

HEARTS AND KIDNEYS AND SUGARS, OH MY!

A DIABETES UPDATE

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ABBREVIATIONS

ACR: albumin:creatinine ratio	DPP4i: dipeptidyl-peptidase 4 inhibitor	KDIGO: Kidney Disease Improving Global Outcomes
ACC: American College of Cardiology	eGFR: estimated glomerular filtration rate	MACCE: major adverse cardiovascular event
ADA: American Diabetes Association	ESKD: end stage kidney disease	MI: myocardial infarction
AGA: American Gastroenterological Association	GIP: glucose-dependent insulinotropic polypeptide	PVD: peripheral vascular disease
AHA: American Heart Association	GLP1a: glucagon-like peptide 1 agonist	SGLT2i: sodium glucose co-transporter 2 inhibitor
ASCVD: atherosclerotic cardiovascular disease	HF: heart failure	SU: sulfonyleurea
BMI: body mass index	HFpEF: heart failure with preserved ejection fraction	T1DM: type 1 diabetes mellitus
CVOI: cardiovascular outcome trial	HFrEF: heart failure with reduced ejection fraction	T2DM: type 2 diabetes mellitus
KKD: chronic kidney disease	HFSA: Heart Failure Society of America	TZD: thiazolidinedione
CVD: cardiovascular disease		

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OBJECTIVES

- Identify new drug approvals related to diabetes management
- Compare and contrast non-glucose lowering benefits of antihyperglycemic medications
- Recall key updates to the 2023 American Diabetes Association Standards of Care
- Apply updated diabetes information to patient scenarios

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KNOW YOUR WHY

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The TikTok Trend That Triggered a Diabetes Drug Shortage

reduces sugar allowed back in

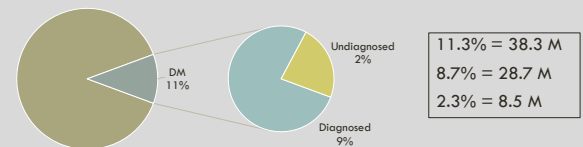
REBIO HEALTH NEWS

Copyright: TM, Copyright: commercial (Dr. Jankovics), YouTube: <https://www.youtube.com/watch?v=8B802214>, Published: October 13, 2019, Accessed: April 29, 2023.
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Kang, D. The TikTok Trend That Triggered a Diabetes Drug Shortage, November 20, 2022, Accessed: April 29, 2023.
<https://www.rebiohealthnews.com/news/2022/11/20/the-tiktok-trend-that-triggered-a-diabetes-drug-shortage>

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IMPACT OF DIABETES

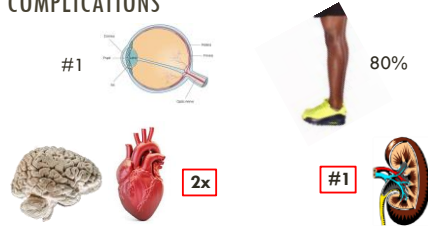
% of US population with diabetes



National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, Centers for Disease Control and Prevention, National Diabetes Statistics Report website, Updated June 29, 2022, Accessed April 21, 2023. <https://www.cdc.gov/diabetes/data/statistics-reports/index.html>

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COMPLICATIONS



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NEW APPROVALS

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TEPLIZUMAB



Indication: delay the onset of Stage 3 T1DM in adults and pediatric patients ≥ 8 years old with Stage 2 T1DM

Class: CD3-directed antibody

MOA: binds CD3 present on T lymphocytes; may deactivate beta cell autoreactive T lymphocytes among other actions

Dose: based on body surface area; 30 minute IV infusion daily over 14 consecutive days

CI: none

Warnings: cytokine release syndrome, lymphopenia, serious infections

AE: (>10%) lymphopenia, leukopenia, rash, headache

<https://tzielD.com/>
TzielD (package insert), Red Bank, NE: PreventionBio, Inc. 2022.

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FINERENONE



Indication: reduce risk of sustained eGFR decline, end stage kidney disease (ESKD), CV death, non-fatal MI, HF hospitalization in adults with chronic kidney disease (CKD) associated with T2DM

Class: non-steroidal mineralocorticoid receptor antagonist (MRA)

MOA: block MR mediated sodium reabsorption and MR overactivation in both epithelial and nonepithelial tissues

Dose: 10 or 20 mg once daily

CI: concomitant CYP3A4 inhibitors; adrenal insufficiency

Warnings: hyperkalemia

AE: (>1%) hyperkalemia, hypnatremia, hypotension

<https://www.kerendia.com/>
Kerendia (package insert), Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc. 2021.

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SEMAGLUTIDE



Indication: improve glycemic control in adults with T2DM; reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established CVD

Class: glucagon-like peptide-1 agonist (GLP1a)

MOA: binds to GLP1 receptors stimulates insulin secretion and lowers glucagon secretion, in a glucose-dependent fashion; delays gastric emptying

Dose: 0.25 mg subcut once weekly; titrated every 4 weeks to 0.5 mg, 1 mg and max 2 mg

CI: personal/family history medullary thyroid carcinoma or MEN2

Warnings: pancreatitis, AKI, acute gallbladder disease, DM retinopathy complications, hypoglycemia in combo with insulin secretagogues or insulin

AE: (>5%) N/V/D, abdominal pain, constipation

<https://www.ozempic.com/diabetes/products/treatment/ozempic.html>
Ozempic (package insert), Princeton, NJ: NovoNordisk, Inc. 2022.

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TIRZEPATIDE



Indication: improve glycemic control in adults with T2DM

Class: glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP1 agonist

MOA: binds to GIP and GLP1 receptors to stimulate insulin secretion and lowers glucagon secretion, in a glucose-dependent fashion; delays gastric emptying

Dose: 2.5 mg subcut once weekly; titrated up by 2.5 mg every 4 weeks to max 15 mg

CI: personal/family history medullary thyroid carcinoma or MEN2

Warnings: pancreatitis, hypoglycemia in combo with insulin secretagogues or insulin, acute kidney injury, DM retinopathy in those with a history, acute gallbladder disease, severe GI disease

AE: (>5%) N/V/D, abdominal pain, constipation, dyspepsia, decreased appetite

<https://www.mounjaro.com/309>
Mounjaro (package insert), Indianapolis, IN: Eli Lilly and Company, 2022.

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BEXAGLIFLOZIN

Indication: improve glycemic control in adults with T2DM

Class: sodium-glucose co-transporter 2 inhibitor (SGLT2i)

MOA: inhibits SGLT2 to reduce renal reabsorption of glucose and lower the renal threshold for glucose which increases urinary glucose excretion

Dose: 20 mg every morning

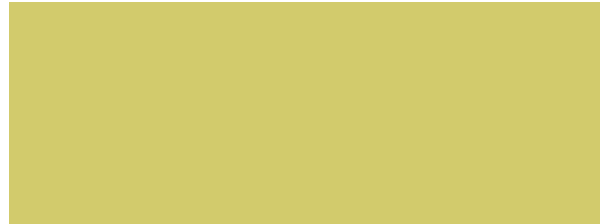
CI: dialysis

Warnings: ketoacidosis, lower limb amputation, volume depletion, genital mycotic infection, Fournier's gangrene, urosepsis/pyelonephritis, hypoglycemia in combo with insulin secretagogues or insulin

AE: (>5%) female genital mycotic infections, UTI, increased urination

Brenzavvy (package insert), Marlborough, MA, Theravance, LLC, 2023. <https://www.theravance.com/>

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NON-GLUCOSE LOWERING BENEFITS

SGLT2 inhibitors
GLP1 agonists

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NON-GLUCOSE LOWERING BENEFITS

CVD
with T2DM

Kidney Disease
with and without T2DM

Heart Failure
with and without T2DM

Obesity
with and without T2DM

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DISCLAIMER



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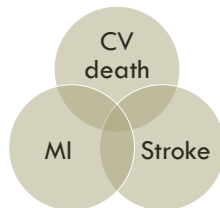
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CARDIOVASCULAR DISEASE

CVOT = cardiovascular outcome trial

Trial Endpoints:

- 3-point composite MACE (major adverse cardiovascular event)
- Individual components



Diabetes Care 2023;46(Suppl. 1):S118-S119

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CVD: GLP1 AGONISTS

	Indicated Population	Composite Outcome
Liraglutide (Victoza®)	T2DM + CVD	MACE (↓13%)
Semaglutide (in.) (Ozempic®)	T2DM + CVD	MACE (↓ 26%)
Dulaglutide (Trulicity®)	T2DM + (CVD or CV risk factors)	MACE (↓ 12%)

Tirzepatide (Mounjaro®, GIP/GLP1 a)- CVOT is ongoing

Product package inserts
Diabetes Care 2023;46(Suppl. 1):S118-S119
<https://clinicaltrials.gov/ct2/show/study/NCT04285423>

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CVD: SGLT2 INHIBITORS

	Indicated Population	Outcome
Canagliflozin (Invokana®)	T2DM + CVD	Composite MACE (↓14%)
Empagliflozin (Jardiance®)	T2DM + CVD	CV death (↓38%)
Dapagliflozin (Farxiga®)	T2DM + (CVD or CV risk factors)	HF hospitalization (↓27%)

Product package inserts
Diabetes Care 2023;46(Suppl. 1):S158-S190
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10200686/>

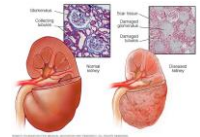
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KIDNEY DISEASE

CVOT data led to follow-up studies in those without T2DM

Trial Endpoints:

- Sustained estimated glomerular filtration rate (eGFR) decline: $\geq 50\%$ decline
- Doubling of serum creatinine
- End-stage kidney disease (ESKD): maintenance dialysis, kidney transplant, sustained eGFR of <15 mL/min/m²
- HF hospitalization
- CV death



Diabetes Care 2023;46(Suppl. 1):S191-S202
Image: <https://www.medschicago.edu/medschool/department-of-internal-medicine/sections/nephrology/>

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KIDNEY DISEASE: SGLT2 INHIBITORS

	Indicated Population	Composite Outcome
Canagliflozin (Invokana®)	T2DM + diabetic nephropathy with albuminuria (ACR >300)	ESKD, doubling of serum creatinine, CV death, and HF hospitalization (↓30%)
Dapagliflozin (Farxiga®)	CKD at risk of progression*	ESKD, sustained eGFR decline, CV death, and HF hospitalization (↓39%)

*independent of diabetes

Empagliflozin (Jardiance®): submitted FDA New Drug Approval request in Jan 2023 to reduce risk of kidney disease progression and CV death in those with CKD (independent of diabetes)

Product package inserts
Diabetes Care 2023;46(Suppl. 1):S158-S202
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10200686/>

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HEART FAILURE

CVOT data in T2DM showed HF benefits

Led to follow-up studies in those without T2DM

Trial Endpoints:

- Worsening HF
- HF hospitalizations
- CV death



Normal heart



Enlarged heart

Diabetes Care 2023;46(Suppl. 1):S158-S190 J Am Coll Cardiol 2022;79(17):e263-e421
Image: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10200686/>

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HF: SGLT2 INHIBITORS

	Indicated Population	Composite Outcome
Empagliflozin (Jardiance®)	HF*	CV death and HF hospitalization (↓25% in rEF, ↓21% in pEF)
Dapagliflozin (Farxiga®)	HF with reduced ejection fraction (NYHA class II-IV)*	CV death, HF hospitalization, urgent HF visit (↓26%)

*independent of diabetes

Canagliflozin (Invokana): reduced patient reported symptoms but no FDA indication

Product package inserts
Diabetes Care 2023;46(Suppl. 1):S158-S190 [doi:10.2337/2023.2846](https://doi.org/10.2337/2023.2846)

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OBESITY

Positive weight benefit in early trials led to follow-up studies in those without T2DM

Trial Endpoints:

- Mean difference in percentage of total body weight loss (TBWL) achieved as compared to placebo
- Percentage of body weight loss at 1+ year
- Percentage of patients achieving 5, 10, 15 or 20% total body weight loss



Cardiovascular Medicine 2022;11(8):1198-1225
Image: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10200686/>

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OBESITY: GLP1 AGONISTS

	Indicated Population	Mean difference % TBWL vs placebo (in adults)
Liraglutide (Saxenda®)	For chronic weight management in: • adults patients with BMI of ≥ 30 kg/m ² or ≥ 27 kg/m ² plus ≥ 1 weight-related comorbid condition	4.8%
Semaglutide (injection) (Wegovy®)	• pediatric patients (12+ years) with BMI at the ≥ 95 th percentile for age and sex	10.8%

Tirzepatide (Mounjaro®, GIP/GLP1 α) – granted FDA “fast track” designation, early data shows ~15% body weight loss and ~57% losing $\geq 20\%$ total body weight on max dose

Diabetes Technology, 2022 Nov; 1:16303:1198-233
Diabetes Care 2023;46(Suppl_1):S128-S131
<https://www.tirzepatide.com/news-releases/news-release-details/tirzepatide-receives-us-fda-fast-track-designation-trapozatide>

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AT A GLANCE: NON-GLYCEMIC INDICATIONS — GLP1 α

		CVD	Obesity
Liraglutide	Victoza®	T2DM + CVD	
	Saxenda®		≥ 12 years old with or without T2DM
Dulaglutide	Trulicity®	T2DM + (CVD or CV risk factors)	
Semaglutide (injection)	Ozempic®	T2DM + CVD	
	Wegovy®		≥ 12 years old with or without T2DM

Product package inserts

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AT A GLANCE : NON-GLYCEMIC INDICATIONS — SGLT2i

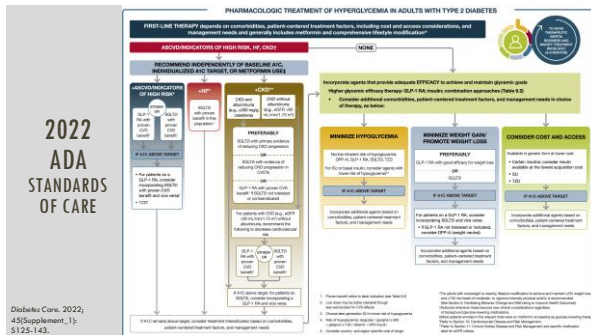
		CVD	HF	Kidney Disease
Canagliflozin	Invokana®	T2DM + CVD		T2DM + diabetic nephropathy with albuminuria
Empagliflozin	Jardiance®	T2DM + CVD	HF with or without T2DM	
Dapagliflozin	Farxiga®	T2DM + (CVD or CV risk factors)	HFrEF with or without T2DM	CKD with or without T2DM

Product package inserts

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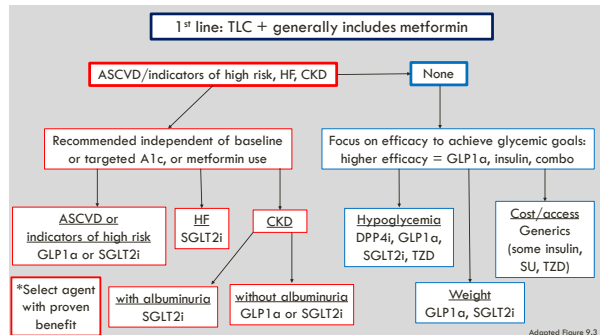
ADA GUIDELINE UPDATES | 2022 vs 2023

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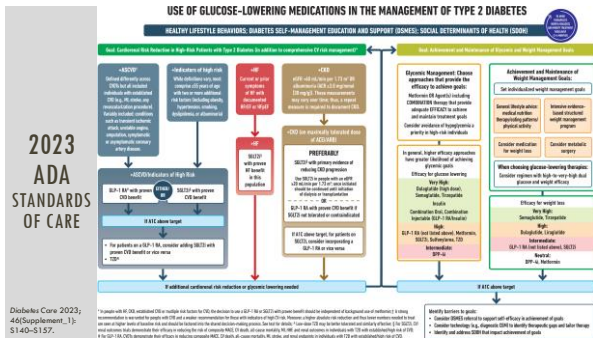
Diabetes Care, 2022; 45(Supplement_1):S123-S142

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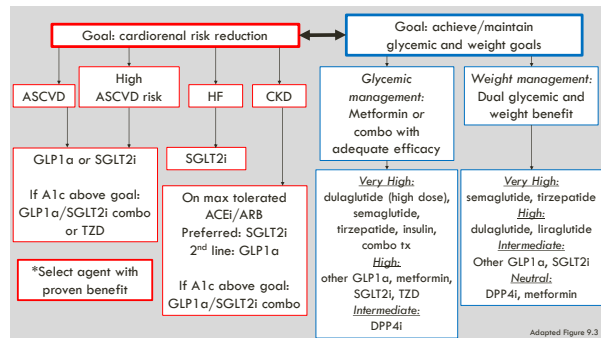


Adapted Figure 9.3

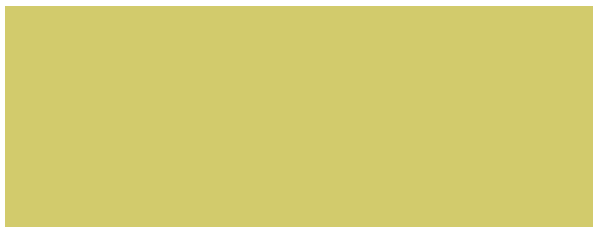
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PATIENT CASES

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MR. CP

CC: 67 year old male with newly diagnosed T2DM
PMH: HTN, PVD, dyslipidemia, obesity, history of MI (age 65)
NKDA
Medications: lisinopril 20 mg daily, amlodipine 10 mg daily, carvedilol 25 mg daily, rosuvastatin 10 mg daily, aspirin 81 mg daily
SH: former tobacco use (quit age 42), one beer most days, denies illicit drugs; Medicare Part D Advantage
FH: unremarkable

Objective:
 BP: 135/80 HR: 75
 BMI: 37
 A1c: 7.5%
 CFR: 48
 Electrolytes WNL

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Q1

According to the 2023 ADA guidelines, is metformin the optimal first line treatment?

- A. Yes
- B. No

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Q1

According to the 2023 ADA guidelines, is metformin the optimal first line treatment?

No- focus on cardiorenal risk reduction, glycemic control, and weight control

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Q2

According to current FDA indications and the 2023 ADA guidelines, which of the following medication classes is preferred for Mr. CP?

- A. GLP1a
- B. GIP/GLP1a
- C. SGLT2i
- D. DPP4i

67 year old male with PMH: new diagnosis T2DM, HTN, PVD, dyslipidemia, obesity, history of MI (age 65)
 Med: lisinopril 20 mg daily, amlodipine 10 mg daily, carvedilol 25 mg daily, rosuvastatin 10 mg daily, aspirin 81 mg daily (NKDA)
 SH: former tobacco use (quit age 42), one beer most days, Medicare Part D Advantage
 BP: 135/80 HR: 75 BMI: 37 A1c: 7.5% GFR: 48
 Electrolytes WNL

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Q2

According to current FDA indications and the 2023 ADA guidelines, which of the following medication classes is preferred for Mr. CP?

	High glycemic efficacy	CV benefit	Weight benefit
★ GLP1a	+++	++	++
GIP/GLP1a	+++	-	+++
SGLT2i	++	++	+
DPP4i	+	-	±

Red indicates FDA approval in this area

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Q3

Of the following GLP1a, which is most appropriate for Mr. CP based on guidelines and FDA approvals?

- A. Victoza®
- B. Saxenda®
- C. Ozempic®
- D. Wegovy®
- E. Rybelsus®
- F. Trulicity®

67 year old male with PMH: new diagnosis T2DM, HTN, PVD, dyslipidemia, obesity, history of MI (age 65)
 Med: lisinopril 20 mg daily, amlodipine 10 mg daily, carvedilol 25 mg daily, rosuvastatin 10 mg daily, aspirin 81 mg daily (NKDA)
 SH: former tobacco use (quit age 42), one beer most days, Medicare Part D Advantage
 BP: 135/80 HR: 75 BMI: 37 A1c: 7.5% GFR: 48
 Electrolytes WNL

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2022 AGA OBESITY

"In adults with overweight (BMI ≥27 kg/m² and weight-related complications) or obesity (BMI ≥30 kg/m²), with inadequate response to lifestyle interventions, add pharmacotherapy"

	Semaglutide	Liraglutide	Phentermine-topiramate ER	Naltrexone-bupropion ER
AGA recommendation	Suggest using			
Mean difference % total body weight loss (95% CI)	10.8%	4.8%	8.5%	3.0%

"Given the magnitude of net benefit, semaglutide 2.4 mg may be prioritized over other approved anti-obesity medications for the long-term treatment of obesity for most patients."

AGA = American Gastroenterological Association

Gastroenterology. 2022;Nov 13(435):1198-225.

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Q3

Which is most appropriate for Mr. CP based on guidelines and FDA approvals?

- A. Victoza® — Liraglutide – FDA approval for MACE prevention and obesity, less weight loss
- B. Saxenda® — Liraglutide – FDA approval for MACE prevention and obesity, less weight loss
- ★ C. Ozempic® — Semaglutide (inj.) – FDA approval for MACE prevention and obesity, strong weight loss
- D. Wegovy® — Semaglutide (inj.) – FDA approval for MACE prevention and obesity, strong weight loss
- E. Rybelsus® — Semaglutide (PO) – no FDA approval for MACE prevention or obesity
- F. Trulicity® — Dulaglutide – FDA approval for MACE prevention but not obesity

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MS. FI – Q4

Ms. FI presents to your community pharmacy stating that her provider insists she must be on Jardiance® no matter what insurance prefers. With further discussion you learn that her blood glucose is normal but "my heart isn't pumping as strong as it should be."

What is the most likely reason to prescribe Jardiance® for this patient?

- A. She has pre-diabetes but doesn't know it
- B. She has HFmrEF
- C. She has HFrEF

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2022 ACC/AHA/HFSA HEART FAILURE

Classification	Pertinent Medication	Class of Recommendation
Stage A (at risk)	SGLT2i if T2DM + (CVD or CVD risk factors)	1 (strong)
HFpEF – Stage C (LVEF ≤40%)	Dapagliflozin or empagliflozin [in addition to beta-blocker, RAAS inhibition, MRA, prn diuretic]	1 (strong)
HFpEF (LVEF ≥50%)	Empagliflozin	2a (moderate)
HFmrEF (LVEF 40-49%)	Empagliflozin	2a (moderate)

LVEF = left ventricular ejection fraction

J Am Coll Cardiol. 2022;79(17):e263-421.

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Q4

Ms. FJ presents to your community pharmacy stating that her provider insists she must be on Jardiance® no matter what insurance prefers. With further discussion you learn that her blood glucose is normal but “my heart isn't pumping as strong as it should be.”

What is the most likely reason to prescribing Jardiance® for this patient?

- A. She has pre-diabetes but doesn't know it – SGLT2i not approved for pre-DM
- ★ B. She has HRmrEF – only empagliflozin has indication for HF regardless of LVEF
- C. She has HFpEF – empagliflozin or dapagliflozin are approved

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MS. LJ – Q5

Ms. LJ, 54 year old female, is a long-time patient who says, “I have heard about some new medicine that can help protect my kidneys. Do you have any suggestions about my medications and anything new I could try?”

PMH: T2DM, CKD stage 3, HTN, atrial fibrillation, overweight, depression

Medications: mefformin ER 500 mg 4 tablets daily, lisinopril 40 mg daily, aspirin 81 mg daily, Eliquis® 5 mg twice daily, bisoprolol 10 mg daily, citalopram 10 mg daily

Allergies: Lipitor- muscle pain

FH: mother- T2, HTN, Afib, breast cancer; father- unknown
SH: denies alcohol, tobacco or illicit drugs; BCBS commercial insurance

Objective:

BP: 110/72 HR: 74

BMI: 27

Electrolytes, CBC WNL

GFR: 34

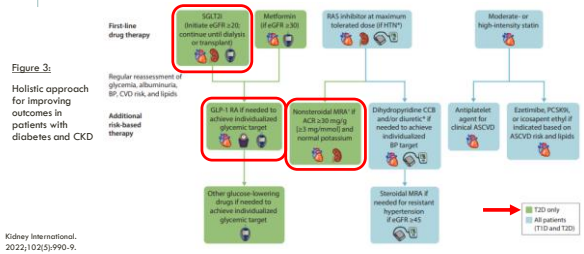
ACR: >300

A1c 6.5%

How would you respond?

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2022 KDIGO CKD IN DIABETES



Kidney International. 2022;102(5):990-9.

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MS. LJ

- Change mefformin to a SGLT2i with proven renal benefit
 - Canagliflozin (Invokana®) or dapagliflozin (Farxiga®) have FDA approval
 - Can potentially maintain glycemic goals with one medication
 - If continue mefformin, renally adjust dose
- Consider addition of finerenone (Kerendia®) after SGLT2i
- Manage other disease states and risk reduction
 - HTN- BP at goal
 - AFib- on appropriate rate control and VTE prophylaxis
 - Re-trial moderate or high intensity statin (rosuvastatin)
 - Encourage healthy weight loss (SGLT2i offers minimal but positive weight loss impact)

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INDICATION CHEAT SHEET

As of May 2023

Indications in addition to glucose lowering in T2DM

Drug	Indication	FDA Approval Date
Liraglutide (Victoza®) (Saxenda®)	To reduce the risk of MACE in adults with T2DM and established CVD	Victoza®: Aug 2017 Saxenda®: Dec 2014 (pediatric: Dec 2020)
Semaglutide, injectable (Ozempic®) (Wegovy®)	For chronic weight management in: <ul style="list-style-type: none"> adults patients with BMI of ≥ 30 kg/m² or ≥ 27 kg/m² plus ≥ 1 weight-related comorbid condition pediatric patients (12+ years) with BMI at the ≥ 95th percentile for age and sex 	Ozempic®: Jan 2020 Wegovy®: June 2021 (pediatric: Dec 2022)
Dulaglutide (Trulicity®)	To reduce the risk of MACE in adults with T2DM and established CVD or multiple CVD risk factors	Feb 2020

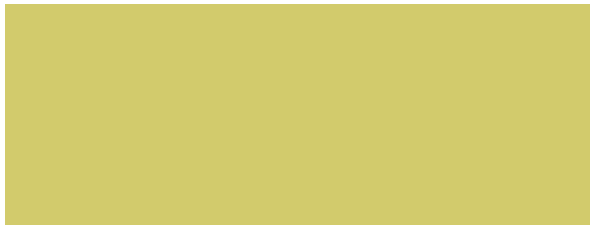
Per package inserts as of May 8, 2023

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Drug	Indication	FDA Approval Date
Canagliflozin (Invokana®)	To reduce the risk of MACE in adults with T2DM and established CVD To reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF in adults with T2DM and diabetic nephropathy with albuminuria (ACR >300)	MACE: Oct 2018 CKD: Sept 019
Empagliflozin (Jardiance®)	To reduce the risk of CV death in adults with T2DM and established CVD To reduce the risk of CV death plus hospitalization for HF in adults with HF and reduced ejection fraction	CV death: Dec 2016 HF alone: Feb 2022
Dapagliflozin (Farxiga®)	To reduce the risk of hospitalization for HF in adults with T2DM and established CVD or multiple CV risk factors To reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF To reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for HF in adults with CKD at risk of progression	HF in DM: Oct 2019 HF alone: May 2020 CKD alone: Apr 2021

Per package inserts as of May 8, 2023

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