Effetti cardiovascolari e renali dei nuovi antidiabetici orali

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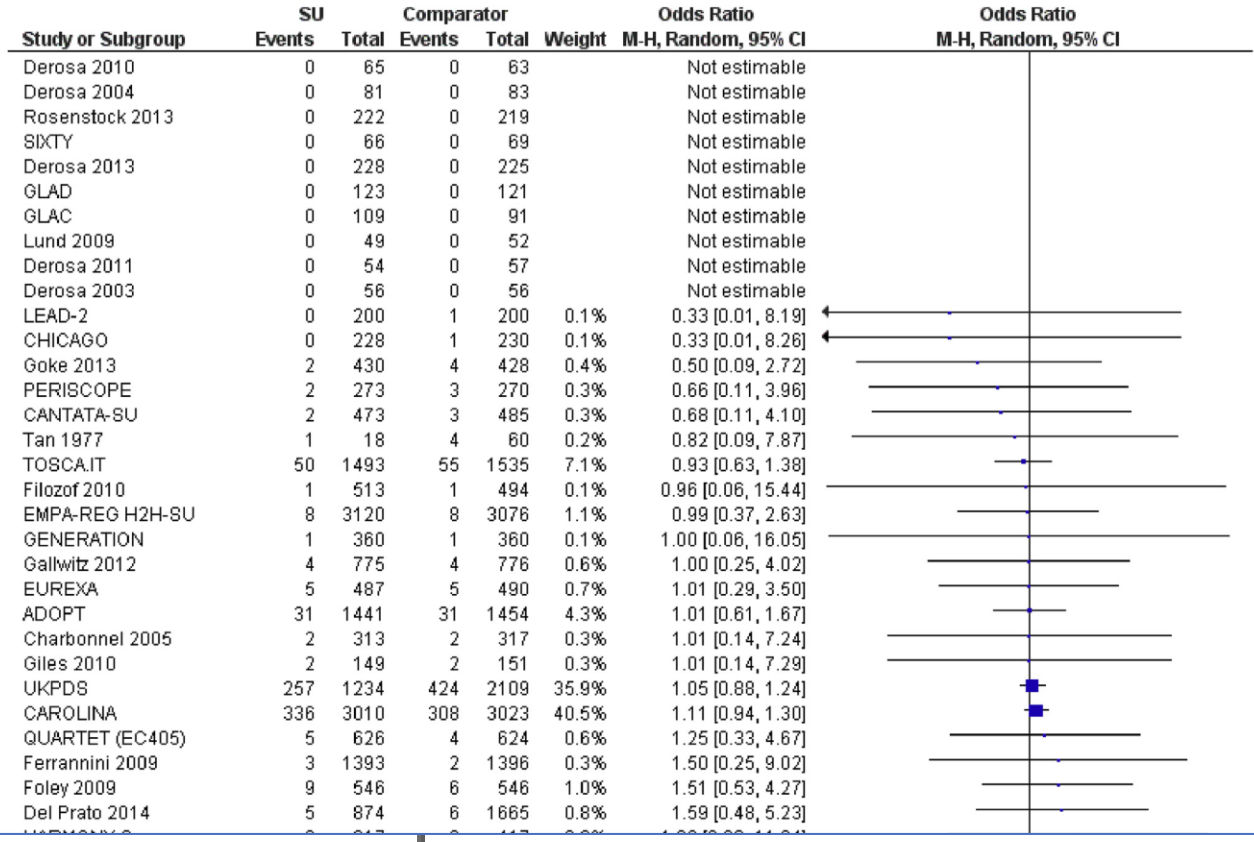
Effect of insulin secretagogues on major cardiovascular events and all-cause mortality: A meta-analysis of randomized controlled trials

Edoardo Mannucci [a,*], Matteo Monami [a], Riccardo Candido [b], Basilio Pintaudi [c], Giovanni Targher [d], on behalf of the SID-AMD joint panel for Italian Guidelines on Treatment of Type 2 Diabetes[1]

Risk of all-cause mortality

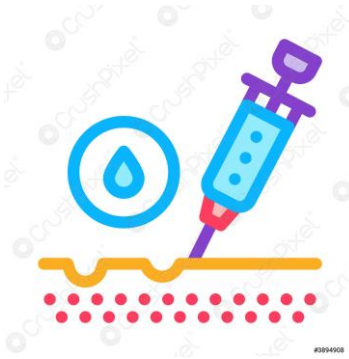


Study or Subgroup	SU Events	SU Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
Derosa 2010	0	65	0	63		Not estimable
Derosa 2004	0	81	0	83		Not estimable
Rosenstock 2013	0	222	0	219		Not estimable
SIXTY	0	66	0	69		Not estimable
Derosa 2013	0	228	0	225		Not estimable
GLAD	0	123	0	121		Not estimable
GLAC	0	109	0	91		Not estimable
Lund 2009	0	49	0	52		Not estimable
Derosa 2011	0	54	0	57		Not estimable
Derosa 2003	0	56	0	56		Not estimable
LEAD-2	0	200	1	200	0.1%	0.33 [0.01, 8.19]
CHICAGO	0	228	1	230	0.1%	0.33 [0.01, 8.26]
Goke 2013	2	430	4	428	0.4%	0.50 [0.09, 2.72]
PERISCOPE	2	273	3	270	0.3%	0.66 [0.11, 3.96]
CANTATA-SU	2	473	3	485	0.3%	0.68 [0.11, 4.10]
Tan 1977	1	18	4	60	0.2%	0.82 [0.09, 7.87]
TOSCA.IT	50	1493	55	1535	7.1%	0.93 [0.63, 1.38]
Filozof 2010	1	513	1	494	0.1%	0.96 [0.06, 15.44]
EMPA-REG H2H-SU	8	3120	8	3076	1.1%	0.99 [0.37, 2.63]
GENERATION	1	360	1	360	0.1%	1.00 [0.06, 16.05]
Gallwitz 2012	4	775	4	776	0.6%	1.00 [0.25, 4.02]
EUREXA	5	487	5	490	0.7%	1.01 [0.29, 3.50]
ADOPT	31	1441	31	1454	4.3%	1.01 [0.61, 1.67]
Charbonnel 2005	2	313	2	317	0.3%	1.01 [0.14, 7.24]
Giles 2010	2	149	2	151	0.3%	1.01 [0.14, 7.29]
UKPDS	257	1234	424	2109	35.9%	1.05 [0.88, 1.24]
CAROLINA	336	3010	308	3023	40.5%	1.11 [0.94, 1.30]
QUARTET (EC405)	5	626	4	624	0.6%	1.25 [0.33, 4.67]
Ferrannini 2009	3	1393	2	1396	0.3%	1.50 [0.25, 9.02]
Foley 2009	9	546	6	546	1.0%	1.51 [0.53, 4.27]
Del Prato 2014	5	874	6	1665	0.8%	1.59 [0.48, 5.23]

Figure 2 Risk of all-cause mortality with insulin secretagogues versus other comparators approved by EMA and currently used in Europe (MHeOR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals). A total of 46 RCTs were included in this pooled primary analysis.

Nutr Metab Cardiovasc Dis . 2020 Sep 24;30(10):1601-1608.

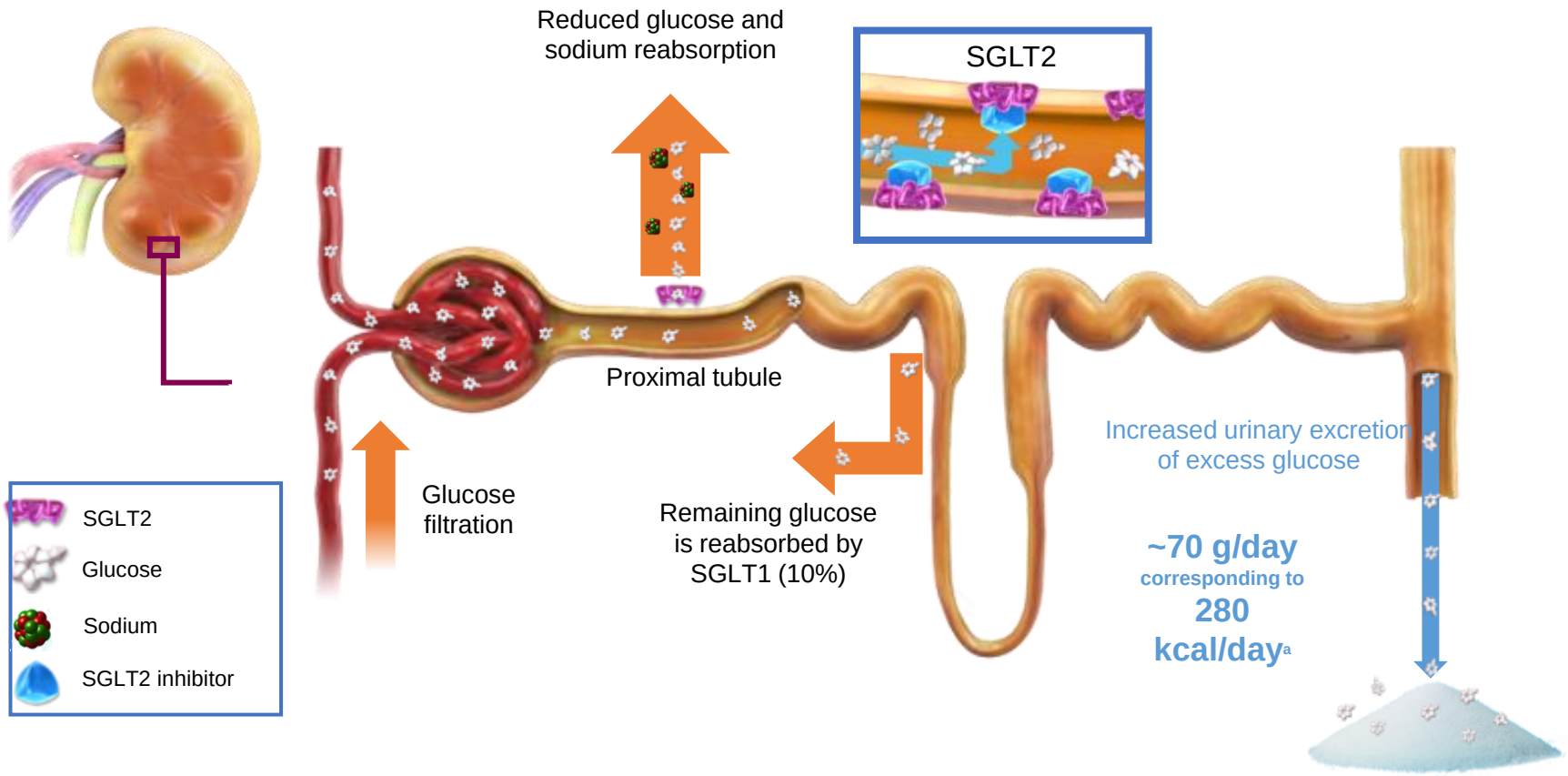
Gli analoghi del GLP-1

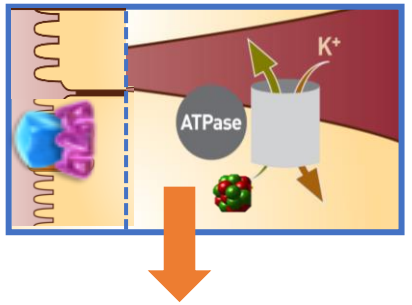


Gli inibitori del SGLT-2

Gli inibitori del SGLT-2

Glifozins Block SGLT2 and Reduces Glucose and Na+ Reabsorption



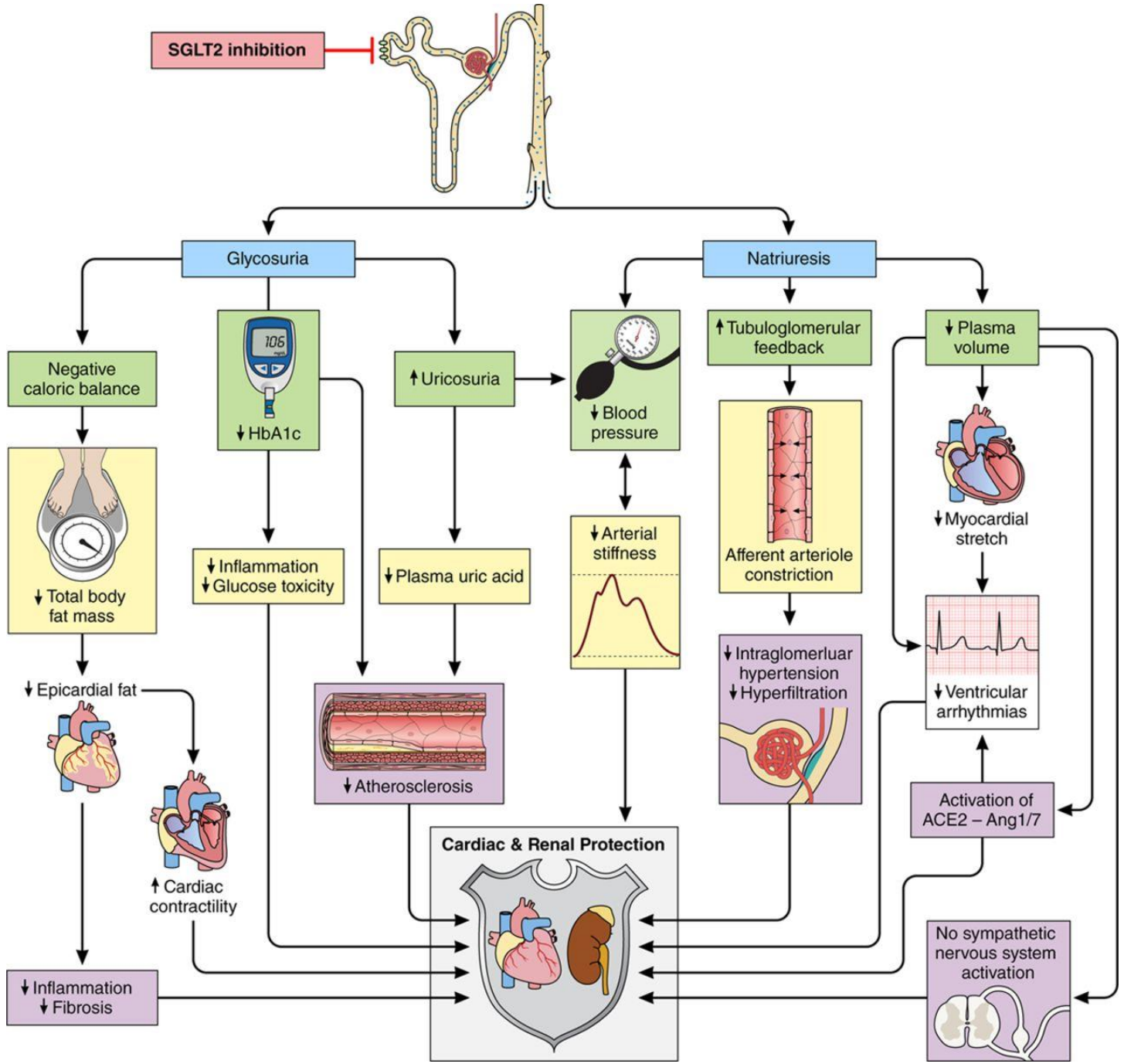


Decrease in intracellular sodium concentration

Based on this MOA, the following occur[3]:

- Diuresis
- Natriuresis
- HbA_{1c} reduction
- Weight loss
- SBP reduction

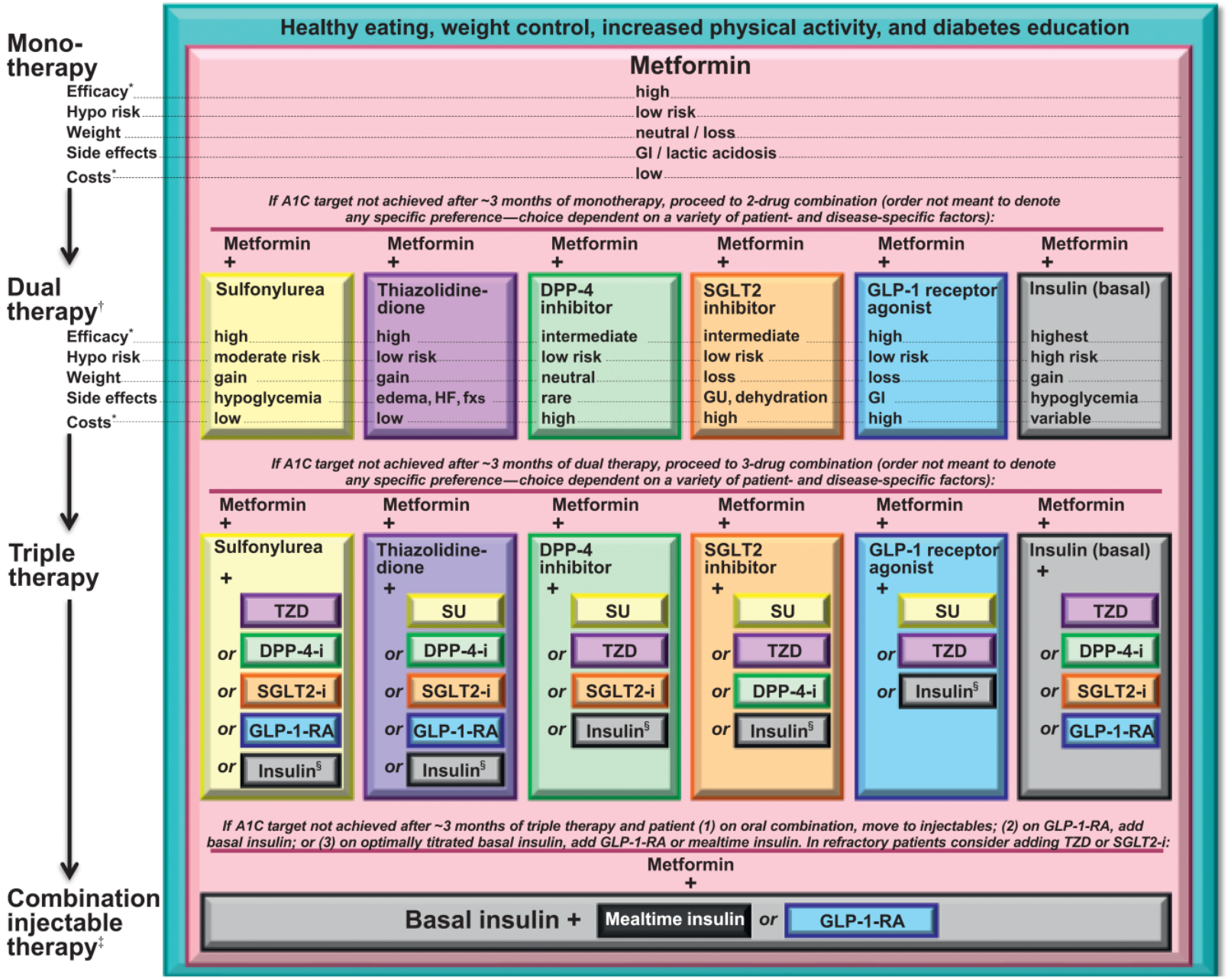
[a]Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy patients and patients with Type 2 diabetes[1] HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure; SGLT, sodium–glucose co-transporter 1. Marsenic O. *Am J Kidney Dis* 2009;53:875–885; 2. FORXIGA. Summary of product characteristics, 2014; 3. Mudaliar S, et al. *Diabetes Care* 2016;39:1115–1122



Circulation. 2016;134:752-772

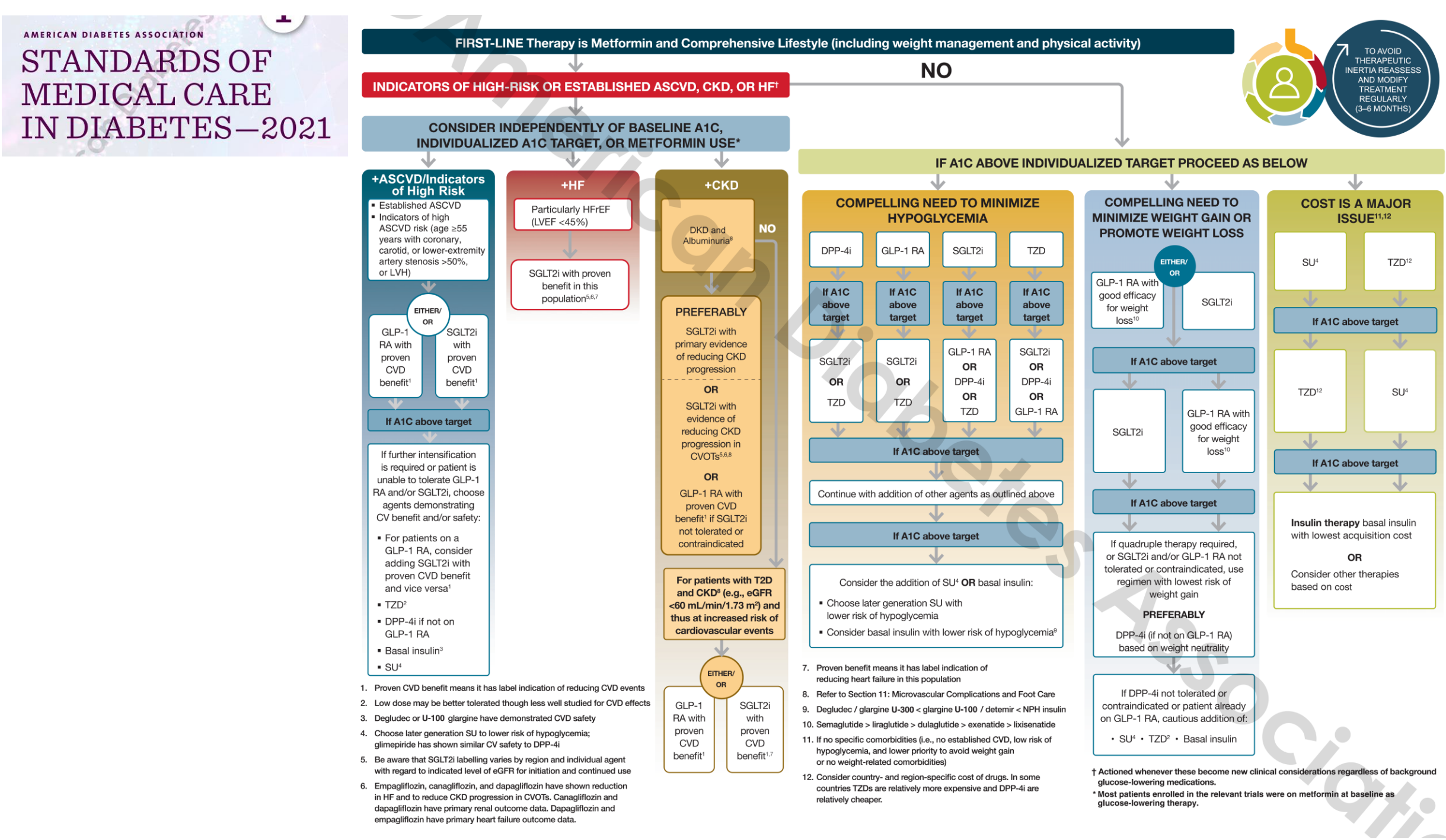
AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2015



AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2021

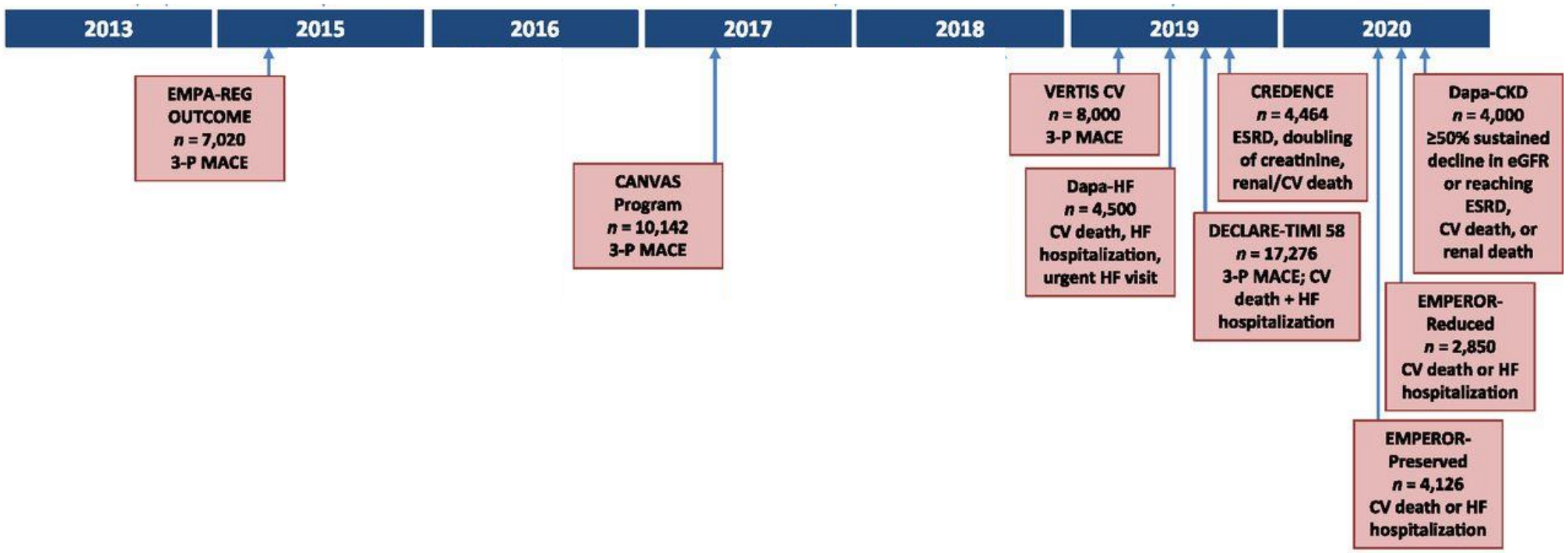


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or **U-100** glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine **U-300** < glargine **U-100** / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

*** Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.**

I trial cardiovascolari degli inibitori del SGLT-2

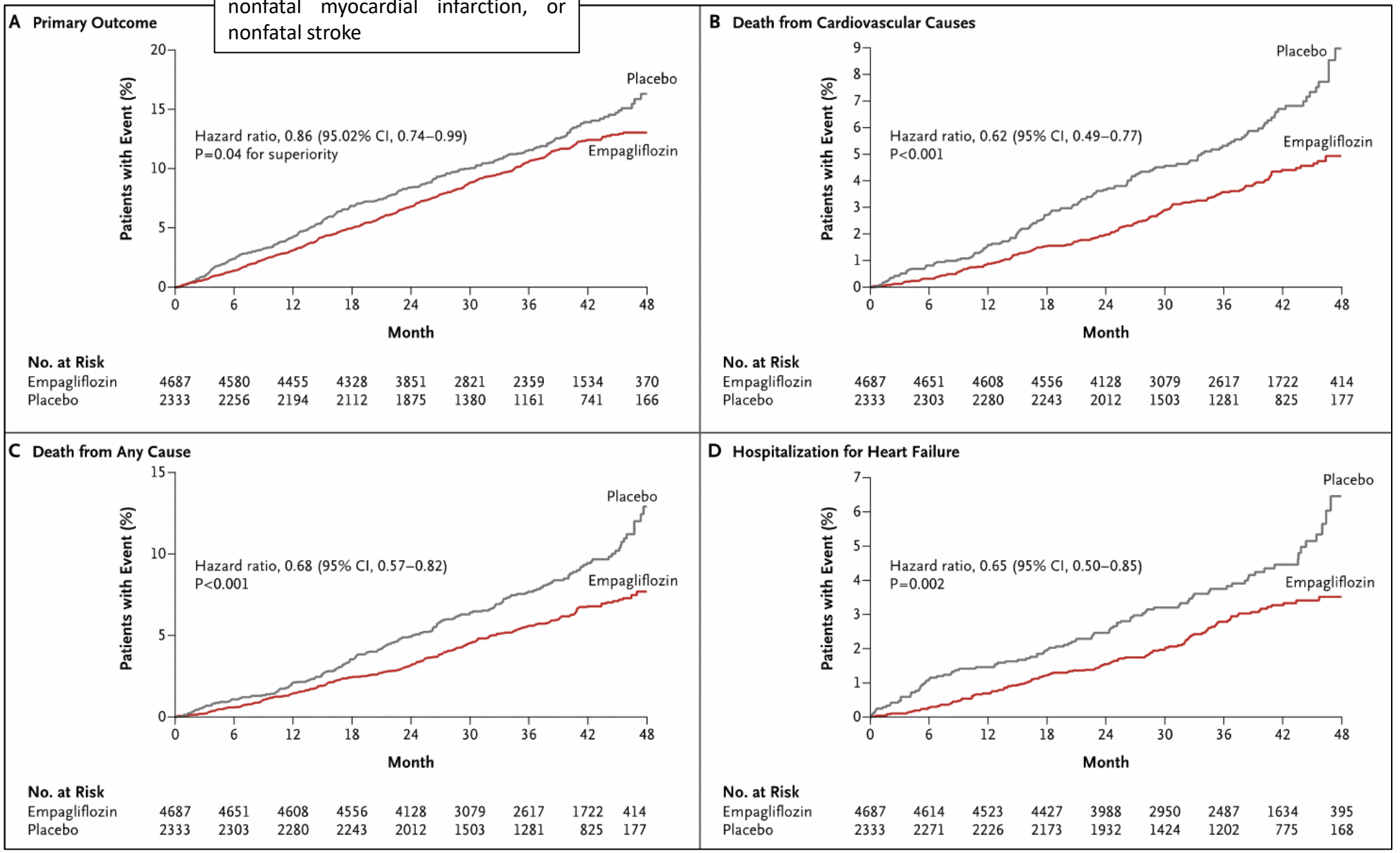


Diabetes Care 2018;41:14–31

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke



N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME®

Empagliflozin riduce il rischio cardiovascolare e migliora la sopravvivenza generale nei pazienti con T2D ad alto rischio CV

14%

↓ 3P-MACE

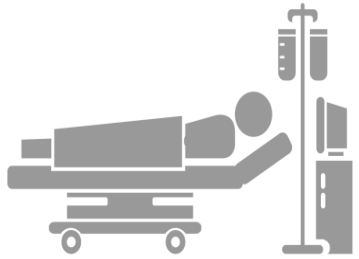
38%

↓ morte CV

32%

↓ Mortalità per tutte le cause

35%



↓ ospedalizzazione per scompenso cardiaco

Zinman B *et al. N Engl J Med* 2015;373:2117 & supplementary appendix

JAMA Cardiology | Original Investigation

Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes

A Meta-analysis

Darren K. McGuire, MD, MHSc; Weichung J. Shih, PhD; Francesco Cosentino, MD, PhD; Bernard Charbonnel, MD; David Z. I. Cherney, MD, PhD; Samuel Dagogo-Jack, MD, DSc; Richard Pratley, MD; Michelle Greenberg, BSc; Shuai Wang, PhD; Susan Huyck, DrPH; Ira Gantz, MD; Steven G. Terra, PharmD; Urszula Masiukiewicz, MD; Christopher P. Cannon, MD

Characteristic	No. (%)[b]			
	EMPA-REG outcome[19] (n = 7020)	CANVAS program[20] (n = 10 142)	DECLARE-TIMI 58[21] (n = 17 160)	VERTIS CV[16] (n = 8246)
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Duration of follow-up, median, y	3.1	2.4	4.2	3.0
Patient characteristics				
Men	5016 (71.5)	6509 (64.2)	10 738 (62.6)	5769 (70.0)
Women	2004 (28.5)	3633 (35.8)	6422 (37.4)	2477 (30.0)
Age, mean (SD), y	63.1 (8.6)	63.3 (8.3)	63.9 (6.8)	64.4 (8.1)
Diabetes characteristics				
HbA_{1c}, mean (SD), %	8.1 (0.8)	8.2 (0.9)	8.3 (1.2)	8.2 (1.0)
Diabetes duration, mean (SD), y	57 > 10[c]	13.5 (7.8)	11.8 (7.8)	13.0 (8.3)
Cardiovascular characteristics				
Established cardiovascular disease	7020 (100)	6656 (65.6)	6974 (40.6)	8246 (100)
History of heart failure	706 (10.1)	1461 (14.4)	1724 (10.0)	1958 (23.7)
Renal characteristics				
Reduced kidney function[d]	1819 (25.9)	2039 (20.1)	1265 (7.4)	1807 (21.9)
Urine ACR≥300 mg/g	769 (11.0)	760 (7.6)	1169 (6.8)	755 (9.2)
Cardiovascular medications				
ACEI or ARB blockade	5666 (80.7)	8116 (80.0)	13 950 (81.3)	6686 (81.1)
β-Blocker	4554 (64.9)	5421 (53.5)	9030 (52.6)	5692 (69.0)
Statin/ezetimibe	5403 (77.0)	7599 (74.9)	12 868 (75.0)	6790 (82.3)

From: JAMA Cardiol. 2021;6(2):148-158

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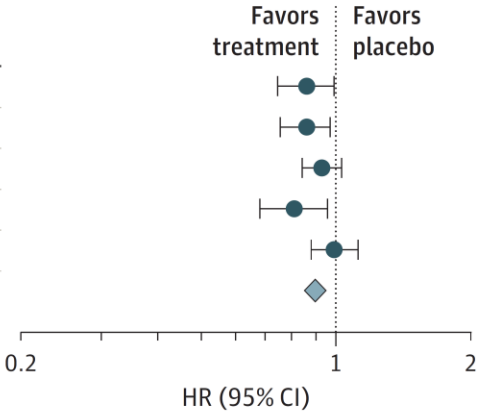
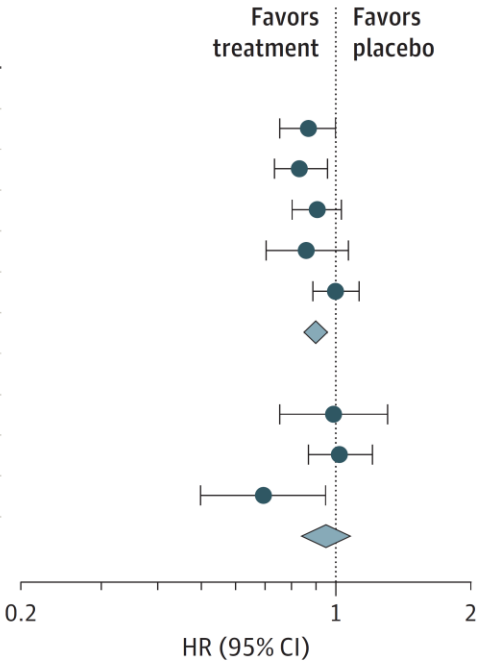
A Overall MACEs (non-fatal MI, non-fatal stroke and CV death)

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)			15.72
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)			20.12
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)			32.02
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)			10.92
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)			21.23
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)			



B MACEs by ASCVD status

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
Patients with ASCVD								
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)			19.19
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)			21.16
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)			24.90
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)			8.82
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)			25.93
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)			
Patients without ASCVD								
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)			21.70
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)			62.07
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)			16.23
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)			



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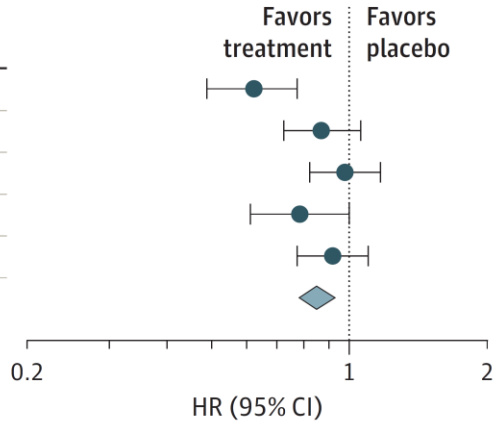
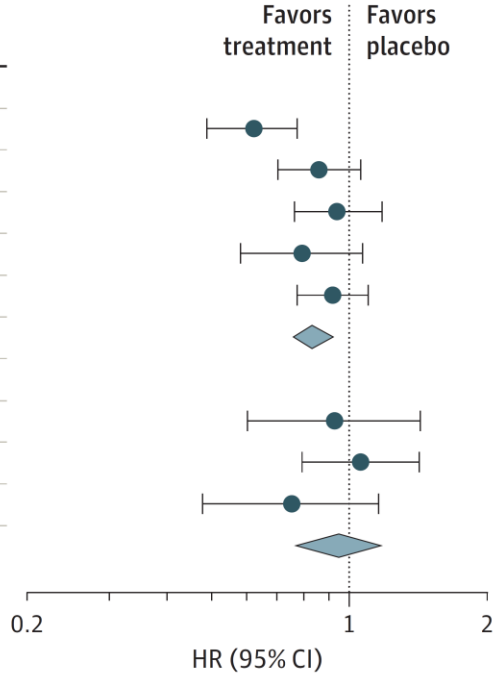
A Overall CV death

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)			15.61
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)			21.32
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)			25.24
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)			13.05
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)			24.77
Fixed-effects model (Q = 11.22; *df* = 4; *P* = .02; I^2 = 64.3%)					0.85 (0.78-0.93)			



B CV death by ASCVD status

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
Patients with ASCVD								
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)			18.61
CANVAS program	NA/3756	14.8	NA/2900	16.8	0.86 (0.70-1.06)			22.08
DECLARE-TIMI 58	153/3474	10.9	163/3500	11.6	0.94 (0.76-1.18)			19.64
CREDENCE	75/1113	25.7	93/1107	32.4	0.79 (0.58-1.07)			10.14
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)			29.52
Fixed-effects model (Q = 9.10; *df* = 4; *P* = .06; I^2 = 56.1%)					0.83 (0.76-0.92)			
Patients without ASCVD								
CANVAS program	NA/2039	6.5	NA/1447	6.2	0.93 (0.60-1.43)			24.02
DECLARE-TIMI 58	92/5108	4.4	86/5078	4.1	1.06 (0.79-1.42)			52.70
CREDENCE	35/1089	12.2	47/1092	16.4	0.75 (0.48-1.16)			23.27
Fixed-effects model (Q = 1.65; *df* = 2; *P* = .44; I^2 = 0.0%)					0.95 (0.77-1.17)			



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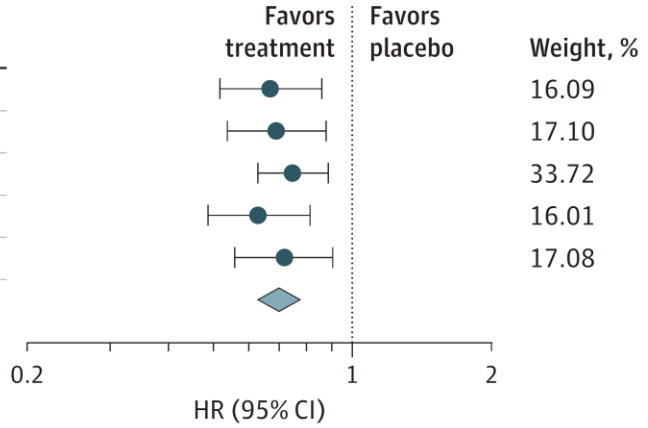
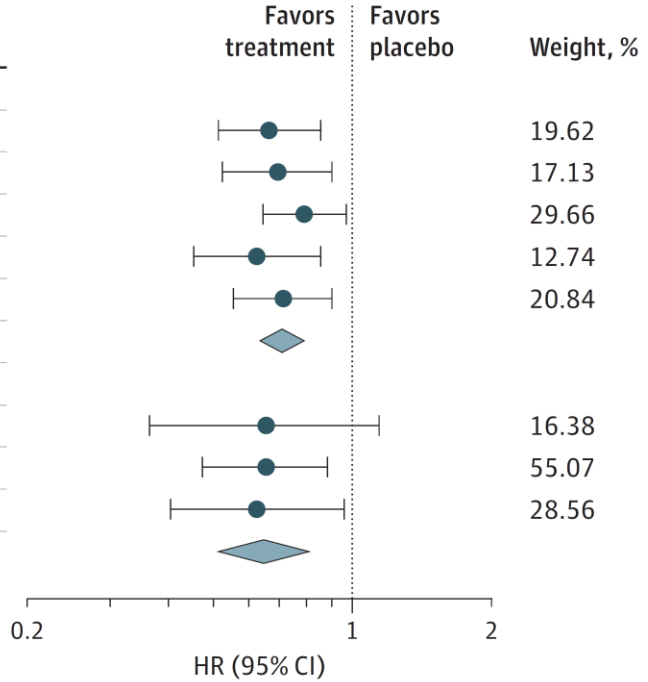
A Overall HHF

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)



B HHF by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.97; *df* = 4; *P* = .74; I^2 = 0.0%)					0.70 (0.62-0.78)
Patients without ASCVD					
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)
Fixed-effects model (Q = 0.03; *df* = 2; *P* = .99; I^2 = 0.0%)					0.63 (0.50-0.80)



SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

Faiez Zannad, João Pedro Ferreira, Stuart J Pocock, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal, Milton Packer

Lancet 2020; 396: 819–29

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76.5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

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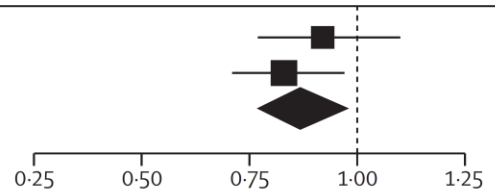
Lancet 2020; 396: 819–29

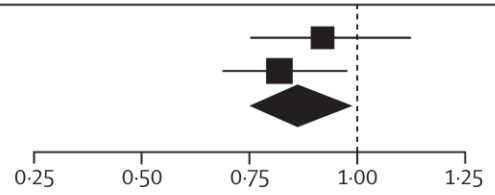
A All-cause mortality

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	249/1863 (13·4%)	266/1867 (14·2%)	0·92 (0·77–1·10)
DAPA-HF	276/2373 (11·6%)	329/2371 (13·9%)	0·83 (0·71–0·97)
Total			**0·87 (0·77–0·98)**
Test for overall treatment effect p=0·018			
Test for heterogeneity of effect p=0·39			



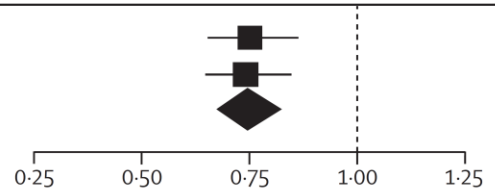
B Cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	187/1863 (10·0%)	202/1867 (10·8%)	0·92 (0·75–1·12)
DAPA-HF	227/2373 (9·6%)	273/2371 (11·5%)	0·82 (0·69–0·98)
Total			**0·86 (0·76–0·98)**
Test for overall treatment effect p=0·027			
Test for heterogeneity of effect p=0·40			



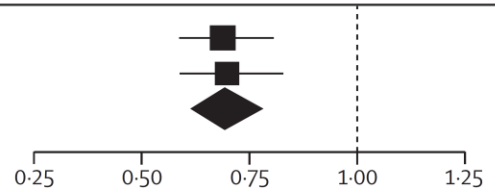
C First hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	361/1863 (19·4%)	462/1867 (24·7%)	0·75 (0·65–0·86)
DAPA-HF	386/2373 (16·3%)	502/2371 (21·2%)	0·74 (0·65–0·85)
Total			**0·74 (0·68–0·82)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·89			



D First hospitalisation for heart failure

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	246/1863 (13·2%)	342/1867 (18·3%)	0·69 (0·59–0·81)
DAPA-HF	231/2373 (9·7%)	318/2371 (13·4%)	0·70 (0·59–0·83)
Total			**0·69 (0·62–0·78)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·90			



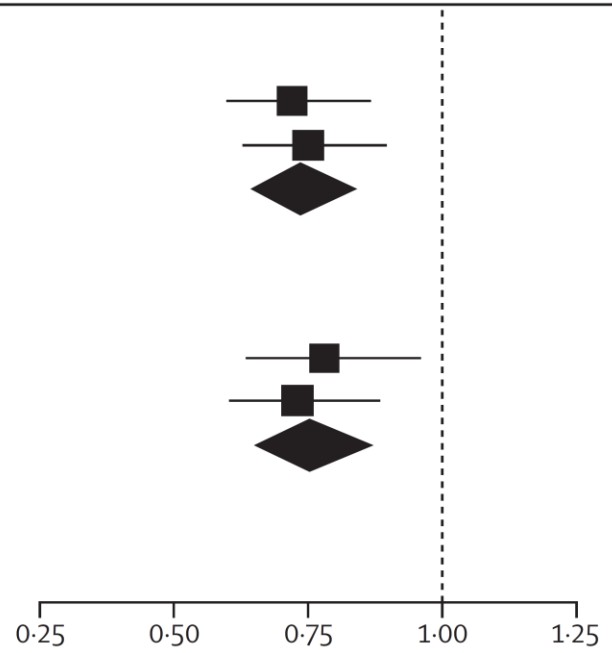
SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

Faiez Zannad, João Pedro Ferreira, Stuart J Pocock, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal, Milton Packer

Pooled treatment effects of empagliflozin and dapagliflozin on the composite of first hospitalisation for heart failure or cardiovascular death in relevant subgroups

A Diabetes status

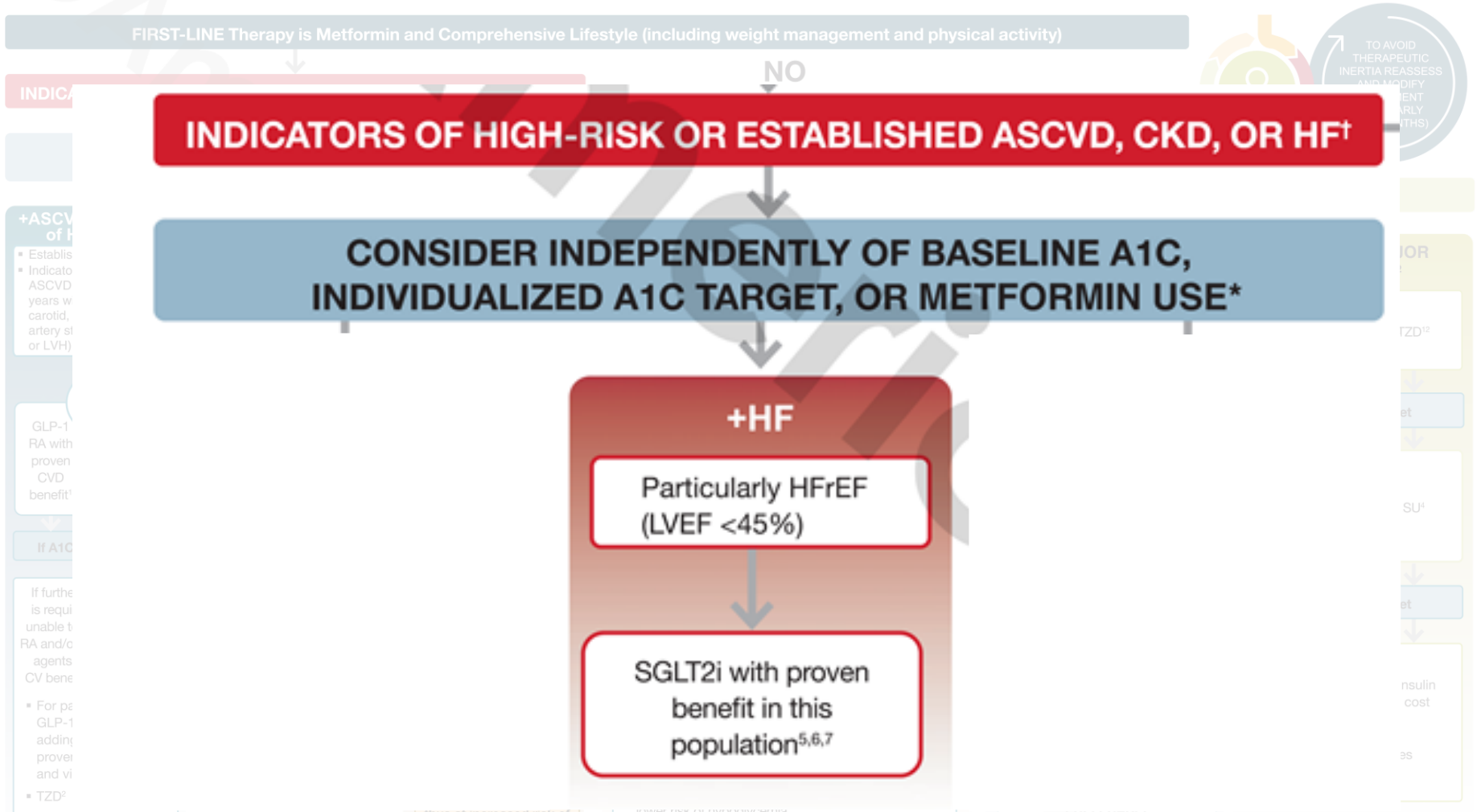
	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
With diabetes			
EMPEROR-Reduced	200/927 (21·6%)	265/929 (28·5%)	0·72 (0·60–0·87)
DAPA-HF	215/1075 (20·0%)	271/1064 (25·5%)	0·75 (0·63–0·90)
Subtotal			**0·74 (0·65–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·76			
Without diabetes			
EMPEROR-Reduced	161/936 (17·2%)	197/938 (21·0%)	0·78 (0·64–0·97)
DAPA-HF	171/1298 (13·2%)	231/1307 (17·7%)	0·73 (0·60–0·88)
Subtotal			**0·75 (0·65–0·87)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·65			
Test for treatment by subgroup interaction p=0·81			



Lancet 2020; 396: 819–29

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2021

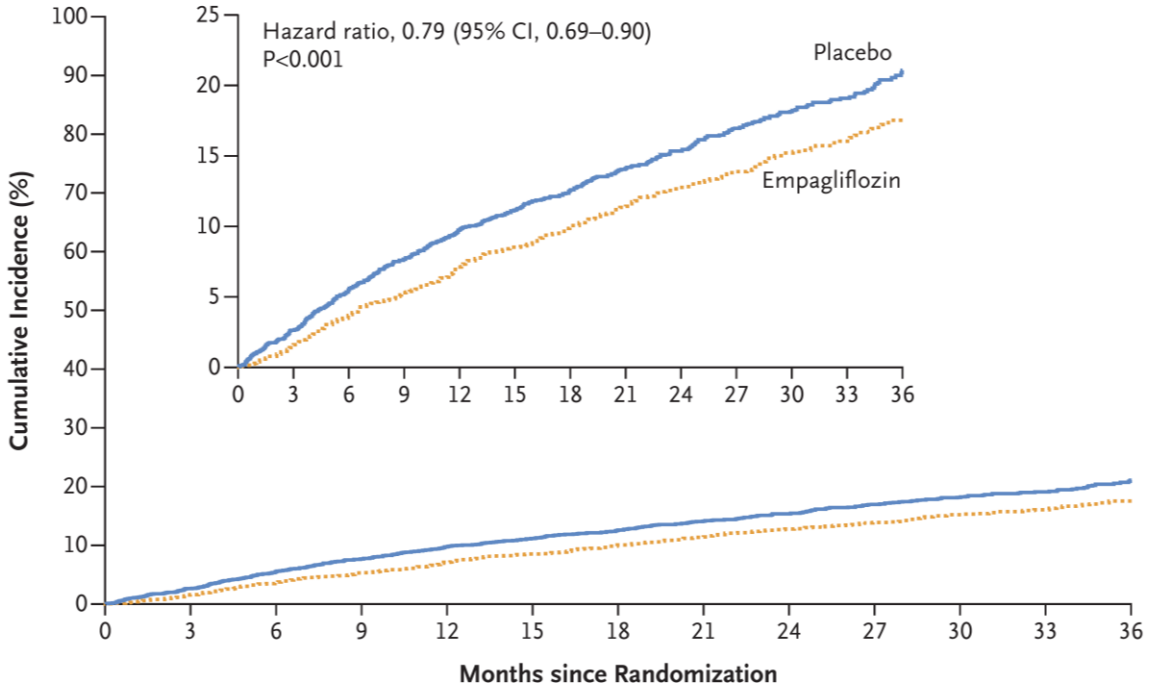


Empagliflozin in Heart Failure with a Preserved Ejection Fraction

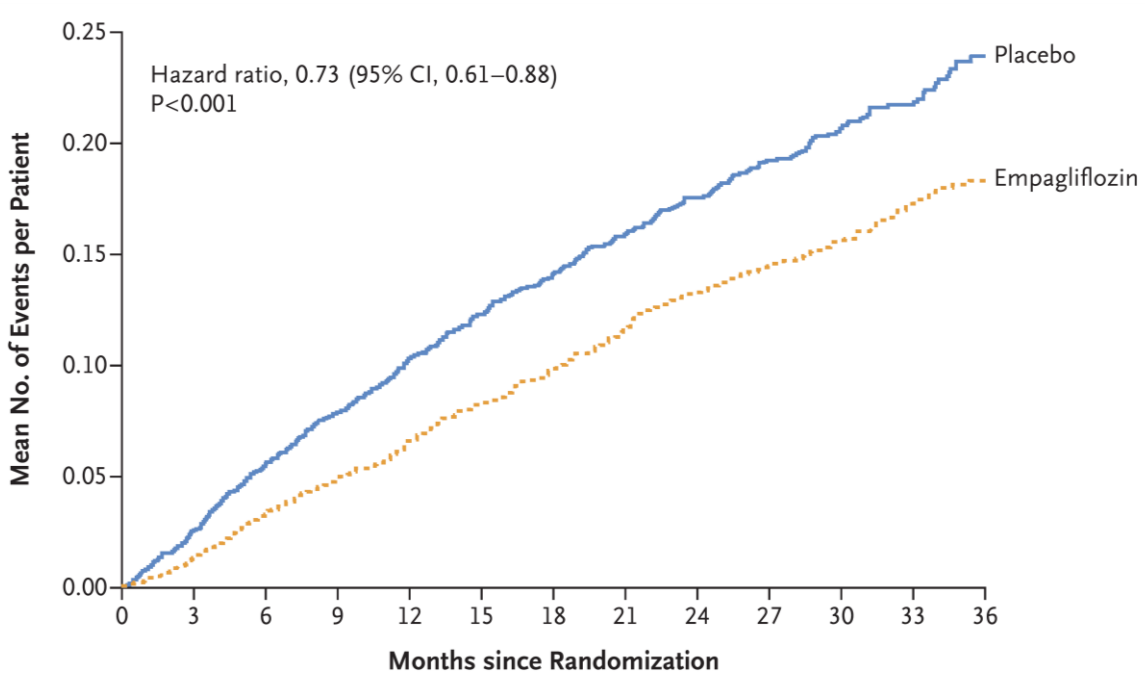
S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators®

EMPEROR-Preserved STUDY

Primary Outcome
(Cardiovascular Death or Hospitalization for Heart Failure)

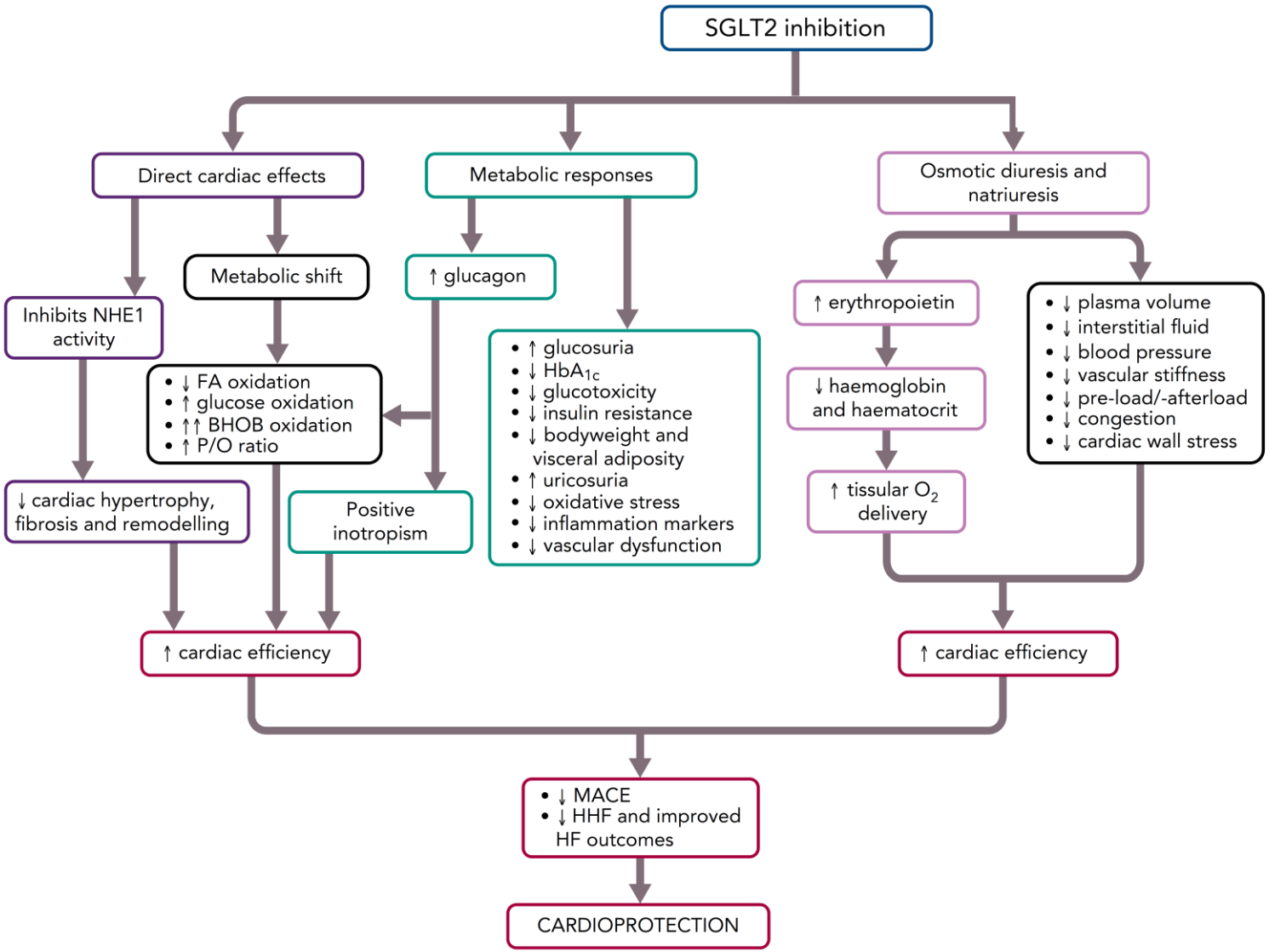


Hospitalizations for Heart Failure.



N Engl J Med. 2021 Aug 27. doi: 10.1056/NEJMoa2107038.

Potential Mechanisms Involved in the Cardioprotective and Renoprotective Effects of Sodium–glucose Cotransporter 2 Inhibitors



JAMA Cardiology | Original Investigation

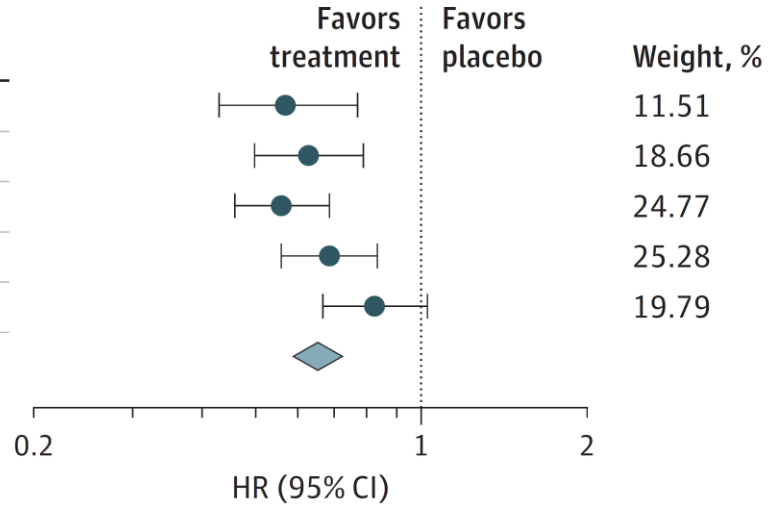
Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes

A Meta-analysis

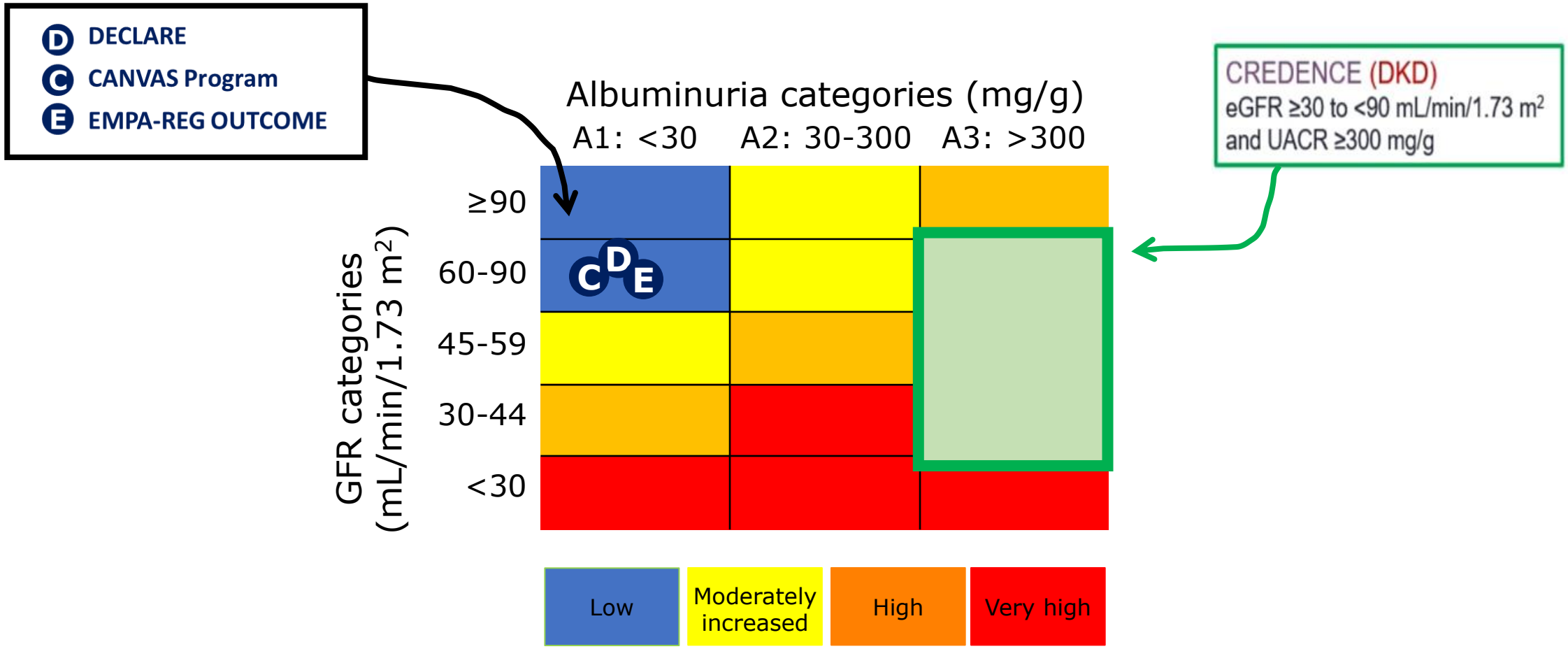
Darren K. McGuire, MD, MHSc; Weichung J. Shih, PhD; Francesco Cosentino, MD, PhD; Bernard Charbonnel, MD; David Z. I. Cherney, MD, PhD; Samuel Dagogo-Jack, MD, DSc; Richard Pratley, MD; Michelle Greenberg, BSc; Shuai Wang, PhD; Susan Huyck, DrPH; Ira Gantz, MD; Steven G. Terra, PharmD; Urszula Masiukiewicz, MD; Christopher P. Cannon, MD

A Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)



Inibitori del SGLT-2 e protezione renale

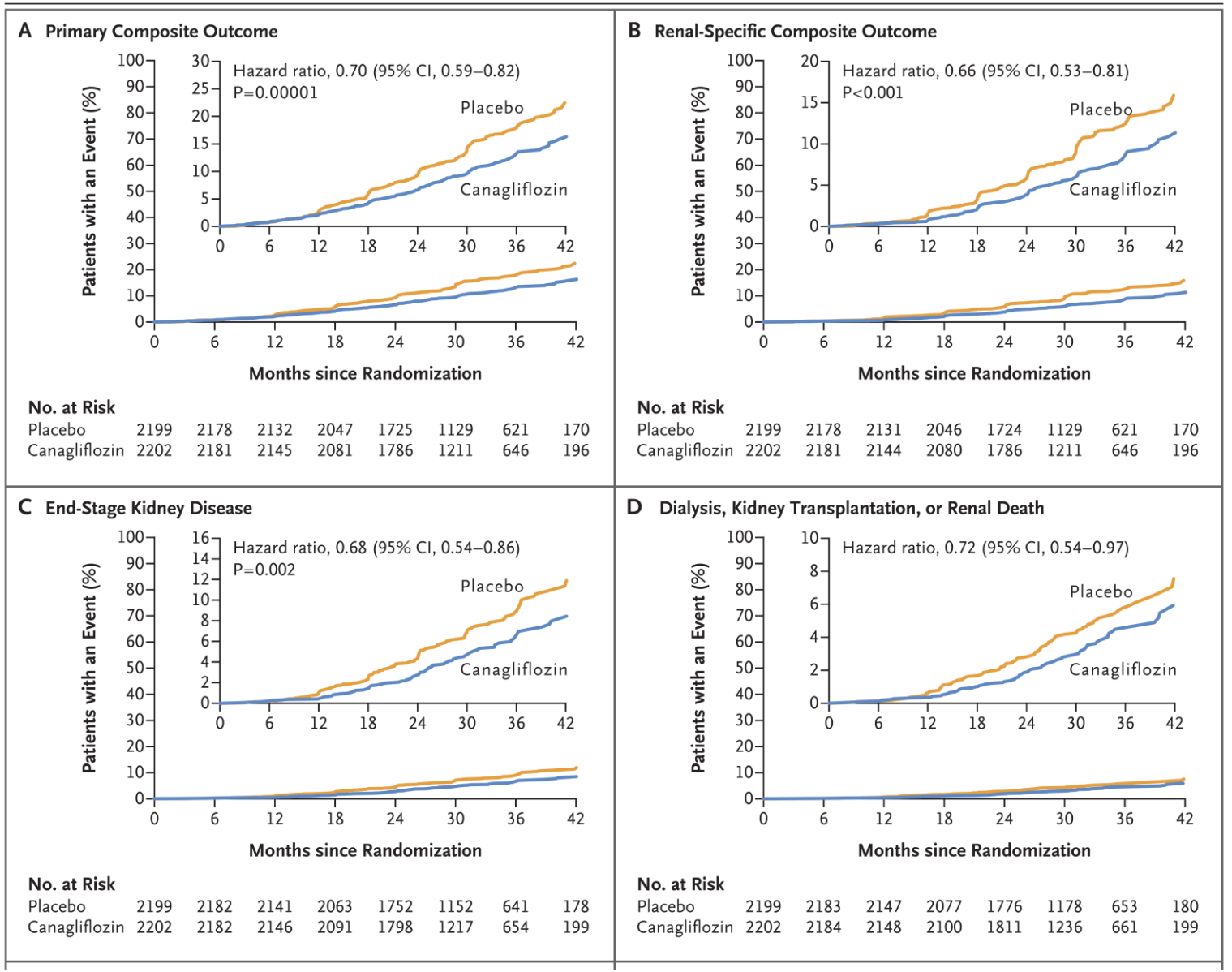


CREDENCE STUDY

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

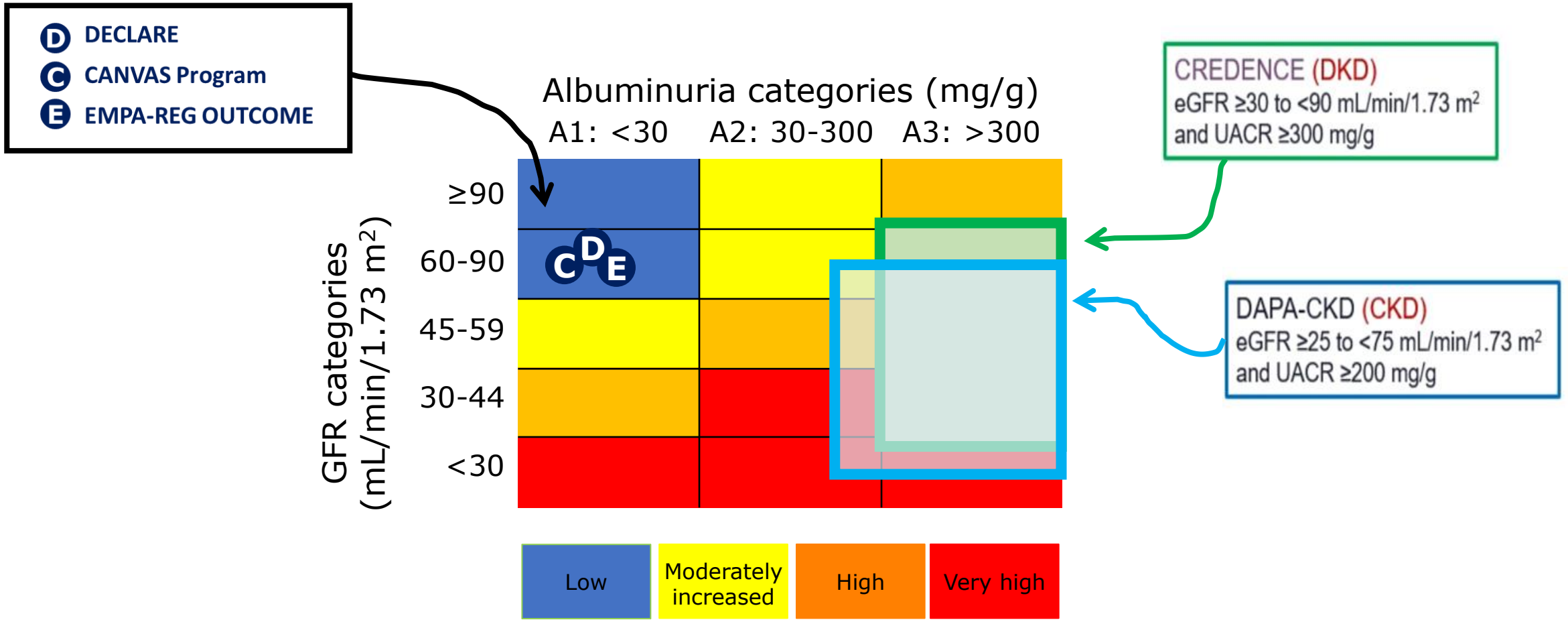
V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

Composite primary outcome:
end stage kidney disease, doubling of the serum creatinine level from baseline, or death from renal or cardiovascular disease.



N Engl J Med 2019;380:2295-306.

Inibitori del SGLT-2 e protezione renale

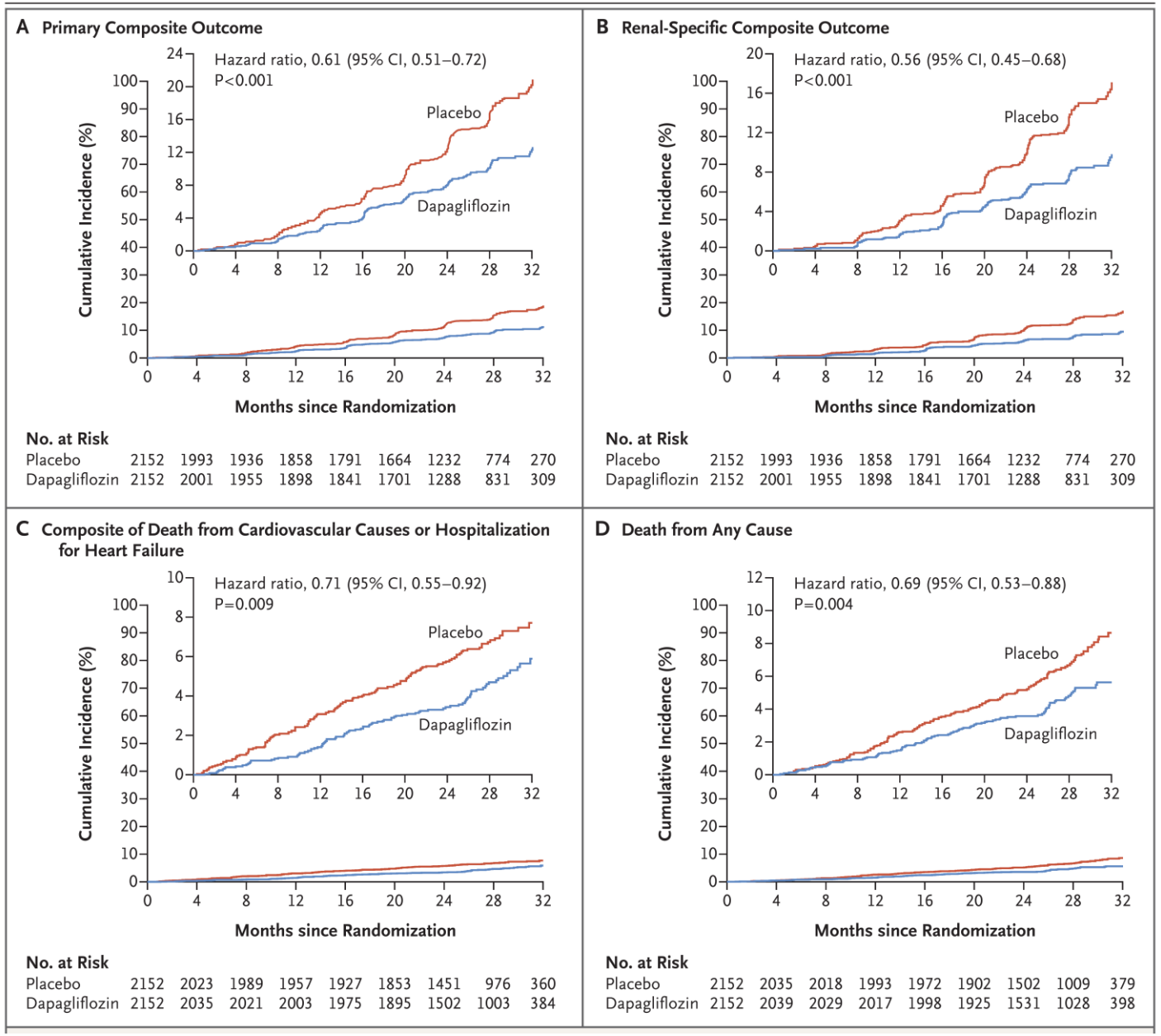


DAPA-CKD STUDY

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

Primary composite outcome:
first occurrence of any of the following: decline of at least 50% in estimated GFR, onset of end-stage kidney disease, death from renal or cardiovascular causes.



N Engl J Med 2020;383:1436-46.

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2021

ALLEGATO I

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

empaglifozin

4.1 Indicazioni terapeutiche

Diabete mellito di tipo 2

[redacted] è indicato, in aggiunta alla dieta e all'esercizio fisico, nel trattamento degli adulti con diabete mellito di tipo 2 non adeguatamente controllato:

- in monoterapia quando l'uso della metformina è considerato non appropriato a causa di intolleranza
- in aggiunta ad altri medicinali per il trattamento del diabete.

Per i risultati degli studi riguardanti le associazioni, gli effetti sul controllo della glicemia e gli eventi cardiovascolari, e le popolazioni studiate, vedere paragrafi 4.4, 4.5 e 5.1.

Insufficienza cardiaca

[redacted] è indicato negli adulti per il trattamento dell'insufficienza cardiaca cronica sintomatica con frazione di eiezione ridotta.

dapaglifozin

4.1 Indicazioni terapeutiche

Diabete mellito di Tipo 2

[redacted] è indicato in pazienti adulti non adeguatamente controllati per il trattamento del diabete mellito di tipo 2 in aggiunta alla dieta e all'esercizio

- in monoterapia quando l'uso di metformina è ritenuto inappropriato a causa di intolleranza.
- in aggiunta ad altri medicinali per il trattamento del diabete di tipo 2.

Per i risultati degli studi clinici rispetto alle associazioni con altri medicinali, agli effetti sul controllo glicemico, agli eventi cardiovascolari e renali, e alle popolazioni studiate vedere paragrafi 4.4, 4.5 e 5.1.

Diabete mellito di Tipo 1

[redacted] è indicato negli adulti nel trattamento del diabete mellito di tipo 1 non sufficientemente controllato in aggiunta all'insulina in pazienti con BMI $\geq$ 27 kg/m^2, quando l'insulina da sola non fornisce un adeguato controllo glicemico nonostante ottimizzazione della terapia insulinica.

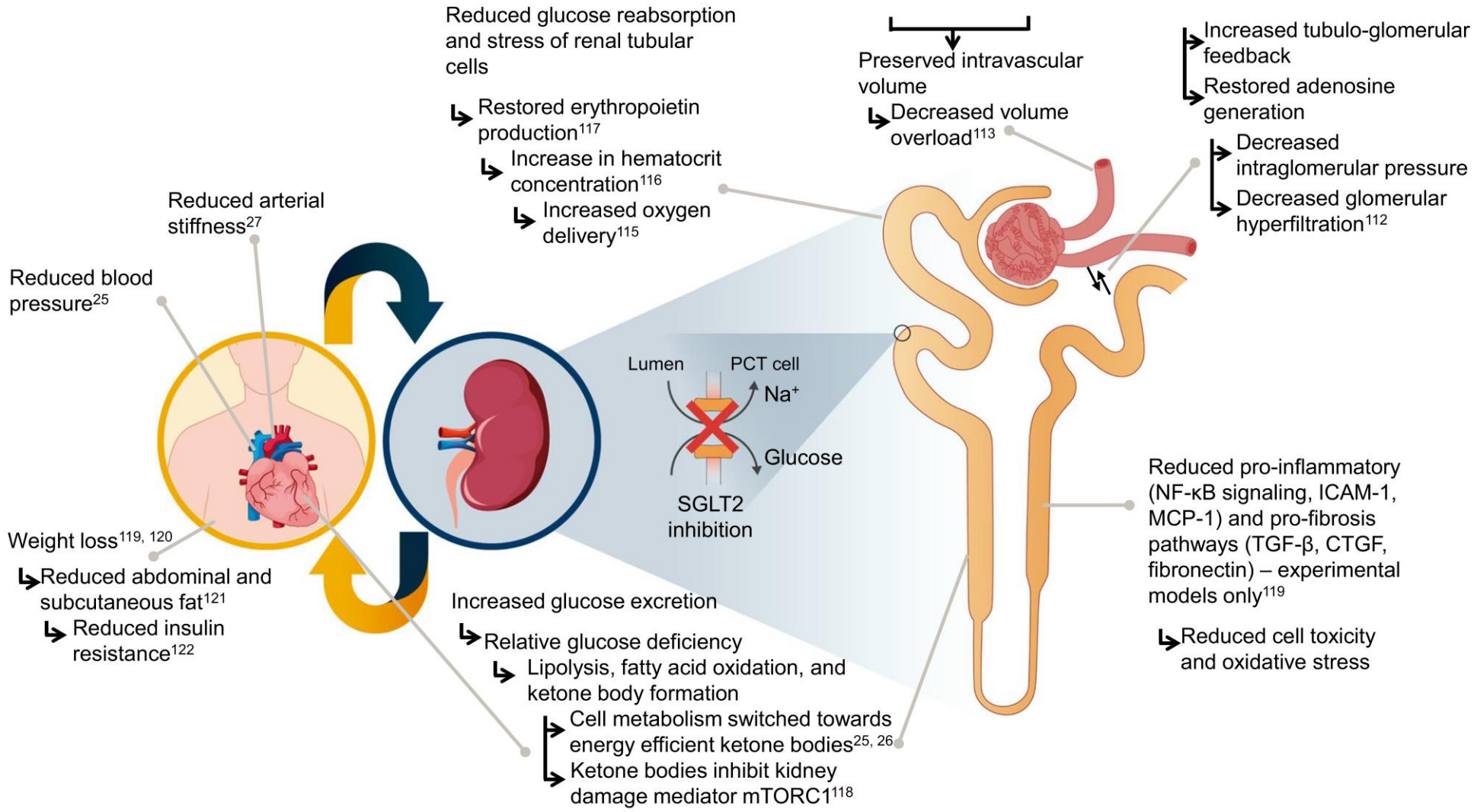
Insufficienza cardiaca

[redacted] è indicato negli adulti per il trattamento dell'insufficienza cardiaca cronica sintomatica con frazione di eiezione ridotta.

Malattia renale cronica

[redacted] è indicato, negli adulti, per il trattamento della malattia renale cronica.

Proposed renal-protective pathways with SGLT2 inhibitors



Giorgino et al. Cardiovasc Diabetol (2020) 19:196

Che cosa NON vi ho detto ?

1.

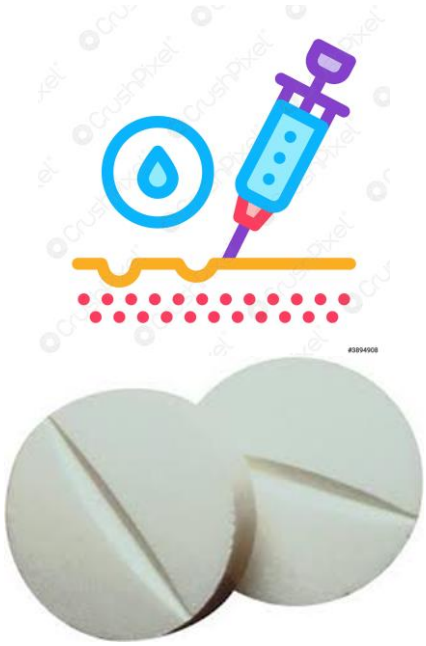
What have we learned about renal protection from the cardiovascular outcome trials and observational analyses with SGLT2 inhibitors?

Vikas S. Sridhar MD[1] | Habib U. Rahman MBBS[1] | David Z.I. Cherney MD, PhD[1,2,3]

Diabetes Obes Metab. 2020;22(Suppl. 1):55–68.

Study	Demographics	Outcomes
Nadkarni et al[67]	• Cohort 1-377 propensity matched SGLT2i users and nonusers. Mean eGFR 63.7 mL/min/1.73 m^2 in users and 60.6 mL/min/1.73 m^2 in non-users • Cohort 2-1207 SGLT2i propensity matched users and nonusers. eGFR 87.4 mL/min/1.73 m^2 in users and 87.2 mL/min/1.73 m^2 in non-users • Agents included: Canagliflozin, dapagliflozin, empagliflozin	• Cohort 1—adjusted HR for AKI_{KDIGO} 0.4 (95% CI 0.2-0.7); P = .004 • Cohort 2—adjusted HR for AKI_{KDIGO} 0.6 (95% CI 0.4-1.1); P = .09 • Trend towards less AKI with SGLT2i • When AKI occurred, severity not worse in SGLT2i users
Cahn et al[68]	N = 6418 and 5604 T2D patients who initiated SGLT2i and DPP-4i, respectively • eGFR 82.7 mL/min/1.73 m^2 in SGLT2i users, 78.1 mL/min/1.73 m^2 in DPP-4i users • 26% and 7.9% of SGLT2i users had microalbuminuria or macroalbuminuria; 23.3% and 7.5% of DPP-4i users had microalbuminuria or macroalbuminuria	• Adjusted OR for ≥30% reduction in eGFR with SGLT2i vs DPP4-i 0.70 (95% CI 0.49-1.00) • Adjusted OR of composite of AKI_{ICD}/initiating dialysis/sustained eGFR<15 0.47 (95% CI 0.27-0.80)
Dekkers et al[72]	N = 69 placebo, 58 dapagliflozin 5 mg, 93 dapagliflozin 10 mg from pooled analysis of 11 phase three RCTs involving patients with T2D and eGFR between 12 and <45 mL/min over 102 wk • Baseline eGFR in placebo, 5 and 10 mg groups were 38.4 (SD 5.7), 37.6 (SD 4.6) and 38.0 (SD 5.0) mL/min/1.73 m^2 • UACR was 52.0, 51.0 and 40.0 mg/g in the placebo, 5 and 10 mg groups	• Significant reductions in weight and blood pressure with both doses of dapagliflozin. • Dapagliflozin did not reduce HbA1c compared to placebo. • Dapagliflozin 5 and 10 mg compared with placebo reduced UACR by 47.1% (95% CI −64.8 to −20.6) and 38.4% (95%CI −57.6 to −10.3), respectively • No significant between-group differences in eGFR
Sugiyama et al[71]	N = 42 patients with T2D and CKD stages 3b-4 on SGLT2i for 1 y • Mean baseline eGFR 40.4 mL/min/1.73 m^2 • Median urine protein to creatinine ratio of 0.36 g/g creatinine in pre-treatment phase • Rates of annual decline in eGFR (−3.8 mL/min/1.73 m^2/y) in the pre-treatment 12-month period (P < .01)	• Non-significant reduction in HbA1c • Significant reductions in weight and blood pressure • Significant decrease in proteinuria with SGLT2i therapy 0.36 g/g Cr pre to 0.23 g/g Cr, P < .01 • Improvement in annual decline in eGFR with SGLT2i: −3.8 mL/min/1.73 m^2/y before SGLT2i compared to 0.1 mL/min/1.73 m^2/y after SGLT2i, P < .01
Brown et al[69]	Patients with T2D who initiated dapagliflozin from a large diabetes registry • Baseline eGFR (n = 1324 patients) 93.4 ± 16.2 mL/min/1.73 m^2 • Among 909 patients with available data, 386 patients (42.5%) had baseline UACR >2 mg/mmol	• Following 3-6 mo of therapy, decrease in HbA1c of −0.9 ± 1.3%, P < .01 • Reduction in body weight by −2.2 ± 3.1 kg, P < .01 • The proportion with uACR ≥2.0 mg/mmol was significantly reduced by 5.9% with dapagliflozin. • Small reduction in eGFR (0.5 ± 9.1 mL/min/1.73 m^2, P = .03)
Kobayashi et al[73]	n = 869 patients with T2D and CKD_{KDOQI} newly initiated on SGLT2i • Mean baseline eGFR of 77.7 ± 23.9 mL/min/1.73 m^2 • Baseline proteinuria (in subgroup of 786 patients) of 47.1 mg/g	• Mean duration of treatment of 13 mo • Reduction in body weight (P < .01) • Decline in median uACR from 47.1 to 41.1 mg/g creatinine with treatment (P < .01) • Fall in eGFR from 77.7 ± 23.9 to 75.0 ± 23.9 mL/min/1.73 m^2 (P < .01)
DARWIN-T2D[74]	n = 473 patients treated with dapagliflozin vs 2973 treated with a comparator, drawn from patients visiting 46 outpatient diabetes clinics. • Baseline eGFR of 87.8 ± 16.4 mL/min/1.73 m^2 in dapagliflozin users vs 79.5 ± 18.7 mL/min/1.73 m^2 in comparators • Baseline albumin excretion rate of 104.9 ± 342.7 mg/g in dapagliflozin users vs 76.2 ± 261.3 mg/g in comparators	• Approximate duration of therapy 6 mo • Among 273 dapagliflozin users and 1380 comparators with available data, there was a 37% reduction in albumin excretion with dapagliflozin (P < .001). There was no reduction in comparators. • Among 393 dapagliflozin users and 2277 comparators with available data, eGFR decreased by 1.1 mL/min/1.73 m^2 (P = .049) during treatment with dapagliflozin. During therapy with a comparator, eGFR fell by 0.6 mL/min/1.73 m^2 (P = .35)
EXSCEL—Exploratory placebo-arm analysis[75]	N = 709 SGLT2i users and 709 propensity matched non-users, all with T2D • Baseline eGFR of 79.2 (21.6) mL/min/1.73 m^2 in SGLT2 users (22% patients with eGFR<60 and 7.1% with eGFR<45) vs 80.1 (21.3) mL/min/1.73 m^2 in non-users (17% patients with eGFR<60 and 2.5% with eGFR<45) • UACR 1.8 (51.4) g/mol in SGLT2i users (20% and 5.5% with microalbuminuria and macroalbuminuria) and 1.7 (45.9) g/mol in non-users (20% and 5.2% with microalbuminuria and macroalbuminuria)	• Median exposure to SGLT2i was 9.2 mo • Using a mixed-model repeated-measures analysis, the estimated increase in eGFR for SGLT2i users was +0.87 (SE 0.37) mL/min/1.73 m^2/y compared with a decrease of −0.91 (SE 0.26) mL/min/1.73 m^2/y in non-users
Zhou et al[76]	N = 990 T2D patients prescribed SGLT2i and 4257 patients prescribed DPP-4i • Baseline eGFR of 76 vs 65.7 mL/min/1.73 m^2 in SGLT2i group vs DPP-4i group • Patients followed for between 9 and 15 mo after first prescription of an SGLT2i or DPP-4i	• SGLT2i users more likely to have preservation of renal function compared to DPP-4i users (adjusted OR 1.27 CI 1.05-1.53, P = .0116, c-statistic = 0.89) • Patient subgroups with greater renal function preservation with SGLT2i compared to DPP-4i: absence of hyperlipidaemia and eGFR ≥79 mL/min/1.73 m^2; eGFR ≥79 mL/min/1.73 m^2 and diabetes duration ≤1.2 y; eGFR ≥75 mL/min/1.73 m^2 and use of antithrombotic agents; and haemoglobin ≤13.4 g/dL and LDL cholesterol ≥95.1 mg/dL

Gli analoghi del GLP-1



+

Gli inibitori del SGLT-2

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2021

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

NO

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

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

EITHER/OR

If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa[1]
- TZD[2]
- DPP-4i if not on GLP-1 RA
- Basal insulin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

+CKD

DKD and Albuminuria[8]

NO

For patients with T2D and CKD[8] (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events

EITHER/OR

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i			TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[9]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/OR

If A1C above target

If A1C above target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU[4] • TZD[2] • Basal insulin

COST IS A MAJOR ISSUE[11,12]

SU[4]	TZD[12]
If A1C above target	
TZD[12]	SU[4]

If A1C above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or **U-100** glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine **U-300** < glargine **U-100** / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

*** Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.**

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REVIEW

Cardiorenal Protection: Potential of SGLT2 Inhibitors and GLP-1 Receptor Agonists in the Treatment of Type 2 Diabetes

Taichi Nagahisa · Yoshifumi Saisho

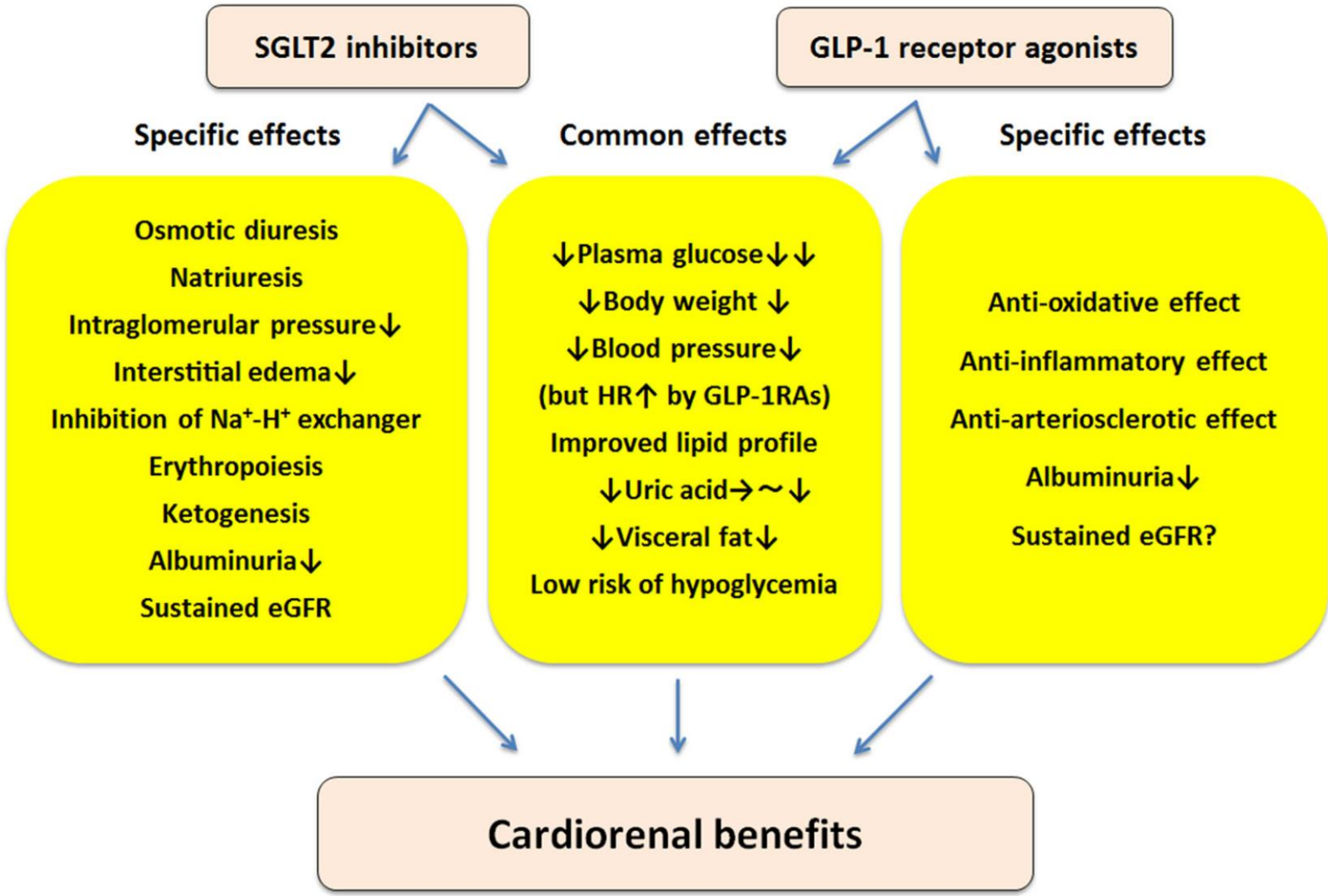
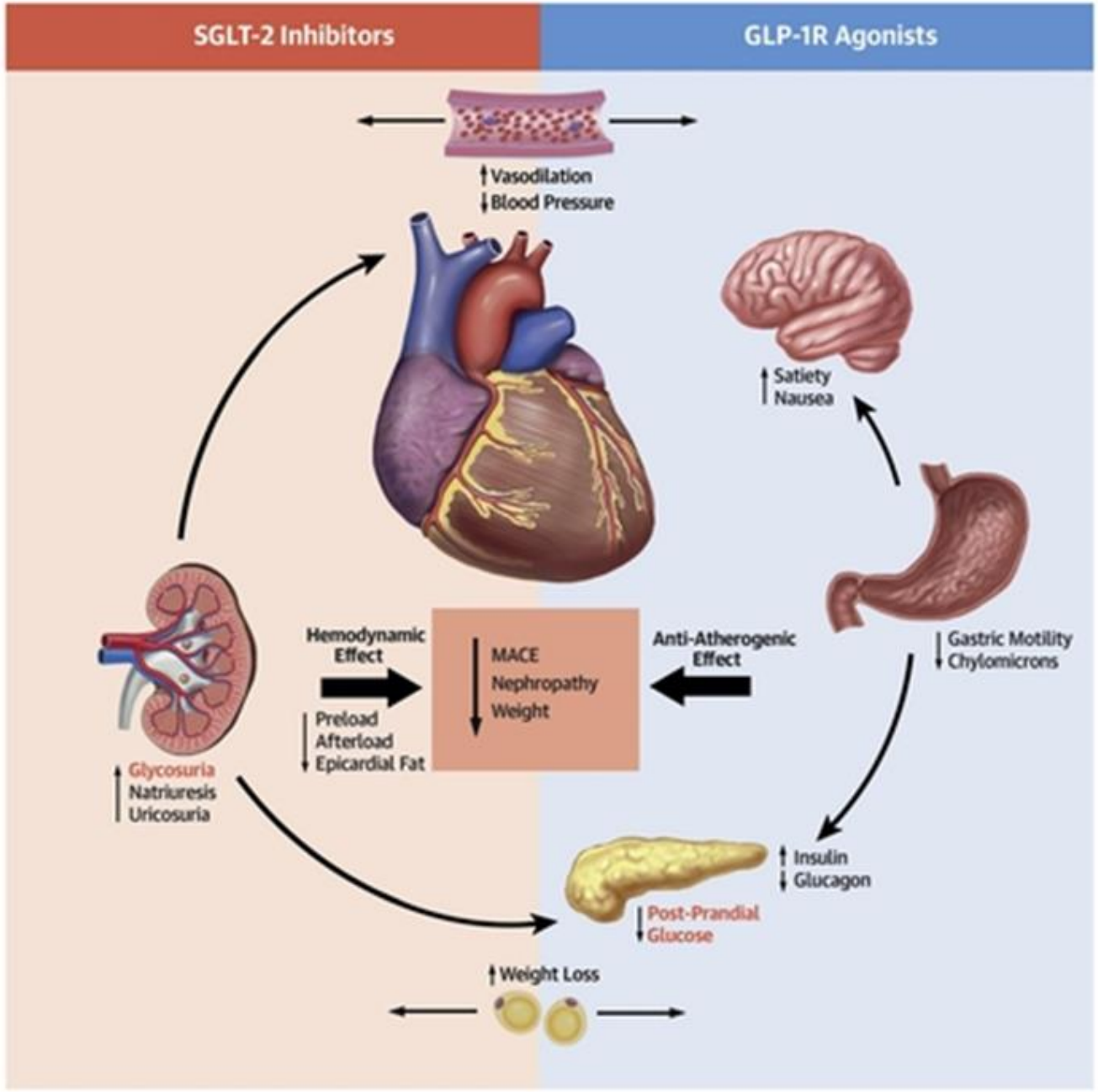


Fig. 1 Proposed key mechanisms of cardiorenal protection by sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with type 2 diabetes and cardiovascular disease. eGFR Estimated glomerular filtration rate, HR heart rate

Conclusioni



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