
 - Remember increased risk of amputations in patients with CKD
- To build on the promising findings to date, a ***dedicated kidney disease outcome trial*** of empagliflozin versus placebo, enrolling >6,600 patients with and without diabetes, including those with low levels of kidney function with and without albuminuria, is under way (***EMPA-KIDNEY***; NCT03594110)

Consider the Patient's BP & Volume Status before Initiating SGLT2i

- Guide from Kidney 360 April 2021
 - If the patient is **hypotensive/hypovolemic**, then SGLT2i must not be initiated
 - In patients who are hypotensive, the antihypertensive medications, including diuretics, may need to be stopped or reduced to restore normotension.
 - If the patient is **hypervolemic/hypertensive**, then SGLT2i therapy can be initiated without adjusting the dose of other antihypertensive medications.
 - If the patient is **euvolemic/normotensive** then the *antihypertensive agents*, including *diuretics*, may need to be reduced or stopped if the BP decreases.
 - In the SGLT2i CV and kidney outcome trials, patients were required to be on the ***maximally tolerated dose of renin-angiotensin system (RAS) blockers*** - A similar strategy to continue RAS blockers must be adopted in clinical practice.
 - ***Monotherapy with SGLT2i*** is reasonable in patients who *are unable to tolerate RAS blockers*.

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 the Patients when initiating SGLT-2 Inhibitor Therapy

- Increase in Urine Output
 - You may notice an increase in your urine output after starting this medication
 - Monitor your weight at home
- Blood Pressure
 - Monitor your blood pressure at home as this medicine may lower blood pressure
 - Inform your doctor if your blood pressure is too low, or if you experience lightheadedness or dizziness
- Blood Glucose
 - Monitor your blood glucose level at home as this medicine may lower blood glucose
 - Inform your doctor if your blood glucose is low
- 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
- Follow the 'Sick Day Rule'
 - On days that you are unable to eat because you are feeling sick due to fever, infection, poor appetite, nausea, vomiting or diarrhea then hold this medicine.
 - You can resume the medicine once you are able to eat and drink.
 - If you continue to feel sick, then call your doctor as you may need to have blood tests to rule out Diabetic ketoacidosis
 - Stop the medication 3 to 4 days before a scheduled surgery that requires you to be NPO (meaning you are instructed to not eat or drink anything for several hours before your surgery) (including colonoscopy)
 - Avoid very low Carbohydrate diet and Keto diet as it 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 as you may need further evaluation

Patient – “Joe”

- 70-year-old male T2D diagnosed 1998, now with “brittle” diabetes
- Weight 165#, BMI 24.2, smokes 2-3 cigs/d, no alcohol, widowed, refuses to change diet
- A1c 9.5% -13.4% range, reported hypoglycemia with low dose prandial insulin
- CAD s/p 2 stents, second degree AV block, Graves’ disease on MMI, chronic GI sx
- Cr 1.21, eGFR 53, UACR 1642; TC 150, HDL 33, TG 471, normal iron studies & ALT
- Meds
 - Metformin 500 mg QD
 - Detemir 32 u QD
 - Methimazole (MMI) 10 mg QD
 - Isosorbide 30 mg
 - Atorvastatin 80 mg QD
 - ASA 81
 - Plavix 75 mg QD
 - Atenolol 25 mg QD
 - Vitamin D 1000 IU QD
- Clinical Question from his primary care clinician
 - Recent bout with an UTI, has chronic GI complaints, patient afraid of low BG, past intolerance of ACEI or ARB; he’s hoping for “a good quality life with minimal interventions” –
 - PCP concerned about adding SGLT2i or GLP1 RA due to above issues - “not sure what to do”



Patient – “Joe” – “What to do?”

- He has stage 3 CKD with UACR >300 mg/g (Cr 1.21, eGFR 53, UACR 1642)
- He has CVD - CAD s/p 2 stents
- He is at risk for heart failure

CKD Stages	GFR	10-29	30-299	>300
1	90+			
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4	29-15			
5	< 15			

CVD, cardiovascular disease; CKD, chronic kidney disease; GFR, glomerular filtration rate. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group³

- The **major risk factors for heart failure** cluster in patients with **type 2 diabetes**, including:
 - Obesity
 - Hypertension – RAAS activation, SNS activation
 - Advanced age
 - Sleep apnea
 - Dyslipidemia
 - Chronic kidney disease +/- anemia
 - a strong risk association between albuminuria and incident heart failure
 - Coronary heart disease
 - Diabetic cardiomyopathy - cardiac dysfunction in the absence of overt macrovascular disease

- He meets criteria to treat with SGLT2i (&/or GLP1 RA) for **non-glycemic** benefits
 - SGLT2i preferred due to CKD -some *glycemic benefits* from SGLT2i also expected at eGFR 53
- Any precautions or concerns?

How to select the next steps/ medication

- Continue or intensify/ modify lifestyle efforts
- Consider glycemic response
- Consider other benefits &/or risks for the *individual* patient –does it potentially improve, worsen or have neutral effect on:
 - Hypoglycemia risk
 - CVD risk
 - Liver disease
 - Renal disease
 - Heart Failure risk
 - Fracture risk and/or Osteoporosis
 - Cancer risk
 - Weight issues
 - Pancreatitis risk
 - Fluid volume issues (edema / dehydration)
 - GI issues (diarrhea, nausea, reflux, gastroparesis)
 - Other risks: DKA, infection
 - Cost, complexity/burden, preferences, etc.

Consider – could he have Adult onset-T1D?

- He has Graves' disease (AITD)
- He is non-obese
- Reasonable to check GAD-65 AB
- Maybe also check for Celiac Disease

UTI risk is not increased by SGLT2i
But UTI is risk for Fournier's gangrene

Think about other auto-immune conditions

“Type 1 diabetes (T1DM) is often associated with autoimmune diseases such as: autoimmune thyroid disease (ATD), celiac disease (CD), autoimmune gastritis (AIG), pernicious anemia (PA) and vitiligo.”

Autoimmune thyroid disease is the most prevalent endocrinopathy among diabetic patients.

- ***Hypothyroidism, celiac disease or Addison's disease*** in patients with type 1 diabetes may *deteriorate glycemic control* and can lead to an increased rate of *hypoglycemia*.
- Autoimmune gastritis, pernicious anemia and celiac disease can cause ***malabsorption*** and anemia which additionally impair the quality of life in patients with T1DM.”

Review Med Wieku Rozwoj Jan-Mar 2012;16(1):23-34.[Type 1 diabetes-associated autoimmune diseases: screening, diagnostic principles and management]

Patient – “Joe”

- 70-year-old male T2D diagnosed 1998, now with “brittle” diabetes
- Weight 165#, BMI 24.2, smokes 2-3 cigs/d, no alcohol, widowed
- A1c 9.5% -13.4% range, reported hypoglycemia with low dose prandial insulin
- CAD s/p 2 stents, second degree AV block, Graves’ disease on MMI, chronic GI sx
- Cr 1.21, eGFR 53, UACR 1642; TC 150, HDL 33, TG 471, normal iron studies & ALT
- Meds
 - Metformin 500 mg QD
 - Detemir 32 u QD
 - Methimazole (MMI) 10 mg QD
 - Isosorbide 30 mg
 - Atorvastatin 80 mg QD
 - ASA 81
 - Plavix 75 mg QD
 - Atenolol 25 mg QD
 - Vitamin D 1000 IU QD
- Follow up
 - Libre CGM – BGs coming down as he adjusts his food (previously refused to change his diet)
 - GAD-65 AB neg – started Empagliflozin for *non-glycemic* benefits + possible *glycemic* benefits



Treatment (ADA Standards of Care)

- 11.3c In patients with chronic kidney disease who are at increased risk for cardiovascular events or chronic kidney disease progression or are **unable to use a SGLT2i**, a **nonsteroidal mineralocorticoid receptor agonist** (finerenone) is recommended to reduce CKD progression & CVD events A
- Nonsteroidal MRA:
 - Less hyperkalemia
 - Much less gynecomastia
 - Minimal BP lowering
 - Anti-fibrosis effects (global – renal, cardiac, islet cells, etc.)
- Need to learn more about combination therapy (RAS blocker + SGLT2i + nonsteroidal MRA)
 - Studied in combo with ACEI/ARB –only a small subset in the studies were also on SGLT2i

eGFR $\geq$ 25mg/min/1.73m²

Normal K⁺

Persistent albuminuria despite max tolerated ACE/ARB

KDIGO Practice Point 1.4.5. A **steroidal** MRA should be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.

11.4 Optimize blood pressure control and reduction in BP variability to reduce the risk or slow the progression of chronic kidney disease. A

The higher the BP, the higher the risk of progression of DKD & CVD events

Increasing data supporting aim for <120/80 whenever tolerated – based on ***standardized*** BP measurement (not routine clinical measurement)

- ADA Standards of Care for Hypertension/ Blood Pressure Control
 - 10.3 For patients with diabetes and HTN, **BP targets should be individualized** through a *shared decision-making process* that addresses CV risk, potential adverse effects of anti-hypertensive medications & patient preference. B
 - 10.4 For individuals with ***diabetes & HTN at higher CV risk*** (existing ASCVD or 10 y ASCVD risk >15%), a **BP target of <130/80 mmHg may be appropriate** if it can be safely attained. B
 - 10.5 For individuals with diabetes & HTN at lower risk for CVD (<15% 10-y ASCVD risk), treat to a BP target of **<140/90 mmHg** A

Optimize blood pressure control to reduce the risk or slow the progression of chronic kidney disease ADA Standards of Care

*“Postural changes in blood pressure and pulse may be evidence of **autonomic neuropathy** and therefore require adjustment of blood pressure targets.*

***Orthostatic blood pressure** measurements should be **checked on initial visit** and as indicated”*

- *“Patients with a **history of or at risk for adverse effects** should have a higher BP target (hypotension/syncope, electrolyte abnormalities, AKI)
 - *In such patients, a **BP target of <140/90 mmHg** is recommended, if it can be safely attained.”**

Treatment (ADA Standards of Care)

- 11.7 In non-pregnant patients with *diabetes and hypertension*, either an **ACE inhibitor or an angiotensin receptor blocker (ARB)** is recommended for those with **modestly elevated UACR (30-299 mg/g creatinine)** B and is **strongly** recommended for those with **UACR $\geq$ 300 mg/g creatinine** and/or **eGFR $<$ 60 ml/min/1.73m²**. A
 - Aim for **maximally tolerated doses** for the most benefit $\rightarrow$ reduced risk for progression to ESRD & reduced risk of cardiovascular event
- 11.8 Periodically **monitor serum creatinine and potassium levels** for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers or diuretics are used. B
- 11.9 An ACE inhibitor or an ARB is **not recommended** for the **primary prevention** of chronic kidney disease *in patients with diabetes who have normal blood pressure, normal UACR and normal eGFR*. A

“The combined use of ACE inhibitors and ARBs should be avoided.”

Two clinical trials found no benefits on CVD or CKD and the combination had higher adverse event rates [hyperkalemia and/or AKI]

Treatment (ADA Standards of Care)

- 11.6 For people with nondialysis-dependent stage 3 or higher CKD, **dietary protein intake** should be a maximum of **0.8 g/kg*** body weight per day (the recommended daily allowance). A (1.0 g/kg/d if nephrotic range proteinuria)
 - For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients. B
- ** Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss and CVD mortality and therefore should be avoided.*
- *Reducing intake to below the RDA of 0.8 g/kg/day provides no additional benefit for glycemia, CVD risk or the course of GFR decline*

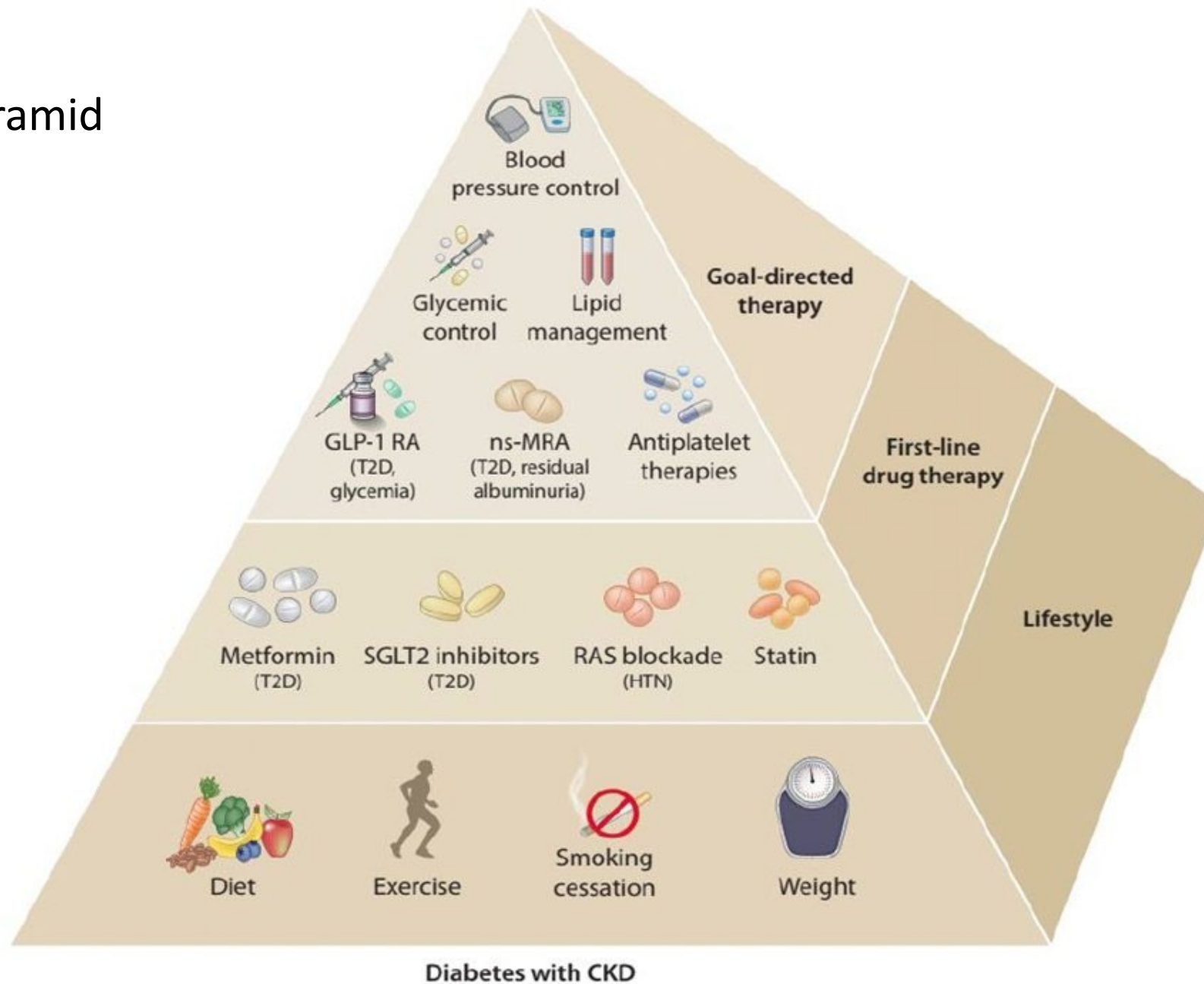
Malnutrition is a risk factor for decline in eGFR

KDIGO

guideline for clinicians caring for patients with diabetes and CKD

- These patients should undertake ***moderate-intensity physical activity*** for a cumulative duration of **at least 150 minutes/week**, or to cardiovascular and physical tolerance, and should be counseled to ***avoid sedentary behavior***.
 - Reduce frailty, disability, mortality
 - Muscle activity helps protect renal function (inflammation, fibrosis, other)
- **Sodium intake** should be less than 2 g/day (<90 mmol sodium/day; <5 g sodium chloride/day) in patients with diabetes and CKD. (CKD retain sodium so need to restrict)
- People with diabetes and CKD should have a **structured self-management educational program**.
- For comprehensive care of patients with diabetes and CKD, policy makers and institutional decision-makers should implement ***team-based, integrated care*** highlighting risk evaluation and patient empowerment.

KDIGO pyramid

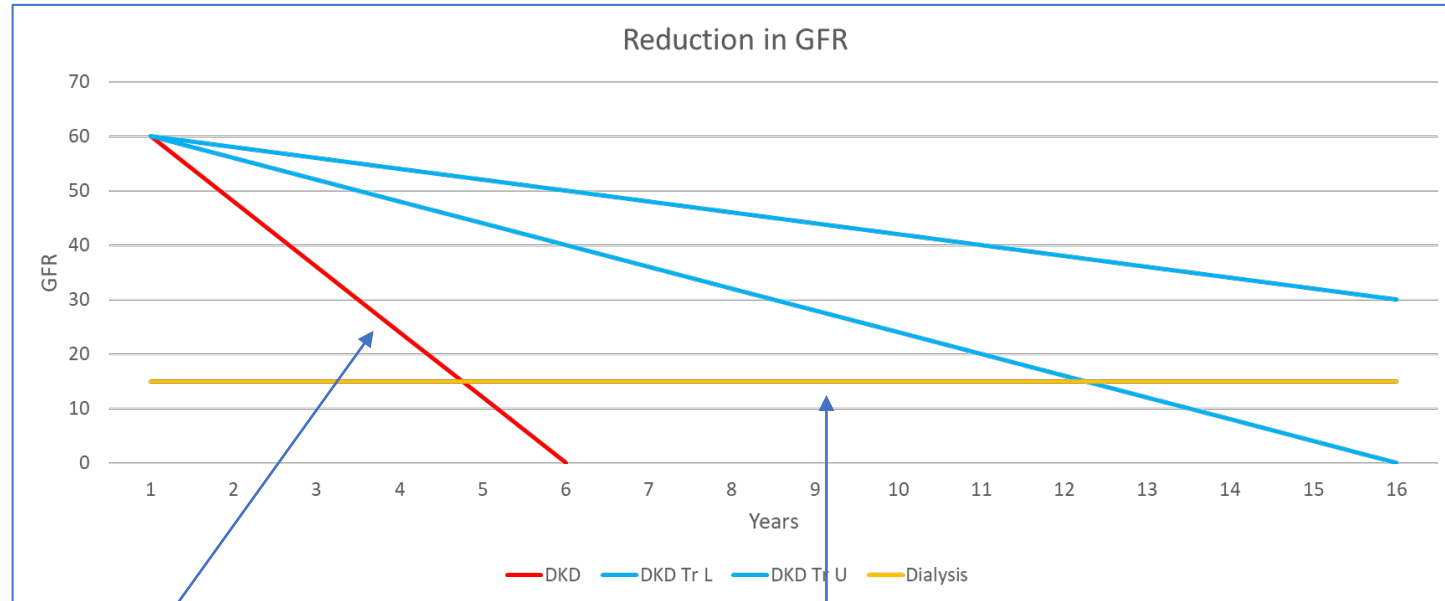


Based on survey done by NKF

- Physicians might consider initiating **risk vs. benefit conversations with patients** when prescribing a new medication to slow disease progression.
 - In order of importance, patients considered the **most critical factors in the decision** of taking a new medication
 - the severity of known adverse events (60.6% very important),
 - the cost or insurance (57.9% very important) and
 - **what their doctor recommends** (55.4% very important)
 - Patients were least concerned about how often they would have to take the medication.

Are you comfortable having that conversation?

Slowing Down the Loss of Kidney Function with Diabetes Kidney Disease



This is how quickly your kidneys will lose function without any treatment

The yellow line is the level where you need to start dialysis

The aqua lines show how much treatment can reduce the rate at which your kidneys lose function

Treatment includes

- Optimal blood pressure, using an ACEI or ARB medication along with other meds if needed
- An SGLT2 inhibitor medication (and/or a GLP1 RA or MRA)
- Blood glucose levels in individualized safe range
- Avoiding drugs that hurt your kidneys such as NSAIDs (ibuprofen, Advil, Motrin, etc.)
- Keeping your muscles strong, avoiding being too sedentary
- Healthy food choices – especially, avoid excess animal protein & fats

Summary – Slowing the Progression of DKD in people with T2D

- Begin the conversation early – consider use of visual aids
 - Late (more advanced stage) treatment is still very beneficial – very often do not receive beneficial Rx
- Lifestyle factors often neglected but are foundational to improve outcomes (smoking, food choices/diet, reduced sedentary time/activity [muscle], weight control)
- Proven benefit of combining ACEI/ARB & SGLT2i
 - Push ACEI/ARB to maximal tolerated dose
 - Add SGLT2i even if no (or minimal) glycemic benefit (eGFR <45)
 - Add SGLT2i even if A1c at goal – if eGFR >45, may need to reduce hypoglycemic meds
 - If patient can't tolerate ACEI/ARB, still use SGLT2i (still beneficial)
 - Become familiar & comfortable with SGLT2i med use (if unsure, consider eConsult)

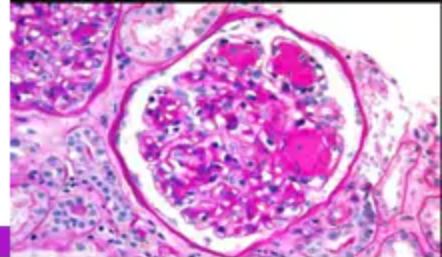


Extra Slides

Pharmacologic Therapy for Adults with T2D

- 9.9 Among individuals with T2D who have **established ASCVD** or indicators of **high cardiovascular risk**, established **kidney disease** or **heart failure** a **SGLT2i** and/or **GLP1 RA with demonstrated CVD benefit*** is recommended as part of the glucose-lowering regimen and the comprehensive CV risk reduction, independent of A1c and in consideration of patient-specific factors. A
- 9.10 In patients with T2D, a **GLP1 RA is preferred to insulin** when possible. A
- 9.11 If insulin is used, combination with a GLP1 RA is recommended for greater efficacy and durability of treatment. A
- *liraglutide, semaglutide (SQ) & dulaglutide
 - Demonstrated CVD benefit, some renal benefit (albuminuria) – trials ongoing
 - No dose adjustment for renal impairment
 - Glycemic benefit even at reduced GFR (unlike SGLT2i)
- Limited by cost & tolerability
- Combination therapy with SGLT2i & GLP1 RA appears to have additive CVD protection

Factors Guiding Decisions on Target A1C



< 6.5%	HbA1c	< 8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

- Glycemic targets should be individualized (<6.5% to as high as <8%) .
- For some patients, metrics derived from CGM (such as time in range, 70–180 mg/dl [3.9–10.0 mmol/l]) may serve as appropriate treatment targets, in addition to or instead of hemoglobin A1c
- Consider medications not associated with hypoglycemia for treatment of T2DM for aggressive glycemic targets for appropriate patients

CKD in T2DM: Screening Frequency and Referral

		Albuminuria →		
		Normal to mildly increased <30 mg/g	Moderately increased 30-299 mg/g	Severely increased ≥300 mg/g
↓ Estimated glomerular filtration rate	Normal or high ≥90 mL/min/1.73 m ²	If CKD 1 screening visit/year	Treat CKD 1 screening visit/year	Consult Nephrologist 2 screening visits/year
	Mildly decreased 60-89 mL/min/1.73 m ²	If CKD 1 screening visit/year	Treat CKD 1 screening visit/year	Consult Nephrologist 2 screening visits/year
	Mildly to moderately decreased 45-59 mL/min/1.73 m ²	Treat CKD 1 screening visit/year	Treat CKD 2 screening visits/year	Refer to Nephrologist 3 screening visits/year
	Moderately to severely decreased 30-44 mL/min/1.73 m ²	Treat CKD 2 screening visits/year	Treat CKD 3 screening visits/year	Refer to Nephrologist 3 screening visits/year
	Severely decreased 15-29 mL/min/1.73 m ²	Consult Nephrologist 3 screening visits/year	Consult Nephrologist 3 screening visits/year	Refer to Nephrologist >4 screening visits/year
	Kidney failure <15 mL/min/1.73 m ²	Refer to Nephrologist >4 screening visits/year	Refer to Nephrologist >4 screening visits/year	Refer to Nephrologist >4 screening visits/year

Fig. 1 Risk of CKD progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best (green) through yellow,

orange, and red to worst (dark red). *CKD* Chronic kidney disease. Modified from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [61], copyright 2013, with permission from Elsevier

ADA Living Standards of Care

Addendum to Section 10, "Cardiovascular Disease and Risk Management"

- "For patients with type 2 diabetes and chronic kidney disease treated with maximum tolerated doses of ACE inhibitors or angiotensin receptor blockers, addition of finerenone should be considered to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. A"
- "Patients with type 2 diabetes and chronic kidney disease should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of chronic kidney disease progression."
- "In patients with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, an SGLT2 inhibitor [with proven benefit in this patient population] is recommended to reduce risk of worsening heart failure, hospitalizations for heart failure, and cardiovascular death. A"

KDIGO recommendations about Non-Steroidal MRA

- Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an $\text{eGFR} \geq 25 \text{ ml/min/1.73 m}^2$, normal serum potassium concentration, and albuminuria despite maximum tolerated dose of RAS inhibitor. (2A)
 - Practice Point 1.4.1: Nonsteroidal MRAs are most appropriate for patients with T2D who are at high risks of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard of care therapies.
 - Practice Point 1.4.2. In general, SGLT2i should be initiated prior to adding a nonsteroidal MRA for treatment of T2D and CKD.
 - Practice Point 1.4.3. To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.
 - Practice Point 1.4.4. The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.
 - Practice Point 1.4.5. A ***steroidal*** MRA should be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.

Yang S, Zhao L, Mi Y, He W. Effects of sodium-glucose cotransporter 2 inhibitors and aldosterone antagonists, in addition to renin-angiotensin system antagonists on major adverse kidney outcomes in patients with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. Published online June 16, 2022. doi:10.1111/dom.14801

- Compared with no treatment or placebo,
 - use of SGLT2 inhibitors in combination with RAS inhibitors was significantly associated with 38% decreased odds of the composite kidney outcome
 - use of the nonsteroidal MRA finerenone in combination with RAS inhibitors was significantly associated with 24% decreased odds of the composite outcome
- The addition of SGLT2 inhibitors or nonsteroidal MRA significantly decreased the odds of heart failure hospitalization by 43% and 22%, respectively, compared with placebo.
 - Use of SGLT2 inhibitors rather than nonsteroidal MRA was significantly associated with 27% decreased odds of heart failure hospitalization
 - SGLT2 inhibitors also were significantly associated with 20% decreased odds of cardiovascular death and
 - 21% decreased odds of all-cause mortality compared with placebo or no treatment.

Yang S, Zhao L, Mi Y, He W. Effects of sodium-glucose cotransporter 2 inhibitors and aldosterone antagonists, in addition to renin-angiotensin system antagonists on major adverse kidney outcomes in patients with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab*. Published online June 16, 2022. doi:10.1111/dom.14801

- Treatment with a nonsteroidal MRA (eg, finerenone) or a non-selective aldosterone antagonist (eg, spironolactone) was significantly associated with 2.3- and 3.2-fold increased odds of hyperkalemia, respectively, compared with placebo or no treatment. These 2 drug classes were significantly associated with 2.7- and 3.9-fold increased odds of hyperkalemia, respectively, compared with SGLT2 inhibitors.
- Non-steroidal MRA was significantly associated with 16.6- and 23.8-fold increased odds of hyponatremia compared with placebo and SGLT2 inhibitors, respectively.
- Close monitoring of potassium and sodium levels is warranted in patients taking an MRA in combination with RAS blockade, according to Yang's team.
- SGLT2 inhibitors were significantly associated with 1.3-fold increased odds of volume reduction. These drugs should not be used in patients with unstable volumetric status or hypovolemia, Yang's team noted.
- The investigators found no increased risk of AKI. According to a SUCRA score analysis, SGLT2 inhibitors were the better choice to reduce the odds of AKI, hyperkalemia, and hyponatremia.

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- ADA Standards of Care 2022: https://diabetesjournals.org/care/issue/45/Supplement_1
- In Depth Article (also available as 2-hour Webinar) [Expert Insights for Primary Care Physicians in Managing Chronic Kidney Disease in T2DM \(medscape.org\)](#)
- Review Diabetes Obes Metab. 2019 Jun;21(6):1291-1298. doi: 10.1111/dom.13670. Epub 2019 Mar 15. Uric acid and the cardio-renal effects of SGLT2 inhibitors Clifford J Bailey PMID: 30762288 DOI: 10.1111/dom.13670
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- Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. Diabetes Obes Metab. 2019 May; 21(5): 1237-1250. Toyama T et al,

Andrassy KM. Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease'. *Kidney Int.* 2013;84:622–3.

- Effective detection and early intervention in DN can help to slow renal function decline. It can also prevent complications, thus improving survival and quality of life in type 2 diabetics. Annual decline in glomerular filtration rate (GFR) in a person varies widely depending on various factors such as ethnicity, age, underlying medical problems, the etiology of chronic kidney disease (CKD), and the presence of comorbidities. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define rapid progression as rate of eGFR declines > 5 mL/min per 1.73m^2 per year [1, 2]. The classical progression of DN is deterioration of renal function over decades with typical rate of GFR decline ranges from between 2 to 20 mL/min per 1.73m^2 per year with a median of 12 mL/min per year [3]. In our report, heavy amount of proteinuria, beside the traditional risk factors like poor glycemic control, hypertension are the leading risk factors for rapid progression of renal disease.

Reference on safety of Empa in CKD

- Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials
- Katherine R. Tuttle; Adeera Levin; Masaomi Nangaku; Takashi Kadowaki; Rajiv Agarwal; Sibylle J. Hauske; Amelie Elsässer; Ivana Ritter; Dominik Steubl; Christoph Wanner; David C. Wheeler
- Diabetes Care 2022;45(6):1445–1452
- <https://doi.org/10.2337/dc21-2034>

Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials

Katherine R. Tuttle Diabetes Care dc212034

<https://doi.org/10.2337/dc21-2034>

- Tuttle et al assess the safety profile of empagliflozin in type 2 diabetic patients with chronic kidney disease (CKD) G3A, G3B and G4 in a pooled analysis across 19 randomized, placebo-controlled trials. The rates of serious adverse events (SAEs) were similar across all stages of CKD compared to placebo, though when stratified by stage, rates were higher in CKD G4; however, their low numbers and wide confidence intervals make these data difficult to interpret. Importantly, rates of drug discontinuation due to SAE, in addition to clinically relevant events such as bone fracture and lower limb amputation, were similar amongst both groups regardless of the stage of CKD. Although hypoglycemia becomes more common as estimated glomerular filtration rate (eGFR) declines and insulin clearance decreases, treated patients did not have significantly higher rates of hypoglycemia. Interestingly, rates of edema and hyperkalemia—common occurrences in the CKD population—were reduced in the intervention arm, although volume depletion and acute renal failure were not increased. Unfortunately, due to low incidence rates, this study was unable to assess the rates of euglycemic diabetic ketoacidosis, which a serious, though rare side effect of sodium–glucose cotransporter 2 inhibitors.
- Empagliflozin is safe in patients with type 2 diabetes with reduced renal function up to CKD G4. Given the safety profile and benefit in edema and hyperkalemia, prescribers should feel comfortable prescribing even for patients with reduced eGFR. The safety of empagliflozin in other non-diabetic forms of kidney disease still needs to be addressed

Lower risk of hyperkalemia, edema & gout with SGLT2i

- Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials Katherine R. Tuttle, et al **Diabetes Care** dc212034 <https://doi.org/10.2337/dc21-2034>
- <https://pubmed.ncbi.nlm.nih.gov/31931526/> Ann Intern Med. 2020 Feb 4;172(3):186-194. doi: 10.7326/M19-2610. Epub 2020 Jan 14. Assessing the Risk for Gout With Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes: A Population-Based Cohort Study Michael Fralick, Sarah K Chen, Elisabetta Patorno, Seoyoung C Kim PMID: 31931526 PMCID: PMC7217750 DOI: 10.7326/M19-2610

Initial Decline in eGFR After Dapagliflozin Initiation and Its Associated Outcomes in Patients With HFrEF

Journal Scan / Research · May 12, 2022, Circulation

- TAKE-HOME MESSAGE

- In this post hoc analysis of the DAPA-HF trial including more than 4000 participants with HFrEF, the mean changes in estimated glomerular filtration rate (eGFR) between days 0 and 14 were $-1.1 \text{ mL/min/1.73m}^2$ and $-4.2 \text{ mL/min/1.73m}^2$ with placebo and dapagliflozin, respectively. Overall, 38.2% of patients — with older age, lower baseline eGFR, higher LVEF, and type 2 diabetes — experienced a $>10\%$ early decline in eGFR with dapagliflozin compared with placebo (OR, 2.36). In the dapagliflozin group, a $>10\%$ initial decline in eGFR was associated with a 27% reduced risk of the primary outcome compared with those with a $\leq 10\%$ decline (HR, 0.73).
- These findings highlight that an early decline in eGFR following dapagliflozin initiation is common, small, and associated with better clinical outcomes in patients with HFrEF.
- Overview written by Steven G. Coca DO, MS
- The hyperfiltration theory of progressive kidney damage is one of the most seminal hypothesis in nephrology.¹ This theory is one of the major mechanisms purported to be operative in renoprotection mediated by antagonists of the renin-angiotensin-aldosterone system, in which a decrease angiotensin-mediated vasoconstriction of the efferent arteriole results in reductions in intraglomerular pressures, and while first abruptly lowering GFR in some, results in long-term improvement in kidney outcomes.² The sodium-glucose cotransporter-2 (SGLT2) inhibitors have also been shown to improve intraglomerular pressures, partially mediated through tubuloglomerular feedback and vasoconstriction of the afferent arterioles.³
- In the post-hoc analysis of the DAPA-HF trial, average eGFR dips, and association of dichotomized dips ($>10\%$ decline in eGFR) in the placebo and dapagliflozin arms with the clinical outcomes were examined.⁴ As shown repeatedly in the literature, in patients with HFrEF, acute declines in eGFR, whether due to RAAS antagonists, aggressive decongestion, and now due to SGLT2i, the “treatment-induced declines” in eGFR are well-tolerated, and often are associated with better outcomes.⁵
- What is remarkable in this analysis of the DAPA-HF trial is that those that had $> 10\%$ decrease in eGFR (38% of dapa-treated), $>20\%$ decrease (13% of dapa-treated), and $> 25\%$ decrease (7% in dapa-treated), changes that in clinical practice may cause clinicians to react with panic and potentially discontinue the SGLT2i due to “hypercreatinemia-phobia”, was associated with 18-39% reduction in risk in the primary outcome. While mechanisms to explain why this profound protection would occur with lowering of GFR (e.g., improvements in metabolic demand, oxygenation of kidney tissue, mitochondrial function), it serves as yet another example to practice a “zen-like” approach to medicine and allow permissive hypercreatinemia prevail in treatment of this high-risk patients to allow for improved clinical outcomes.⁶

For Patients & Families

- <https://www.kidneyfund.org/kidney-disease/chronic-kidney-disease-ckd/stages-of-chronic-kidney-disease/>
- [11-10-1813 abe patbro gfr b.pdf \(kidney.org\)](#)

CKD in T2DM: Screening Frequency and Referral

		Albuminuria		
		Normal to mildly increased <30 mg/g	Moderately increased 30-299 mg/g	Severely increased ≥300 mg/g
Estimated glomerular filtration rate ↓	Normal or high ≥90 mL/min/1.73 m ²	If CKD 1 screening visit/year	Treat CKD 1 screening visit/year	Consult Nephrologist 2 screening visits/year
	Mildly decreased 60-89 mL/min/1.73 m ²	If CKD 1 screening visit/year	Treat CKD 1 screening visit/year	Consult Nephrologist 2 screening visits/year
	Mildly to moderately decreased 45-59 mL/min/1.73 m ²	Treat CKD 1 screening visit/year	Treat CKD 2 screening visits/year	Refer to Nephrologist 3 screening visits/year
	Moderately to severely decreased 30-44 mL/min/1.73 m ²	Treat CKD 2 screening visits/year	Treat CKD 3 screening visits/year	Refer to Nephrologist 3 screening visits/year
	Severely decreased 15-29 mL/min/1.73 m ²	Consult Nephrologist 3 screening visits/year	Consult Nephrologist 3 screening visits/year	Refer to Nephrologist >4 screening visits/year
	Kidney failure <15 mL/min/1.73 m ²	Refer to Nephrologist >4 screening visits/year	Refer to Nephrologist >4 screening visits/year	Refer to Nephrologist >4 screening visits/year

Fig. 1 Risk of CKD progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best (green) through yellow,

orange, and red to worst (dark red). *CKD* Chronic kidney disease. Modified from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [61], copyright 2013, with permission from Elsevier

- <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.048057>
- Vol. 142, No. 11 Sodium-Glucose Cotransporter-2 Inhibitors and Loop Diuretics for Heart Failure
- Sodium-Glucose Cotransporter-2 Inhibitors and Loop Diuretics for Heart Failure; Priming the Natriuretic and Metabolic Reserve of the Kidney
- Justin L. Grodin and W.H. Wilson Tang
- Originally published 14 Sep 2020 <https://doi.org/10.1161/CIRCULATIONAHA.120.048057> Circulation. 2020;142:1055–1058

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