GRAND ROUNDS:
SGLT2 INHIBITORS

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learning OBJECTIVES

01 SUMMARIZE LANDMARK TRIALS OF SGLT2I IN T2DM, CVD, HF, CKD

02 APPLY GUIDELINE RECOMMENDATIONS FOR SGLT2I USE IN DM, CVD, HF, AND CKD

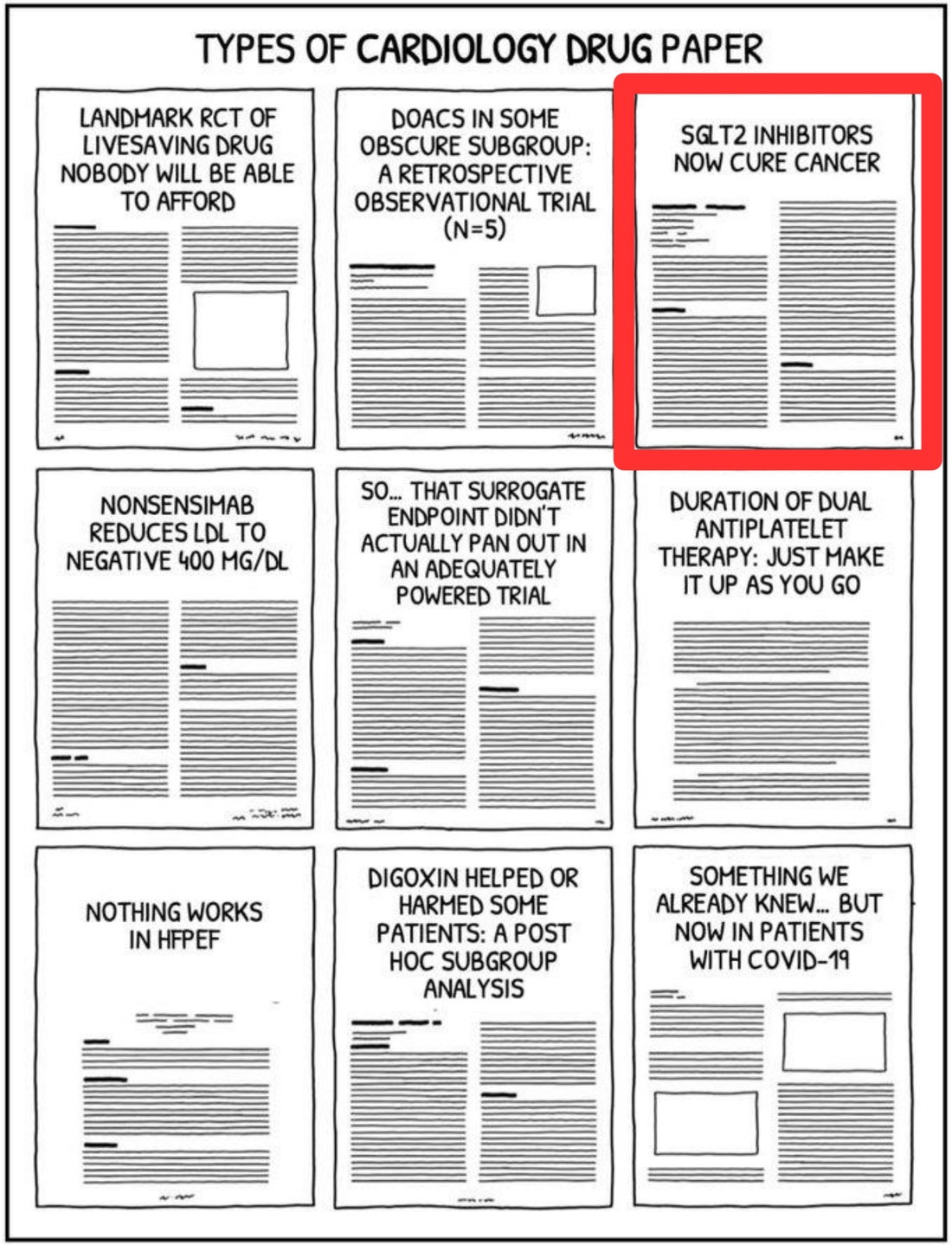
03 RISK STRATIFY AND COUNSEL ON ADVERSE EFFECTS OF SGLT2I

04 IDENTIFY STRATEGIES TO MITIGATE SGLT2I RISKS

05 APPLY EVIDENCE AND CLINICAL JUDGEMENT IN PRESCRIBING SGLT2IS IN VARIOUS CLINICAL SETTINGS

sglt2i

IN THE NEWS



mechanism of **ACTION**

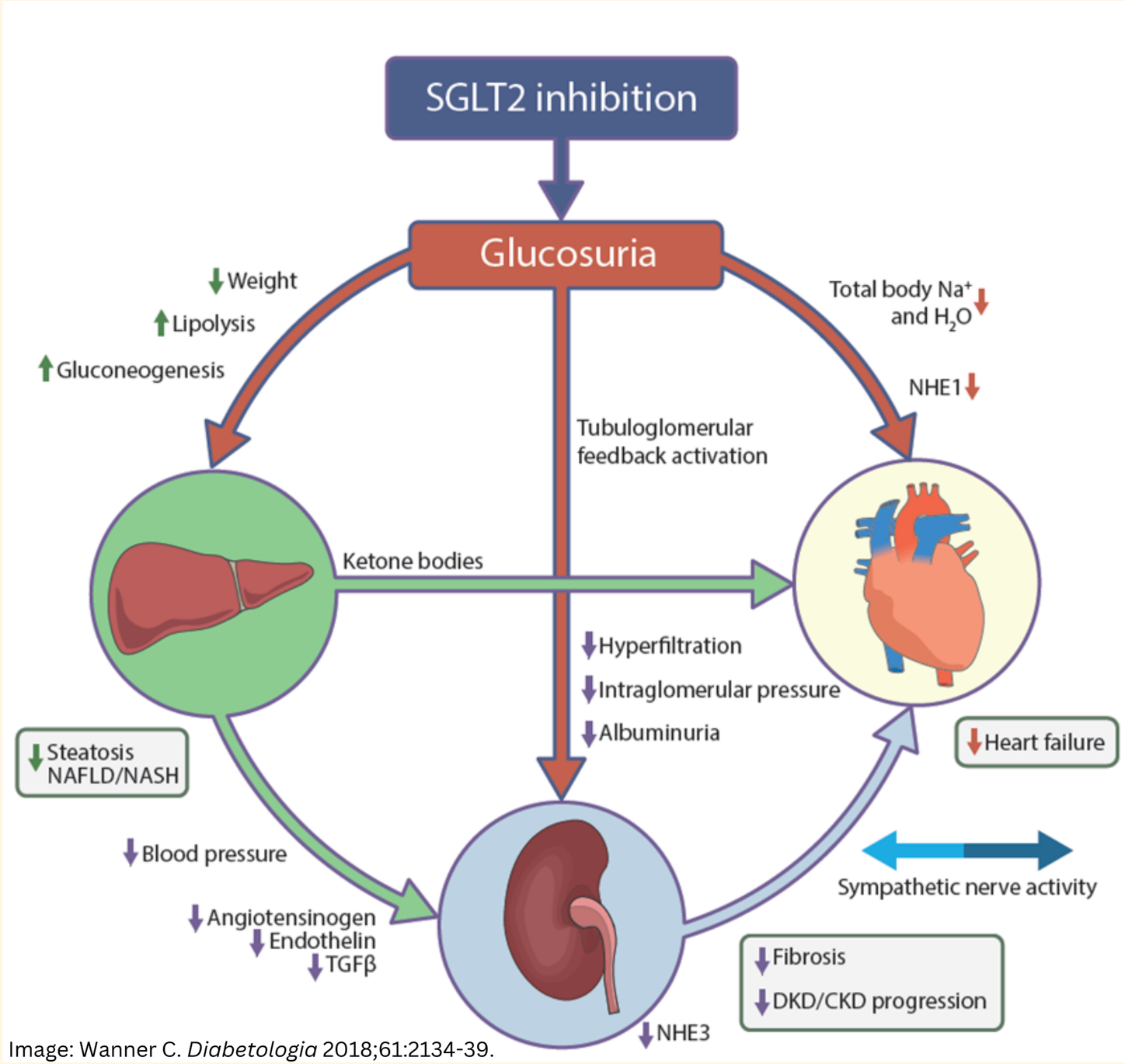


Image: Wanner C. *Diabetologia* 2018;61:2134-39.

patient CASE

60 y/o M with a PMH of HTN, CAD s/p PCI (3 yrs ago), gallstone pancreatitis, and type II DM. His A1C is 8.5%.

How would you optimize their DM management?

1) GLP-1 RA
2) Sulfonylurea
3) TZD
4) SGLT2i
5) No additional medications

Current medications:

- Metformin 1000mg BID
- Lisinopril 20mg Daily
- Atorvastatin 40mg Daily

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+CKD

eGFR <60 mL/min per 1.73 m^2 OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+ASCVD/Indicators of High Risk

GLP-1 RA‡ with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

SGLT2i§ with proven HF benefit in this population

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

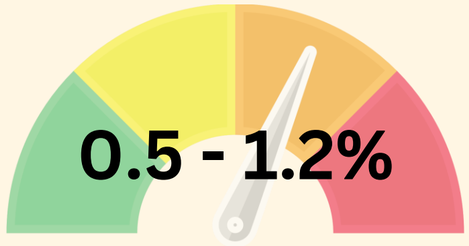
Neutral:
DPP-4i, Metformin

ADA Standards of Care 2023

type 2 DIABETES

- Primarily lowers fasting > post-prandial sugars

- 5 SGLT2i approved in the US for T2DM:
  - empagliflozin (Jardiance)
  - dapagliflozin (Farxiga)
  - canagliflozin (Invokana)
  - ertugliflozin (Steglatro)
  - bexagliflozin (Brenzavvy)



A1c Reduction Potential

Hypoglycemia Risk

ASCVD & HF Benefit

CKD Benefit

Weight Loss Potential

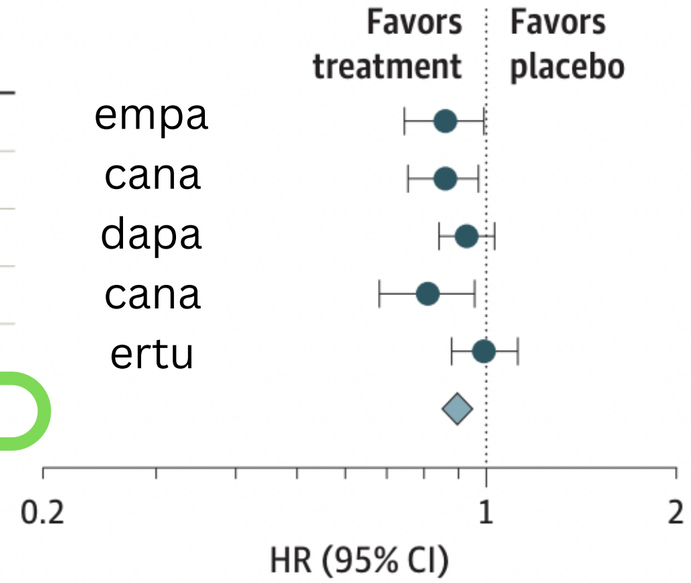
Cost

cvot DATA

Pooled data for composite 3-point Major Adverse Cardiovascular Event (MACE): MI, stroke, CV death

A Overall MACEs

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model ($Q = 5.22$; $df = 4$; $P = .27$; $I^2 = 23.4\%$)					0.90 (0.85-0.95)



CVOT: cardiovascular outcomes trials

McGuire DK, et al. *JAMA Cardiol* 2021;6(2):148-158.

cvot DATA

Only **empagliflozin** and **canagliflozin** have FDA approvals for reducing risk of **MACE (both)** and **CV death (empa)**

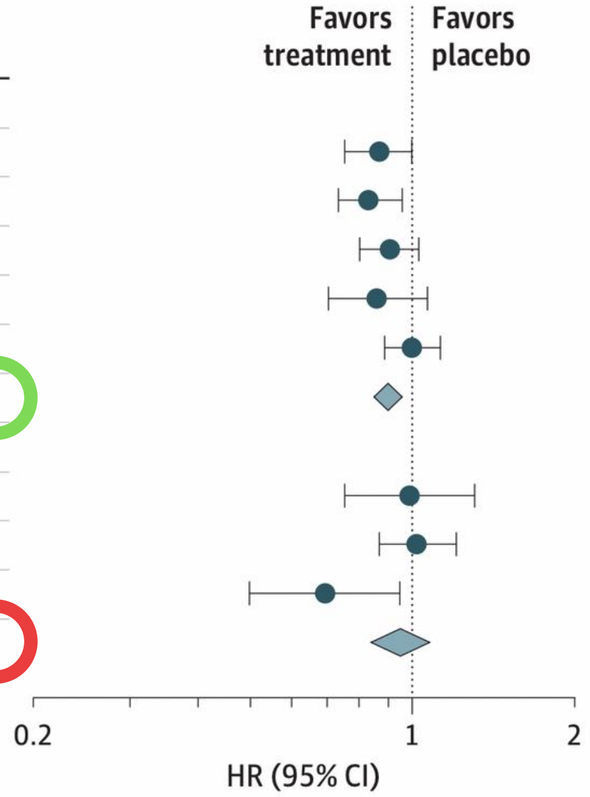
	EMPA-REG OUTCOME (2015)	**CANVAS Program (2017)**	**DECLARE-TIMI (2018)**
Intervention	empa vs placebo	cana vs placebo	dapa vs placebo
Population	T2DM + ASCVD	T2DM + ASCVD, or >2 risk factors	T2DM + ASCVD or risk factors
Primary Outcome HR (95% CI)	3-point MACE 0.86 (0.74 - 0.99)	3-point MACE 0.86 (0.75 - 0.97)	3 pt MACE 0.93 (0.84 - 1.03) CV death/HF hosp 0.83 (0.73-0.95)

cvot DATA

MACE benefit is greater in patients with **pre-existing ASCVD**

B MACEs by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)



McGuire DK, et al. *JAMA Cardiol* 2021;6(2):148-158.

cvot DATA

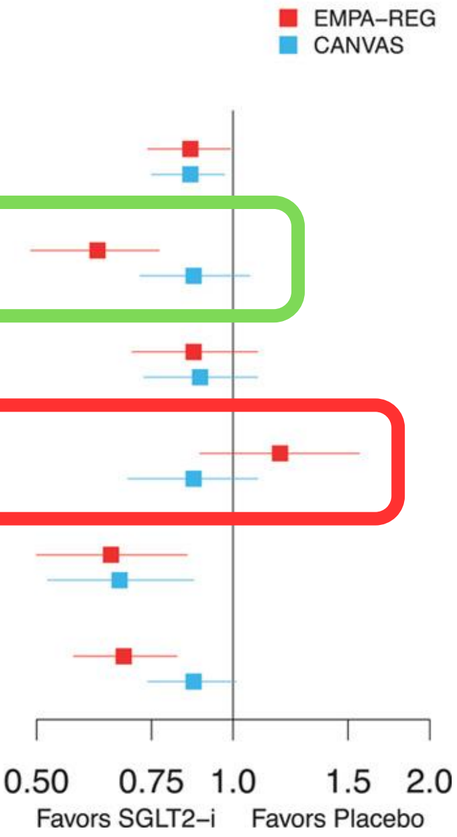
EMPA-REG OUTCOME only enrolled patients with ASCVD

MACE outcome driven primarily by reduction in CV death

No benefit in fatal and nonfatal stroke

B Summary of key cardiovascular outcomes

	Active Rate per 1000 patient-years	Placebo Rate per 1000 patient-years	Hazard Ratio (95% CI)
MACE-3	37.4	43.9	0.86 (0.74 – 0.99)
	26.9	31.5	0.86 (0.75 – 0.97)
CV Death	12.4	20.2	0.62 (0.49 – 0.77)
	11.6	12.8	0.87 (0.72 – 1.06)
Fatal and nonfatal MI	16.8	19.3	0.87 (0.70 – 1.09)
	11.2	12.6	0.89 (0.73 – 1.09)
Fatal and nonfatal stroke	12.3	10.5	1.18 (0.89 – 1.56)
	7.9	9.6	0.87 (0.69 – 1.09)
Heart failure hospitalization	19.4	14.5	0.65 (0.50 – 0.85)
	5.5	8.7	0.67 (0.52 – 0.87)
All cause mortality	19.4	28.6	0.68 (0.57 – 0.82)
	17.3	19.5	0.87 (0.74 – 1.01)



Bethel MA. *Circulation* 2018;2018;137(12):1218-1220.

patient CASE

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also lowers ASCVD risk, but relatively contraindicated due to hx of gallstone pancreatitis

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take home POINTS

Empagliflozin, canagliflozin reduce risk of 3-point MACE

Benefit is greater for secondary ASCVD prevention

Empagliflozin reduces risk of CV death and all-cause mortality

These SGLT2is are recommended regardless of A1c to reduce CV risk

patient CASE

60 y/o M with a pmhx of CKD stage 3 with microalbuminuria and type II DM. His A1C is 8.5%.

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KDIGO 2022

Recommendation 1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

SGLT2i have safety and benefit in CKD patients, **even for those without T2DM**

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.

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Choice of SGLT2i should prioritize agents with **documented kidney or CV benefits**

It is reasonable to **withold SGLT2i during times of prolonged fasting, surgery, or critical medical illness** (greater risk for ketosis)

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A **reversible decrease in eGFR** when starting SGLT2i may occur and is generally **not an indication to discontinue therapy**

Reasonable to **continue SGLT2i even if eGFR falls <20 mL/min/1.73m2,** unless not tolerated or kidney replacement therapy started

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Choice of SGLT2i should prioritize agents with **documented kidney or CV benefits**

A **reversible decrease in eGFR** when starting SGLT2i may occur and is generally **not an indication to discontinue therapy**

If a patient is at risk for hypovolemia, **consider decreasing thiazide or loop diuretic** dosages before starting SGLT2i

It is reasonable to **withold SGLT2i during times of prolonged fasting, surgery, or critical medical illness** (greater risk for ketosis)

Reasonable to **continue SGLT2i even if eGFR falls <20 mL/min/1.73m2,** unless not tolerated or kidney replacement therapy started

Recommendations to use SGLT2i do not apply to kidney transplant recipients

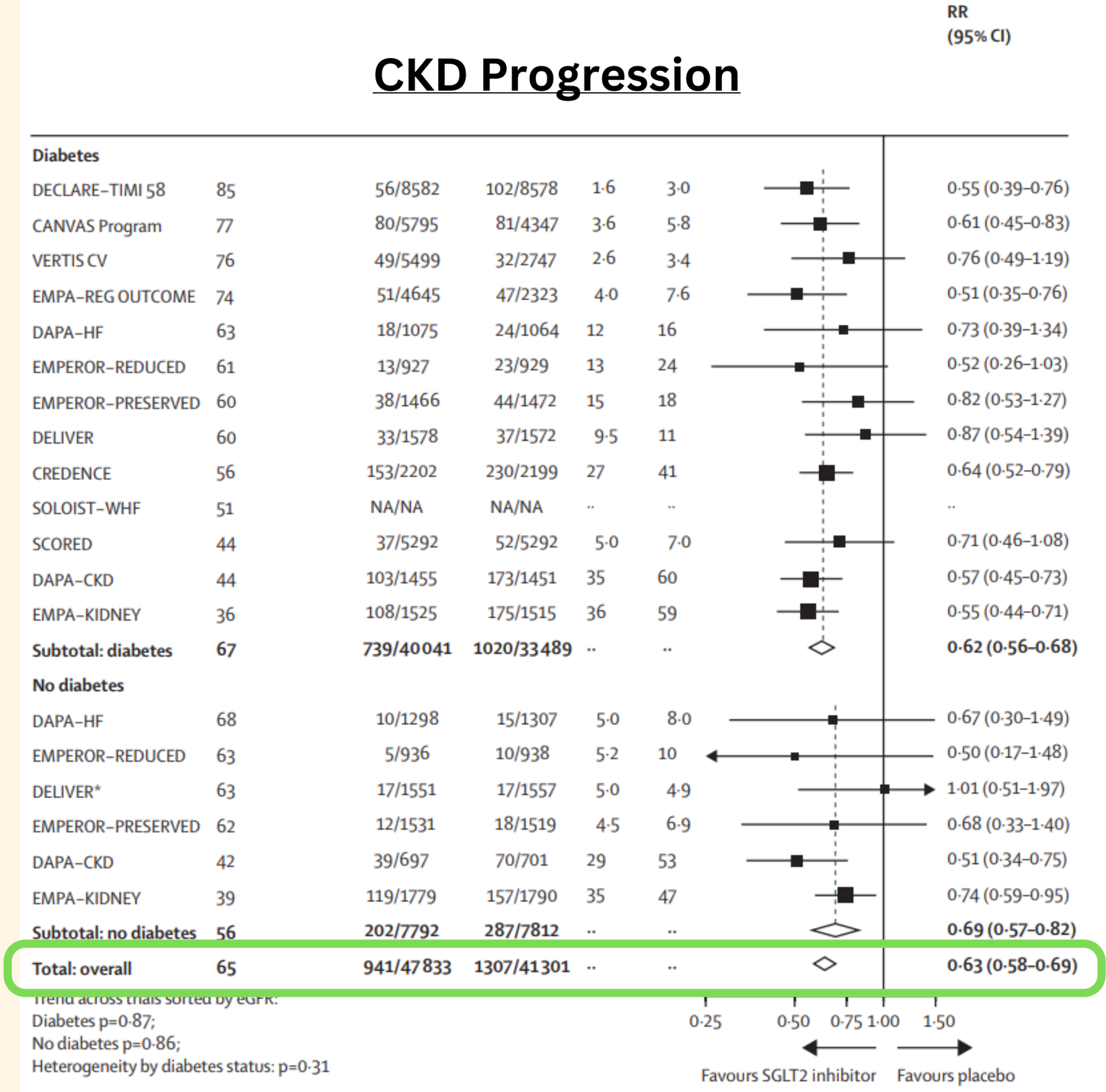
KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.

ckd DATA

SGLT2i users had a **37% risk reduction in CKD progression,** regardless of DM status

Benefits appear greater in patients with higher albuminuria (EMPA-KIDNEY)

CKD Progression



Nuffield Department of Population Health Renal Studies Group: SGLT2i Meta-Analysis CardioRenal Trialists' Consortium. *Lancet* 2022;400:1788-1801.

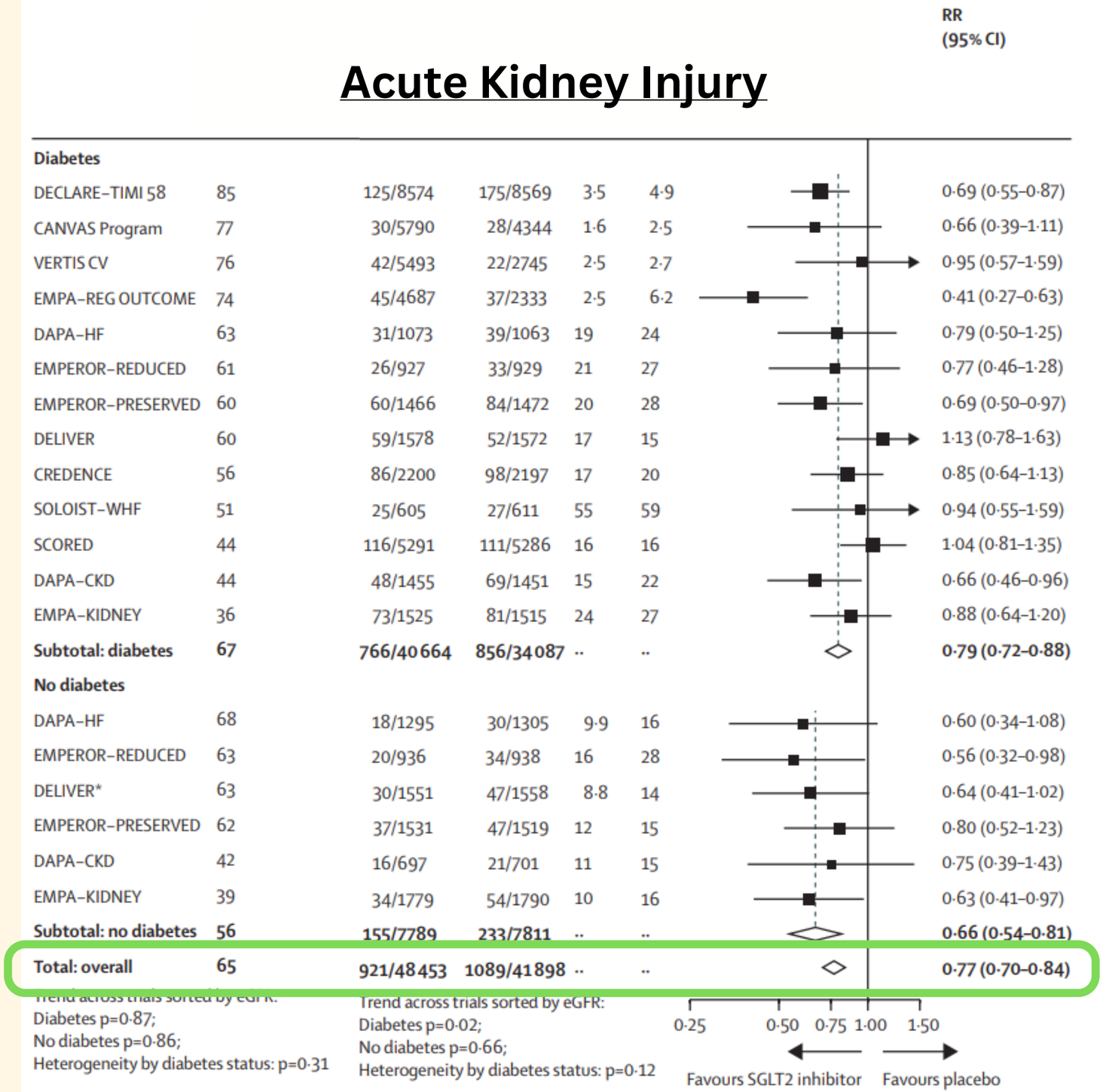
ckd

DATA

SGLT2i users had a **23% risk reduction in AKI**, regardless of DM status

None of the large trials found increased risk for AKI

Acute Kidney Injury



Nuffield Department of Population Health Renal Studies Group: SGLT2i Meta-Analysis CardioRenal Trialists' Consortium. *Lancet* 2022;400:1788-1801.

KDIGO 2023

Recommendation 3.6.2: We recommend treating adults with CKD and heart failure or eGFR ≥20 ml/min per 1.73 m^2 with urine albumin-to-creatinine ratio (ACR) ≥200 mg/g with an SGLT2i (1A).

Recommendation 3.6.3: We suggest treating adults with eGFR ≥20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g with an SGLT2i (2B).

July 2023 public draft for review

"This recommendation places **high value** on the **large relative reductions in risk for kidney disease progression** in a series of large, placebo controlled RCTs"

"This recommendation places **high value** on **demonstrable net absolute benefits versus absolute harms** in people with CKD (particularly in those without DM at very low risk of ketoacidosis"

"This recommendation places **moderate value** on the benefits of SGLT2i on risk of AKI, CV death, hospitalization for HF and MI, risk of hospitalization from any cause"

KDIGO 2023 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: Public Review Draft July 2023

patient CASE

60 y/o M with a pmhx of CKD stage 3 with microalbuminuria and type II DM. His A1C is 8.5%.

How would you optimize their DM management?

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take home POINTS

Empa, cana, and dapa reduce kidney disease progression*

*benefit may be greater in those with more albuminuria

These SGLT2i are recommended in CKD regardless of T2DM status

Reversible drop in eGFR may occur; generally can continue SGLT2i

KDIGO 2023 CKD Guideline coming soon

patient CASE

67 y/o F with a pmhx of HFpEF from uncontrolled HTN. She presents to clinic for follow up of her HF.

Current medications:
Spironolactone 25mg daily
Chlorthalidone 25mg daily
Lasix 40mg daily

VS: Normal

PE: Euvolemic

Labs: BMP normal except eGFR 40

How would you optimize their HF management?

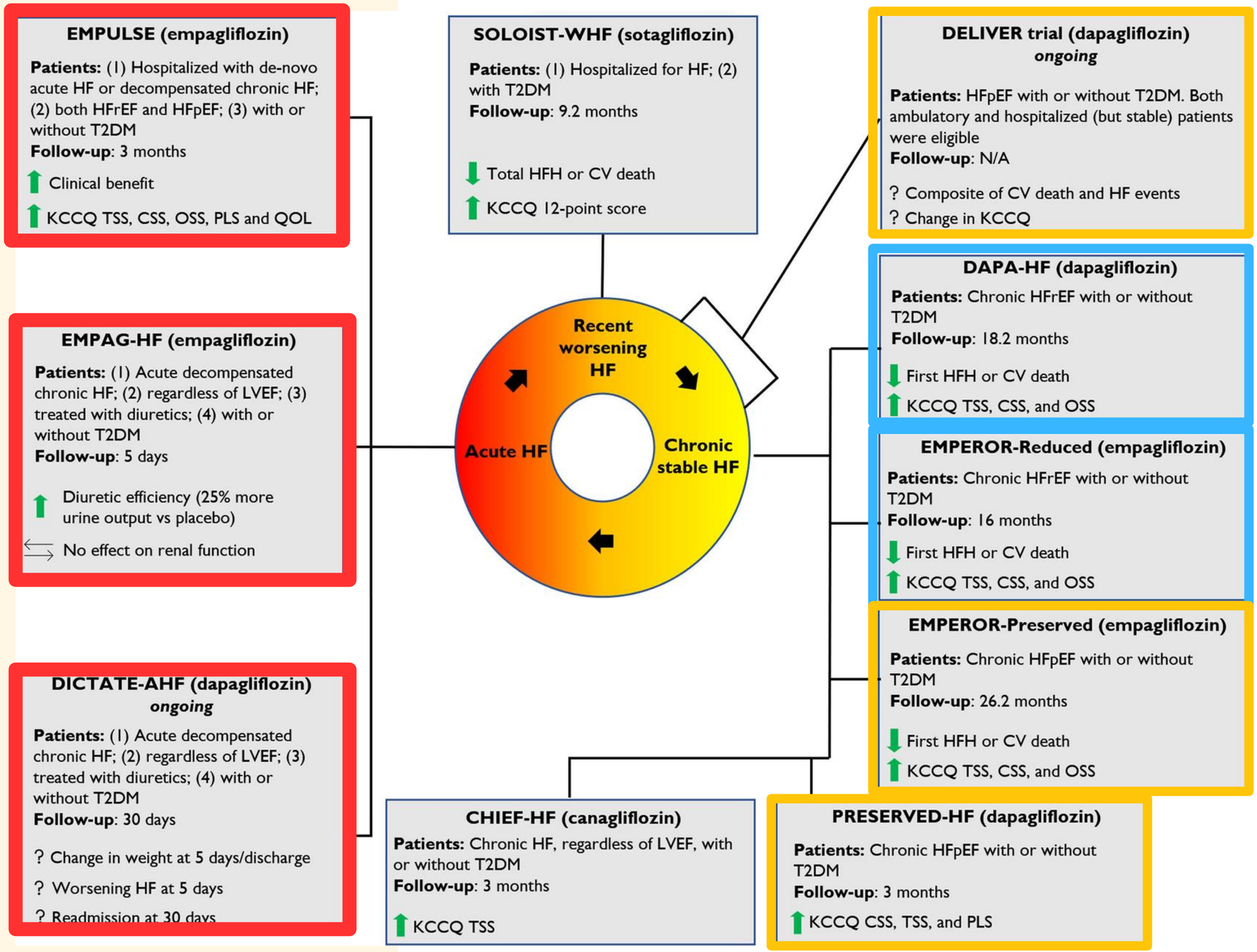
heart FAILURE

SGLT2i have been studied across the HF spectrum

HFrEF trials

HFpEF trials

ADHF trials



Anker SD. *Circulation* 2022;146(4):299-302.

HFrEF

LVEF ≤40%

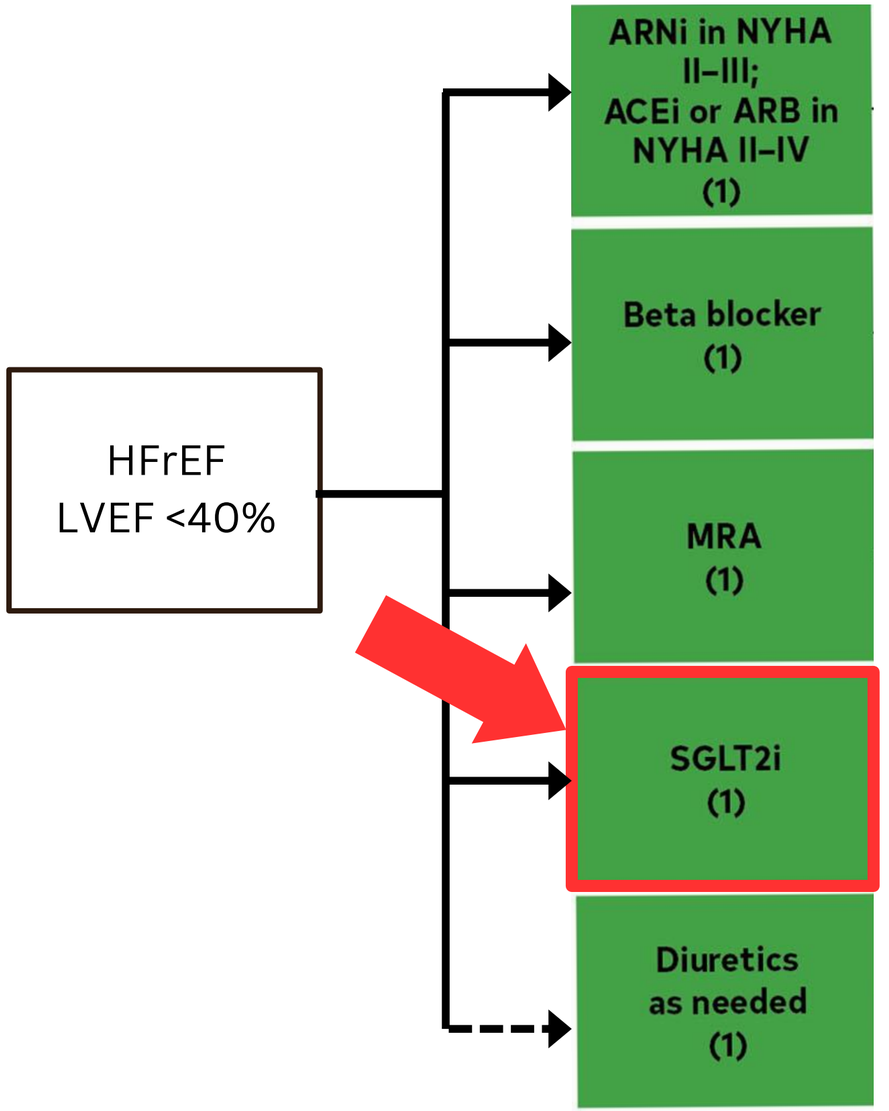
Data based on DAPA-HF (**dapa**; 2019) and EMPEROR-REDUCED (**empa**; 2020)

Dapa and empa reduce risk of **CV death** and **HF hospitalizations** by **25%**

Benefit primarily driven by **HF hospitalization reduction**

Benefit similar regardless of T2DM status

Treatment of HFrEF



2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure
Vaduganathan M. *Lancet* 2022;400:757-767.

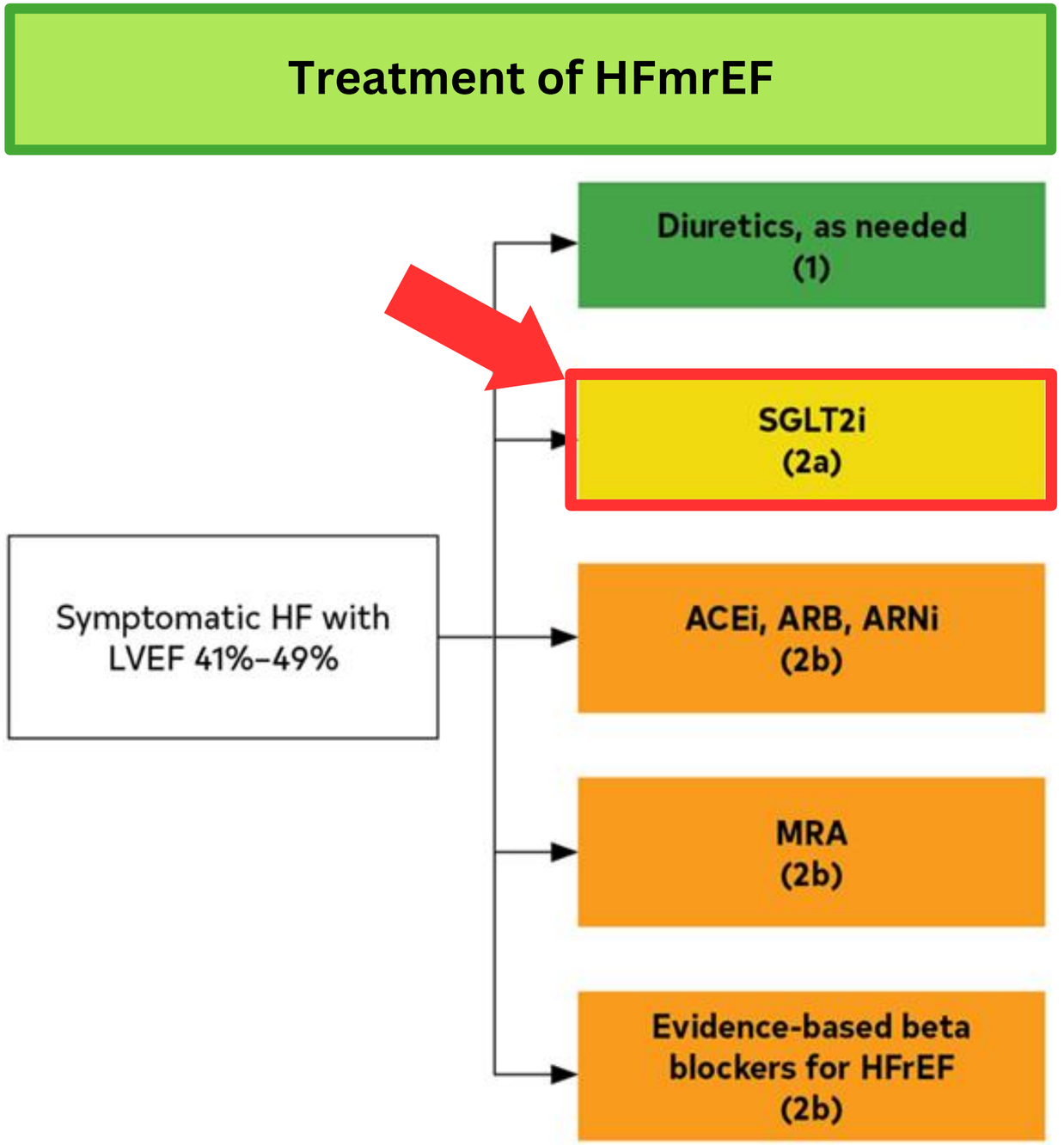
HFmrEF

LVEF 41-49%

No prospective RCTs exclusively in HFmrEF

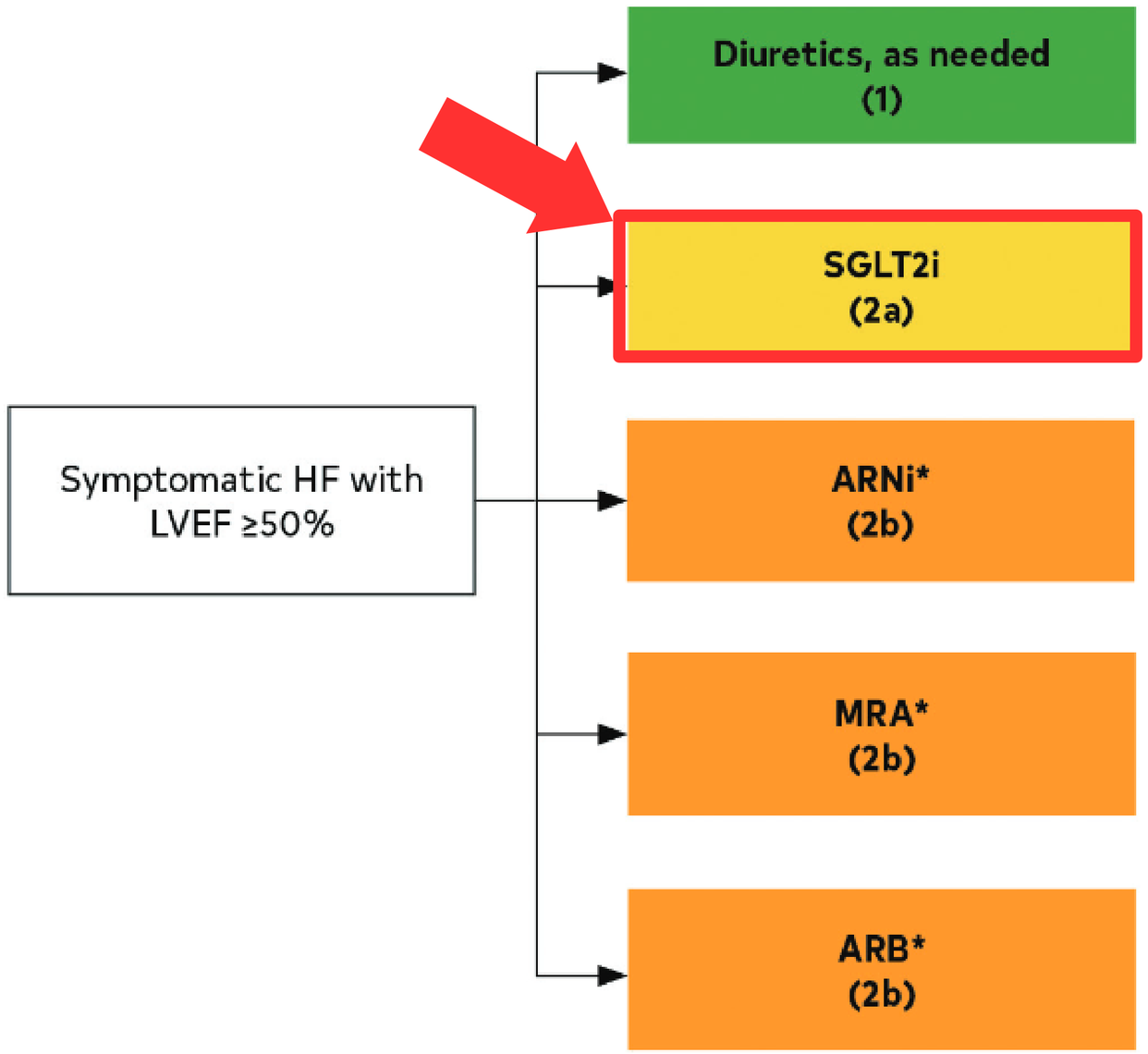
Data based on subgroup/post-hoc analyses of EMPEROR-Preserved trial (**empa** in HFpEF)

Largest benefit (CV death, HF hospitalizations) among patients with HFmrEF
(vs LVEF 50-60%, ≥60%)



2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Treatment of HFpEF



HFpEF

LVEF ≥ 50%

Data based on EMPEROR-Preserved (**empa**; 2020) and DELIVER (**dapa**; 2022)

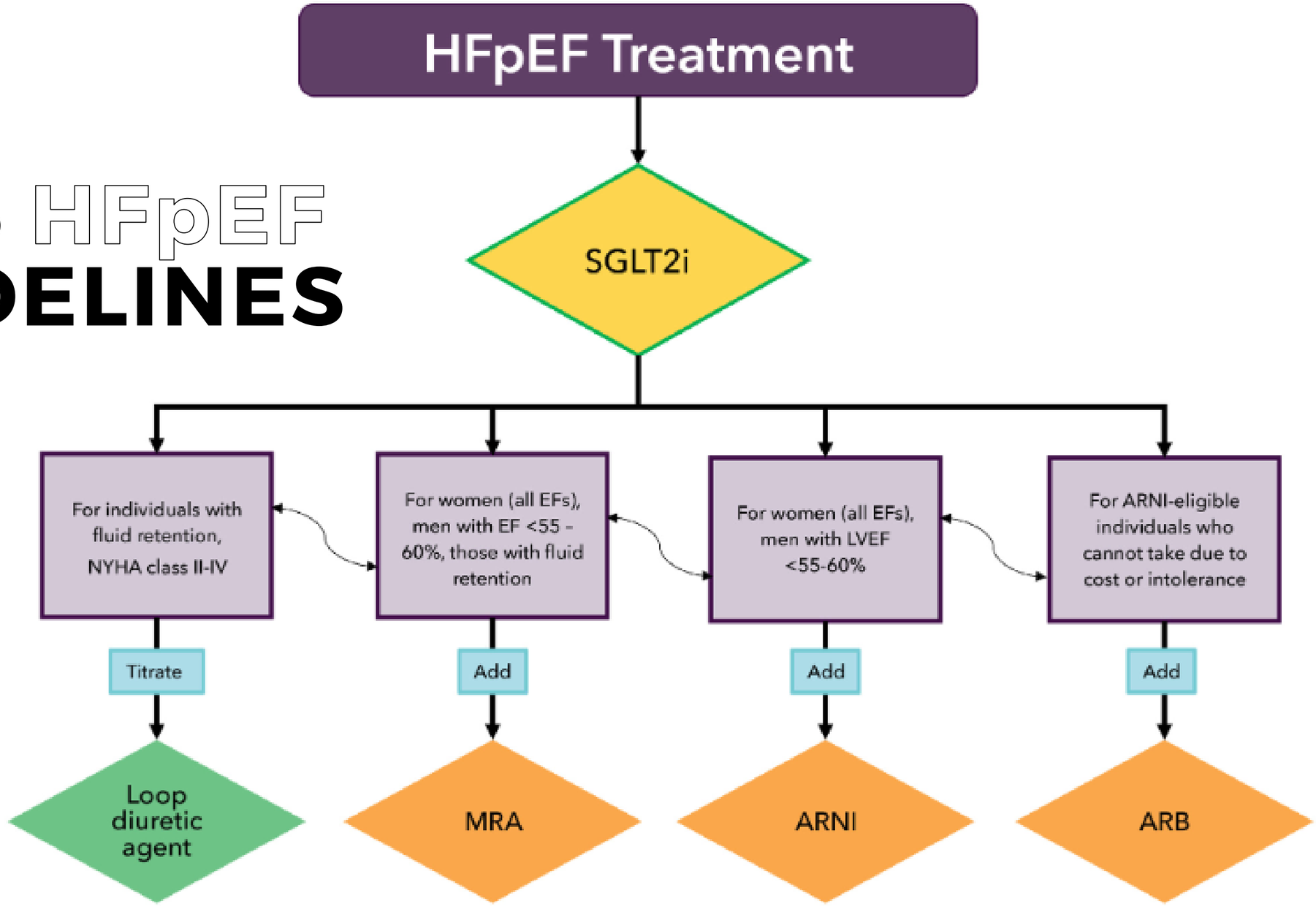
Empa and dapa reduce risk of **CV death** and **HF hospitalizations** by **20%**

Benefit primarily driven by **HF hospitalization reduction**

Benefit similar regardless of T2DM status

Kittleson MM, et al. *J Am Coll Cardiol* 2023
Vaduganathan M. Lancet 2022;400:757-767.

2023 HFpEF GUIDELINES



2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction

patient CASE

67 y/o F with a pmhx of HFpEF from uncontrolled HTN. She presents to clinic for follow up of her HF.

How would you optimize their HF management?

1) Add ARNI
2) Increase Lasix
3) Add SGLT2i
4) Add ARB

Current medications:
Spironolactone 25mg daily
Chlorthalidone 25mg daily
Lasix 40mg daily

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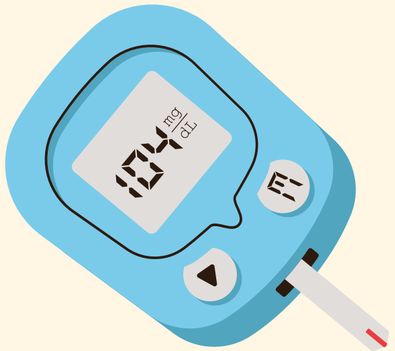
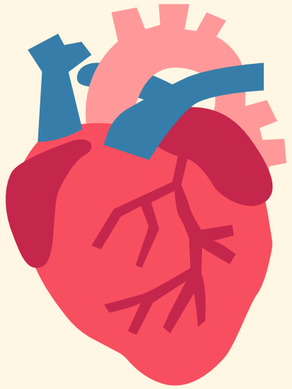
take home **POINTS**

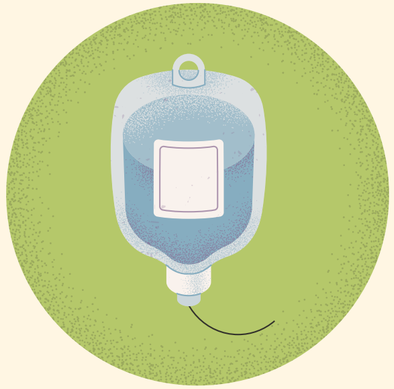
SGLT2i (empa, dapa) are mainstay of therapy in HF <u>regardless of:</u>



Diabetes



LVEF



HF status*

*except cardiogenic shock

audience QUESTION

67 y/o with pmhx of HFpEF. You plan to start an SGLT2i to optimize HF management.

Which of the following side effects would you counsel on?

1) Increased risk of genital mycotic infections
2) Increased risk of UTIs
3) Increased risk of amputations
4) Euglycemic DKA

urinary tract INFECTIONS

Multiple systematic reviews show **no increased risk for UTI with SGLT2i**

SGLT2i **do** increase risk for **genital infections**

Urinary Tract Infections	
	Relative Risk (95% CI)
SGTL2i vs control	1.05 (0.98 - 1.12)
Subgroup by individual SGLT2i (interaction p=0.03)	
canagliflozin	1.13 (0.97 - 1.33)
dapagliflozin	1.34 (1.11 - 1.63)
empagliflozin	1.00 (0.93 - 1.08)

Genital Infections	
	Relative Risk (95% CI)
SGTL2i vs control	3.30 (2.74 - 3.99)
Subgroup by individual SGLT2i (interaction p=.04)	
canagliflozin	1.13 (0.97 - 1.33)
dapagliflozin	1.34 (1.11 - 1.63)
empagliflozin	1.00 (0.93 - 1.08)

Liu J. *Sci Rep* 2017;2824:doi:10.1038/s41598-017-02733-w

urinary tract INFECTIONS

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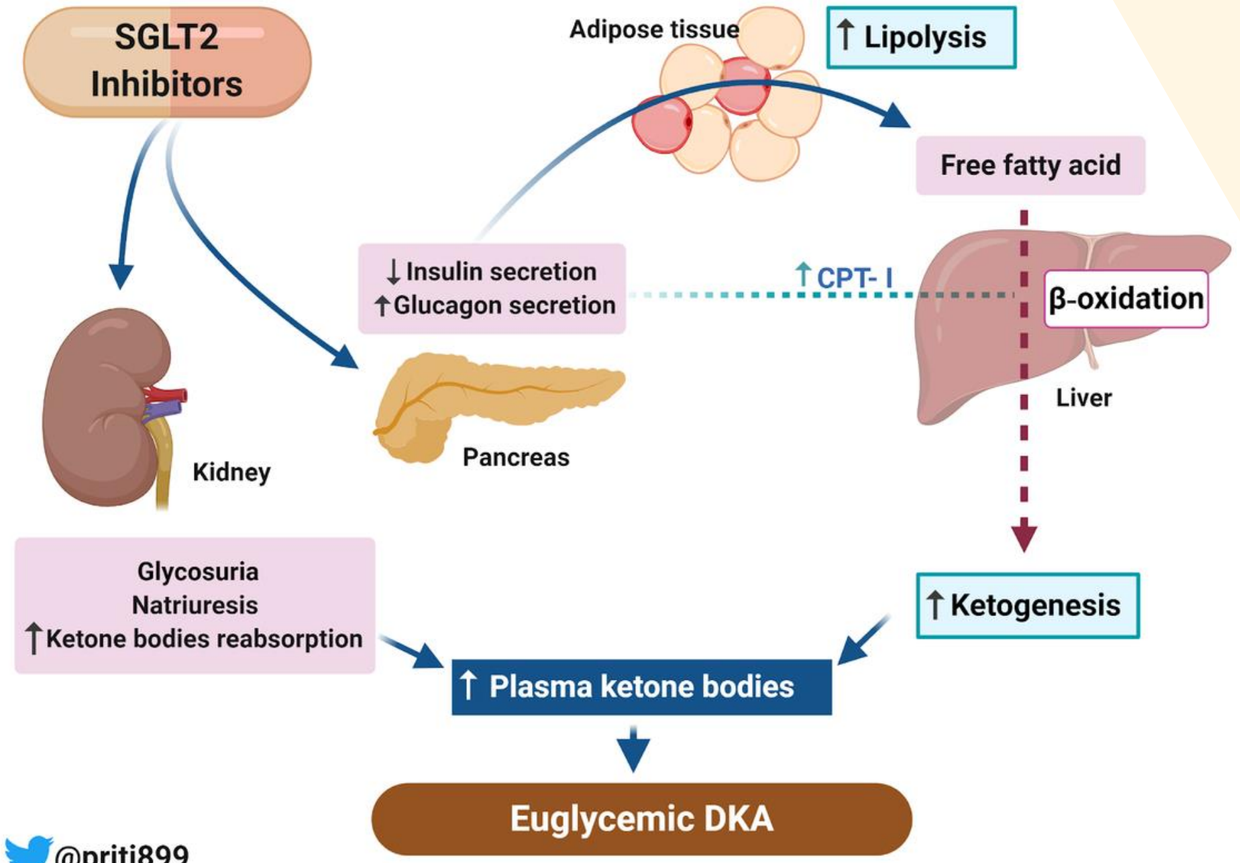
Genital Infections	
	Relative Risk (95% CI)
SGTL2i vs control	3.30 (2.74 - 3.99)
Subgroup by individual SGLT2i (interaction p=.03)	
canagliflozin	4.45 (3.49 - 5.67)
dapagliflozin	3.22 (1.95 - 5.32)
empagliflozin	3.14 (2.29 - 4.30)

Liu J. *Sci Rep* 2017;2824:doi:10.1038/s41598-017-02733-w

euglycemic DKA



@priti899

01 Epidemiology

- 50% cases associated with precipitating event
- Low documented rates for T2DM (~0.1%)
- **Median time after SGLT2i initiation: 2 weeks**

02 Mechanism

- ↓blood glucose
- ↓insulin,↑glucagon → lipolysis
- **volume depletion** → lipolysis and ketogenesis
- SGLT2i may↓urinary ketone excretion

03 Risk Factors

- Reduced PO intake
- Acute illness
- ↓insulin dose
- Use in T1DM, LADA

Blau JE. *Diabetes Metab Res Rev* 2017;33(8):10.1002
Qiu H. *Diabetes Metab Res Rev* 2017;33:0.

eDKA

RISK MITIGATION

Sick Day Protocol

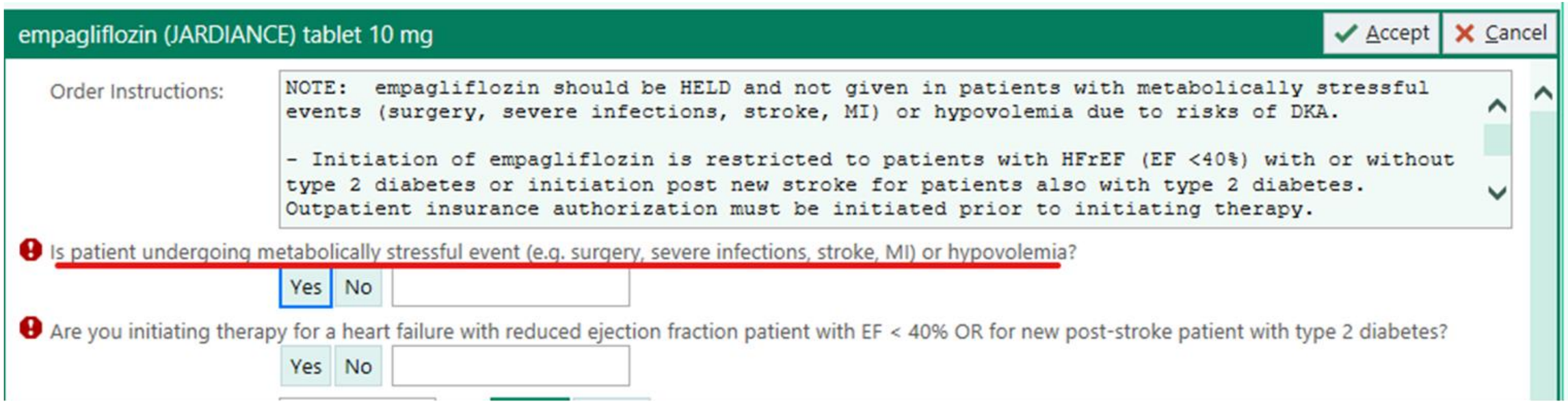
- temporarily **hold SGLT2i**
- keep drinking and eating, if possible
- **check BG, blood ketone** levels more often
- seek medical help early

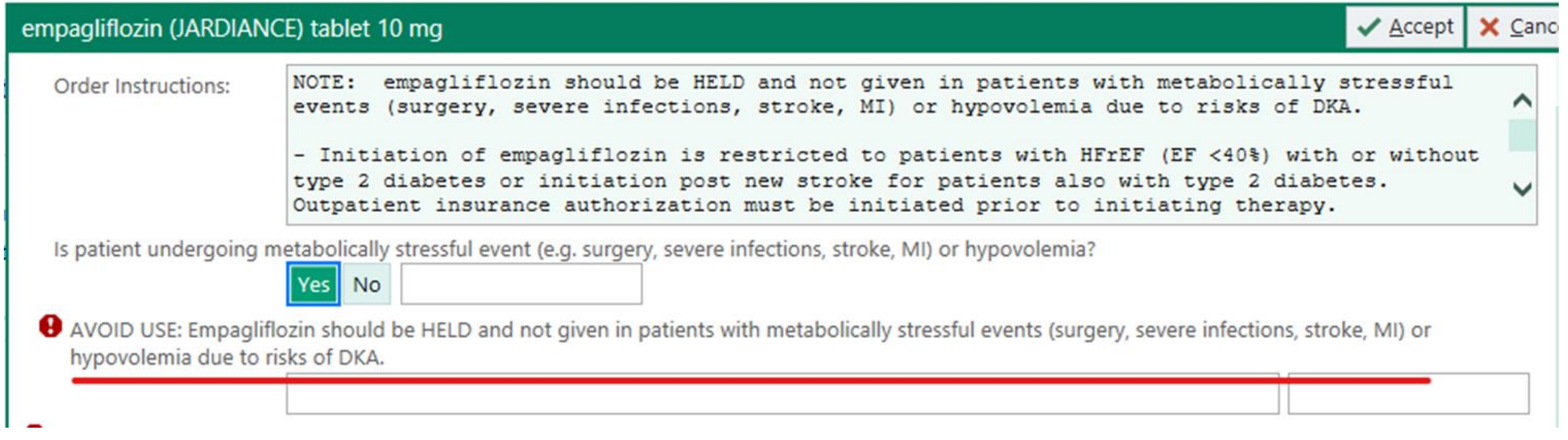
Perioperative Care

- hold SGLT2i day of day-stay procedures
- **limit fasting** to minimum required
- **hold SGTL2i ≥2 days before procedure** requiring hospital stay and/or bowel prep
- **check BG, ketone levels** on admission
- **restart SGLT2i when eating/drinking normally**

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.

eDKA RISK MITIGATION





other rare
SIDE EFFECTS

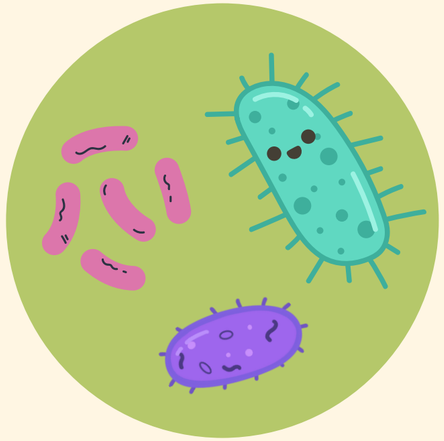
Higher rates of amputations, fracture reported in CANVAS (canagliflozin), however **not observed in other RCTs**

Multiple systematic reviews found **no increased risk** for hypovolemia, lower limb amputations, and bone fracture vs placebo

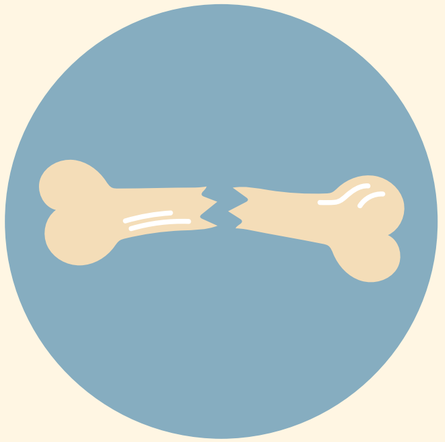
Benefits generally outweigh these rare, potential risks

Hypovolemia

Amputations



Fournier's Gangrene



Fracture

D'Andrea E. *JAMA Intern Med* 2023;183(3):242-54.
Vukadinovic D. *Eur J Heart Fail* 2022;24:1625-32.
Donnan JR. BMJ Open 2019;9:e022577.

audience QUESTION

67 y/o with pmhx of HFpEF. You plan to start an SGLT2 to optimize HF management.

Which of the following side effects would you counsel on?

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sglt2i SUMMARY

		ASCVD	HF	CKD
Efficacy				
SGLT2i	empa (Jardiance)			
	cana (Invokana)			
	dapa (Farxiga)			
Current Guideline Recommendations				

sglt2i SUMMARY

		ASCVD	HF	CKD
Efficacy		↓ 3-pt MACE		
SGLT2i	**empa (Jardiance)**			
	cana (Invokana)			
	dapa (Farxiga)			
Current Guideline Recommendations		First line in T2DM + ASCVD, <u>regardless of A1c</u>		

sglt2i SUMMARY

		ASCVD	HF	CKD
Efficacy		↓ 3-pt MACE	↓ HF hospitalization and CV mortality	
SGLT2i	**empa (Jardiance)**			
	cana (Invokana)			
	dapa (Farxiga)			
Current Guideline Recommendations		First line in T2DM + ASCVD, <u>regardless of A1c</u>	HFrEF: <u>1A</u> HFpEF: <u>2A</u>	

sglt2i SUMMARY

		ASCVD	HF	CKD
Efficacy		↓ 3-pt MACE	↓ HF hospitalization and CV mortality	↓ CKD progression and AKI
SGLT2i	**empa (Jardiance)**	✓	✓	✓
	cana (Invokana)	✓		✓
	dapa (Farxiga)		✓	✓
Current Guideline Recommendations		First line in T2DM + ASCVD, regardless of A1c	HFrEF: 1A	CKD (GFR >20) + T2DM: 1A
			HFpEF: 2A	

thank YOU!

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