From Guidelines to General Practice – SGLT2i and GLP-1RA for Cardiovascular and Kidney Disease

Sandeep Das, M.D., M.P.H.
Nicholas Hendren, M.D.
Ildiko Lingvay, M.D., M.P.H., M.S.C.S.
Robert Toto, M.D.
Vlad G. Zaha, M.D., Ph.D.

Disclosures

Sandeep Das, M.D., M.P.H.

Associate Editor, *Circulation*

Nicholas Hendren, M.D.

None

Ildiko Lingvay, M.D., M.P.H., M.S.C.S.

Grant or Contract: NovoNordisk, Pfizer, Merck, Mylan, Sanofi

Independent Contractor: NovoNordisk, AstraZeneca, BI, Lilly, Valeritas, Intarcia, Mannkind, ADA, Janssen, Intercept, Zealand Pharma, Bayer, TARGETPharma, Duke CRI

Robert Toto, M.D.

Employment: Reata Pharmaceuticals

Independent Contractor: Amgen, Boehringer-Ingelheim, Bayer, Astra-Zeneca, Quintiles, Quest Diagnostics, MedScape, Relypsa

Vlad G. Zaha, M.D., Ph.D.

Associate Editor, *Circulation*

Objectives

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i) and Glucagon-like Peptide 1 Receptor Antagonists (GLP-1RA) in type 2 diabetes, ischemic cardiomyopathy, chronic kidney disease, heart failure

- When to consider
- Why to consider
- Which one to pick (or both), additional benefits
- Treatment consideration
  - SGLT2i – how to handle side effects, when to stop, "AKI"
  - GLP-1RA – titration, GI adverse effects

Case 1

Case Presentation DM

Your 58-year-old patient with a history of type 2 diabetes, hypertension, obesity, and hypercholesterolemia and a prior myocardial infarction was admitted recently with pneumonia, but is now asymptomatic and fully recovered. They mentioned a "low" while undergoing physical therapy, but has not had a second episode since.

BP is 122/68, HR 68, BMI 32.2

Medication regimen: glipizide 5 mg, atorvastatin 40 mg, aspirin 81 mg, lisinopril 40 mg

Recent labs: eGFR 78, LDL 68, HbA1c 6.6%

Ejection fraction post-procedure was 55%

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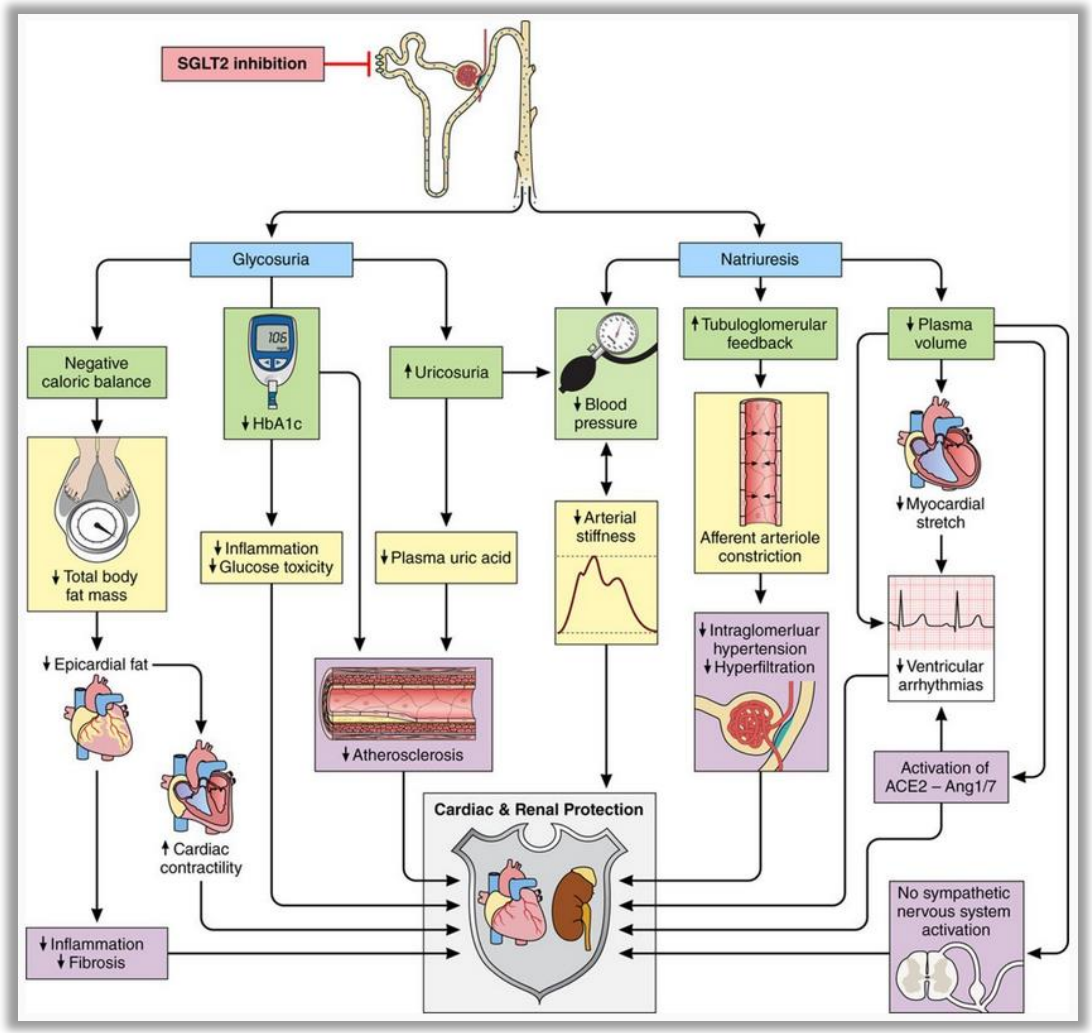
What changes, if any, would you recommend to this pharmacologic regimen?

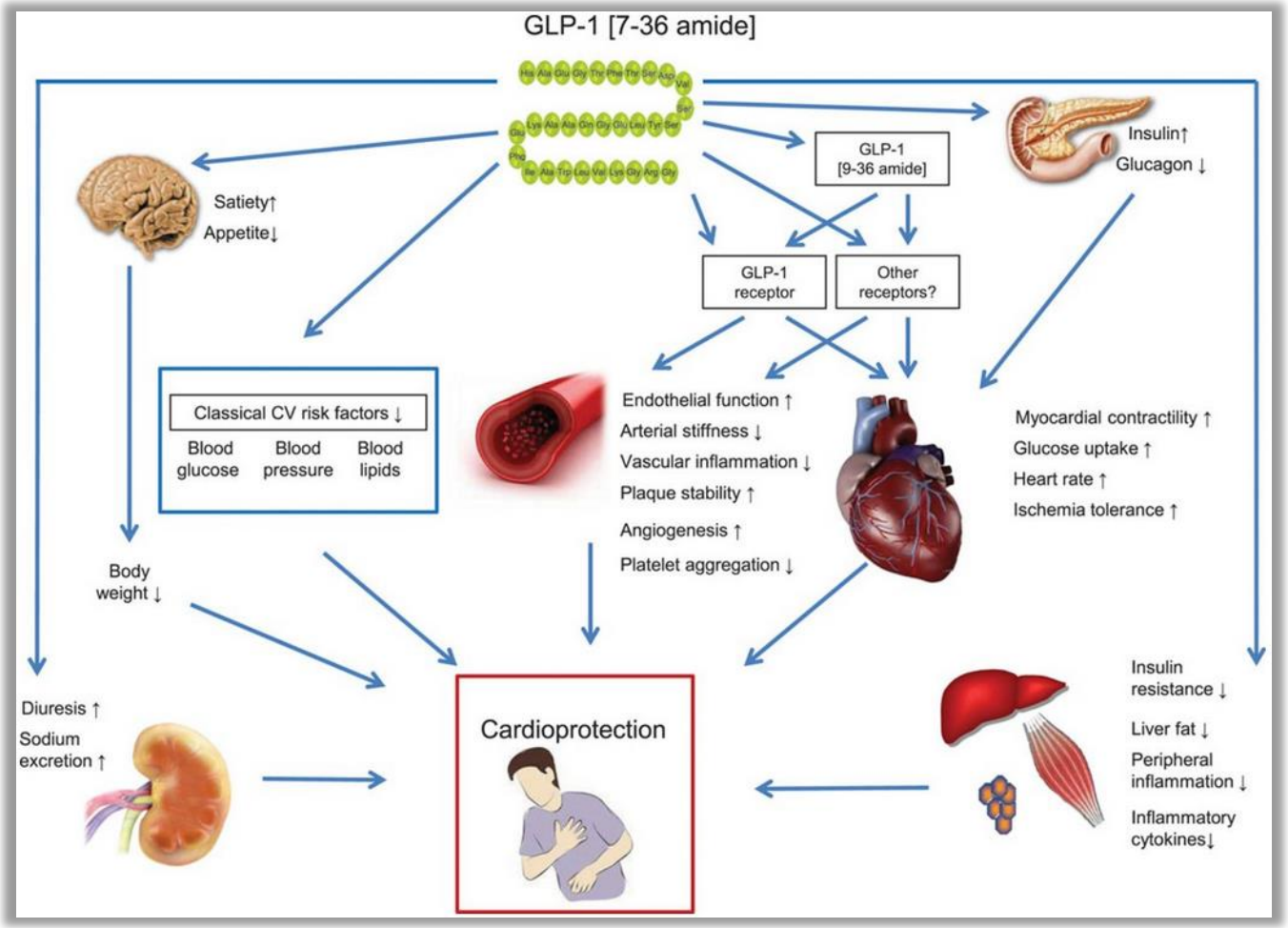
SGLT2i



- Block uptake of glucose and sodium in the proximal renal tubule
- Glucosuria
  - Weight loss
  - Glycemic control
  - Uricosuria
- Natriuresis
  - BP control
  - Volume control
  - Decrease glomerular hyperfiltration

Heerspink HJL, et al. Circulation. 2016;134:752–772

GLP-1RA



Nauck MA, et al. Circulation. 2017;136:849–870

SGLT2i – Practical Tips

- Recommend holding 3 days before surgery
- Hold if vomiting and unable to keep down food – “Sick day” rule
- Avoid in type I diabetes
- Avoid in very low calorie or ketogenic diets

- DKA risk is low but 2-10x higher than placebo
- No difference in UTI rates in EMPAREG, EMPEROR-Reduced, or DAPA-HF trials

GLP-1RA – Practical Tips

- Glycemic management and care coordination
  - Hypoglycemia risk if used with insulin or sulfonylureas
  - Overlap mechanistically with DPP4 inhibitors
- Caution in patients with a history of
  - Diabetic gastroparesis
  - Prior gastric surgery
  - Acute pancreatitis
  - ESRD
- Contraindications
  - Medullary thyroid CA or MEN2
  - Pregnant or breast feeding

SGLT2i/GLP1-RA in Diabetes – Take Home Points

- Both glycemic control (HbA1c) and weight management are co-primary treatment goals for diabetes management
- Metformin no longer recommended as the only first line option
- In patients at high-risk of CV disease, GLP1-RA/SGLT2i should be added irrespective of glycemic control (HbA1c)
- Consider de-escalating other agents without proven CV benefits, especially if they carry a risk for hypoglycemia

Case 2

Case Presentation MI

Your 56 year old patient presents for post hospital follow up after a recent myocardial infarction (MI) and percutaneous coronary intervention (PCI).

- Medical Hx: Prior to his MI he “never had any health problems”
- Physical exam: BMI is 31 kg/m^2, BP is 122/76
- Discharge medications: aspirin 81 mg, prasugrel 10 mg, losartan 50 mg, atorvastatin 80 mg daily; metoprolol tartrate 25 mg, metformin 500 mg twice a day
- Labs during his admission: Cr 1.5, UA protein +, LDL of 155, A1C of 7.8%
- Echocardiogram - normal ejection fraction

He wants to do anything possible to avoid having another heart attack.

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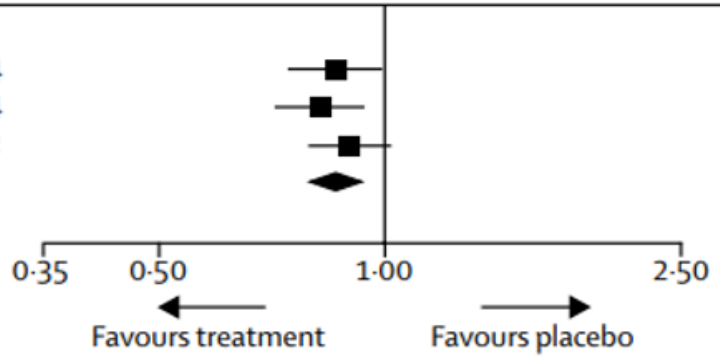
What medication changes, if any, would you recommend?

SGLT2i – Major Adverse Cardiovascular Events (MACE)

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**

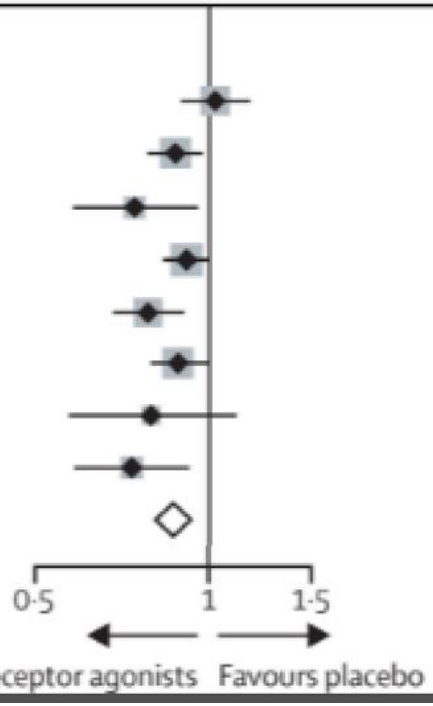


~14% MACE benefit in secondary prevention

Zelniker, et al. Lancet 2019; 393: 31-39

Meta Analysis of GLP-1RA RCTs – MACE

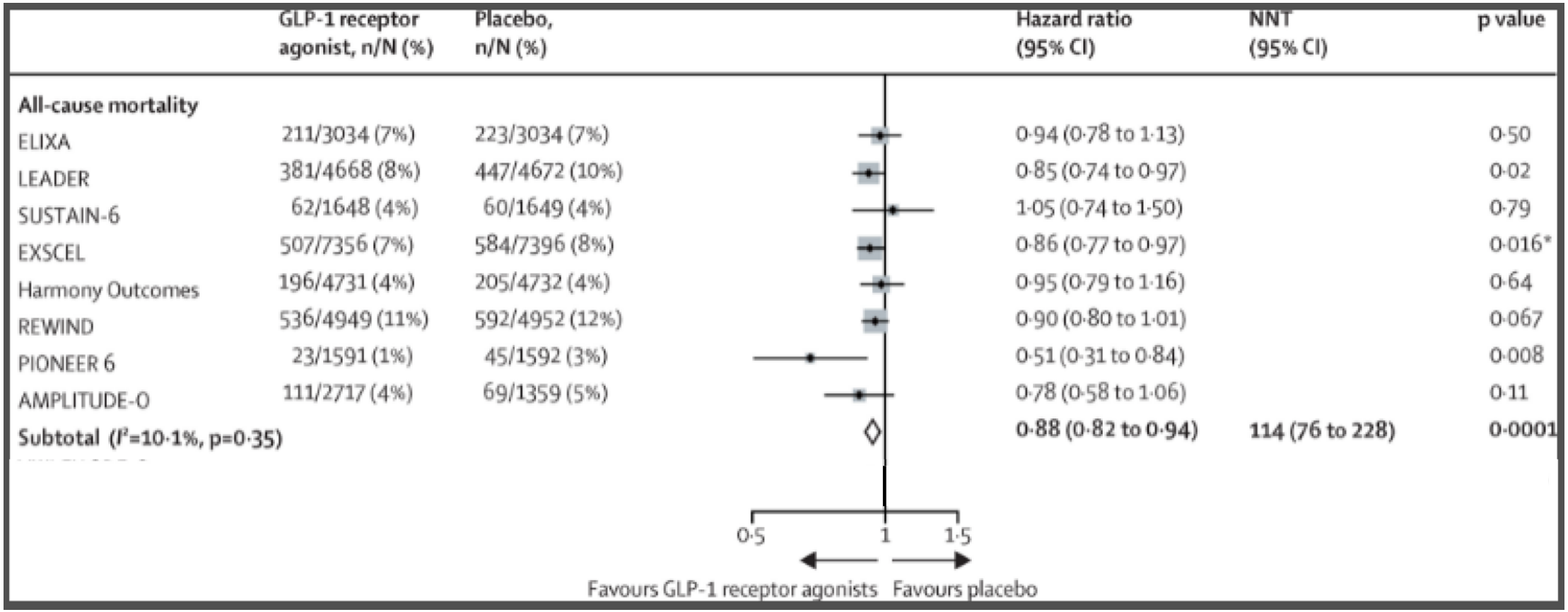
	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**



14% reduction in MACE

Sattar N, et al. Lancet Diabetes Endocrinol 2021;9(10):653-662

Meta Analysis of GLP-1 RA RCTs – All Cause Mortality



	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78 to 1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74 to 0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74 to 1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77 to 0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	205/4732 (4%)	0·95 (0·79 to 1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80 to 1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31 to 0·84)		0·008
AMPLITUDE-O	111/2717 (4%)	69/1359 (5%)	0·78 (0·58 to 1·06)		0·11
Subtotal (I^2=10·1%, p=0·35)			**0·88 (0·82 to 0·94)**	**114 (76 to 228)**	**0·0001**

12% reduction in all-cause mortality

Sattar N, et al. Lancet Diabetes Endocrinol 2021;9(10):653-662

SGLT2i and GLP-1RA – Take Home Points

~15% reduction in MACE (both) and 12% reduction in all cause mortality (GLP1-RA) in patients with ASCVD and T2D

Case 3

Case Presentation CKD

- 68 y/o man with T2D x 20 years with hypertension, hyperlipidemia, erectile dysfunction, NSTEMI (2016), retinopathy, neuropathy, NASH, smokes marijuana daily to reduce pain of DPNP.
- Current meds: metformin 500 mg BID, glipizide 20 mg q hs, atorvastatin 80 mg, ASA 81, losartan 100 mg, duloxetine 60 mg
- Physical exam: BMI 32 kg/m^2, BP 128/74 mmHg. Fundoscopic exam: non-proliferative retinopathy. Neuro exam: Loss of vibratory and temperature sensation feet bilaterally
- Labs: A1c: 7.8 %, eGFR: 42 $ml/min/1.73\ m^2$, Hgb: 12.2 g, ACR: 398 mg/g; LVEF 42%

Case Presentation CKD

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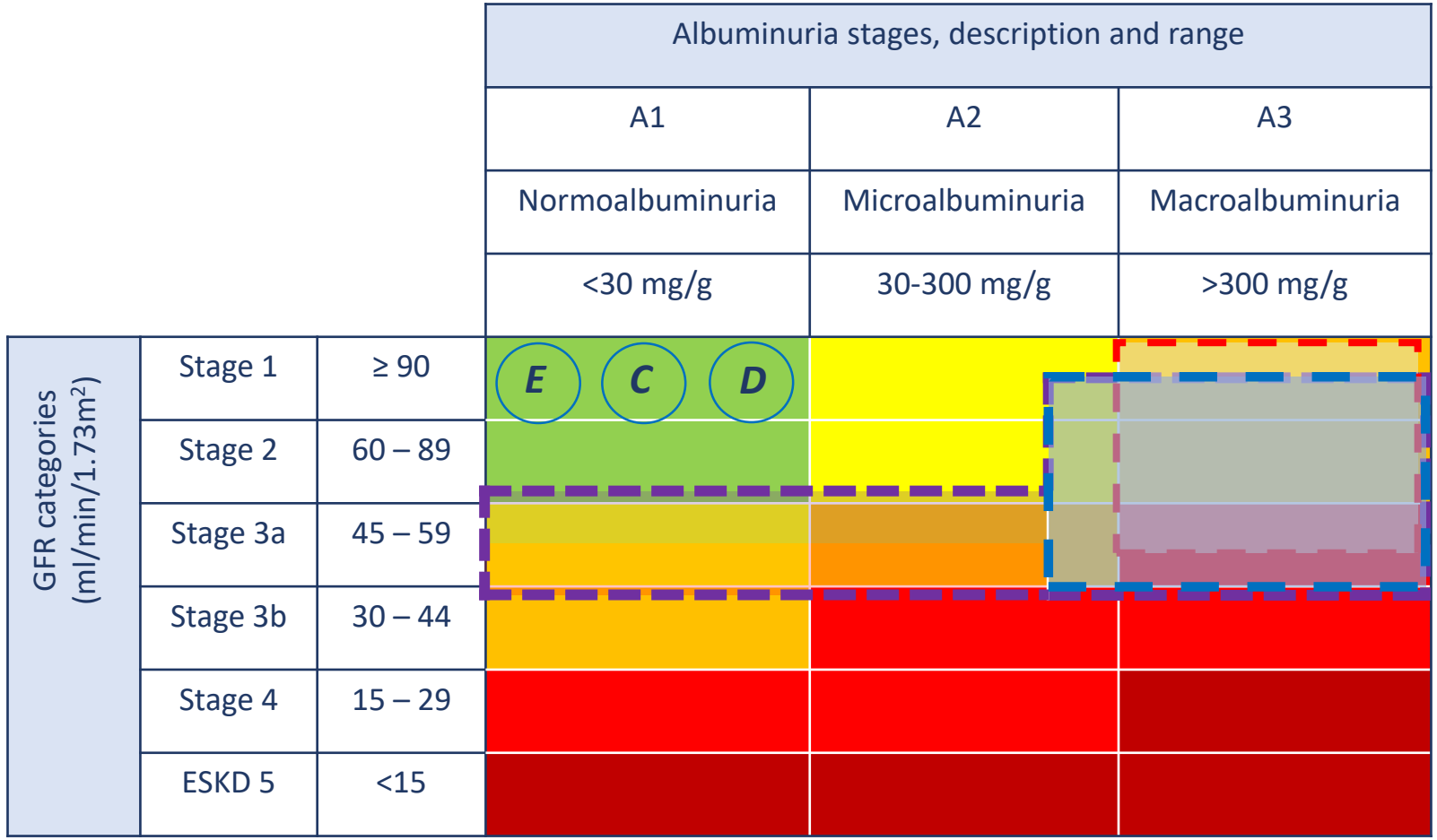
- Current meds: metformin 500 mg BID, glipizide 20 mg q hs, atorvastatin 80 mg, ASA 81, losartan 100 mg, duloxetine 60 mg
- Physical exam: BMI 32 kg/m^2, BP 128/74 mmHg. Fundoscopic exam: non-proliferative retinopathy. Neuro exam: Loss of vibratory and temperature sensation feet bilaterally
- Labs: A1c: 7.8 %, eGFR: 42 ml/min/1.73 m^2, Hgb: 12.2 g, ACR: 398 mg/g; LVEF 42%

What medication changes, if any, would you recommend?

The Consistent Benefit of SGLT2i on Kidney Health from Three Major Large Scale Clinical Trials, N = 15,314



CREDENCE (DKD only) N =4401
eGFR ≥30 to <90 ml/min/1.73m²
and UACR ≥300 mg/g

DAPA-CKD (CKD) N = 4304
eGFR ≥25 to <75 ml/min/1.73m²
and UACR ≥200 mg/g

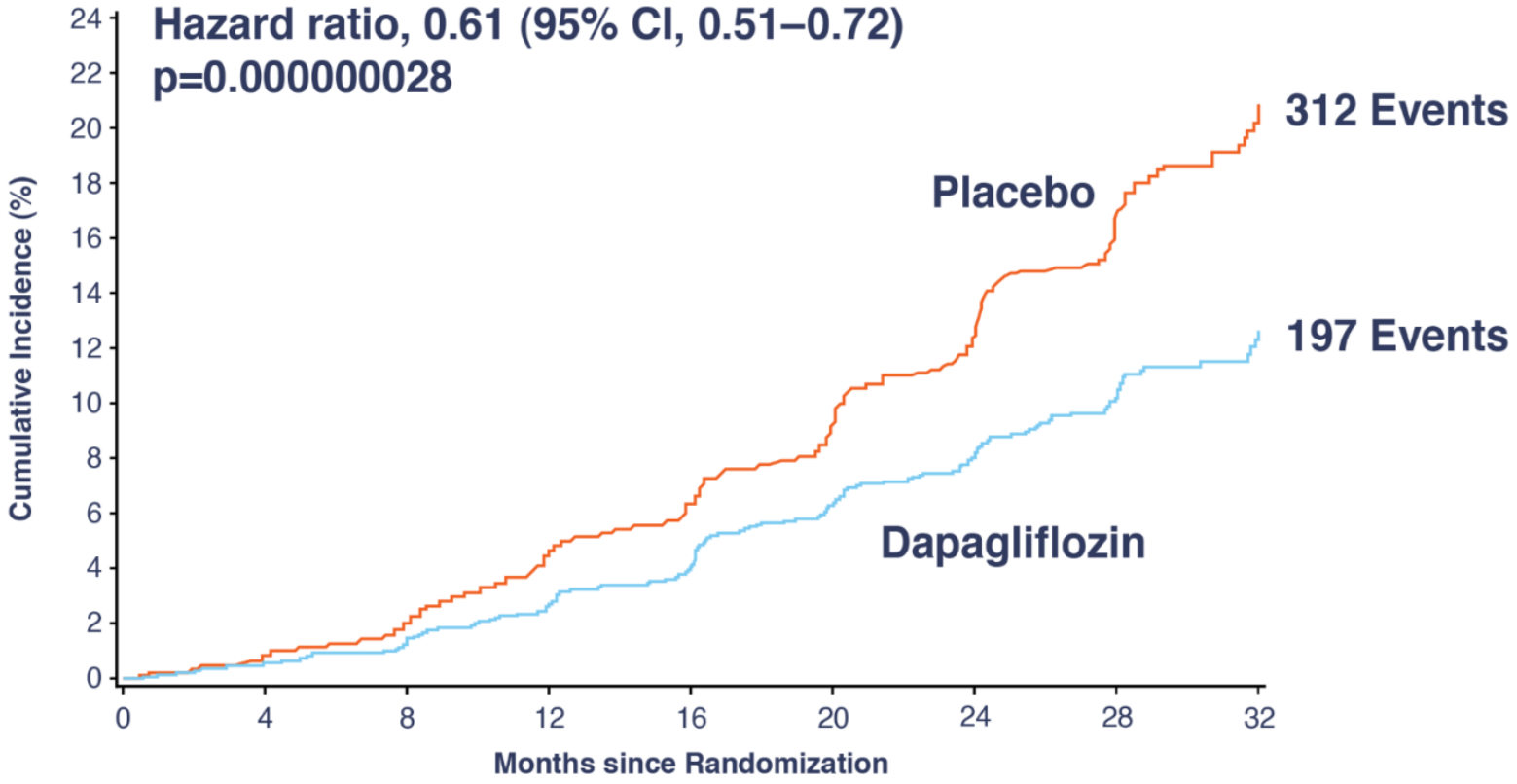
EMPA-KIDNEY (CKD) N = 6609
eGFR ≥45 to <75 ml/min/1.73m²
and UACR ≥200 mg/g
OR
eGFR ≥20 to <45 ml/min/1.73m²

E=EMPAREG-Outcome; C=CANVAS; D=DECLARE TIMI-58

CKD, chronic kidney disease; DKD, diabetic kidney disease, eGFR, glomerular filtration rate; GFR, glomerular filtration rate

Heerspink HJL, et.al. Nephrol Dial Transplant 2020;35:274–282

DAPA CKD: Primary Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or Cardiovascular Death



No. at Risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

Heerspink HJL, et.al. N Engl J Med 2020;383:1436–1446

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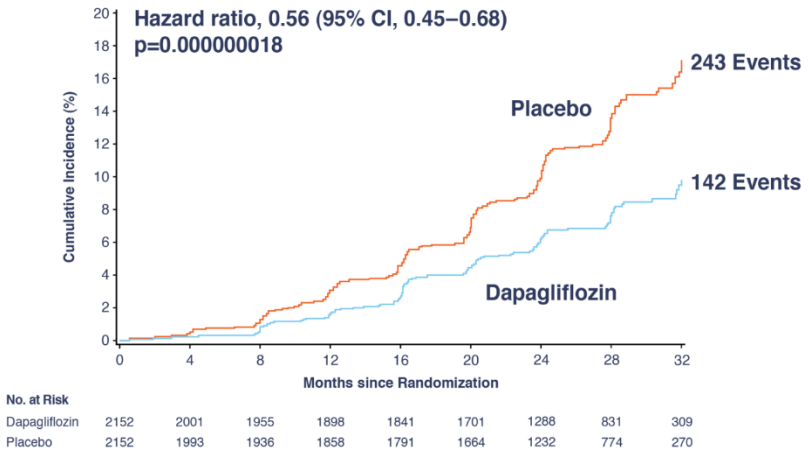
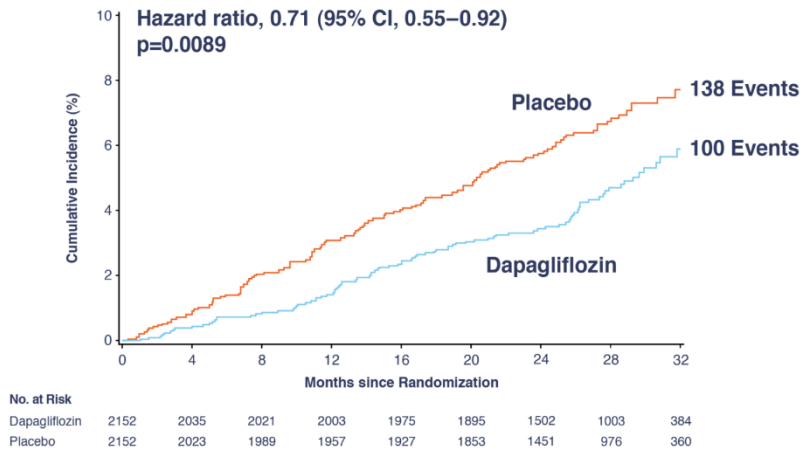
DAPA CKD: Secondary Outcomes

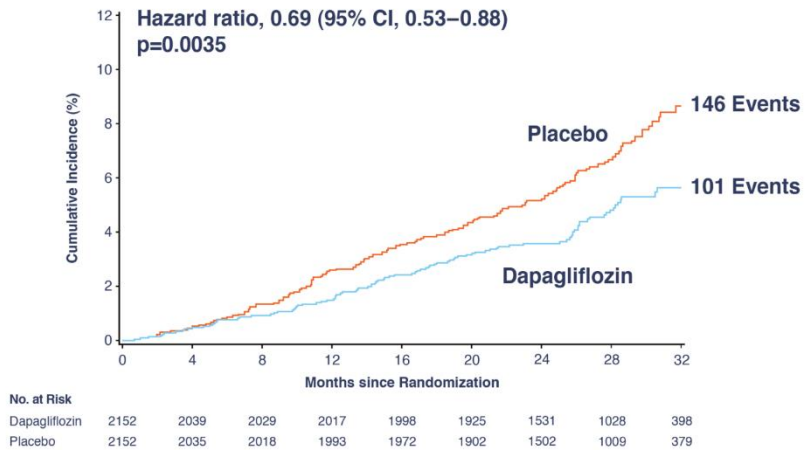
Sustained ≥50% eGFR decline, ESKD, renal death



Cardiovascular death or heart failure hospitalization



All-cause mortality



Heerspink HJL, et.al. N Engl J Med 2020;383:1436–1446

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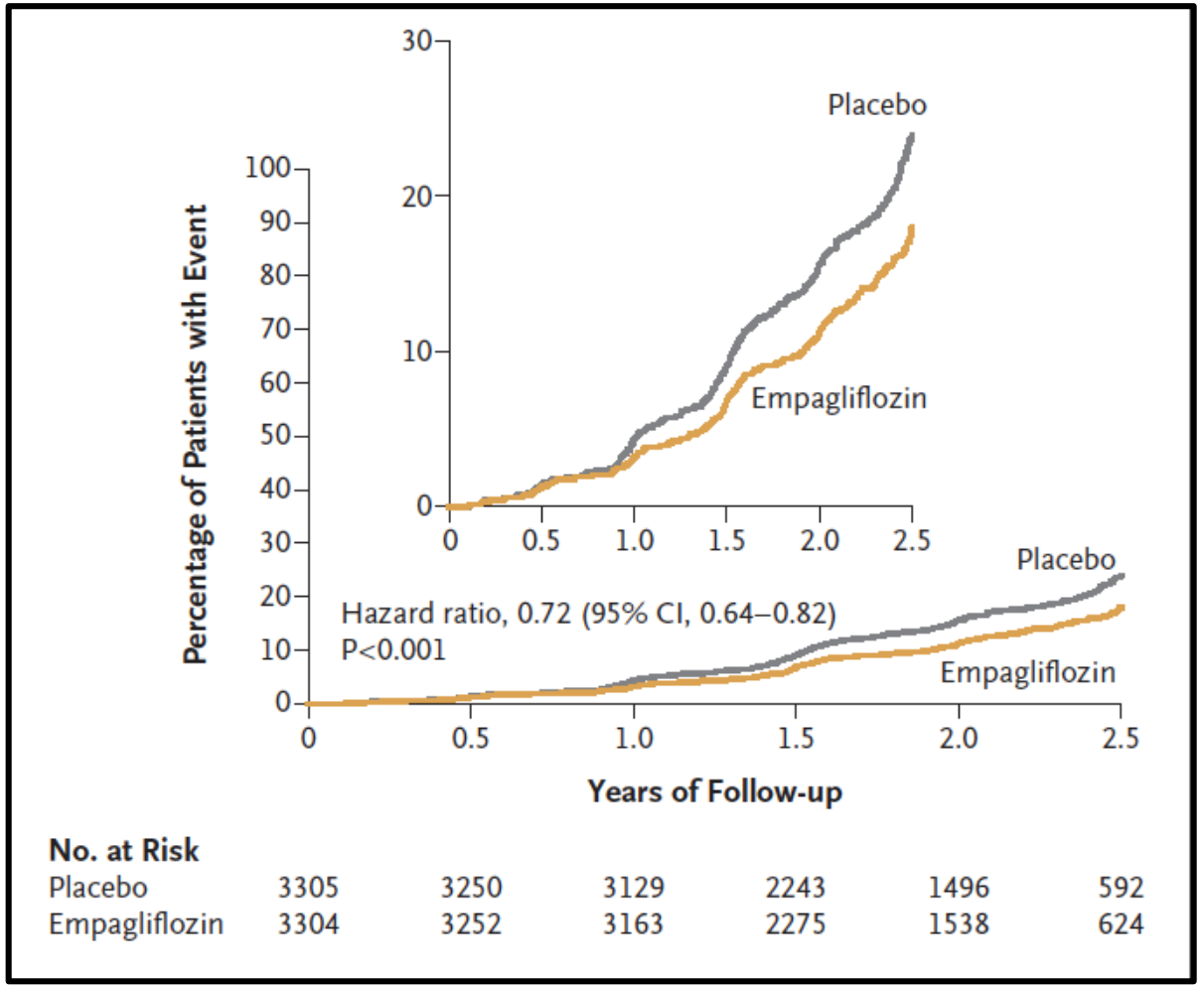
EMPA CKD Primary Outcome



EMPA CKD Collaborative Group published on November 4, 2022, at NEJM.org

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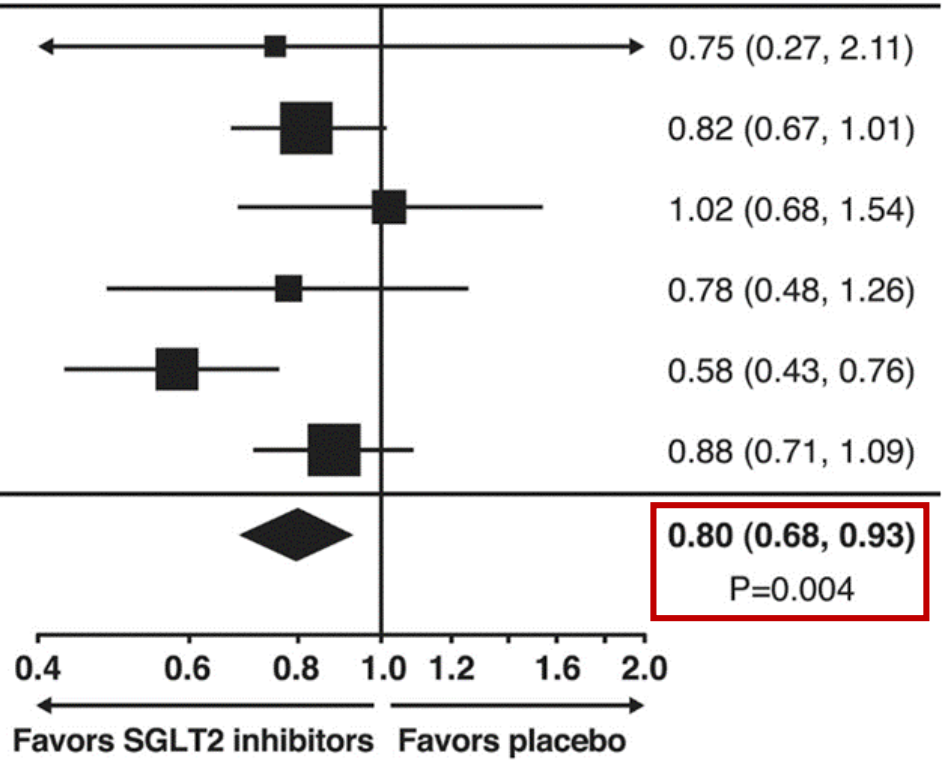
Practical Tips – Hyperkalemia

	SGLT2 inhibitors		Placebo		
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	Hazard Ratio (95% CI)
CANVAS Program	8/5795	0.4	7/4347	0.6	0.75 (0.27, 2.11)
CREDENCE	169/2202	30.7	203/2199	37.4	0.82 (0.67, 1.01)
DAPA-CKD	48/1455	33.0	47/1451	32.0	1.02 (0.68, 1.54)
DECLARE-TIMI 58	30/8582	0.9	38/8578	1.1	0.78 (0.48, 1.26)
EMPA-REG OUTCOME	104/4687	7.7	88/2333	13.4	0.58 (0.43, 0.76)
VERTIS CV	243/5493	15.4	134/2745	17.7	0.88 (0.71, 1.09)
Overall (I^2=29.5%; $P_{heterogeneity}$=0.21)					**0.80 (0.68, 0.93)** P=0.004



SGLT2i results in ↓20% of hyperkalemia

SGLT2i and Risk of Hyperkalemia PMID 35394821

Practical tips – CKD & Hyperkalemia

- Helps preserve renal function
- Can initiate SGLT2i with eGFR ≥20 ml/min/1.73 m^2
- No toxic effects likely with lower eGFR
- 50% metabolism via GI tract
- Reduce risk of hyperkalemia with ACEi/ARB/ARNI or MRA

SGLT2i – Take Home Point

35% reduction in adverse kidney outcomes

Case 4

Case Presentation Heart Failure

A 45-year-old woman with a history of hypertension, CKD (eGFR 32) and HFpEF (LVEF 48%) presents to your clinic for medical care.

Blood pressure: 95/61 mmHg Heart Rate: 55 bpm

Medications:

- Losartan 25 mg daily
- Carvedilol 6.25 mg twice daily
- Spironolactone 25 mg daily

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Medications:

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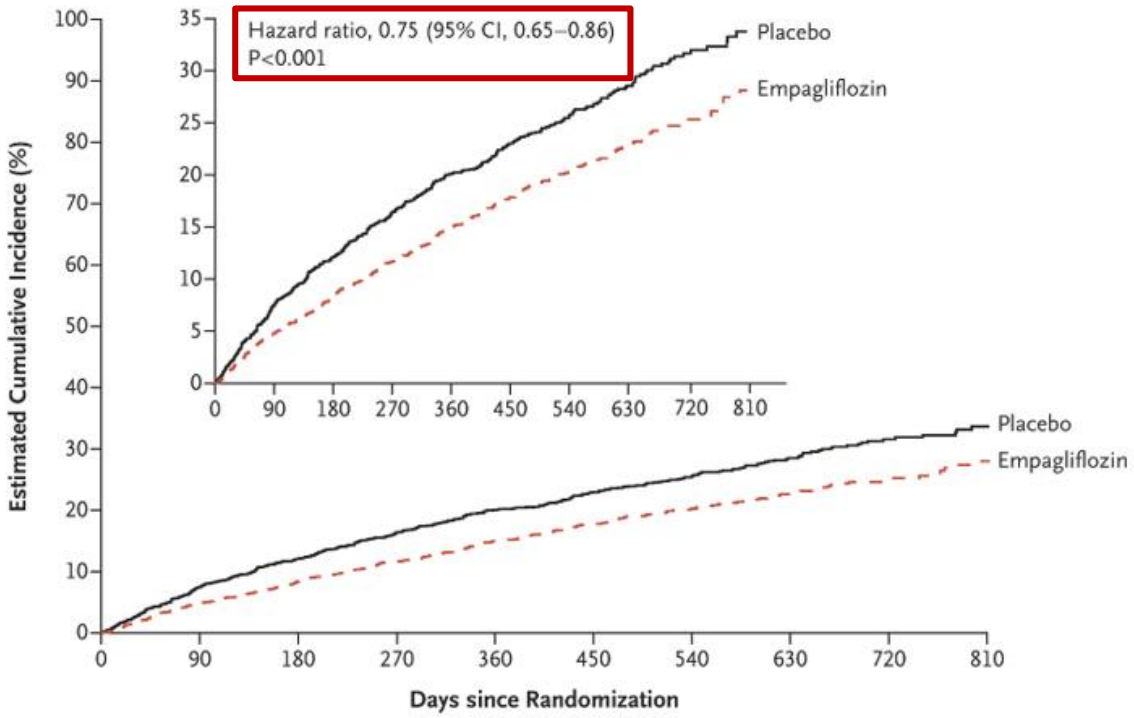
- Spironolactone 25 mg daily

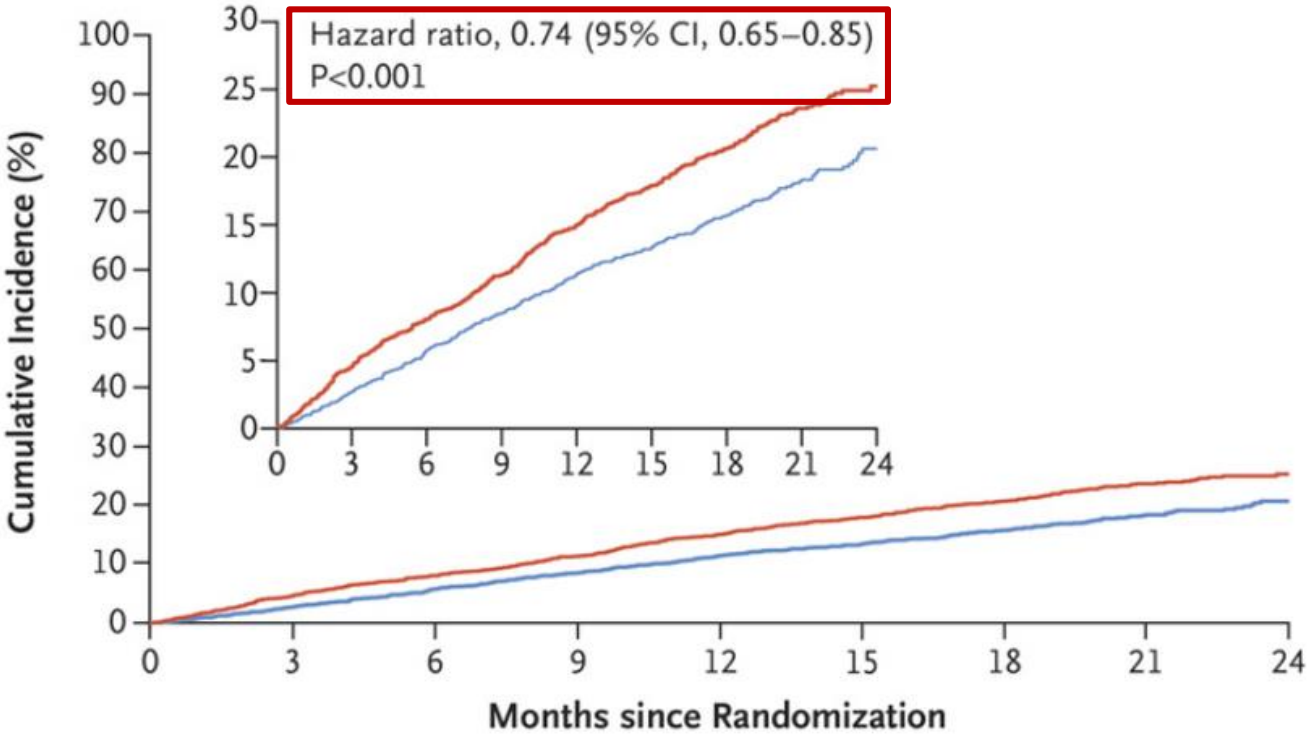
She asks: “What else can I do to lower my risk of death or heart failure hospitalization?”

SGLT2i in Systolic Heart Failure (LVEF <40%)

EMPEROR-Reduced (Empagliflozin)
1º Endpoint: CV Death or HF Hospitalization



DAPA-HF (Dapagliflozin)
1º Endpoint: CV Death, Urgent HF visit or HF Hospitalization



EMPEROR-Reduced PMID 32865377; **DAPA-HF** PMID 31535829

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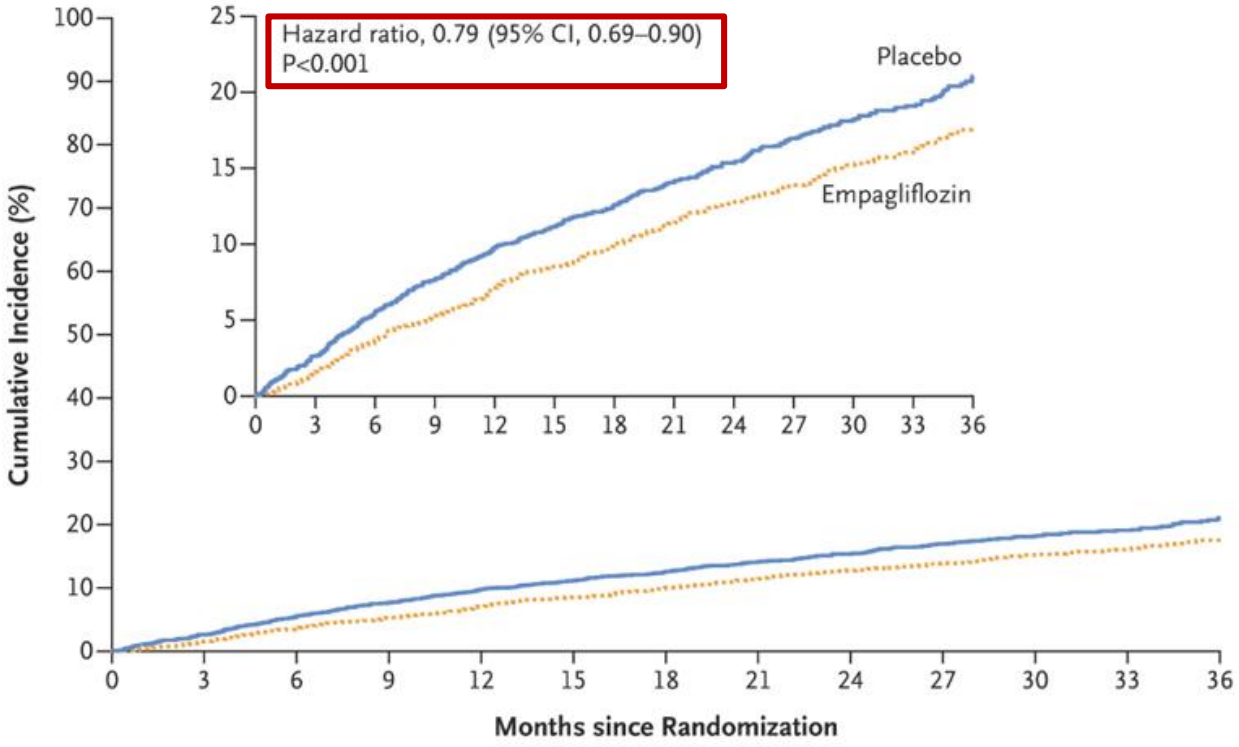
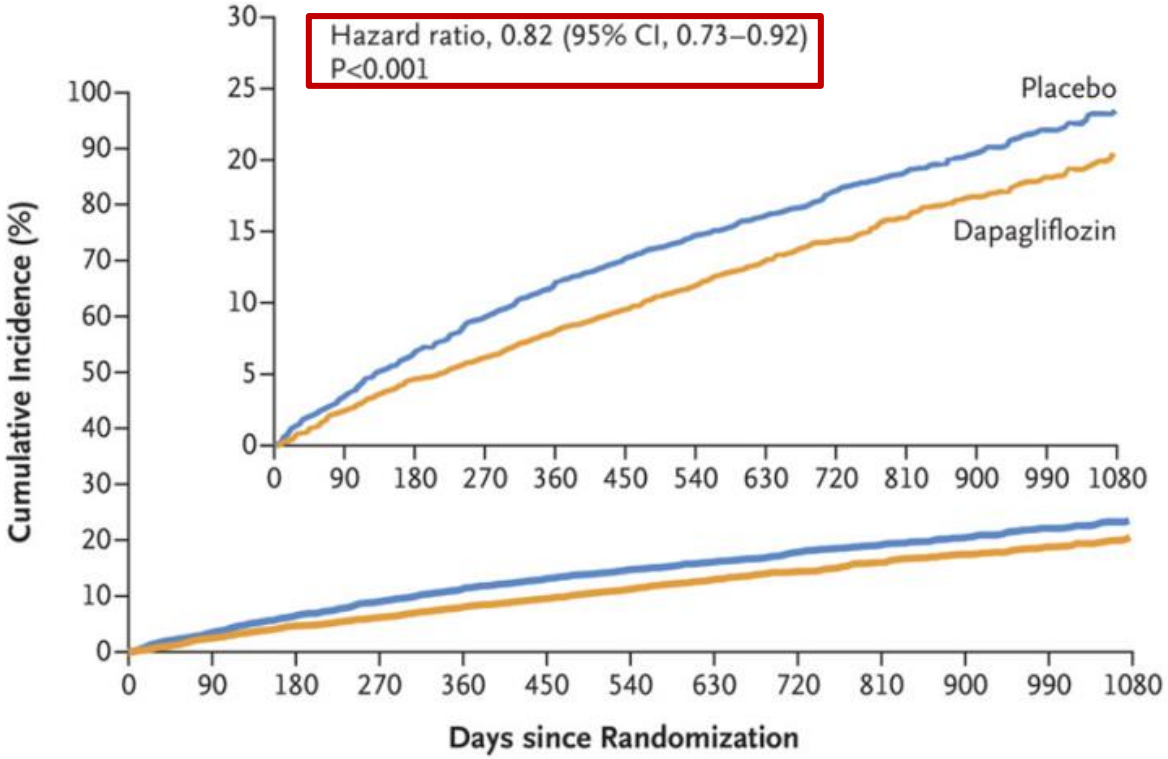
SGLT2i in HFpEF (LVEF >40%)

EMPEROR-Preserved (Empagliflozin)
1º Endpoint: CV Death or HF Hospitalization



DELIVER (Dapagliflozin)
1º Endpoint: CV Death, Urgent HF vist or HF Hospitalization



EMPEROR-Preserved PMID 34449189; **DELIVER** PMID 36027570

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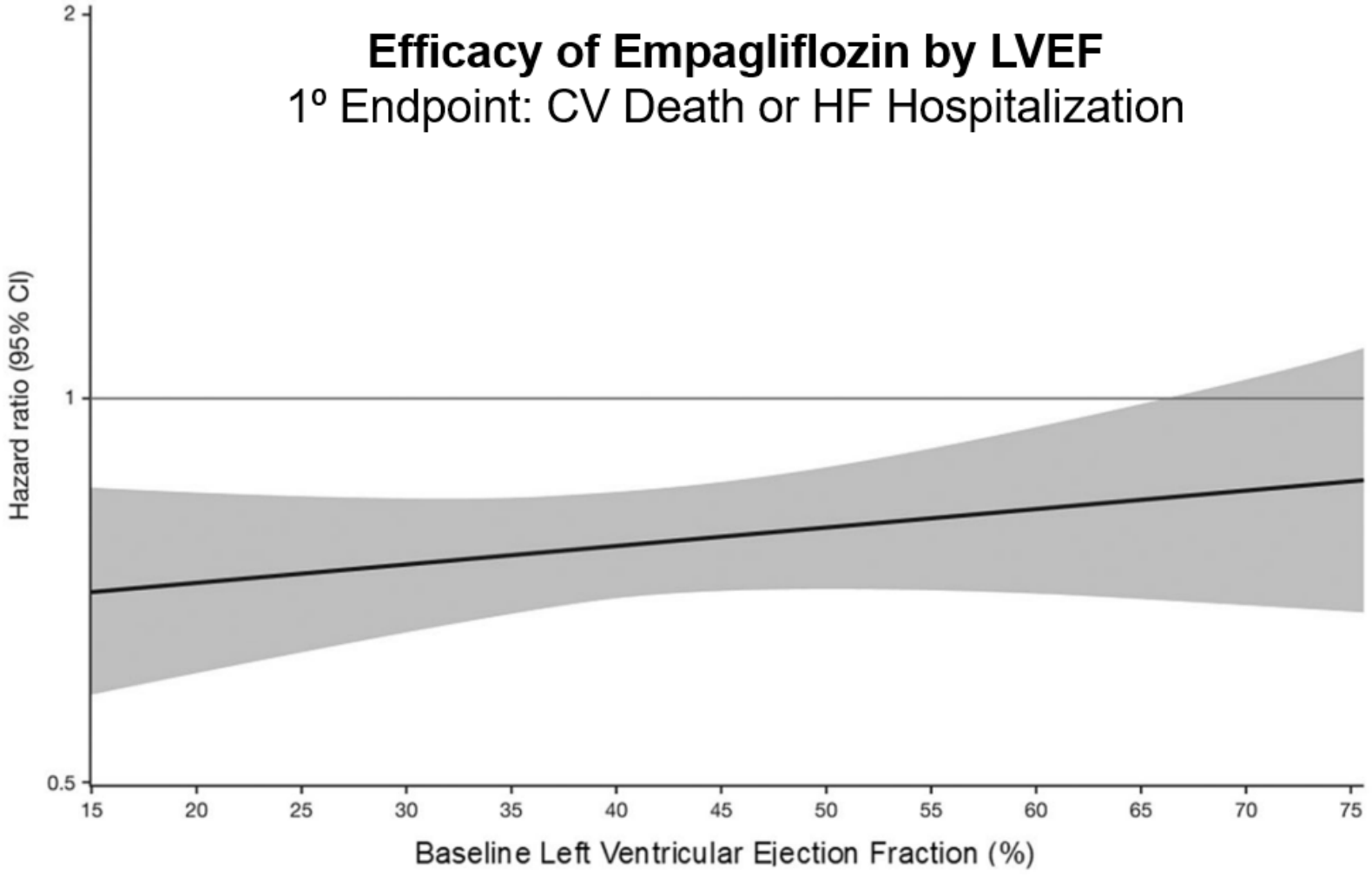
SGLT2i Efficacy in Heart Failure



Empagliflozin in patients with heart failure. PMID 34878502

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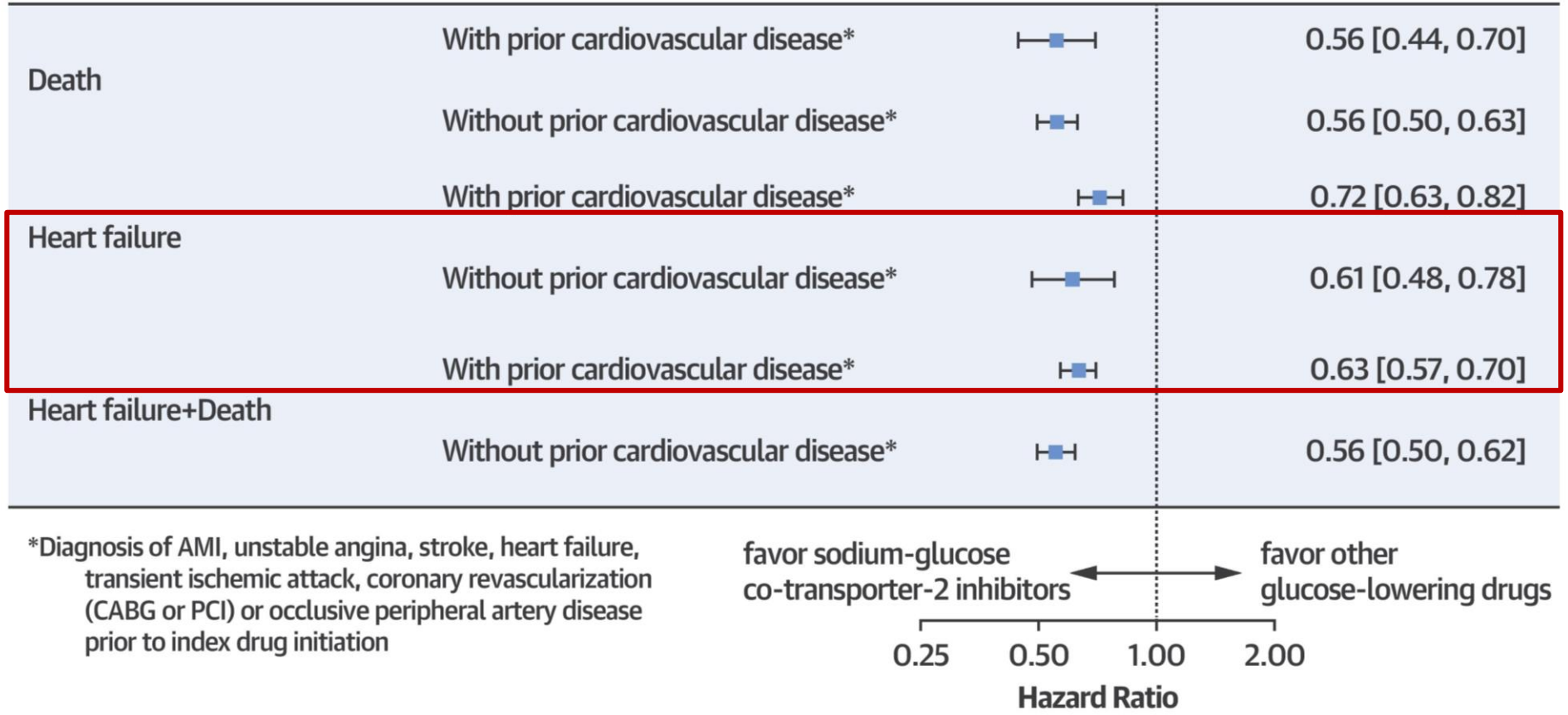
SGLT2i in Preventing Heart Failure

CENTRAL ILLUSTRATION: Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease



SGLT2i & Analysis for CVD-REAL. PMID 29852973

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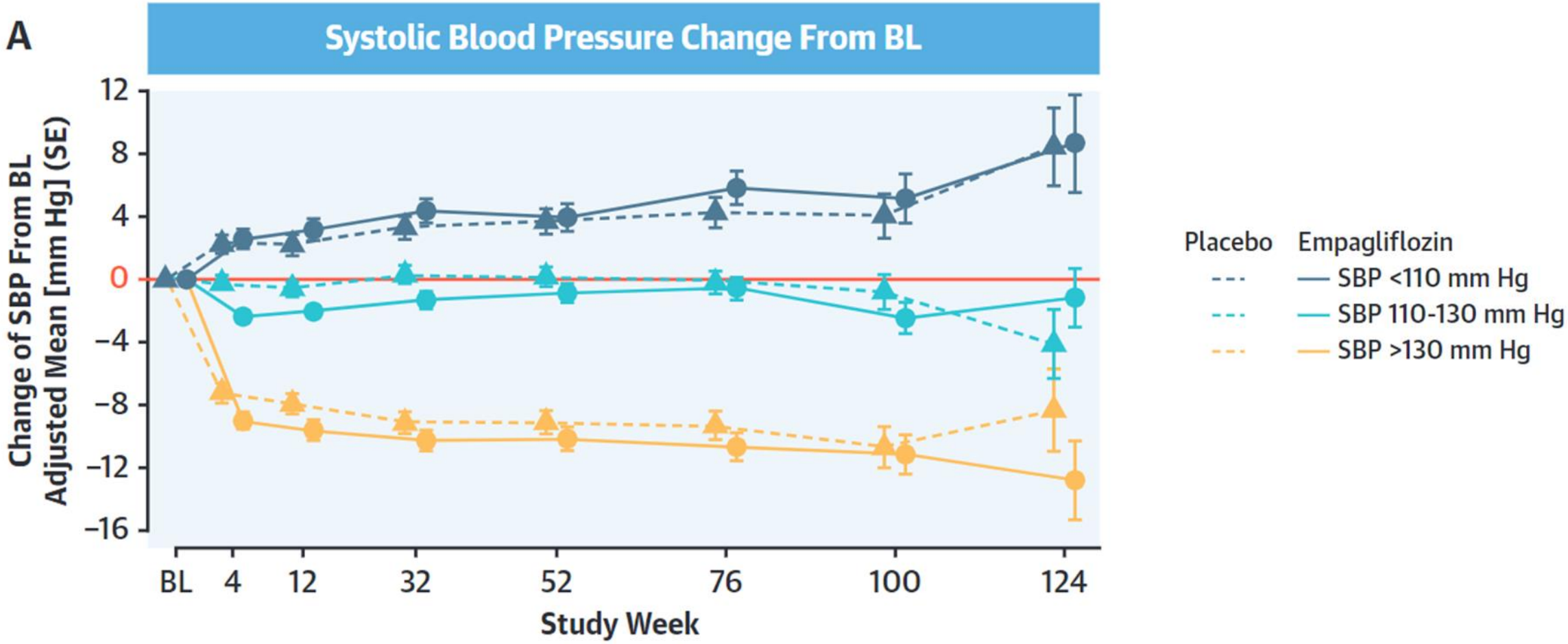
Practical Tips – ”Hypotensive" Patient



EMPEROR-Reduced - Empagliflozin and Systolic BP PMID 34556320

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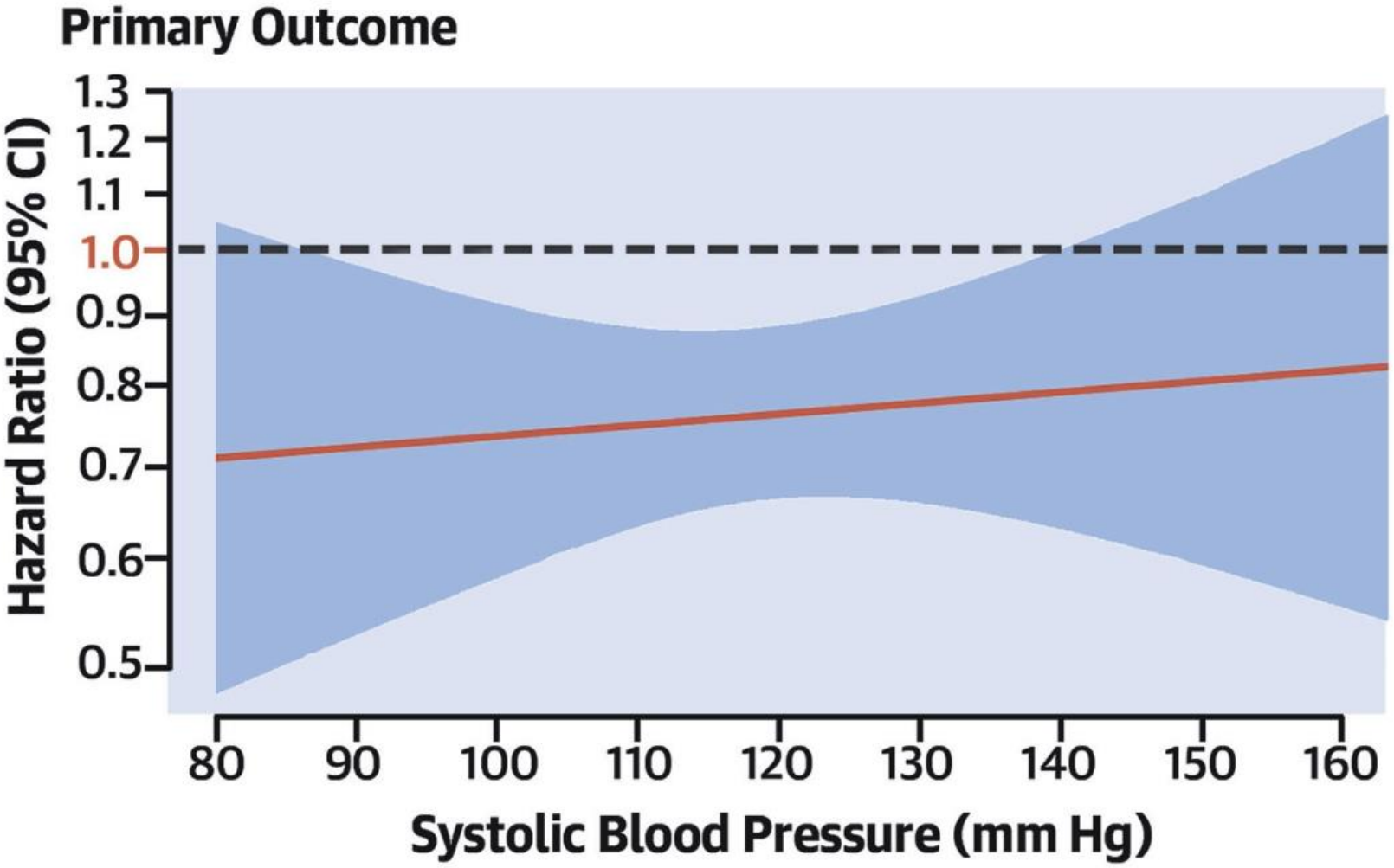
Practical Tips – ”Hypotensive" Patient



EMPEROR-Reduced - Empagliflozin and Systolic BP PMID 34556320

SGLT2i – Take Home Point

20-25% reduction in death or HF hospitalization (regardless of EF)

SGLT2i/GLP-1RA in CVD and CKD – Summary

- SGLT2i
  - 15% reduction in MACE
  - 20-25% reduction in death or HF hospitalization (regardless of EF)
  - Prevent new HF
  - Reduce hyperkalemia
  - Preserve renal function (can initiate if eGFR >20)
  - Often well tolerated in "hypotensive" patients with heart failure
- GLP-1RA
  - 14% reduction in MACE
  - 12% reduction in all-cause mortality

Post-Test Questions

Turn on camera app

Frame the QR

Click the pop-up

Case Presentation DM

Your 58-year-old patient with a history of type 2 diabetes, hypertension, obesity, and hypercholesterolemia and a prior myocardial infarction was admitted recently with pneumonia, but is now asymptomatic and fully recovered. They mentioned a "low" while undergoing physical therapy, but has not had a second episode since.

BP is 122/68, HR 68, BMI 32.2

Medication regimen: glipizide 5 mg, atorvastatin 40 mg, aspirin 81 mg, lisinopril 40 mg

Recent labs: eGFR 78, LDL 68, HbA1c 6.6%

Ejection fraction post-procedure was 55%

Question

What changes, if any, would you recommend to this pharmacologic regimen:

(a) None, meets all goals

(b) Switch glipizide to metformin

(c) Switch glipizide to a GLP-1RA

(d) Add pioglitazone

Ques esults

Answer

What changes, if any, would you recommend to this pharmacologic regimen:

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(c) Switch glipizide to a GLP-1RA

(d) Add pioglitazone

Case Presentation MI

Your 56 year old patient presents for post hospital follow up after a recent myocardial infarction (MI) and percutaneous coronary intervention (PCI).

- Medical Hx: Prior to his MI he “never had any health problems”
- Physical exam: BMI is 31 kg/m^2, BP is 122/76
- Discharge medications: aspirin 81 mg, prasugrel 10 mg, losartan 50 mg, atorvastatin 80 mg daily; metoprolol tartrate 25 mg, metformin 500 mg twice a day
- Labs during his admission: Cr 1.5, UA protein +, LDL of 155, A1C of 7.8%
- Echocardiogram - normal ejection fraction

He wants to do anything possible to avoid having another heart attack.

Question

Which of the following is FALSE:

(a) Selected GLP-1RA have been proven to reduce future heart attacks in patients with T2D and MI

(b) Selected SGLT2 inhibitors have been proven to reduce incident heart failure in patients with T2D and MI

(c) Use of GLP-1RA, albeit at doses higher than those studied in CV outcomes trials, can facilitate weight loss

(d) SGLT2 inhibitors and GLP-1RA with proven CV benefit can be used with or without background metformin

(e) SGLT2 inhibitors are contraindicated in patients with CKD3 and proteinuria

Ques sults

Answer

(a) is correct, multiple trials, e.g. LEADER for liraglutide.

(b) is correct, multiple trials, e.g. EMPA REG OUTCOME for empagliflozin.

(c) is correct, in people with or without T2D, e.g. STEP 1 trial for semaglutide.

(d) is correct, current ADA standards of care recommend selected SGLT2 inhibitors and GLP-1RA regardless of background metformin in patients with T2D and prior MI.

(e) is false. Selected SGLT2 inhibitors have been shown to improve CV and renal outcomes in patients with CKD 3 and proteinuria, e.g. DAPA CKD trial, dapagliflozin

Case Presentation CKD

- 68 y/o man with T2D x 20 years with hypertension, hyperlipidemia, erectile dysfunction, NSTEMI (2016), retinopathy, neuropathy, NASH, smokes marijuana daily to reduce pain of DPNP.
- Current meds: metformin 500 mg BID, glipizide 20 mg q hs, atorvastatin 80 mg, ASA 81, losartan 100 mg, duloxetine 60 mg
- Physical exam: BMI 32 kg/m^2, BP 128/74 mmHg. Fundoscopic exam: non-proliferative retinopathy. Neuro exam: Loss of vibratory and temperature sensation feet bilaterally
- Labs: A1c: 7.8 %, eGFR: 42 ml/min/1.73 m^2, Hgb: 12.2 g, ACR: 398 mg/g; LVEF 42%

Question

What changes, if any, would you recommend to this pharmacologic regimen:

(a) None, meets all goals

(b) Switch glipizide to SGLT2i

(c) Switch glipizide to a GLP-1RA

(d) Switch glipizide to SGLT2i + GLP-1RA

Ques sults

Answer

What changes, if any, would you recommend to this pharmacologic regimen:

(a) None, meets all goals

(b) Switch glipizide to SGLT2i

(c) Switch glipizide to a GLP-1RA

(d) Switch glipizide to SGLT2i + GLP-1RA

Case Presentation HF

A 45-year-old woman with a history of hypertension, CKD (eGFR 32) and HFpEF (LVEF 48%) presents to your clinic for medical care.

Blood pressure: 95/61 mmHg Heart Rate: 55 bpm

Medications:

- Losartan 25 mg daily
- Carvedilol 6.25 mg twice daily
- Spironolactone 25 mg daily

She asks: “What else can I do to lower my risk of death or heart failure hospitalization?”

Question

"What else can I do to lower my risk of death or heart failure hospitalization?"

(a) Increase carvedilol 12.5 mg twice daily

(b) Start aspirin 81 mg daily

(c) Increase diuretics

(d) Start dapagliflozin 10 mg daily

(e) Start digoxin 125 mcg daily

Ques esults

Answer

(a) Increase carvedilol 12.5 mg twice daily

(b) Start aspirin 81 mg daily

(c) Increase diuretics

(d) Start dapagliflozin 10 mg daily

(e) Start digoxin 125 mcg daily

SGLT2i/GLP-1RA in CVD and CKD – Summary

- SGLT2i
  - 15% reduction in MACE
  - 20-25% reduction in death or HF hospitalization (regardless of EF)
  - Prevent new HF
  - Reduce hyperkalemia
  - Preserve renal function (can initiate if eGFR >20)
  - Often well tolerated in "hypotensive" patients with heart failure
- GLP-1RA
  - 14% reduction in MACE
  - 12% reduction in all-cause mortality