Gestione del PAZIENTE DIABETICO DI TIPO 2 in MEDICINA GENERALE: dal concetto di COMPETENZA all'AUDIT CLINICO

Protezione cardiorenale nel paziente diabetico tipo 2: dalle evidenze alla pratica clinica

SIMG COLLEGE
LIFELONG - LIFEWIDE LEARNING
Take the next step in your family medicine career

SIMG
SOCIETÀ ITALIANA DI MEDICINA GENERALE E DELLE CURE PRIMARIE

SIMG ALTA FORMAZIONE

SIMGLab
SIMULATION LABORATORY

Type 2 Diabetes: Treatment Goals

- Achieve HbA1c Targets

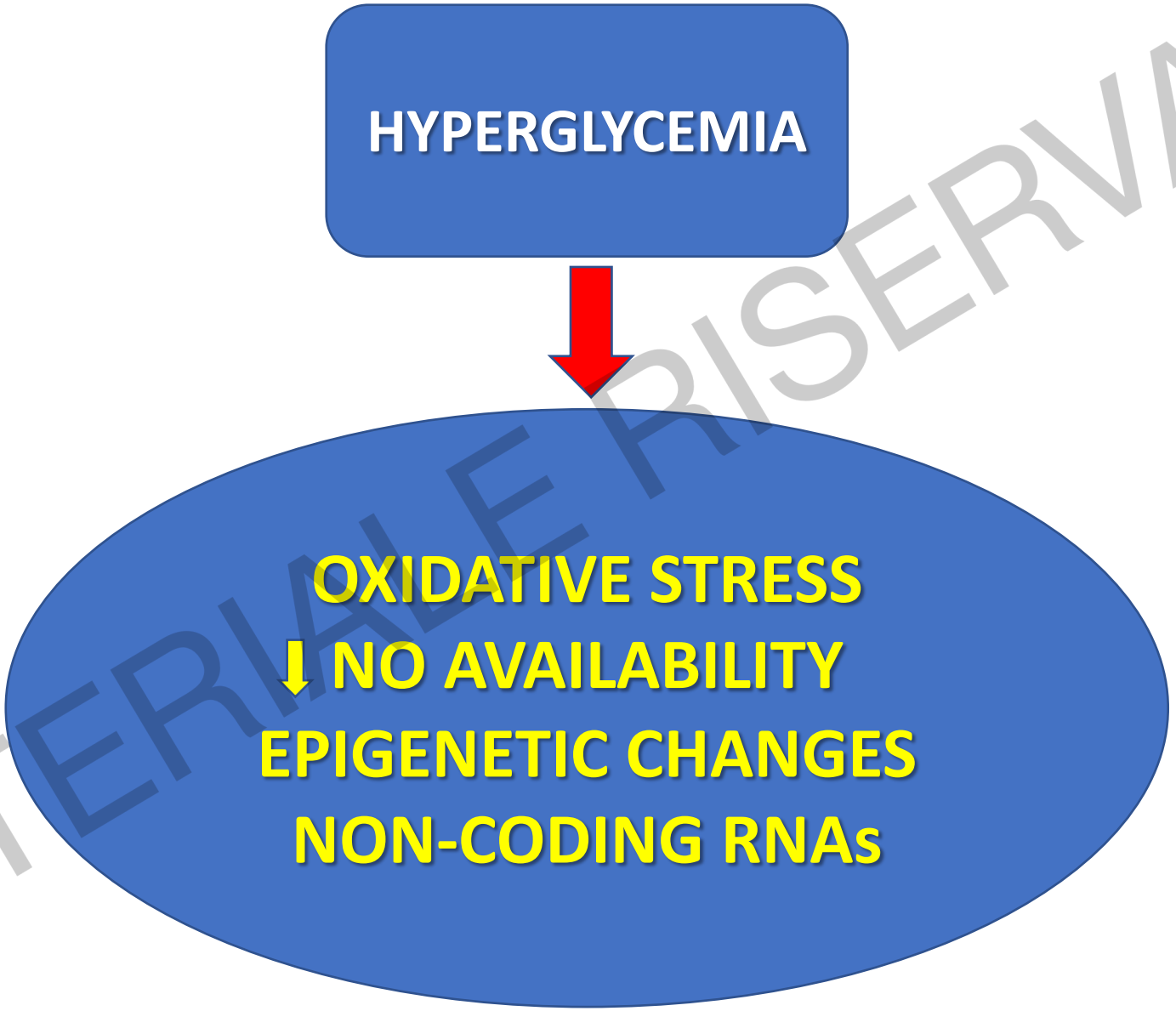
- Achieve a Composit Target:
  - ✓Target HbA1, no Hypoglycemia, no Weight Gain

- Prevent/delay macro- and micro-vascular complications

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies,[1,2] David A. D'Alessio,[3] Judith Fradkin,[4] Walter N. Kernan,[5] Chantal Mathieu,[6] Geltrude Mingrone,[7,8] Peter Rossing,[9,10] Apostolos Tsapas,[11] Deborah J. Wexler,[12,13] and John B. Buse[14]

Diabetes Care Publish Ahead of Print, published online October 4, 2018



Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

La terapia del diabete mellito di tipo 2

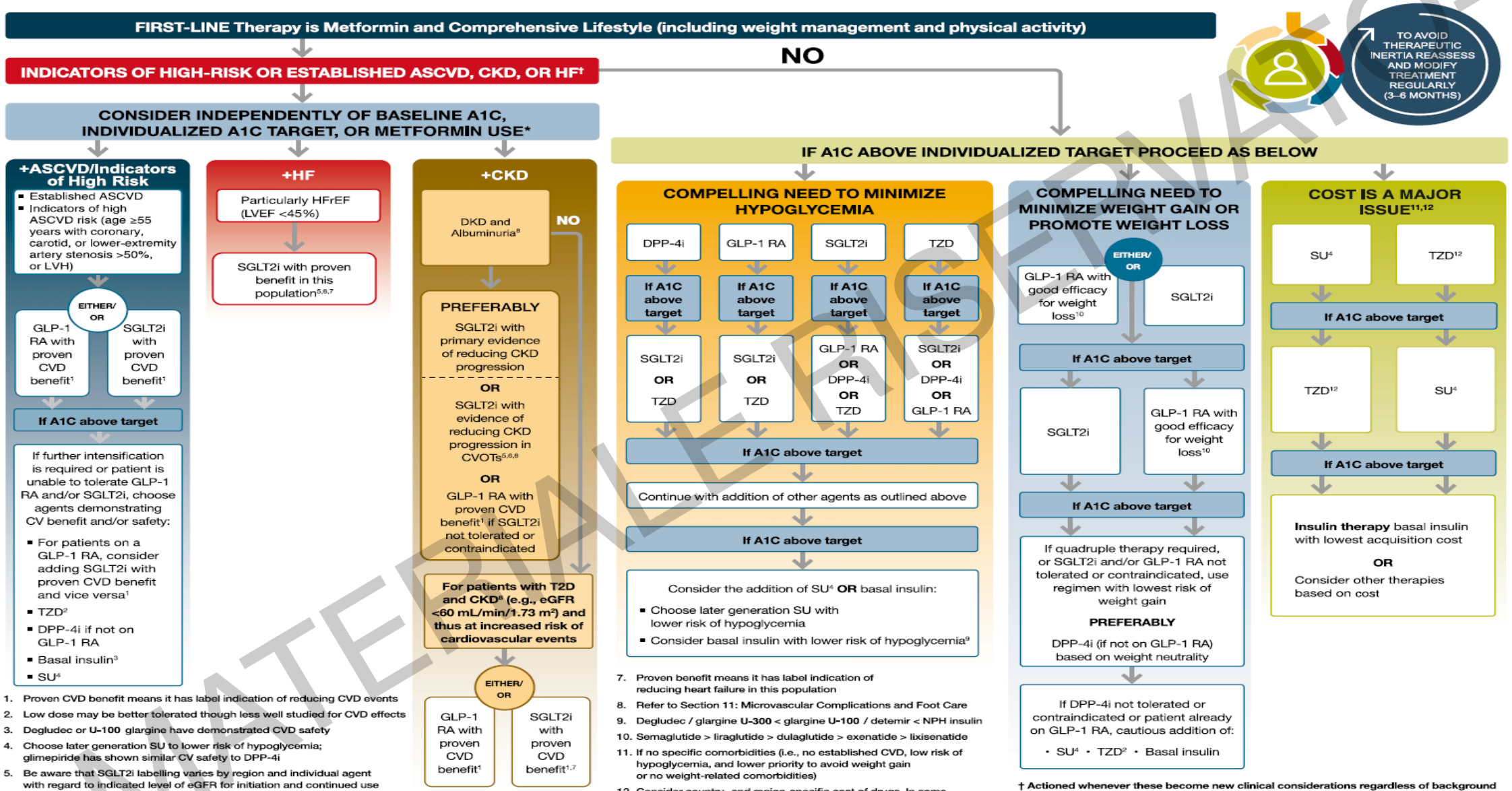
1.2.1. Si raccomanda un target di HbA1c inferiore 53 mmol/mol (7%) in pazienti con diabete di tipo 2 trattati con farmaci non inducenti ipoglicemia.

1.2.2. Si suggerisce un target di HbA1c inferiore o uguale a 48 mmol/mol (6.5%) in pazienti con diabete di tipo 2 trattati con farmaci non associati ad ipoglicemia.

Characteristics of the "ideal" diabetes drug

- **EFFICACY** *
- **«EASINESS»** *
  - Easy administration
  - No need for titration
- **TOLERABILITY** *
  - Very Little Side Effects
- **SAFETY** *
  - No hypoglycemia risk
  - No weight gain
  - No documentable serious adverse effects on any organ or apparatus

- **DOCUMENTED POSITIVE EFFECTS ON DIABETES COMPLICATIONS**



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.

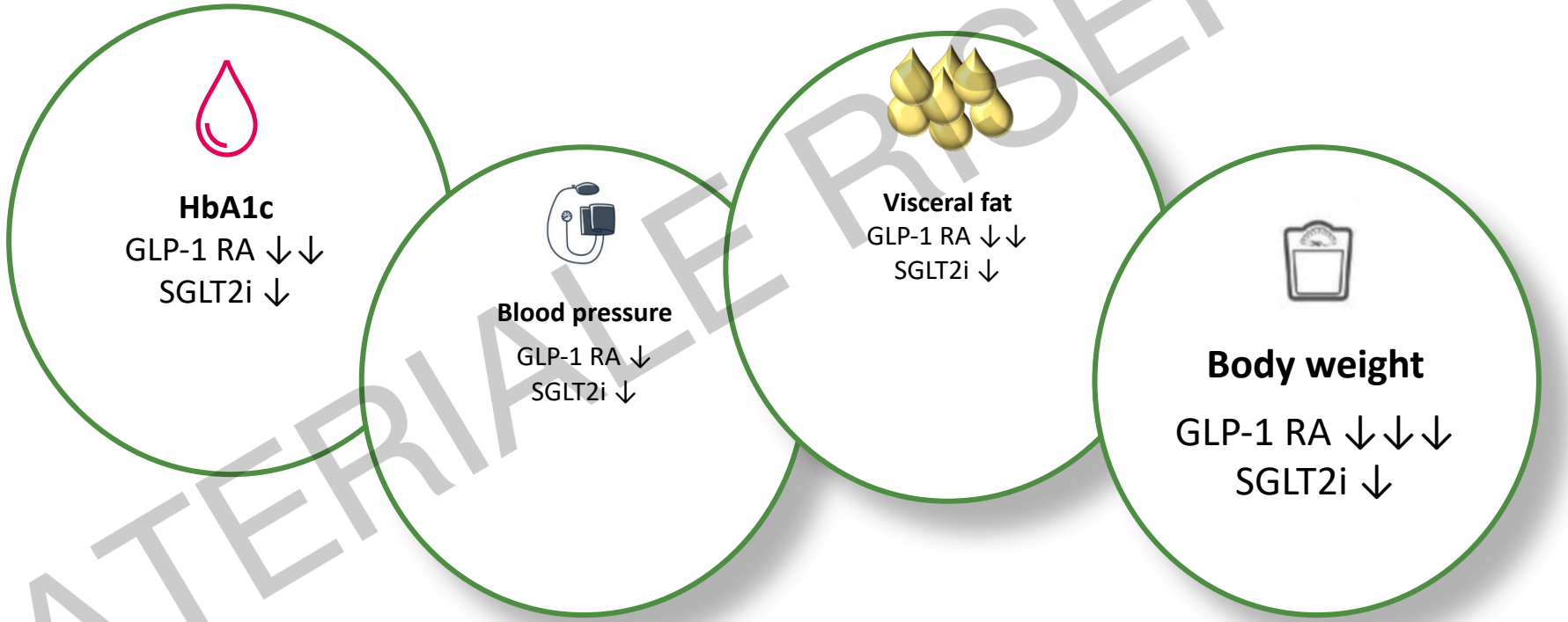
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

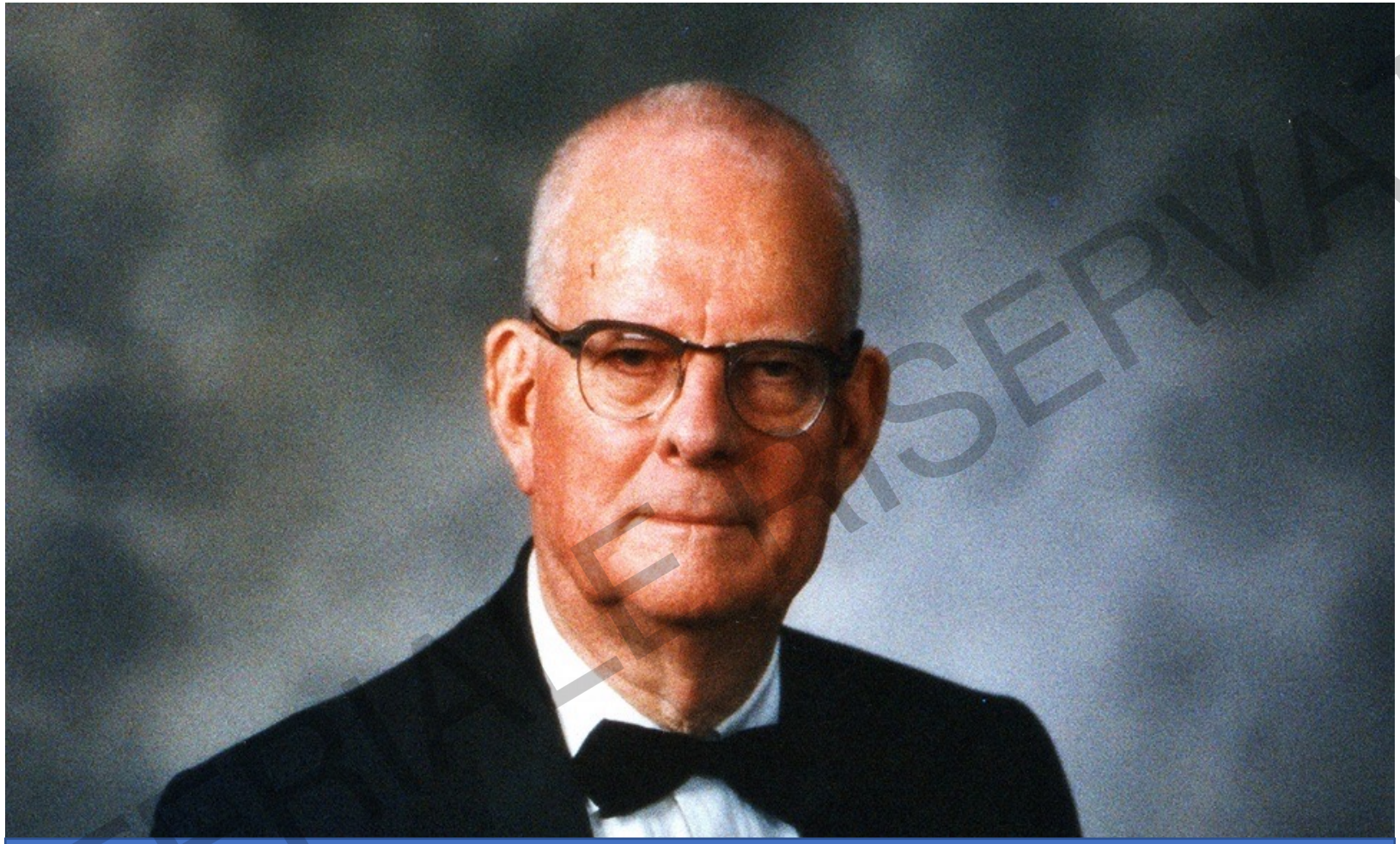
Diabetes Care 2021;44(Suppl. 1):S111–S124

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

Metabolic effects of GLP-1 RA and SGLT2 inhib



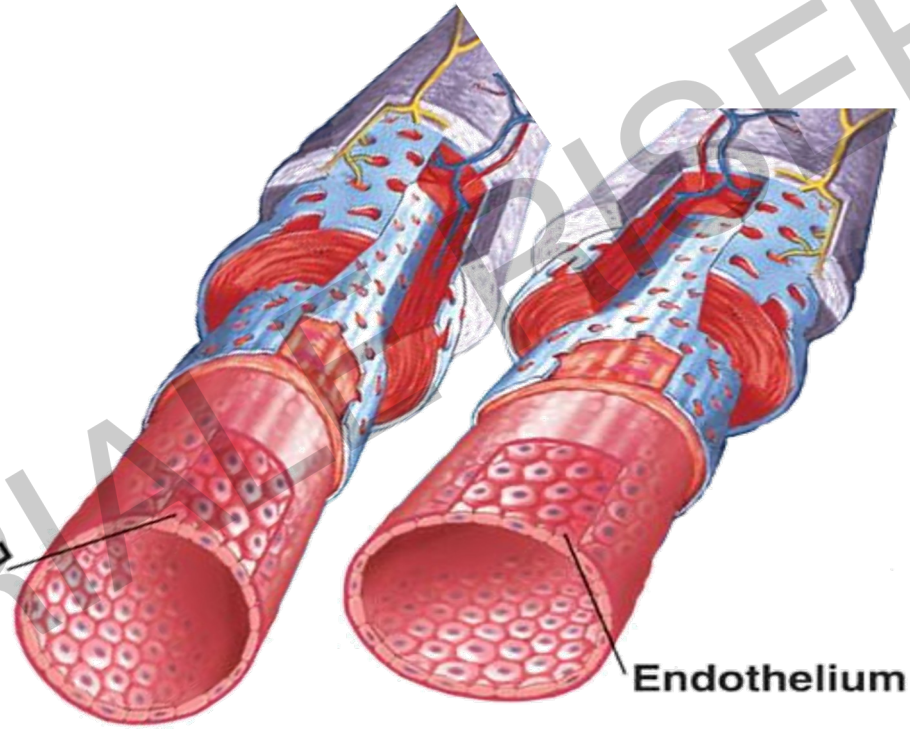


IN GOD WE TRUST
ALL OTHERS MUST SHOW DATA

W.E. Demings

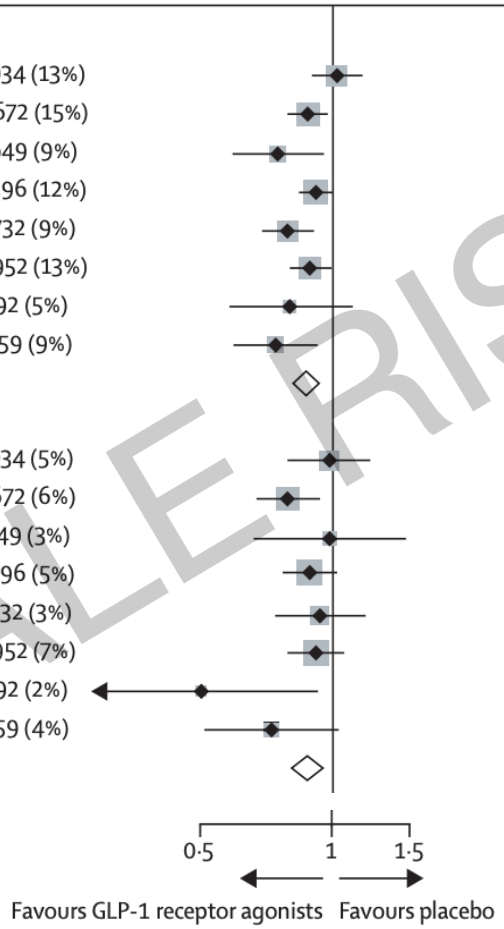
GLP-1 RAs

MACE



GLP-1, MACE e Morte CV

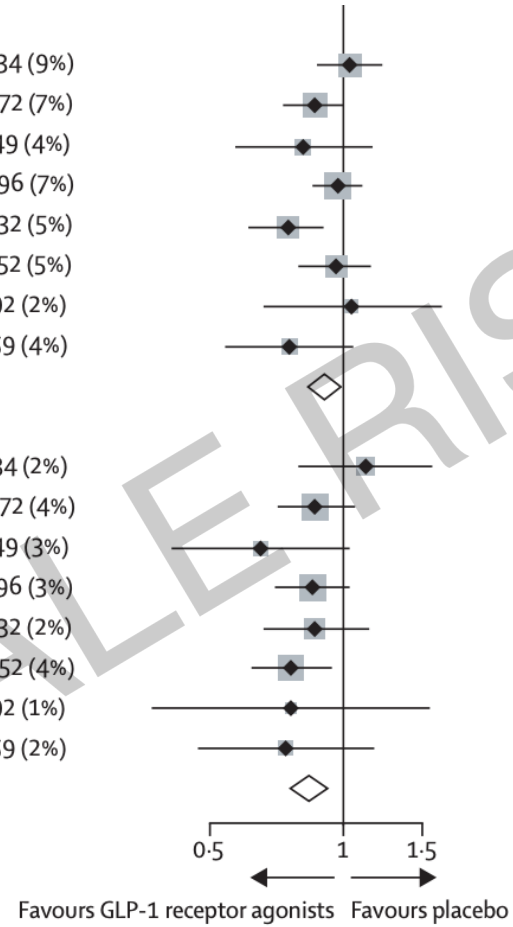
	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I^2=13·4%, p=0·33)			**0·87 (0·80–0·94)**	**163 (103–353)**	**0·0010**



Sattar et al. 2021

GLP-1, Infarto non fatale e stroke

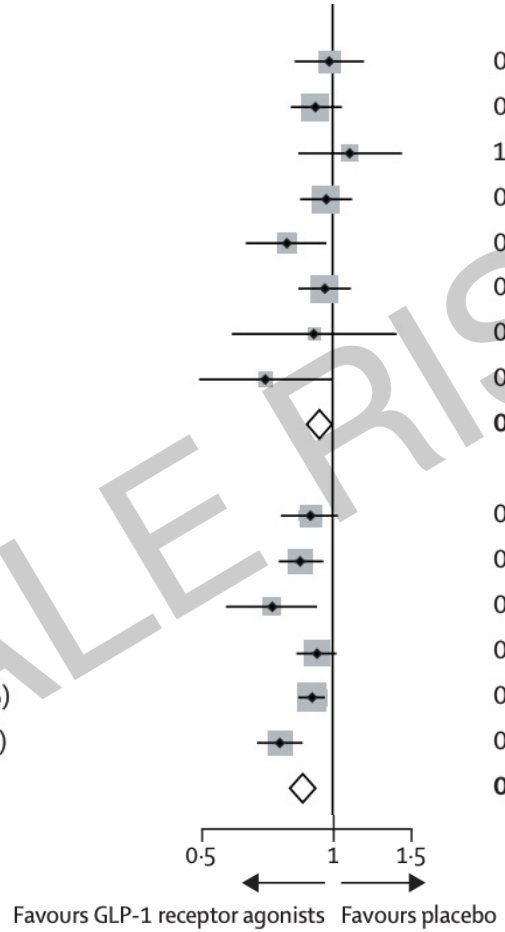
Fatal or non-fatal myocardial infarction					
ELIXA	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)		0·71
LEADER	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)		0·046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)		0·26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)		0·62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I^2=26·9%, p=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I^2=0·0%, p=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**



Sattar et al. 2021

GLP-1RA, Ospedalizzazione per infarto e CKD

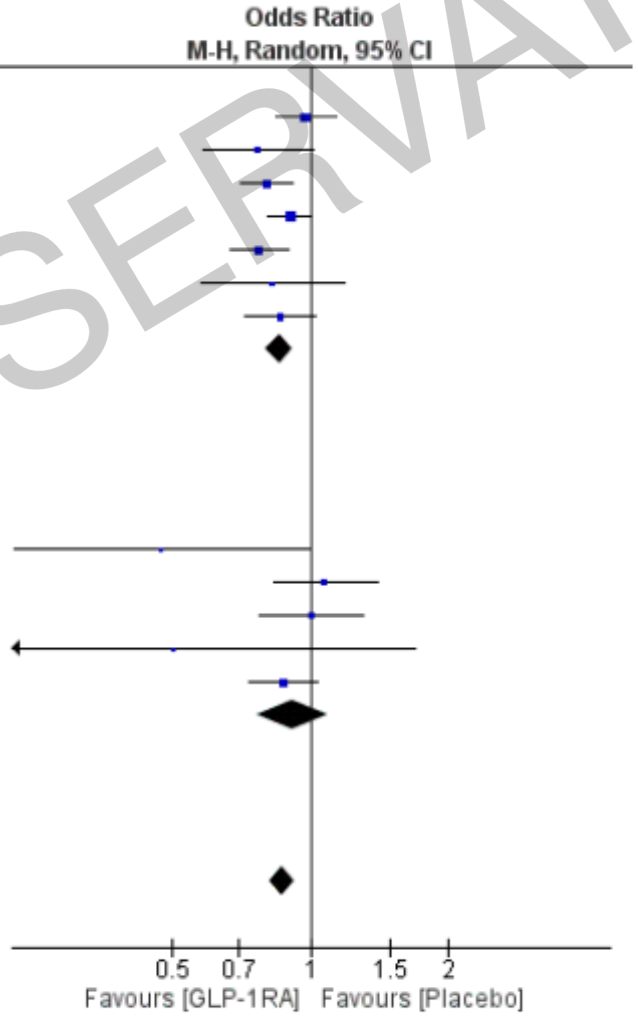
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75 to 1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73 to 1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77 to 1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78 to 1·13)		0·49
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53 to 0·94)		0·019
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77 to 1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48 to 1·55)		0·59
AMPLITUDE-O	40/2717 (1%)	31/1359 (2%)	0·61 (0·38 to 0·98)		0·04
Subtotal (I^2=3·0%, p=0·41)			**0·89 (0·82 to 0·98)**	**258 (158 to 1422)**	**0·013**
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68 to 1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67 to 0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46 to 0·88)		0·005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76 to 1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77 to 0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0·68 (0·57 to 0·79)		<0·0001
Subtotal (I^2=47·5%, p=0·090)			**0·79 (0·73 to 0·87)**	**47 (37 to 77)**	**<0·0001**



Sattar et al. 2021

Meta-analysis of GLP-1RA Trials on the Composite of MI, Stroke, and CV Death by the Presence of ASCVD

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
11.1.1 Established CVD							
ELIXA	389	3034	397	3034	12.8%	0.98 [0.84, 1.13]	2015
SUSTAIN-6	97	1262	124	1271	4.9%	0.77 [0.58, 1.02]	2016
LEADER	480	3403	571	3372	15.0%	0.81 [0.71, 0.92]	2016
EXSCEL	722	5394	786	5388	18.6%	0.90 [0.81, 1.01]	2017
HARMONY OUTCOMES	338	4731	428	4732	12.9%	0.77 [0.67, 0.90]	2018
PIONEER-6	57	1350	68	1345	3.1%	0.83 [0.58, 1.19]	2019
REWIND	280	1560	315	1554	10.0%	0.86 [0.72, 1.03]	2019
Subtotal (95% CI)		**20734**		**20696**	**77.3%**	**0.86 [0.80, 0.92]**	
Total events	2363		2689				
Heterogeneity: Tau² = 0.00; Chi² = 7.15, df = 6 (P = 0.31); I² = 16%							
Test for overall effect: Z = 4.52 (P < 0.00001)							
11.1.2 Multiple risk factors							
SUSTAIN-6	11	386	22	378	0.8%	0.47 [0.23, 0.99]	2016
LEADER	128	1265	123	1300	5.5%	1.08 [0.83, 1.40]	2016
EXSCEL	117	1962	119	2008	5.4%	1.01 [0.77, 1.31]	2017
PIONEER-6	4	241	8	247	0.3%	0.50 [0.15, 1.70]	2019
REWIND	277	3093	317	3128	10.8%	0.87 [0.74, 1.03]	2019
Subtotal (95% CI)		**6947**		**7061**	**22.7%**	**0.92 [0.77, 1.10]**	
Total events	537		589				
Heterogeneity: Tau² = 0.01; Chi² = 6.27, df = 4 (P = 0.18); I² = 36%							
Test for overall effect: Z = 0.95 (P = 0.34)							
Total (95% CI)		**27681**		**27757**	**100.0%**	**0.87 [0.81, 0.93]**	
Total events	2900		3278				
Heterogeneity: Tau² = 0.00; Chi² = 14.45, df = 11 (P = 0.21); I² = 24%							
Test for overall effect: Z = 4.13 (P < 0.0001)							
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.50), I² = 0%							



Mannucci E et al, Diabetes Obes Metab. 2020

SGLT2 inhib

MACE

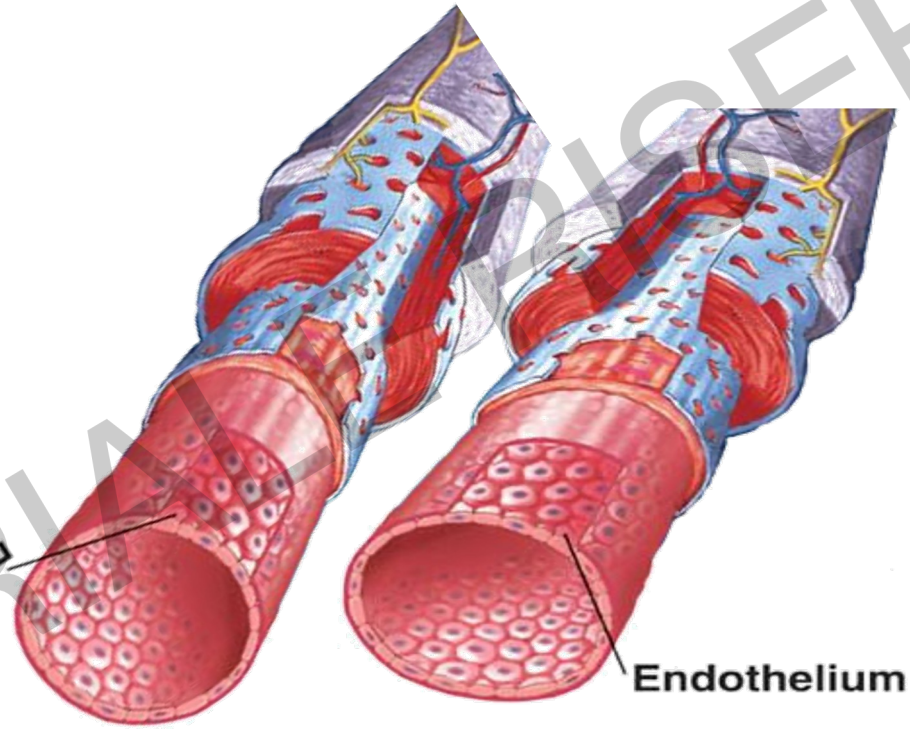
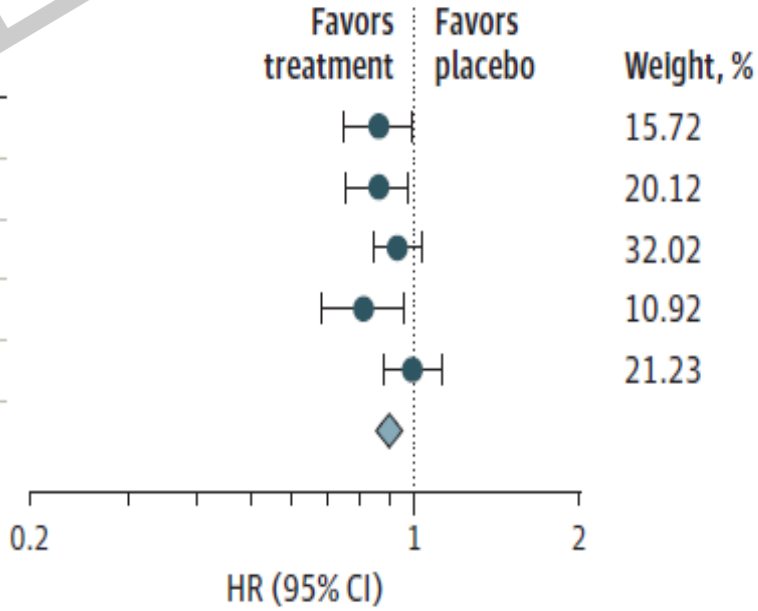


Figure 1. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events–Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

A Overall MACEs

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

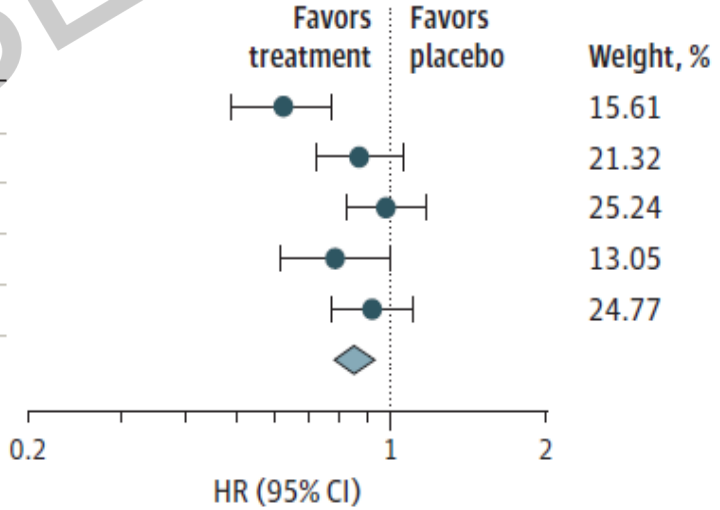


Mc Guire et al., *JAMACardiol*. 2021;6(2):148-158

Figure 2. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular Death

A Overall CV death

	Treatment		Placebo		Hazard ratio (95% CI)	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years		
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)	

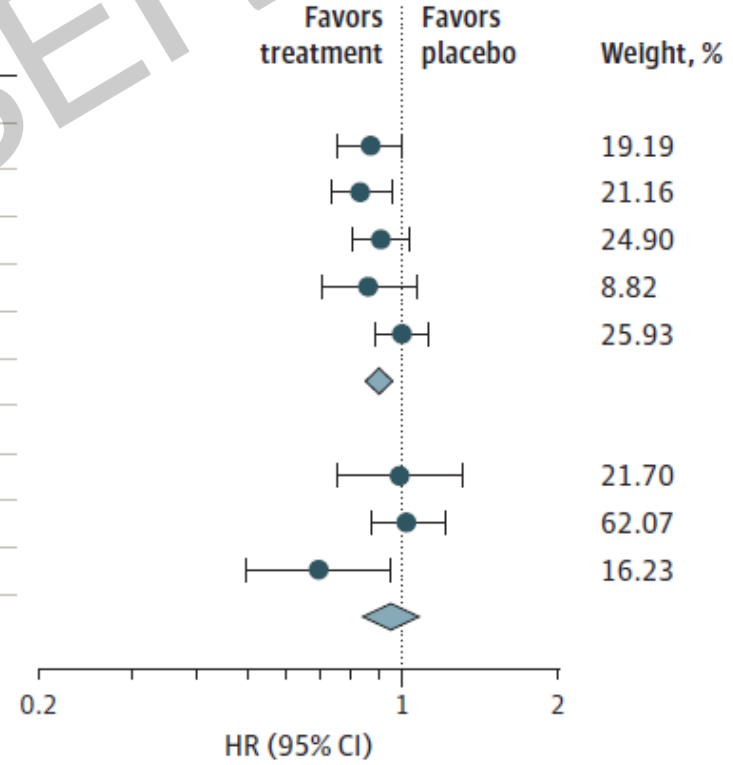


Mc Guire et al., *JAMACardiol*. 2021;6(2):148-158

Figure 1. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

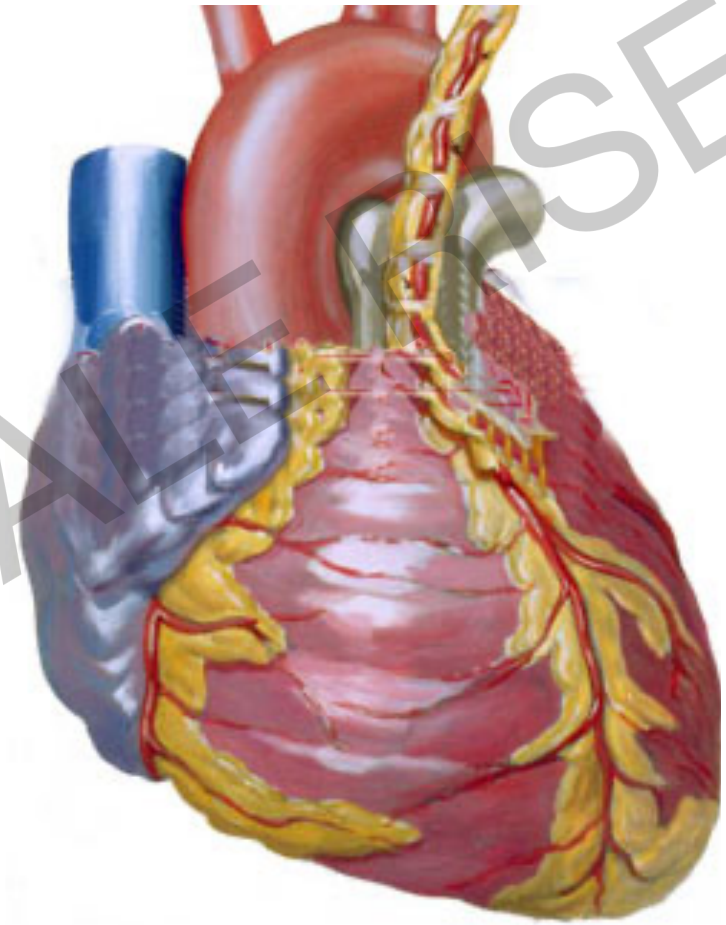
B MACEs by ASCVD status

	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	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
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)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)



Mc Guire et al., *JAMACardiol*. 2021;6(2):148-158

HEART FAILURE

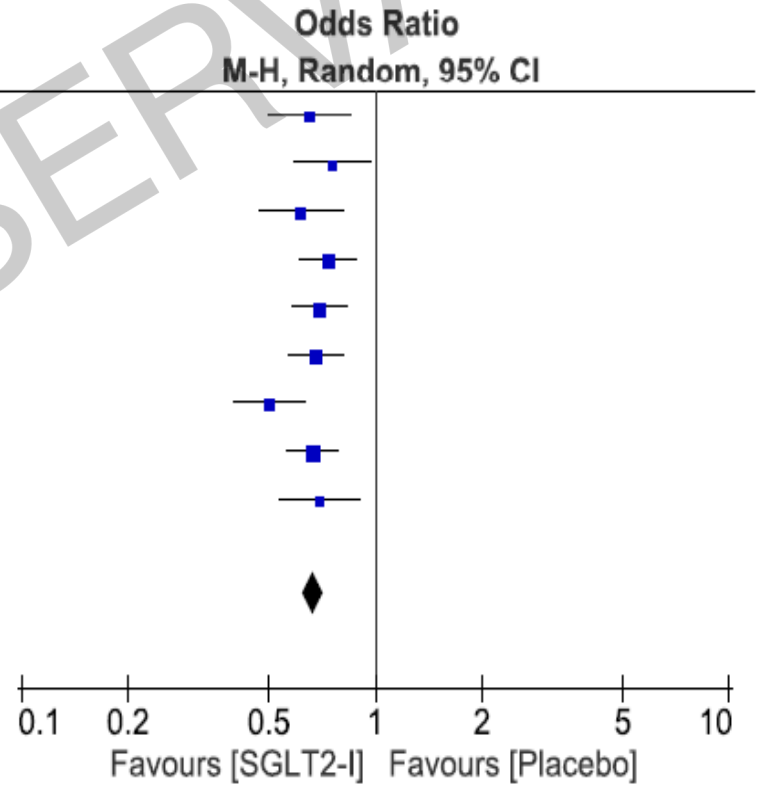


Hospitalization for heart failure in participants of 10 CVOTs

Study or Subgroup	SGLT2-I Events	SGLT2-I Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
EMPA-REG OUTCOME	126	4687	95	2333	6.9%	0.65 [0.50, 0.85]	2015
CANVAS and CANVAS-R	124	5795	122	4347	7.9%	0.76 [0.59, 0.98]	2017
CREDENCE	89	2202	141	2199	6.9%	0.61 [0.47, 0.81]	2019
DECLARE-TIMI 58	212	8582	286	8578	14.7%	0.73 [0.61, 0.88]	2019
DAPA-HF	237	2373	326	2371	15.1%	0.70 [0.58, 0.83]	2019
EMPEROR-Reduced	246	1863	342	1867	15.1%	0.68 [0.57, 0.81]	2020
SOLOIST-WHF	194	608	297	614	9.2%	0.50 [0.40, 0.63]	2020
SCORED	245	5292	360	5292	16.9%	0.67 [0.56, 0.79]	2020
VERTIS-CV	139	5499	99	2747	7.4%	0.69 [0.53, 0.90]	2020
Total (95% CI)		**36901**		**30348**	**100.0%**	**0.67 [0.62, 0.72]**	
Total events	1612		2068				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.65$, df = 8 (P = 0.37); $I^2 = 8\%$

Test for overall effect: Z = 10.83 (P < 0.00001)

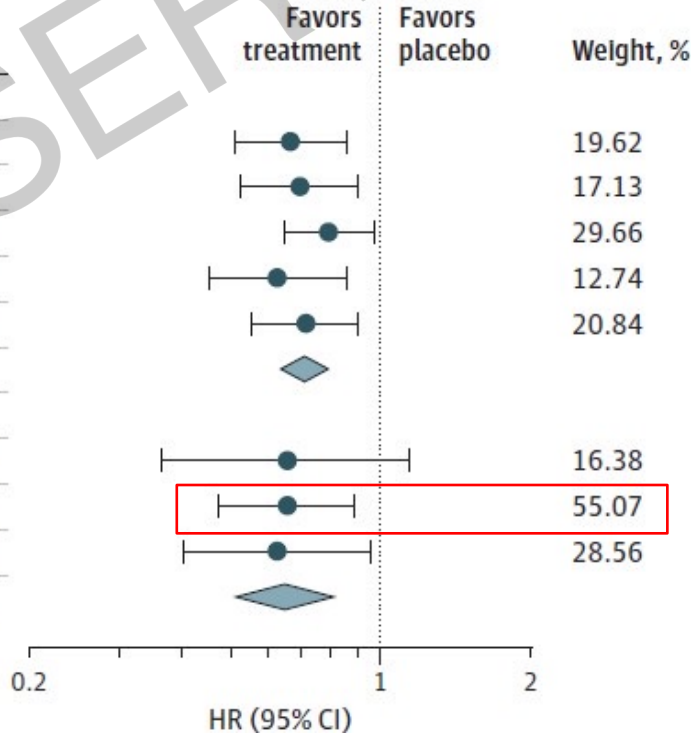


Bhattarai M et al., *JAMA Network Open.* 2022;5(1):

Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

B HHF by ASCVD status

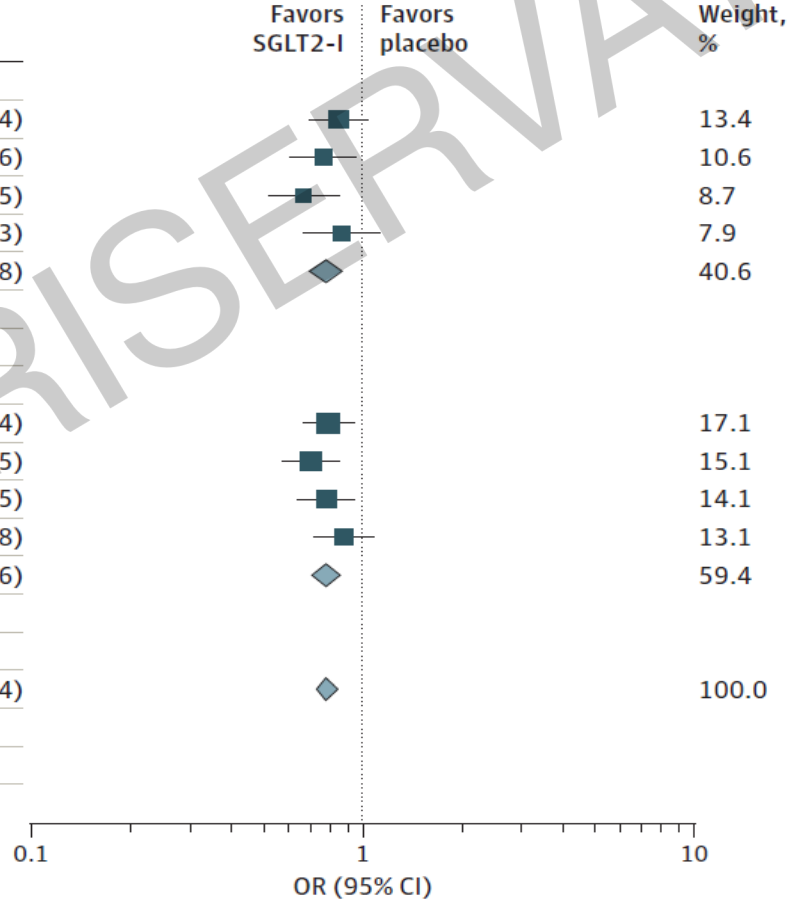
	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)			17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)			29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)			12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			20.84
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)			16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)			55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)			28.56
Fixed-effects model (Q = 0.03; *df* = 2; *P* = .99; I^2 = 0.0%)					0.63 (0.50-0.80)			



Mc Guire et al., *JAMACardiol*. 2021;6(2):148-158

CV death or hospitalization for heart failure in participants of five CVOTs younger or older than 65 years

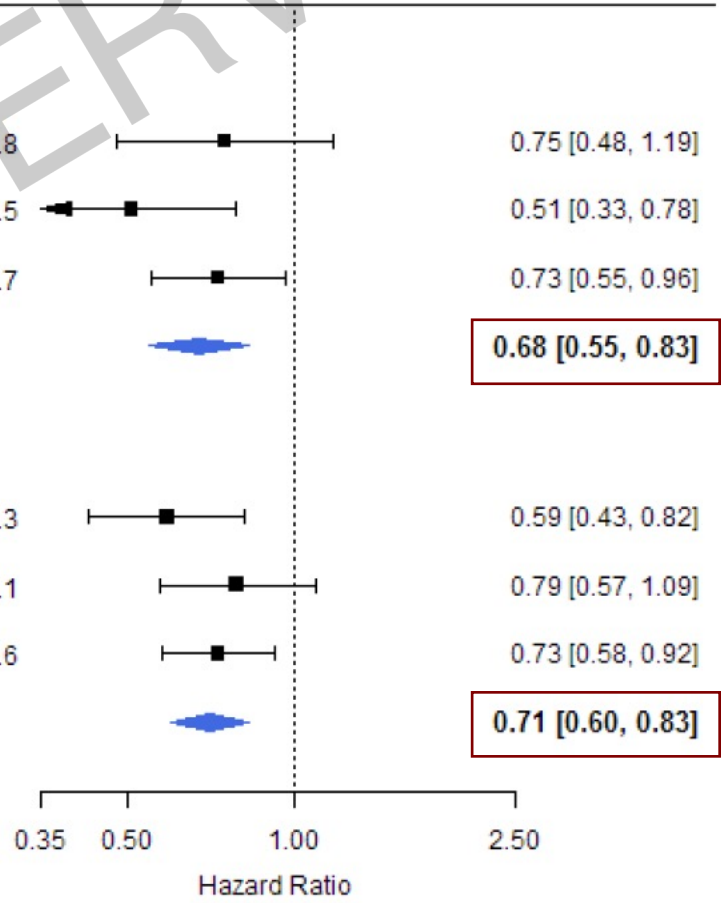
Source	SGLT2-I No. of events	SGLT2-I Total	Placebo No. of events	Placebo Total	OR (95% CI)
Age <65 y					
Wiviott et al,[6] 2019	180	4631	211	4622	0.85 (0.69-1.04)
McMurray et al,[9] 2019	162	1032	196	998	0.76 (0.61-0.96)
Packer et al,[10] 2020	128	675	193	740	0.66 (0.52-0.85)
Cannon et al,[7] 2020	159	2719	92	1376	0.87 (0.66-1.13)
Subtotal	629	9057	692	7736	0.79 (0.70-0.88)
Heterogeneity: $\tau^2=0.00$; $\chi^2_3=2.82$ ($P=.42$); $I^2=0\%$					
Test for overall effect: $z=4.06$ ($P<.001$)					
Age ≥65 y					
Wiviott et al,[6] 2019	228	3951	285	3956	0.79 (0.66-0.94)
McMurray et al,[9] 2019	224	1341	306	1373	0.70 (0.58-0.85)
Packer et al,[10] 2020	233	1188	269	1127	0.78 (0.64-0.95)
Cannon et al,[7] 2020	285	2780	158	1371	0.88 (0.71-1.08)
Subtotal	970	9260	1018	7827	0.78 (0.71-0.86)
Heterogeneity: $\tau^2=0.00$; $\chi^2_3=2.50$ ($P=.47$); $I^2=0\%$					
Test for overall effect: $z=5.03$ ($P<.001$)					
Total	1599	18317	1710	15563	0.78 (0.73-0.84)
Heterogeneity: $\tau^2=0.00$; $\chi^2_1=5.33$ ($P=.62$); $I^2=0\%$					
Test for overall effect: $z=6.46$ ($P<.001$)					
Test for subgroup differences: $\chi^2_1=0.01$ ($P=.94$); $I^2=0\%$					



Bhattarai M et al., *JAMA Network Open.* 2022;5(1):

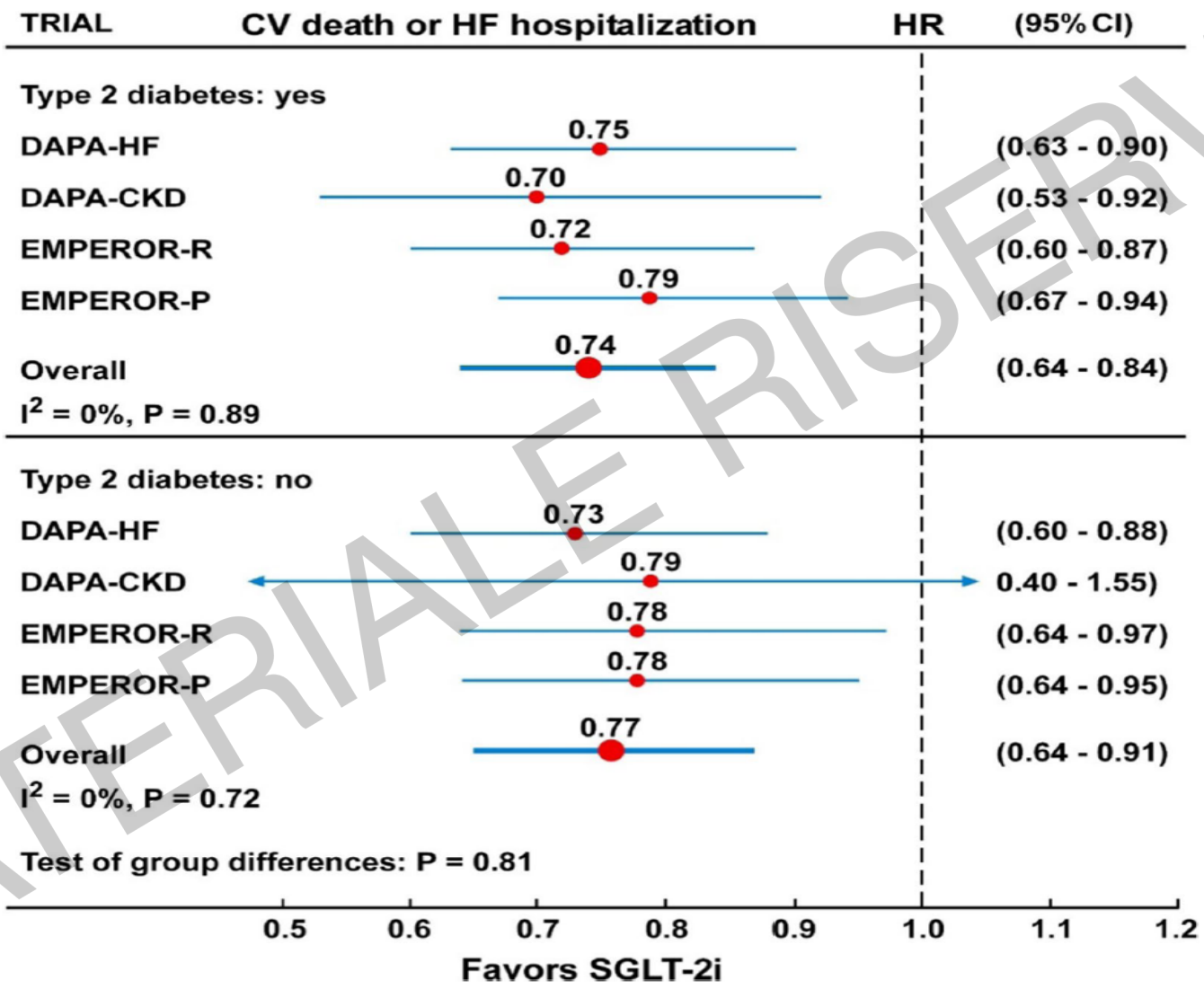
Hospitalization for heart failure stratified by history of heart failure
Metanalysis of 3 CVOTs

HHF	Patients	Events	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	Weights (%)	HR [95% CI]
History of Heart Failure:						
EMPA-REG OUTCOME	706	78	40.7	52.4	20.8	0.75 [0.48, 1.19]
CANVAS Program	1461	NA	14.1	28.1	23.5	0.51 [0.33, 0.78]
DECLARE-TIMI 58	1724	202	27.7	37.2	55.7	0.73 [0.55, 0.96]
FE Model for history of HF (P-value = 0.0002)						**0.68 [0.55, 0.83]**
No History of Heart Failure:						
EMPA-REG OUTCOME	6314	143	6.4	10.8	25.3	0.59 [0.43, 0.82]
CANVAS Program	8681	NA	4.3	5.7	25.1	0.79 [0.57, 1.09]
DECLARE-TIMI 58	15436	296	4.0	5.6	49.6	0.73 [0.58, 0.92]
FE Model for no history of HF (P-value <0.0001)						**0.71 [0.60, 0.83]**



Zelniker TA et al. Lancet 5;393(10166):31-39, 2019

CV death or hospitalization for heart failure in participants of four CVOTs with or without type 2 diabetes

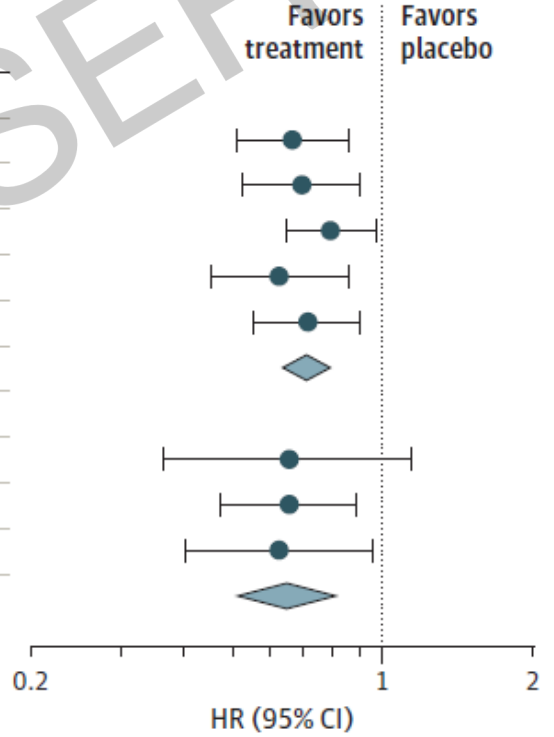


Giugliano *et al. Cardiovascular Diabetology* (2021) 20:236

Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

B HHF 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	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)			17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)			29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)			12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			20.84
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)			16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)			55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)			28.56
Fixed-effects model (Q = 0.03; *df* = 2; *P* = .99; I^2 = 0.0%)					0.63 (0.50-0.80)			

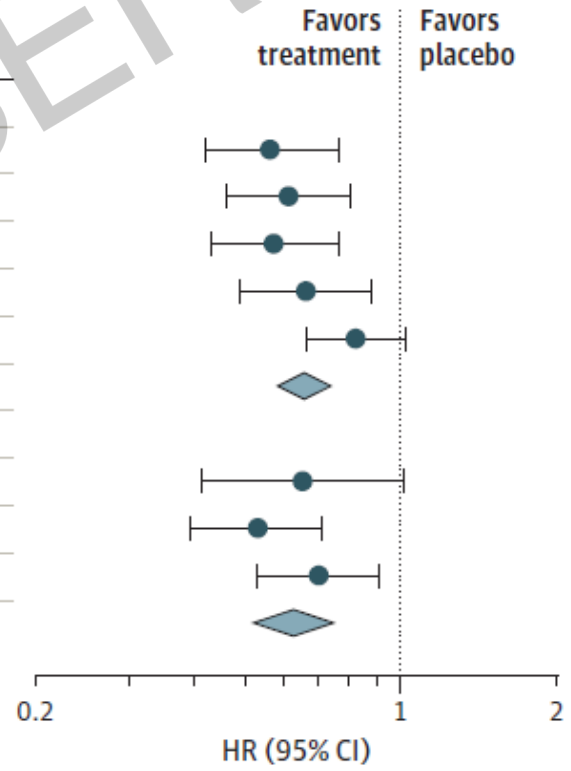


Mc Guire et al., *JAMACardiol*. 2021;6(2):148-158

Figure 4. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Kidney-Related Outcomes

B Kidney outcomes by ASCVD status

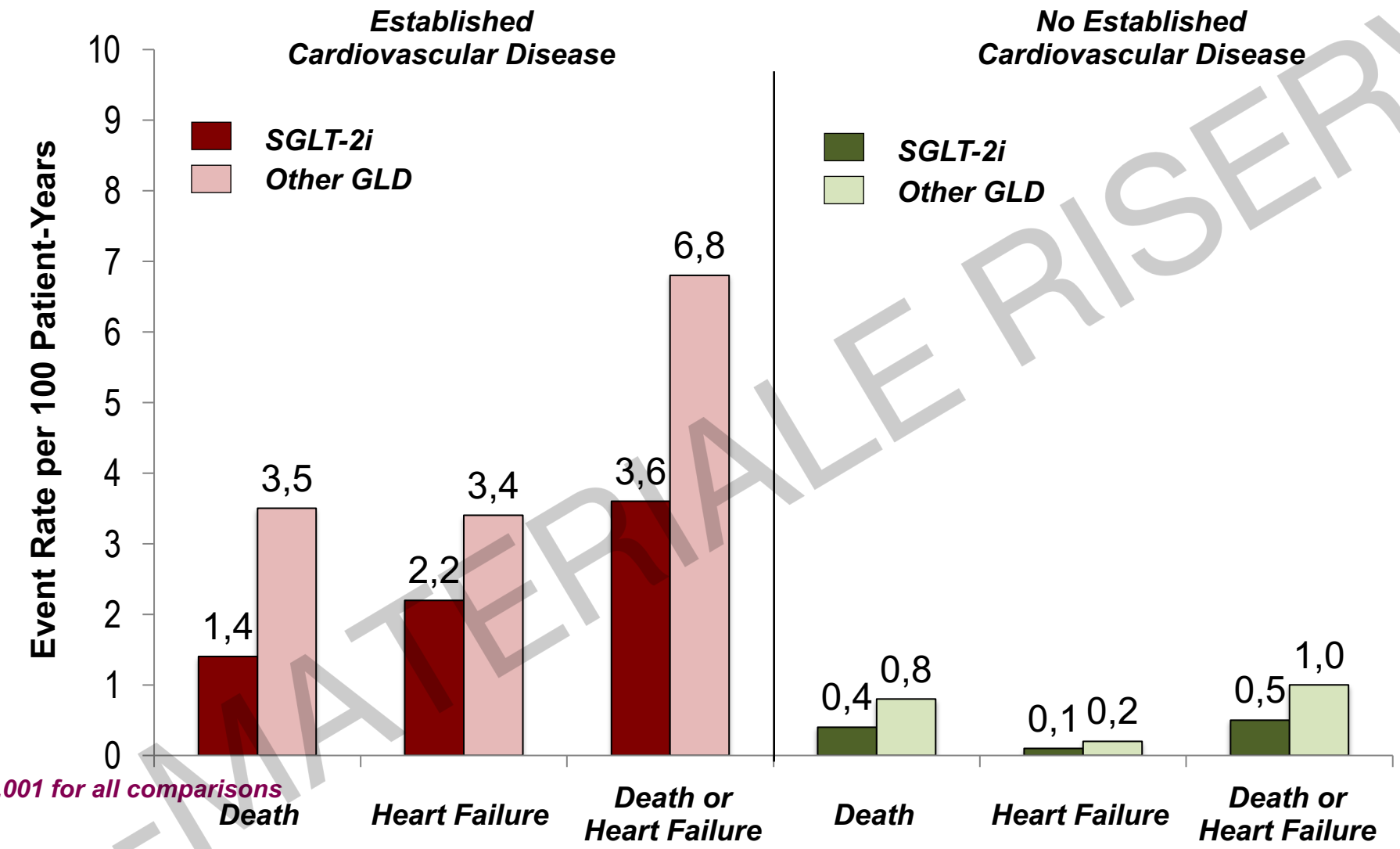
	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)			16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)			19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)			18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)			17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)			28.66
Fixed-effects model ($Q = 6.09$; $df = 4$; $P = .19$; $I^2 = 34.4\%$)					0.64 (0.56-0.72)			
Patients without ASCVD								
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)			15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)			37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)			46.87
Fixed-effects model ($Q = 1.86$; $df = 2$; $P = .40$; $I^2 = 0.0\%$)					0.60 (0.50-0.73)			



Mc Guire et al., *JAMACardiol*. 2021;6(2):148-158

CVD Real

CVD in DM2 Patients Treated With SGLT-2i vs Other GLD



p<0.001 for all comparisons

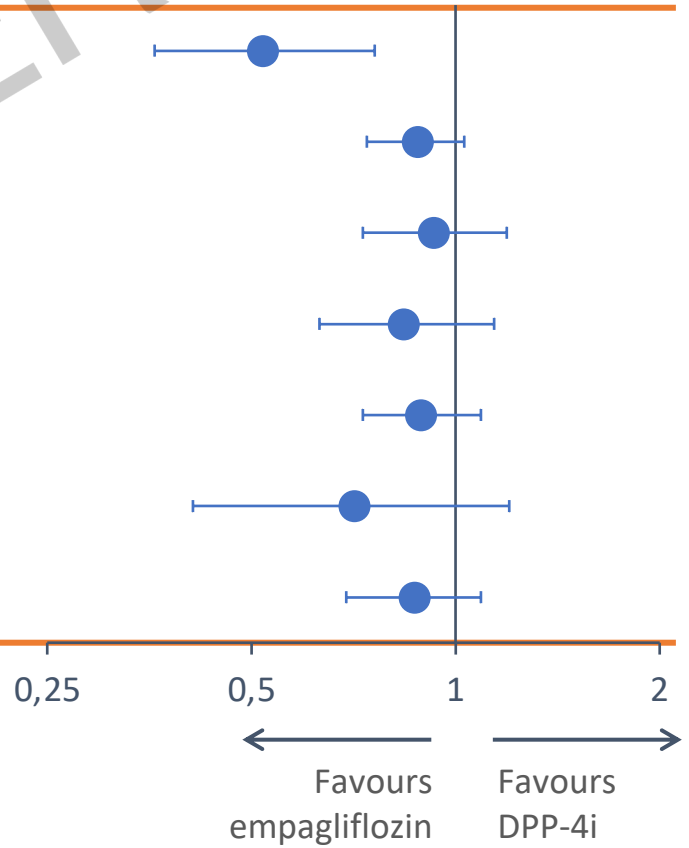
- **In DM2, SGLT2i exert additional CV protection when compared to other GLD, in patients with and without established CVD, homogenously across databases**
- **The observed lower risk of events was consistent across subgroups**

*Dapagliflozin is not indicated for the reduction of CV mortality. CVD-REAL is supportive evidence of dapagliflozin not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus.

RESULTS YEAR 3: *Empa vs DPP-4i*

All Cause Death and CV events (w/o CV death)

	Empagliflozin (n=39,169)		DPP-4i (n=39,169)		
	n event	IR/ 1000 PY	n event	IR/ 1000 PY	HR (95% CI)
All-cause mortality*[1]	42	8.3	83	15.9	0.52 (0.36, 0.76)
Atherosclerotic CV event†[2]	278	14.56	305	17.6	0.88 (0.74, 1.03)
MI[2]	128	6.69	133	7.54	0.93 (0.73, 1.19)
Stroke[2]	83	4.33	95	5.39	0.84 (0.63, 1.14)
MI or stroke[1]	192	10.0	209	11.9	0.89 (0.73, 1.09)
Unstable angina[2]	27	1.41	36	2.04	0.71 (0.41, 1.20)
Coronary revascularisation[2]	145	7.59	157	8.91	0.87 (0.69, 1.09)



Kidney function

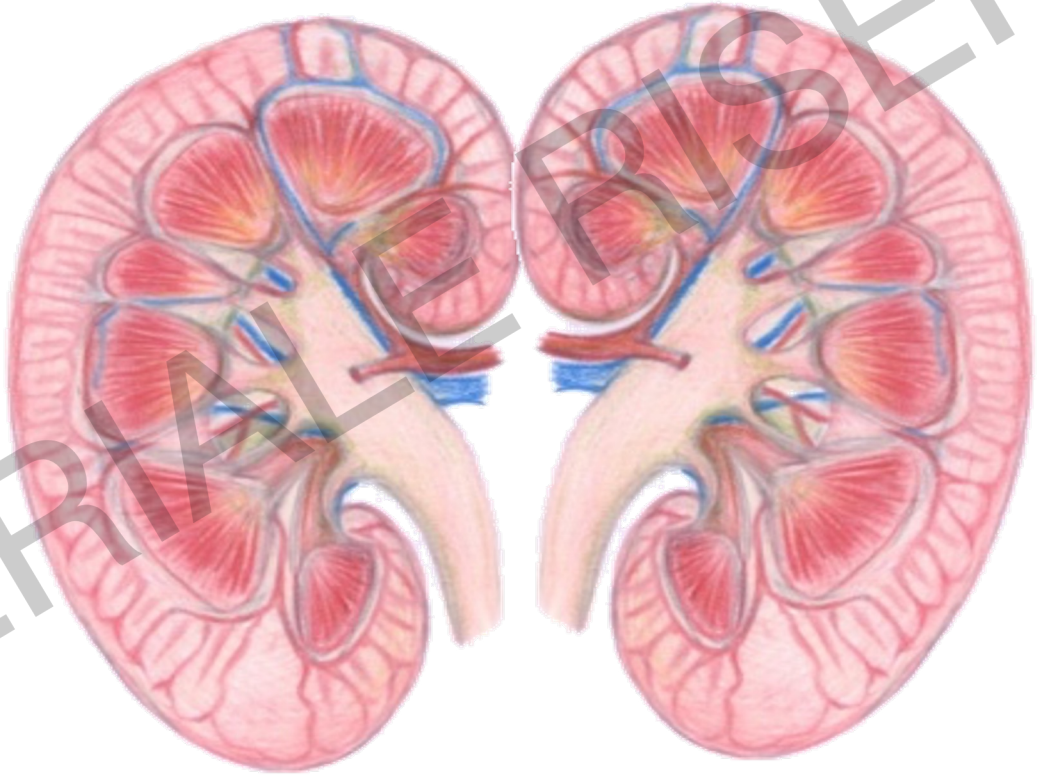
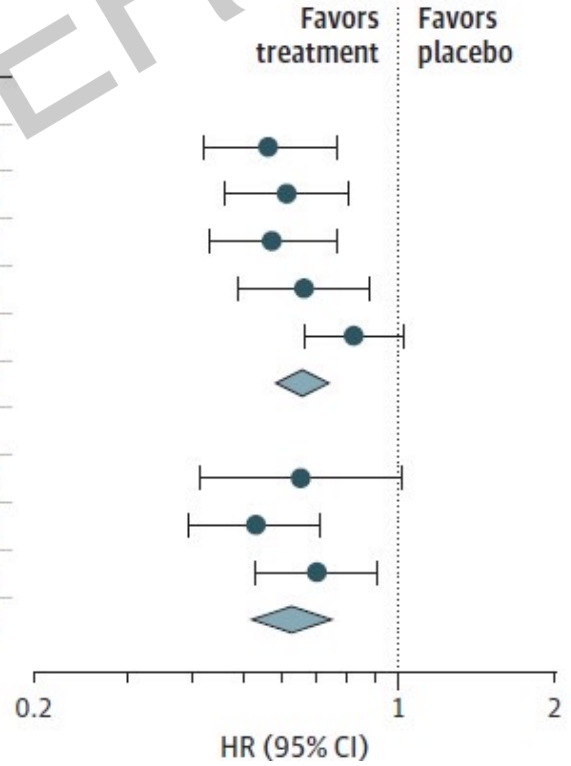


Figure 4. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Kidney-Related Outcomes

B Kidney outcomes 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	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)			16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)			19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)			18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)			17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)			28.66
Fixed-effects model ($Q = 6.09$; $df = 4$; $P = .19$; $I^2 = 34.4\%$)					0.64 (0.56-0.72)			
Patients without ASCVD								
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)			15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)			37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)			46.87
Fixed-effects model ($Q = 1.86$; $df = 2$; $P = .40$; $I^2 = 0.0\%$)					0.60 (0.50-0.73)			

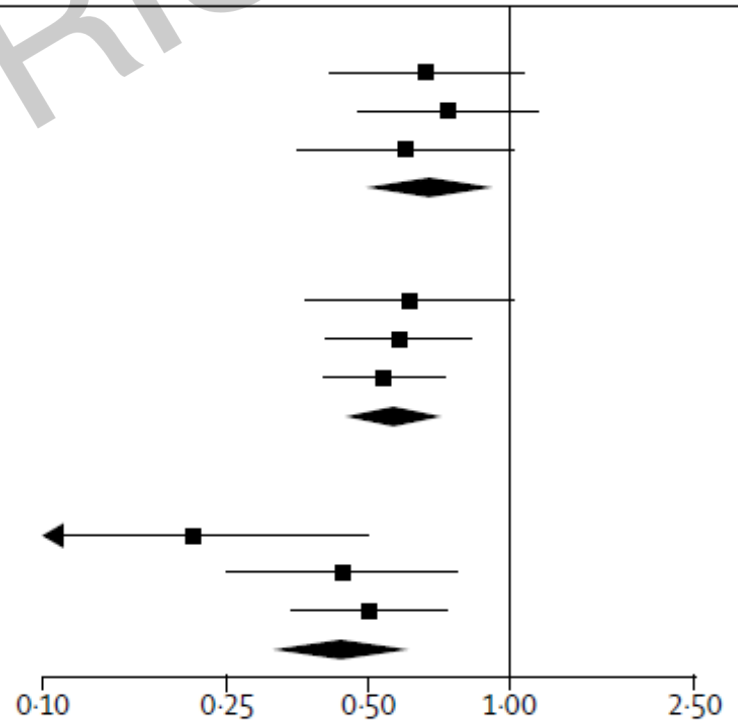


Mc Guire et al., *JAMACardiol*. 2021;6(2):148-158

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

Renal Endpoint

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196	605	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA	NA	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606	659	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406	1232	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA	NA	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838	3894	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043	486	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA	NA	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137	4025	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**



Zelniker et al. Lancet 2019; 393:31

Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials

the bmj | *BMJ* 2021;372:m4573

- A core finding suggests that there is high certainty that SGLT-2 inhibitors reduce all cause and cardiovascular mortality, nonfatal myocardial infarction, kidney failure, and admission to hospital for heart failure.
- GLP-1 receptor agonist treatment reduces all cause and cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and kidney failure.
- SGLT-2 inhibitor treatment reduces all cause mortality and admission to hospital for heart failure to a greater extent than GLP-1 receptor agonist treatment.

GRADE summary of findings to illustrate absolute effects for all cause mortality for SGLT-2 inhibitors compared with placebo

		Anticipated absolute effects over five years					
Comparison	Relative effect (odds ratio (95% CI))	Baseline risk*	Risk with control	Risk with intervention	Anticipated absolute effects (95% CI) over five years	Certainty in treatment effects (GRADE)	Plain text summary
SGLT-2 inhibitor *v* placebo	0.77 (0.71 to 0.83)	Very low	Placebo: 20 per 1000	SGLT-2 inhibitor: 15 per 1000	5 fewer per 1000 (from 3 fewer to 6 fewer)	Moderate due to indirectness	SGLT-2 inhibitor treatment probably reduces all cause mortality in people with diabetes and few or no cardiovascular risk factors
		High	Placebo: 170 per 1000	SGLT-2 inhibitor: 136 per 1000	34 fewer per 1000 (from 25 fewer to 43 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and chronic kidney disease
		Very high	Placebo: 265 per 1000	SGLT-2 inhibitor: 217 per 1000	48 fewer per 1000 (from 35 fewer to 61 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and established cardiovascular disease and chronic kidney disease

- 56.000 morti in 5 anni !!

thebmj | *BMJ* 2021;372:m4573

GRADE summary of findings to illustrate absolute effects for all cause mortality for GLP-1 RAs compared with placebo

Comparison	Relative effect (odds ratio (95% CI))	Anticipated absolute effects over five years: Baseline risk*	Risk with control	Risk with intervention	Anticipated absolute effects (95% CI) over five years	Certainty in treatment effects (GRADE)	Plain text summary
GLP-1 receptor agonist *v* placebo	0.88 (0.83 to 0.94)	Very low	Placebo: 20 per 1000	GLP-1 receptor agonist: 18 per 1000	2 fewer per 1000 (from 1 fewer to 3 fewer)	Moderate due to indirectness	GLP-1 receptor agonist treatment probably reduces all cause mortality in people with diabetes and few or no cardiovascular risk factors
		High	Placebo: 170 per 1000	GLP-1 receptor agonist: 153 per 1000	17 fewer per 1000 (from 9 fewer to 25 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and chronic kidney disease
		Very high	Placebo: 265 per 1000	GLP-1 receptor agonist: 241 per 1000	24 fewer per 1000 (from 12 fewer to 35 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and established cardiovascular disease and chronic kidney disease

- 30.000 morti in 5 anni !!

thebmj | *BMJ* 2021;372:m4573

THE VIS INSITA, OR INNATE FORCE OF MATTER, IS A POWER OF RESISTING BY WHICH EVERY BODY, AS MUCH AS IN IT LIES, ENDEAVOURS TO PRESERVE ITS PRESENT STATE,