SGLT-2 Inhibitors and Diabetic Kidney Disease

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Objectives

- Epidemiology of diabetic kidney disease
- Treatment of diabetic kidney disease
- Recommendations for use of SGLT-2 inhibitors in clinical guidelines
- Mechanism of action of SGLT-2 inhibitors
- Advantages and indications for use of SGLT-2 inhibitors
- Dosing of available SGLT-2 inhibitors and adjustment for renal function
- Adverse effects of SGLT-2 inhibitor use and patient counseling
- Monitoring of a patient on an SGLT-2 inhibitor

Epidemiology of Diabetic Kidney Disease

- CKD is diagnosed by presence of:
  - Persistent elevation of urinary albumin excretion (albuminuria)
  - Low estimated glomerular filtration rate (eGFR)
  - Other manifestations of kidney damage
- Occurs in 20-40% of patients with diabetes
- Diabetic kidney disease 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 blood pressure variability
- ACE inhibitor or angiotensin receptor blocker (ARB)
- ***Sodium-glucose cotransporter 2 (SGLT-2) inhibitors***
  - In patients who cannot tolerate SGLT-2 inhibitors, consider finerenone (a nonsteroidal mineralocorticoid receptor antagonist)

American Diabetes Association Standards of Medical Care in Diabetes - 2022

Chronic Kidney Disease and Risk Management

11.3a For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥25 mL/min/1.73 m^2 and urinary albumin ≥300 mg/g creatinine is recommended to reduce chronic kidney disease progression and cardiovascular events. **A**

11.3b In patients with type 2 diabetes and chronic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors additionally for cardiovascular risk reduction when estimated glomerular filtration rate and urinary albumin creatinine are ≥25 mL/min/1.73 m^2 or ≥300 mg/g, respectively (**Fig. 9.3**). **A**

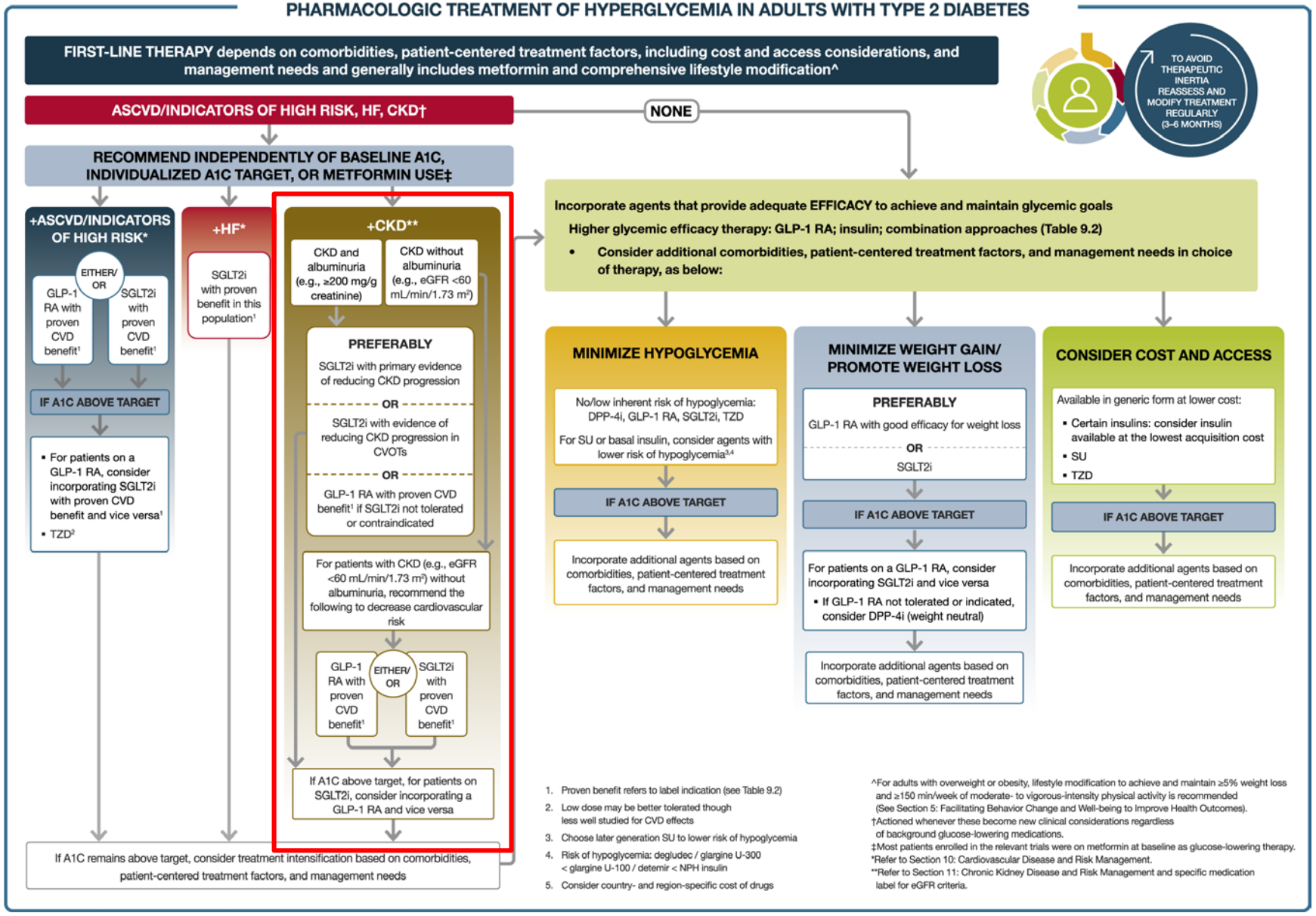
WELL-AHEAD

Project ECHO

American Diabetes Association®

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022**

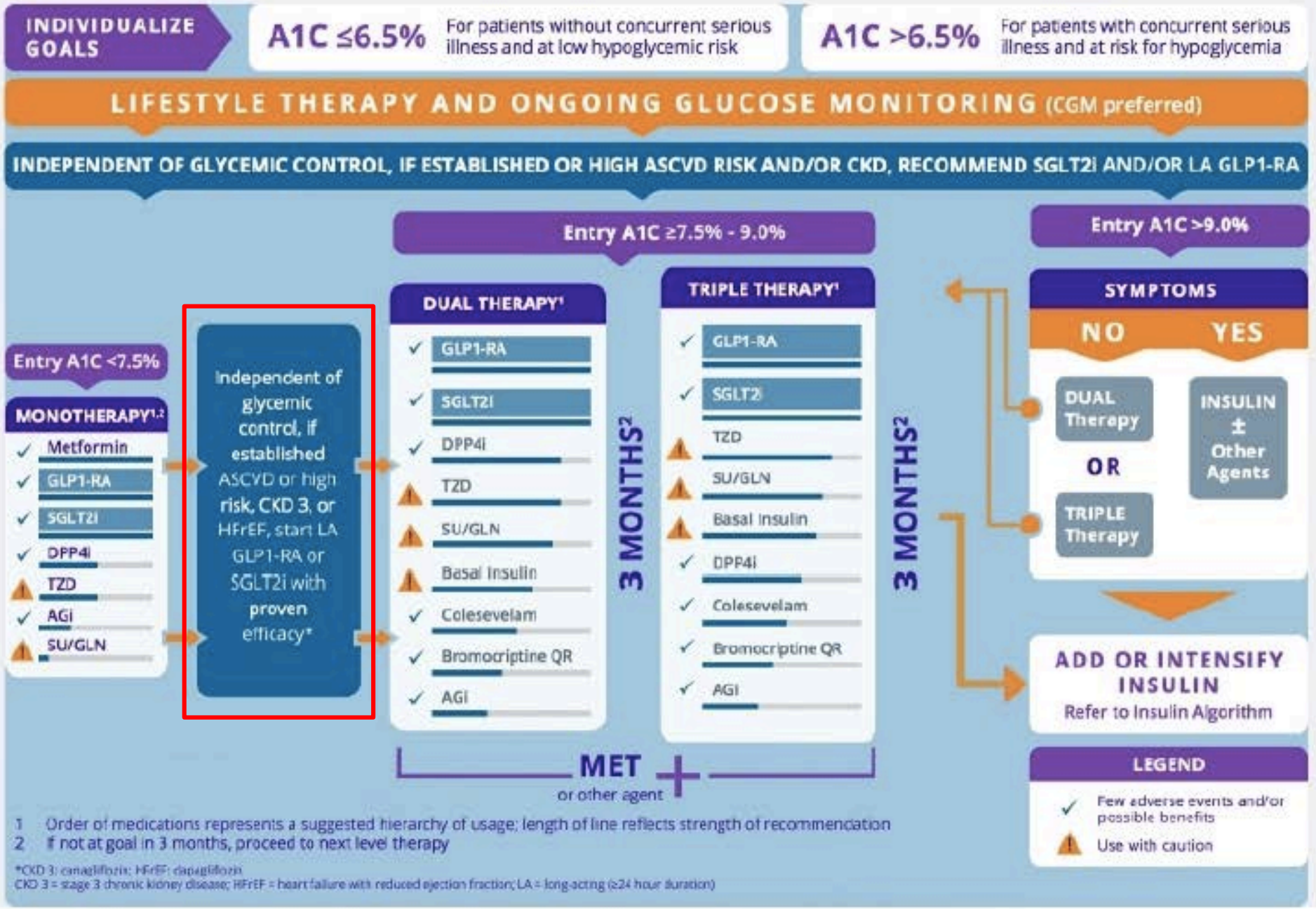
Diabetes Care. 2021;45(Supplement_1):S125-S143. doi:10.2337/dc22-S009



COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM (2020)

https://pro.aace.com/disease-state-resources/diabetes/ guidelines

GLYCEMIC CONTROL ALGORITHM



Mechanism of Action of SGLT-2 Inhibitors

Lower the renal threshold for glucose excretion

Suppress renal glucose reabsorption

Increase urinary glucose excretion

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

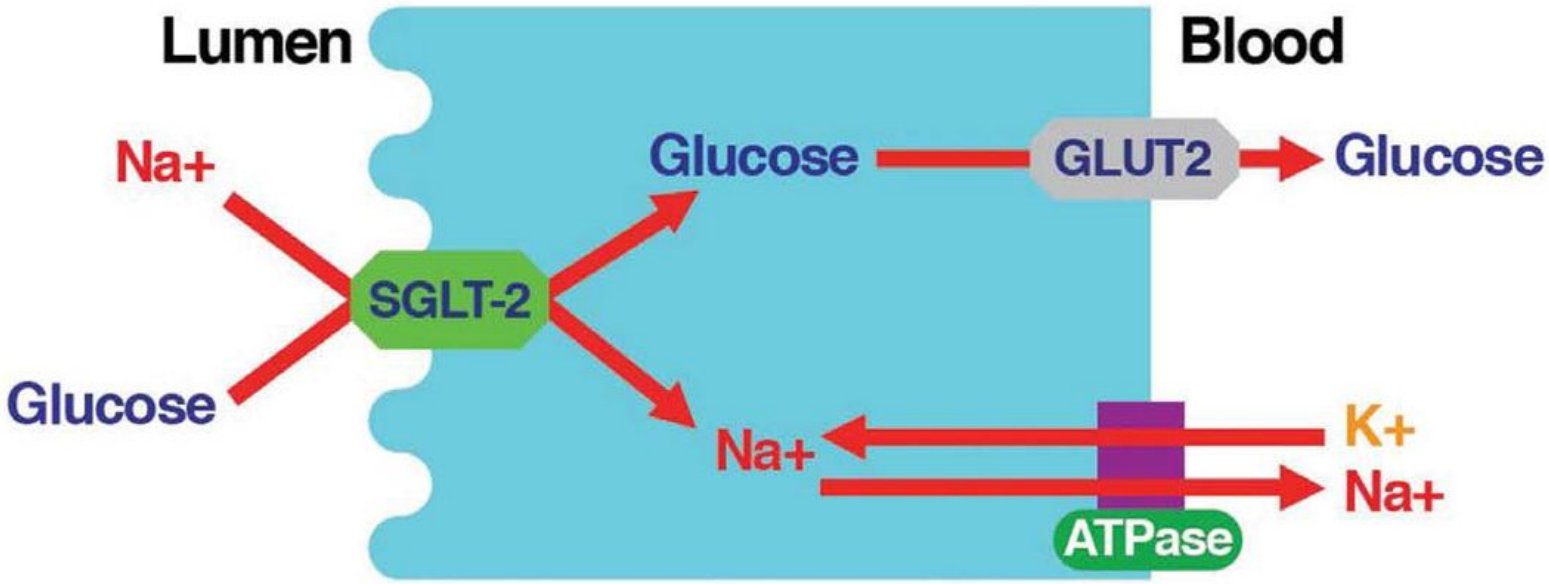


Figure Legend:

SGLT-2 mediates glucose reabsorption in the kidney. SGLT-2 catalyzes the active transport of glucose (against a concentration gradient) across the luminal membrane by coupling it with the downhill transport of Na+. The inward Na+ gradient across the luminal epithelium is maintained by active extrusion of Na+ across the basolateral surface into the intracellular fluid. Glucose diffuses out of the cell down a concentration gradient via the basolateral facilitative transporter GLUT2.[20] Adapted from Ref. 20.

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

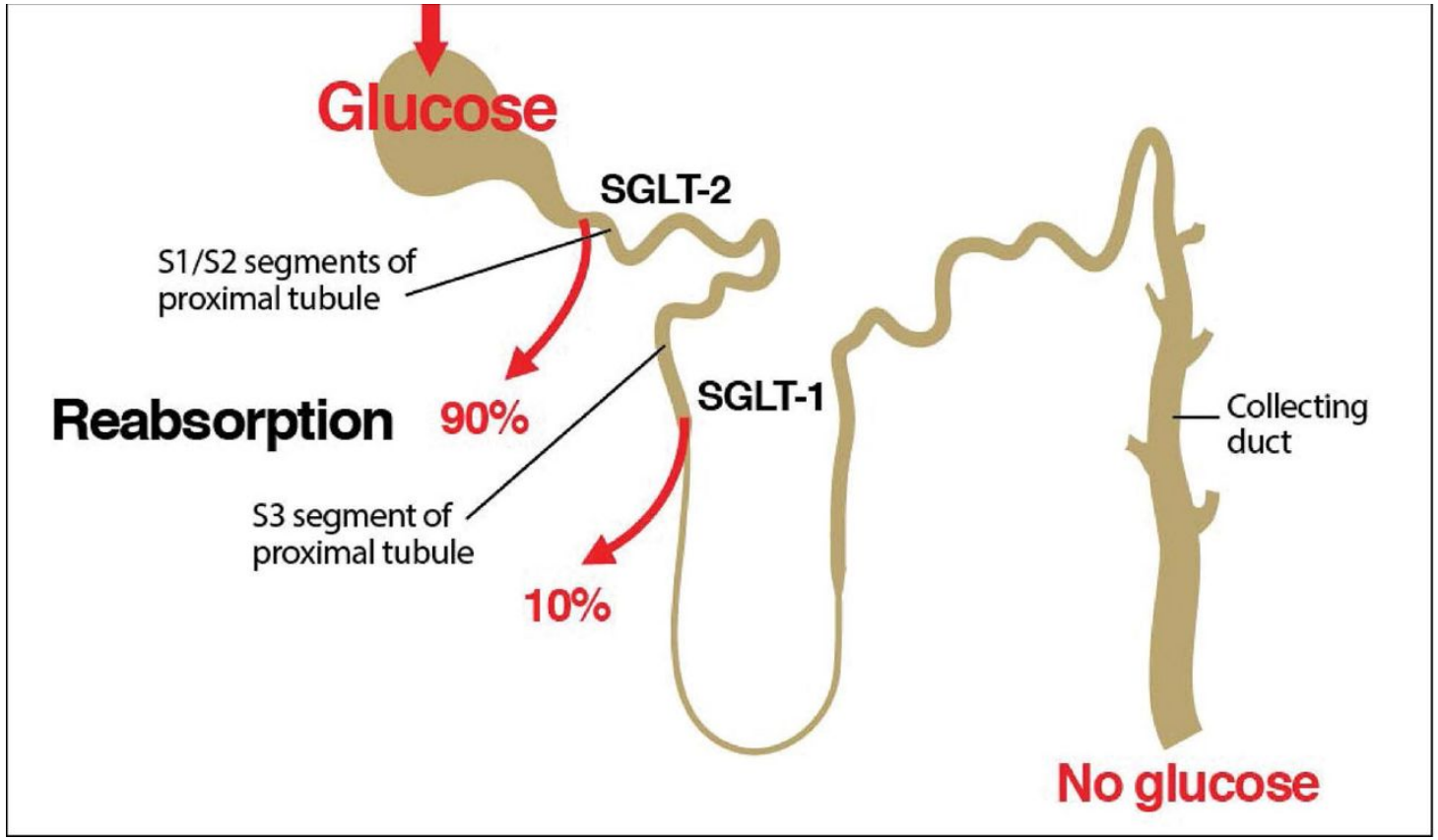


Figure Legend:

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]

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

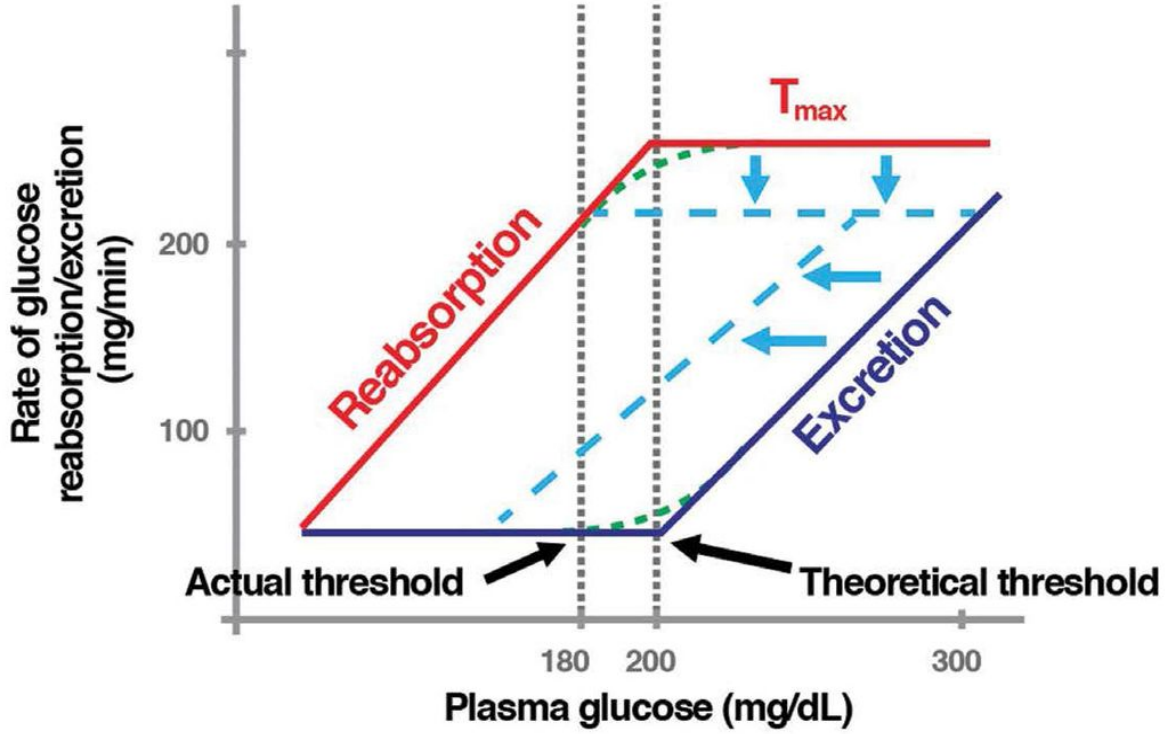


Figure Legend:

Renal glucose handling before and following inhibition of SGLT-2. As the plasma glucose concentration increases, renal glucose reabsorption increases, following the line marked "Reabsorption" (in red). At plasma glucose concentrations greater than ~ 200 mg/dl, all the filtered glucose is reabsorbed, and there is no excretion. When glucose reaches a threshold, at ~ 200 mg/dl, the maximum capacity of the renal tubule to reabsorb glucose—or T_{max}—is exceeded. Once past this threshold, glucose begins to be excreted via the urine (dark blue line, labeled "Excretion"). The actual thresholds for both reabsorption and excretion differ from the theoretical thresholds because of physiological variation among individual nephrons (i.e., slight differences in their glucose-handling abilities). This is known as "splay" (green dashed lines). The dashed light blue lines depict renal glucose handling after SGLT-2 inhibition. SGLT-2 inhibitors lower the renal glucose threshold, leading to urinary glucose excretion.[16] Adapted from Ref. 16.

Advantages of SGLT-2 Inhibitors

- Improve hyperglycemia (A1c reduction of 0.5-0.7%)
  - Effective at any degree of insulin resistance or beta cell dysfunction
- Act independently of insulin and confer no risk of hypoglycemia
- 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	Average monthly cost (max dose)
Empagliflozin	Yes	Yes	Yes	$658
Canagliflozin	Yes	Yes	Yes	$652
Dapagliflozin	Yes	No	Yes	$639
Ertugliflozin	No	No	Yes	$372

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

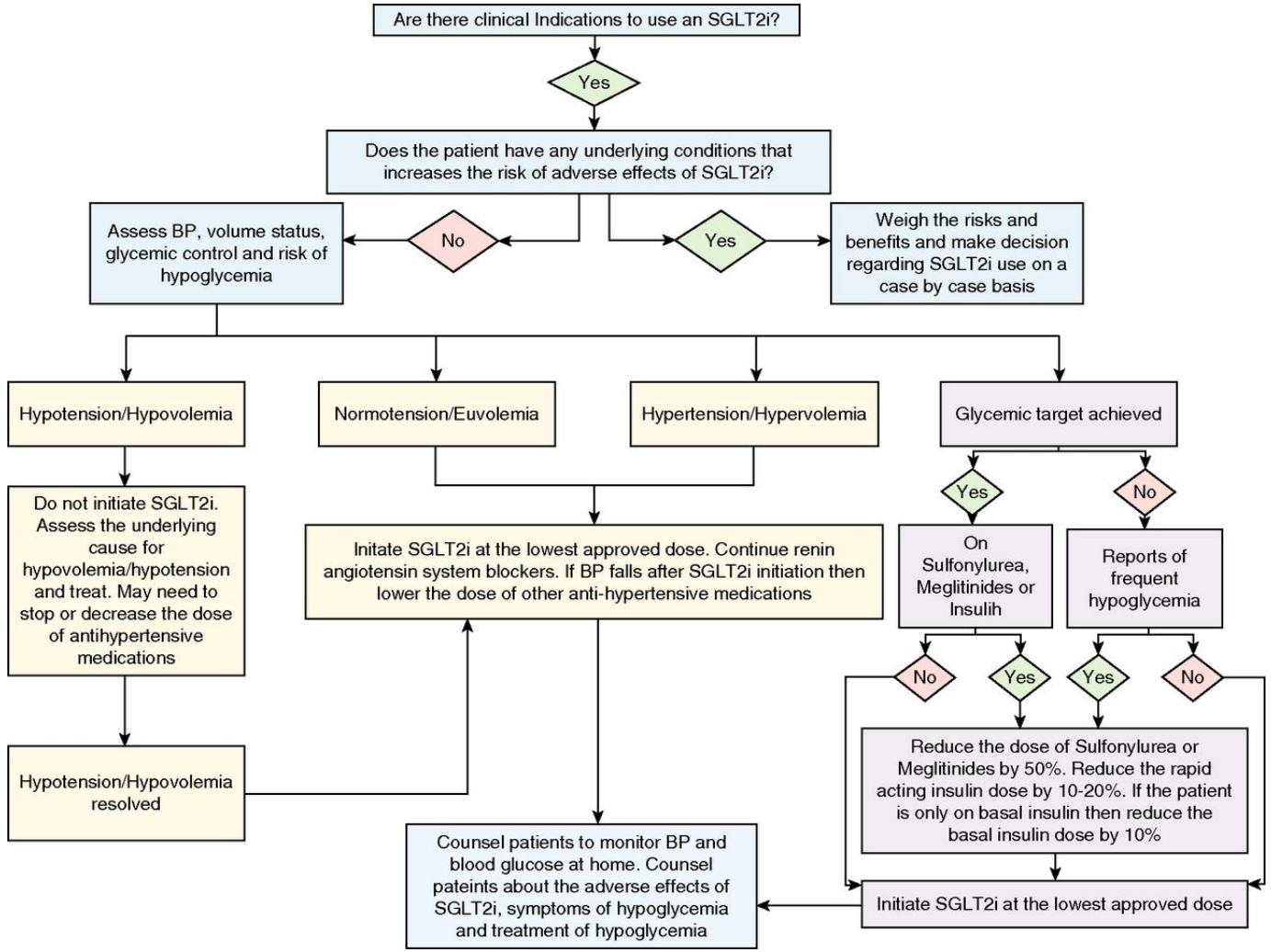
SGLT2 inhibitors have less glycemic benefit in patients with more severe kidney disease at initiation

	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	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

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. Has not been seen in other large trials of SGLT-2 inhibitors.

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

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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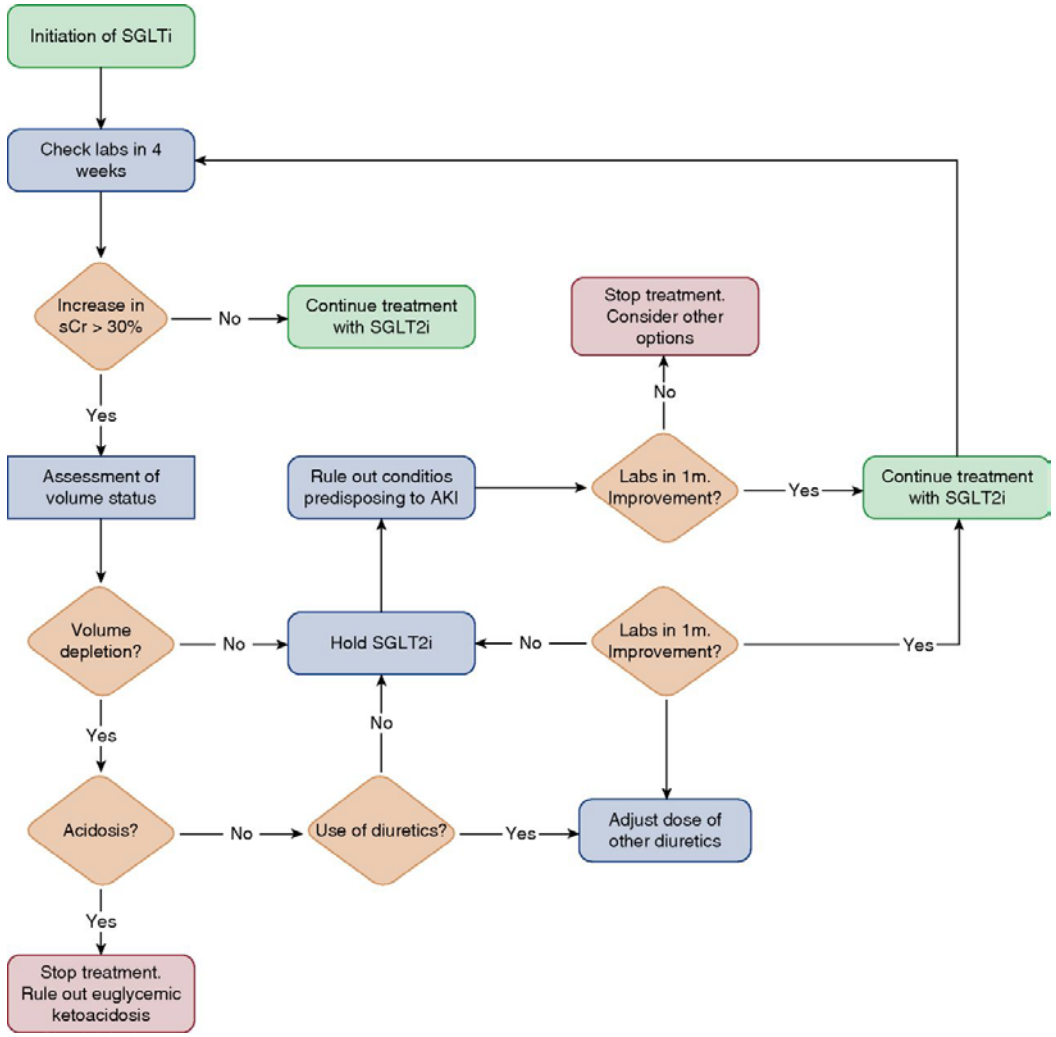
What to expect?

- 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
- Followed by attention of the slope of eGFR decline when compared to placebo
- If decrease in eGFR is > 30%, look for other factors that may be contributing

How does decrease in eGFR lead to nephroprotection?

- This is believed to be a hemodynamic effect, and is not related to direct renal injury.
- Decrease in hyperfiltration in the nephron → less proteinuria and glomerular sclerosis

Proposed algorithm for initiation and surveillance of treatment with SGLT2is.



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

Future of SGLT-2 Inhibitors

- Use in non-diabetic patients with CKD?
- Agents that inhibit both SGLT-1 and SGLT-2
- Treatment of HFrEF and HFpEF

Summary

- SGLT-2 inhibitors should be use in all patients with diabetic kidney disease
- Benefits include improvement in Hgb A1c, delayed progression of CKD, and improvement in cardiovascular outcomes
- Doses may need adjustment for declines in eGFR
- Monitor for development of adverse effects of the medication
- Expect a mild, early decline in eGFR after initiating an SGLT-2 inhibitor. This effect is expected to plateau and is not an indication for discontinuing the drug.

References

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