DIABETE
OGGI

Benefici degli Sodium-glucose co-transporter 2 inhibitors: glicemia e molto altro

SISTEMA SANITARIO REGIONALE
ASL VITERBO

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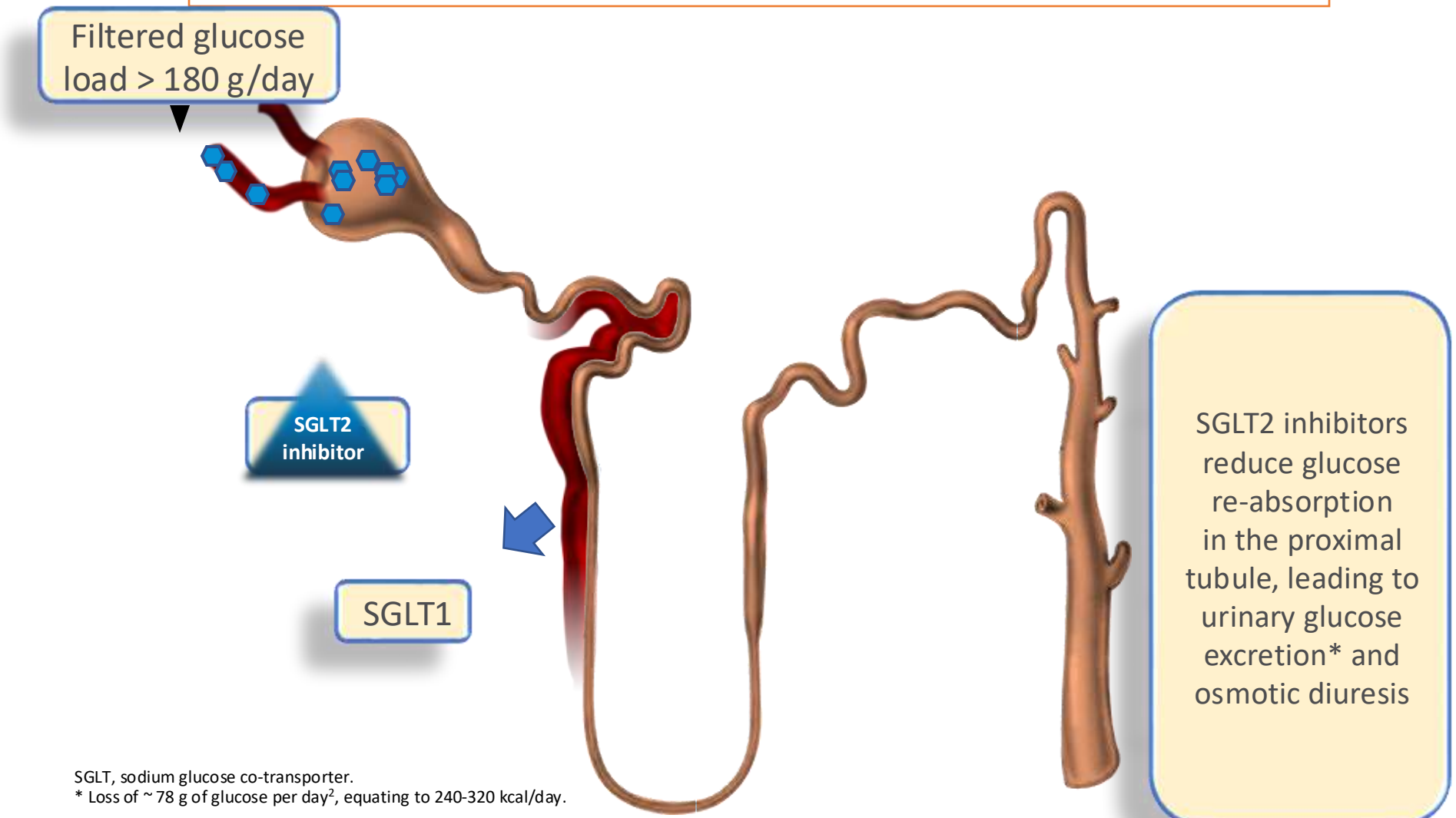
Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti anche per partecipazioni a congressi dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- ABBOTT
- Movi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Urinary glucose excretion via SGLT2 inhibition[1]



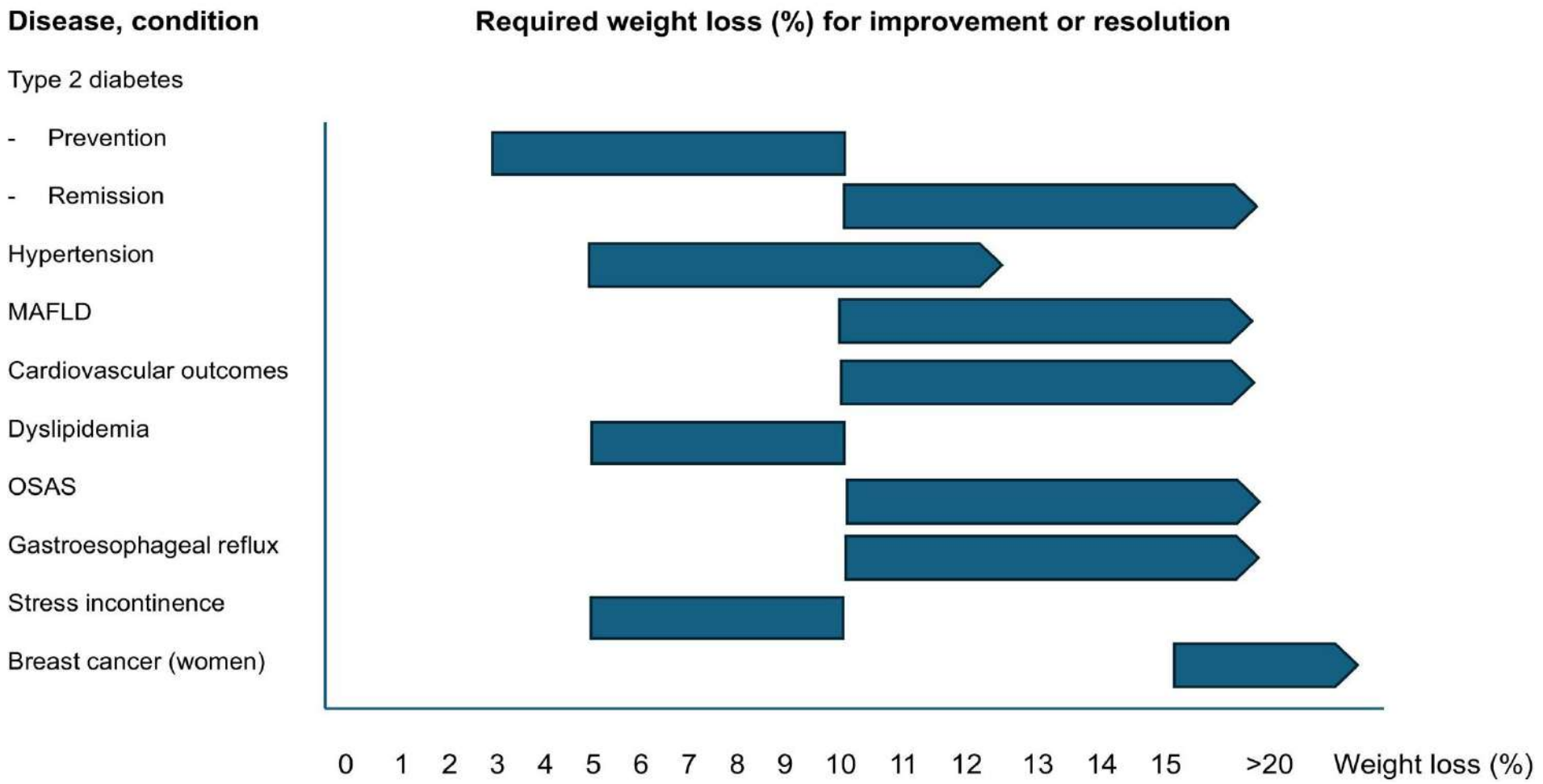
SGLT, sodium glucose co-transporter.
* Loss of ~ 78 g of glucose per day[2], equating to 240-320 kcal/day.

References
1. Bakris GL, *et al. Kidney Int*. 2009;**75**;1272–1277.

Comparing Agents

Medication	Average A1C lowering	Hypoglycemic Agent	Weight Gain/Loss
Metformin	1.5%	No	Loss
Sulfonylureas	1.5%	Yes	Gain
Glinides	1-1.5%	No	Gain
SGLT-2 Inhibitors	1%	No	Loss
TZDs	0.5-1.4%	No	Gain
α-Glucosidase Inhibitor	0.5-0.8%	No	Neutral
DPP-4 Inhibitors	0.5-1%	No	Neutral

An overview of obesity-related complications: The epidemiological evidence linking body weight and other markers of obesity to adverse health outcomes



Diabetes Obesity Metabolism, First published: 11 March 2025, DOI: (10.1111/dom.16263)

SGLT2-i e perdita di Peso Corporeo

TABLE 1 Weight change achieved in published Phase III trials with available glucagon-like peptide receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2i)

Drug	Properties	Route of Administartion/Dosing	Weight Change in T2DM Trials: Absolute (kg)
GLP-1 RA			
Dulaglutide	GLP-1 RA peptide fused to IgG4 molecule	sc 0.75-1.5 mg weekly	−0.8 to 2.9[12]
Exenatide	39 AA peptide	sc 5-10mcg bd	−1.4 to 4[13-18]
Exenatide-QW	Encapsulated in biodegradable polymer microspheres	sc 2 mg weekly	−1.6 to 3.7[12,13,18]
Liraglutide	C-16 fatty acid to lys26, non-covalent bond to albumin	sc 1.2 mg-1.8 mg od	−2 to 5.0[11,14,19-21]
Liraglutide	C-16 fatty acid to lys26, non-covalent bond to albumin	sc titrate in 0.6 mg weekly increments to 3 mg od	−6.0[19]
Lixisenatide	44 AA derivative of exenatide	sc 10-20mcg od	−1.3 to 3.0[15]
SGLT2i	**SGLT2:SGLT1 relative specificity**		
Canagliflozin			
Dapagliflozin			
Empagliflozin			
Ertugliflozin			

75 gr/die di escrezione di glucosio≃ 300 kcal

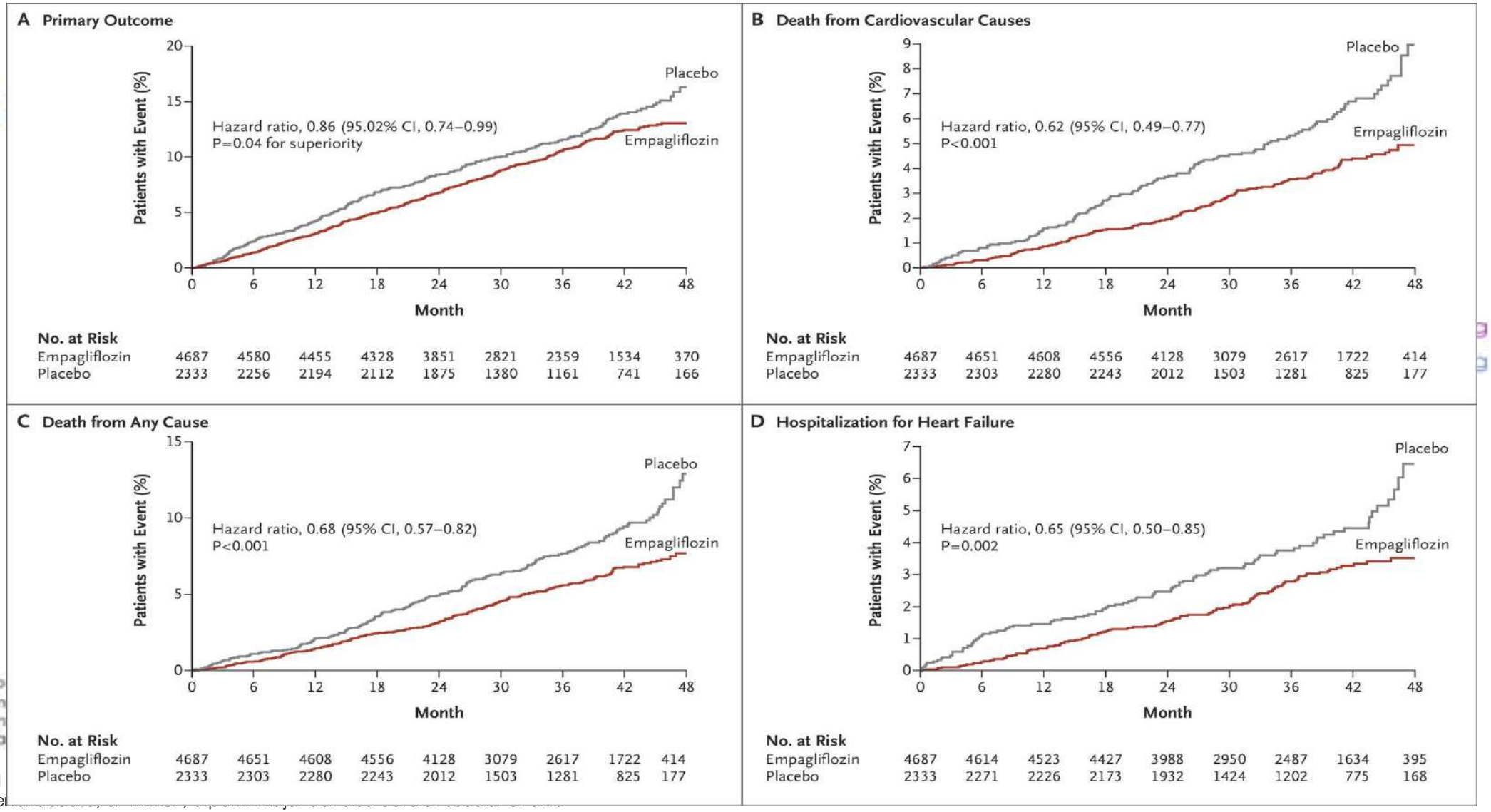
↓ Glicemia e Insulina
↑Glucagone con stimolo alla lipolisi
↑ FAO (ossidazione acidi grassi)
↑ della glicogenolisi e della gluconeogenesi

Abbreviations: bd, twice daily; od, once daily; po, oral; sc, subcutaneous. These data are from separately published studies and, therefore, are not intended to indicate comparative efficacy.

E- Brown Obesity Reviews. 2019;20:816–828

Non solo Glicemia….

EMPA-REG OUTCOME: Summary



*Defined
due to re

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. N Engl J Med* 2016 (submitted)

SGLT2 INHIBITORS: CARDIOVASCULAR OUTCOMES TRIALS

	EMPA-REG OUTCOME 2016	CANVAS Program 2017	DECLARE-TIMI 58 2019	VERTIS CV 2020
DRUG	Empagliflozin 10-25 mg daily	Canagliflozin 100-300 mg daily	Dapagliflozin 10 mg daily	Ertugliflozin 5-15 mg daily
# RANDOMIZED	7020 (active, n=4687; placebo, n=2333)	10,141 (active, n=5764; placebo, n=4347)	17,160 (active, n=8582; placebo, n=8578)	8246 (active, n=5499; placebo, n=2747)
INCLUSION CRITERIA	• Type 2 diabetes; HgA1c 7.0-10% • Established cardiovascular disease • eGFR ≥30 mL/min	• Type 2 diabetes; HgA1c 7.0-10.5% • Established cardiovascular disease, or ≥2 risk factors • eGFR >30 mL/min	• Type 2 diabetes; HgA1c 6.5-12% • Established cardiovascular disease, or multiple risk factors • CrCl ≥60 mL/min	• Type 2 diabetes • HgA1c 7.0-10.5% • Established cardiovascular disease
BASELINE CHARACTERISTICS	• Age ~63 years; male ~71% • HgA1c ~8.1% • CAD ~76%; prior MI ~47%	• Age ~63 years; male ~64% • HgA1c ~8.2% • Established ASCVD ~72%	• Age ~64 years; male ~63% • HgA1c ~8.3% • Established ASCVD ~41%	• Age ~64 years; male ~70% • HgA1c ~8.2% • CAD ~76%
DURATION	Median follow-up period of 3.1 years	Median follow-up period of ~3.6 years	Median follow-up period of ~4.2 years	Mean follow-up period of 3.5 years
PRIMARY OUTCOME	Composite of cardiovascular death, non-fatal MI and non-fatal stroke	Composite of cardiovascular death, non-fatal MI and non-fatal stroke	Composite of cardiovascular death, myocardial infarction and stroke	Composite of cardiovascular death, non-fatal MI and non-fatal stroke
RESULTS	**Primary Composite Outcome:** 490 (10.5%) vs 282 (12.1%) HR 0.86 (95% CI 0.74-0.99) p=0.04; ARR 1.63%; NNT ~62	**Primary Composite Outcome:** 26.9 vs 31.5 (# pts per 1000 pt-years) HR 0.86 (95% CI 0.75-0.97); p=0.02	**Primary Composite Outcome:** NSD 756 (8.81%) vs 803 (9.36%); HR 0.93 (95% CI 0.84-1.03); p=0.17	**Primary Composite Outcome:** NSD 653/5493 (11.9%) vs 327/2745 (11.9%) HR 0.97 (95.6% CI 0.85-1.11)
MORBIDITY OUTCOMES	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 126 (2.69%) vs 95 (4.07%) HR 0.65 (95% CI 0.50-0.85) p=0.002; ARR 1.38%; NNT ~73	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 5.5 vs 8.7 (# pts per 1000 pt-years) HR 0.67 (95% CI 0.52-0.87)	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 212 (2.47%) vs 286 (3.33%) HR 0.73 (95% CI 0.61-0.88) ARR 0.86%; NNT ~116	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 139 (2.53%) vs 99 (3.60%) HR 0.70 (95% CI 0.54-0.90)
MORTALITY OUTCOMES	Cardiovascular Death: 172 (3.67%) vs 137 (5.87%) HR 0.62 (95% CI 0.49-0.77) p<0.001; ARR 2.20%; NNT ~46	Cardiovascular Death: NSD	Cardiovascular Death: NSD	Cardiovascular Death: NSD

Cardiovascular Outcomes in the integrated CANVAS Program

Neal B et al. N Engl J Med ;377:644-657

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

0.5 1.0 2.0

Canagliflozin Better Placebo Better

Major Cardiovascular and Renal Outcomes and Death from Any Cause: DECLARE TIMI 58.

Wiviott SD et al. N Engl J Med2019;380:347-357

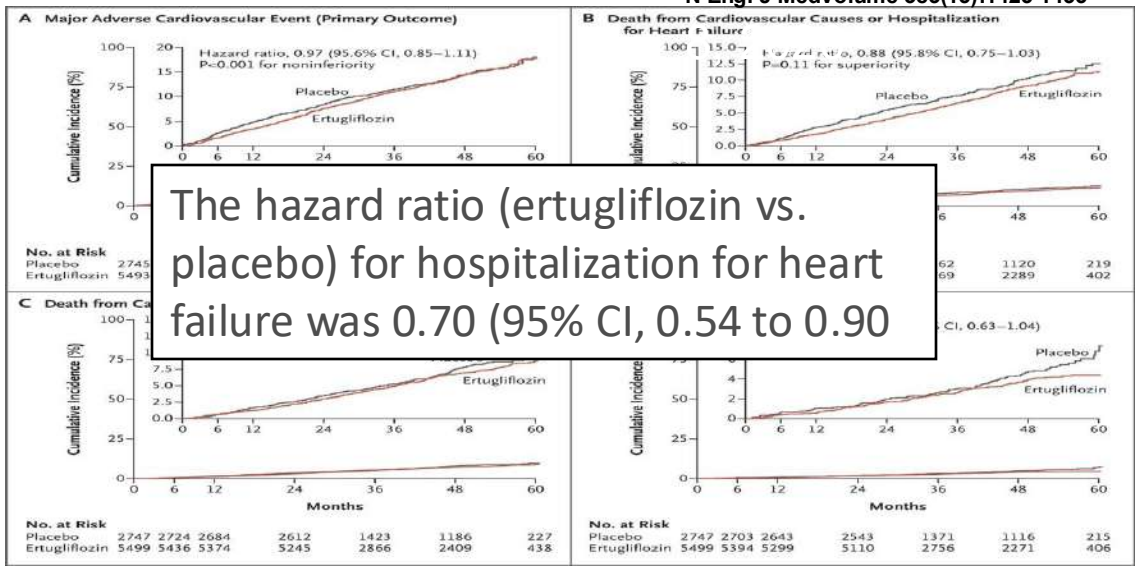
Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

0.40 0.50 1.0 1.5

Dapagliflozin Better Placebo Better

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

N Engl J MedVolume 383(15):1425-1435



The hazard ratio (ertugliflozin vs. placebo) for hospitalization for heart failure was 0.70 (95% CI, 0.54 to 0.90

Effetto favorevole sull'insufficienza cardiaca

Kim et al. Cardiovasc Diabetol (2018) 17:91
https://doi.org/10.1186/s12933-018-0737-5

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Association between sodium glucose co-transporter 2 inhibitors and a reduced risk of heart failure in patients with type 2 diabetes mellitus: a real-world nationwide population-based cohort study

Young-Gun Kim[1,2], Seung Jin Han[3], Dae Jung Kim[3], Kwan-Woo Lee[3] and Hae Jin Kim[3*]

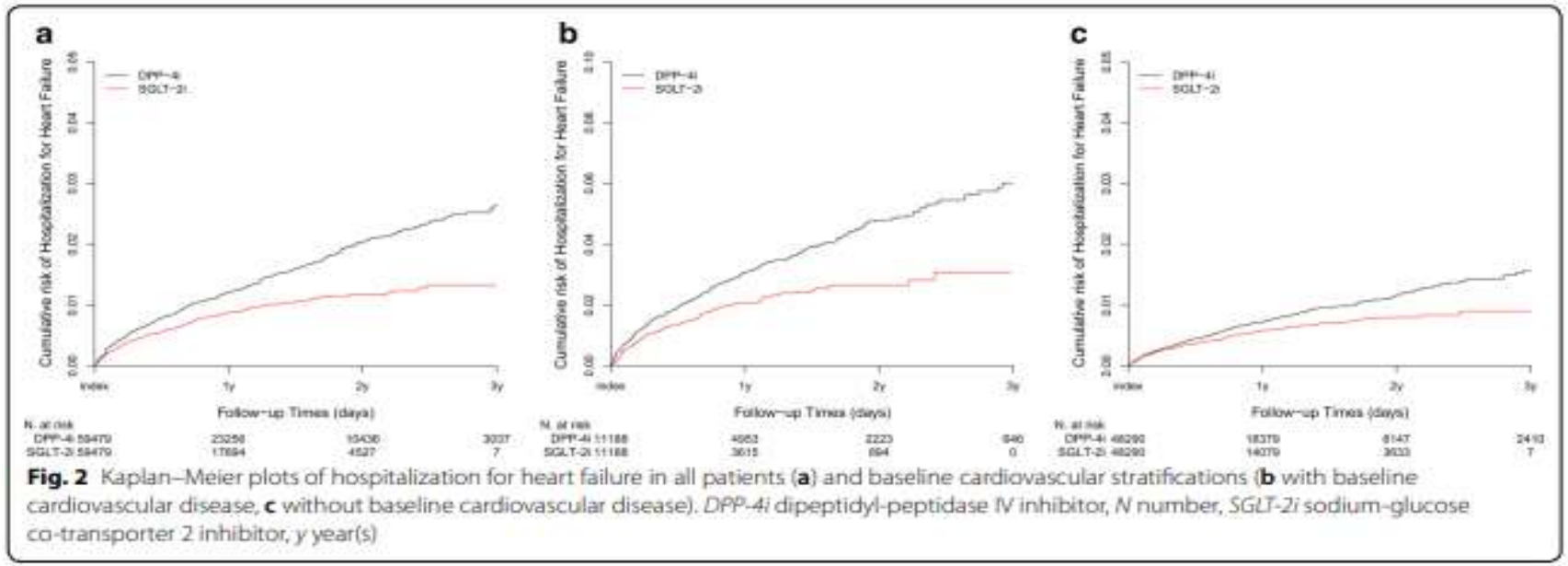


Fig. 2 Kaplan–Meier plots of hospitalization for heart failure in all patients (**a**) and baseline cardiovascular stratifications (**b** with baseline cardiovascular disease, **c** without baseline cardiovascular disease). *DPP-4i* dipeptidyl-peptidase IV inhibitor, *N* number, *SGLT-2i* sodium-glucose co-transporter 2 inhibitor, *y* year(s)

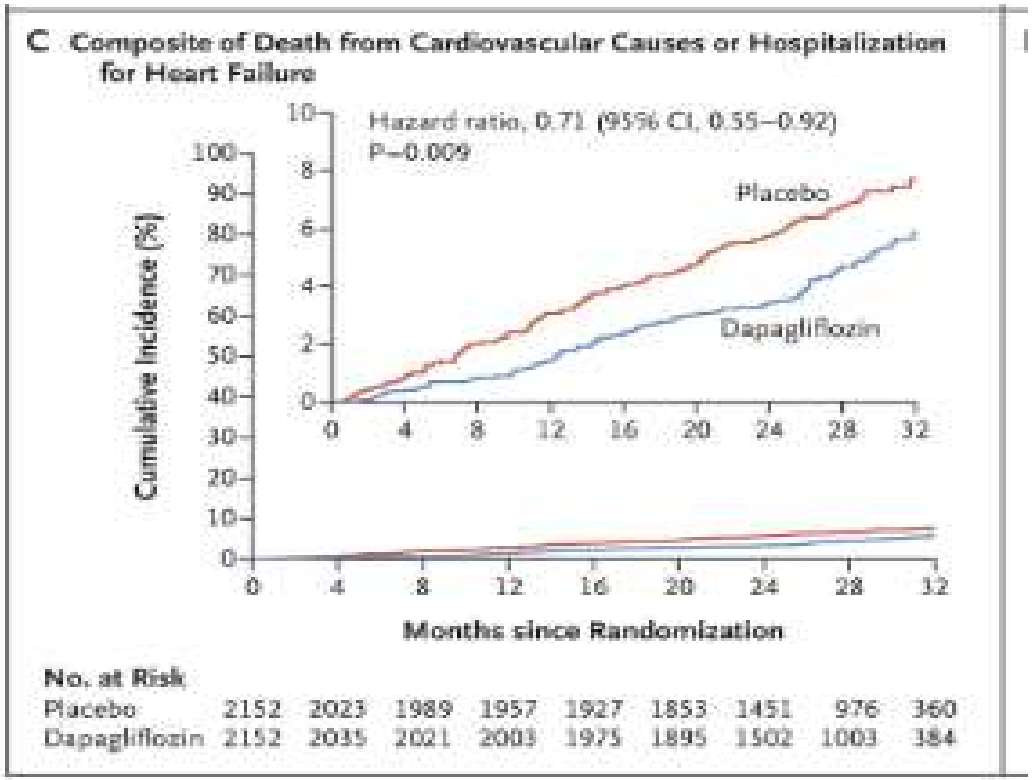
Conclusions

Our results suggest that SGLT-2i reduced hHF compared with DPP-4i. A HF protective effect of SGLT-2i vs. DPP-4i was shown 30 days after initiating the SGLT-2i among patients with established CVD, but this effect appeared later in patients without established CVD.

Benefici su Outcome CV in pazienti con Diabete Mellito e Malattia Renale Cronica

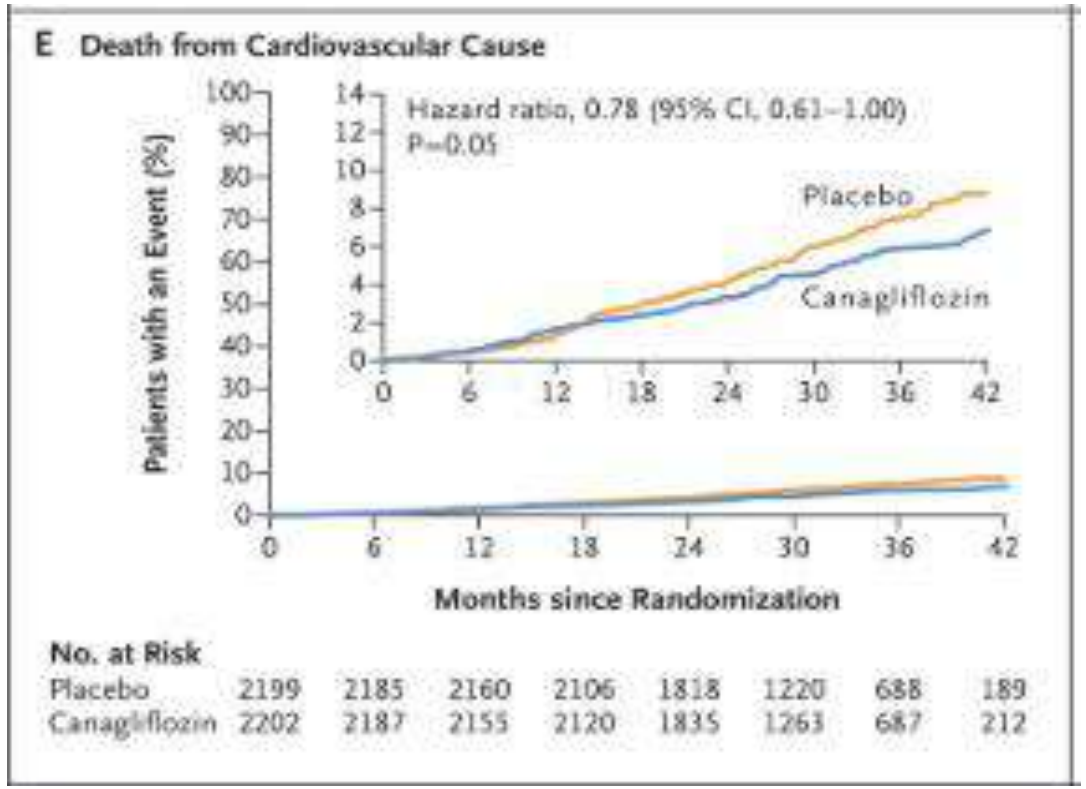
Dapagliflozin in Patients with Chronic Kidney Disease

N ENGL J MED 383;15 NEJM.ORG OCTOBER 8, 2020



Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

N ENGL J MED 380;24 NEJM.ORG JUNE 13, 2019



JAMA Cardiology | Original Investigation

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

A Meta-analysis

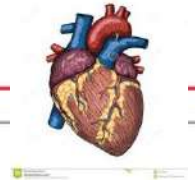
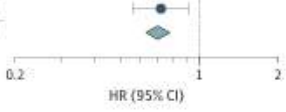


Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

A Overall HHF

	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, %
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)		16.09
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)		17.10
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)		33.72
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)		16.01
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)		17.08
Fixed-effects model ($Q = 1.39$; $df = 4$; $P = .85$; $I^2 = 0.0\%$)					0.68 (0.61-0.76)		



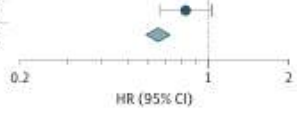
B HHF by ASCVD status

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

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

A Overall kidney outcomes

	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, %
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)		11.51
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)		18.66
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)		24.77
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)		25.28
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)		19.79
Fixed-effects model ($Q = 7.96$; $df = 4$; $P = .09$; $I^2 = 49.7\%$)					0.62 (0.56-0.70)		



B Kidney outcomes by ASCVD status

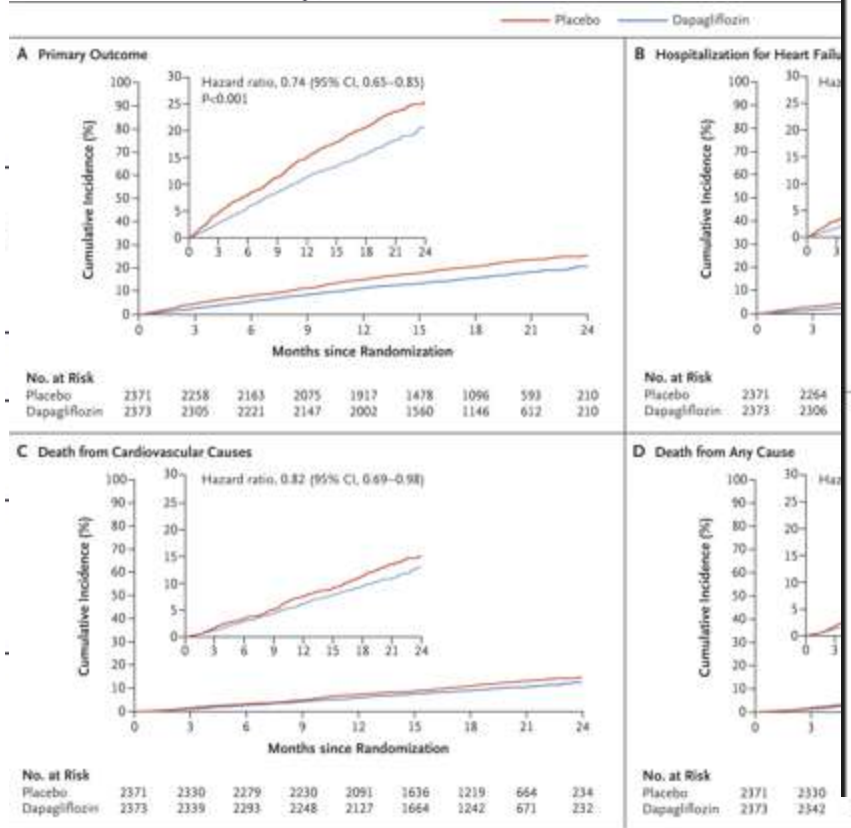
	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
Patients with ASCVD							
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)		16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (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)		

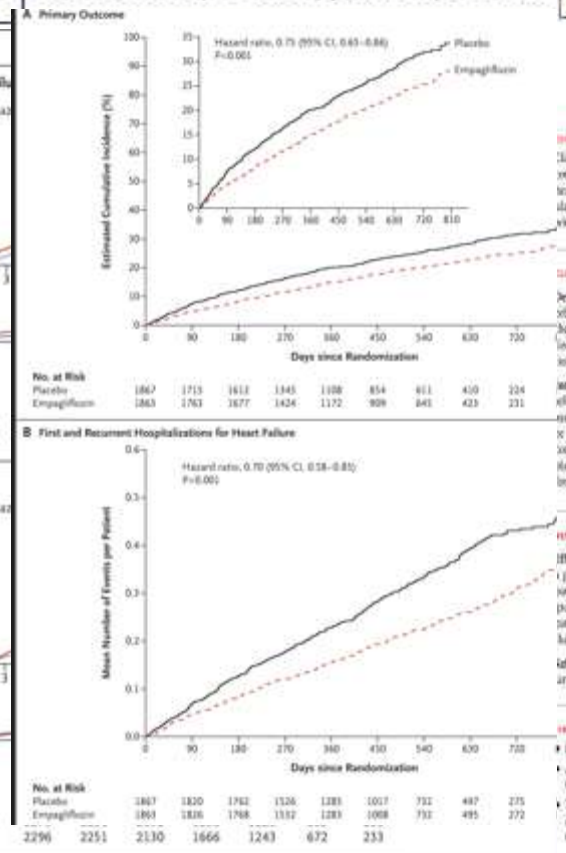
CONCLUSIONS AND RELEVANCE In this meta-analysis, SGLT2 inhibitors were associated with a reduced risk of major adverse CV events; in addition, results suggest significant heterogeneity in associations with CV death. The largest benefit across the class was for an associated reduction in risk for HHF and kidney outcomes, with benefits for HHF risk being the most consistent observation across the trials.

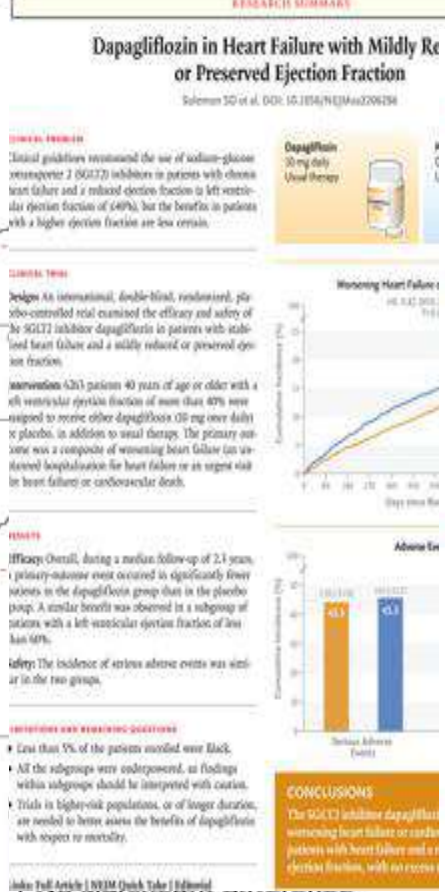
JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511
Published online October 7, 2020.

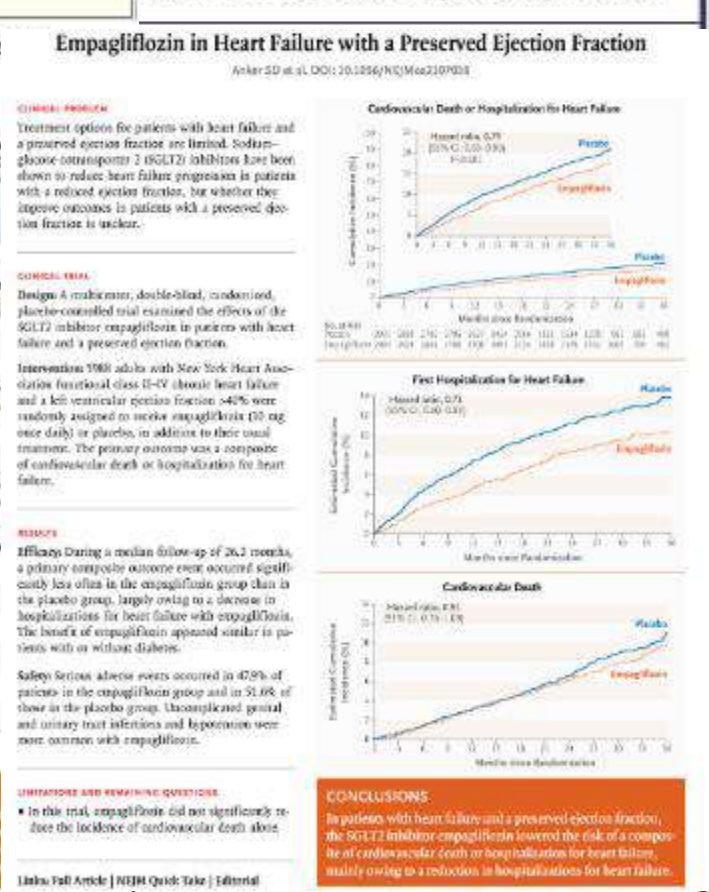
SGLT2 INHIBITORS: SUMMARY OF HEART FAILURE TRIALS

	DAPA-HF 2019	EMPEROR-Reduced 2020	DELIVER 2022	EMPEROR-Preserved 2021
DRUG	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily
# RANDOMIZED	4744 (active, n=2373; placebo, n=2371)	3730 (active, n=1863; placebo, n=1867)	[illegible]	5988 (active, n=2997; placebo, n=2991)
MORTALITY OUTCOMES	Cardiovascular Death: 227 (9.57%) vs 273 (11.5%) HR 0.82 (95% CI 0.69-0.98) ARR 1.95%; NNT ~52	Cardiovascular Death: No significant difference	Cardiovascular Death: No significant difference	Cardiovascular Death: No significant difference





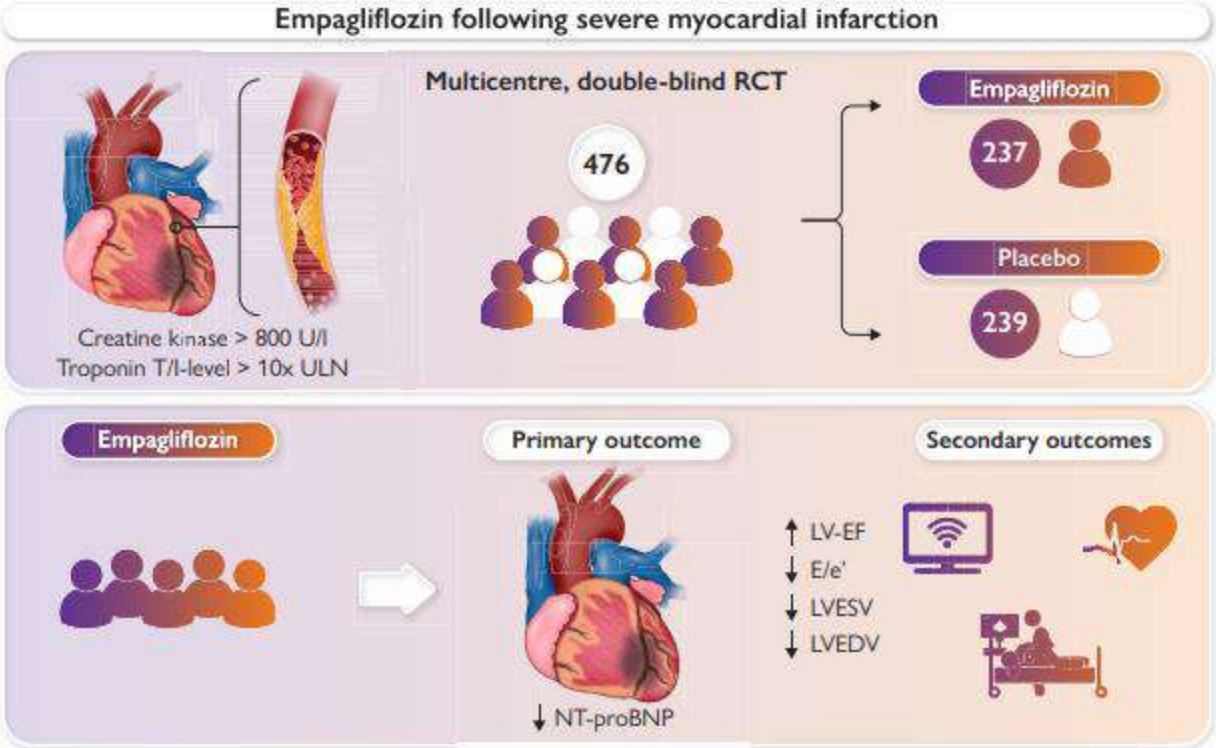




ESC European Society of Cardiology
European Heart Journal (2022) **43**, 4421–4432
https://doi.org/10.1093/eurheartj/ehac494

.....molto altro

Empagliflozin in acute myocardial infarction: the EMMY trial



Conclusion In patients with a recent myocardial infarction, empagliflozin was associated with a significantly greater NT-proBNP reduction over 26 weeks, accompanied by a significant improvement in echocardiographic functional and structural parameters.

RESEARCH SUMMARY

Empagliflozin after Acute Myocardial Infarction

Butler J et al. DOI: 10.1056/NEJMoa2314051

CONCLUSIONS

Among adults at high risk for heart failure after an acute myocardial infarction, daily treatment with empagliflozin did not result in a significantly lower risk of a first hospitalization for heart failure or death from any cause than placebo.

Links: Full Article | NEJM Quick Take | Editorial

Early initiation of SGLT2 inhibitors after acute myocardial infarction

ESC Working Group Cardiovascular Pharmacotherapy

Andeas Hammer [1], Samuel Sossalla [2,3], and Patrick Sulzgruber [1,*]

EMPACT-MI	1:1 RCT	DAPA-MI
Inclusion: Newly LVEF ↓/Congestion Exclusion: History of HF	Acute MI (NSTEMI/STEMI)	Inclusion: LVEF ↓ or Q-wave MI Exclusion: History of HF/DM
6522 Patients 78% with LVEF <45%		4017 Patients 67% with LVEF 30–49%
Placebo / 10mg o.d. Empagliflozin		Placebo / 10mg o.d. Dapagliflozin
Composite Endpoint: First hospitalization for HF / all-cause death		**Composite Endpoint:** Death, HF-hosp., nonfatal MI, AFIB onset, DM onset, NYHA reduction, weight loss >5%
HR 0.90 (95% CI 0.76-1.06, p=0.21)		Win-Ratio: 1.34 (95% CI 1.20-1.50, p<0.001)

2 Years

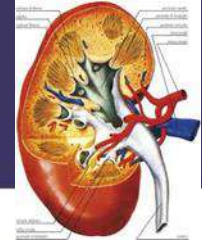
In conclusion, while SGLT2 inhibitors offer promising cardiometabolic and HF benefits in post-AMI patients, their long-term impact on robust outcomes such as mortality remains unclear. However, the absence of a mortality signal in both DAPA-MI and EMPACT-MI raises questions about their routine post-AMI use of SGLT2 inhibitors, especially considering cost and safety concerns

The DAPA-MI trial investigated the effect of dapagliflozin on cardiometabolic outcomes in patients with AMI without a history of diabetes mellitus (DM) or HF

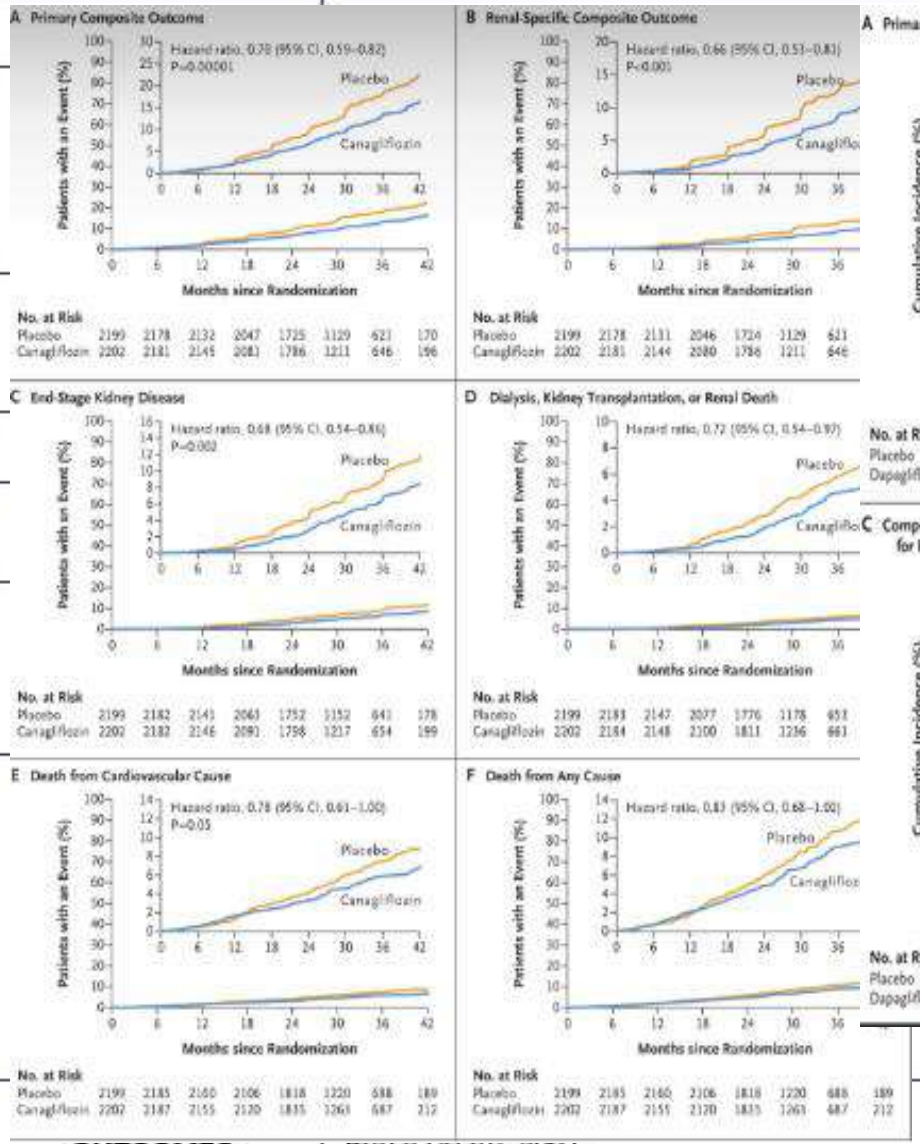
CONCLUSIONS

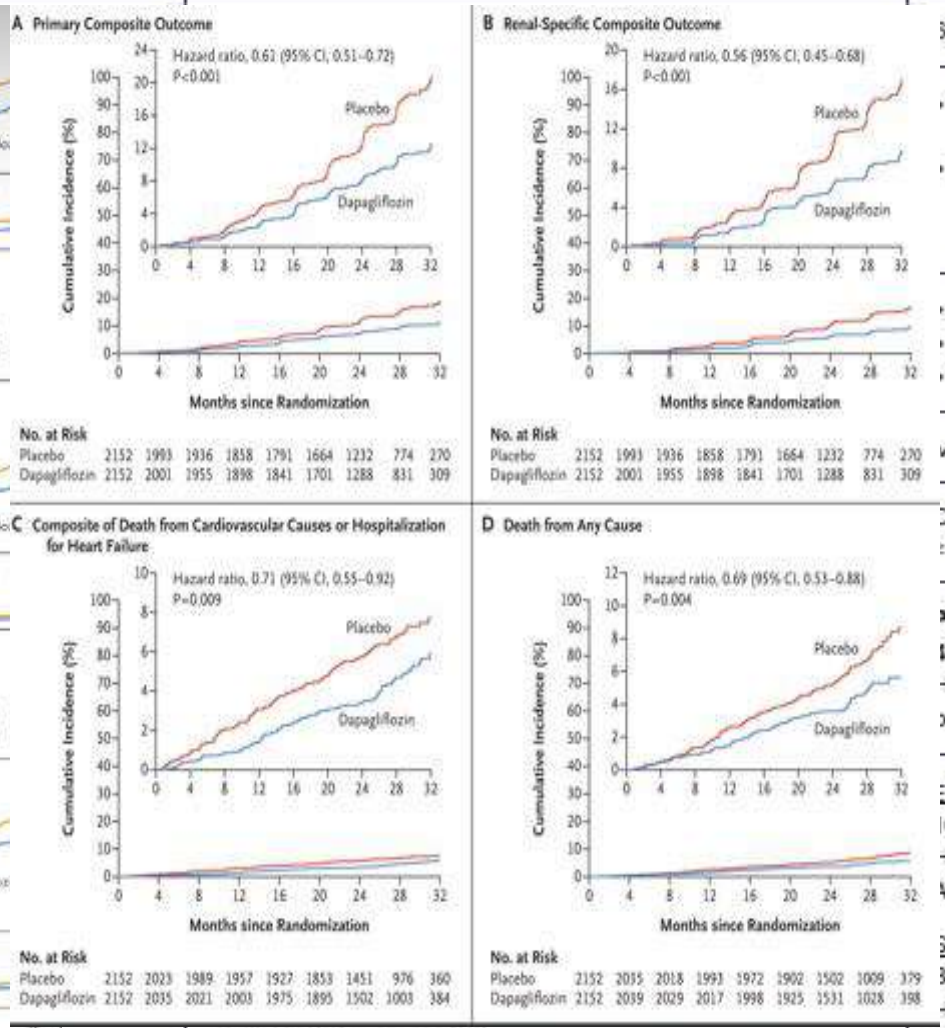
In patients with acute MI as noted above, after approximately 1 year of treatment with dapagliflozin there were significant benefits with regard to improvement in cardiometabolic outcomes but no impact on the composite of cardiovascular death or hospitalization for heart failure compared with placebo.

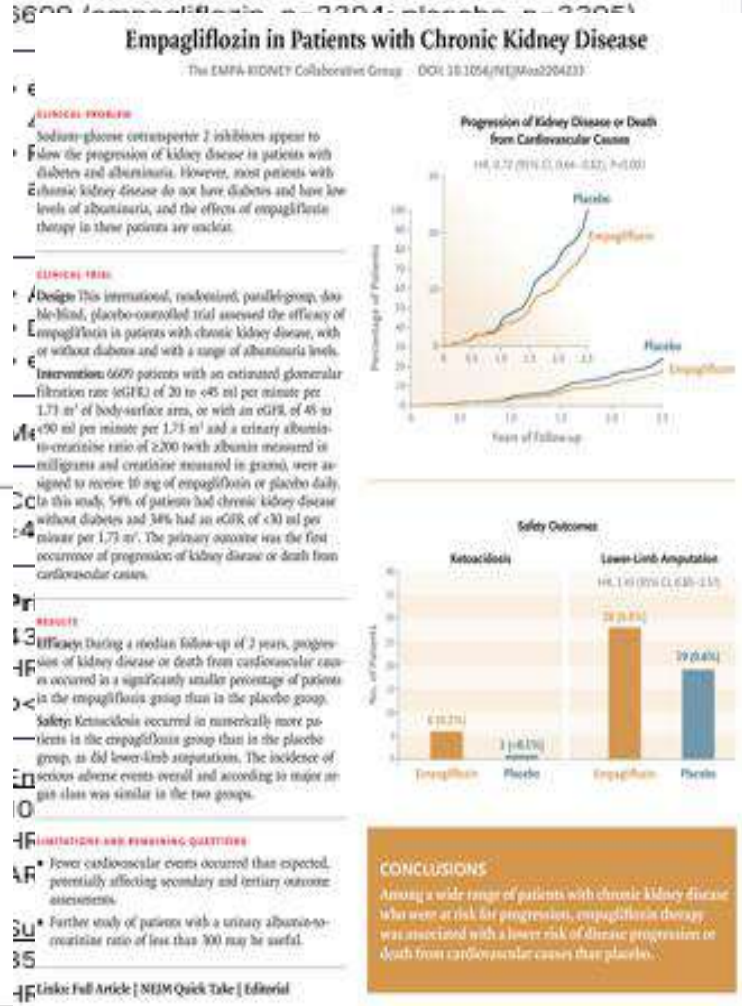
SGLT2 INHIBITORS: SUMMARY OF RENAL TRIALS



	CREDENCE 2019	DAPA-CKD 2020	EMPA-KIDNEY 2023
DRUG	Canagliflozin 100 mg daily	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily
OUTCOMES	Renal Death: NSD	ARR 4.14%; NNT ~25 Cardiovascular Death: NSD Renal Death: NSD	Cardiovascular Death: NSD Renal Death: NSD

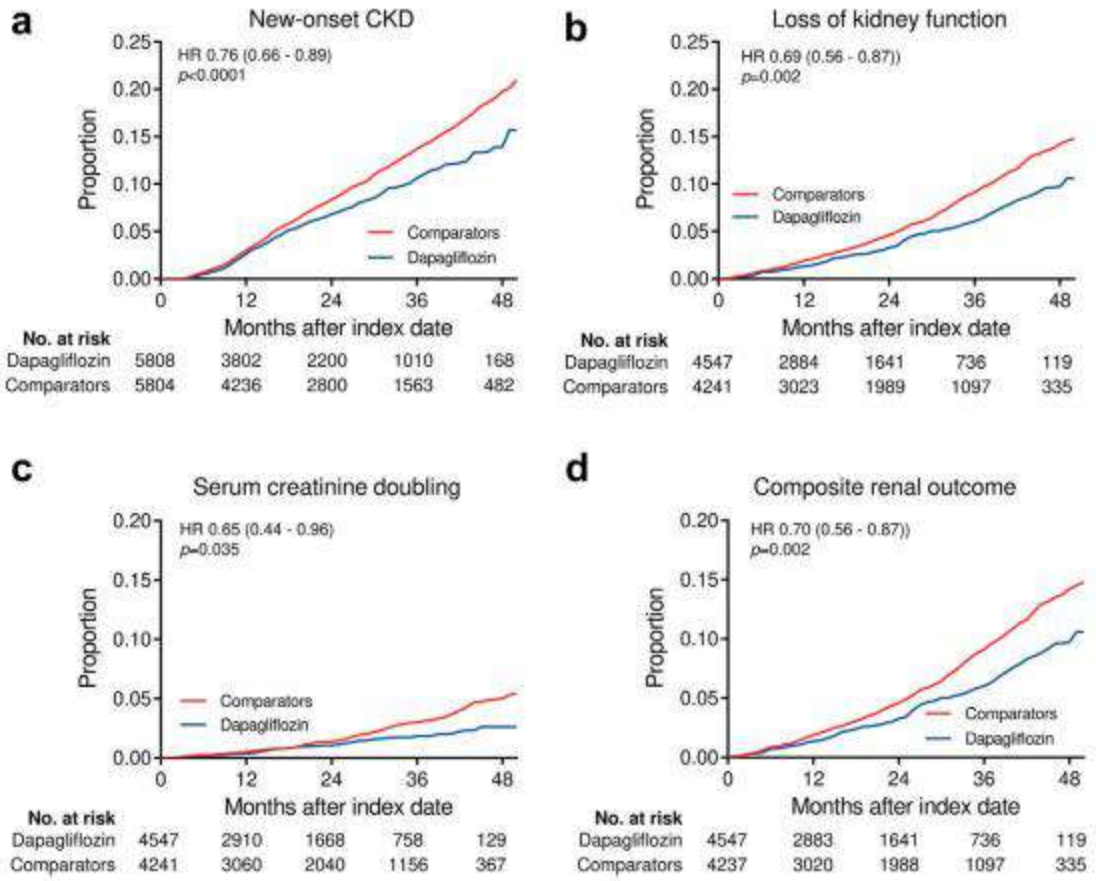






Long-term benefits of dapagliflozin on renal outcomes of type 2 diabetes under routine care: a comparative effectiveness study on propensity score matched cohorts at low renal risk

Gian Paolo Fadini,[a,b,f,*] Enrico Longato,[c,f] Mario Luca Morieri,[a] Stefano Del Prato,[d] Angelo Avogaro,[a] and Anna Solini[e]
DARWIN-Renal Study Investigators



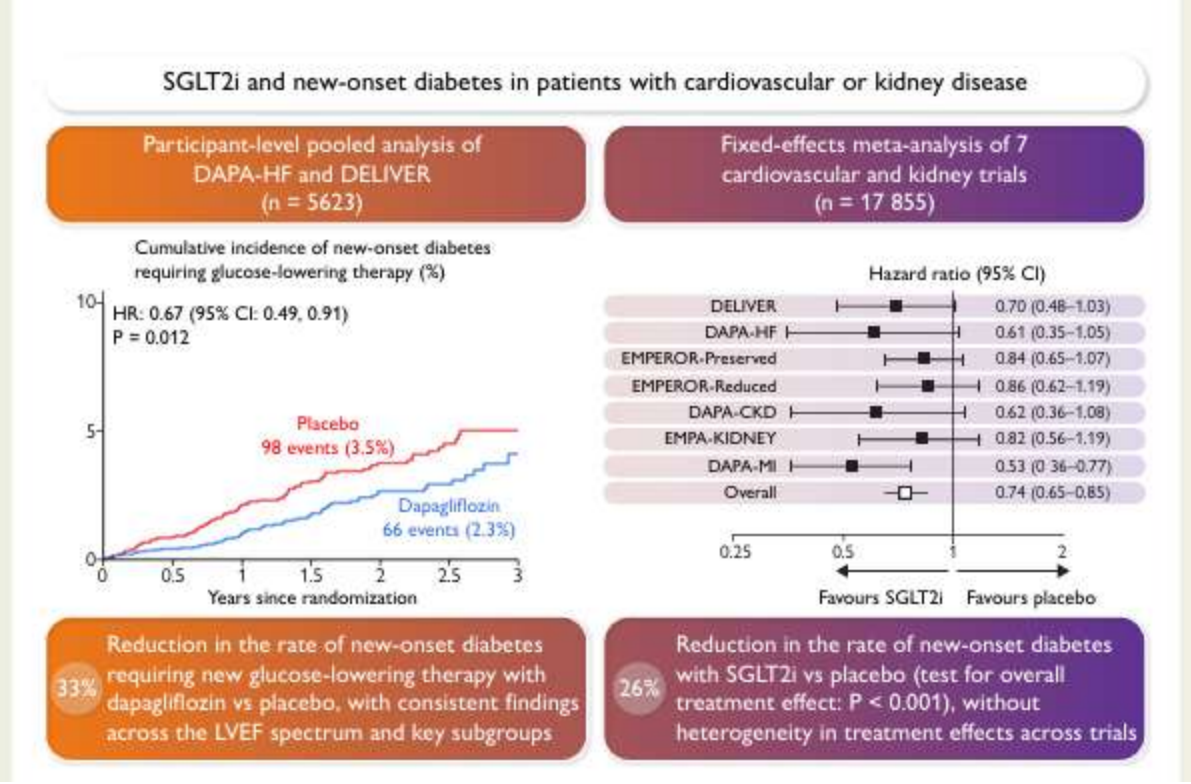
In summary, our study, designed to overcome some issues with prior observational research, supports the strong protective effects of dapagliflozin against the loss of kidney function under routine care, even in patients without baseline CKD. Based on real-world evidence, it is expected that broadening the population of patients with T2D who are receiving SGLT2i will drive a change in the epidemiology of ESKD in the next decades.

ESC European Society of Cardiology
European Heart Journal (2025) **46**, 1321–1331
https://doi.org/10.1093/eurheartj/ehae780

.....molto altro

Sodium-glucose co-transporter 2 inhibitors and new-onset diabetes in cardiovascular or kidney disease

- Effetto glicosurico
- ↓ del peso corporeo e della adiposità viscerale
- ↑ della sensibilità insulinica e della funzione β cellulare



Conclusions

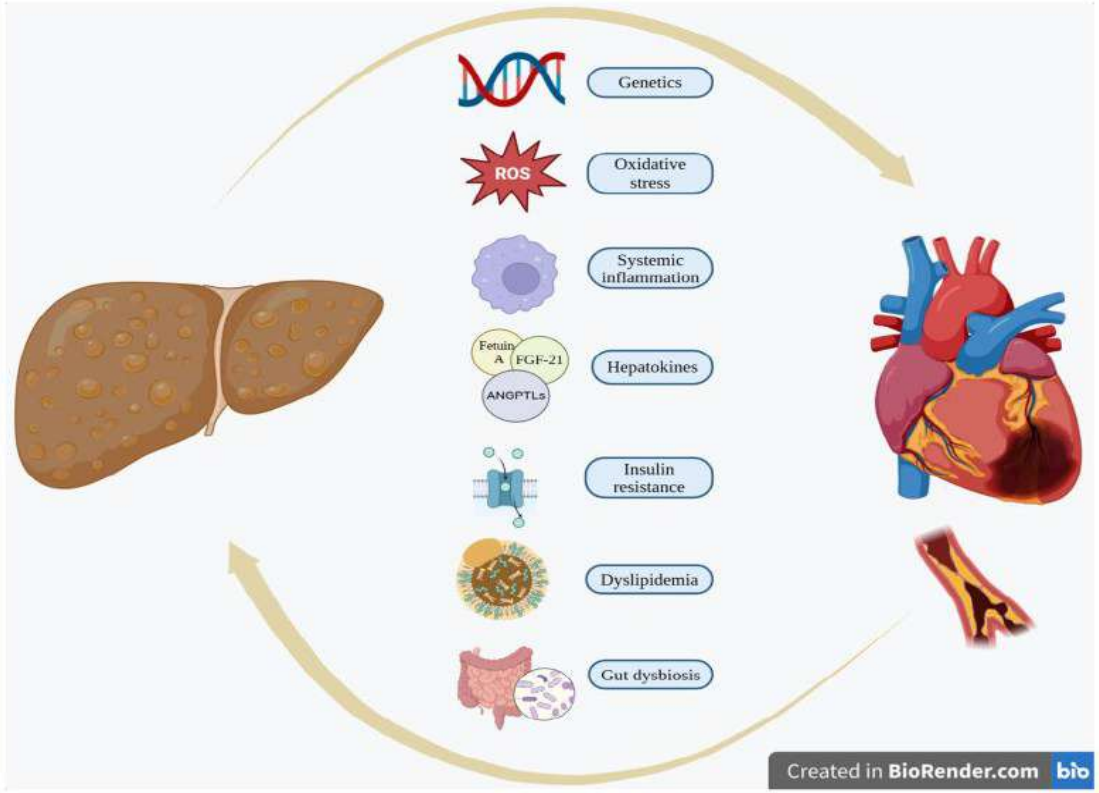
SGLT2i reduced incident diabetes necessitating the initiation of GLT in patients with HF across the LVEF spectrum, without excess risk of major hypoglycaemia. In a comprehensive meta-analysis of seven trials of patients with cardiovascular or kidney diseases, we estimate that SGLT2i reduce risk of new-onset diabetes by 26%. These findings further emphasize the role of SGLT2i as a core component of comprehensive strategies to improve cardiovascular-kidney-metabolic health.

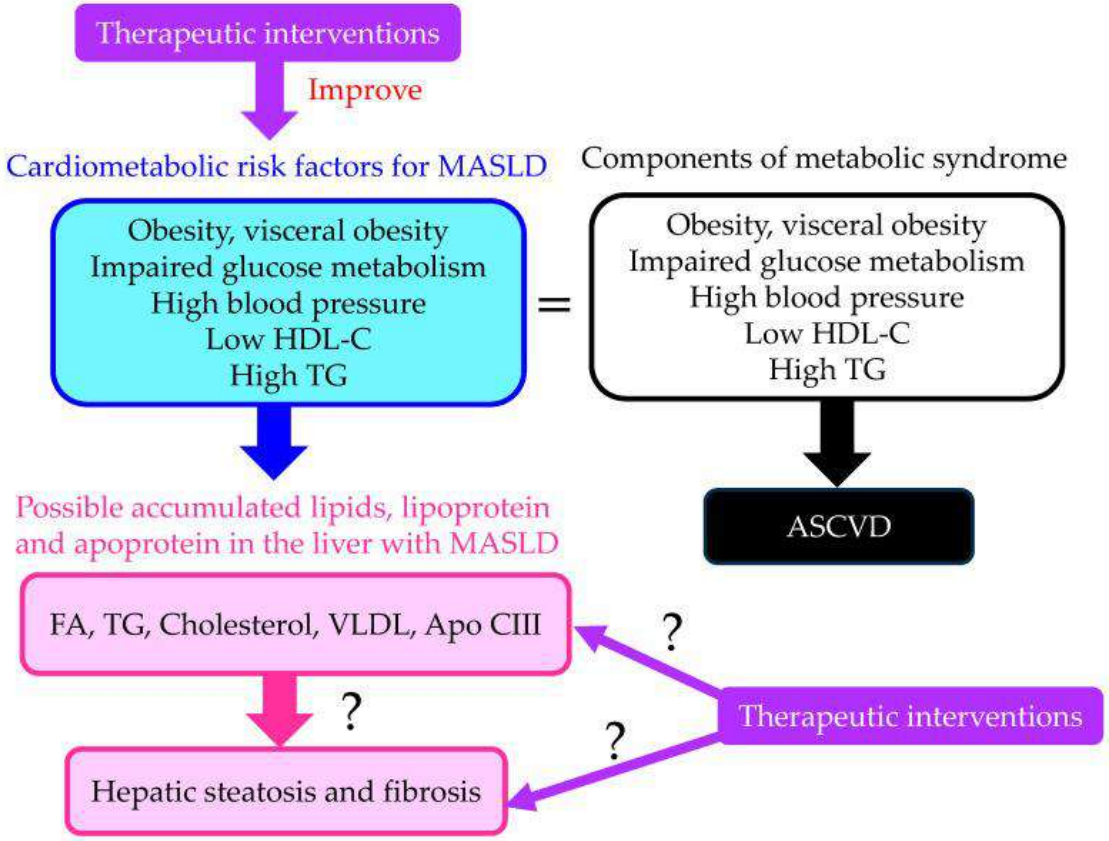
Review

Linking Cardiovascular Disease and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): The Role of Cardiometabolic Drugs in MASLD Treatment

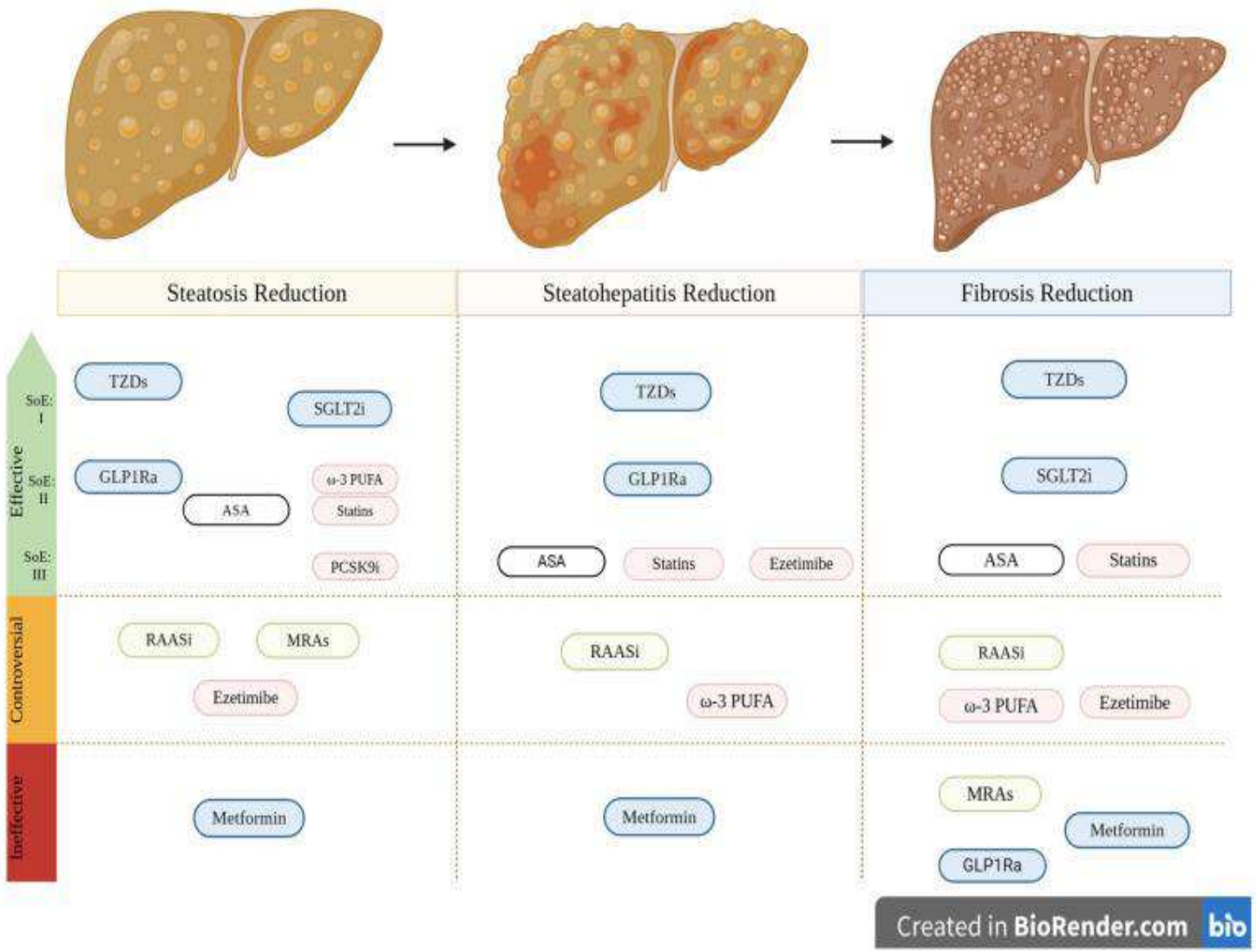
Marios Zisis [1], Maria Eleni Chondrogianni [2,3,†], Theodoros Androutsakos [4,†], Ilias Rantos [1], Evangelos Oikonomou [5], Antonios Chatzigeorgiou [6] and Eva Kassi [2,3,*]

.....molto altro





https://doi.org/10.3390/biom15030324



SGLT2i

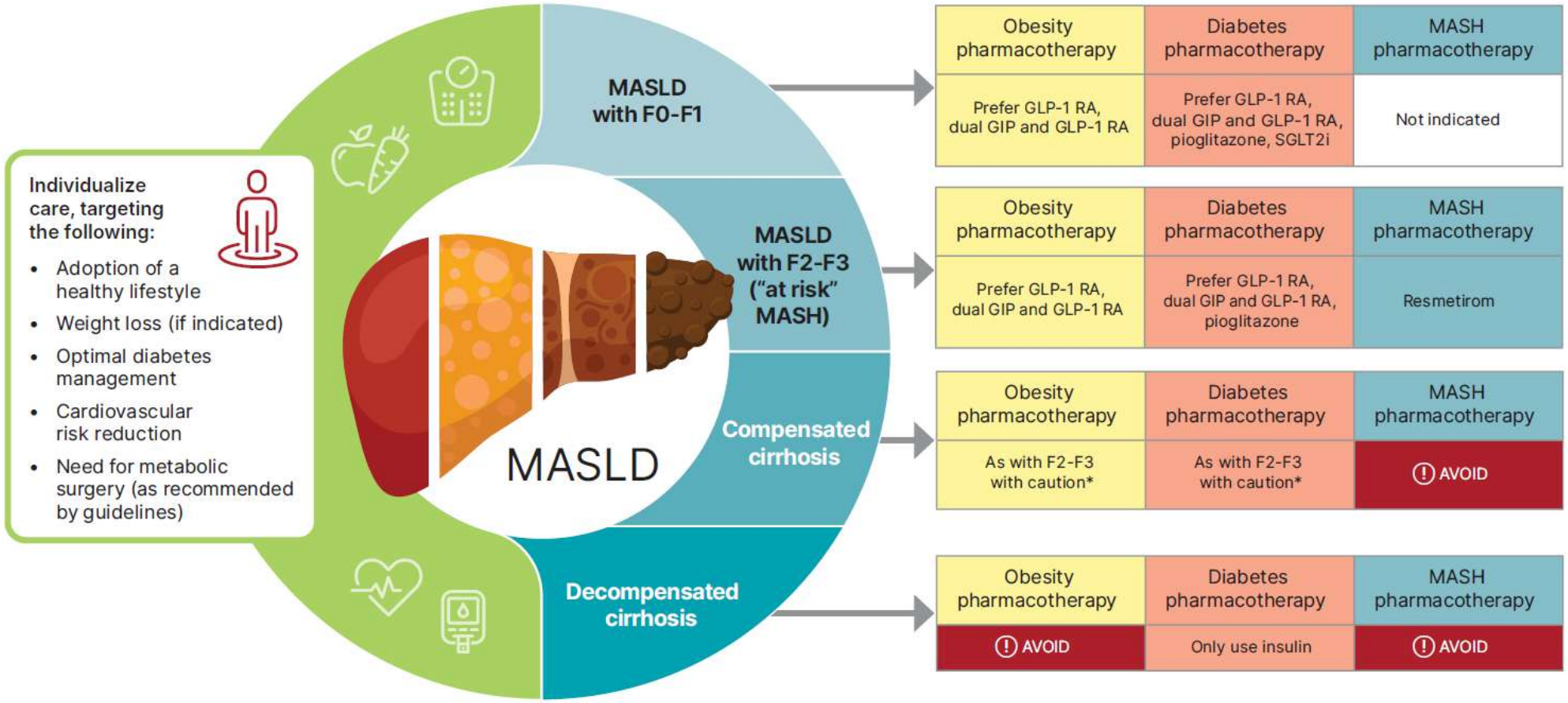
- ↓ Insulina e ↓ lipogenesi
- α cells ↑glucagone: β ossidazione FFA con ↓ trigliceridi epatici
- ↓glucotossicità e ROS e induzione di enzimi antiossidanti

SGLT2i

- ↓ Steatosi epatica
- ↓livelli di aminotransferasi
- ↓ Peso corporeo

https://doi.org/10.3390/biom15030324

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

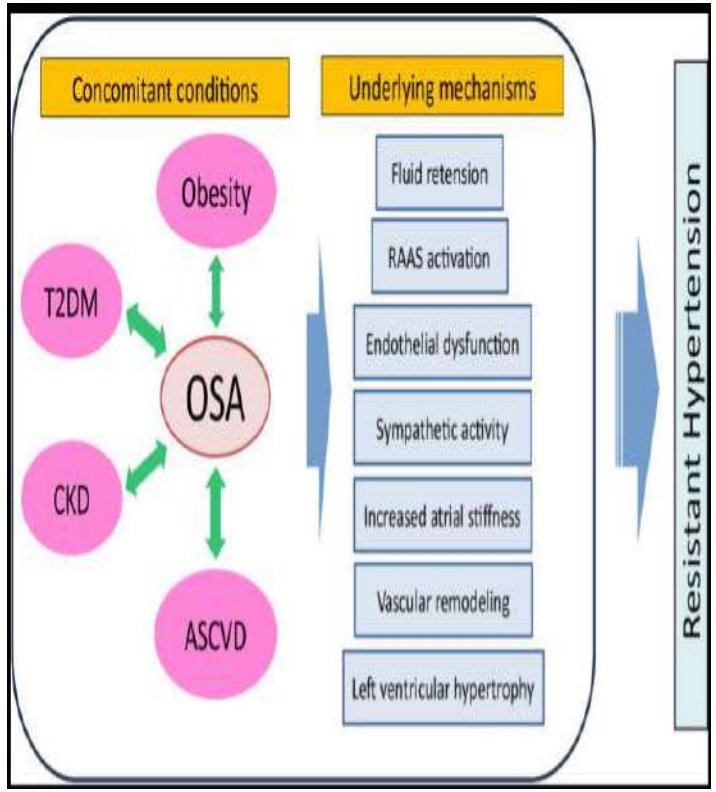
Figure 4.3—Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

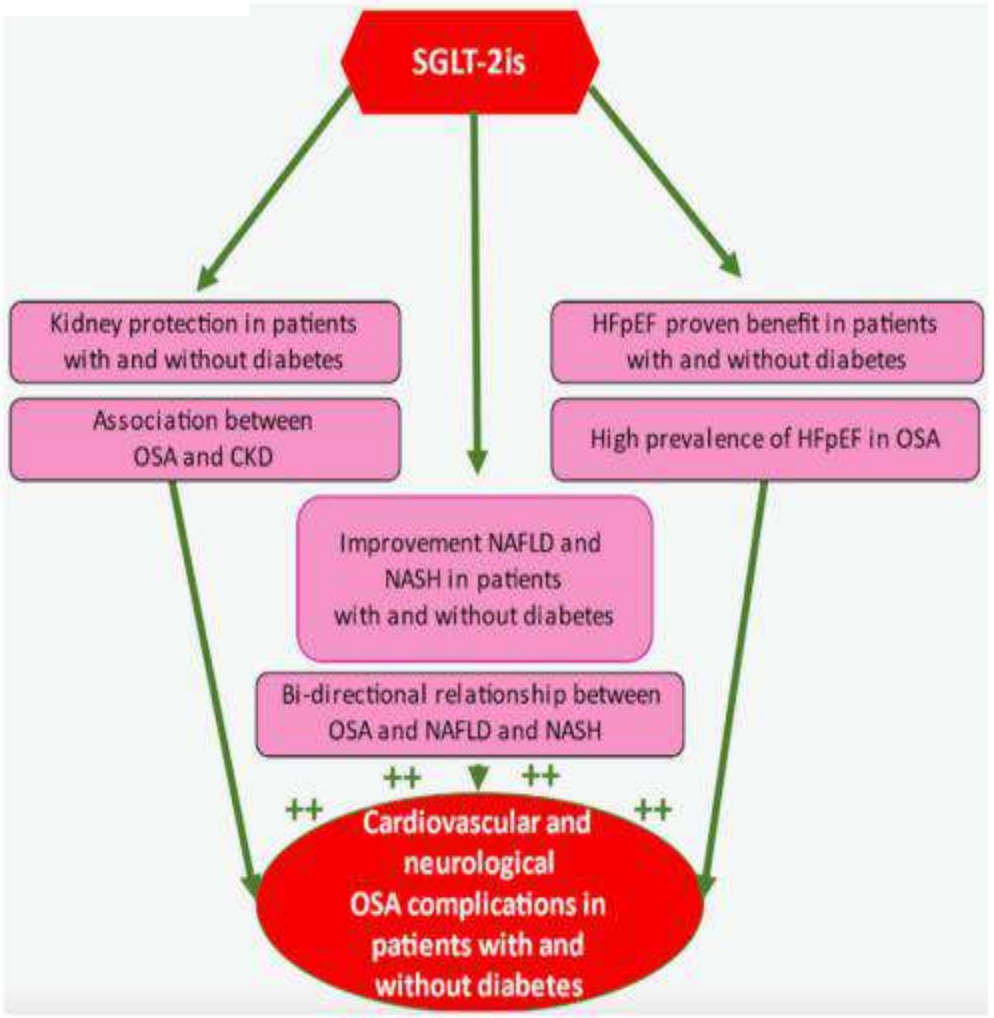
Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Care in Diabetes - 2025. Diabetes Care 2025;48(Suppl. 1):S59-S85

Heart Failure with Preserved Ejection Fraction and Obstructive Sleep Apnea: A Novel Paradigm for Additional Cardiovascular Benefit of SGLT2 Inhibitors in Subjects With or Without Type 2 Diabetes

Vincenzo Maria Monda · Sandro Gentile · Francesca Porcellati · Ersilia Satta · Alessandro Fucili · Marcello Monesi · Felice Strollo

.....molto altro ancora





In conclusion, the putative favorable effect of SGLT2is in patients with OSA is likely due to the ability to reduce cardiovascular events inpatients with HFpEF [31] and improve renal function independently of diabetes [37, 38].

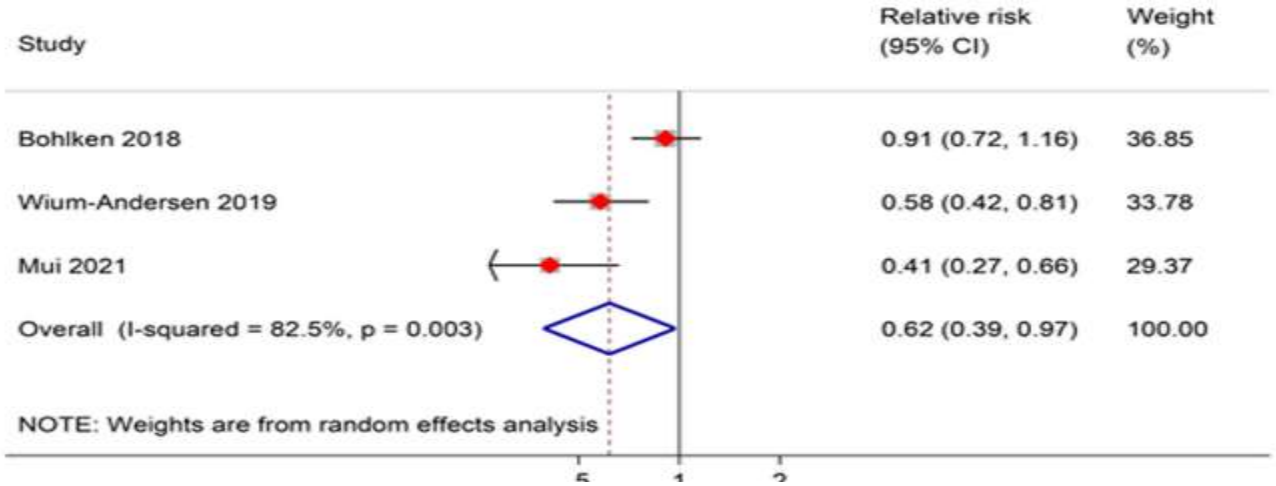
Considering the close association between OSA and HFpEF, SGLT2is might also be promising for OSA prevention, treatment, and rehabilitation regardless of coexisting T2DM, as well as for the often-associated NAFLD when T2DM is present.

……molto altro ancora

Newer glucose-lowering drugs and risk of dementia: A systematic review and meta-analysis of observational studies

Huilin Tang MSc, Hui Shao MD, PhD, C. Elizabeth Shaaban PhD, Keming Yang PhD, Joshua Brown PharmD, PhD, Stephen Anton PhD, Yonghui Wu PhD ... See all authors

First published: 23 February 2023 | https://doi.org/10.1111/jgs.18306 | Citations: 51



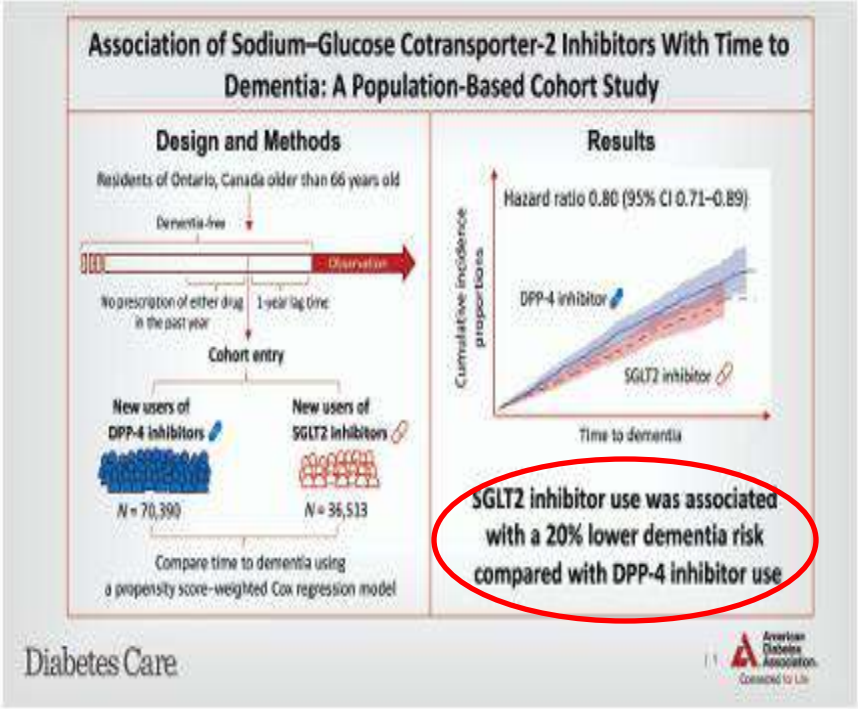
Our meta-analysis of the three observational studies showed that SGLT2 inhibitor use was significantly associated with a decreased risk of all-cause dementia, compared to nonSGLT2 inhibitor users (RR, 0.62; 95% CI, 0.39–0.97) (Figure 2). However, a high level of heterogeneity between studies was observed in this meta-analysi

Diabetes Care
American Diabetes Association.

Association of Sodium–Glucose Cotransporter 2 Inhibitors With Time to Dementia: A Population-Based Cohort Study

Che-Yuan Wu, Carina Iskander, Christa Wang, Lisa Y. Xiong, Baiju R. Shah, Jodi D. Edwards, Moira K. Kapral, Nathan Herrmann, Krista L. Lanctôt, Mario Masellis, Richard H. Swartz, Hugo Cogo-Moreira, Bradley J. MacIntosh, Jennifer S. Rabin, Sandra E. Black, Refik Saskin, and Walter Swardfager

Diabetes Care 2023;46(2):297–304 | https://doi.org/10.2337/dc22-1705



JAMA Neurology | Original Investigation

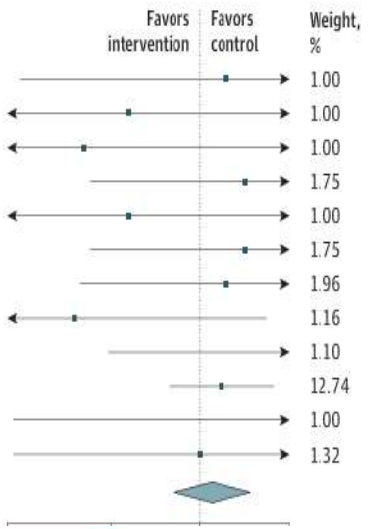
Cardioprotective Glucose-Lowering Agents and Dementia Risk
A Systematic Review and Meta-Analysis

Allie Seminer, MSc; Alfredi Mulihano; Clare O'Brien, MD; Finn Krewer, PhD; Maria Costello, PhD; Conor Judge, PhD; Martin O'Donnell, PhD; Catriona Reddin, MD

Figure 1. Association of Glucose-Lowering Therapy With All-Cause Dementia

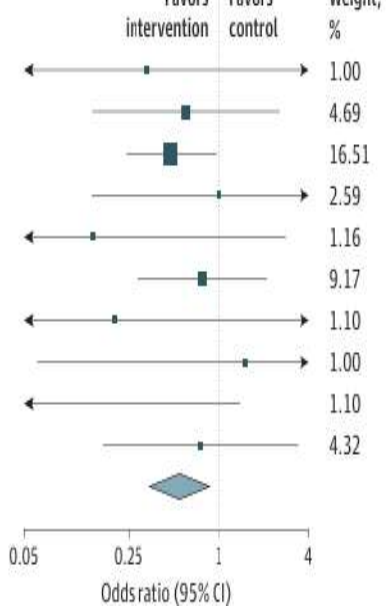
A SGLT2i

Study	Intervention event	Total	Control event	Total	ARR (95% CI)	Odds ratio (95% CI)	Weight, %
Zinman et al,[28] 2015	1	4687	0	2333	-0.01 (-0.09 to 0.07)	1.49 (0.06 to 36.68)	1.00
Neal et al,[29] 2017	0	2907	1	2905	0.03 (-0.06 to 0.13)	0.33 (0.01 to 8.18)	1.00
Neal et al,[29] 2017	0	2888	1	1442	0.09 (-0.09 to 0.26)	0.17 (0.01 to 4.09)	1.00
Wiviott et al,[32] 2019	2	8582	1	8578	-0.01 (-0.05 to 0.03)	2.00 (0.18 to 22.05)	1.75
McMurray et al,[31] 2019	0	2373	1	2371	0.04 (-0.07 to 0.16)	0.33 (0.01 to 8.18)	1.00
Perkovic et al,[30] 2019	2	2202	1	2199	-0.05 (-0.20 to 0.11)	2.00 (0.18 to 22.05)	1.75
Cannon et al,[35] 2020	3	5499	1	2747	-0.02 (-0.11 to 0.08)	1.50 (0.16 to 14.42)	1.96
Packer et al,[34] 2020	0	1863	3	1867	0.16 (-0.05 to 0.37)	0.14 (0.01 to 2.77)	1.16
Heerspink,[33] 2020	2	2152	0	2152	-0.09 (-0.25 to 0.06)	5.00 (0.24 to 104.30)	1.10
Anker et al,[36] 2021	14	2997	10	2991	-0.13 (-0.45 to 0.19)	1.40 (0.62 to 3.15)	12.74
Peikert et al,[37] 2022	1	3131	0	3132	-0.03 (-0.12 to 0.06)	3.00 (0.12 to 73.72)	1.00
Herrington et al,[38] 2023	1	3304	1	3305	0.00 (-0.08 to 0.08)	1.00 (0.06 to 16.00)	1.32
RE model for subgroup: Q = 6.40; *df* = 11; *P* = .85; I^2 = 0%					-0.01 (-0.04 to 0.02)	1.20 (0.67 to 2.17)	



B GLP-1RA

Study	Intervention event	Total	Control event	Total	ARR (95% CI)	Odds ratio (95% CI)	Weight, %
Pfeffer et al,[39] 2015	0	3034	1	3034	0.03 (-0.06 to 0.12)	0.33 (0.01 to 8.18)	1.00
Marso et al,[51] 2016	3	1648	5	1649	0.12 (-0.21 to 0.46)	0.60 (0.14 to 2.51)	4.69
Marso et al,[40] 2016	12	4668	25	4672	0.28 (0.02 to 0.53)	0.48 (0.24 to 0.95)	16.51
Holman et al,[41] 2017	2	7356	2	7396	0.00 (-0.05 to 0.05)	1.01 (0.14 to 7.14)	2.59
Hernandez et al,[47] 2018	0	4731	3	4732	0.06 (-0.02 to 0.15)	0.14 (0.01 to 2.77)	1.16
Gerstein et al,[42] 2019	7	4949	9	4952	0.04 (-0.12 to 0.20)	0.78 (0.29 to 2.09)	9.17
Husain et al,[43] 2019	0	1591	2	1592	0.13 (-0.09 to 0.34)	0.20 (0.01 to 4.17)	1.10
Gerstein et al,[44] 2021	1	2717	0	1359	-0.02 (-0.15 to 0.12)	1.50 (0.06 to 36.88)	1.00
Frias et al,[45] 2022	0	304	2	102	2.26 (-0.74 to 5.27)	0.07 (0.00 to 1.39)	1.10
Lincoff et al,[48] 2023	3	8803	4	8801	0.01 (-0.05 to 0.07)	0.75 (0.17 to 3.35)	4.32
RE model for subgroup: Q = 4.72; *df* = 9; *P* = .86; I^2 = 0%					0.07 (0.02 to 0.1)	0.55 (0.35 to 0.86)	



Conclusions

In this meta-analysis of randomized clinical trials, glucose-lowering therapy with GLP1-RAs, but not SGLT2is or pioglitazone, was associated with a statistically significant reduction in dementia or cognitive impairment.

RESEARCH ARTICLE | September 18, 2024 |

SGLT2 Inhibitor Use and Risk of Dementia and Parkinson Disease Among Patients With Type 2 Diabetes

Hae Kyung Kim, MD, Geert Jan Biessels, MD, PhD, Min Heui Yu, MS, Namki Hong, MD, PhD, Yong-ho Lee, MD, PhD, Byung-Wan Lee, MD, PhD, Eun Seok Kang, MD, PhD, Bong-Soo Cha, MD, PhD, Eun Jig Lee, MD, PhD, and Minyoung Lee, MD, PhD AUTHORS INFO & AFFILIATIONS

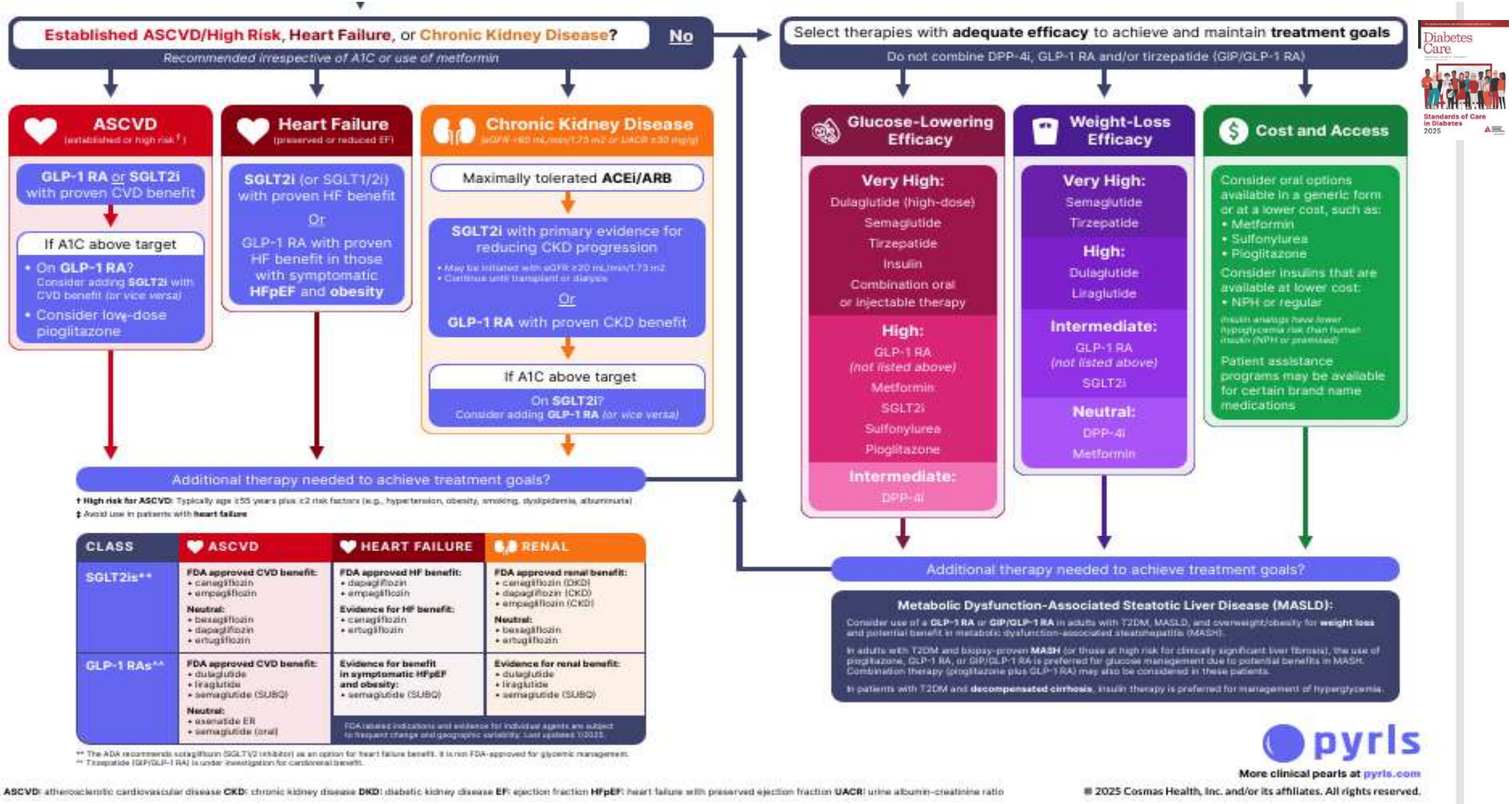
October 22, 2024 issue • 103 (8) • https://doi.org/10.1212/WNL.0000000000209805

Results

From the 358,862 participants analyzed (mean [SD] age, 57.8 [9.6] years; 58.0% male), 6,837 incident dementia or PD events occurred. Regarding the individual endpoints, SGLT2i use was associated with reduced risks of AD (adjusted hazard ratio [aHR] 0.81, 95% CI 0.76–0.87), VaD (aHR 0.69, 95% CI 0.60–0.78), and PD (aHR 0.80, 95% CI 0.69–0.91) with a 6-month drug use lag period. In addition, use of SGLT2i was associated with a 21% lower risk of all-cause dementia (aHR 0.79, 95% CI 0.69–0.90) and a 22% lower risk of all-cause dementia and PD than use of other OADs (aHR 0.78, 95% CI 0.73–0.83). The association between the use of SGLT2i and the lowered risk of these neurodegenerative disorders was not affected by sex, Charlson Comorbidity Index, diabetic complications, comorbidities, and medications. Sensitivity analysis further

Discussion

In this nationwide population-based study, SGLT2i use significantly reduced the risks of neurodegenerative disorders in patients with type 2 diabetes independent of various factors including comorbidities and bioclinical parameters.



† **High risk for ASCVD:** Typically age ≥55 years plus ≥2 risk factors (e.g., hypertension, obesity, smoking, dyslipidemia, albuminuria)

‡ Avoid use in patients with **heart failure**

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is**	**FDA approved CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • bexagliflozin • dapagliflozin • ertugliflozin	**FDA approved HF benefit:** • dapagliflozin • empagliflozin **Evidence for HF benefit:** • canagliflozin • ertugliflozin	**FDA approved renal benefit:** • canagliflozin (DKD) • dapagliflozin (CKD) • empagliflozin (CKD) **Neutral:** • bexagliflozin • ertugliflozin
GLP-1 RAs**	**FDA approved CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • semaglutide (oral)	**Evidence for benefit in symptomatic HFpEF and obesity:** • semaglutide (SUBQ)	**Evidence for renal benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)

FDA-labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 1/2025.

** The ADA recommends sotagliflozin (SGLT1/2 inhibitor) as an option for heart failure benefit. It is non FDA-approved for glycemic management.

** Tirzepatide (GIP/GLP-1 RA) is under investigation for cardiorenal benefit.

ASCVD: atherosclerotic cardiovascular disease **CKD:** chronic kidney disease **DKD:** diabetic kidney disease **EF:** ejection fraction **HFpEF:** heart failure with preserved ejection fraction **UACR:** urine albumin-creatinine ratio

Diabetes Care

Standards of Care in Diabetes 2025

pyrls

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Key practice points:

- *Discuss the relative benefits and risks of SGLT2i therapy with the person you are treating.*
- *Use dual first-line SGLT2i therapy with metformin (unless contraindicated). Initiate 4 weeks after metformin, post-date the SGLT2i prescription and do not wait for HbA1c assessment at 3 months after metformin initiation.*
- *Emphasise the importance of ongoing hydration and good personal hygiene.*
- *Give written information/electronic resources to support advice on the management of T2DM medicines during periods of acute or dehydrating illness.*
- *If symptomatic of hyperglycaemia, start rescue therapy and then reassess initiation of SGLT2i when symptoms resolved.*
- *For planned surgery or procedures requiring nil by mouth, advise on the importance of pausing SGLT2i treatment 3–7 days prior to surgery or liaise with pre-operative team.*
- *Please refer to the relevant SmPC before prescribing any SGLT2i therapy.*
- *Discussion with an expert clinician is advisable for more complex cases.*

Initial assessment

- QRISK®3 calculator
- QRISK®3-lifetime calculator
- Kidney function (eGFR and UACR)

Consider SGLT2i therapy

- Frailty/older people/cognitive impairment
- Ketogenic/very low calorie/low carbohydrate diet
- BMI <25 kg/m² (adjust according to ethnic variation)
- Recurrent genital mycotic infections and UTIs
- Symptomatic hyperglycaemia
- History of PAD and/or lower limb amputation (discuss with local specialist foot team)
- QRISK®3 (where available or QRISK®2) <10%

Do not prescribe SGLT2i therapy

- Acute illness with risk of dehydration
- Current or previous diabetic ketoacidosis
- Low beta-cell function (low C peptide levels)
- Rapid progression to insulin (within 1 year)
- Excessive alcohol intake
- Suspected LADA or slowly evolving immune-related diabetes
- Chronic pancreatitis and/or PEI
- Type 3c diabetes
- Suspected pancreatic cancer
- Pregnancy/suspected pregnancy, planning pregnancy or breastfeeding
- Planned surgery or procedure requiring starvation/ nil by mouth (3–7 days prior to planned surgery)
- Type 1 diabetes
- Unclear diagnosis of diabetes

Offer SGLT2i therapy

First-line combination therapy with metformin* or as monotherapy if metformin is contraindicated or not tolerated in people with one of the following:

- QRISK®3 (where available or QRISK®2) >10%
- HF
- Established ASCVD
- CKD/DKD

*If using with metformin, initiate metformin first and titrate over a 4-week period and then start SGLT2i therapy

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Combination therapy with other oral glucose-lowering therapies in people with:

- QRISK®3 (where available or QRISK®2) >10%
- CVD
- HF
- CKD

Young onset T2DM (aged 18–40 years), unless planning pregnancy

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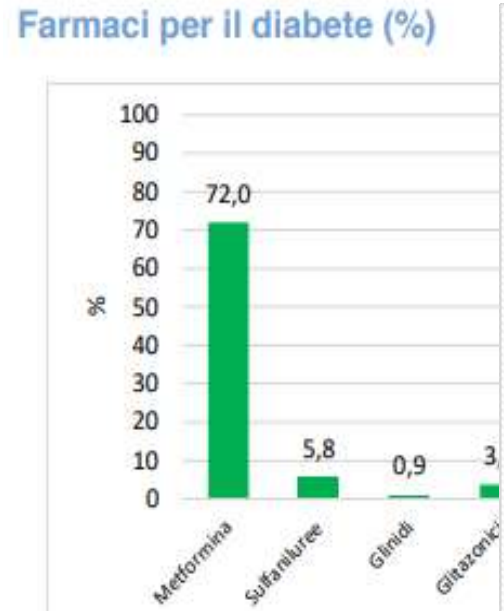
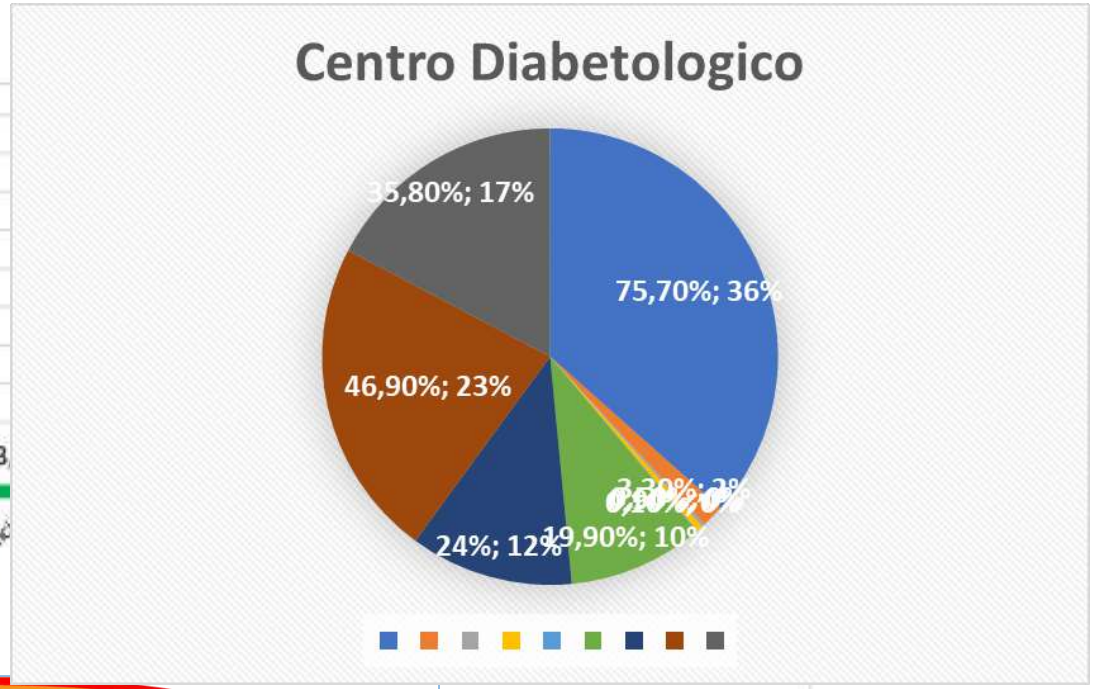
Overweight or obesity in the absence of GLP-1 RA

Vulnerable to the effects of hypoglycaemia

IMPORTANT – this decision tool is for guidance only. The final clinical decisions are the responsibility of the prescriber.





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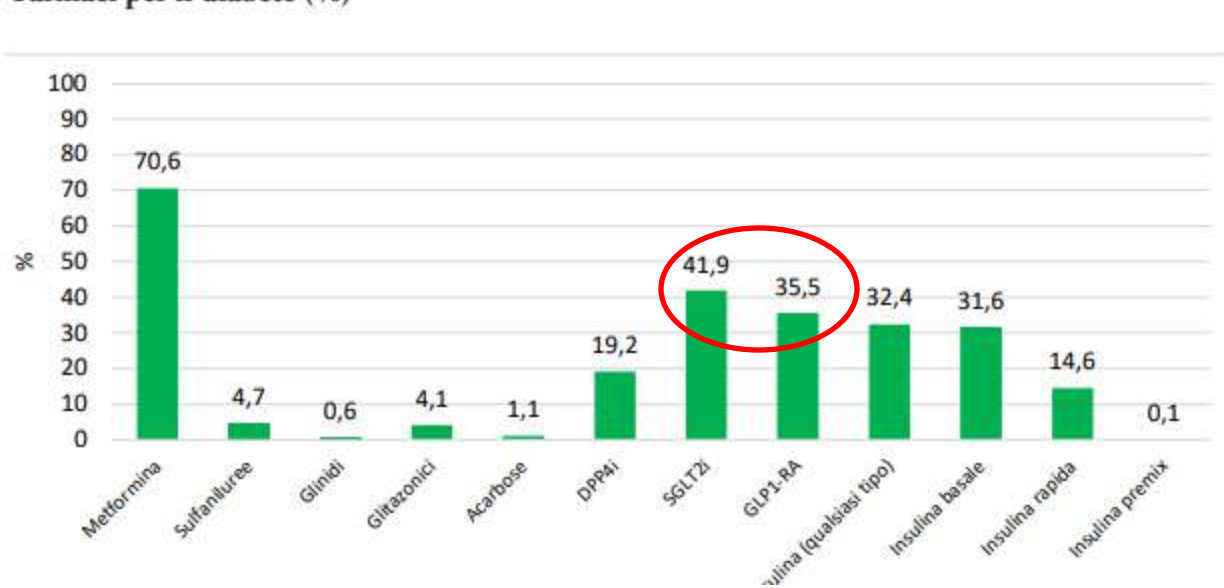

Grazie