| | Canagliflozin | Dapagliflozin | Empagliflozin |
|---|---|---|---|
| **eGFR Cut-Off for Initiation** | | | |
| **Dose** | | | |
| **Renal Benefits** | | | |
| **Use in Type 2 Diabetes Only?** | | | |

# SGLT“2” Good to be True?
# Renal Outcomes of SGLT2 Inhibitors

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# Disclosure

- The speaker has no conflicts of interest to disclose
- Non-FDA approved indications will be discussed

# Learning Objectives

1. Outline current guidelines and the role of SGLT2 inhibitors in kidney disease
2. Review the literature regarding SGLT2 inhibitors and their place in patients with kidney disease
3. Define optimal patients to initiate on SGLT2 inhibitors

# Chronic Kidney Disease

- Chronic kidney disease (CKD) defined as abnormalities of kidney structure or function for > 3 months
- Diabetes (DM) is the leading cause of kidney failure




KDIGO Diabetes Work Group. Kidney Int. 2020 Oct;98(4S):S1-S115.
Alicic RZ, et al. Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2032-2045.

# KDIGO 2020 Guideline for DM in CKD

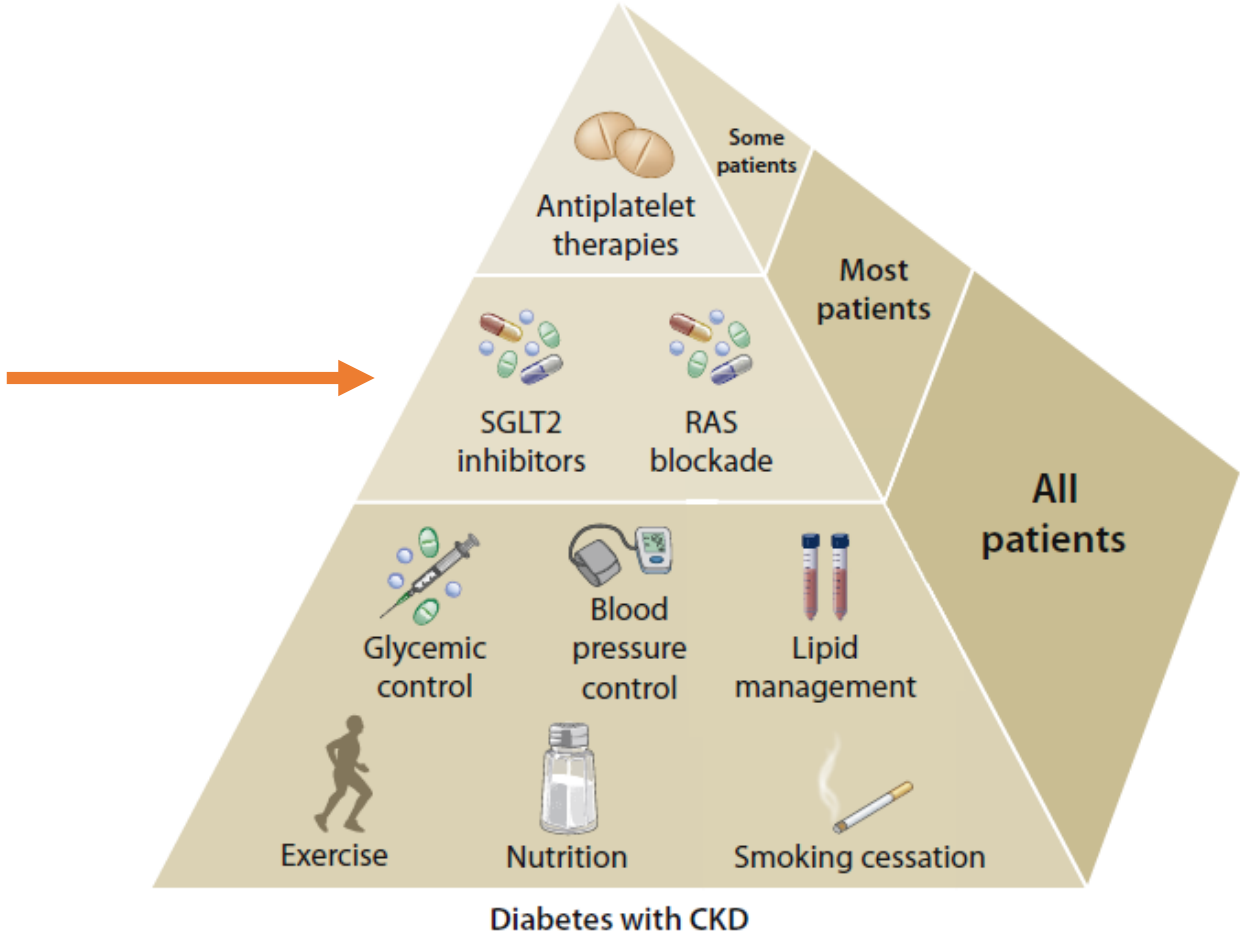
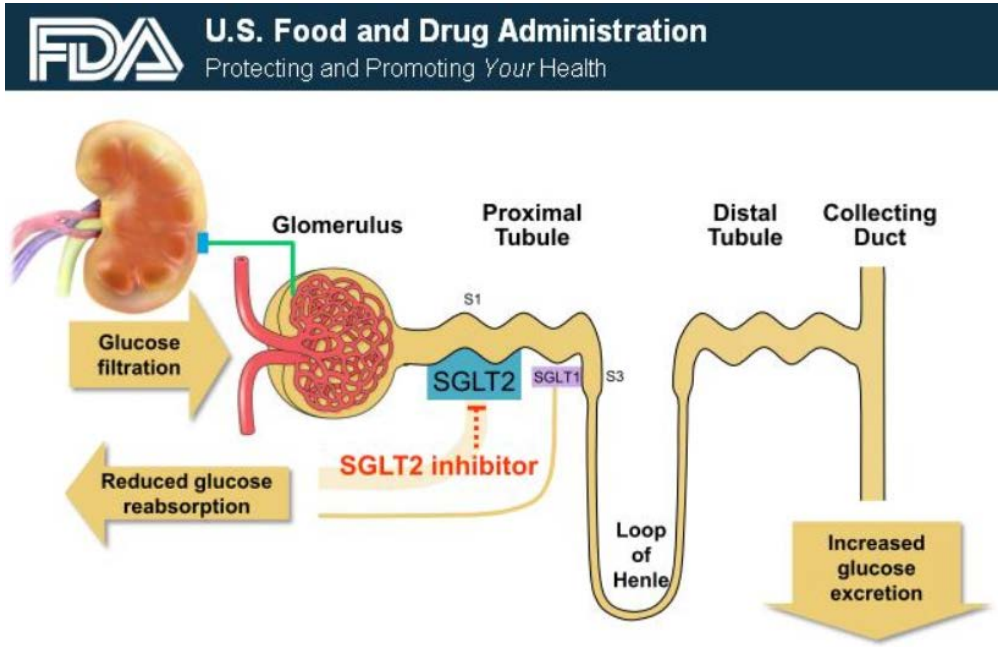





Image used with permission from: KDIGO Diabetes Work Group. Kidney Int. 2020 Oct;98(4S):S1-S115.

# SGLT2 Inhibitors




| | |
|---|---|
| Drugs | Canagliflozin Ertugluflozin<br>Dapagliflozin Sotagliflozin*<br>Empagliflozin |
| HbA1c Reduction | 0.5-1% |
| MOA | Inhibits SGLT2 in the proximal and renal tubules, thus reducing the reabsorption of filtered glucose |
| Side Effects | Risk of UTI, increased urination, dehydration |
| Notes | Previous BBW for canagliflozin which warned of higher risk of lower extremity amputations; Removed August 2020 |

*not FDA approved; SGLT1 and SGLT2 inhibitor



Canagliflozin; Dapagliflozin; Empagliflozin. Lexicomp.
Image from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sodium-glucose-cotransporter-2-sglt2-inhibitors

# Renal Protective Mechanism

SGLT2 inhibitors reduce sodium reabsorption in the proximal tubule

Causes afferent arteriole vasoconstriction

Leads to a reduction in hyperfiltration



Dekkers CCJ, et al. Nephrol Dial Transplant. 2020 Jan; 35(Suppl 1): i33–i42.

# KDIGO 2020 Guideline for DM in CKD

- Most patients with type 2 diabetes, CKD, and eGFR $\geq$ 30 ml/min/1.73m$^2$ would benefit from treatment with both metformin and an **SGLT2 inhibitor**
- Prioritize SGLT2 inhibitors with documented kidney or cardiovascular benefits
- A reversible decrease in eGFR with initiation of SGLT2 inhibitor treatment may occur and is not an indication to stop therapy
- It is reasonable to continue an SGLT2 inhibitor even if the eGFR falls below 30 ml/min/1.73m$^2$, unless renal replacement therapy is needed



KDIGO Diabetes Work Group. Kidney Int. 2020 Oct;98(4S):S1-S115.

# Assessment Question #1

In patients with type 2 diabetes and CKD, the 2020 KDIGO guideline recommends:

A. starting an SGLT2 inhibitor in all patients regardless of eGFR
B. continuing an SGLT2 inhibitor even with a reversible decrease in eGFR
C. maintaining SGLT2 inhibitor therapy even if patients require dialysis
D. initiating any SGLT2 inhibitor for proposed renal benefits

# Literature

Canagliflozin

Dapagliflozin

Empagliflozin

# Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

| | |
|---|---|
| Inclusion | Type 2 diabetes and high cardiovascular risk, eGFR > 30 ml/min/1.73m$^2$ |
| Intervention | Canagliflozin 100 mg daily vs matching placebo |
| Renal Outcome(s) | - Progression of albuminuria<br>- Composite renal outcome of 40% reduction in eGFR, need for renal replacement therapy (RRT), or death from renal causes |
| N | 10,142 |
| Results | - Less progression of albuminuria in canagliflozin group (HR 0.73, 95% CI 0.67–0.79)<br>- Lower incidence of composite renal outcome in canagliflozin group (HR 0.60, 95% CI 0.47–0.77) |
| Conclusion | Patients treated with canagliflozin had a lower risk of progression of albuminuria and loss of kidney function versus placebo. Outcomes not viewed as significant on the basis of the prespecified testing sequence. |



Bruce Neal MB, et al. N Engl J Med 2017; 377:644-657.

# Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

| | |
|---|---|
| Objective | Assess the renal effects of canagliflozin in patients with type 2 diabetes |
| Design | Randomized, double-blind, placebo-controlled, multicenter trial |
| Inclusion | - Type 2 diabetes, CKD with eGFR 30 to 90 ml/min/1.73m$^2$ and albuminuria<br>- Receiving angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for ≥ 4 weeks |
| Intervention | Canagliflozin 100 mg daily vs matching placebo |
| N | 4,401 |
| Outcome(s) | Primary: composite of end stage renal disease (ESRD), doubling of serum creatinine (SCr) from baseline, or death from renal or cardiovascular (CV) disease |



Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

| Outcome | Canagliflozin (N = 2202) | Placebo (N = 2199) | HR (95% CI) |
|---|---|---|---|
| Primary Composite, n | 245 | 340 | 0.70 (0.59–0.82) |
| Doubling of SCr, n | 118 | 188 | 0.60 (0.48–0.76) |
| ESRD, n | 116 | 165 | 0.68 (0.54–0.86) |
| Renal Death, n | 2 | 5 | - |

- Trial stopped early on a planned interim analysis
- 4,401 patients randomized with median follow-up 2.62 years
- Patients with type 2 diabetes and CKD who received canagliflozin had lower risk of primary composite outcome



Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

| | Canagliflozin | Dapagliflozin | Empagliflozin |
|---|---|---|---|
| eGFR Cut-Off for Initiation | ≥ 30 | | |
| Dose | 100 mg daily | | |
| Renal Benefits | Lower risk of ESRD including need for HD, and increasing SCr | | |
| Use in Type 2 Diabetes Only? | Yes | | |

# Literature

Canagliflozin

**Dapagliflozin**

Empagliflozin

# Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

| | |
|---|---|
| Inclusion | Type 2 diabetes and risk factors for or having CV disease, CrCl ≥ 60 ml/min |
| Intervention | Dapagliflozin 10 mg daily vs matching placebo |
| Renal Outcome(s) | Renal composite outcome: ≥ 40% decrease in eGFR to < 60 ml/min/1.73m$^2$, new ESRD, or death from renal cause |
| N | 17,160 |
| Results | - Lower incidence of composite renal outcome in dapagliflozin group<br>  - 1.5% dapagliflozin vs 2.8% placebo (HR 0.53, 95% CI 0.43-0.66) |
| Conclusion | Dapagliflozin resulted in a lower incidence of eGFR decrease, new ESRD, or death from renal cause, supporting a possible lower rate of adverse renal outcomes in patients with type 2 diabetes. |



Wiviott SD, et al. N Engl J Med 2019; 380:347-357.

# Dapagliflozin in Patients with Chronic Kidney Disease

| | |
|---|---|
| Objective | Assess the effect of dapagliflozin in patients with CKD, with or without type 2 diabetes |
| Design | Randomized, double-blind, placebo-controlled, multicenter trial |
| Inclusion | - Adults with or without type 2 diabetes and eGFR 25 to 75 ml/min/1.73m2, and urinary albumin-to-creatinine ratio of 200 to 5000 mg/g<br>- Receiving ACEi or ARB for ≥ 4 weeks |
| Intervention | Dapagliflozin 10 mg daily vs matching placebo |
| N | 4,304 |
| Outcome(s) | - Primary composite: first occurrence of 50% decline in eGFR, new ESRD, or death from renal or CV causes<br>- Secondary composite: same as primary composite sans death from CV causes |



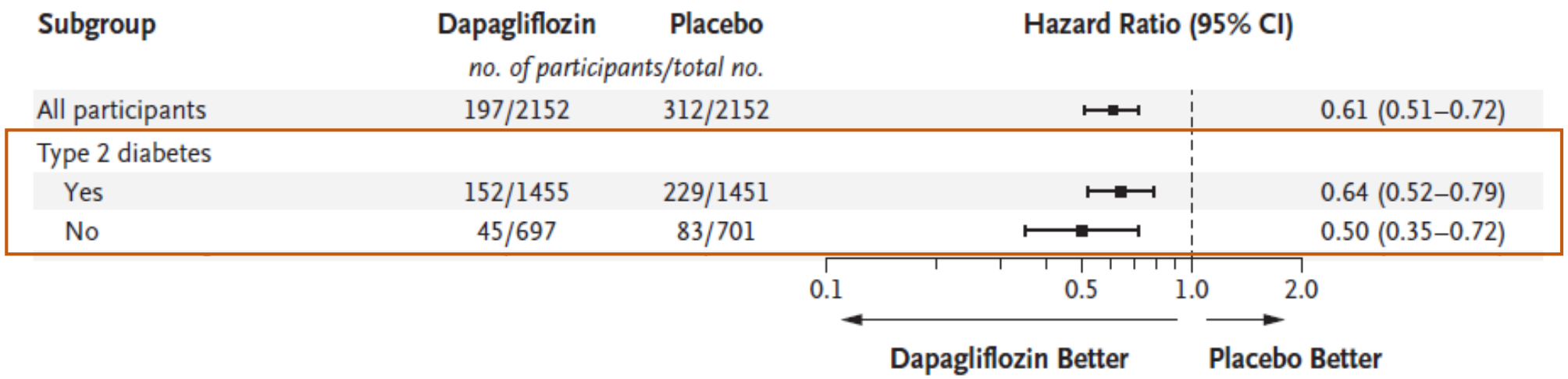
Heerspink HJL, et al. N Engl J Med. 2020 Oct 8;383(15):1436-1446.

| Outcome | Dapagliflozin, n (N = 2152) | Placebo, n (N = 2152) | HR (95% CI) |
|---|---|---|---|
| Primary Composite, n (%) | 197 (9.2) | 312 (14.5) | 0.61 (0.51–0.72) |
| Secondary Composite, n (%) | 142 (6.6) | 243 (11.3) | 0.56 (0.45–0.68) |
| CV Death or HF Hospitalization, n (%) | 100 (4.6) | 138 (6.4) | 0.71 (0.55–0.92) |

- Event rates for all components of composite outcome favored dapagliflozin
- Number needed to treat for primary outcome = 19



Heerspink HJL, et al. N Engl J Med. 2020 Oct 8;383(15):1436-1446.




- Effect of dapagliflozin on primary outcome consistent across prespecified subgroups
- Renal benefit in CKD patients with or without type 2 diabetes
- Patients with CKD, regardless of type 2 diabetes, who received dapagliflozin had lower risk of primary composite outcome



Heerspink HJL, et al. N Engl J Med. 2020 Oct 8;383(15):1436-1446.

| | Canagliflozin | Dapagliflozin | Empagliflozin |
|---|---|---|---|
| eGFR Cut-Off for Initiation | ≥ 30 | ≥ 25 (DAPA-CKD) | |
| Dose | 100 mg daily | 10 mg daily | |
| Renal Benefits | Lower risk of ESRD including need for HD, and increasing SCr | Slower decline in eGFR, lower risk of new ESRD | |
| Use in Type 2 Diabetes Only? | Yes | No (as per DAPA-CKD) | |

# Literature

Canagliflozin

Dapagliflozin

Empagliflozin

# Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

| | |
|---|---|
| Inclusion | Type 2 diabetes and established CV disease, eGFR $\geq$ 30 ml/min/1.73m$^2$ |
| Intervention | Empagliflozin 10 mg or 25 mg daily vs matching placebo |
| Renal Outcome(s) | Incident or worsening nephropathy (progression to macroalbuminuria, doubling of SCr and eGFR $\leq$ 45, initiation of RRT, death from renal disease) |
| N | 7,020 |
| Results | - Incident or worsening nephropathy: 12.7% empagliflozin vs 18.8% placebo (P < 0.001, HR 0.61, 95% CI 0.53-0.70)<br>- Consistent benefit of empagliflozin across the two doses |
| Conclusion | Patients with type 2 diabetes at high risk for CV events who received empagliflozin had a lower rate of incident or worsening nephropathy as compared to placebo. Various renal outcomes, including progression to macroalbuminuria, doubling of SCr, and initiation of RRT were also lower. |



Wanner C, et al. N Engl J Med. 2016 Jul 28;375(4):323-34.

# Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

| | |
|---|---|
| Objective | Assess the effects of empagliflozin in patients with heart failure with reduced ejection fraction (HFrEF) |
| Design | Randomized, double-blind, parallel-group, placebo-controlled trial |
| Inclusion | - Heart failure with reduced ejection fraction and NYHA class II-IV on guideline directed medical therapy<br>- Excluded if eGFR < 20 ml/min/1.73m$^2$ |
| Intervention | Empagliflozin 10 mg daily vs matching placebo |
| N | 3,730 |
| Renal Outcome(s) | - Rate of decline in eGFR during treatment<br>- Composite renal outcome (need for chronic dialysis, renal transplantation, or reduction of $\geq$ 40% in eGFR) |



Packer M, et al. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

| Outcome | Empagliflozin (N = 1863) | Placebo (N = 1867) | HR (95% CI) |
|---|---|---|---|
| Decline in eGFR, ml/min/1.73m$^2$ | –0.55±0.23 | –2.28±0.23 | 1.73 (1.10–2.37) |
| Renal Composite, n (%) | 30 (1.6) | 58 (3.1) | 0.50 (0.32–0.77) |

- Empagliflozin slowed the rate of decline in the eGFR
- Risk of composite renal outcome was lower in empagliflozin group
  - Not included in testing hierarchy
- No prespecified subgroup analysis comparing diabetes vs no diabetes



Packer M, et al. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

| | Canagliflozin | Dapagliflozin | Empagliflozin |
|---|---|---|---|
| eGFR Cut-Off for Initiation | ≥ 30 | ≥ 25 (DAPA-CKD) | ≥ 30 (EMPA-REG OUTCOME)<br>≥ 20 (EMPEROR-Reduced) |
| Dose | 100 mg daily | 10 mg daily | 10 mg daily |
| Renal Benefits | Lower risk of ESRD including need for HD, and increasing SCr | Slower decline in eGFR, lower risk of new ESRD | Lower risk of worsening nephropathy, slower decline in eGFR |
| Use in Type 2 Diabetes Only? | Yes | No (as per DAPA-CKD) | No (as per EMPEROR-Reduced, but no pre-specified subgroup) |

# Future Studies

| The Study of Heart and Kidney Protection with Empagliflozin | Renohemodynamic Effects Empagliflozin in Various Populations |
|---|---|
| **EMPA-KIDNEY** | **REGROUP** |
| Multicenter, international, randomized, double-blind, placebo-controlled trial | Single-center, prospective, placebo-controlled, double-blind, randomized, cross-over trial |
| Objective: to assess cardio-renal outcomes in patients with CKD using empagliflozin once daily | Objective: to investigate the effect of empagliflozin on kidney function in people with preserved or impaired renal function with or without type 2 diabetes |
| Outcomes: time to first occurrence of kidney disease progression or cardiovascular death | Outcomes: measured eGFR |
| Estimated study completion date: December 2022 | Estimated study completion date: March 2022 |



NCT03594110. NCT04243850. ClinicalTrials.gov

# Assessment Question #2

Landmark trials regarding renal outcomes have demonstrated that all SGLT2 inhibitors:

A. Have the same eGFR cut off of $\geq$ 30 ml/min/1.73m$^2$
B. Can be used in patients with or without type 2 diabetes
C. Have shown a slower decline in eGFR or doubling of SCr
D. Need to be titrated to their maximum and optimal dose

# FDA Approved Indications

| Canagliflozin | Dapagliflozin | Empagliflozin |
|---|---|---|
| • Type 2 DM<br>• Type 2 DM with CV disease<br>• Diabetic kidney disease | • Type 2 DM<br>• Diabetic kidney disease<br>• **Chronic kidney disease**<br>• HFrEF | • Type 2 DM<br>• Type 2 DM with CV disease |



Canagliflozin; Dapagliflozin; Empagliflozin. Lexicomp.

| Contraindications |
| --- |
| History of serious hypersensitivity reaction to drug |
| Severe renal impairment, ESRD, or dialysis |

| Cautions |
| --- |
| Intravascular volume contraction, particularly in patients with renal impairment or low systolic blood pressure, those on diuretics, or the elderly |
| Increased incidence of bone fractures reported with canagliflozin |
| Hypoglycemia risk increased with insulin and insulin secretagogues (e.g., sulfonylureas) |
| Mycotic genital infections |
| Euglycemic ketoacidosis in vulnerable patients |
| History of osteoporosis (canagliflozin) |



Das SR, et al. J Am Coll Cardiol. 2018 Dec 18;72(24):3200-3223.

# Who Should Receive an SGLT2 Inhibitor?

| Assessment | Intervention | Follow-Up |
|---|---|---|
| Eligible Patients<br>- eGFR ≥ 30 ml/min/1.73m$^2$<br><br>High priority features<br>- UACR ≥ 200 mg/g<br>- Heart failure<br><br>Potential Contraindications<br>- Genital infection risk<br>- Diabetic ketoacidosis<br>- Foot ulcers<br>- Immunosuppression | Low-dose SGLT2 inhibitor with proven benefits<br>- Canagliflozin 100 mg<br>- Dapagliflozin 10 mg<br>- Empagliflozin 10 mg<br><br>Education<br>- Sick day protocol<br>- Perioperative care<br>- Foot care | - Assess adverse effects<br>- Review knowledge<br>- Anticipate an acute drop in eGFR, which is generally not a reason to stop the SGLT2 inhibitor |



Zoungas S, et al. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):631-633.

| Assessment | Intervention | Follow-Up |
|---|---|---|
| Hypoglycemia risk?<br>- Insulin or sulfonylurea<br>- History of severe hypoglycemia<br>- HbA1c at or below goal | Education<br>- Hypoglycemia symptoms<br>- Glycemia monitoring<br>- Consider insulin/sulfonylurea dose reduction | - Ask about hypoglycemia<br>- Reduce sulfonylurea or insulin if needed |

If high

| Assessment | Intervention | Follow-Up |
|---|---|---|
| Volume depletion risk?<br>- Concurrent diuretic use<br>- Tenuous volume status<br>- History of acute kidney injury | Education<br>- Volume depletion symptoms<br>- Consider diuretic dose reduction | - Re-assess volume<br>- Reduce concomitant diuretic if needed |



Zoungas S, et al. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):631-633.

# Patient Case

A 69 YO M with PMH type 2 DM, HTN, HLD, OSA, and back pain was referred to your clinic for declining eGFR. He was diagnosed with DM 32 years prior to referral and developed retinopathy and nephropathy over time. Urine albumin-creatinine ratio initially elevated 10 years prior. eGFR has declined over the years.

| Current Labs | |
|---|---|
| UACR | 2291 mg/g |
| eGFR | 32 ml/min/1.73m$^2$ |
| HbA1c | 7.2% |
| BP | 132/68 |

| Current Medications | |
|---|---|
| Metformin | Losartan |
| Glipizide | Amlodipine |
| Insulin | HCTZ |
| | Spironolactone |



Zoungas S, et al. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):631-633.

# Assessment Question #3

Should this patient be started on an SGLT2 inhibitor?

A. Yes, given their decline in eGFR and increase in UACR in the past years
B. No, their HbA1c is too close to goal which increases hypoglycemia risk
C. No, they take insulin and a sulfonylurea which increases hypoglycemia risk
D. No, their eGFR is too close to the guideline recommended cut off

# Patient Case

A 69 YO M with PMH **type 2 DM**, HTN, HLD, OSA, and back pain was referred to your clinic for **declining eGFR**. He was diagnosed with DM 32 years prior to referral and developed retinopathy and **nephropathy** over time. Urine albumin-creatinine ratio initially elevated 10 years prior. eGFR has declined over the years.

| Current Labs | |
|---|---|
| **UACR** | **2291 mg/g** |
| **eGFR** | **32 ml/min/1.73m$^2$** |
| HbA1c | 7.2% |
| BP | 132/68 |

| Current Meds | |
|---|---|
| **Metformin** | Losartan |
| Glipizide | Amlodipine |
| Insulin | HCTZ |
| | Spironolactone |



Zoungas S, et al. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):631-633.

# Summary

| |
|---|
| Canagliflozin, dapagliflozin, and empagliflozin have shown renal benefit in patients with type 2 diabetes and CKD |
| Dapagliflozin has shown renal benefit in patients with CKD with or without type 2 diabetes |
| SGLT2 inhibitors should be started when eGFR $\geq$ 30 ml/min/1.73m$^2$, and can be continued until patient requires renal replacement therapy |
| Monitor for hypoglycemia and volume depletion risk, especially if patient taking insulin, sulfonylurea, and/or diuretics concurrently |

# Special Acknowledgement:

Jennifer Austin Szwak, PharmD, BCPS
Clinical Pharmacy Specialist, Internal Medicine
University of Chicago Medicine

# Questions