The Growing Role of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

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DISCLOSURE

All presenters of this session have no potential conflict of interest

Learning Objectives

- Identify patients who are indicated for the expanded role of SGLT2 inhibitors
- Explain the potential mechanism of action of SGLT2 inhibitors in heart failure and renal protection
- Recognize situations where use of SGLT2 inhibitors should be avoided

ABBREVIATIONS

- ACEi = angiotensin-converting enzyme inhibitor
- ADA = American Diabetes Association
- ARB = angiotensin II receptor blocker
- (AS)CV(D) = (atherosclerotic) cardiovascular (disease)
- (C)HF = (congestive) heart failure
- CKD = chronic kidney disease
- eGFR = estimated glomerular filtration rate
- ESRD = end stage renal disease
- FDA = Food and Drug Administration
- HbA1c = hemoglobin A1c
- HHF = heart failure hospitalization

ABBREVIATIONS

- KCCQ = Kansas City Cardiomyopathy Questionnaire
- MACE = major adverse cardiovascular events
- MRA = mineralocorticoid receptor antagonist
- NNT = number needed to treat
- RAAS = renin-angiotensin-aldosterone system
- RRT = renal replacement therapy
- SBP = systolic blood pressure
- SCr = serum creatinine
- SGLT2 = sodium-glucose cotransporter 2
- T2DM = type 2 diabetes mellitus
- UACR = urine albumin-to-creatinine ratio

BACKGROUND

- Originated from the 19th century: Phlorizin
- Positive cardiovascular, heart failure, and renal outcomes have been demonstrated since
- FDA-approved indications:
  - Treatment of type 2 diabetes mellitus (2013)
  - To slow the progression of diabetic kidney disease in patients with diabetic nephropathy (Canagliflozin, 2019)
  - Adjunctive treatment for heart failure with reduced ejection fraction (Dapagliflozin, 2020)

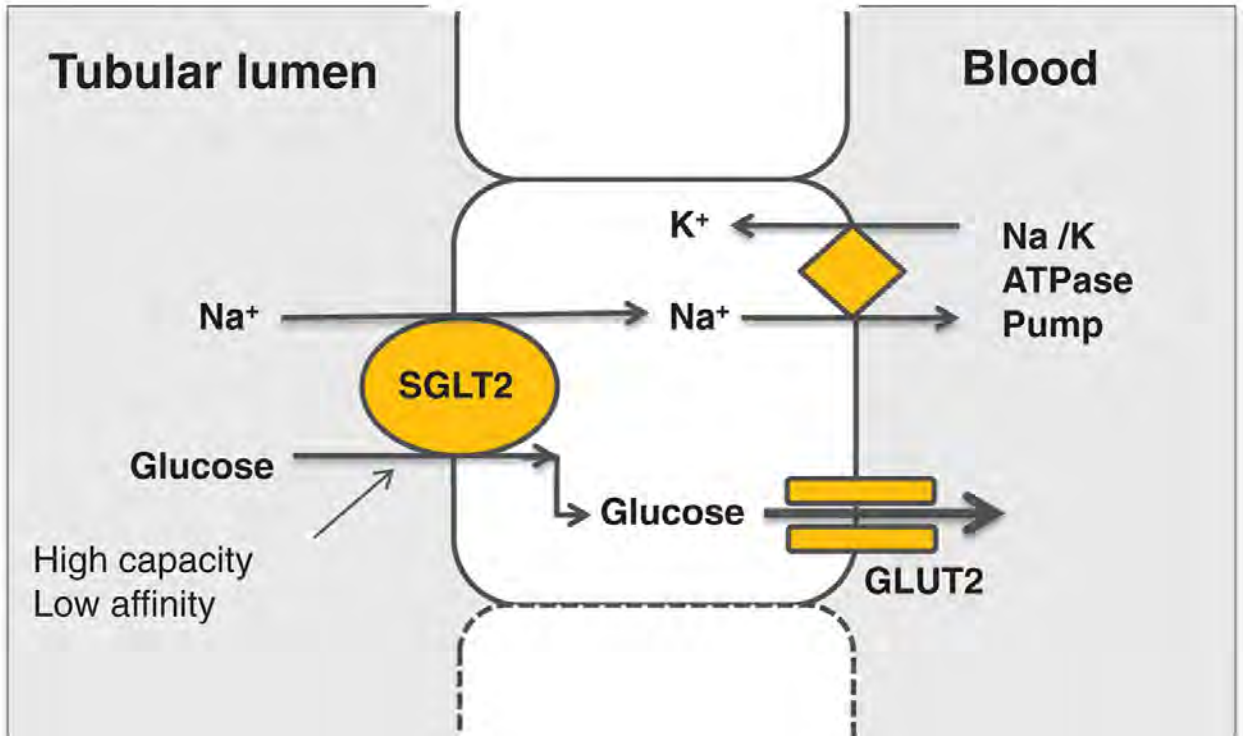
SGLT2 Inhibitor: Mechanism of Action

Inhibition of SGLT2

↓ Reabsorption of filtered glucose and sodium

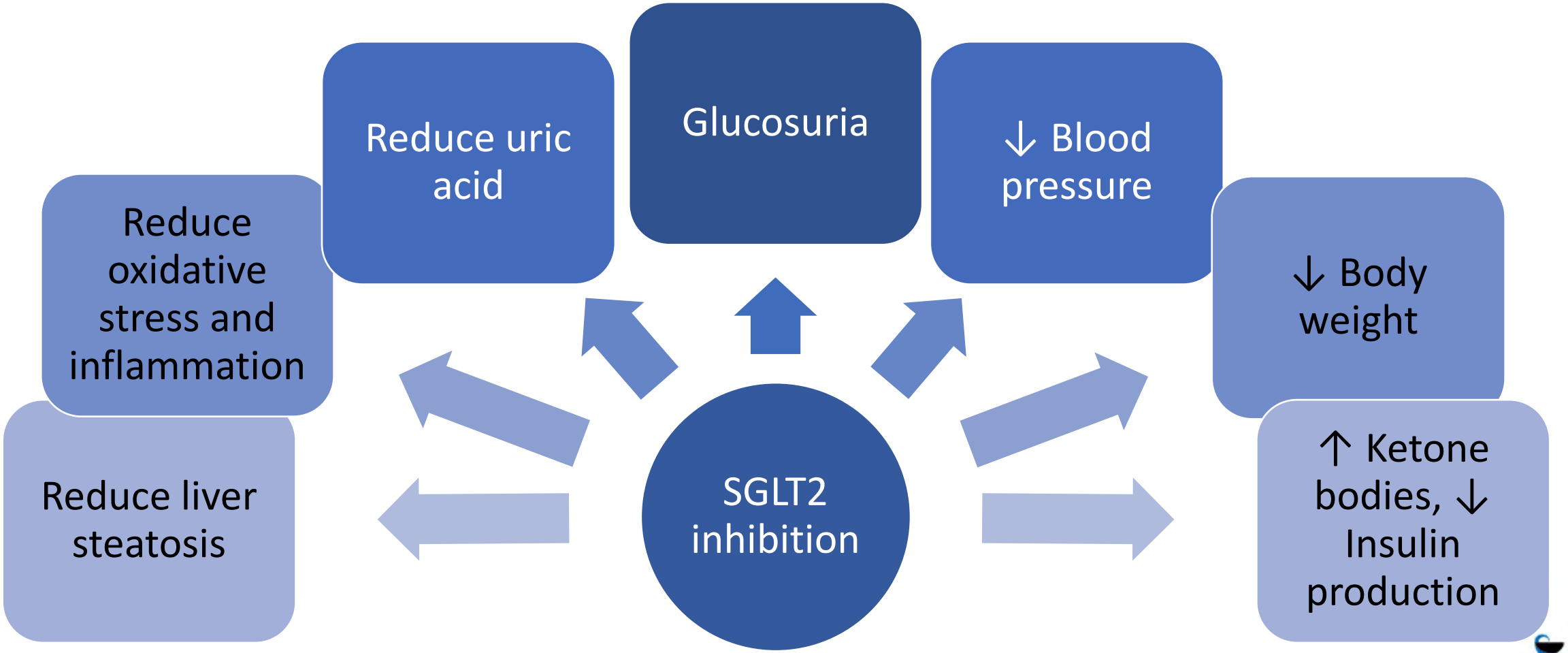
↑ Urinary glucose excretion

↓ Fasting and post-prandial blood glucose



1. Brown E, et al. *Diabetes Obes Metab*. 2019.

Clinical Effects



2. Bonora, et al. *Diabetes Metab Syndr Obes.* 2020

ADA 2020 Recommendation:

SGLT2 inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists with demonstrated cardiovascular disease benefit are recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors such as:

- Established atherosclerotic cardiovascular disease
- Indicators of high risk, established kidney disease
- Heart failure

3. American Diabetes Association. *Diabetes Care*. 2020

SGLT2 Inhibitors: CV Outcomes Trials

CARDIOVASCULAR OUTCOMES

EMPA-REG Empagliflozin	
100% ASCVD	Mean eGFR 74

3.1 years

3-point MACE
0.86 (0.74 to 0.99)
CV Death
0.62 (0.49 to 0.77)
HHF
0.65 (0.50 to 0.85)

CANVAS Canagliflozin	
66% ASCVD	Mean eGFR 76

2.4 years

3-point MACE
0.86 (0.75 to 0.97)
CV Death
0.87 (0.72 to 1.06)
HHF
0.67 (0.52 to 0.87)

DECLARE-TIMI 58 Dapagliflozin	
41% ASCVD	Mean eGFR 85

4.2 years

3-point MACE
0.93 (0.84 to 1.03)
CV Death
0.98 (0.82 to 1.17)
HHF
0.73 (0.61 to 0.88)

4. Zelnicker TA, et al. *Lancet.* 2019.

Renal Outcomes

EMPA-REG Empagliflozin		CANVAS Canagliflozin		DECLARE-TIMI 58 Dapagliflozin	
100% ASCVD	Mean eGFR 74	66% ASCVD	Mean eGFR 76	41% ASCVD	Mean eGFR 85
3.1 yrs		2.4 yrs		4.2 yrs	
Progression to macroalbuminuria, doubling of SCr with eGFR ≤45, RRT, or renal death 0.61 (0.53 to 0.70)		**40% reduction in eGFR, RRT, or renal death** 0.60 (0.47 to 0.77)		**≥40% eGFR decrease to <60, ESRD, or renal death** 0.53 (0.43 to 0.66)	

4. Zelnicker TA, et al. *Lancet.* 2019.

RENAL BENEFIT

CREDENCE

- Prospective, double-blind, randomized controlled trial
- Setting: 690 sites in 34 countries
- Canagliflozin 100mg vs placebo
- Median follow-up: 2.6 years
- Analysis: Intention-to-treat

5. Perkovic V, et al. *N Engl J Med.* 2019

CREDENCE (POPULATION)

Inclusion Criteria

- Age ≥30 years old with T2DM
- HbA1c 6.5-12.0% (6.5-10.5% in Germany)
- eGFR 30-89 mL/min/1.73 m^2
- Urinary albumin:creatinine 300-5000 (mg/g)
- On an ACEi/ARB at the maximum tolerable dose

Exclusion Criteria

- Diabetic ketoacidosis or Type 1 diabetes
- Suspected non-diabetic kidney disease
- Dialysis
- History of CHF
- Blood potassium level >5.5 mmol/L

5. Perkovic V, et al. *N Engl J Med.* 2019

CREDENCE (BASELINE CHARACTERISTICS)

	Canagliflozin (N=2202)	Placebo (N=2199)
Age — yr	62.9±9.2	63.2±9.2
Female sex—no. (%)	762 (34.6)	732 (33.3)
eGFR — ml/min/1.73 m^2	56.3±18.2	56.0±18.3
Median UACR – mg/g	923	931
Drug therapy—no. (%)		
RAAS inhibitor	2201 (>99.9)	2194 (99.8)
Diuretic	1026 (46.6)	1031 (46.9)
Glycated hemoglobin—%	8.3 ± 1.3	8.3 ± 1.3
Blood pressure—mmHg	139.8/78.2	140.0/78.3

5. Perkovic V, et al. *N Engl J Med.* 2019

CREDENCE (PRIMARY OUTCOME)

	Hazard Ratio (95% CI)	P Value
Primary composite outcome	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	0.68 (0.54–0.86)	0.002
Cardiovascular death	0.78 (0.61–1.00)	0.05
Renal death	0.39 (0.08–2.03)	NA

5. Perkovic V, et al. *N Engl J Med.* 2019

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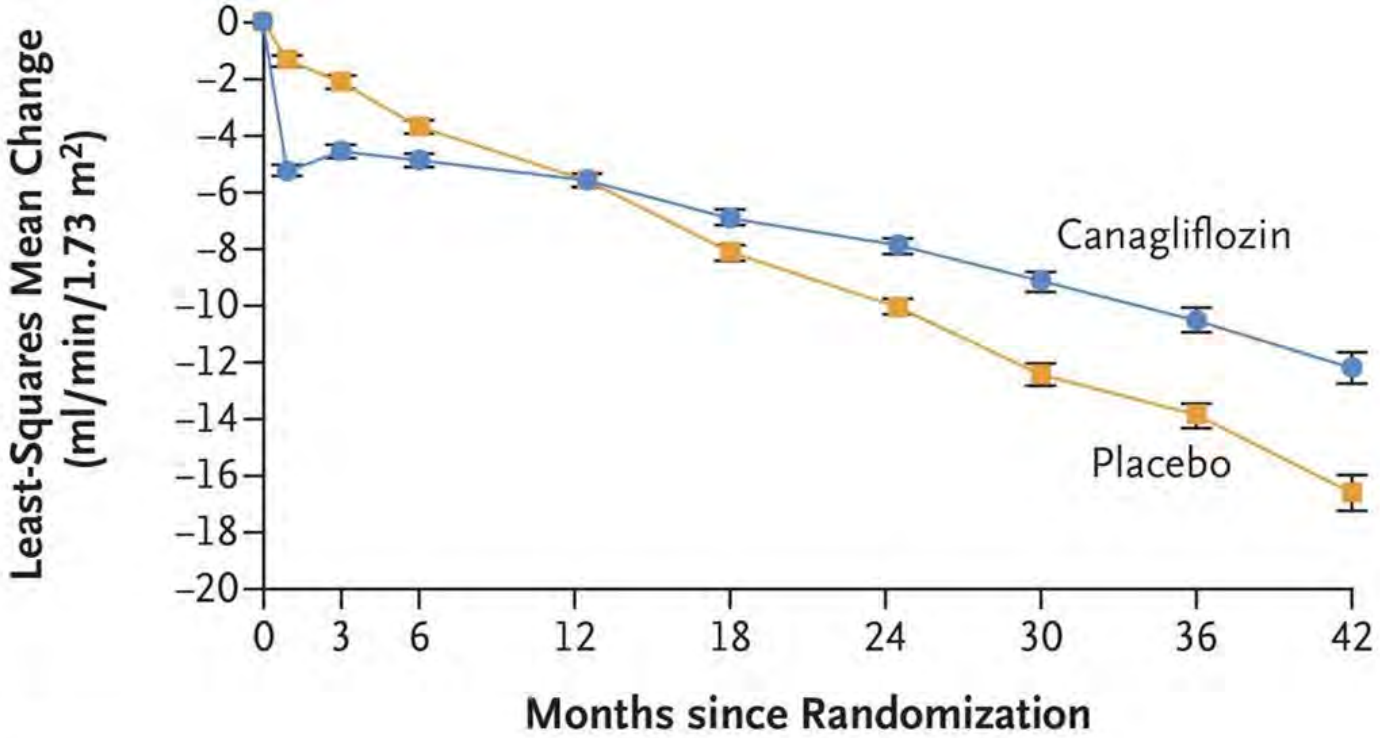
Renal death	0.39 (0.08–2.03)	NA

NNT= 22 over 2.6 years

5. Perkovic V, et al. *N Engl J Med.* 2019

CREDENCE (MEAN CHANGE IN EGFR)



No. of Patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

5. Perkovic V, et al. *N Engl J Med.* 2019

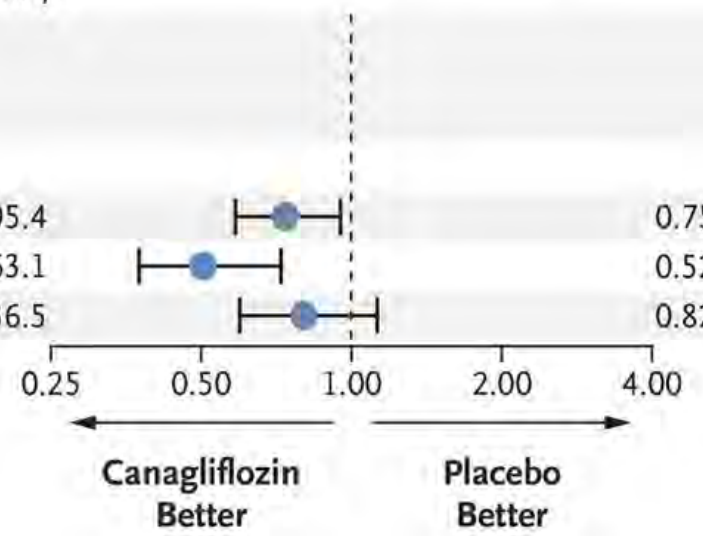
CREDENCE (SAFETY)

	Hazard Ratio (95% CI)
Any adverse event	0.87 (0.82–0.93)
Any serious adverse event	0.87 (0.79–0.97)
Amputation	1.11 (0.79–1.56)
Fracture	0.98 (0.70–1.37)
Bladder cancer	1.10 (0.45–2.72)
Acute kidney injury	0.85 (0.64–1.13)
Diabetic ketoacidosis	10.80 (1.39–83.65)

5. Perkovic V, et al. *N Engl J Med.* 2019

CREDENCE (SUBGROUP ANALYSIS)

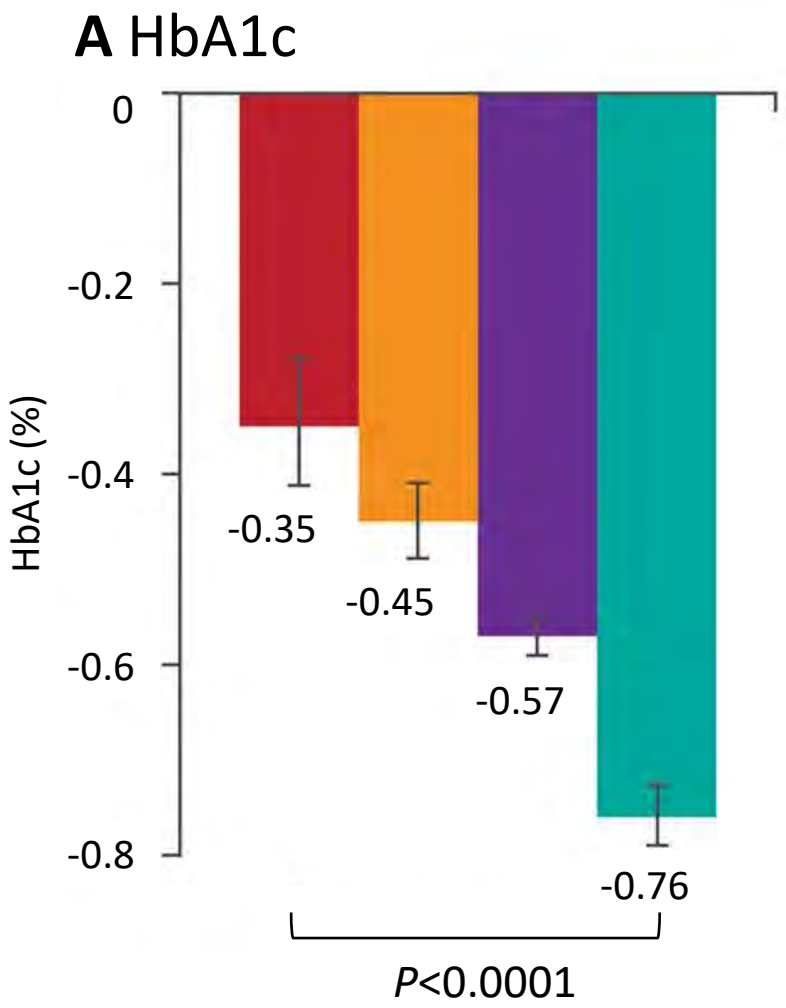
Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	

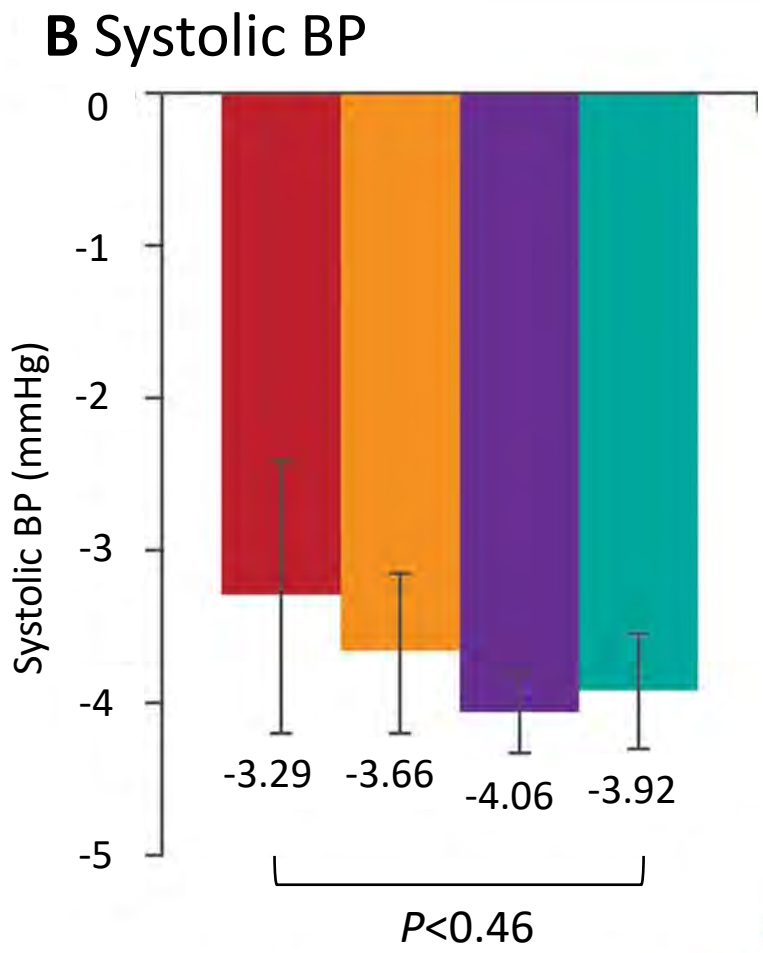


5. Perkovic V, et al. *N Engl J Med.* 2019

SGLT2 INHIBITORS: A1C & SBP REDUCTION

- eGFR <45 mL/min/1.73m^2
- eGFR 45 to <60 mL/min/1.73m^2
- eGFR 60 to <90 mL/min/1.73m^2
- eGFR ≤90 mL/min/1.73m^2





6. Neuen BL et al. *Circulation.* 2018

Nephroprotective Mechanisms

Reduction in hyperfiltration (restoration of tubuloglomerular feedback)

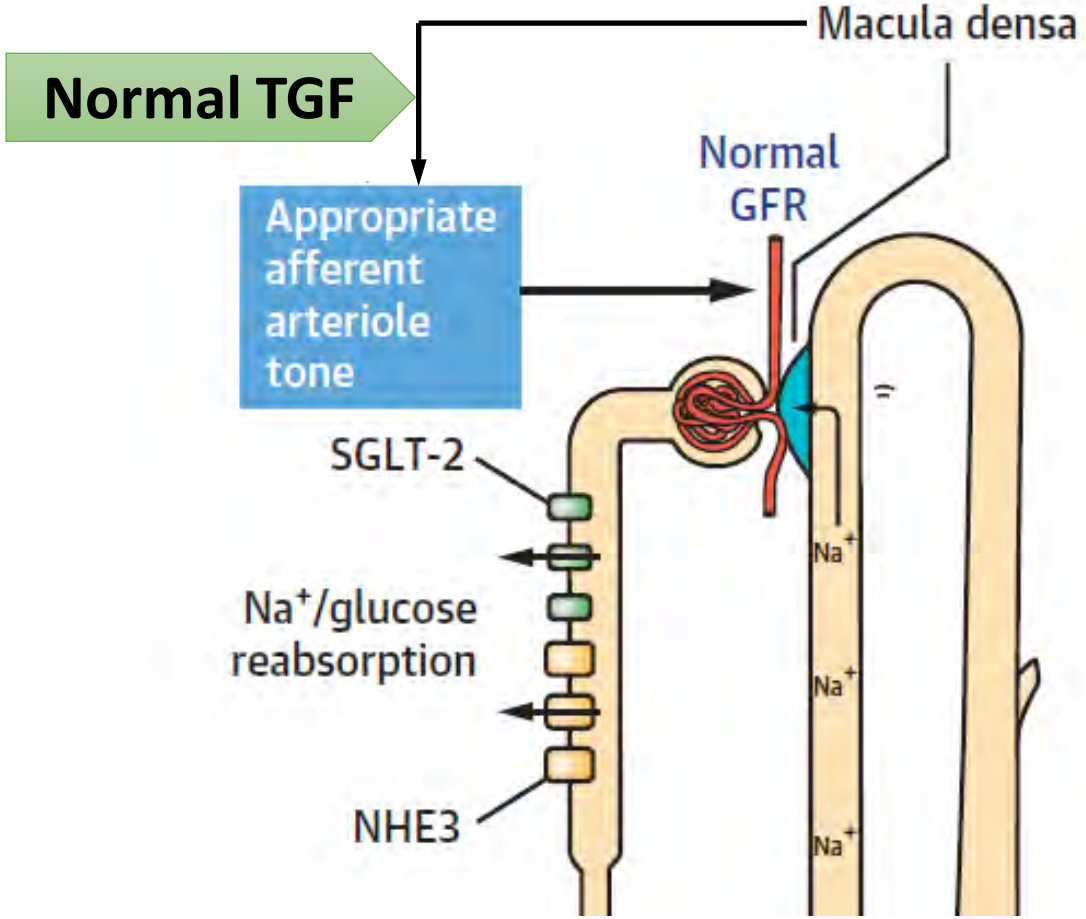
Reduction in blood pressure and vascular stiffness

Attenuation of renal hypoxia (upregulate erythropoiesis)

Reduction in inflammation (increase uric acid secretion, decrease inflammatory markers, weight loss)

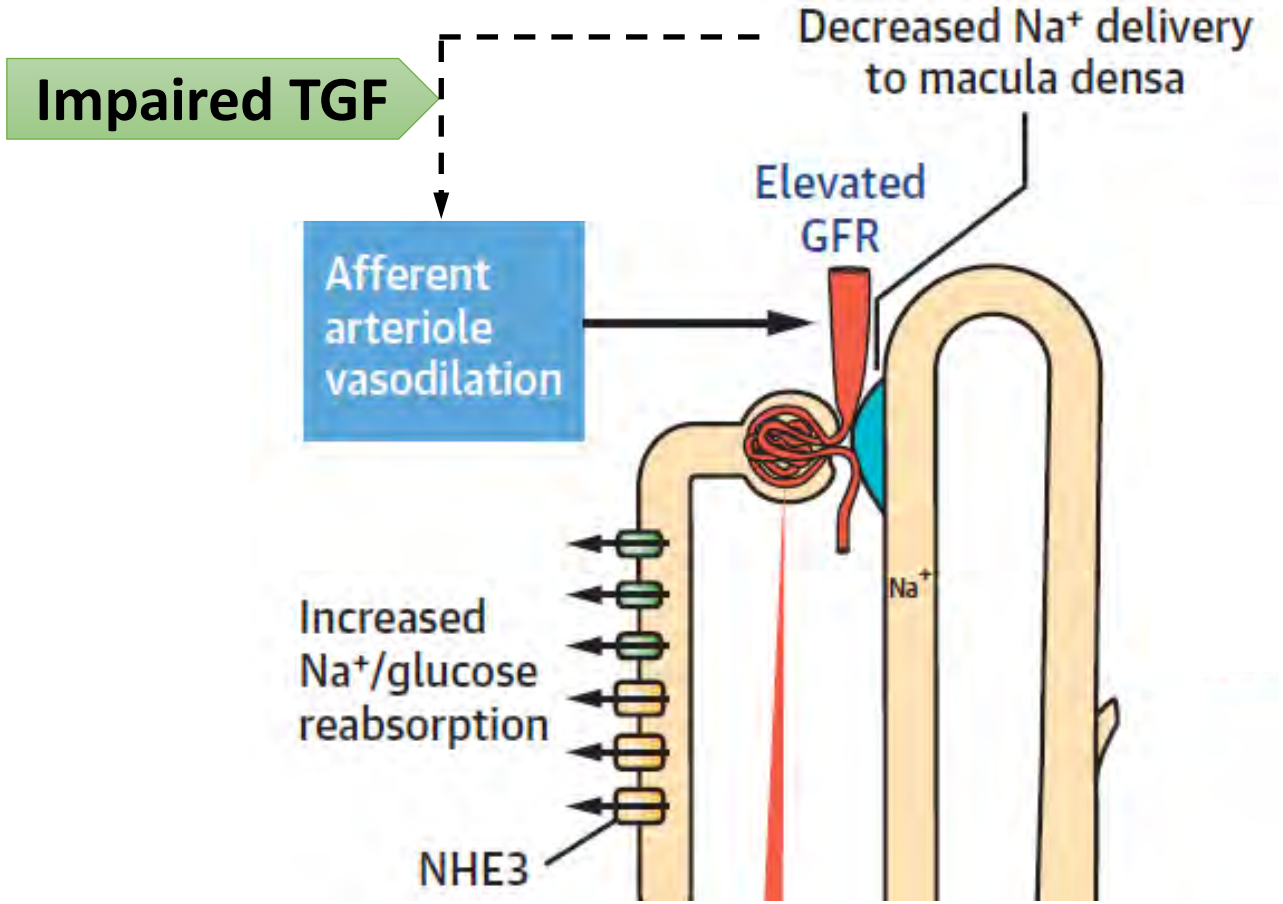
7. Cherney et al. *Journal of the American College of Cardiology*. 2019

Restoration of Tubuloglomerular Feedback (TGF)



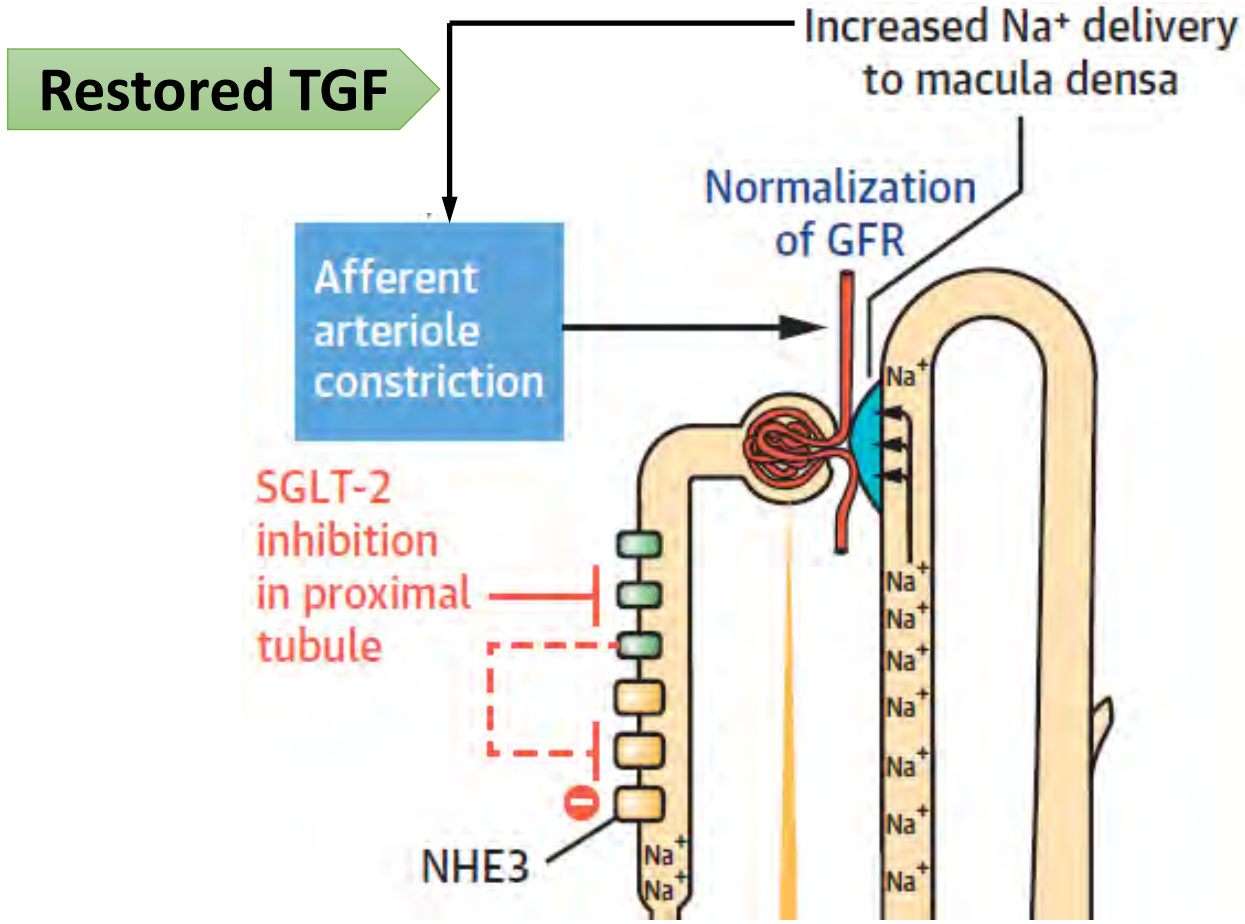
7. Cherney et al. *Journal of the American College of Cardiology*. 2019

RESTORATION OF TUBULOGLOMERULAR FEEDBACK



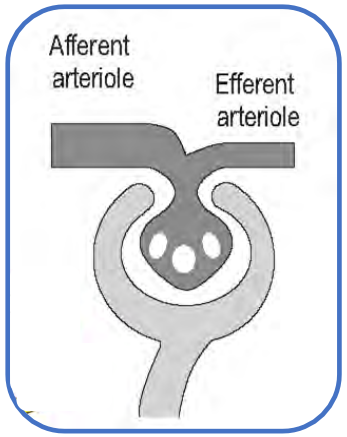
7. Cherney et al. *Journal of the American College of Cardiology*. 2019

Restoration of Tubuloglomerular Feedback

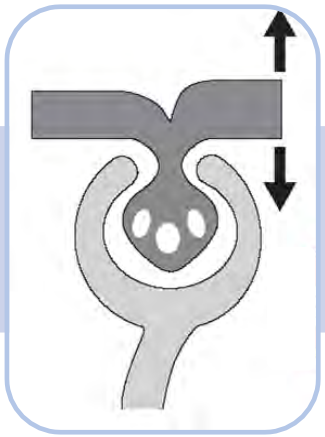


7. Cherney et al. *Journal of the American College of Cardiology*. 2019

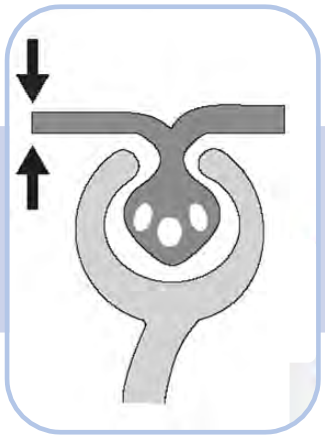
Nephroprotective Mechanisms



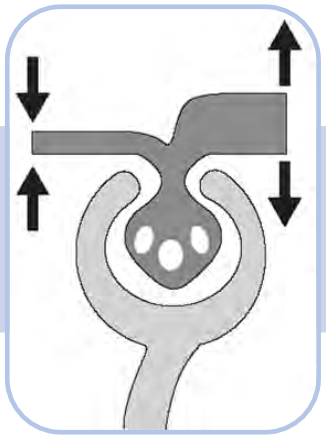
Normal glomerulus



RAAS Blockade
Efferent Dilation



SGLT2 Inhibition
Afferent Constriction



Combined SGLT2 + RAAS Inhibition
Afferent Constriction + Efferent Dilation

7. Cherney et al. *Journal of the American College of Cardiology*. 2019

KEY POINTS

- SGLT2 inhibitors provide nephroprotection in addition to RAAS inhibitors
- Nephroprotective benefit persists at lower renal function (eGFR < 45 mL/min/1.73m^2) irrespective of glycemic control

PLACE IN THERAPY

ADA Recommendation

Consider use of a SGLT2 inhibitor in pts with an eGFR ≥30 mL/min/1.73m^2 and urinary albumin >30 mg/g creatinine, particularly in those with urinary albumin >300 mg/g creatinine, to reduce risk of CKD progression, CV events, or both. **A**

FDA Indication (Canagliflozin)

Reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria

2. American Diabetes Association. *Diabetes Care.* 2020

TIMELINE: FUTURE RENAL TRIALS

CREDENCE

Canagliflozin

(Completed October 2018)

Diabetic CKD

DAPA-CKD

Dapagliflozin

(Completed March 2020)

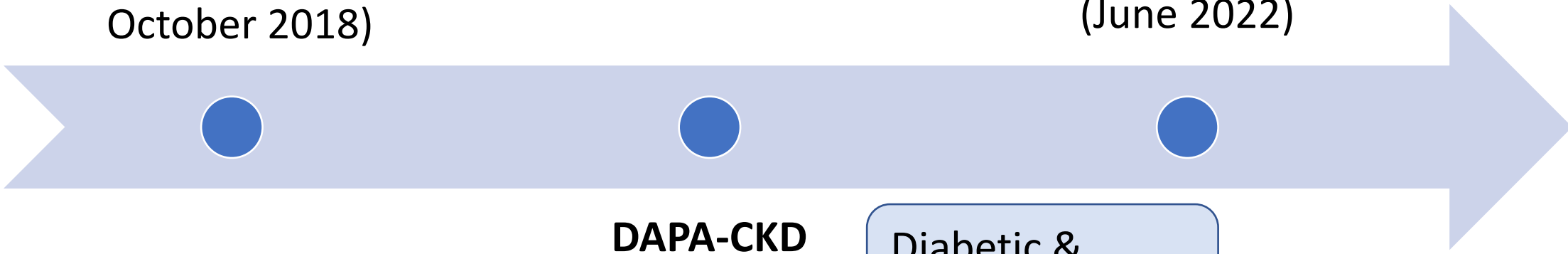
Diabetic & Nondiabetic CKD

EMPA-KIDNEY

Empagliflozin

(June 2022)

Diabetic & Nondiabetic CKD



HEART FAILURE BENEFIT

DAPA HF

- Multicenter, double-blind, parallel-group, randomized, controlled trial
- Dapagliflozin 10mg vs Placebo (n=2,371)
- Setting: 410 centers in 20 countries (14% North America)
- Median follow-up: 18.2 months
- Analysis: Intention-to-treat
- Primary outcome: Composite of worsening HF or CV death

8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (Population)

Inclusion Criteria

- Age of at least 18 years
- Ejection fraction of ≤40%
- NYHA Class II, III, or IV symptoms
- Plasma NT-proBNP level of:
  - ≥ 600pg/mL OR
  - ≥ 400pg/mL if they were hospitalized for HF within the past 12 months

Exclusion Criteria

- Type 1 Diabetes
- Hypotension/SBP <95 mmHg
- eGFR ≤30 ml/m/1.73m^2
- Current decompensated HF or HF hospitalization <4 weeks prior

8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (Baseline Characteristics)

	Dapagliflozin (N=2373)	Placebo (N=2371)
Age — yr	66.2±11.0	66.5±10.8
Female sex—no. (%)	564 (23.8)	545 (23.0)
NYHA classification II/ III/ IV , %	68/ 32/ 1	67/ 32/ 1
Median NT-proBNP (IQR) — pg/ml	1428 (857–2655)	1446 (857–2641)
Ischemic etiology, %	55.5	57.3
Diabetes mellitus diagnosis, %	41.8	41.8
Systolic blood pressure — mm Hg	122.0±16.3	121.6±16.3

8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (Baseline Characteristics)

	Dapagliflozin (N=2373)	Placebo (N=2371)
Heart failure medication, %		
Diuretic	93.4	93.5
ACE inhibitor	56.1	56.1
ARB	28.4	26.7
Sacubitril–valsartan	10.5	10.9
Beta-blocker	96.0	96.2
MRA	71.5	70.6
Digitalis	18.8	18.6

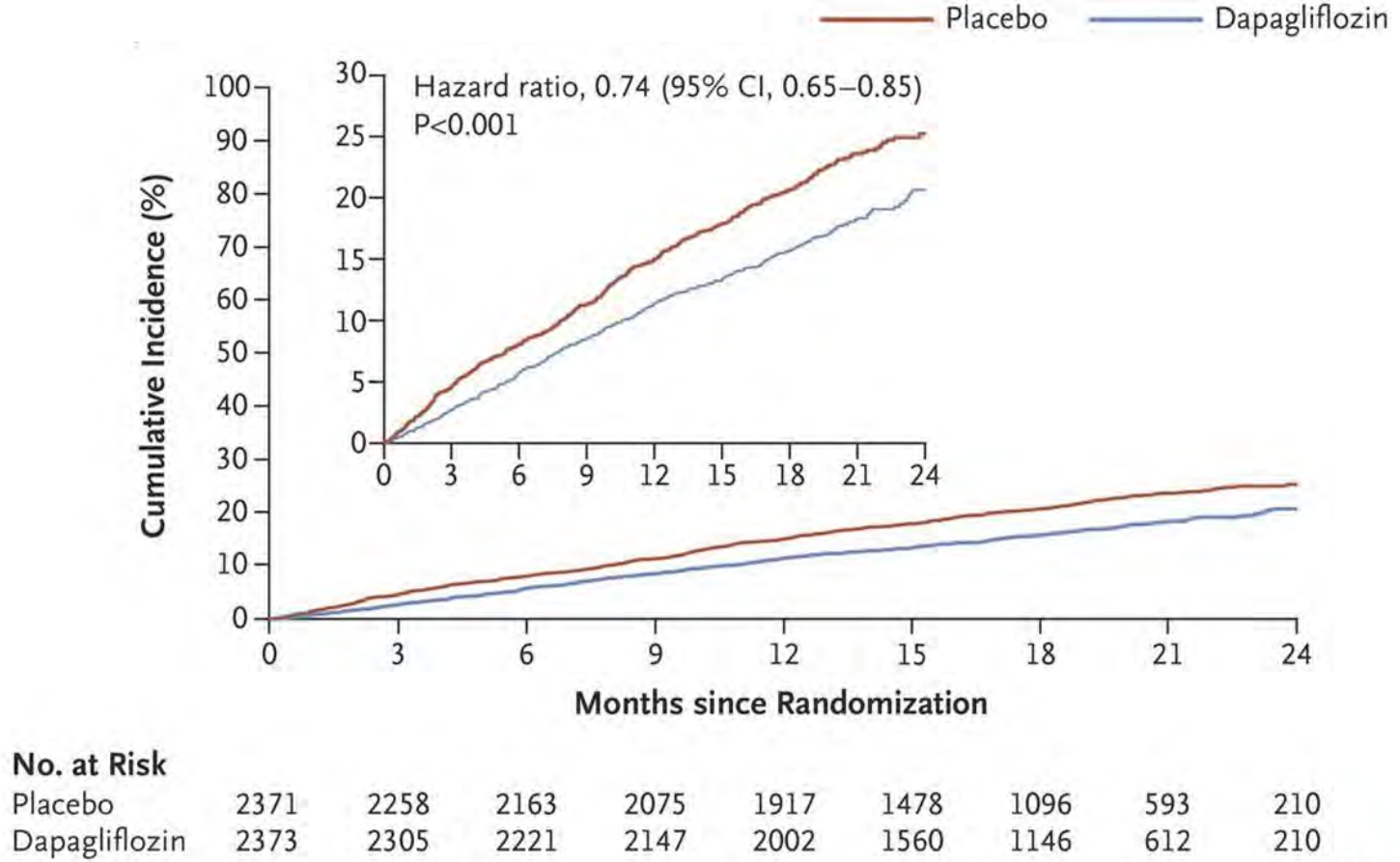
8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (Primary Composite Outcome)

Primary Outcomes

Worsening heart failure (hospitalization or urgent visit resulting in IV therapy for HF) or CV mortality

NNT = 62 over 18.2 months

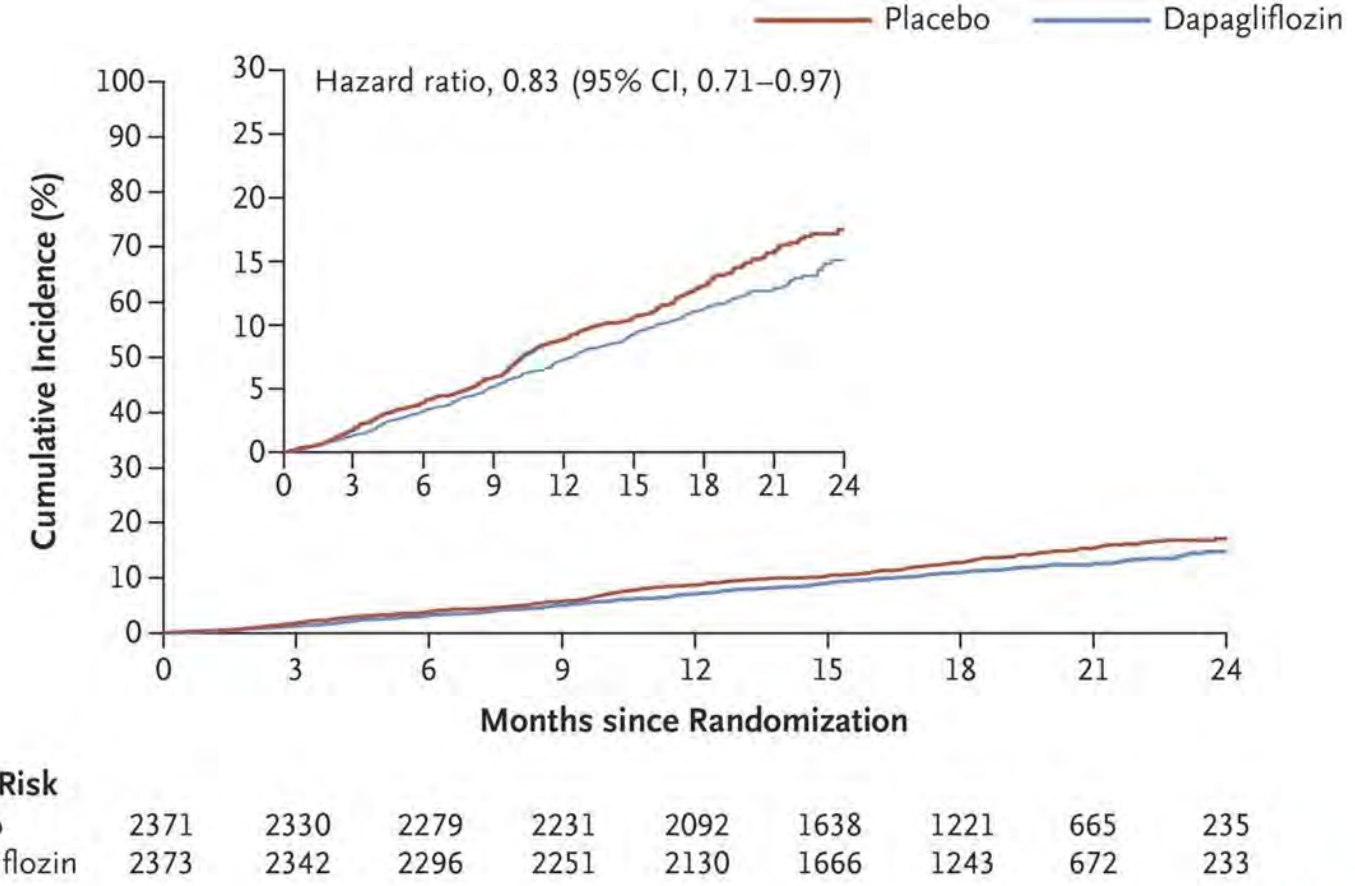


8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (CV MORTALITY)

CV MORTALITY

NNT= 45 OVER
18.2 MONTHS



8. McMurray JJV et al. *N Engl J Med.* 2019

EVIDENCE-BASED THERAPIES FOR PATIENTS WITH HFrEF

DAPAGLIFLOZIN

NNT = 66
STANDARDIZED TO
12 MONTHS

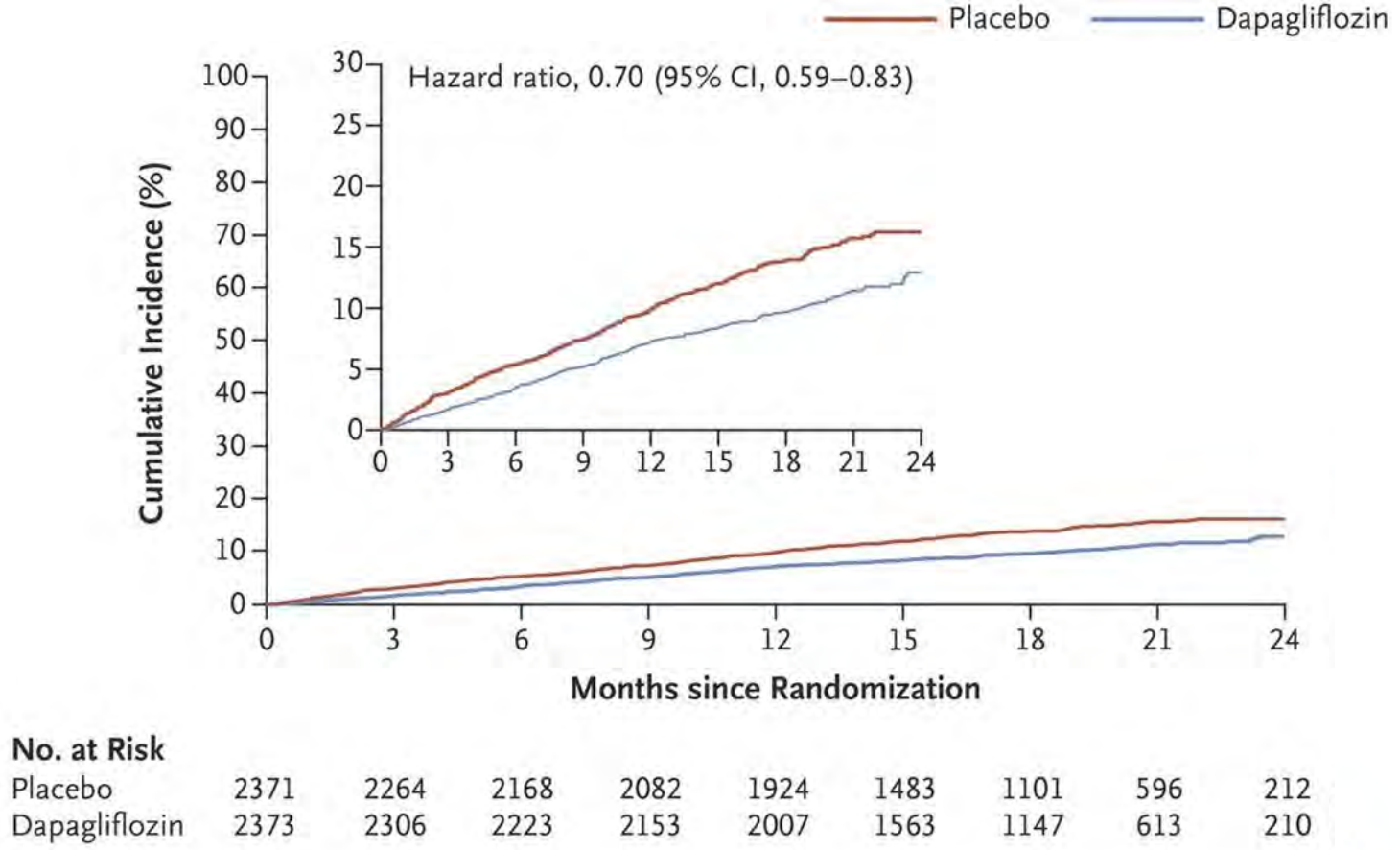
Table. Demonstrated Benefits of Evidence-Based Therapies for Patients With Heart Failure and Reduced Ejection Fraction

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal Randomized Clinical Trial(s), %	NNT to Prevent All-Cause Mortality Over Time	NNT for All-Cause Mortality[a]
ACEI/ARB	17	22 over 42 mo	77
ARNI[b]	16	36 over 27 mo	80
β-Blocker	34	28 over 12 mo	28
Aldosterone antagonist	30	9 over 24 mo	18
Hydralazine/ nitrate	43	25 over 10 mo	21
CRT	36	12 over 24 mo	24
ICD	23	14 over 60 mo	70

9. Fonarow, G. C et al. *JAMA Cardiology.* 2018

DAPA HF (Hospitalization for Heart Failure)

HOSPITALIZATION FOR HEART FAILURE



8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (KCCQ Result)

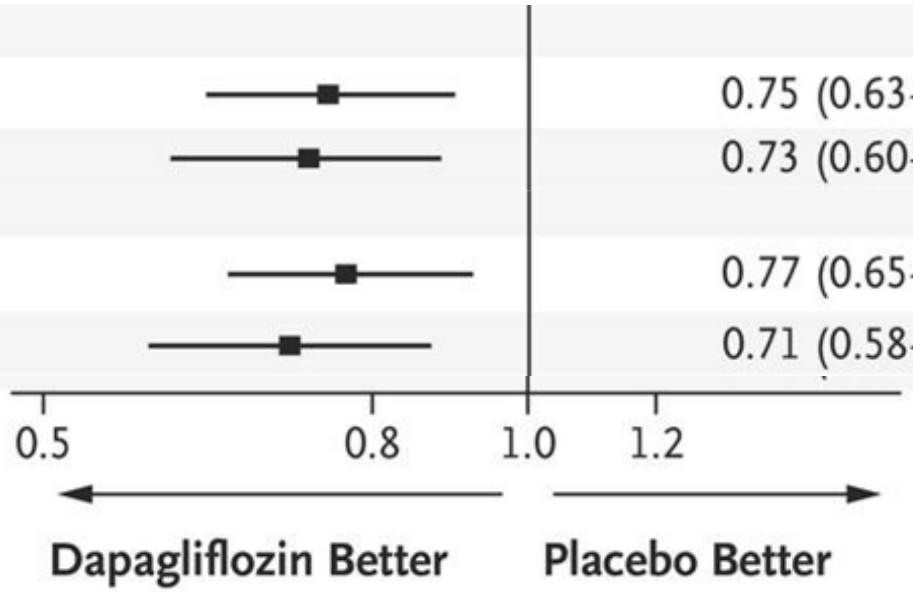
Treatment	Change in KCCQ Score
Dapagliflozin	6.1±18.6
Placebo	3.3±19.2

Win Ratio: 1.18 (1.11 to 1.26)
P value <0.001

8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (PRESPECIFIED SUBGROUP)

Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		
Type 2 diabetes at baseline			
Yes	215/1075	271/1064	0.75 (0.63–0.90)
No	171/1298	231/1307	0.73 (0.60–0.88)
Main cause of heart failure			
Ischemic	223/1316	289/1358	0.77 (0.65–0.92)
Nonischemic or unknown	163/1057	213/1013	0.71 (0.58–0.87)



8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (SAFETY)

Adverse events of interest, %	Dapagliflozin	Placebo	P Value
Volume depletion	7.5	6.8	0.40
Renal adverse event	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycemia	0.2	0.2	NA
Diabetic ketoacidosis	0.1	0	NA

8. McMurray JJV et al. *N Engl J Med.* 2019

DAPA HF (LABORATORY AND OTHER MEASURES)

Change from baseline to 8 months	Dapagliflozin	Placebo	Difference	P Value
Hematocrit — %	2.31±3.90	−0.19±3.81	2.41 (2.21 to 2.62)	<0.001
NT-proBNP — pg/ml	−196±2387	101±2944	−303 (−457 to −150)	<0.001
Weight — kg	−0.88±3.86	0.10±4.09	−0.87 (−1.11 to −0.62)	<0.001

8. McMurray JJV et al. *N Engl J Med.* 2019

KEY POINTS

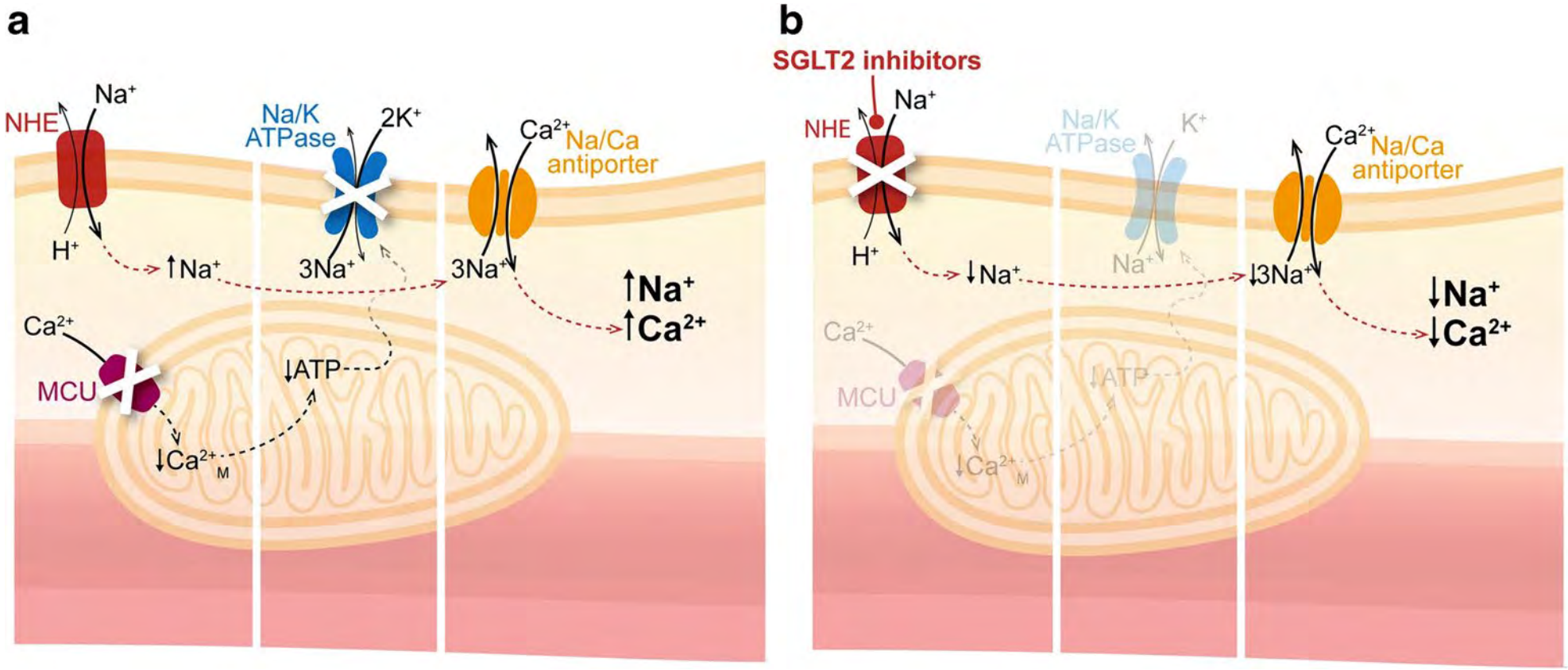
- Benefits heart failure with reduced ejection fraction (HFrEF) irrespective of HbA1c reduction
- Benefit is in addition to guideline-directed medical therapy
  - Angiotensin receptor–neprilysin inhibitor (ARNI) used in ~10% of the patient population
- Multiple theories for cardioprotective mechanism
  - Benefits both ischemic and non-ischemic causes of heart failure

Cardioprotective Mechanisms

Hemodynamic effects	Direct cardiac effects	Increased hematocrit
• ↓ preload via natriuresis and osmotic diuresis • ↓ afterload via reduction in blood pressure and arterial stiffness • ↓ sympathetic overdrive	• NHE1 inhibition – minimize myocyte injury and cardiomyopathy • CaMKII reduction – improving contractility	• SGLT2 inhibitors alleviate metabolic stress in the proximal tubule • Allows myofibroblasts to revert back to erythropoietin-producing cells

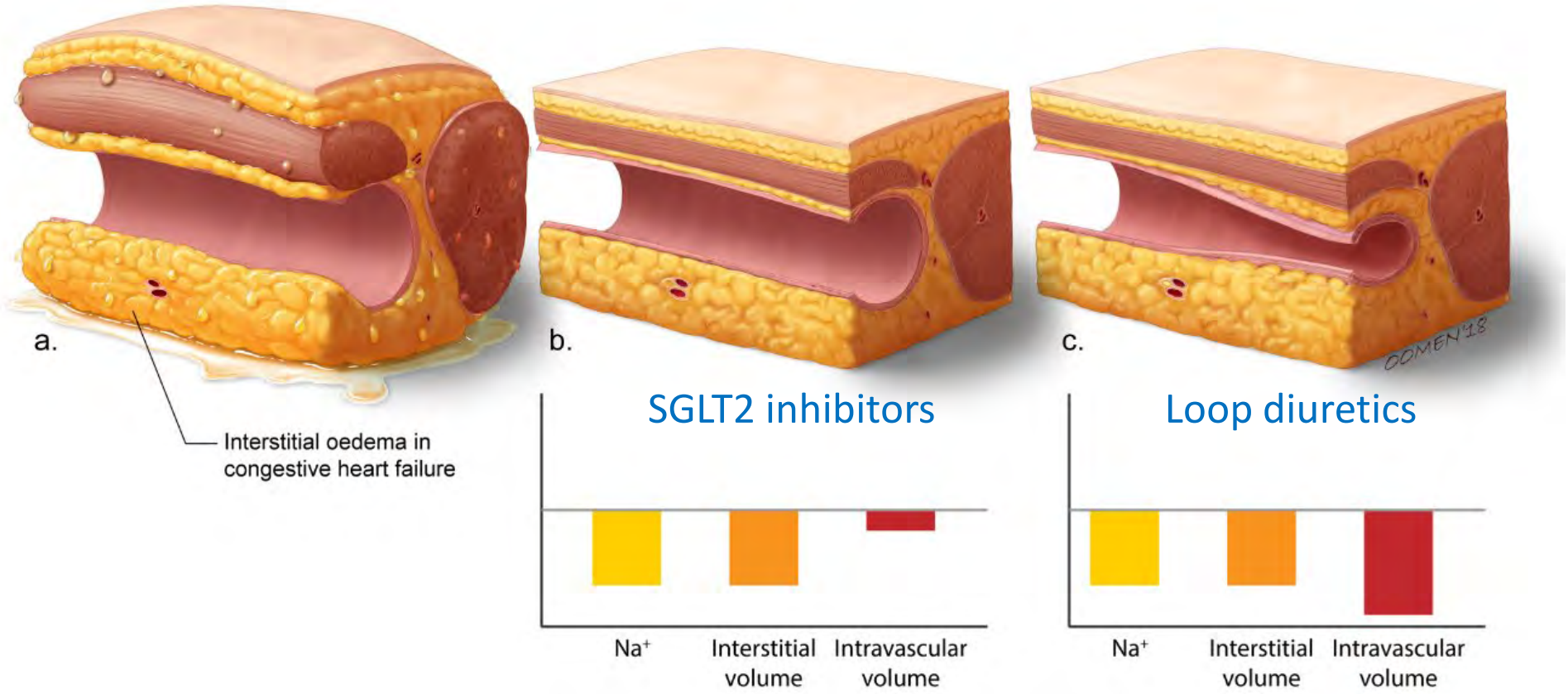
10. Zelniker TA, Braunwald E. *JACC.* 2020

Na^+/H^+ EXCHANGE



11. Verma S, McMurray JJV. *Diabetologia*. 2019

SGLT2 Inhibitors vs. Diuretics



12. Verma S. *Am J Cardiology.* 2019

Cardioprotective Mechanisms

Reduction in inflammation	Improvement in myocardial efficiency	Metabolic Effects
• Restoration of equilibrium between pro- and anti-inflammatory adipokines • Increased uric acid excretion	• SGLT2 inhibition promotes ketogenesis via increased glucagon and reduced insulin production • Improves cardiac efficiency and contractility	• Lower HbA1c, blood pressure, body weight

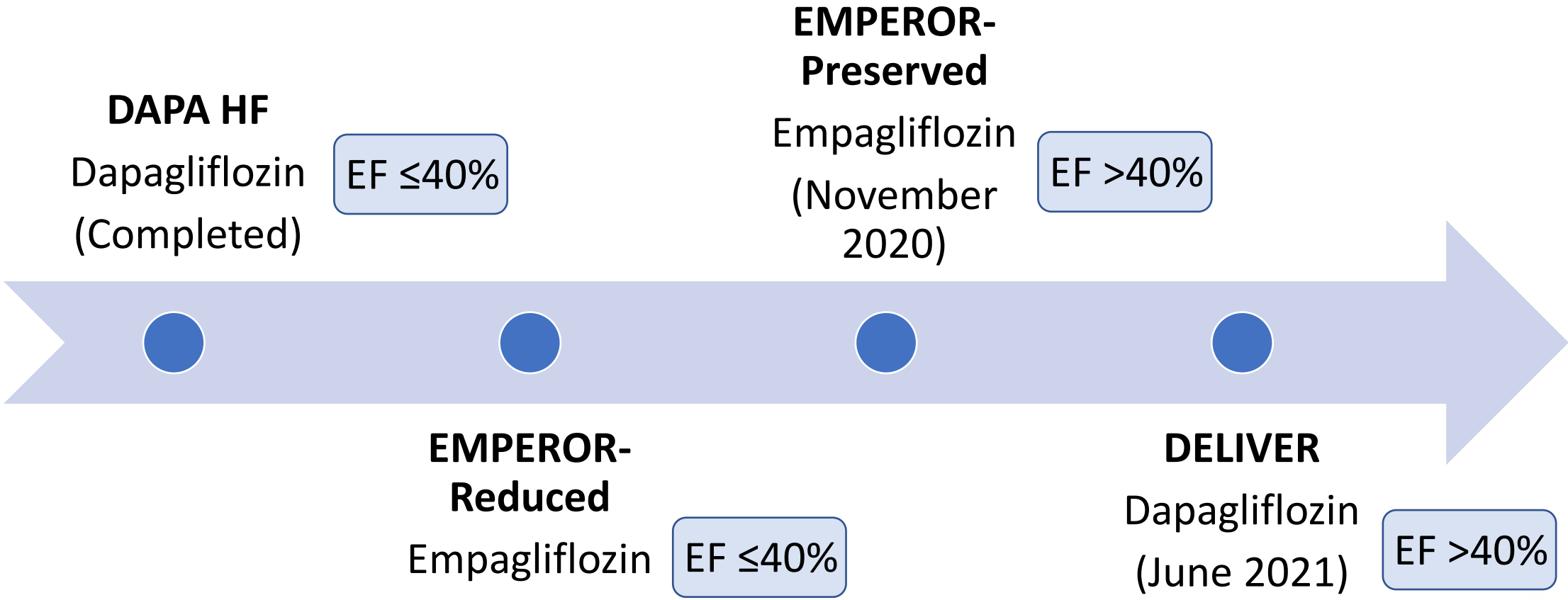
10. Zelniker TA, Braunwald E. *JACC.* 2020

Place in Therapy

FDA Indication (Dapagliflozin)

Treatment of heart failure with reduced ejection fraction (HFrEF) in adults with and without type 2 diabetes mellitus

TIMELINE: FUTURE HEART FAILURE TRIALS



Cardio-Metabolic-Renal Effects

	HF	CVD	CKD
Glucose lowering			x
Reduction in weight	x	x	x
Lowering BP	x	x	x
Natriuresis	x		x
Anti-inflammation	x	x	x
Antifibrotic	x		x
Reduce renal hypoxia			x
Tubuloglomerular feedback			x
Reduce natriuretic peptides	x		x
Reduce energy demand	x		x

10. Zelniker TA, Braunwald E. *JACC*. 2020

PRECAUTIONS

Caution	Risk Factors
Intravascular volume contraction	Renal impairment or low SBP, diuretic use, or the elderly
Bone fractures (canagliflozin)	Osteoporosis
Genitourinary infections	Prior h/o UTI (females), or uncircumcised males
Euglycemic ketoacidosis	Insulin deficiency, insulin dose reduction, caloric restriction, alcohol abuse, acute illness
Lower limb amputation (canagliflozin and ertugliflozin)	Prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers
Fournier gangrene	Diabetes, obesity, poor hygiene

OTHER BENEFITS

NON-ALCOHOLIC FATTY LIVER DISEASE

- Improvement shown in small studies
  - Improve serum liver enzymes
  - Positive benefit through non-invasive image techniques (MRI-PDFF and liver/spleen attenuation ratio)
- Very small studies show histopathological improvement

13. Gharaibeh, N. E et al. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2019

NON-ALCOHOLIC FATTY LIVER DISEASE

Mechanism

- Decrease blood glucose, blood insulin levels, and body mass → decrease hepatic insulin resistance
- Reduction of hepatic de novo lipid synthesis
- Stimulates release of glucagon from pancreatic alpha cells → increase beta-oxidation and hepatic ketone production

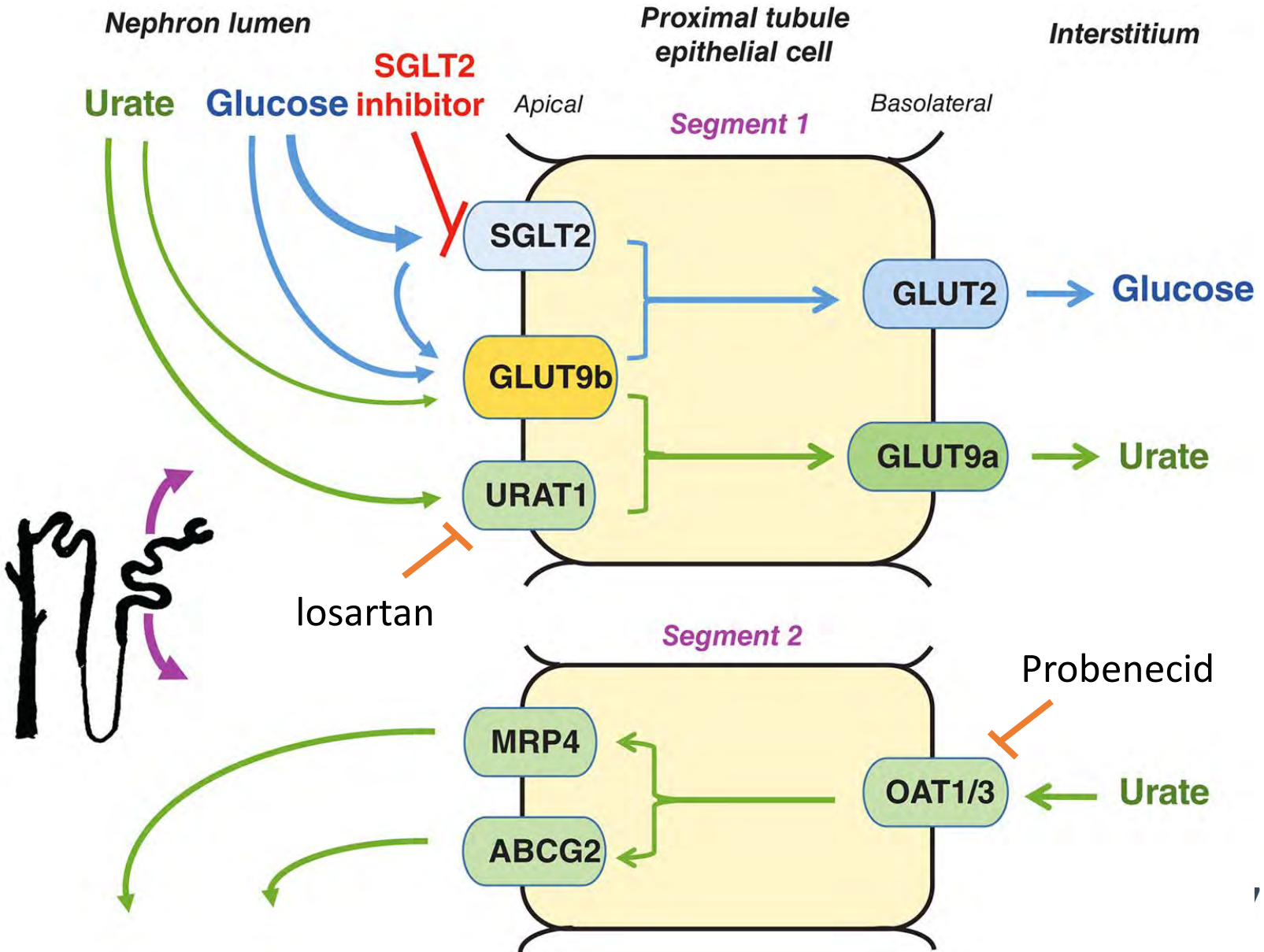
13. Gharaibeh, N. E et al. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2019

GOUT

- SGLT2 inhibitors shown to decrease uric acid levels
- Using an insurance claims database, researchers compared adults with type 2 diabetes prescribed SGLT2 inhibitors versus prescribed GLP-1 receptor agonists
  - After a mean follow-up of 260 to 300 days, rate of incident gout was significantly lower among those prescribed SGLT2 inhibitors

14. Fralick, M et al. *Annals of Internal Medicine.* 2020

GOUT



15. Chino, Y. et al. *Biopharmaceutics & Drug Disposition.* 2014

Summary / Key Points

- SGLT2 inhibitors can be beneficial for patients with heart failure, chronic kidney disease, and diabetes
- However, benefits and risks need to be assessed in every patient
- Mechanisms of these benefits are likely multifactorial

Patient Case

- 58-year-old Caucasian male with T2DM for 15 years
- History of CHF for 4 years: 2 admissions in the past year
- NSTEMI January 2017
- History of pancreatitis due to alcohol in 2012
- States taking glipizide PRN d/t hypoglycemia
- Laboratory:
  - A1c: 7.3%
  - LDL: 106 mg/dL, TG: 165 mg/dL, HDL: 35mg/dL
  - eGFR: 49 mL/min/1.73m^2
  - Echo: EF 35%

Patient Case

- Physical Examination
  - Weight: 234 lbs.; BMI 33.57
  - BP: 140/84 Pulse 82
  - Neck: no JVD
  - Cardiac: no murmurs, NML S1S2
  - Abdomen: no hepatomegaly
  - Extremities: 1-2+ edema, intact peripheral pulses
  - CNS: loss of vibratory sensation in feet intact ankle reflexes and hot and cold sensation

- Meds
  - Metformin 1000mg BID
  - Glargine 34 units QHS
  - Glipizide 5mg BID
  - Metoprolol 25mg BID
  - Aspirin 81mg daily
  - Atorvastatin 80mg daily
  - Lisinopril 20mg daily
  - Clopidogrel 75mg daily
  - Spironolactone 25mg daily
  - Hydralazine 25mg BID
  - Isosorbide 20mg BID

TEST QUESTION 1

Which of the following comorbidities is relevant in deciding if an SGLT2 inhibitor is a good treatment option?

A. CKD
B. CHF
C. DM
D. All of the above

TEST QUESTION 1

Which of the following comorbidities is relevant in deciding if an SGLT2 inhibitor is a good treatment option?

A. CKD
B. CHF
C. DM
D. **All of the above**

TEST QUESTION 2

Which of the following medications would be most appropriate to add for this patient?

A. Saxagliptin
B. Dapagliflozin
C. Dulaglutide
D. Pioglitazone

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B. **Dapagliflozin**
C. Dulaglutide
D. Pioglitazone

TEST QUESTION 3

Which of the following is **not** an effect of SGLT2 inhibitors?

A. Dilation of afferent renal arteries
B. Increase uric acid excretion
C. Reduction of both preload and afterload
D. Increase in epoetin production

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