SGLT2 inhibitors: established and emerging indications

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Background

- Despite current standard-of-care therapies, a high burden of cardiovascular disease and ESKD exists in this population leading to:

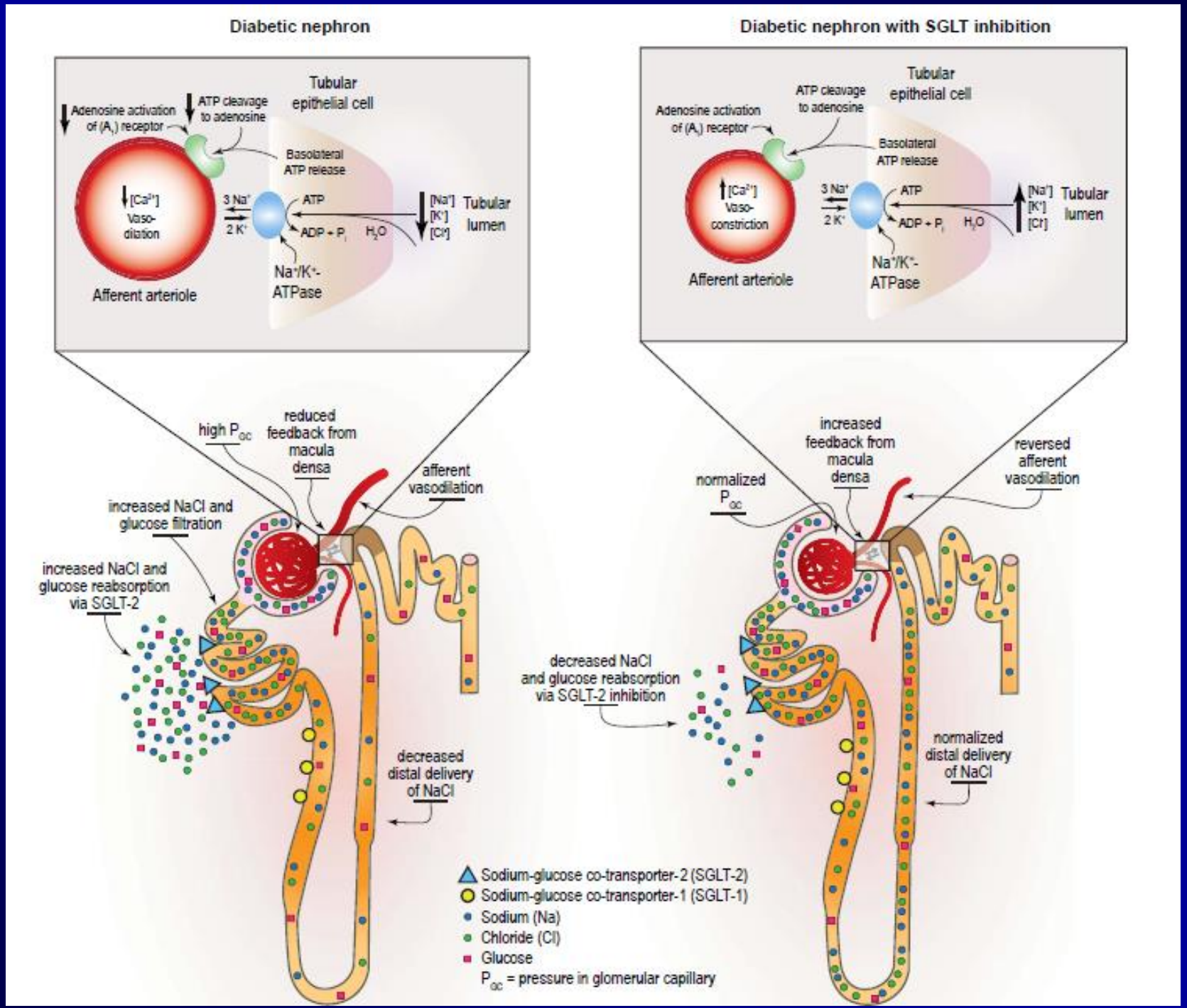
- High morbidity, mortality, healthcare resource use
- Poor health-related quality of life.

Background

Chronic kidney disease (CKD) in patients with type 2 diabetes is a major public health problem, resulting in significant cardiovascular and kidney adverse outcomes and endstage kidney disease worldwide.

New Strategies

- Here we describe the current evidence for the **cardiorenal protective effects** of the newer classes of antidiabetic agents, including **SGLT2** (sodium glucose cotransporter 2) inhibitors

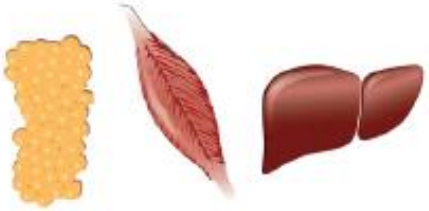


Perkovic V, et al. N Engl J Med.2019;

Insulin-dependent mechanisms

1 Insulin action

- Thiazolidinediones
- Metformin



Adipose tissue, muscle, and liver

2 Insulin release

- Sulphonylureas
- GLP-1 agonists*
- DPP-4 inhibitors*
- Meglitinides

Pancreas

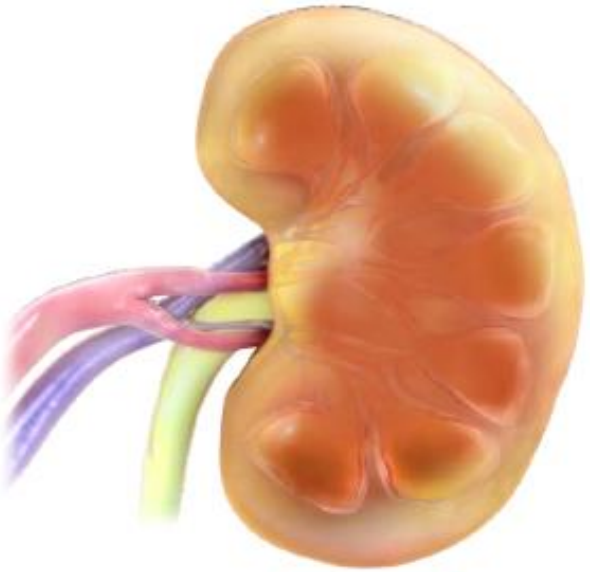
3 Insulin replacement

- Insulin

Enhance glucose utilisation

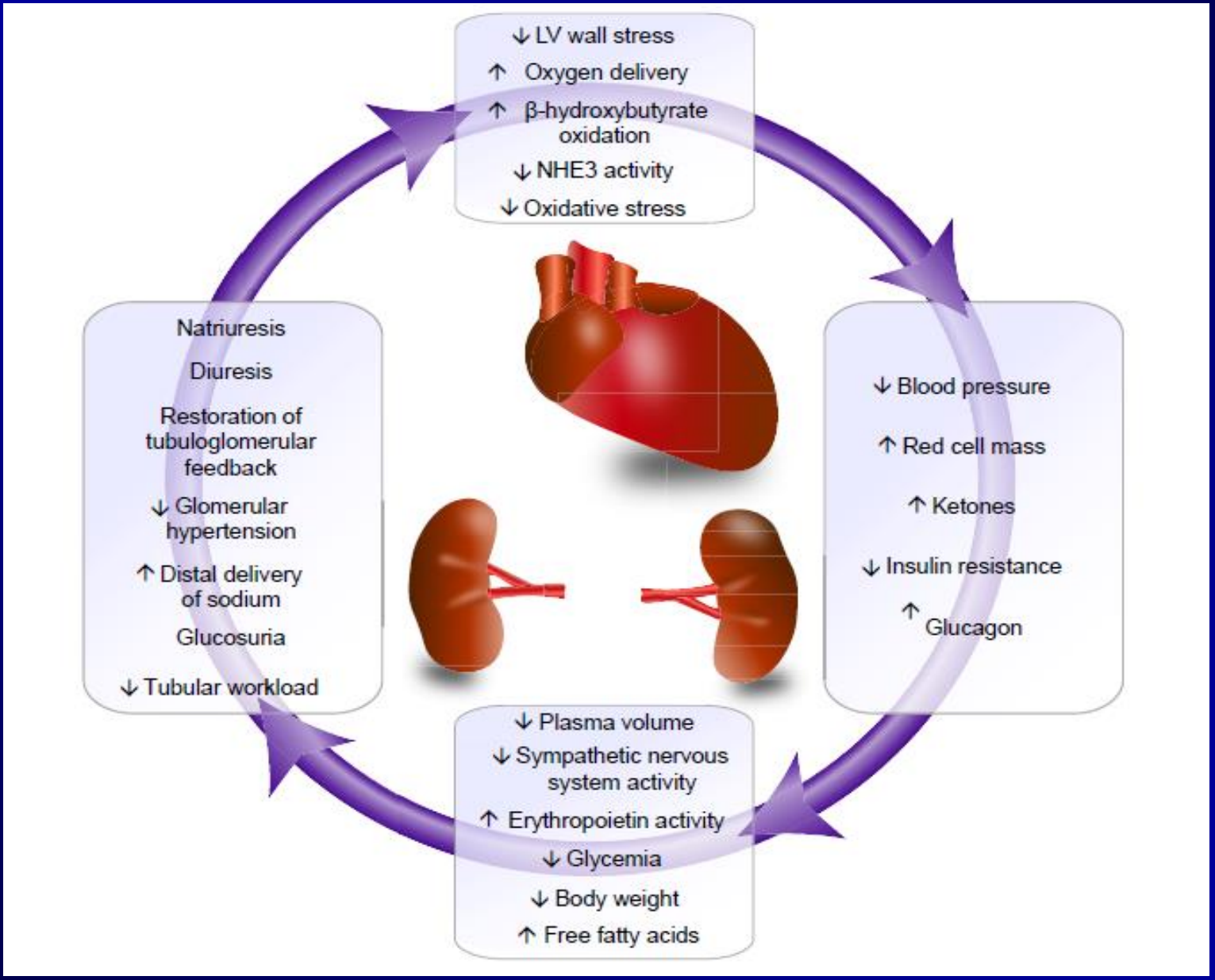
Insulin-independent mechanism

SGLT2 Inhibition



Glucose excretion

MECHANISMS OF CARDIORENAL PROTECTION WITH SGLT2i



Perkovic V, et al. N Engl J Med.2019;

Cardiovascular Outcomes Trials of SGLT2is

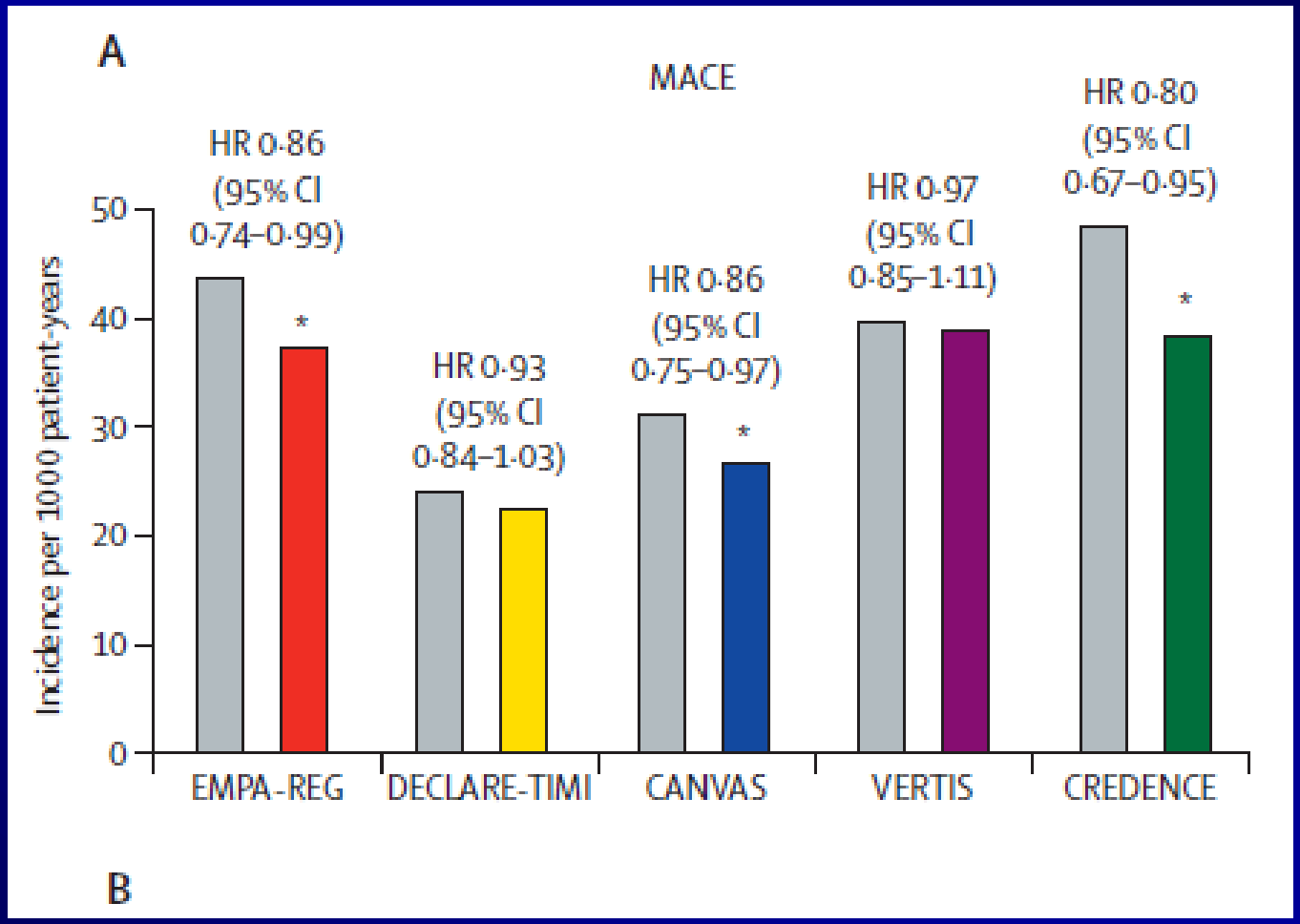
Stopped early

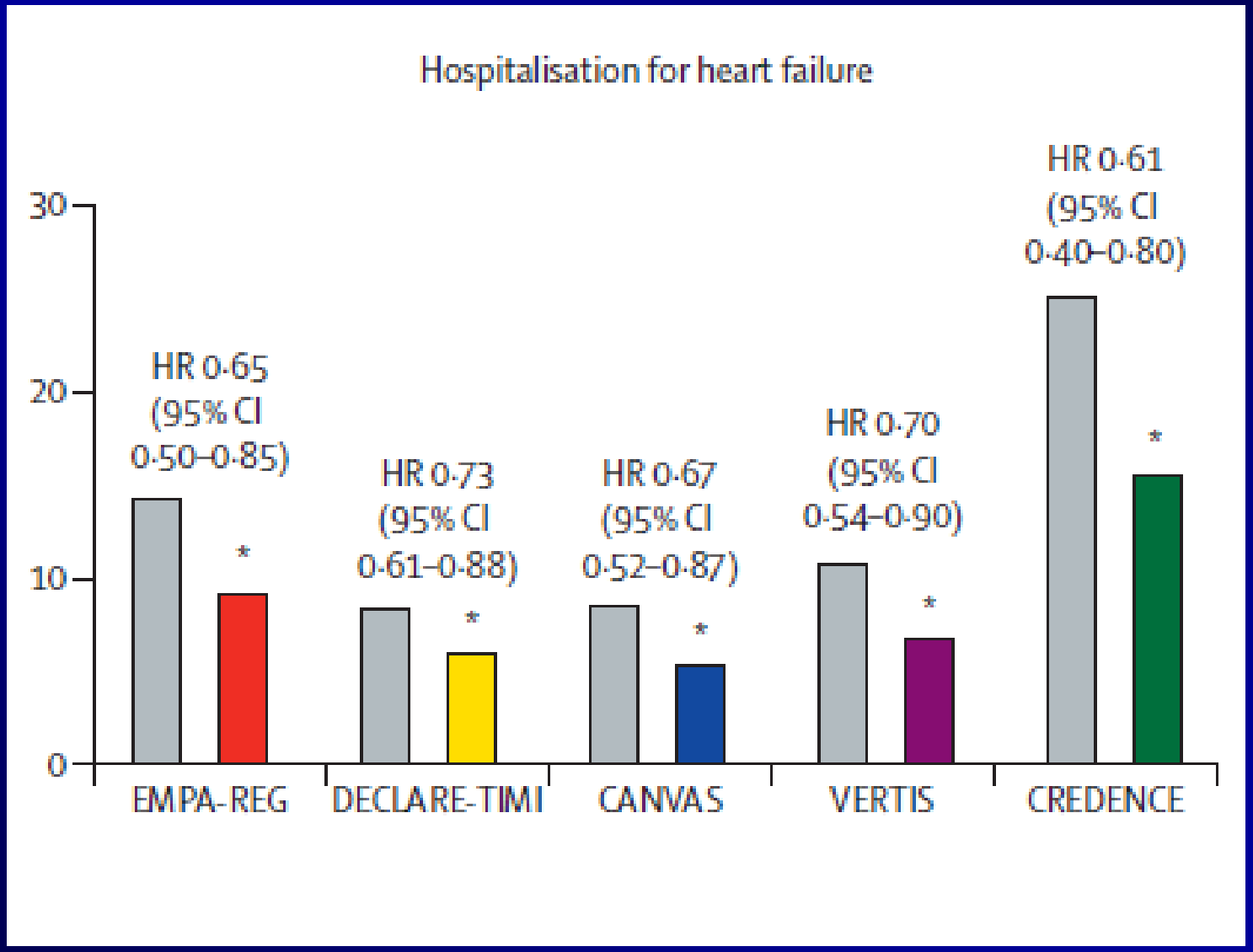
	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58	CREDENCE	DAPA-HF	VERTIS-CV*
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin	Ertuglifloz
n	7020	10 142	17 160	4401	4744	8238
Study dose, mg	25, 10	300, 100	10	100	10	5, 15
Duration of T2D, mean±SD or median (IQR), y	≥10 (4011 [57% had T2D >10 y])	13.5±7.8	11 (6–16)	15.8±8.6	NA; only 42% had T2D	12.9±8.3
Median follow-up, y	3.1	2.4	4.2	2.62	1.52	3.5
Statin use (baseline), n (%)	5403 (77)	7599 (75)	12 868 (75)	3036 (69)	…	6705 (81)
ACE inhibitor/ARB, n (%)	5666 (81)	8116 (80)	13 950 (81)	4395 (100)	3968 (84)	6705 (81)
MRA, n (%)	441 (6)	…	…	…	3370 (71)	675 (8.2)
ARNi, n (%)	…	…	…	…	508 (11)	
Metformin, n (%)	5193 (74)	7825 (77)	14 068 (82)	2545 (58)	1016 (51)	6285 (76)

Janani Rangaswami,et al. Circulation.2020;142.

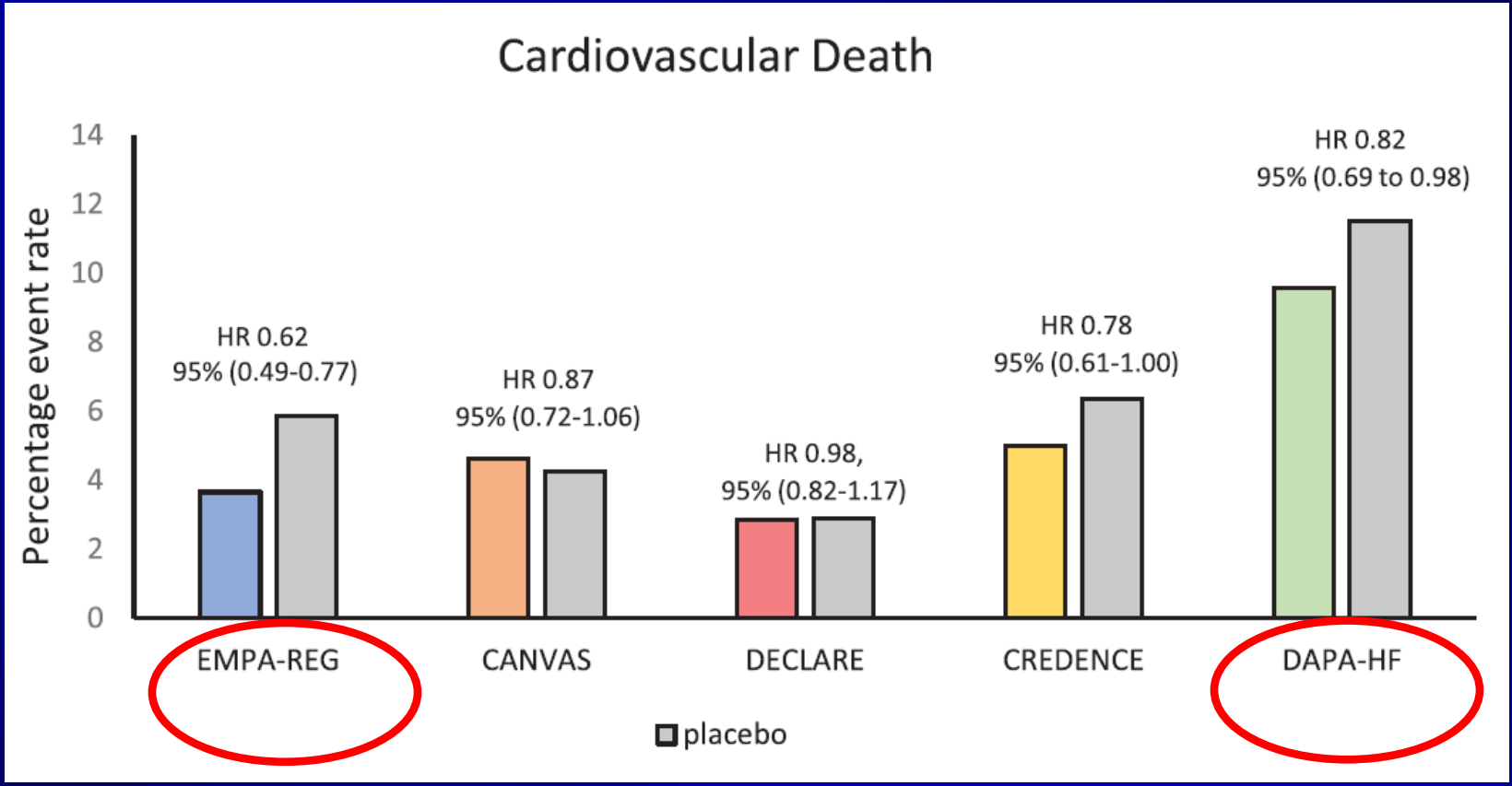
	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58	CREDENCE	DAPA-HF	VERTIS-CV*
Entry eGFR (lower limit), mL·min^{-1}·1.73 m^{-2}	30	30	60	30	30	30
eGFR threshold/criteria for drug discontinuation	If eligibility criteria are violated (GFR <30 mL·min^{-1}·1.73 m^{-2})	eGFR <15 mL·min^{-1}·1.73 m^{-2}	CrCl <30 mL/min	Initiation of dialysis or kidney transplantation	No specific GFR cutoff for drug discontinuation	eGFR <15 mL·min^{-1}·1.73 m^{-2}
Baseline UACR, n (%)						
≥300 mg/g	769 (11)	760 (8)	1169 (7)	3874 (88)		75 (9)
>300 mg/g	2012 (29)	2266 (23)	4029 (24)	496 (11)		2486 (30)
Baseline established CVD, n (%)	6964 (99)	7324 (72)	6974 (41)	2220 (50)	4744 (100)	8236 (99)

Janani Rangaswami,et al. Circulation.2020;142


A
MACE
HR 0·86
(95% CI
0·74–0·99)
HR 0·93
(95% CI
0·84–1·03)
HR 0·86
(95% CI
0·75–0·97)
HR 0·97
(95% CI
0·85–1·11)
HR 0·80
(95% CI
0·67–0·95)
*
*
*
*
Incidence per 1000 patient-years
50
40
30
20
10
0
EMPA-REG
DECLARE-TIMI
CANVAS
VERTIS
CREDENCE
B

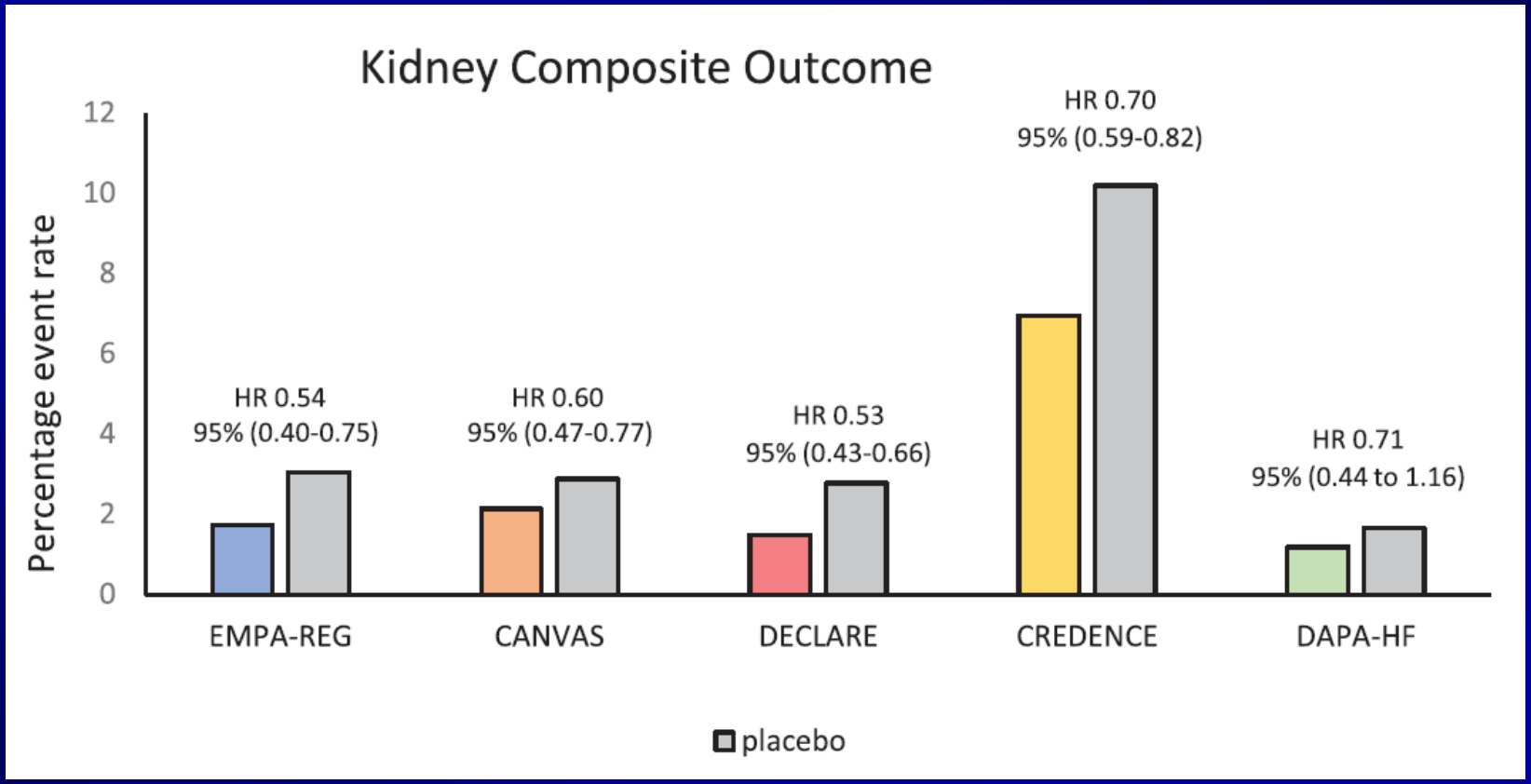

Hospitalisation for heart failure
30
20
10
0
HR 0·65
(95% CI
0·50–0·85)
HR 0·73
(95% CI
0·61–0·88)
HR 0·67
(95% CI
0·52–0·87)
HR 0·70
(95% CI
0·54–0·90)
HR 0·61
(95% CI
0·40–0·80)
*
*
*
*
*
EMPA-REG
DECLARE-TIMI
CANVAS
VERTIS
CREDENCE

Cardiovascular Death



Janani Rangaswami,et al. Circulation.2020;142

Kidney Composite Outcome

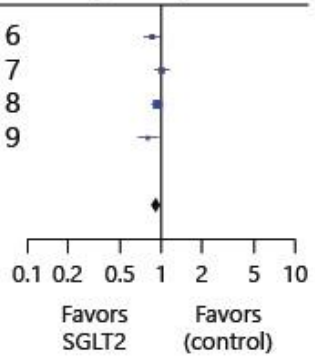


Janani Rangaswami,et al. Circulation.2020;142

Composite cardiovascular outcome in patients with type 2 diabetes with either CVD or CV risk factors.

Study or subgroup	SGLT2 events	SGLT2 total	Control events	Control total	Weight, %	Risk ratio M-H, fixed, 95% CI	Year
EMPA-REG OUTCOME	490	4,687	282	2,333	19.5	0.86 (0.75, 0.99)	2016
CANVAS	585	5,795	426	4,347	25.1	1.03 (0.92, 1.16)	2017
DECLARE-TIMI 58	756	8,582	803	8,578	41.5	0.94 (0.86, 1.03)	2018
CREDENCE	217	2,202	269	2,199	13.9	0.81 (0.68, 0.95)	2019
Total (95% CI)		21,266		17,457	100.0	0.93 (0.87, 0.99)	
Total events	2,048		1,780				

Heterogeneity: $\chi^2 = 6.76$, df = 3, $p = 0.08$; $I^2 = 56\%$
Test for overall effect: $Z = 2.35$, $p = 0.02$



NNT=167

Kevin Bryan Lo, et al. Cardiorenal Med 2020;10:1–10

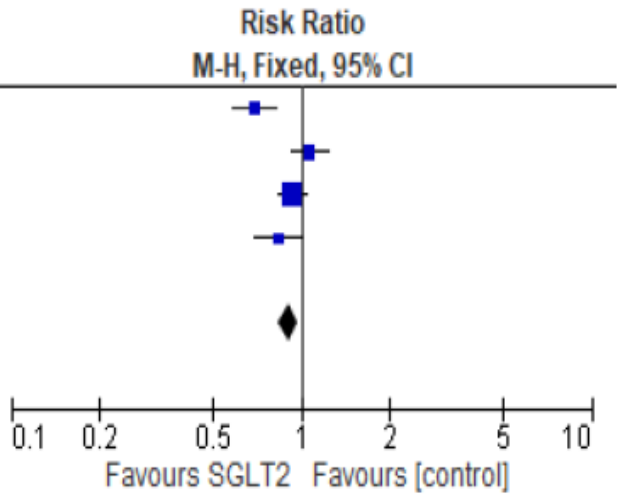
All-cause mortality in patients with type 2 diabetes with either established CVD or CV risk factors

Study or Subgroup	SGLT2 Events	SGLT2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
EMPA-REG OUTCOME	269	4687	194	2333	19.2%	0.69 [0.58, 0.82]	2016
CANVAS	400	5795	281	4347	23.8%	1.07 [0.92, 1.24]	2017
DECLARE-TIMI 58	529	8582	570	8578	42.2%	0.93 [0.83, 1.04]	2018
CREDENCE	168	2202	201	2199	14.9%	0.83 [0.69, 1.02]	2019
Total (95% CI)		**21266**		**17457**	**100.0%**	**0.90 [0.84, 0.97]**	
Total events	1366		1246				

Heterogeneity: Chi² = 14.57, df = 3 (P = 0.002); I² = 79%

Test for overall effect: Z = 2.73 (P = 0.006)

NNT = 143



Kevin Bryan Lo, et al. Cardiorenal Med 2020;10:1–10

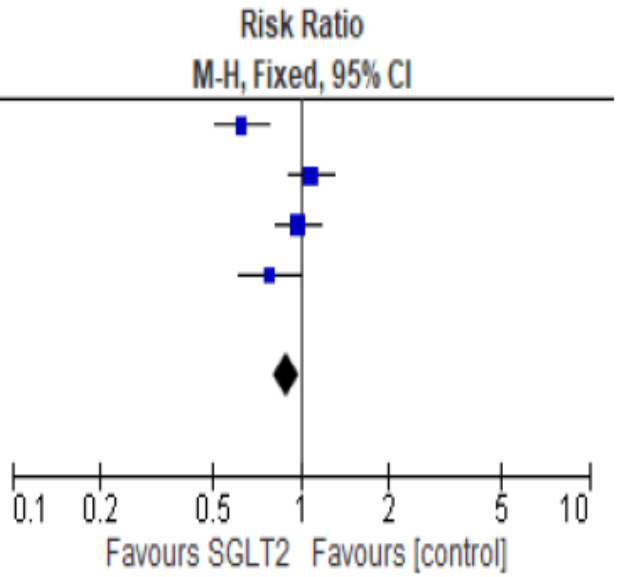
Death from cardiovascular causes alone in patients with type 2 diabetes with either established CVD or CV risk factors

Study or Subgroup	SGLT2 Events	SGLT2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
EMPA-REG OUTCOME	172	4687	137	2333	23.3%	0.62 [0.50, 0.78]	2016
CANVAS	268	5795	185	4347	27.0%	1.09 [0.90, 1.31]	2017
DECLARE-TIMI 58	245	8582	249	8578	31.8%	0.98 [0.83, 1.17]	2018
CREDENCE	110	2202	140	2199	17.9%	0.78 [0.62, 1.00]	2019
Total (95% CI)		**21266**		**17457**	**100.0%**	**0.89 [0.81, 0.99]**	
Total events	795		711				

Heterogeneity: $Chi^2 = 16.90$, $df = 3$ ($P = 0.0007$); $I^2 = 82\%$

Test for overall effect: $Z = 2.26$ ($P = 0.02$)

NNT = 250



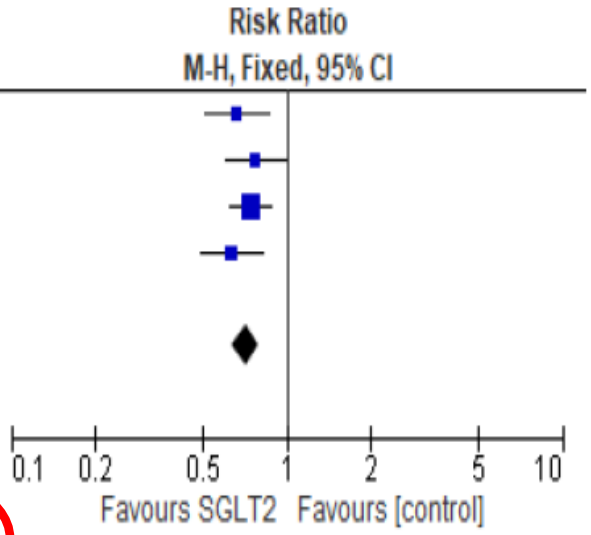
Kevin Bryan Lo, et al. Cardiorenal Med 2020;10:1–10

Heart failure hospitalization in patients with type 2 diabetes with either established CVD or CV risk factors

Study or Subgroup	SGLT2 Events	SGLT2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
EMPA-REG OUTCOME	126	4687	95	2333	18.4%	0.66 [0.51, 0.86]	2016
CANVAS	123	5795	120	4347	19.8%	0.77 [0.60, 0.99]	2017
DECLARE-TIMI 58	212	8582	286	8578	41.4%	0.74 [0.62, 0.88]	2018
CREDENCE	89	2202	141	2199	20.4%	0.63 [0.49, 0.82]	2019
Total (95% CI)		**21266**		**17457**	**100.0%**	**0.71 [0.63, 0.79]**	
Total events	550		642				

Heterogeneity: $Chi^2 = 1.73$, $df = 3$ ($P = 0.63$); $I^2 = 0\%$

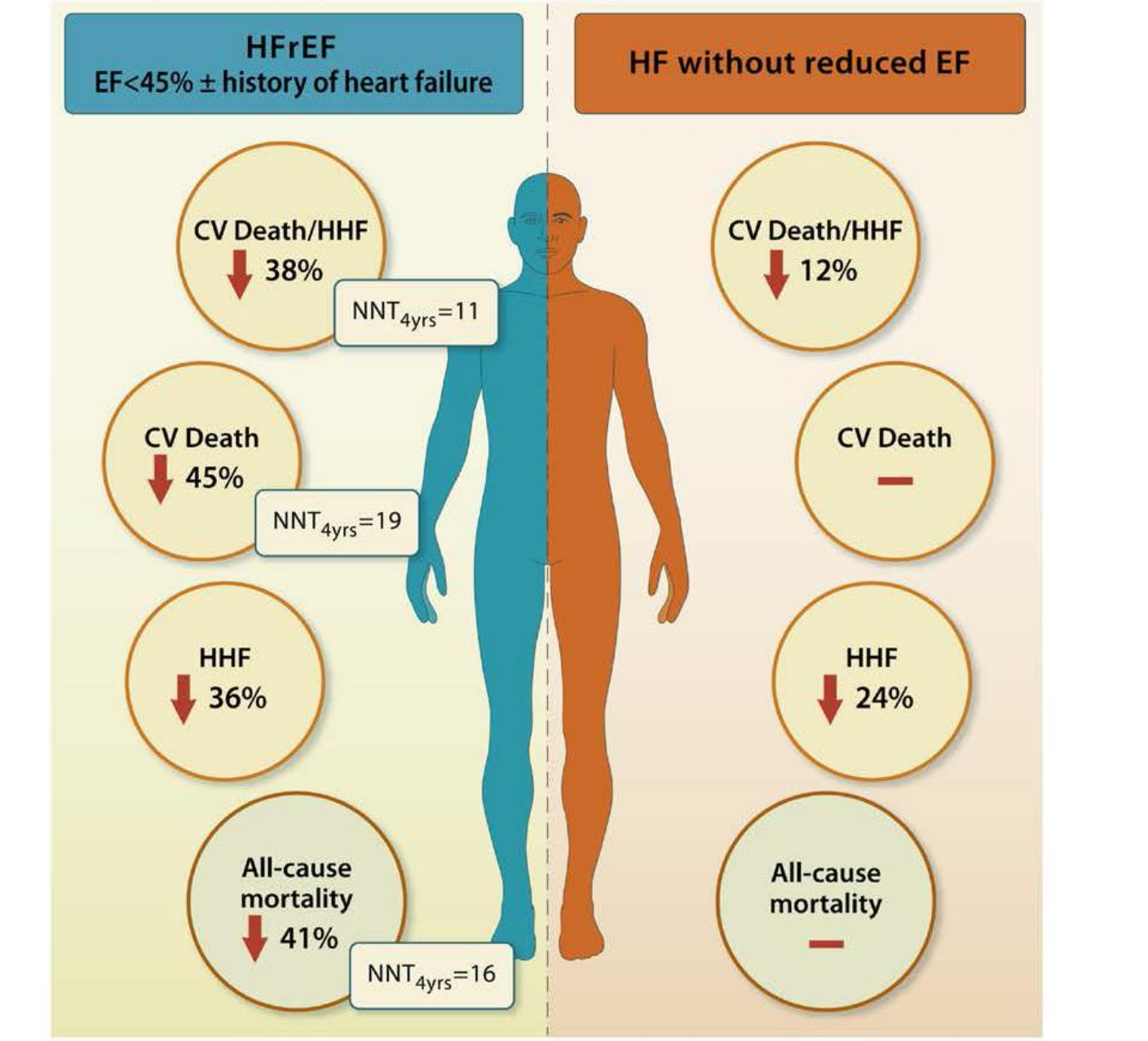
Test for overall effect: $Z = 5.97$ ($P < 0.00001$)



NNT = 91

Kevin Bryan Lo, et al. Cardiorenal Med 2020;10:1–10

DECLARE-TIMI 58

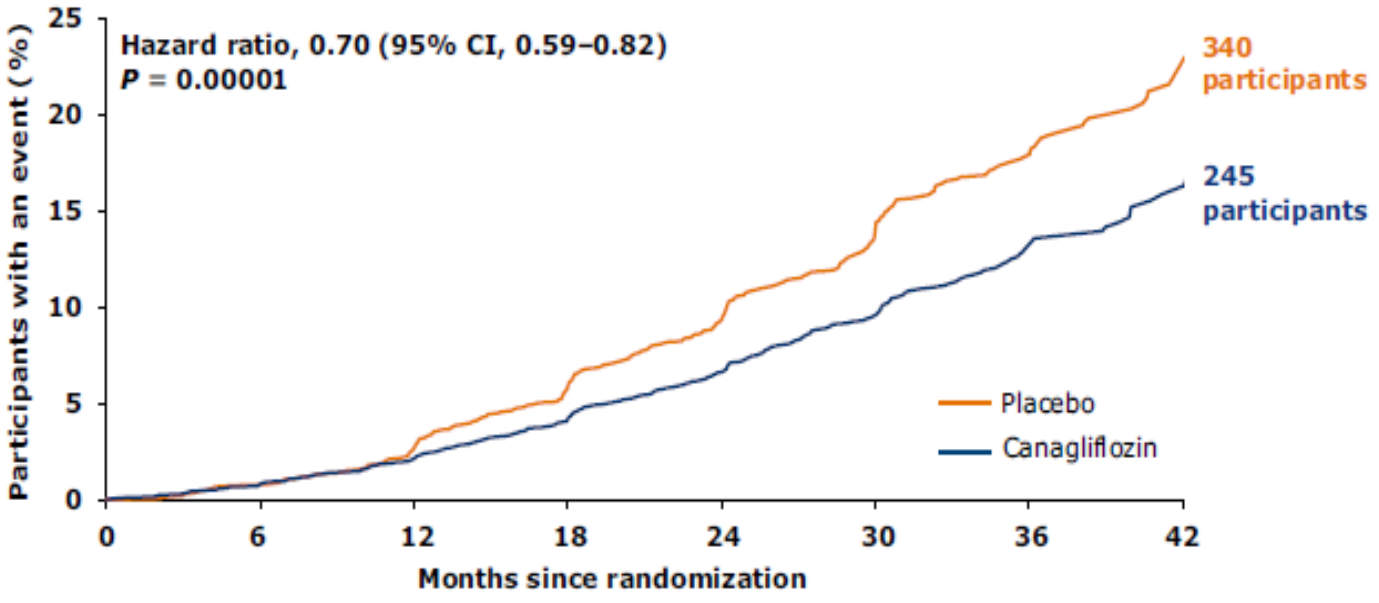


Circulation. 2019;139:2537–2541. DOI: 10.1161/CIRCULATIONAHA.119.040514

Renal Outcomes

Outcomes	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI-58	CREDENCE	DAPA-HF
Progression of albuminuria definition	Progression to macroalbuminuria	New-onset micro/macroalbuminuria or microalbuminuria to macroalbuminuria or with an ACR value increase of ≥30% from baseline	New-onset micro/macroalbuminuria or microalbuminuria to macroalbuminuria		…
Progression of albuminuria, HR (95% CI)	0.62 (0.54–0.72)	0.73 (0.67–0.79)	0.73 (0.67–0.79)	…	…
Kidney composite outcome definition	Doubling of serum creatinine, initiation of kidney replacement therapy, or death caused by kidney disease	40% Decrease in eGFR, death resulting from kidney disease, or kidney replacement therapy requirement	40% Decrease in eGFR, ESKD, or death caused by kidney disease	ESKD, doubling of serum creatinine, death caused by kidney disease	Sustained decline in the eGFR of ≥50%, ESKD, dialysis, or kidney transplantation
Kidney composite outcome, HR (95% CI)	0.54 (0.40–0.75)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	0.70 (0.59–0.82)	0.71 (0.44–1.16)

Renal Outcome in CREDENCE



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

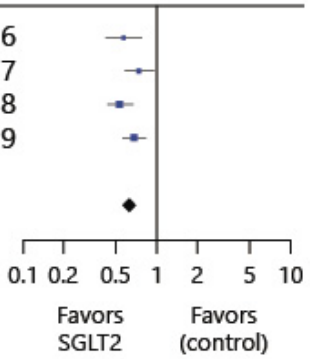
Figure 4. CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) primary outcome: kidney failure, serum creatinine doubling, kidney or cardiovascular disease death. Adapted with permission from Perkovic et al[14] with permission of the copyright holder; original graphic © 2019 Massachusetts Medical Society.

Perkovic V, et al. N Engl J Med.2019;380(24):2295-2306.

Composite renal outcome with either established cardiovascular disease or cardiovascular risk factors.

Study or subgroup	SGLT2 events	SGLT2 total	Control events	Control total	Weight, %	Risk ratio M-H, fixed, 95% CI	Year
EMPA-REG OUTCOME	81	4,645	71	2,323	13.5	0.57 (0.42, 0.78)	2016
CANVAS	124	5,795	125	4,347	20.4	0.74 (0.58, 0.95)	2017
DECLARE-TIMI 58	127	8,582	238	8,578	34.0	0.53 (0.43, 0.66)	2018
CREDENCE	153	2,202	224	2,199	32.0	0.68 (0.56, 0.83)	2019
Total (95% CI)		21,224		17,447	100.0	0.63 (0.56, 0.71)	
Total events	485		658				

Heterogeneity: $\chi^2 = 5.12$, df = 3, $p = 0.16$; $I^2 = 41\%$
Test for overall effect: $Z = 7.85$, $p < 0.00001$



NNT = 67

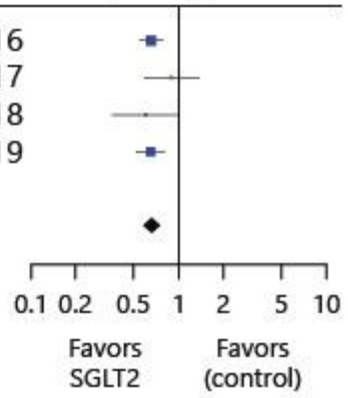
Kevin Bryan Lo, et al. Cardiorenal Med 2020;10:1–10

Composite renal outcome in patients with type 2 DM and **eGFR <60**

Study or subgroup	SGLT2 events	SGLT2 total	Control events	Control total	Weight, %	Risk ratio M-H, fixed, 95% CI	Year
EMPA-REG OUTCOME	207	998	161	507	45.0	0.65 (0.55, 0.78)	2016
CANVAS	43	1,110	40	929	9.2	0.90 (0.59, 1.37)	2017
DECLARE-TIMI 58	21	606	38	659	7.7	0.60 (0.36, 1.01)	2018
CREDENCE	118	1,297	181	1,295	38.2	0.65 (0.52, 0.81)	2019
Total (95% CI)		4,011		3,390	100.0	0.67 (0.59, 0.76)	
Total events	389		420				

Heterogeneity: $\chi^2 = 2.19$, df = 3, $p = 0.53$; $I^2 = 0\%$

Test for overall effect: $Z = 6.13$, $p < 0.00001$



NNT = 37

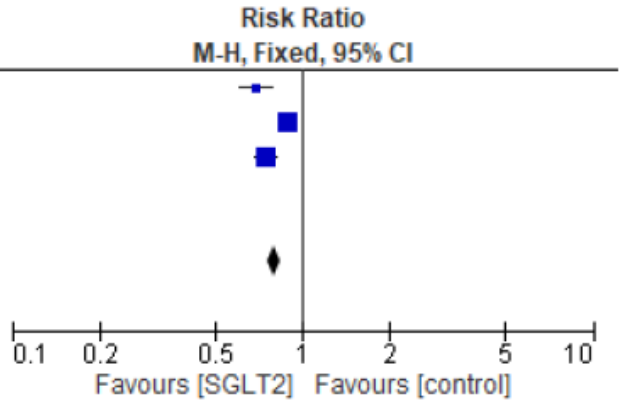
Kevin Bryan Lo, et al. Cardiorenal Med 2020;10:1–10

Progression of albuminuria in patients with type 2 diabetes with either established CVD or CV risk factors

Study or Subgroup	SGLT2 Events	SGLT2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
EMPA-REG OUTCOME	459	4091	330	2033	14.9%	0.69 [0.61, 0.79]	2016
CANVAS	1341	5196	1114	3819	43.3%	0.88 [0.83, 0.95]	2017
DECLARE-TIMI 58	928	7836	1243	7838	41.9%	0.75 [0.69, 0.81]	2018
CREDENCE	0	0	0	0		Not estimable	2019
Total (95% CI)		**17123**		**13690**	**100.0%**	**0.80 [0.76, 0.84]**	
Total events	2728		2687				

Heterogeneity: $Chi^2 = 16.27$, $df = 2$ ($P = 0.0003$); $I^2 = 88\%$

Test for overall effect: $Z = 9.21$ ($P < 0.00001$)



NNT = 27

Kevin Bryan Lo, et al. Cardiorenal Med 2020;10:1–10

Non-alcoholic fatty liver disease

- Randomised controlled trials with SGLT2 inhibitors and GLP-1 receptor agonists have shown improved liver enzymes and reductions in liver fat in patients with type 2 diabetes,
- But only GLP-1 receptor agonists (liraglutide and semaglutide) have shown reversal

or improvements of the histological features of NAFLD

Combination therapy

- Overall, the evidence supports combination therapy with a GLP-1 receptor agonist and SGLT2 inhibitor with the additive benefits of glycaemic improvement and weight loss reflecting distinct and complementary mechanisms of action.

Emily Brown , et al. ***Lancet*** **2021; 398: 262–76**

SGLT2 inhibitors as treatment adjunct in type 1 diabetes

- In Europe, dapagliflozin and sotagliflozin have been approved for patients with a suboptimal control of insulin and a BMI of more than 27 kg/m²

Yamada T, et al. Diabetes Obes Metab 2018; 20: 1755–61

SGLT2 inhibitors as treatment adjunct in type 1 diabetes

- SGLT2 inhibitors should be avoided in patients who are poorly compliant or those with recurrent diabetic ketoacidosis and should be discontinued during acute illness or surgical intervention

Clinical use of SGLT2 inhibitors in patients without diabetes

- DAPA-CKD examined the effects of dapagliflozin on CKD in patients with and without type 2 diabetes. The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes.
- EMPA-KIDNEY (NCT03594110), has been initiated in people with and without type 2 diabetes

Hiddo J.L. Heerspink,et al. N Engl J Med 2020; 383:1436-1446

Clinical use of SGLT2 inhibitors in patients without diabetes

- The results of the DAPA-HF and EMPEROR-reduced trials strongly support the use of an SGLT2 inhibitor in the treatment of patients wit established HFrEF with reductions in worsening HFrEF or cardiovascular deaths with or without type 2 diabetes

McMurray JJV ,et al. *N Engl J Med* 2019; **381:** 1995–2008.
Packer M,et al. *N Engl J Med* 2020; **383:** 1413–24.

Clinical use of SGLT2 inhibitors in patients without diabetes

- FDA and European regulators have approved the use of dapagliflozin to reduce the risk of cardiovascular death or worsening heart failure in patients with HFrEF, with and without type 2 diabetes.

- Dapagliflozin also reduced the risk of new onset of type 2 diabetes by 32% (hazard ratio [HR] 0·68; 95% CI 0·50–0·94) compared with those receiving placebo among at risk patients with prediabetes and HFrEF;
- a similar effect size to that seen with metformin in diabetes prevention studies (approximately 31%).

Silvio E Inzucchi,et al. DiabetesCare. 2021Feb;44(2):586-594

ADVERSE EVENTS AND RISK/BENEFIT PROFILE WITH SGLT2i

- Genital mycotic infections
- Urinary tract infections
- Euglycemic diabetic ketoacidosis
- Increased risk of amputation (CANVAS trial)
- Fournier gangrene: ≈1 case per 10,000 men treated with SGLT2is
- Fracture risk
- AKI: The initial decrease in eGFR when SGLT2is are initiated is consistent with these hemodynamic effects.

Genital mycotic infections:

- The most common adverse event of SGLT2is.
- Advice given for daily hygienic measures such as rinsing the genital area after voiding and before bedtime significantly lessened the risk for genital mycotic infections (6 of 125 versus 51 of 125; P=0.015) and improved compliance with SGLT2i treatment

Urinary tract infections

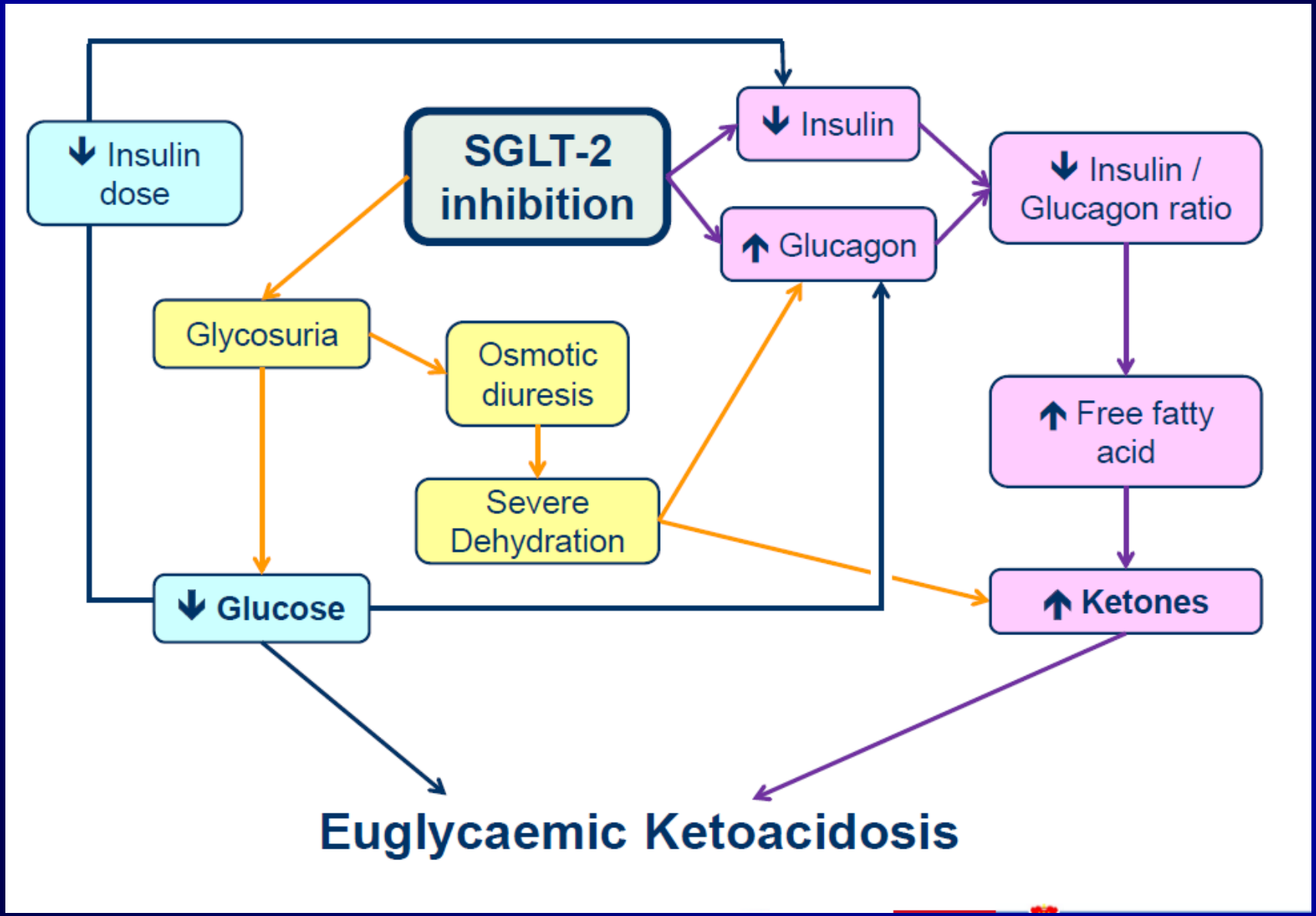
- Urinary tract infections also have been reported with SGLT2is, but the risk of urinary tract infections has not been higher compared with placebo in clinical trials.

Euglycemic diabetic ketoacidosis

- Patients with signs or symptoms of ketoacidosis such as nausea, vomiting, and abdominal pain should be discontinue SGLT2is and evaluate for ketoacidosis.

- Holding SGLT2i during periods of low oral intake or before elective surgeries

Euglycemic diabetic ketoacidosis



Increased risk of amputation

- It is unknown whether amputation risk is causally related to canagliflozin or extends to other drugs in this class.
- Frequent foot care along with self-examination should be promoted.
- Therapy should be stopped in patients with active ulceration or foot lesions

Risk of Fournier gangrene

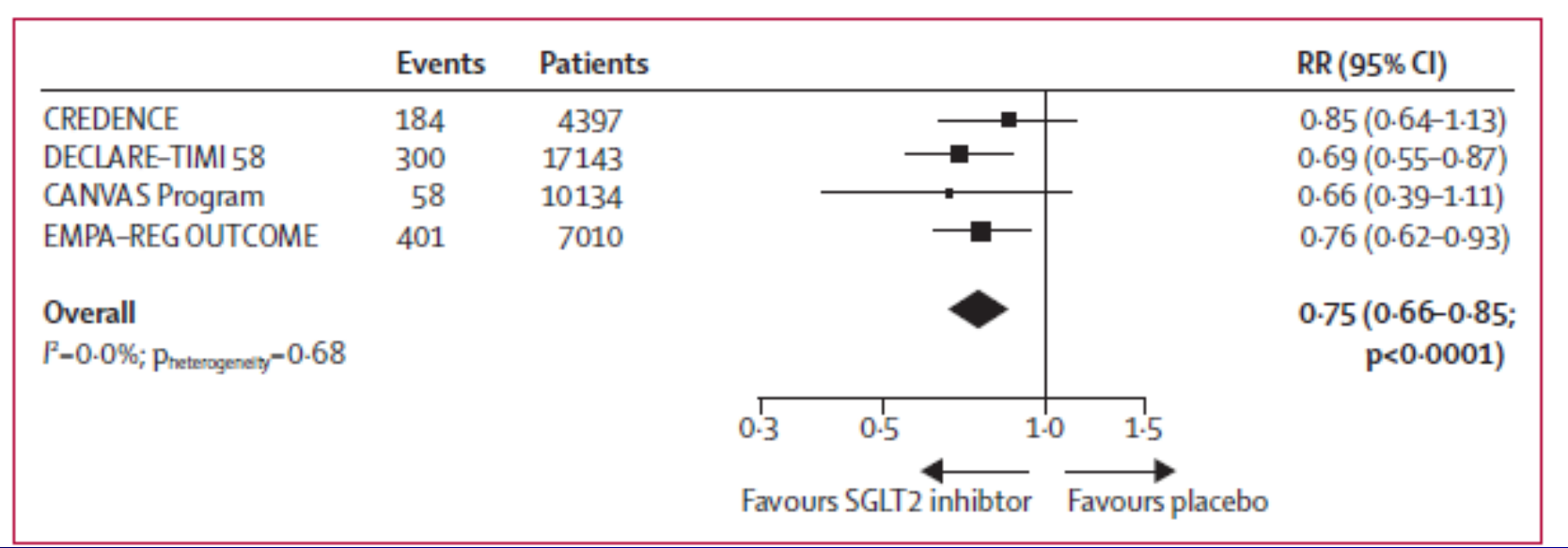
- A slightly higher (but not statistically significant) risk of Fournier gangrene of ≈1 case per 10 000 men treated with SGLT2is compared with men treated with other antihyperglycemic agents.

Dave CV, et al. *JAMA Intern Med*. 2019

Risk of AKI

- Decrease in eGFR when SGLT2is are initiated is consistent with these hemodynamic effects.

Effect of SGLT2 inhibitors on acute kidney injury



Brendon L Neuen, et al. ***Lancet Diabetes Endocrinol*** **2019**

ADVERSE EFFECTS(AE)	EMPA-REG OUTCOME		CANVAS		DECLARE-TIMI 58		CREDENCE		DAPA-HF	
	EMPA n(%)	Placebo n(%)	CANA event rate per 1000 patient-year	Placebo event rate per 1000 patient-year	DAPA n(%)	Placebo n(%)	CANA n(%)	Placebo n(%)	DAPA n(%)	Placebo n(%)
Male genital infection	166 (5.0) ↑	25 (1.5)	34.9↑	10.8	76 (0.9) ↑	9 (0.1)	28 (0.2) ↑	3 (0.0)		
Female genital infection	135 (10.0) ↑	17 (2.6)	68.8↑	17.5			22 (0.3) ↑	10 (0.0)		
Hypoglycemia	1303 (27.8)	650 (27.9)	50	46.4	58 (0.7)	83 (1.0)	225 (1.0)	240 (0.1)	4 (0.2)	4 (0.2)
Urinary tract infection	842 (18.0)	423 (18.1)	40	37	127 (1.5)	133 (1.6)	245 (1.1)	221 (0.1)	11 (0.5)	17 (0.7)
Fracture	179 (3.8)	91 (3.9)	15.4↑	11.9	457 (5.3)	440 (5.1)	67 (0.3)	68 (0.0)	49 (2.1)	50 (2.1)
Hyperkalemia			6.9	4.4			151	181		
Amputation			6.3↑	3.4	123 (1.4)↑	113 (1.3)	70 (0.3)	63 (0.0)	13 (0.5)	12 (0.5)
Acute kidney injury	45 (1.0)	37 (1.6)	3	4.1	125 (1.5)	113 (1.3)	86 (0.4)	98 (0.0)	23 (1.0)	46 (1.9)
Breast Cancer			3.1	2.6	36 (0.4)	113 (1.3)	8 (0.1)	3 (0.0)	1 (0)	2 (0.1)
Bladder Cancer			1	1.1	26 (0.3)	45 (0.5)	10 (0.0)	9 (0.0)	1 (0)	2 (0.1)
Diabetic Ketoacidosis	4 (0.1)	1 (<0.1)	0.6	0.3	27 (0.3) ↑	12 (0.1)	11 (0.0) ↑	1 (0.0)	3 (0.1)	0

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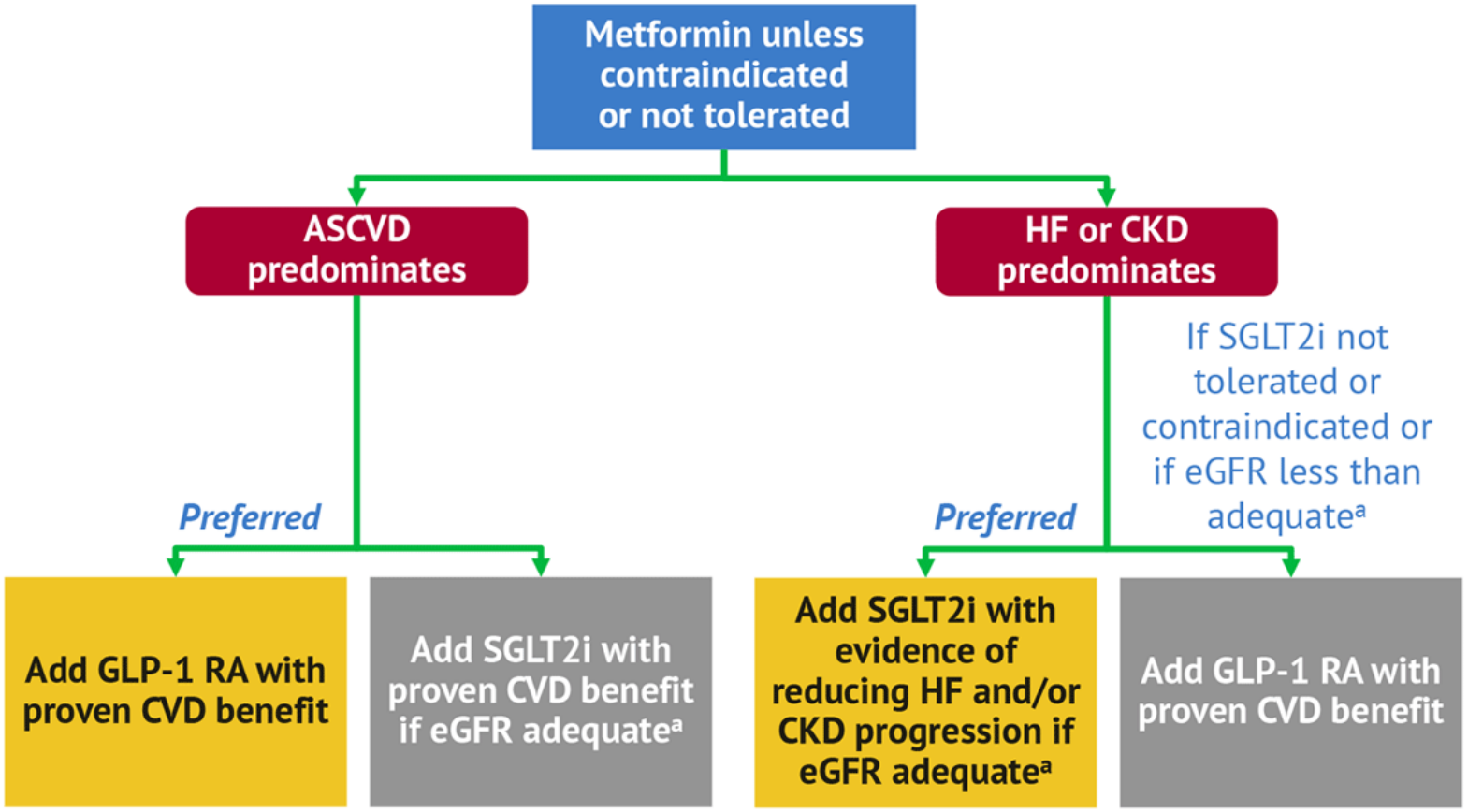
ADA Guidelines: Glucose-Lowering Medications in Patients at High Risk



[a] SGLT1i labeling varies by region and individual agent with regard to indicated level of eGFR.

Current position in treatment algorithms

- SGLT2 inhibitors and GLP-1 receptor agonists were positioned as first-line treatment for naive patients with existing CVD or at a high risk of this, irrespective of HbA1c.

- GLP-1 receptor agonists should be considered in patients with type 2 diabetes and those at a high risk or with established CVD,
- SGLT2 inhibitors considered for patients with HFrEF or CKD (with or without established CVD)

European Society for Cardiology in collaboration with the European Association for the Study of Diabetes

Identify Patients with T2D at High Risk for Kidney Events

- Screening eGFR & albuminuria
- Consider individualized risk scores*
- With or without concomitant treatment with RASi

Selection of Specific SGLT2i

	Canagliflozin**	Dapagliflozin	Empagliflozin	Ertugliflozin
Use above eGFR (mL/min/1.73 m2)	30	30	45	60
Starting in eGFR<60mL/min/1.73 m2 (all once daily)	100mg	5-10mg	10mg	5mg
Stop if eGFR (60mL/min/1.73 m2) falls below	Dialysis	Dialysis	45	30

Adjustment of Concomitant Therapies

- Expect average 2–4mmHg systolic blood pressure lowering
- Consider reduction in daily diuretic dose with close monitoring of congestive signs/symptoms
- Closely monitor for hypoglycemia especially with concomitant insulin or sulfonylureas

Patient Counseling

- Interrupt therapy during periods of poor oral intake or in anticipation of elective surgery
- Avoid excessive alcohol or ketogenic diets
- Volume depletion and orthostatic hypotension
- Perineal hygiene and foot care. Hold therapy if any concern for active ulcers.

Longitudinal Follow-up

- Cross-disciplinary communication
- Monitor kidney function periodically and adjust dose accordingly
- Ensure continued access and adherence

PCP/Internal Medicine

Nephrology

Endocrinology

Cardiology

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Thank you