	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

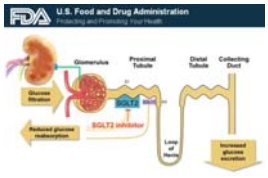
DM and ↑blood glucose → Alterations in the kidneys → CKD or diabetic kidney disease (DKD)

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

SGLT2 Inhibitors



Drugs	Canagliflozin Dapagliflozin Empagliflozin Ertugluflozin Sotagliflozin*
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 ≥ 30 ml/min/1.73m² 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/1.73m², 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

CANVAS

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Inclusion	Type 2 diabetes and high cardiovascular risk, eGFR > 30 ml/min/1.73m²
Intervention	Canagliflozin 100 mg daily vs matching placebo
Renal Outcome(s)	- Progression of albuminuria - 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) - 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

CREDENCE

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/1.73m² and albuminuria - 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

CREDENCE

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

DECLARE-TIMI 58

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 - 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.

DAPA-CKD

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 - 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 - 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.

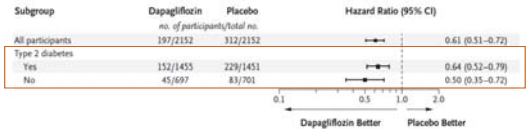
DAPA-CKD

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.

DAPA-CKD



- 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**

EMPA-REG OUTCOME

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Inclusion	Type 2 diabetes and established CV disease, eGFR ≥ 30 ml/min/1.73m²
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 ≤ 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) - 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.

EMPEROR-Reduced

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 - Excluded if eGFR < 20 ml/min/1.73m²
Intervention	Empagliflozin 10 mg daily vs matching placebo
N	3,730
Renal Outcome(s)	- Rate of decline in eGFR during treatment - Composite renal outcome (need for chronic dialysis, renal transplantation, or reduction of ≥ 40% in eGFR)

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

EMPEROR-Reduced

Outcome	Empagliflozin (N = 1863)	Placebo (N = 1867)	HR (95% CI)
Decline in eGFR, ml/min/1.73m²	–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) ≥ 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

EMPA-KIDNEY
Multicenter, international, randomized, double-blind, placebo-controlled trial
Objective: to assess cardio-renal outcomes in patients with CKD using empagliflozin once daily
Outcomes: time to first occurrence of kidney disease progression or cardiovascular death
Estimated study completion date: December 2022

Renohemodynamic Effects Empagliflozin in Various Populations

REGROUP
Single-center, prospective, placebo-controlled, double-blind, randomized, cross-over trial
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: measured eGFR
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 ≥ 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 • Type 2 DM with CV disease • Diabetic kidney disease	• Type 2 DM • Diabetic kidney disease • **Chronic kidney disease** • HFrEF	• Type 2 DM • 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 - eGFR ≥ 30 ml/min/1.73m^2 High priority features - UACR ≥ 200 mg/g - Heart failure Potential Contraindications - Genital infection risk - Diabetic ketoacidosis - Foot ulcers - Immunosuppression	Low-dose SGLT2 inhibitor with proven benefits - Canagliflozin 100 mg - Dapagliflozin 10 mg - Empagliflozin 10 mg Education - Sick day protocol - Perioperative care - Foot care	- Assess adverse effects - Review knowledge - 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? - Insulin or sulfonylurea - History of severe hypoglycemia - HbA1c at or below goal	Education - Hypoglycemia symptoms - Glycemia monitoring - Consider insulin/sulfonylurea dose reduction	- Ask about hypoglycemia - Reduce sulfonylurea or insulin if needed

If high

Assessment	Intervention	Follow-Up
Volume depletion risk? - Concurrent diuretic use - Tenuous volume status - History of acute kidney injury	Education - Volume depletion symptoms - Consider diuretic dose reduction	- Re-assess volume - 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

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Clinical Pharmacy Specialist, Internal Medicine
University of Chicago Medicine

Questions