SGLT-2 Inhibitors for the Family Physician

KEY DOUTHITT, MD

ASSOCIATE PROFESSOR, UNIVERSITY OF KENTUCKY DEPARTMENT OF FAMILY AND COMMUNITY MEDICINE

MEDICAL DIRECTOR, NORTH FORK VALLEY COMMUNITY HEALTH CENTER

Faculty Disclosures

- None

Educational Need/Practice Gap

- Gaps
  - Studies and indications for sodium-glucose co-transporter 2 inhibitors (SGLT-2s) have been developing at a rapid pace.
  - Unfamiliarity with these newer diabetic agents, their side effects, and studies showing secondary benefits has resulted in less integration or inappropriate integration of these medications into management plans.
- Needs
  - Providers need to be familiar with SGLT-2s to discuss their risks and benefits with patients and recommend tailored therapy based on their underlying health conditions.

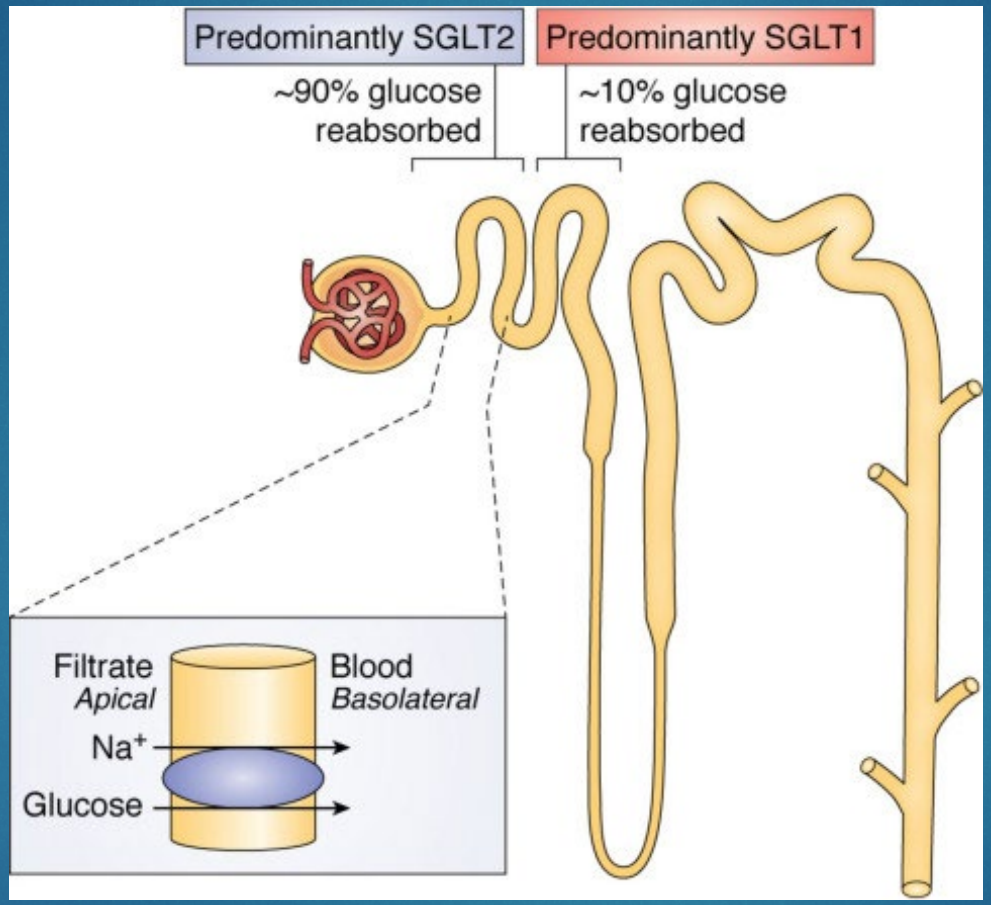
Objectives

- Upon completion of this educational activity, you will be able to:
  - 1. Compare the efficacy of sodium-glucose co-transporter 2 inhibitors in the treatment of type 2 diabetes, congestive heart failure, and chronic kidney disease.
  - 2. Describe potential uses for SGLT-2 inhibitors in other disease states.

Kahoot Question 1:

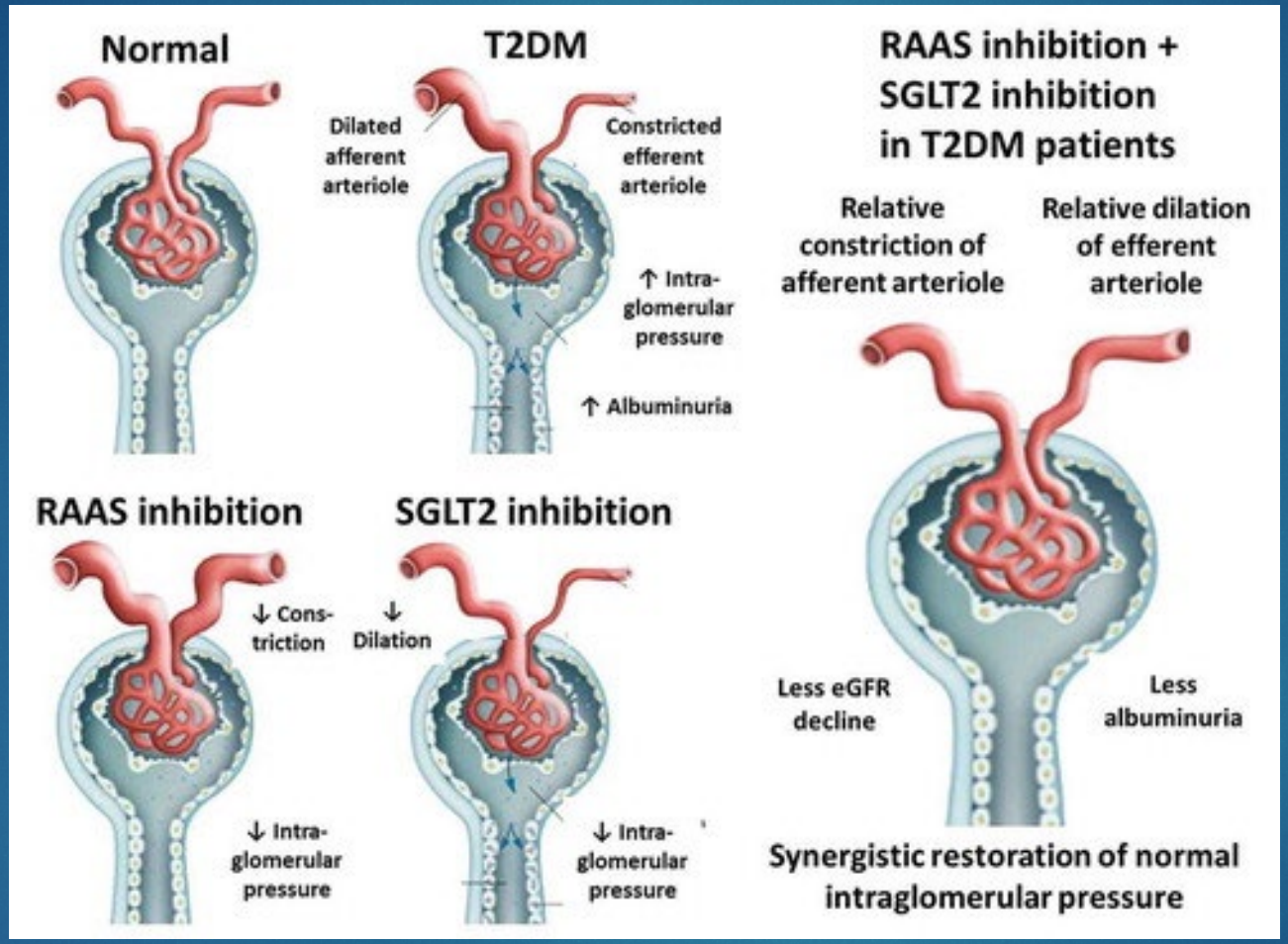
- Go to Kahoot.it
- Enter the game code shown
- Put in a nickname
- Points are given for correct answers.
- The faster the correct answer is given, the more points that are awarded
- No points taken away for incorrect answers
- Be first. Be right.

SGLT-2s: Mechanism of Action



- Perry RJ, et al. J Biol Chem. 2020 Oct 16;295(42):14379-14390.

SGLT-2s: Mechanism of Action



- Delanaye, P., & Scheen, A. J. (2018). Preventing and treating kidney disease in patients with type 2 diabetes. *Expert Opinion on Pharmacotherapy*, *20*(3), 277–294.

SGLT-2s

- 6 Currently on the market:
  - Empagliflozin (Jardiance ®)
  - Canagliflozin (Invokana ®)
  - Dapagliflozin (Farxiga ®)
  - Ertugliflozin (Steglatro ®)
  - Bexagliflozin (Brenzavvy ®)
  - Sotagliflozin (Inpefa ®)

Kahoot Question 2-4:

- Go to Kahoot.it
- Enter the game code shown
- Put in a nickname
- Points are given for correct answers.
- The faster the correct answer is given, the more points that are awarded
- No points taken away for incorrect answers
- Be first. Be right.

SGLT-2s: Side effects and Contraindications

- Side effects:
  - 2-4 fold increase in vulvovaginal candidiasis
  - Increased rate of UTIs (8.8% vs 6.1%)
  - Increased incidence of Fournier's gangrene
  - Avoid giving to patients with HbA1C > 9.0%
  - For canagliflozin – increased incidence of lower limb amputation and bone fracture
- Contraindications:
  - Type I diabetes or history of DKA
  - For A1C lowering, limited benefit if GFR < 60.

SGLT-2s

- Benefits:
  - Average A1C lowering 0.6-1%.
  - Weight loss (~ 5 lbs)
  - Blood pressure lowering
  - No hypoglycemia

SGLT-2s: Understanding the Facts

- Do SGLT-2s reduce the risk of cardiovascular events in patients with type 2 diabetes:
  - With known cardiovascular disease?
  - With risk factors for cardiovascular disease?

Kahoot Question 5:

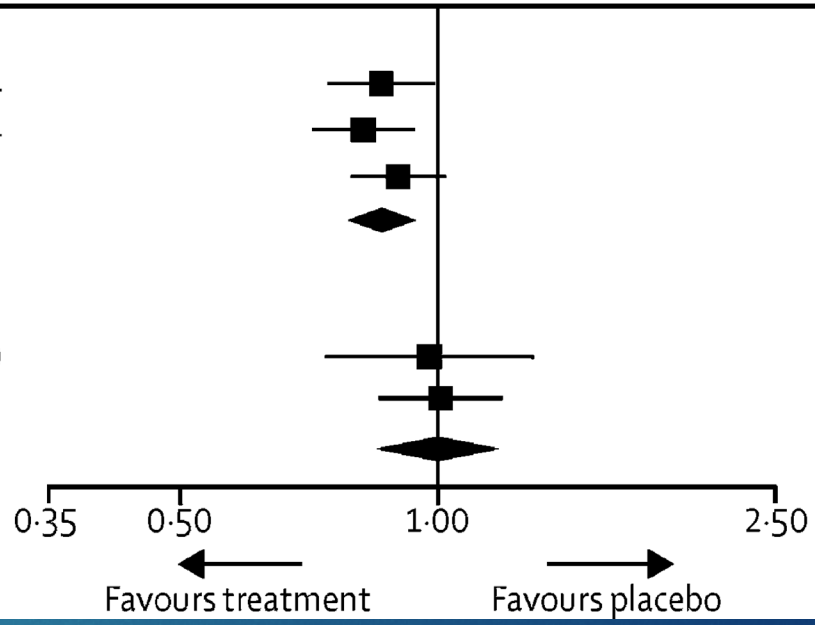
- Go to Kahoot.it
- Enter the game code shown
- Put in a nickname
- Points are given for correct answers.
- The faster the correct answer is given, the more points that are awarded
- No points taken away for incorrect answers
- Be first. Be right.

Zelniker et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

- Included 34,322 patients from the major trials for Empagliflozin (EMPA-REG Outcome), Canagliflozin (CANVAS Program) and Dapagliflozin (DECLARE-TIMI 58).
- All patients had type 2 diabetes.
- Categorized into those with known cardiovascular disease and those with no known cardiovascular disease but multiple risk factors.
- Evaluated for the presence of cardiovascular events (myocardial infarction, stroke or CVD death).

Zelniker et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

	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)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**

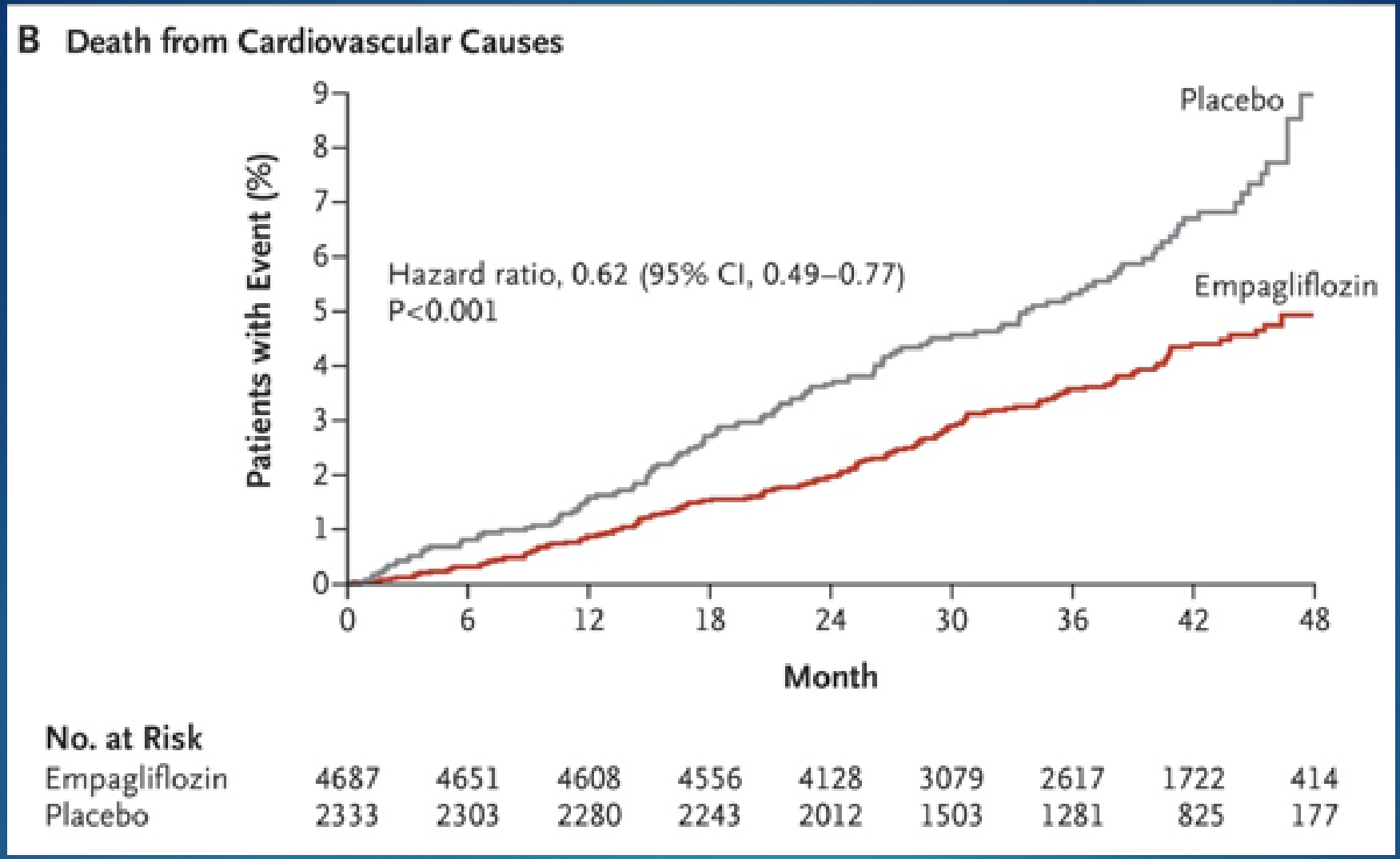


Zelniker et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

- SGLT-2 treatment reduced the risk of cardiovascular death by 16% (p=0.0023) and myocardial infarction by 11% (p=0.0177).
- SGLT-2 treatment did not reduce the incidence of stroke.
- SGLT-2 treatment did not reduce the incidence of CVD events in those without a history of cardiovascular disease.

EMPA-REG OUTCOME: Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117.

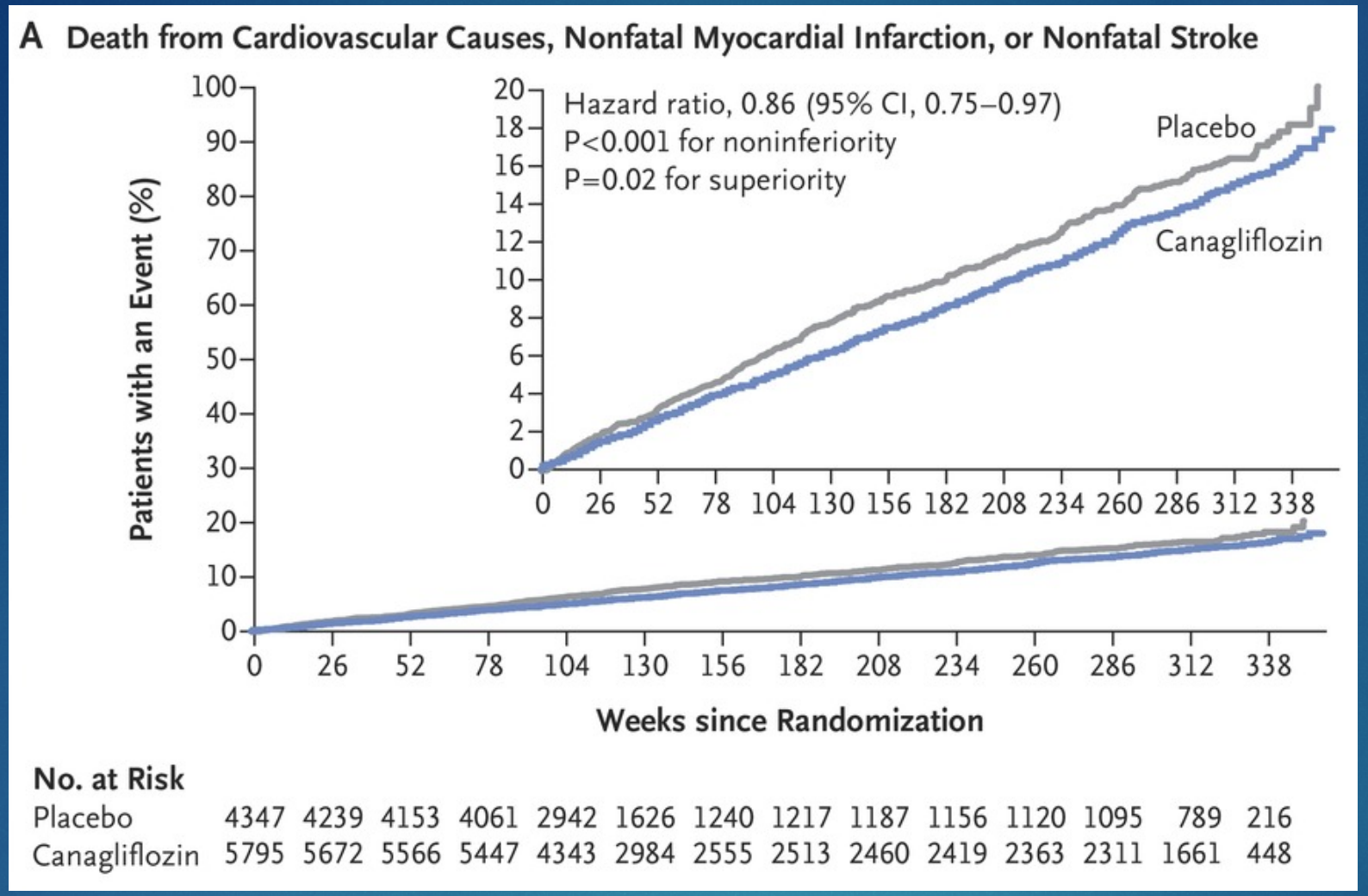
- 7020 patients with type 2 diabetes with known cardiovascular disease
- Placebo vs. empagliflozin
- A1C 7.0 - 9.0%



Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117.

CANVAS Program: Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644.

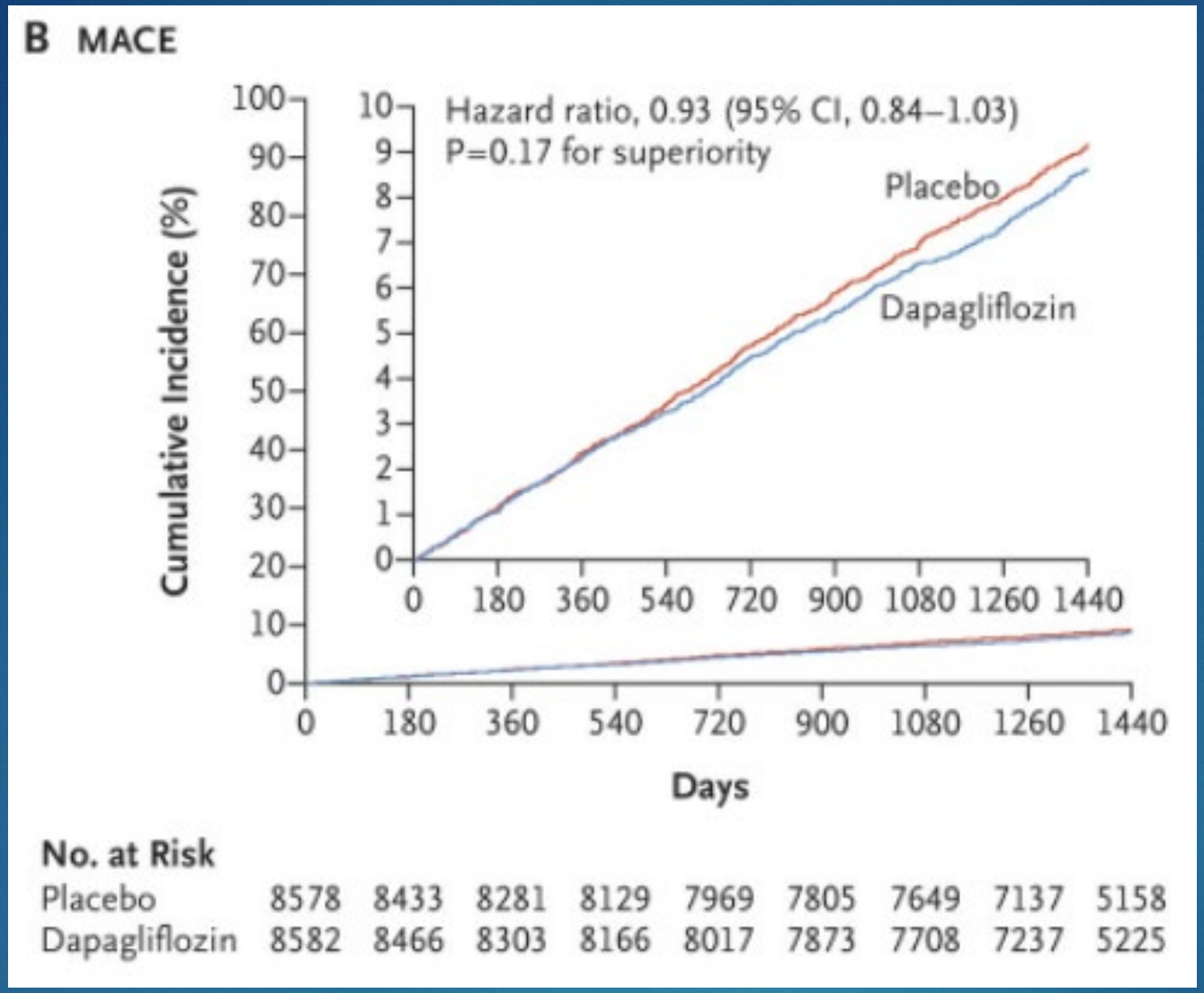
- 10,142 patients with type 2 diabetes and high cardiovascular risk (65.6% had a history of cardiovascular disease and 34.4% had at least two risk factors).
- Placebo vs. canagliflozin.
- A1C 7.0 – 10.5%.



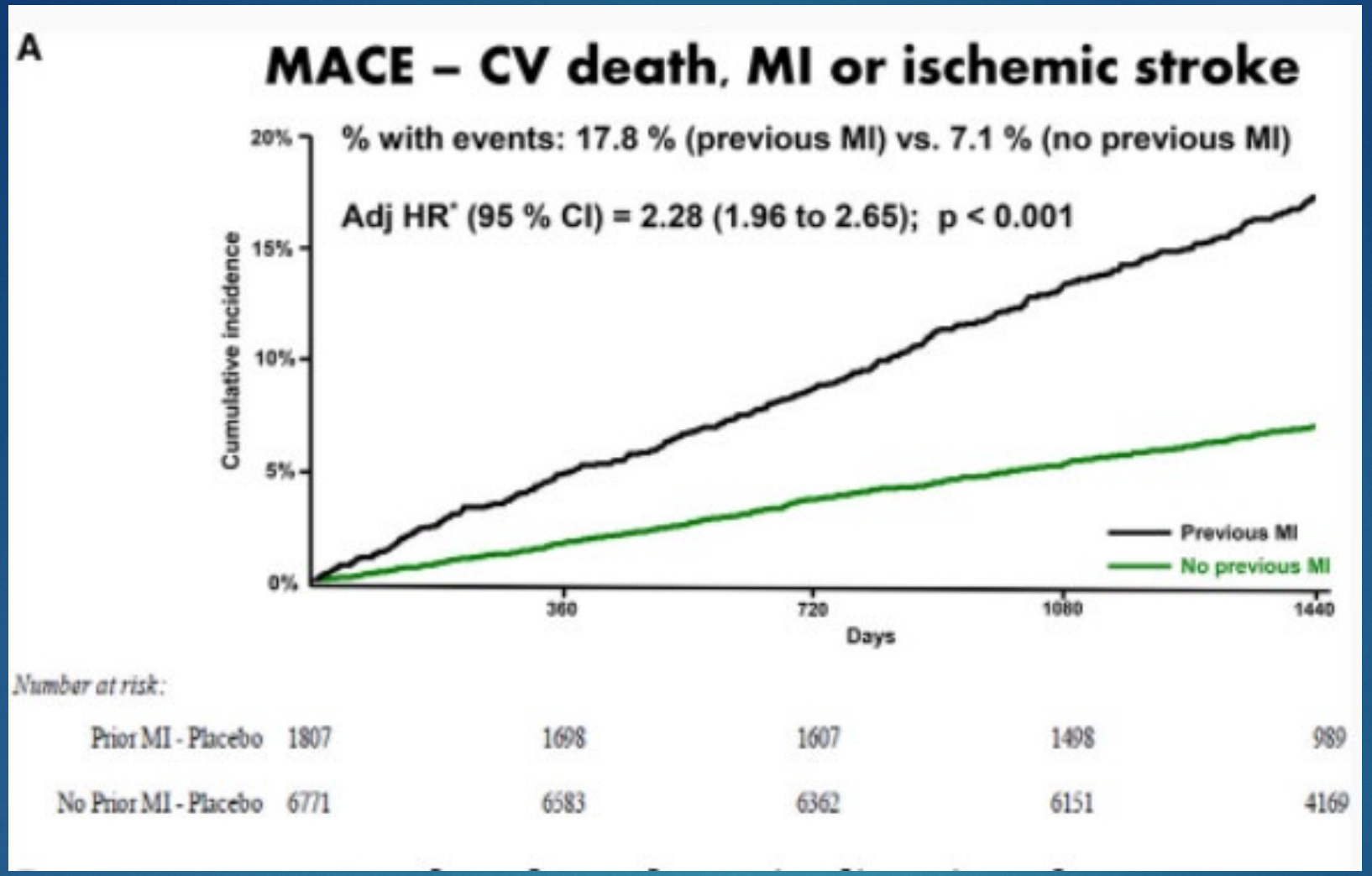
Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644.

DECLARE-TIMI 58: Wiviott et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357.

- 17,160 patients with type 2 diabetes and high cardiovascular risk (40.6% had cardiovascular disease and 59.4% had at least one additional risk factor).
- Placebo vs. Dapagliflozin.
- A1C 6.5 – 12.0%.



Wiviott et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357.



Furtado et al. Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. Circulation. 2019 May 28;139(22):2516-2527.

SGLT-2s: Understanding the Facts

- Do SGLT-2s reduce the risk of cardiovascular events in patients with type 2 diabetes:
  - With known cardiovascular disease? Yes!
  - With risk factors for cardiovascular disease? No!

Sodium-glucose co-transporter 2 inhibitors

Medication	CV event risk reduction in those with CVD
Dapagliflozin	No?
Empagliflozin	Yes
Canagliflozin	Yes
SGLT-2s	Yes

SGLT-2s: Understanding the Facts

- Do SGLT-2s reduce the risk of hospitalization for heart failure:
  - In patients with type 2 diabetes:
    - With known heart failure?
    - With risk factors for heart failure?
  - In patients without type 2 diabetes?
  - In patients with heart failure with reduced ejection fraction HFrEF?
  - In patients with heart failure with preserved ejection fraction HFpEF?

Kahoot Question 6-7:

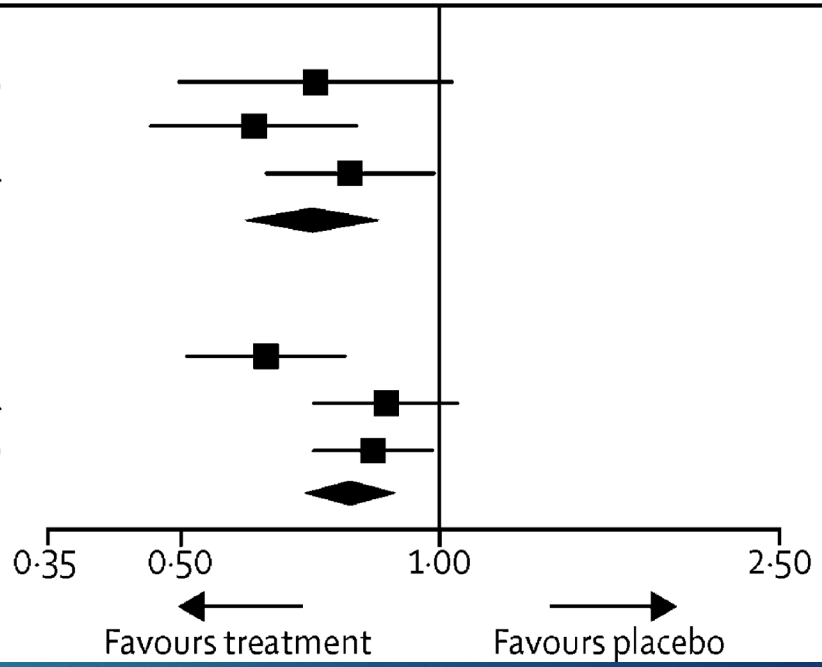
- Go to Kahoot.it
- Enter the game code shown
- Put in a nickname
- Points are given for correct answers.
- The faster the correct answer is given, the more points that are awarded
- No points taken away for incorrect answers
- Be first. Be right.

Zelniker et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

- Included 34,322 patients from the major trials for Empagliflozin (EMPA-REG Outcome), Canagliflozin (CANVAS Program), and Dapagliflozin (DECLARE-TIMI 58).
- All patients had type 2 diabetes.
- Categorized into those with history of heart failure and those with no known history of heart failure but multiple risk factors.
- Evaluated for the presence of hospitalization for CHF.

Zelniker et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462	244	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803	658	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852	872	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225	2089	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992	3689	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730	7706	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**



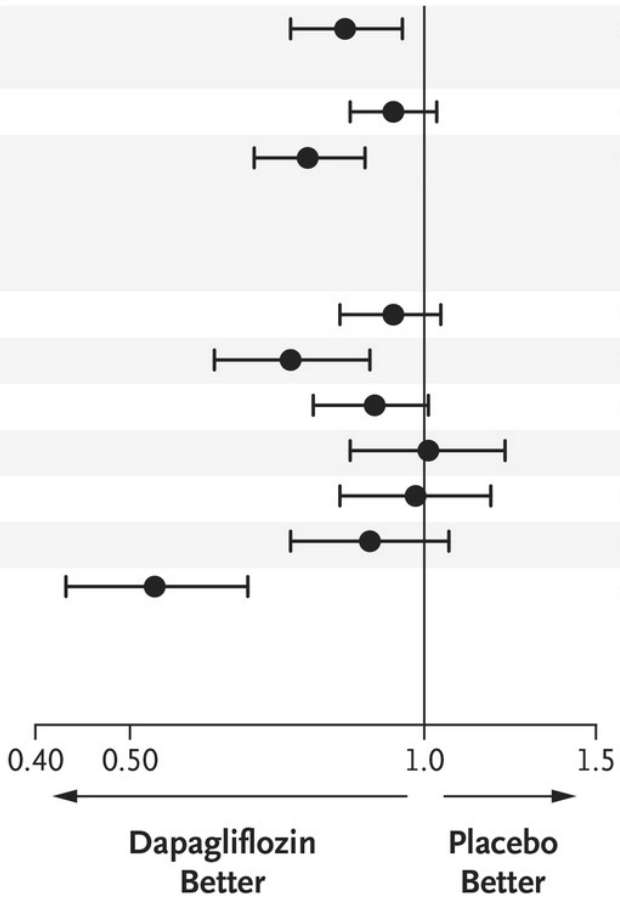
Zelniker et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

- SGLT-2 treatment reduced the risk of hospitalization for heart failure by 23% with a similar benefit in patients with or without cardiovascular disease and with or without a history of heart failure.

DECLARE-TIMI 58: Wiviott et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357.

- 17,160 patients with type 2 diabetes and high cardiovascular risk (40.6% had cardiovascular disease and 59.4% had at least one additional risk factor).
- Placebo vs. Dapagliflozin.
- A1C 6.5 – 12.0%.

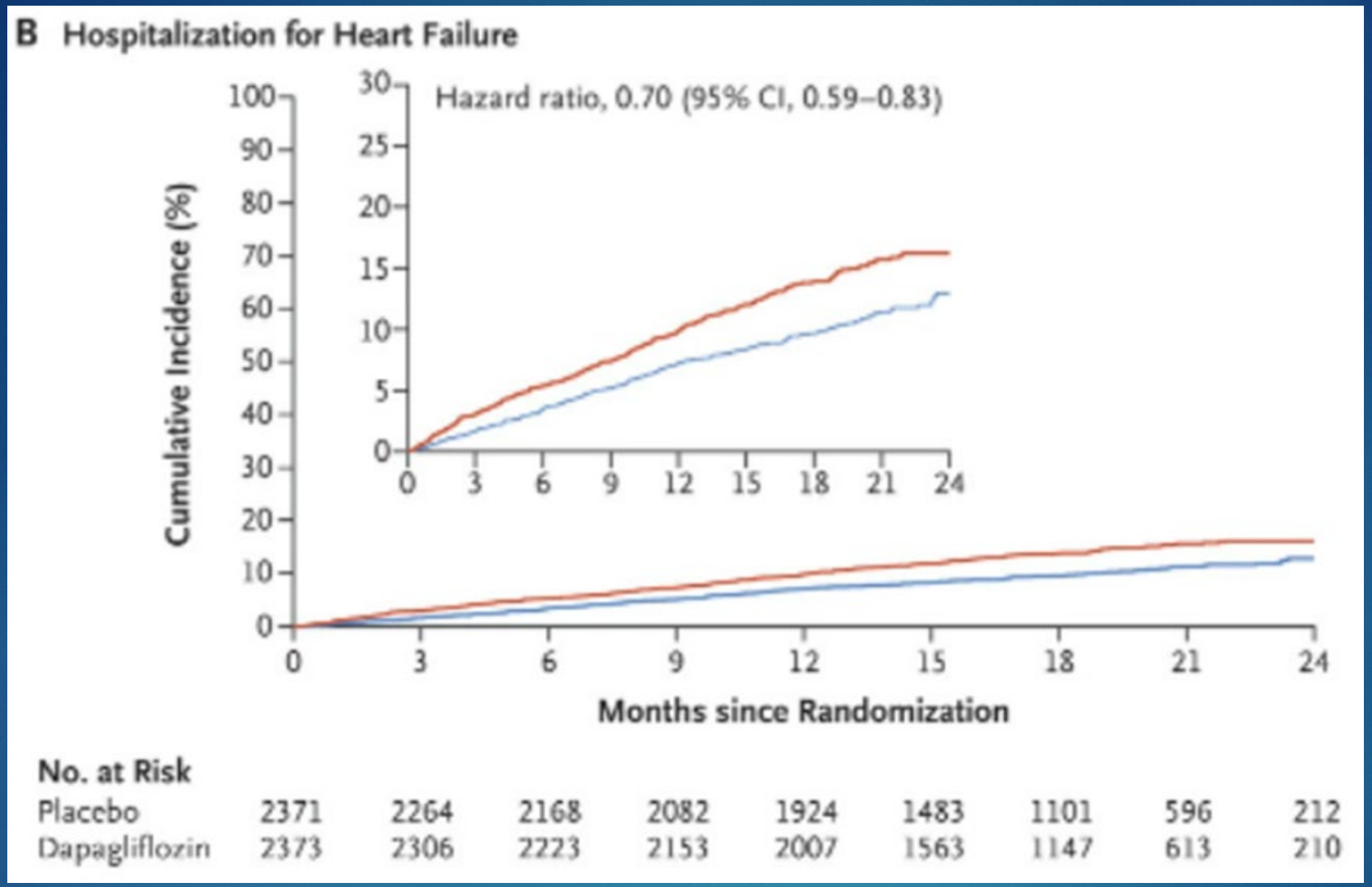
Outcome	Dapagliflozin (N=8582)		Placebo (N=8578)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	



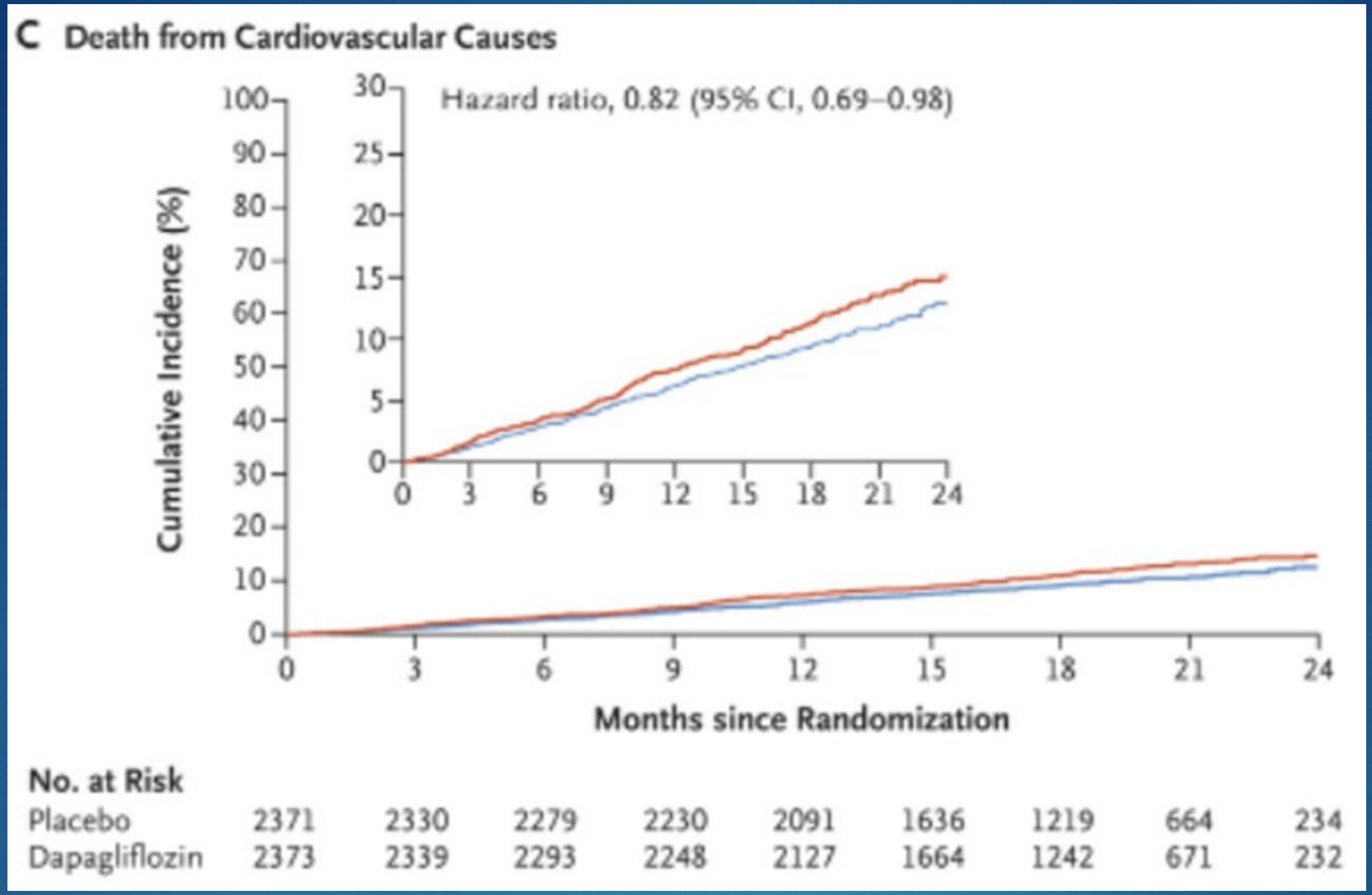
Wiviott et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357.

DAPA-HF: McMurray et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

- 4,744 patients with NYHA class II-IV CHF with ejection fraction of 40% or less.
- 42% of patients had type 2 diabetes.
- Randomly assigned to standard of care and dapagliflozin or standard of care and placebo.



McMurray et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.



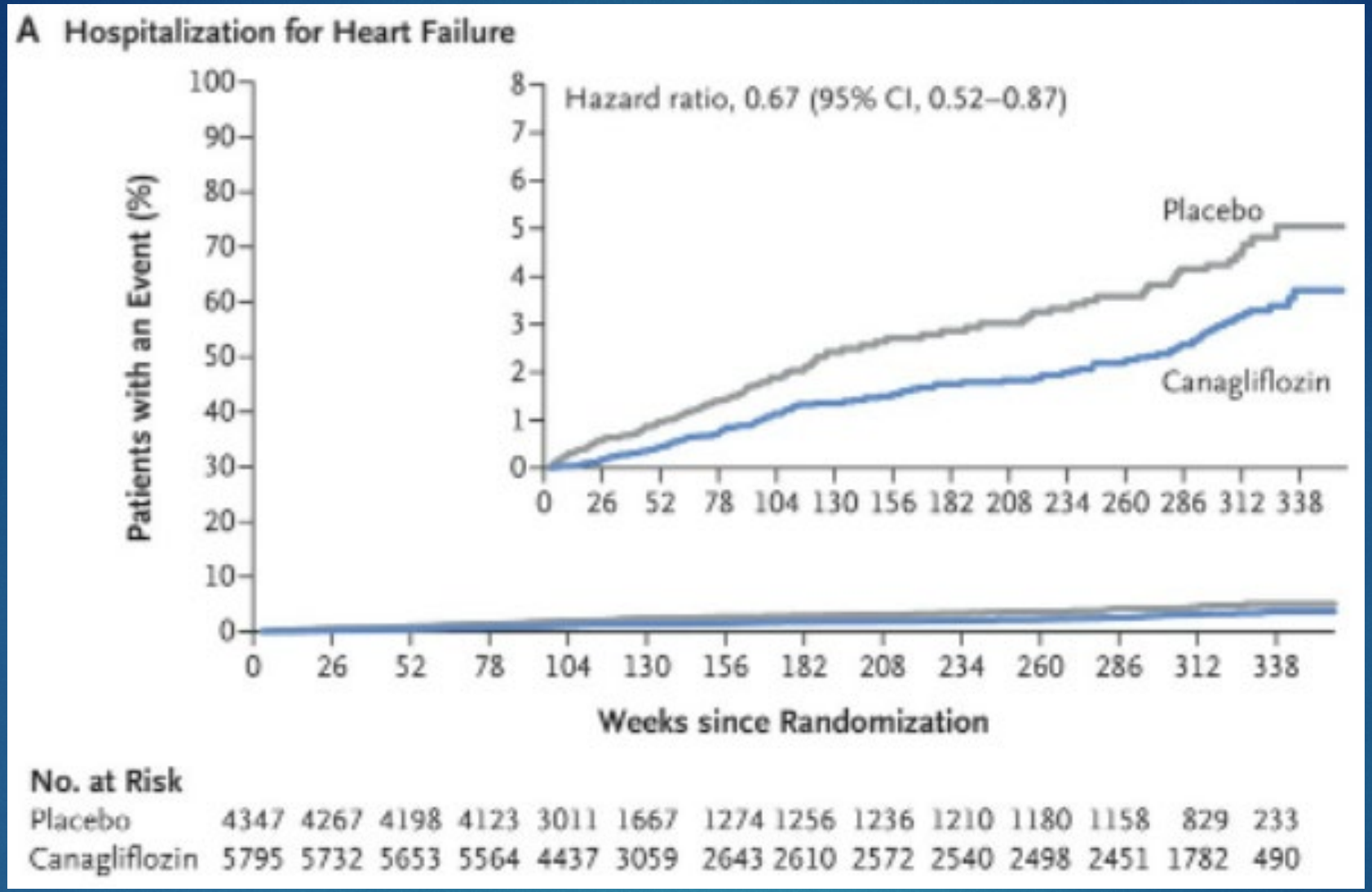
McMurray et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

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)

McMurray et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

CANVAS Program: Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644.

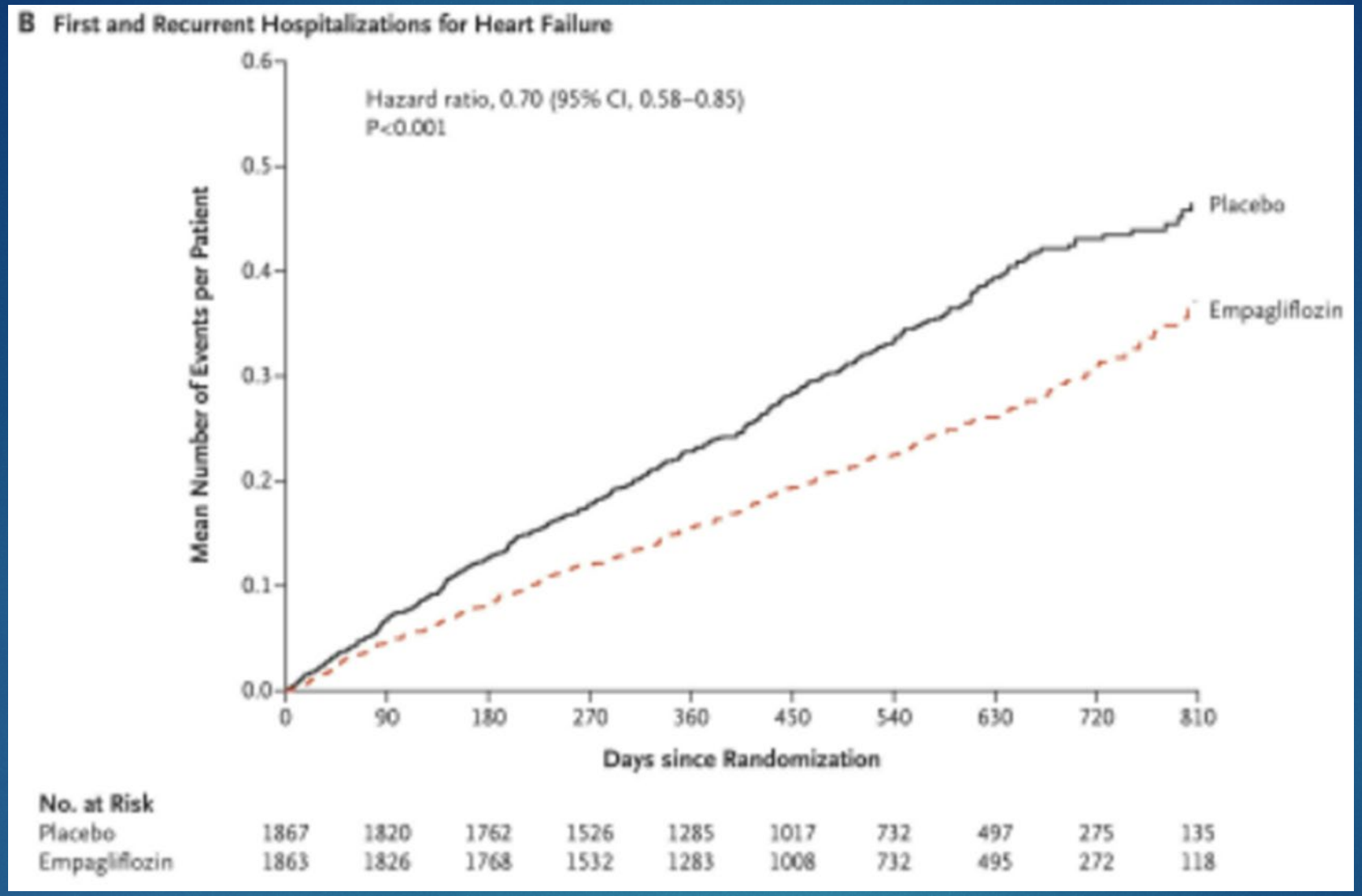
- 10,142 patients with type 2 diabetes and high cardiovascular risk (65.6% had a history of cardiovascular disease and 34.4% had at least two risk factors).
- Placebo vs. canagliflozin.
- A1C 7.0 – 10.5%.



Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644.

EMPEROR-Reduced: Packer et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

- 3,730 patients with NYHA class II-IV CHF with ejection fraction of 40% or less (73% had an EF of 30% or less).
- 50% of patients had type 2 diabetes.
- Randomly assigned to standard of care and empagliflozin or standard of care and placebo.



Packer et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

Baseline diabetes status				
Diabetes	200/927	265/929		0.72 (0.60–0.87)
No diabetes	161/936	197/938		0.78 (0.64–0.97)

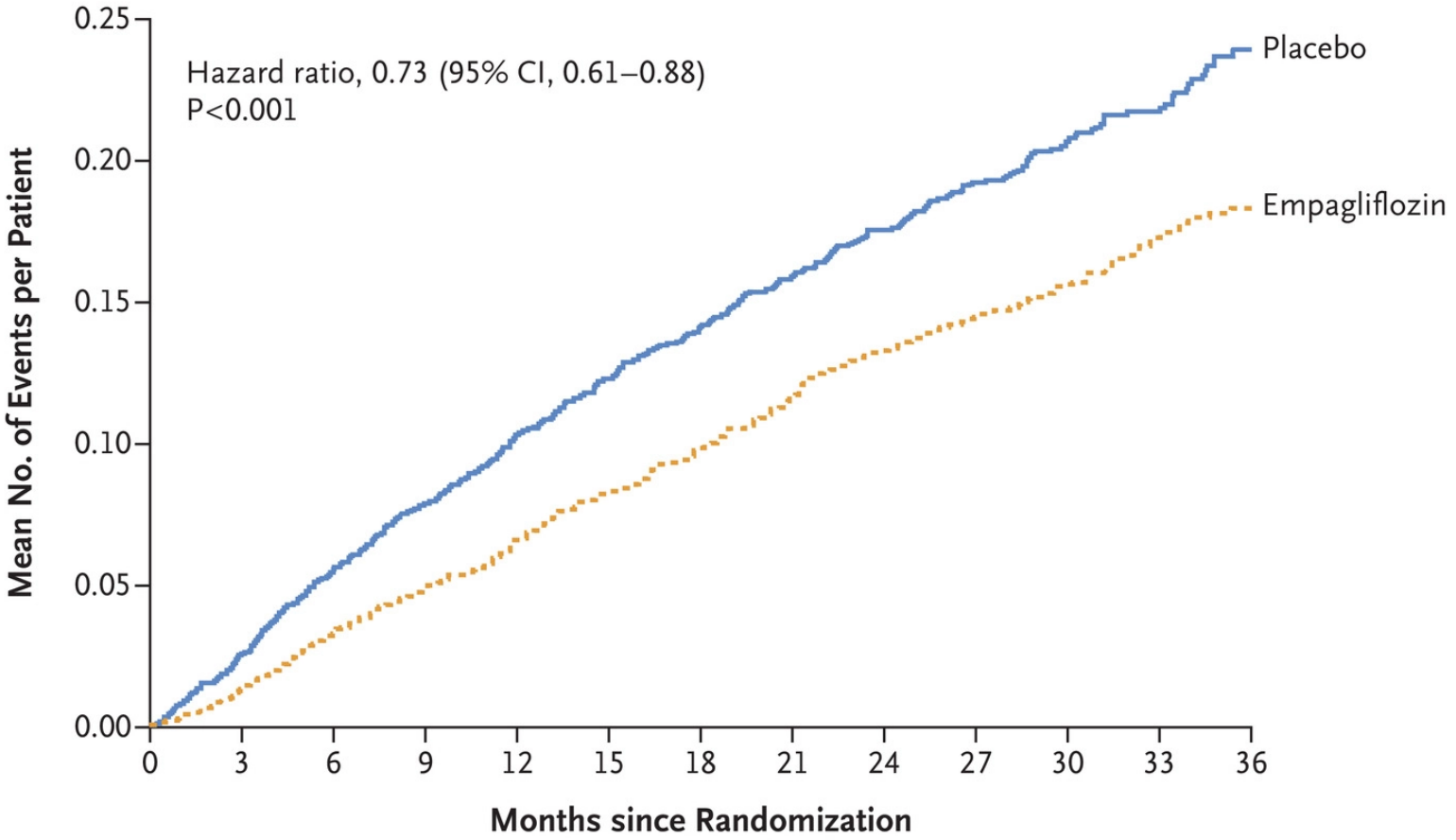
Packer et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

Variable	Empagliflozin (N=1863)		Placebo (N=1867)		Hazard Ratio or Absolute Difference (95% CI)†	P Value
		events/100 patient-yr		*events/100 patient-yr*		
Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	

Packer et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

EMPEROR-Preserved: Anker et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021; 385:1451-1461.

- 5,988 patients with NYHA class II-IV heart failure with preserved ejection fraction (EF > 40%).
- 49% had type 2 diabetes.
- Empagliflozin 10 mg vs. placebo.

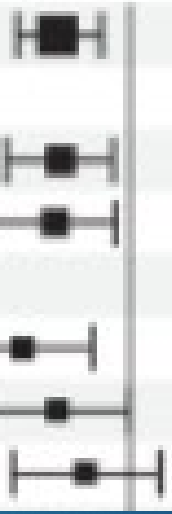


No. at Risk

Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Anker et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021; 385:1451-1461.

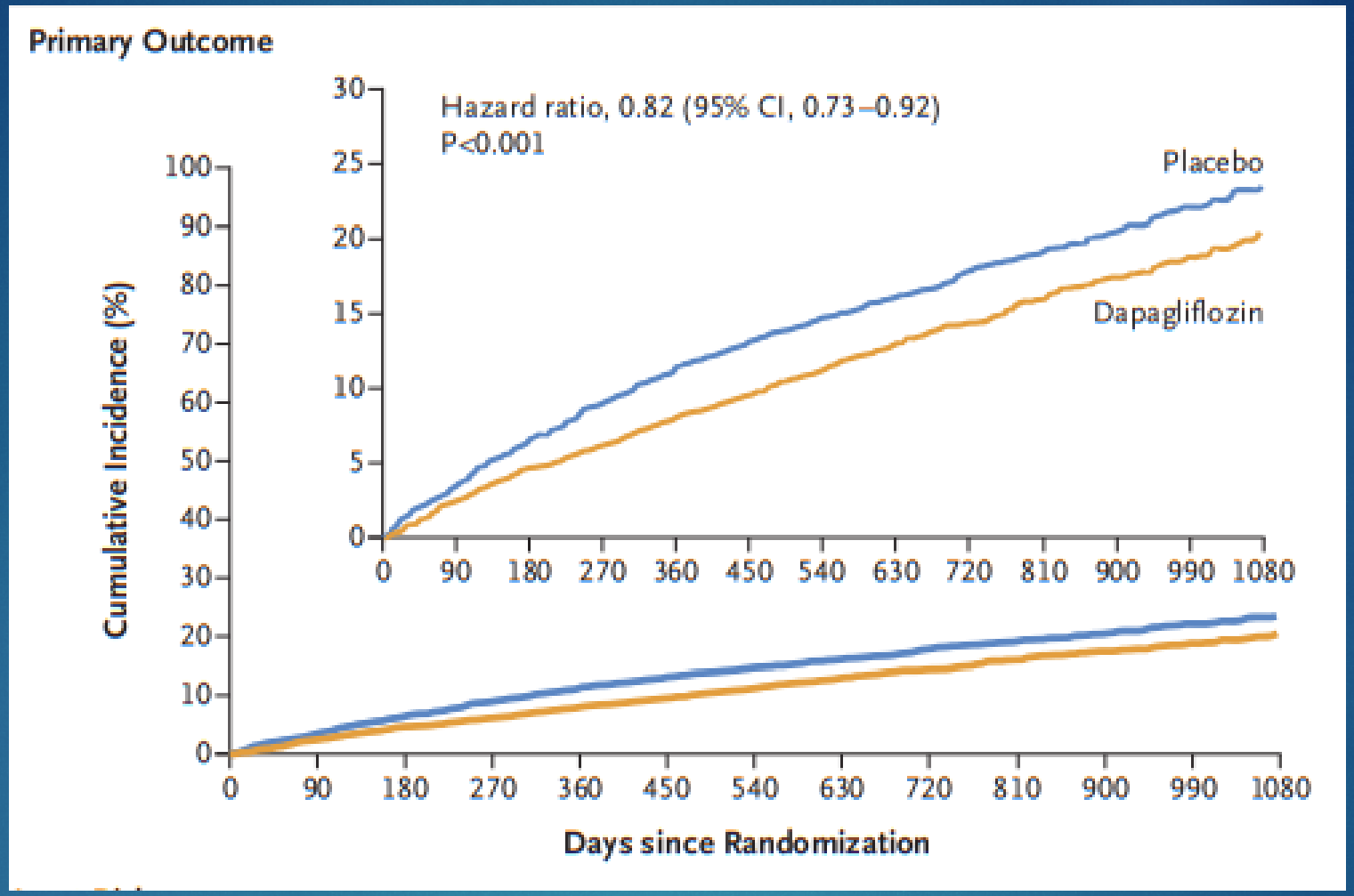
Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)



Anker et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021; 385:1451-1461.

DELIVER: Solomon SD et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22; 387(12): 1089-1098.

- 6,263 patients with NYHA class II-IV heart failure with preserved ejection fraction (EF > 40%).
- 45% had type 2 diabetes.
- Dapagliflozin 10 mg vs. placebo.
- Primary outcome was a composite of hospitalization or urgent treatment for heart failure and cardiovascular death.



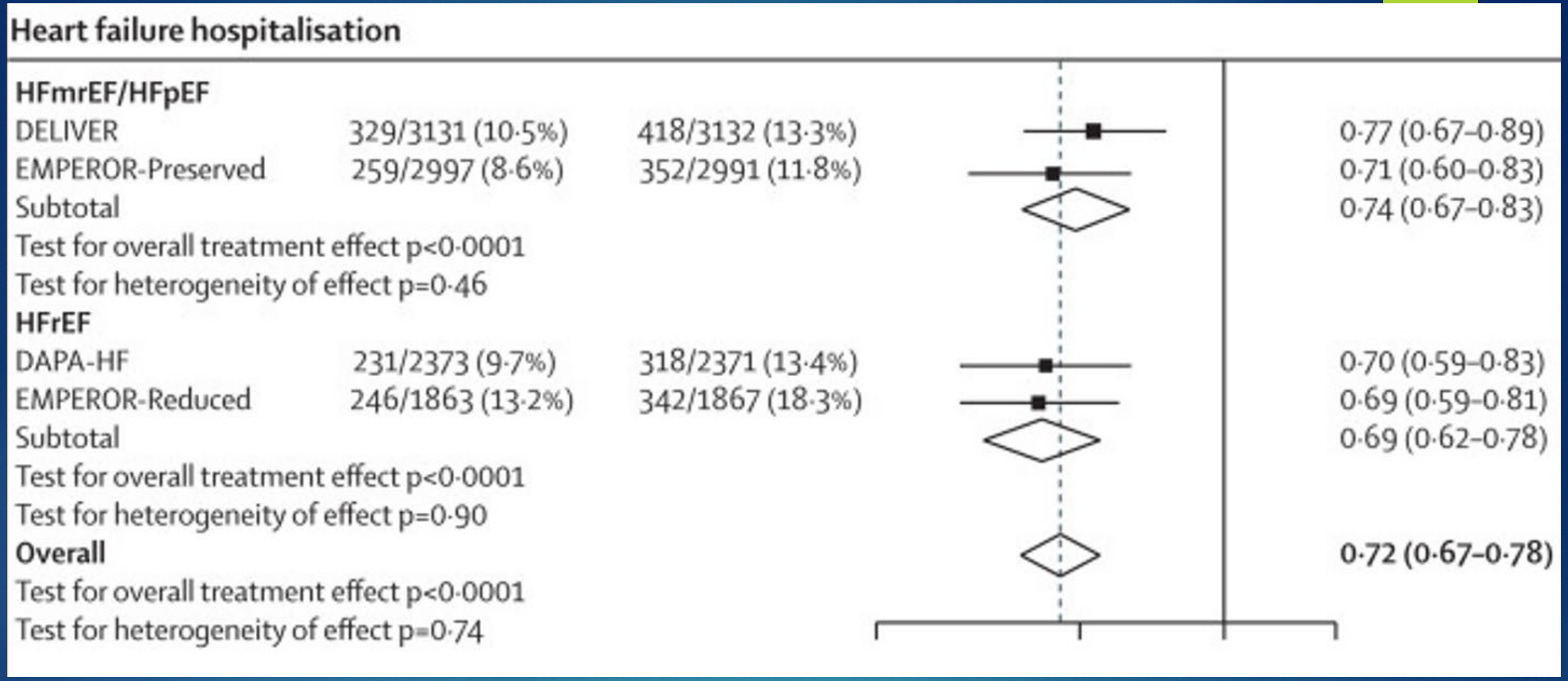
- Solomon SD et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22; 387(12): 1089-1098.

Type 2 diabetes mellitus at enrollment				
No	242/1730	293/1727		0.81 (0.68–0.96)
Yes	270/1401	317/1405		0.83 (0.70–0.97)

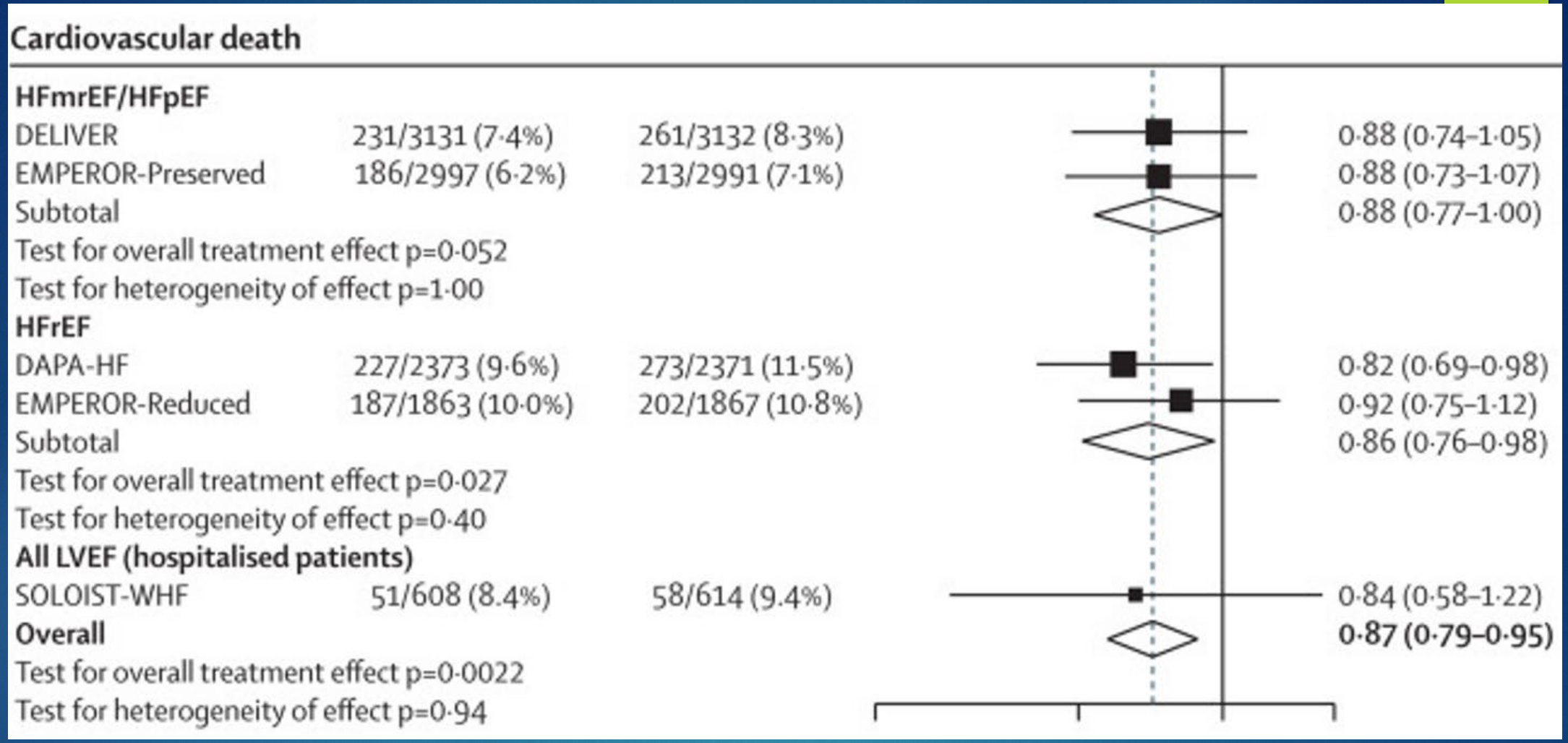
- Solomon SD et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22; 387(12): 1089-1098.

Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, McMurray JJV, Solomon SD. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022 Sep 3;400(10354):757-767.

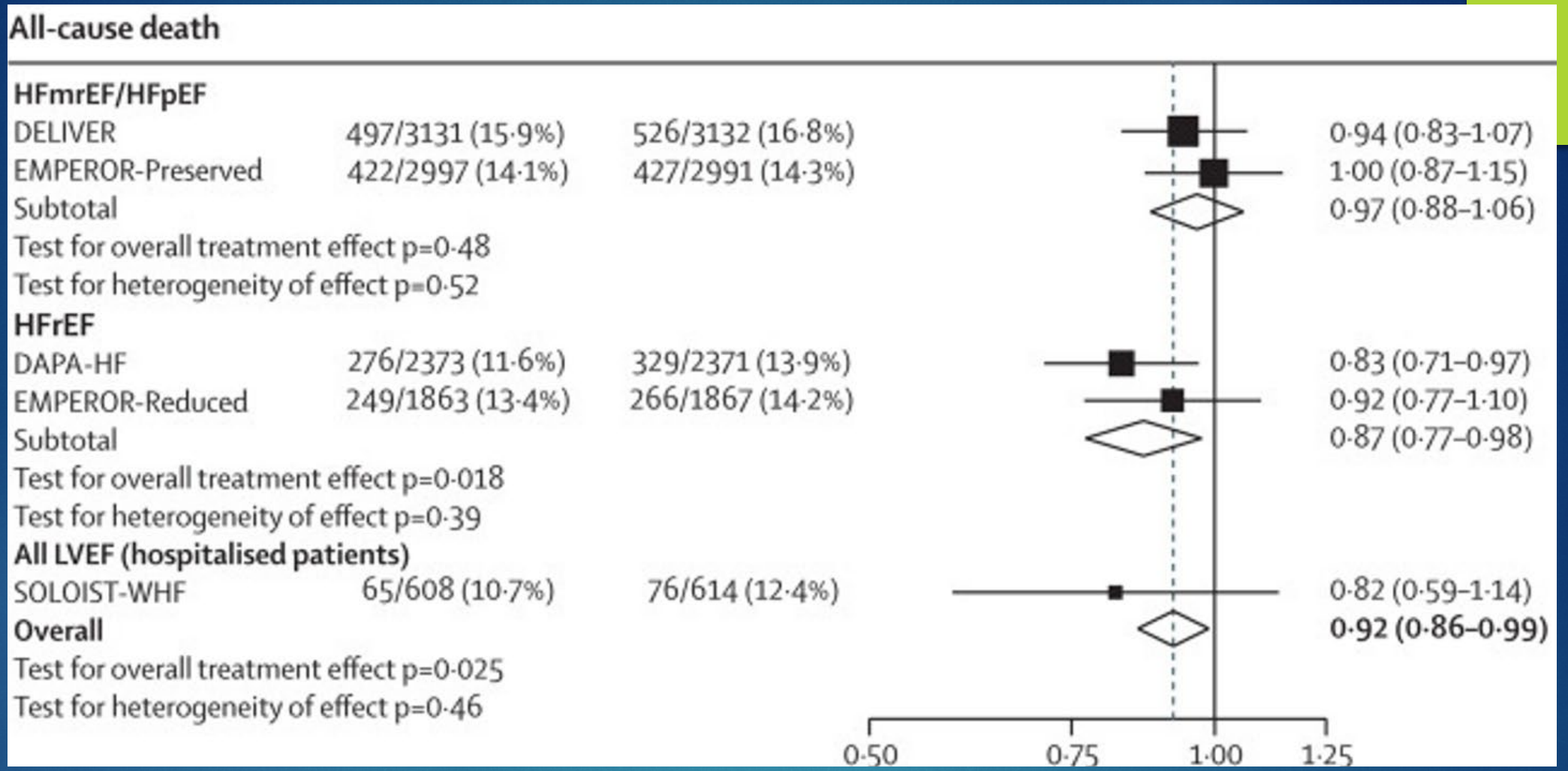
- Metanalysis of 5 trials looked at the effect of SGLT-2s on patients with Heart Failure with preserved ejection fraction.
- 12,251 patients.



- Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, McMurray JJV, Solomon SD. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022 Sep 3;400(10354):757-767.



- Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, McMurray JJV, Solomon SD. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022 Sep 3;400(10354):757-767.



- Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, McMurray JJV, Solomon SD. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022 Sep 3;400(10354):757-767.

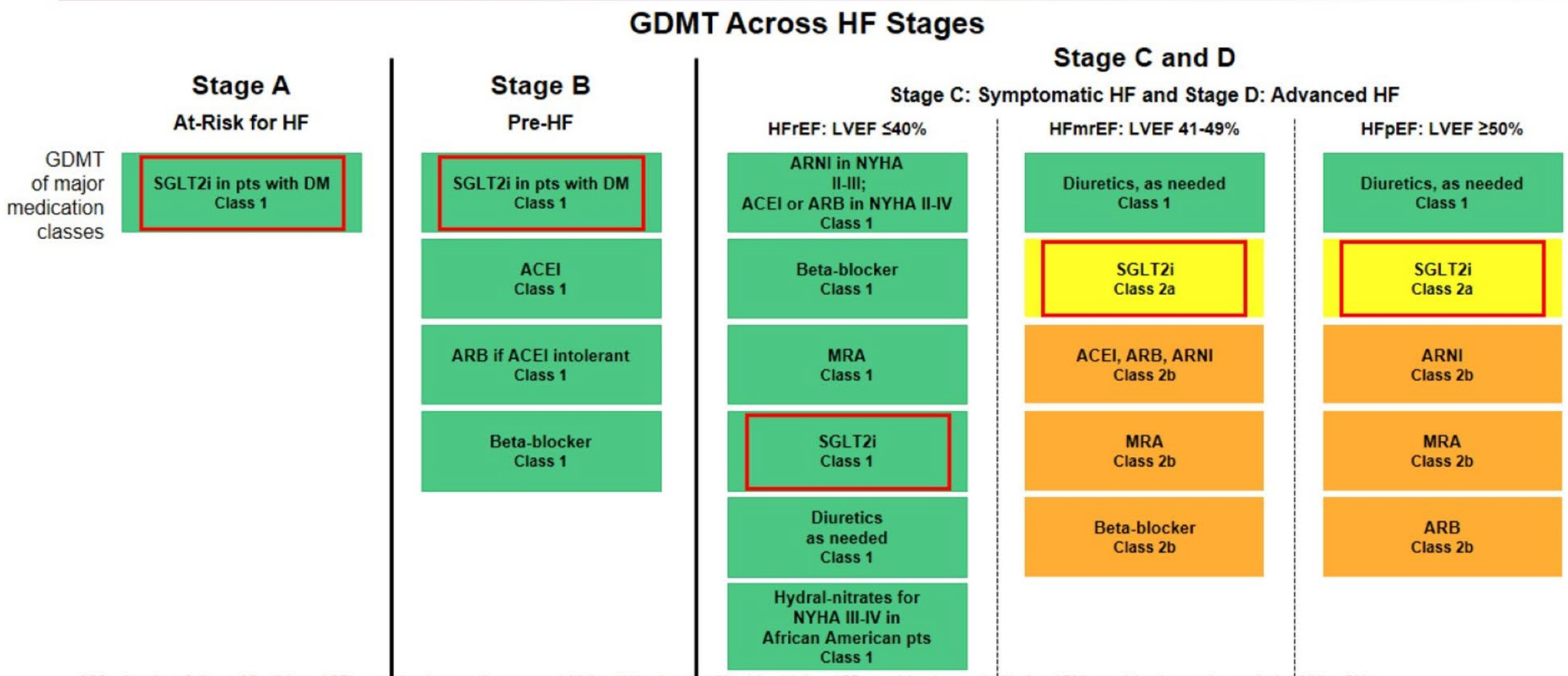
SGLT-2s: Understanding the Facts

- Do SGLT-2s reduce the risk of hospitalization for heart failure:
  - In patients with type 2 diabetes: Yes!
    - With known heart failure? Yes!
    - With risk factors for heart failure? Yes!
  - In patients without type 2 diabetes? Yes!
  - In patients with heart failure with reduced ejection fraction HFrEF? Yes!
  - In patients with heart failure with preserved ejection fraction HFpEF? Yes!

Sodium-glucose co-transporter 2 inhibitors

Medication	CV event risk reduction in those with CVD in pts w/ DMII	Primary prevention of hospitalization for HF in pts w/ DMII	Secondary prevention of hospitalization for HF		
			HFrEF		HFpEF
			w/ DMII	w/o DMII	w/ or w/o DMII
Dapagliflozin	No?	Yes	Yes*	Yes*	Yes
Empagliflozin	Yes	No	Yes	Yes	Yes
Canagliflozin	Yes	No	Yes	No	No
SGLT-2s	Yes	Yes	Yes	Yes	Yes

2022 AHA/ACC/HFSA HF Guidelines: SGLT2i are Now Recommended Across All Stages and Types of HF



ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; DM = diabetes mellitus; GDMT = guideline-directed medical therapy; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; Hydral-nitrates: hydralazine and isosorbide dinitrate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

Adapted from Heidenreich PA et al. Central Illustration. Online ahead of print. *J Am Coll Cardiol.* 2022.

SGLT-2s: Understanding the Facts

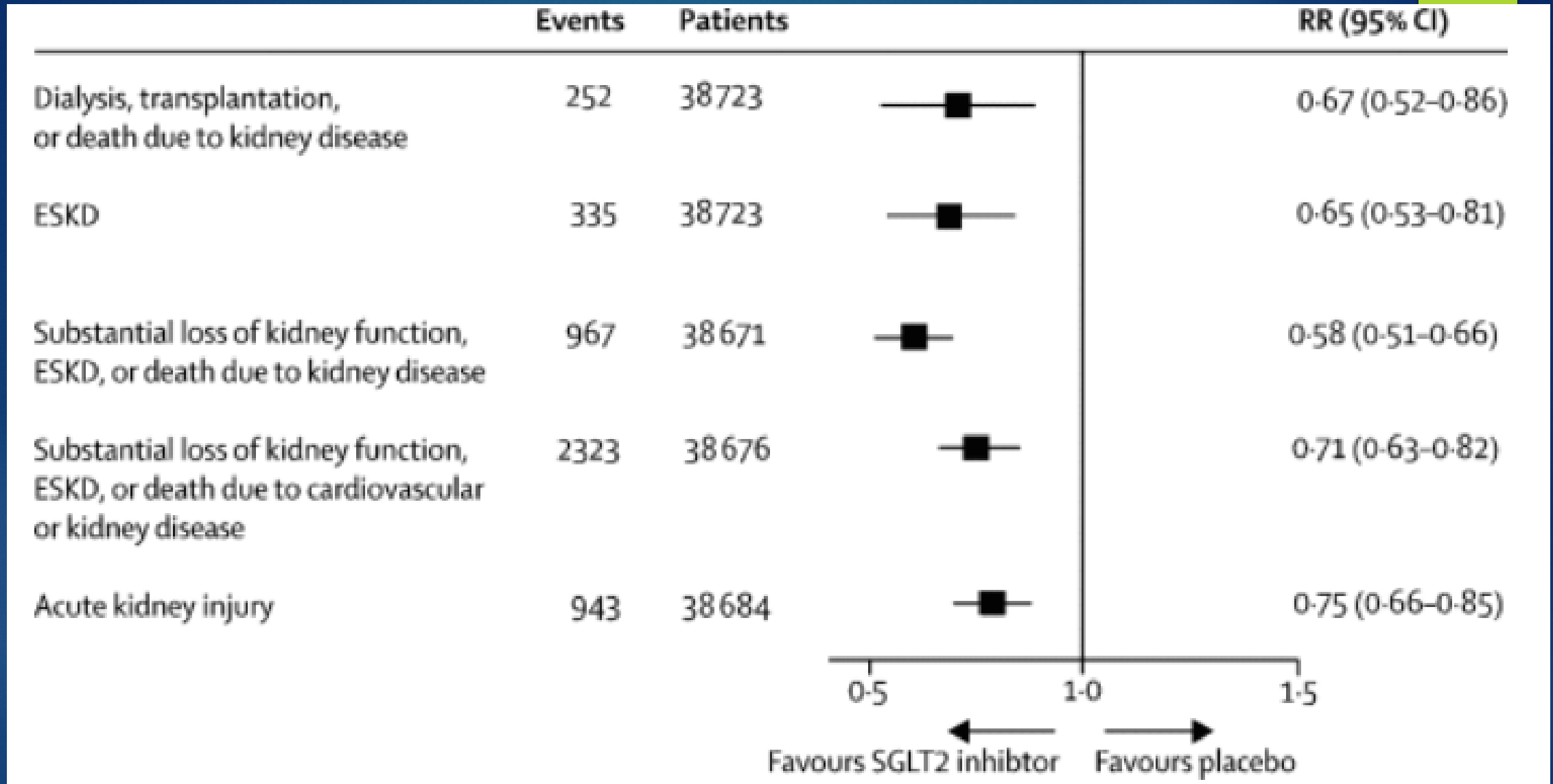
- Do SGLT-2s reduce the risk of progression of kidney disease:
  - In patients with type 2 diabetes?
  - In patients without type 2 diabetes?
- Do SGLT-2s reduce the risk of cardiovascular death in patients with kidney disease?

Kahoot Question 8-9:

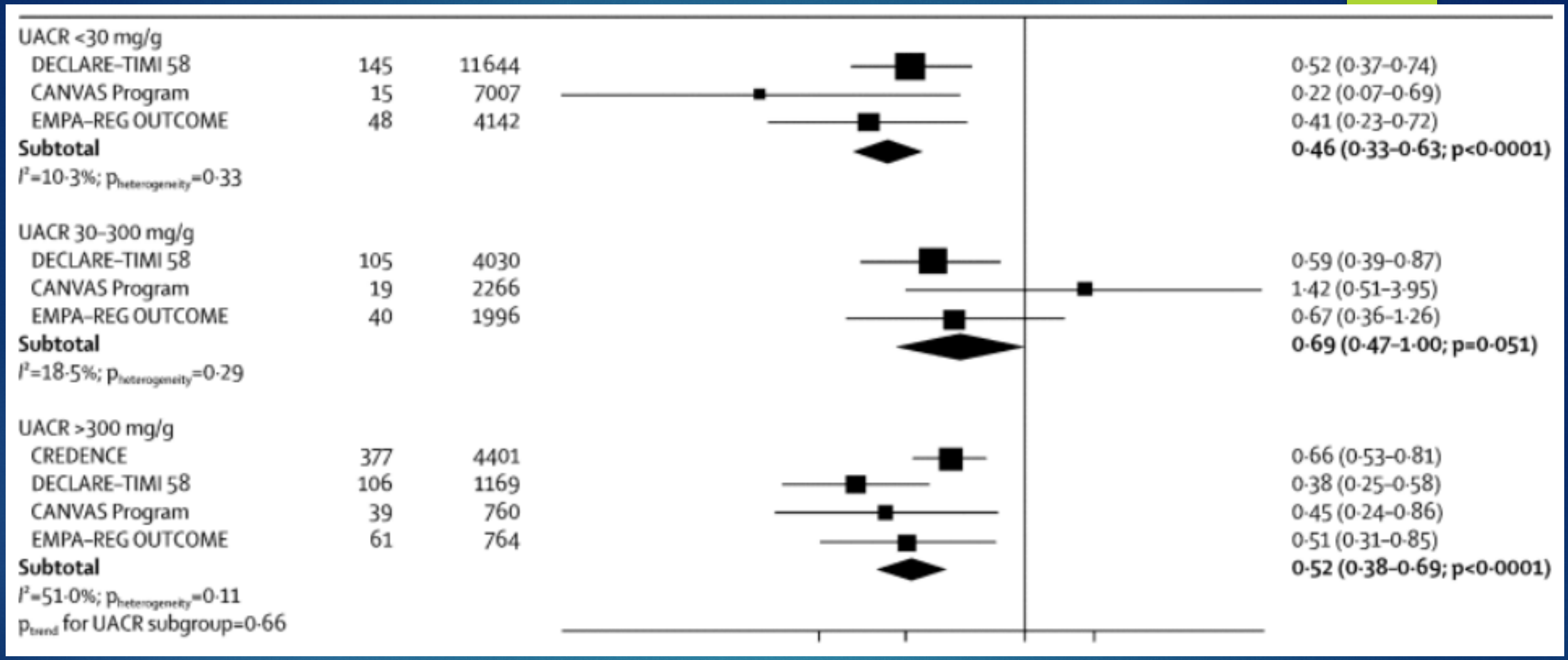
- Go to Kahoot.it
- Enter the game code shown
- Put in a nickname
- Points are given for correct answers.
- The faster the correct answer is given, the more points that are awarded
- No points taken away for incorrect answers
- Be first. Be right.

Neuen et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.

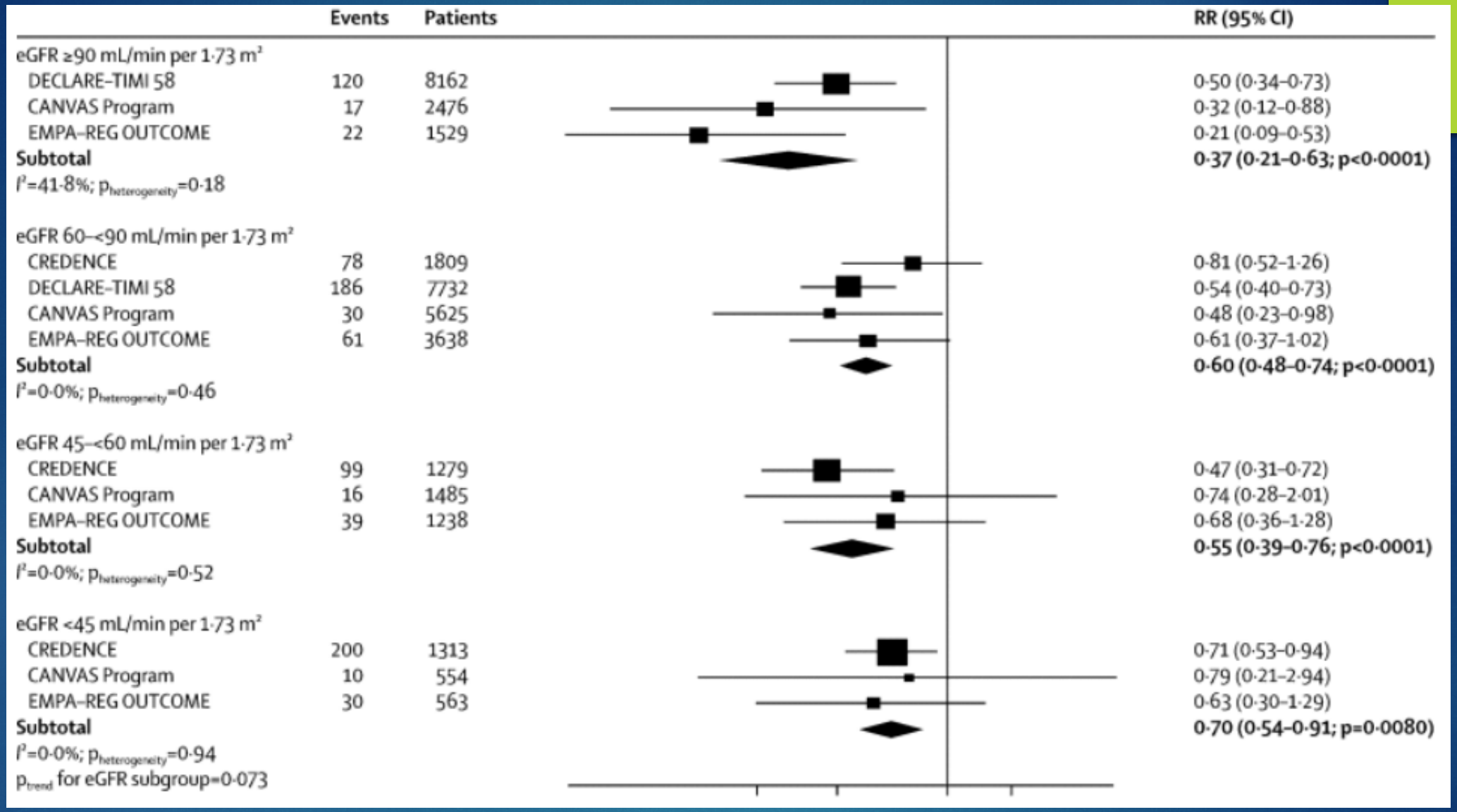
- Metanalysis of 4 trials looked at the effect of SGLT-2s on diabetic kidney disease.
- 38,723 patients.



Neuen et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.



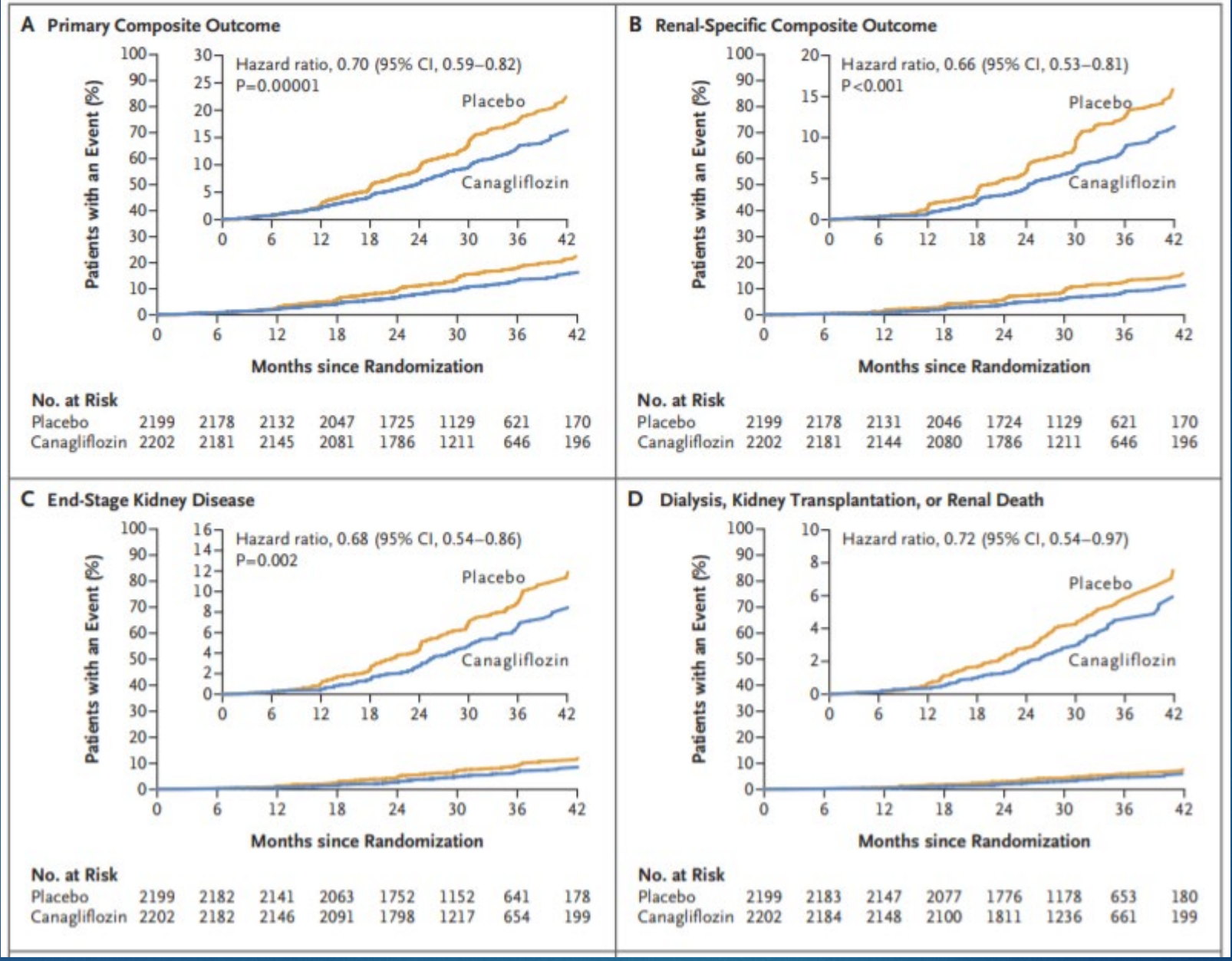
Neuen et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.



Neuen et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.

CREDENCE: Perkovic V, Jardine M, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019; 380:2295.

- 4,401 patients with diabetes and eGFR < 90 and urine albumin/creatinine > 300 mg/g.
- Compared canagliflozin 100 mg to placebo.
- Looked at a variety of renal outcomes.



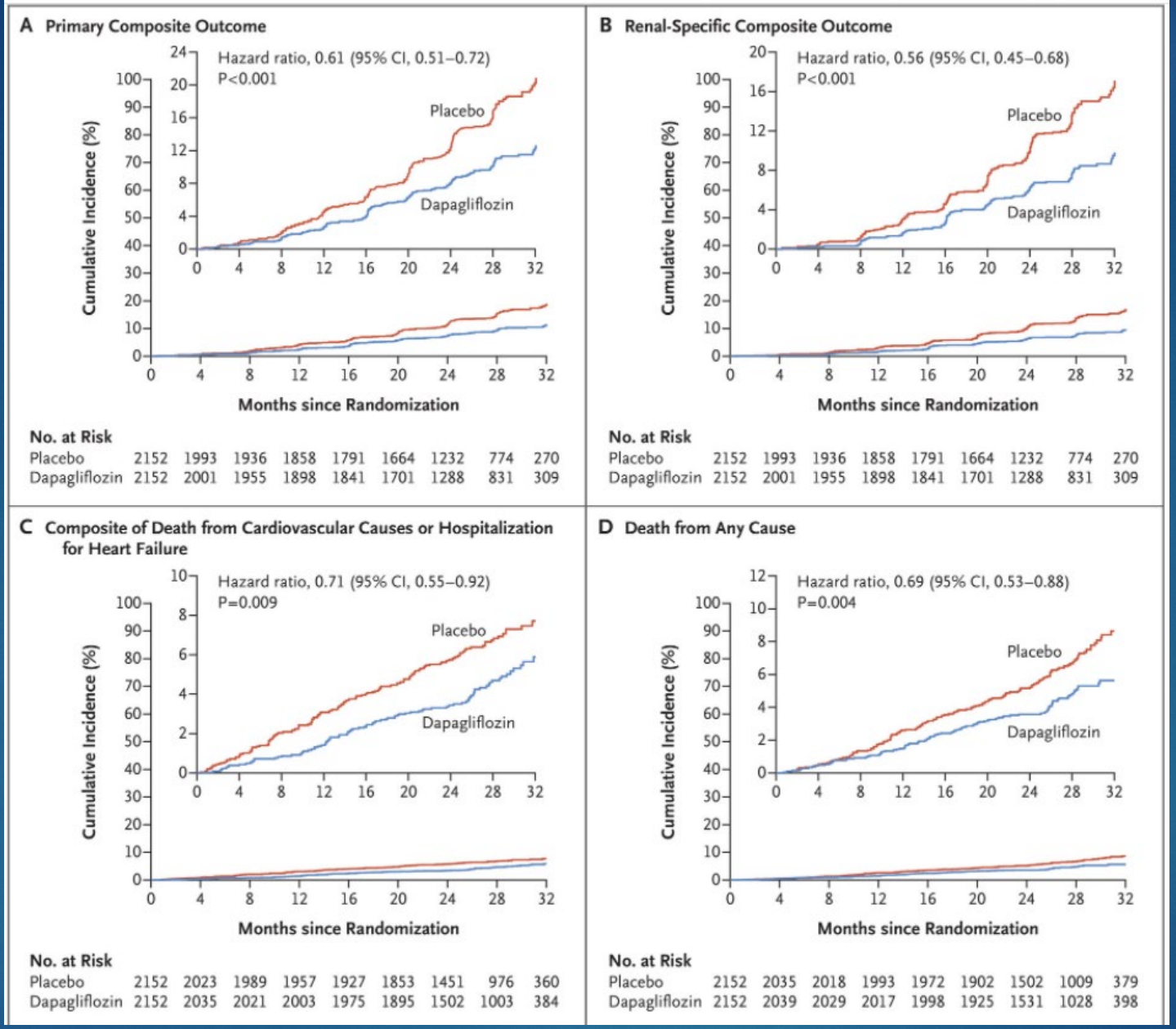
Perkovic V, Jardine M, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019; 380:2295.

CREDENCE: Perkovic V, Jardine M, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019; 380:2295.

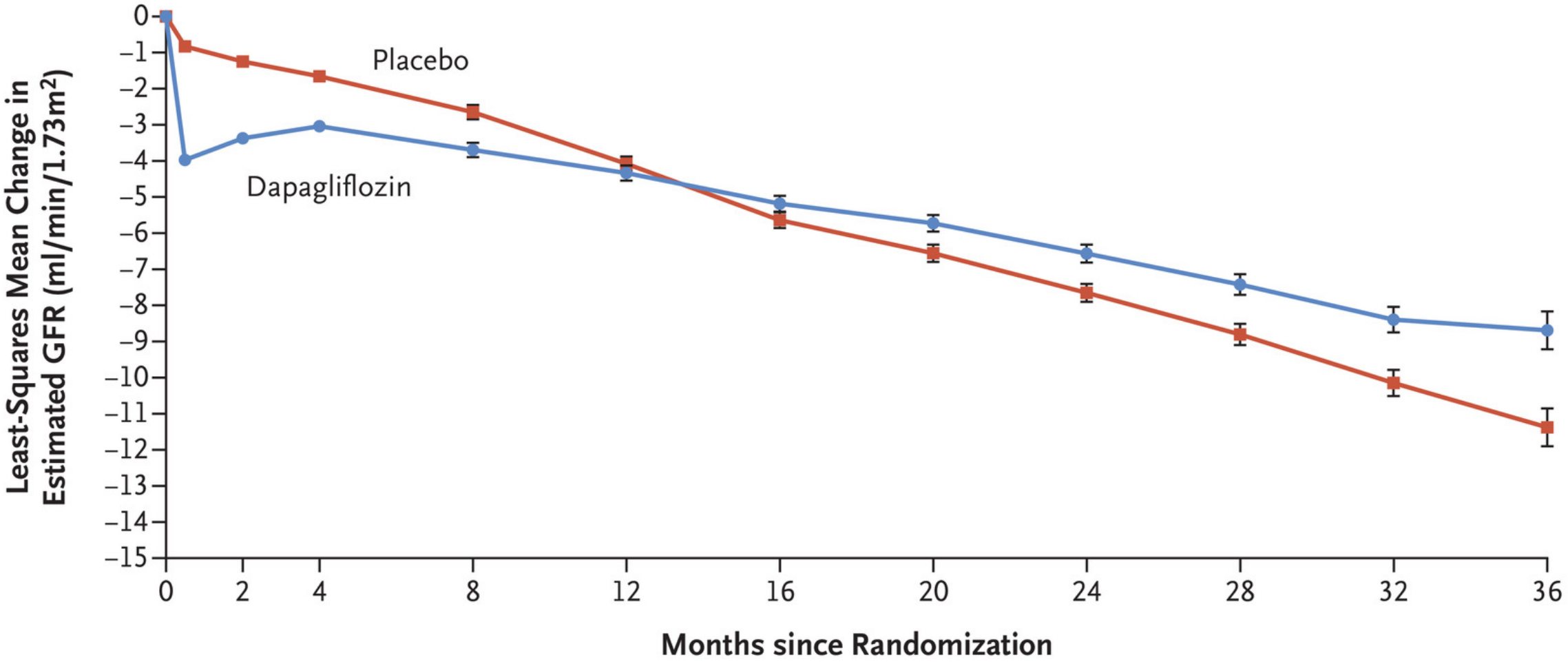
- Reduced the incidence of ESKD (5.3 vs 7.5%).
- Reduced doubling of serum creatinine (5.4 vs 8.5%).
- Reduced hospitalization for heart failure (4.0 vs 6.4%).
- Reduction in cardiovascular death not statistically significant.

DAPA-CKD: Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436.

- 4,304 individuals with eGFR 25-75 and urine albumin/creatinine ratio of > 200 mg/g.
- Type 2 diabetes in 67.5% of patients.
- 10 mg dapagliflozin vs. placebo.



Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436.



No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436.

Type 2 diabetes				
Yes	152/1455	229/1451		0.64 (0.52–0.79)
No	45/697	83/701		0.50 (0.35–0.72)
Estimated GFR				
<45 ml/min/1.73 m^2	152/1272	217/1250		0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902		0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio				
≤1000	44/1104	84/1121		0.54 (0.37–0.77)
>1000	153/1048	228/1031		0.62 (0.50–0.76)

Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436.

DAPA-CKD: Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436.

- Reduced the incidence of end stage kidney disease (5.1 vs. 7.5%).
- Reduced the risk of 50% of greater decline in CKD (5.2 vs. 9.3%).
- Reduced all cause mortality (4.7 vs. 6.8%).
- Reduction in cardiovascular death not statistically significant.

EMPA-KIDNEY: Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436.

- 6,609 individuals with eGFR 20-44 regardless of urine albumin/creatinine ratio or those with eGFR 45-89 with albumin/creatinine ratio of > 200 mg/g.
- Patients with and without Type 2 diabetes.
- 10 mg empagliflozin vs. placebo.

EMPA-KIDNEY: Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436.

- Empagliflozin reduced the incidence of ESKD (3.3 versus 4.8 percent)
- Reduce the incidence of a sustained decline in eGFR to <10 mL/min/1.73 m^2 (3.5 versus 5.1 percent)
- Reduced the incidence of a sustained decrease in eGFR of 40 percent or more (10.9 versus 14.3 percent)
- Reduction in cardiovascular death not statistically significant

SGLT-2s: Understanding the Facts

- Do SGLT-2s reduce the risk of progression of kidney disease:
  - In patients with type 2 diabetes? Yes!
  - In patients without type 2 diabetes? Yes!
- Do SGLT-2s reduce the risk of cardiovascular death in patients with kidney disease? No!

Sodium-glucose co-transporter 2 inhibitors

Medication	CV event risk reduction in those with CVD in pts w/ DMII	Primary prevention of hospitalization for HF in pts w/ DMII	Secondary prevention of hospitalization for HF			Reduction in worsening of CKD	
			HFrEF		HFpEF		
			w/ DMII	w/o DMII	w/ or w/o DMII	w/ DMII	w/o DMII
Dapagliflozin	No?	Yes	Yes	Yes	Yes	Yes	Yes
Empagliflozin	Yes	No	Yes	Yes	Yes	Yes	Yes
Canagliflozin	Yes	No	Yes	No	No	Yes	No
SGLT-2s	Yes	Yes	Yes	Yes	Yes	Yes	?

SGLT-2's: Understanding the Facts

- SGLT-2's and the hospitalized patient:
  - When should they be stopped?
  - When should they be started?

Kahoot Question 10:

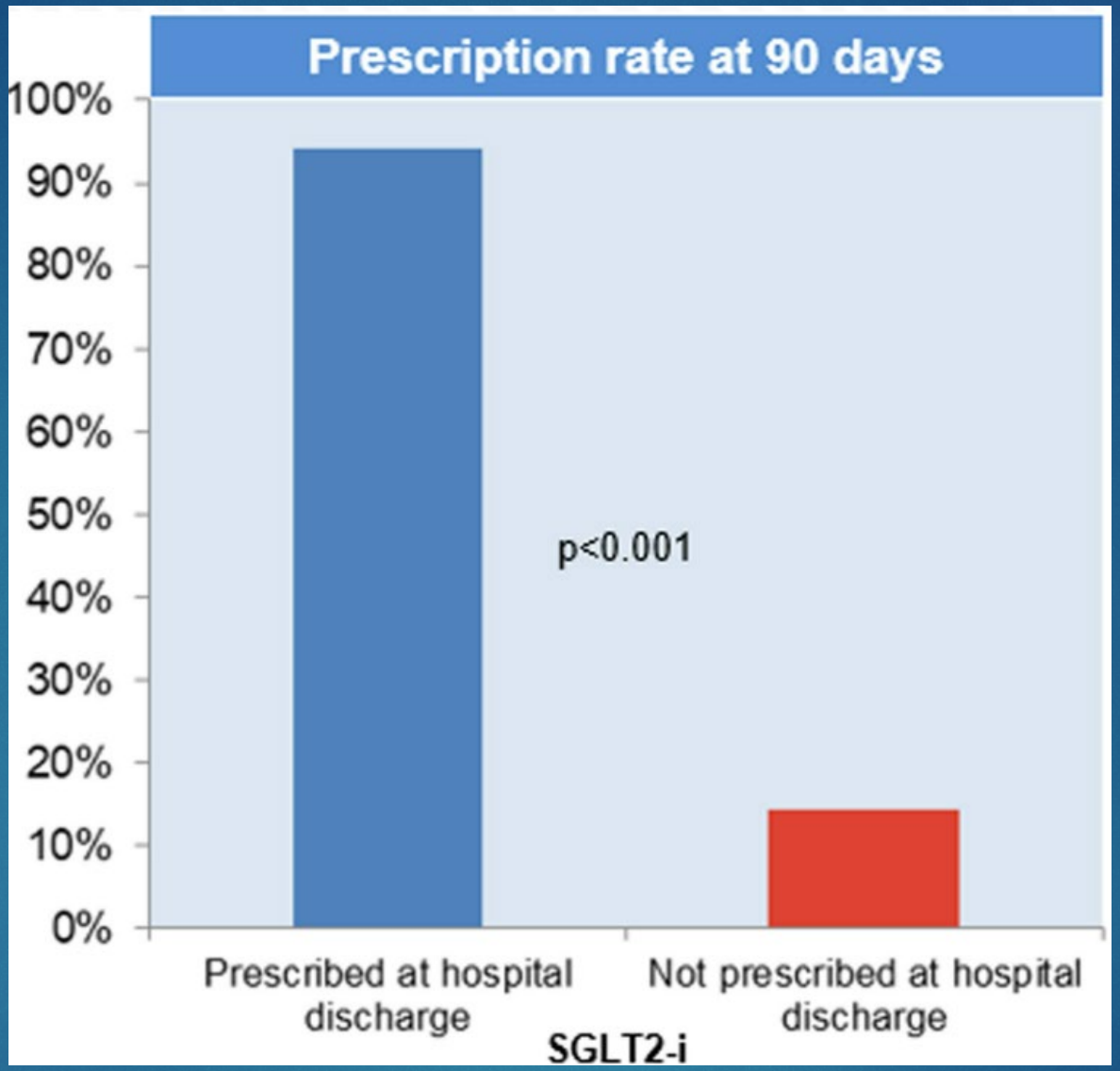
- Go to Kahoot.it
- Enter the game code shown
- Put in a nickname
- Points are given for correct answers.
- The faster the correct answer is given, the more points that are awarded
- No points taken away for incorrect answers
- Be first. Be right.

American Diabetes Association. 15. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S211-S220.

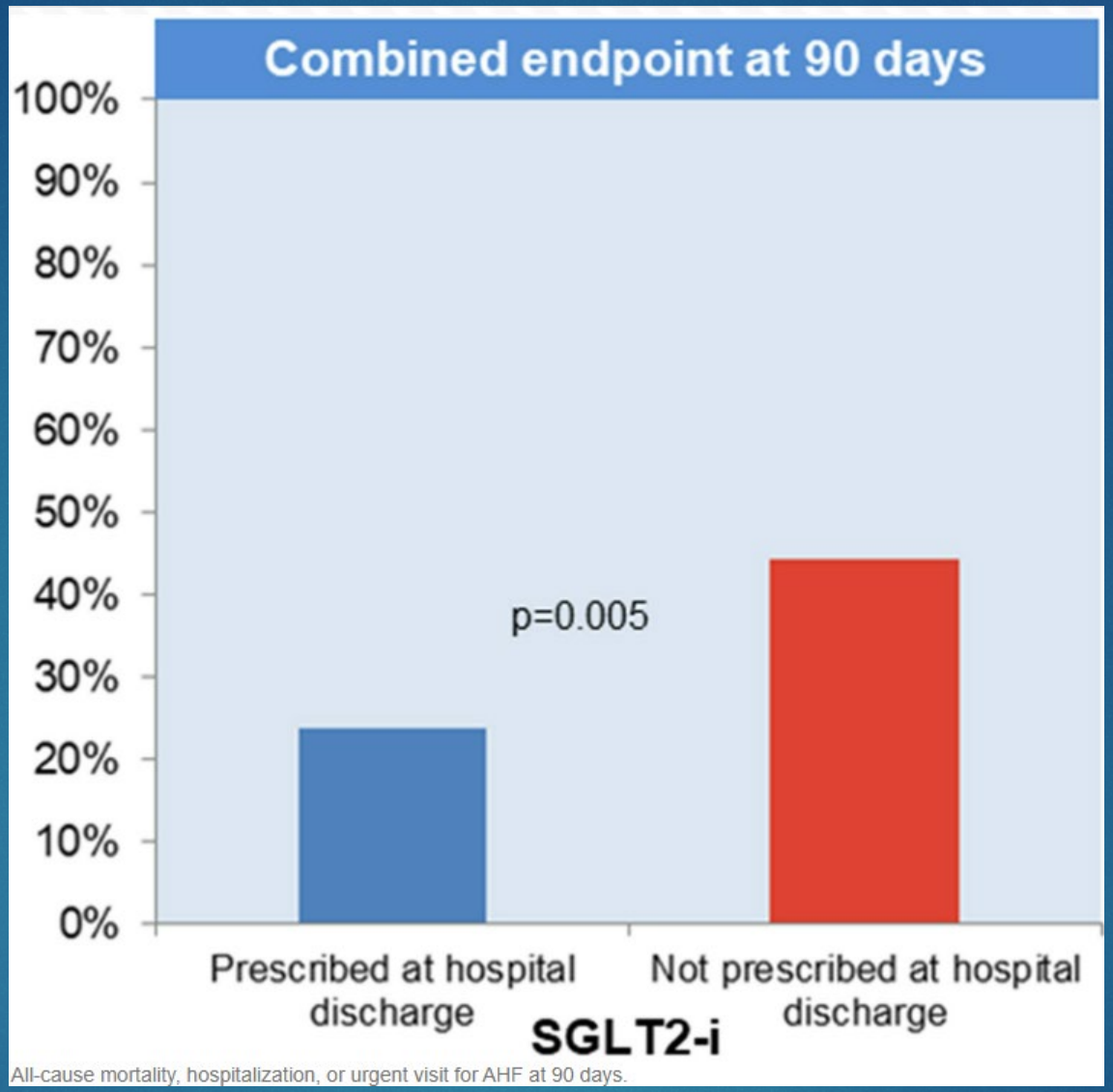
- SGLT-2s should be stopped 3 days prior to a surgical procedure.
  - SGLT-2's may worsen post-surgical hypovolemia and lead to unrecognized euglycemic DKA.
  - SGLT-2's should be held in patients with severe illness.

Burgos LM, Ballari FN, Spaccavento A, Ricciardi B, Suárez LL, Baro Vila RC, De Bortoli MA, Conde D, Diez M. In-hospital initiation of sodium-glucose cotransporter-2 inhibitors in patients with heart failure and reduced ejection fraction: 90-day prescription patterns and clinical implications. Curr Probl Cardiol. 2024 Oct;49(10):102779.

- Evaluated 237 patients and looked at 90 day prescription rates for SGLT-2s in persons with HFrEF.



Burgos LM, Ballari FN, Spaccavento A, Ricciardi B, Suárez LL, Baro Vila RC, De Bortoli MA, Conde D, Diez M. In-hospital initiation of sodium-glucose cotransporter-2 inhibitors in patients with heart failure and reduced ejection fraction: 90-day prescription patterns and clinical implications. Curr Probl Cardiol. 2024 Oct;49(10):102779.



Burgos LM, Ballari FN, Spaccavento A, Ricciardi B, Suárez LL, Baro Vila RC, De Bortoli MA, Conde D, Diez M. In-hospital initiation of sodium-glucose cotransporter-2 inhibitors in patients with heart failure and reduced ejection fraction: 90-day prescription patterns and clinical implications. Curr Probl Cardiol. 2024 Oct;49(10):102779.

SGLT-2's: Understanding the Facts

- SGLT-2's and the hospitalized patient:
  - When should they be stopped?
    - 3 days prior to surgery or in severe illness
  - When should they be started?
    - On discharge if treating HF

SGLT-2's: Other Things to Know

- SGLT-2's reduced the incidence of contrast induced nephropathy in patients undergoing cardiac angiography and PCI from 16.1% to 9.6% ($p = 0.012$).

Keskin B, Hakgor A, Akhundova A, Savur U, Dursun A, Arman ME, Duman AB, Tanyeri S, Kenger MZ, Dervis E, Boztosun B. Do sodium-glucose cotransporter-2 inhibitors provide protection against contrast-induced nephropathy in patients with acute coronary syndrome? J Cardiovasc Med (Hagerstown). 2025 Oct 1;26(10):536-543.

SGLT-2's: Other Things to Know

- SGLT-2's have been shown to have a mild increase in serum magnesium levels and may be particularly helpful in those with treatment resistant hypomagnesemia due to renal magnesium wasting.

Tang H, Zhang X, Zhang J, Li Y, Del Gobbo LC, Zhai S, Song Y. Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials. Diabetologia. 2016 Dec;59(12):2546-2551.

SGLT-2's: Other Things to Know

- SGLT-2's may helpful in SIADH. A small randomized, double-blinded, placebo-controlled cross over trial show improvement in serum sodium with empagliflozin in patients with mild SIADH by 4.1 mmol.

Refardt J, Imber C, Nobbenhuis R, Sailer CO, Haslbauer A, Monnerat S, Bathelt C, Vogt DR, Berres M, Winzeler B, Bridenbaugh SA, Christ-Crain M. Treatment Effect of the SGLT2 Inhibitor Empagliflozin on Chronic Syndrome of Inappropriate Antidiuresis: Results of a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J Am Soc Nephrol. 2023 Feb 1;34(2):322-332.

SGLT-2's: Other Things to Know

- SGLT-2's may be helpful in diuretic resistant ascites in patients with DM II. Case reports show reductions in ascites and peripheral edema.

Montalvo-Gordon I, Chi-Cervera LA, García-Tsao G. Sodium-Glucose Cotransporter 2 Inhibitors Ameliorate Ascites and Peripheral Edema in Patients With Cirrhosis and Diabetes. Hepatology. 2020 Nov;72(5):1880-1882.

SGLT-2's: Other Things to Know

- A metanalysis of 16 cohort studies involving over 400,000 participants. SGLT-2's reduced the risk of diabetic retinopathy progression compared to other treatments ($p < 0.001$).

Goodarzi S, Soltani Abhari F, Azarinoush G, Rafiei MA, Yousefian H, Heidari E, Ekramipour E, Mirzaei A, Namakin K, Shafiee A. SGLT2 inhibitors for delaying diabetic retinopathy: a systematic review and meta-analysis. Int Ophthalmol. 2025 Oct 3;45(1):406.

SGLT-2's: Other Things to Know

- SGLT-2's reduced proteinuria by 37.6% and reduce GFR decline ($p < 0.001$) in patients with lupus nephritis.

- Ramírez-Mulhern I, Navarro-Sánchez V, Rivero-Otamendi E, Sánchez-Mejía DE, Zavala-Miranda MF, Mejia-Vilet JM. Effects of sodium-glucose transporter 2 inhibitors in patients with lupus nephritis: a before-and-after retrospective cohort study. Rheumatology (Oxford). 2025 Oct 16:keaf548.

Summary

- SGLT-2s can be prescribed for secondary prevention of CV death in patients with type 2 diabetes and known cardiovascular disease.
- SGLT-2s can be prescribed for primary and secondary prevention of hospitalization for heart failure in patients with or without type 2 diabetes with either HFrEF or HFpEF.
- SGLT-2s can be used to reduce the development of CKD in patients with type 2 diabetes and to reduce the progression of CKD in patients with or without type 2 diabetes and albuminuria.
- SGLT-2s can reduce the risk of cardiovascular death and all cause mortality in patients with HFrEF
- SGLT-2s should not be prescribed for primary prevention of CV death in patients with type 2 diabetes.
- SGLT-2s should not be prescribed for reduction in CV death in patients with CKD.

Questions?