Nuove frontiere nell'uso degli SGLT2i

Franco Tuccinardi

Diabetologia Casa del Sole Formia

DISCLOSURE

Il dr.Franco Tuccinardi dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Eli Lilly
- Boehringer
- Savio
- MSD
- Daiichi Sankyo
- Bayer

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.).

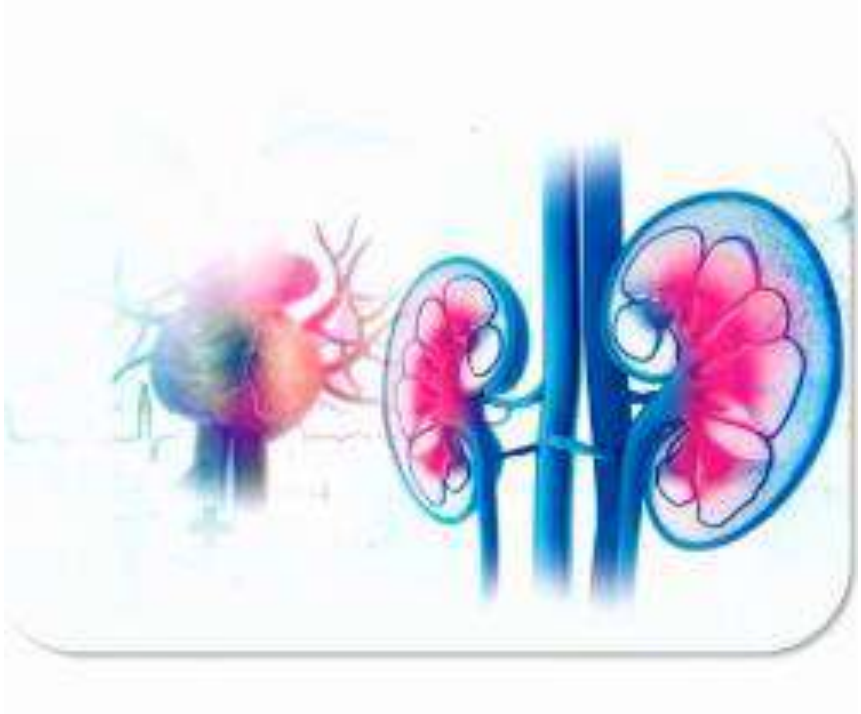
SGLT2 inhibitors have demonstrated…

Phase III trials — Metabolic benefits in people **with T2D**[1–4]

CVOTs — CV and kidney benefits in people **with T2D** and CVD[5–14]

HF trials — CV benefits in people **with HFrEF and HFpEF**, independent of T2D*[15–17]

CKD trials — Kidney benefits in people **with CKD**, independent of T2D*[18,19]

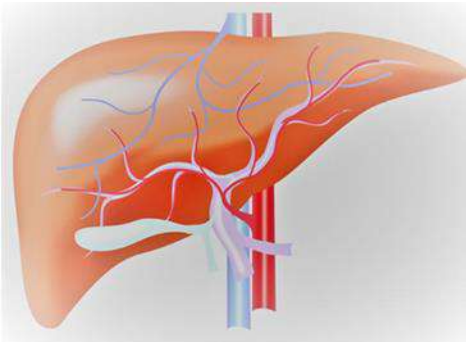


1. Häring H-U et al. Diabetes Care 2014;37:1650 2. Lavelle-Gonzalez FJ et al. Diabetologia 2013;56:2582 3. Bailey CJ et al. Lancet 2010;375:2223 4. Rosenstock J et al. Diabetes Obes Metab 2018;20:520 5. McGuire DK et al. JAMA Cardiol 2021;6:148 6. Neal B et al. N Engl J Med 2017;377:644 7. Radholm K et al. Circulation 2018;138:458 8. Wiviott S et al. N Engl J Med 2019;380:347 9. Zinman B et al. N Engl J Med 2015;373:2117 10. Wanner C et al. N Engl J Med 2016;375:323 11. Cannon CP et al. N Engl J Med 2020;383:1425 12. Cosentino F et al. Circulation 2020;142:2205 13. Cherney DZI et al. Diabetologia 2021;64:1256 14. Perkovic V et al. N Engl J Med 2019;380:2295 15. Packer M et al. N Engl J Med 2020;383:1413 16. McMurray JJV et al. N Engl J Med 2019;381:1995 17. Anker SD et al. N Engl J Med 2021;385:1451 18. Heerspink HJL et al. N Engl J Med 2020;383:1436 19. The EMPA-KIDNEY Collaborative Group. N Engl J Med 2022; 20. American Diabetes Association. Diabetes Care 2023;46:S1

Nuove evidenze con SGLT2 inibitori ?

- SGLT2i e MASLD
- SGLT2i e demenza
- SGLT2i in dialisi
- SGLT2i e IMA
- SGLT2i e retinopatia
- SGLT2i e cancro
- …..

background



- Il legame della NAFLD con disordini metabolici (obesità, T2D) è così stretto che è stata recentemente rinominata come MASLD (disfunzione metabolica associata a malattia epatica steatosica)

- La forte connessione tra T2D e MASLD si evidenzia dai dati epidemiologici : la prevalenza di MASLD nel T2D è superiore al 70% mentre nella popolazione generale è del 25%.

JAMA Internal Medicine | Original Investigation

Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease

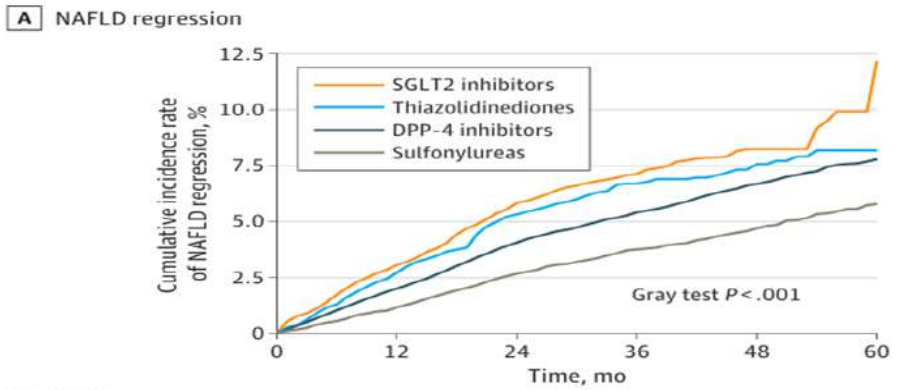
Retrospective non randomized interventional cohort study (80178 patients) to investigate which OAD is associated with the best patient outcomes in NAFLD and type 2 diabetes (T2D)

The primary outcome was **NAFLD regression** assessed by the Fatty Liver Index

The secondary end point2 was **Composite liver-related outcome** (defined as liver-related hospitalization, liver-related mortality,liver transplant, and hepatocellular carcinoma) .

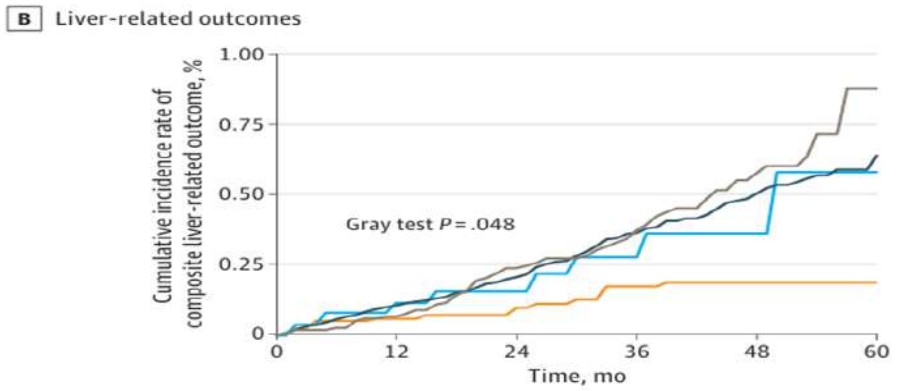
JAMA Intern Med. 2024;184(4):375-383.

Weighted Cumulative Incidence Function According to Oral Antidiabetic Drug Class



No. at risk

SGLT2 inhibitors	9418	8958	5760	2700	956	144
Thiazolidinediones	2180	2077	1552	1079	633	158
DPP-4 inhibitors	55 179	53 120	38 698	23 795	11 035	2604
Sulfonylureas	13 154	12 864	10 268	7171	4049	1054



No. at risk

SGLT2 inhibitors	9418	9236	6111	2902	1040	164
Thiazolidinediones	2180	2133	1636	1154	683	171
DPP-4 inhibitors	55 179	54 153	40 257	25 066	11 766	2806
Sulfonylureas	13 154	13 007	10 525	7423	4224	1109

JAMA Intern Med. 2024;184(4):375-383.

Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial)

Mohammad Shafi Kuchay,[1] Sonal Krishan,[2] Sunil Kumar Mishra,[1] Khalid Jamal Farooqui,[1] Manish Kumar Singh,[3] Jasjeet Singh Wasir,[1] Beena Bansal,[1] Parjeet Kaur,[1] Ganesh Jevalikar,[1] Harmendeep Kaur Gill,[1] Narendra Singh Choudhary,[4] and Ambrish Mithal[1]

Diabetes Care 2018;41:1801–1808 | https://doi.org/10.2337/dc18-0165

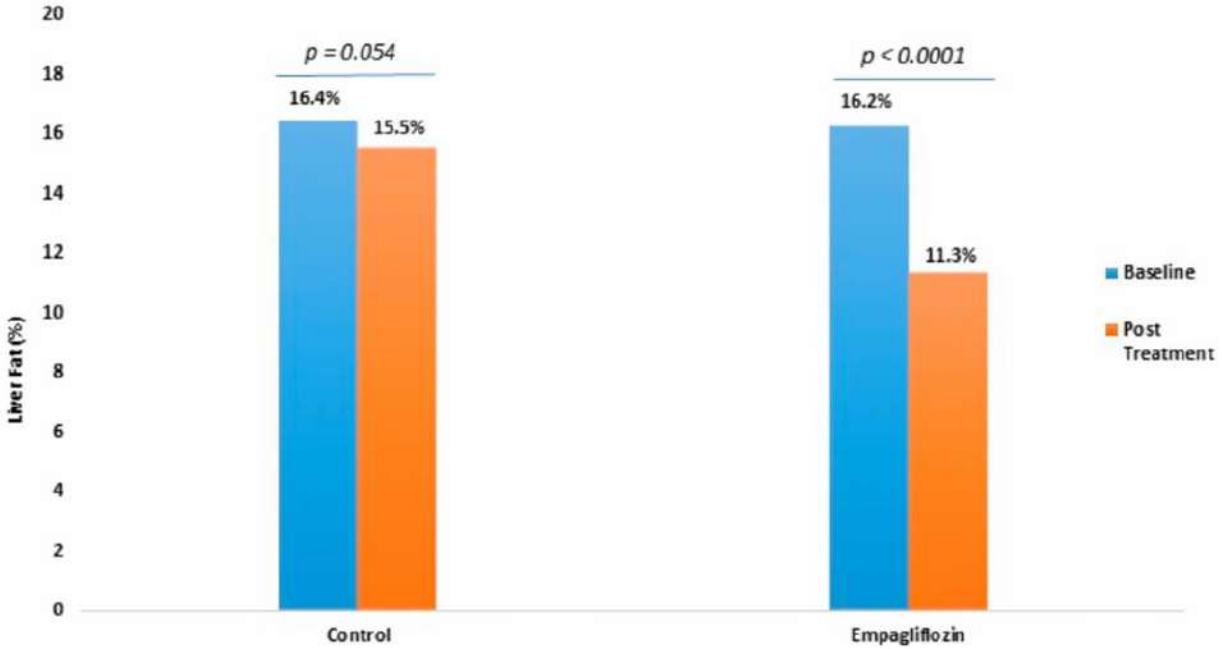
50 pazienti con diabete di tipo 2 e NAFLD sono stati assegnati in modo casuale al gruppo empagliflozin (empagliflozin 10 mg al giorno) o al gruppo di controllo .

L' outcome primario era la variazione del contenuto di grasso epatico rispetto al basale, quantificato mediante MRI-PDFF

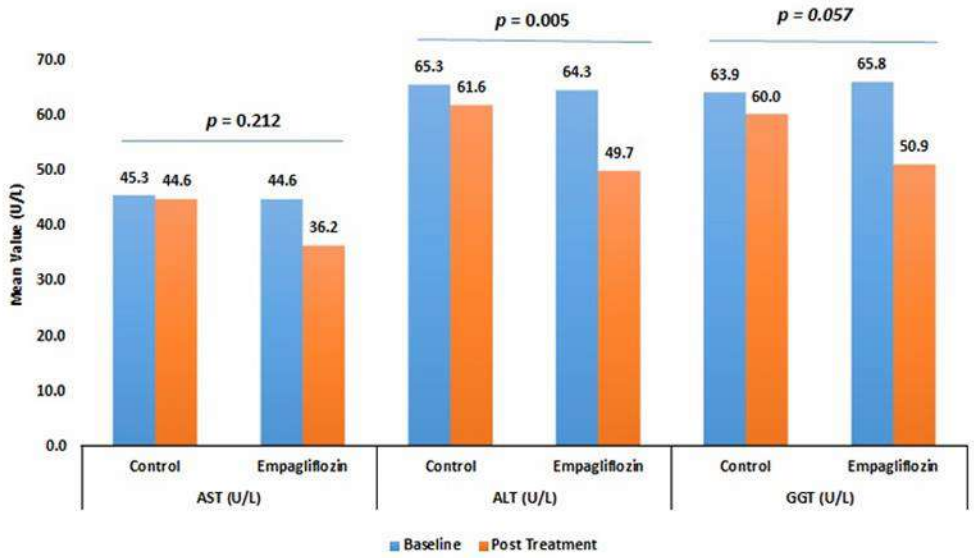
L'outcomes secondari erano la variazione dei livelli sierici di AST, ALT e GGT.

Diabetes Care 2018;41:1801–1808

Baseline and post-treatment changes in liver fat in the empagliflozin and control groups assessed by MRI-PDFF



Change in serum AST, ALT and GGT levels relative to baseline



Diabetes Care 2018;41:1801–1808

The effect of ertugliflozin in patients with nonalcoholic fatty liver disease associated with type 2 diabetes mellitus

A randomized controlled trial

Adil Khaliq, PharmD, MPhil[a], Haroon Badshah, PhD[a,*], Yasar Shah, PhD[a], Inayat Ur Rehman, PhD[a,b], Kashif Ullah Khan, PhD[b], Long Chiau Ming, PhD[c], Maong Hui Cheng, MD[c]

to determine the **effectiveness** of 15 mg of ertugliflozin versus 30 mg of the standard therapy pioglitazone versus placebo in NAFLD patients with T2DM after 24 weeks of clinical study.

Comparison among the grades of fatty liver at initial assessment and after 24 weeks of interventional treatment in NAFLD patients

	Pre-treatment			Post-treatment		
	Pioglitazone (n = 60)	Ertugliflozin (n = 60)	Placebo (n = 60)	Pioglitazone (n = 60)	Ertugliflozin (n = 60)	Placebo (n = 60)
Grade 0	0 (0%)	0 (0%)	0 (0%)	6 (10.00%)	10 (16.6%)	1 (1.6%)
Grade 1	16 (26.6%)	16 (26.6%)	17 (28.4%)	26 (43.4%)	32 (53.4%)	15 (25%)
Grade 2	25 (41.7%)	27 (45%)	24 (40%)	16 (26.6%)	14 (23.4%)	24 (40%)
Grade 3	19 (31.7%)	17 (28.4%)	19 (31.6%)	12 (20.0%)	4 (6.6%)	20 (33.4%)

NAFLD = nonalcoholic fatty liver diseases.

Medicine 2024;103:45(e40356).

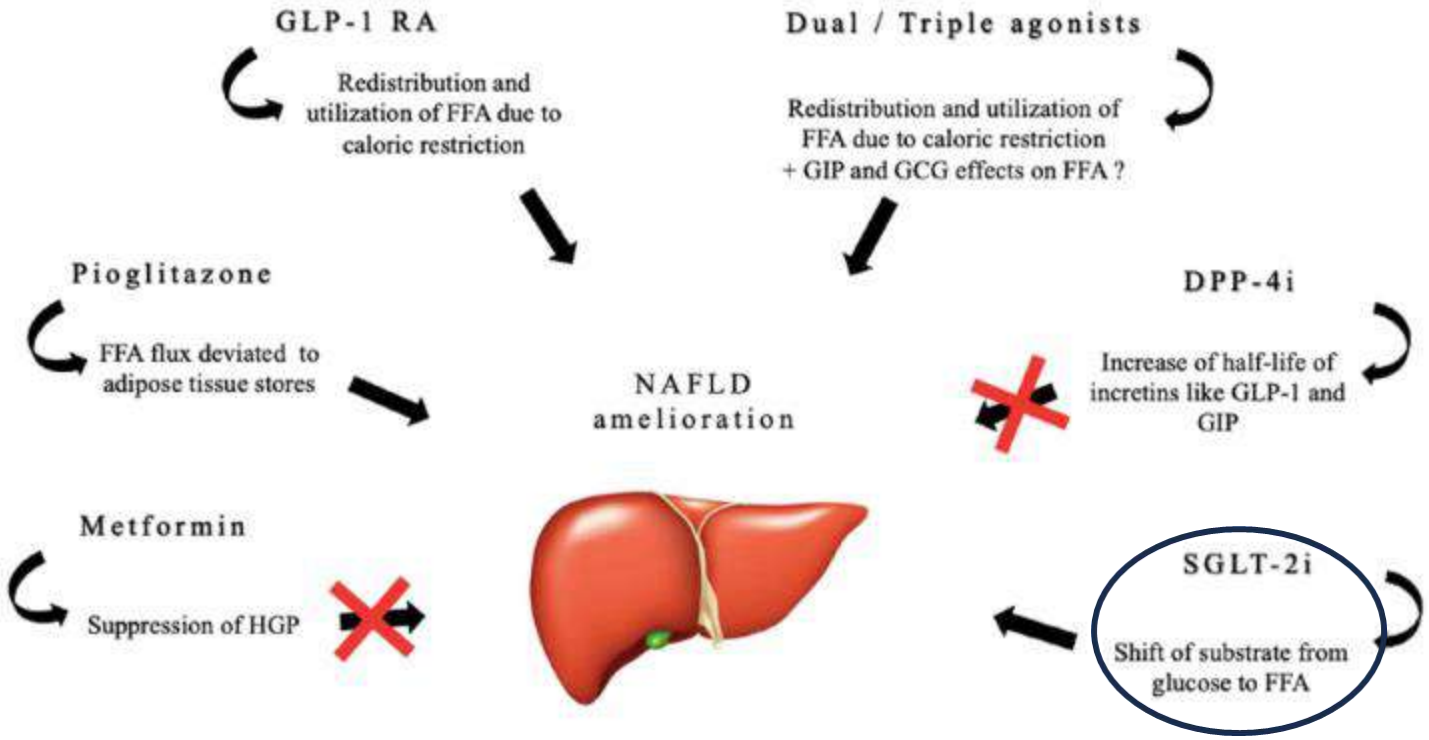
Diabetes/Metabolism Research and Reviews

REVIEW ARTICLE | Open Access

Volume 39, Issue 7
October 2023
e3668

Why do some glucose-lowering agents improve non-alcoholic fatty liver disease whereas others do not? A narrative review in search of a unifying hypothesis

Gea Ciccarelli, Gianfranco Di Giuseppe, Francesca Cinti, Simona Moffa, Teresa Mezza, Andrea Giaccari



Il miglioramento del metabolismo degli acidi grassi liberi possa essere il meccanismo unificante alla base dell'efficacia di alcuni agenti ipoglicemizzanti sulla NAFLD.

Gli SGLT2i provocano lo spostamento del substrato dall'ossidazione del glucosio a quella dell'FFA invertendo di conseguenza l'accumulo patologico di lipidi nel fegato

Diabetes Metab Res Rev. 2023;39:e3668.

SGLT2i e demenza

I pazienti diabetici hanno un rischio di sviluppare quadri di malattia di Alzheimer e in particolare di demenza vascolare molto più alti rispetto alla popolazione generale

Gli attori principalmente coinvolti nella patogenesi del decadimento cognitivo legato al diabete sembrano essere le complicanze acute (iper- e ipoglicemia), l'insulino-resistenza e la vasculopatia

L'insulino-resistenza favorisce l'accumulo di β-amiloide, aumentando il rischio di malattia di Alzheimer

JDI Journal of Diabetes Investigation
Official Journal of the Asian Association for the Study of Diabetes

Original Article | Open Access

Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies

To investigate the association between diabetes and the **risk** of all type dementia (ATD), Alzheimer's disease (AD) and vascular dementia (VaD).

1,148,041 participants, of whom 89,708 participants were having diabetes and 1,058,333 were non-diabetics

Type of dementia	No. studies pooled	Pooled estimate		Level of significance of pooled RR	Tests of heterogeneity			Tests of publication bias
		RR	95% CI	*P*	*Q* value (d.f.)	*P*-value	I^2 (%)	Egger's *P*
All type dementia	20	1.73	1.65–1.82	<0.001	76.5 (22)	<0.01	71.25	0.12
Alzheimer's disease	20	1.56	1.41–1.73	<0.001	23.3 (21)	0.32	9.8	0.93
Vascular dementia	13	2.27	1.94–2.66	<0.001	12.0 (12)	0.52	0	0.41

Journal of Diabetes Investigation Volume 4 Issue 6 November 2013

Home > Diabetes Therapy > Article

Risk of Dementia in Patients with Diabetes Using Sodium-Glucose Transporter 2 Inhibitors (SGLT2i): A Systematic Review, Meta-Analysis, and Meta-Regression

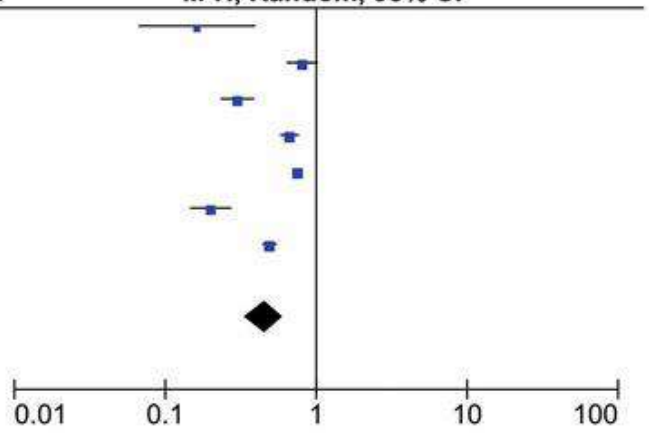
Diabetes Therapy

pooled analysis from seven observational studies examine the **association** between the use of SGLT2i and the risk of dementia in patients with diabetes.

	SGLT-2i		No SGLT-2i			Odds Ratio	Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Akimoto H et al. 2020	5	1574	1245	64511	6.7%	0.16 [0.07, 0.39]	
Bohlken J et al. 2018	141	315	8135	16237	15.2%	0.81 [0.64, 1.01]	
Mui JV et al. 2021	72	13276	652	36554	14.9%	0.30 [0.24, 0.38]	
Secnik J et al. 2020	244	3824	12040	129494	16.1%	0.66 [0.58, 0.76]	
Siao WZ et al. 2022	3426	103247	4507	103247	16.6%	0.75 [0.72, 0.79]	
Wium-Andersen IK et al. 2019	44	912	11575	57183	14.1%	0.20 [0.15, 0.27]	
Wu CY et al. 2023	560	36513	2171	70390	16.4%	0.49 [0.45, 0.54]	
Total (95% CI)		**159661**		**477616**	**100.0%**	**0.45 [0.3, 0.61]**	
Total events	4492		40325				

Heterogeneity: Tau² = 0.13; Chi² = 186.68, df = 6 (P < 0.00001); I² = 97%

Test for overall effect: Z = 5.28 (P < 0.00001)



Diabetes Ther (2024) 15:663–675

Risk of dementia after initiation of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in adults aged 40-69 years with type 2 diabetes: population based cohort study

Anna Shin,[1] Bo Kyung Koo,[2] Jun Young Lee,[3] Eun Ha Kang[4]

To compare the risk of dementia associated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors in adults aged 40-69 years with type 2 diabetes.

110.885 propensity score matched pairs of adults with type 2 diabetes aged 40-69 years who were **initiators** of either an SGLT-2 inhibitor or a DPP-4 inhibitor (**free of known dementia** and followed-up for a mean 670 days)

The primary outcome was new onset dementia.

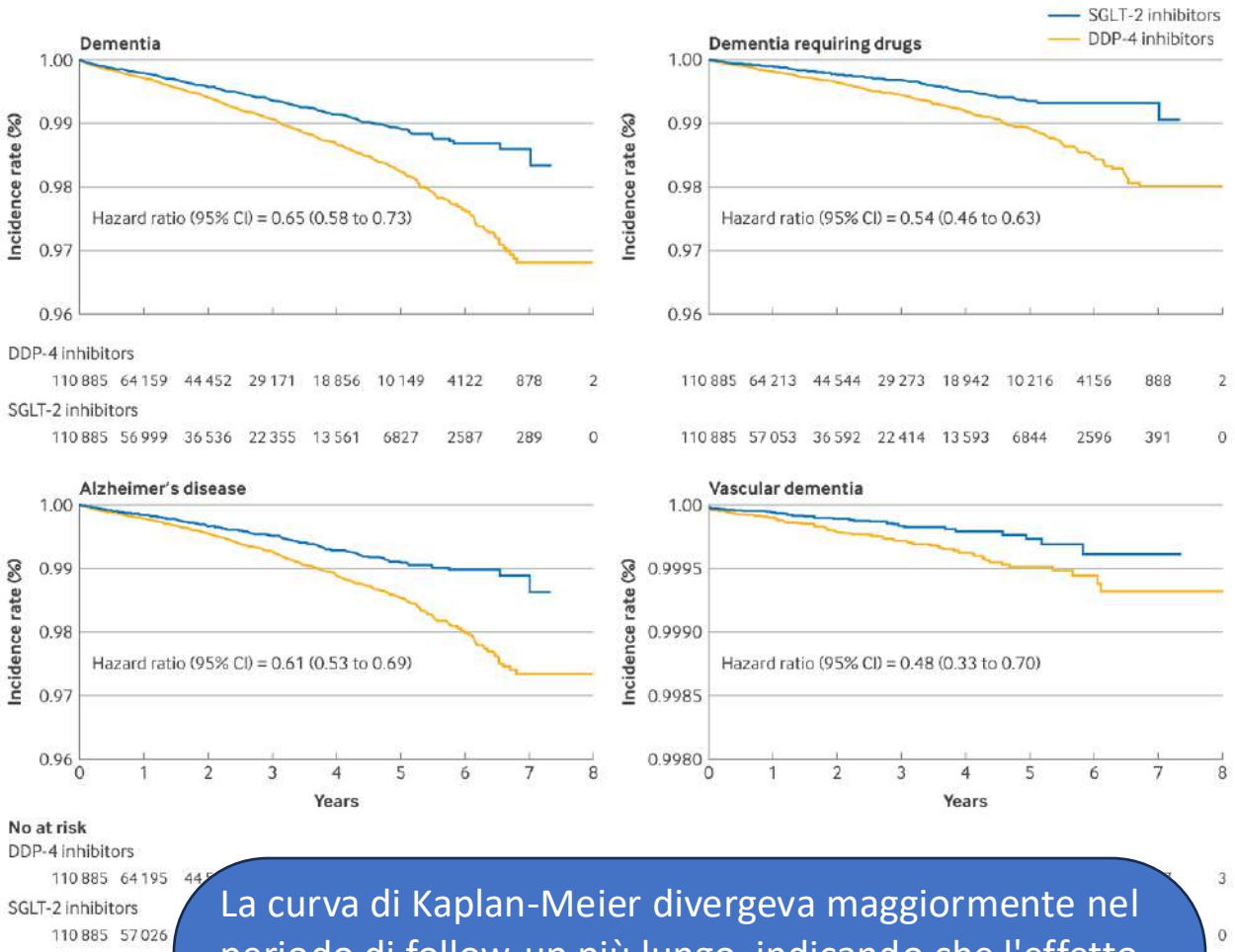
Secondary outcomes were dementia requiring drug treatment and individual types of dementia, including Alzheimer's disease and vascular dementia.

BMJ 2024;386:e079475

Kaplan-Meier curves for dementia-free survival comparing propensity score matched initiators of SGLT-2 inhibitors with initiators of DPP-4 inhibitors

-35%

- 39%



- 46%

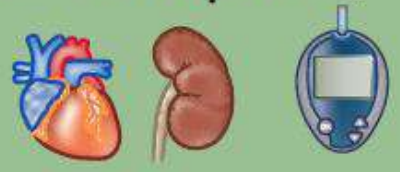
- 52%

La curva di Kaplan-Meier divergeva maggiormente nel periodo di follow-up più lungo indicando che l'effetto sarebbe maggiore con un trattamento più lungo

BMJ 2024;386:e079475

C’è spazio per gli SGLT2i nei pazienti in dialisi?

SGLT2i
(Initiate eGFR ≥20; continue until dialysis or transplant)



DAPA-CKD:

Key Inclusion Criteria

- **≥18 years of age**
- **eGFR ≥25 to ≤75 mL/min/1.73m^2**
- **UACR ≥200 to ≤5000 mg/g**
- **Stable max tolerated dose of ACEi/ARB for ≥4 weeks**
- **With and without T2D**

EMPA-KIDNEY design

Population: a broad range of patients with chronic kidney disease at risk of progression

(**eGFR 20-44; or 45-90 mL/min/1.73 m^2 with UACR ≥200 mg/g**)

JOURNAL ARTICLE

#3382 REASONS FOR DIALYSIS INITIATION AND SAFETY OF DAPAGLIFLOZIN AMONG DIALYSIS PARTICIPANTS: NEW INSIGHTS FROM DAPA-CKD

...in contrast to most other trials, participants who reached dialysis were allowed to continue study medication with dapagliflozin or placebo

During median 2.4 years follow-up, 68/2152 (3.2%) and 99/2152 (4.6%) participants in the dapaglifozin and placebo groups respectively required chronic dialysis

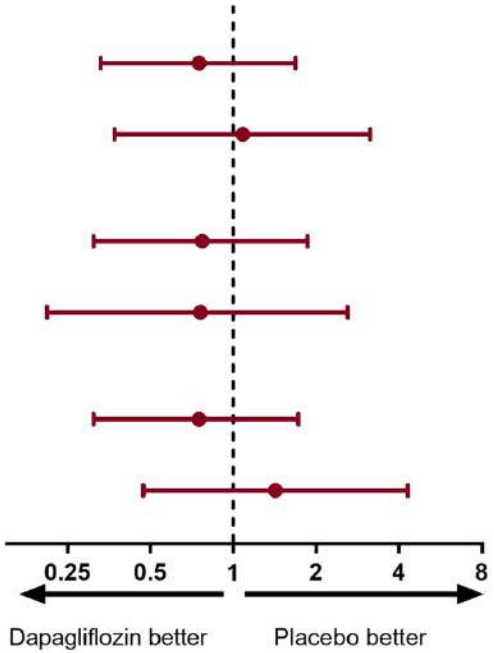
In the dapagliflozin and placebo groups, 25/68 (37%) and 41/99 (41%) continued the blinded study medication while receiving chronic dialysis.

In this pre-specified analysis of the DAPA-CKD trial, we assessed reasons for dialysis initiation and serious adverse events (**SAEs**) among participants who initiated dialysis and continued the study medication.

Nephrology Dialysis Transplantation, Volume 38, Issue Supplement_1, June 2023,

Similar Rates of Serious Adverse Events Occurred in Patients Who Continued Dapagliflozin or Placebo During Chronic Dialysis[a]

Safety Outcomes	Patients Initiated on Dialysis			OR (95% CI)	Interaction p-value
	DAPA (n=68)	PBO (n=99)			
Any adverse event					
Discontinued treatment	15/40	28/63		0.75 (0.33, 1.68)	0.60
Continued treatment	9/28	11/36		1.08 (0.37, 3.13)	
Any serious adverse event					
Discontinued treatment	10/40	19/63		0.77 (0.31, 1.86)	0.99
Continued treatment	5/28	8/36		0.76 (0.21, 2.60)	
Any serious adverse event, including death					
Discontinued treatment	12/40	23/63		0.75 (0.31, 1.72)	0.36
Continued treatment	9/28	9/36		1.42 (0.47, 4.30)	



[a]Chronic dialysis defined as the need for dialysis for at least 28 days.

CI = confidence interval; DAPA = dapagliflozin; OR = odds ratio; PBO = placebo.

Heerspink HJL et al. Presented at: 60th ERA Congress; June 15-18, 2023; Milan, Italy and Virtual.

Pharmacokinetic Properties of Dapagliflozin in Hemodialysis and Peritoneal Dialysis Patients

Joaquim Barreto,[1] Cynthia Borges,[2] Tais Betoni Rodrigues,[3] Daniel C. Jesus,[1] Alessandra M. Campos-Staffico,[4] Wilson Nadruz,[5] Jose Luiz da Costa,[3,6] Rodrigo Bueno de Oliveira,[2] and Andrei C. Sposito[1]

Studio prospettico, monocentrico, in aperto, finalizzato a valutare **le proprietà farmacocinetiche la dializzabilità e la sicurezza** del dapagliflozin nei pazienti con insufficienza renale sottoposti a regimi di dialisi regolari rispetto a quelli con diabete di tipo 2 con funzionalità renale normale

CJASN 18: 1051–1058, 2023

What are the pharmacokinetic properties of dapagliflozin in hemodialysis and peritoneal dialysis patients?

CJASN
Clinical Journal of the American Society of Nephrology

Methods

Prospective, sin
open-label trial

N=7 adults with kidney
failure on dialysis
5 on hemodialysis
2 on peritoneal dia

N=7 adults with type 2
diabetes and eGFR ≥60
Control group

Sampling protocol

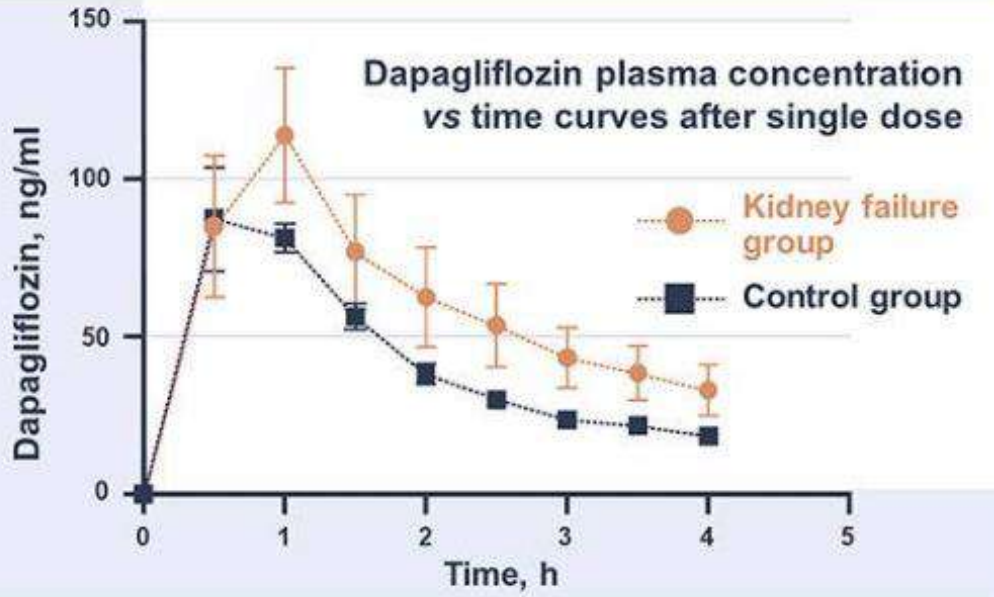
Le concentrazioni di picco del dapagliflozin non hanno mostrato differenze clinicamente significative tra i gruppi.

Sebbene dapagliflozin non abbia dimostrato di essere dializzabile non è stato osservato alcun accumulo clinicamente significativo entro 7 giorni dall'esposizione al farmaco.

6 daily doses

Dapagliflozin 10 mg
every day, for 6 days

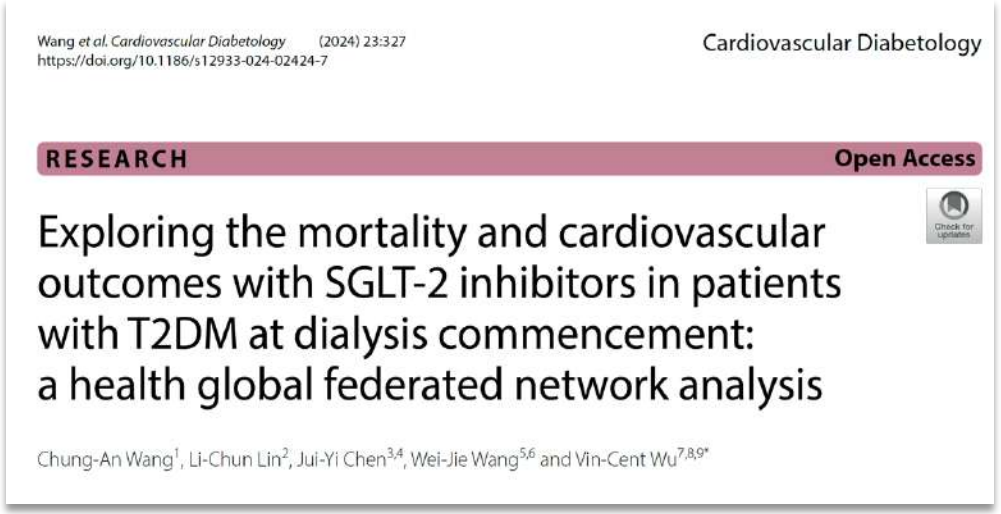
Blood samples
at day 7



Low dialyzability
Dialysis clearance of 20 mL/min
<0.10% of administered dapagliflozin dose was removed by the dialysate

No serious adverse events reported

CJASN 18: 1051–1058, 2023



Wang et al. Cardiovascular Diabetology (2024) 23:327
https://doi.org/10.1186/s12933-024-02424-7

Cardiovascular Diabetology

RESEARCH Open Access

Exploring the mortality and cardiovascular outcomes with SGLT-2 inhibitors in patients with T2DM at dialysis commencement: a health global federated network analysis

Chung-An Wang[1], Li-Chun Lin[2], Jui-Yi Chen[3,4], Wei-Jie Wang[5,6] and Vin-Cent Wu[7,8,9*]

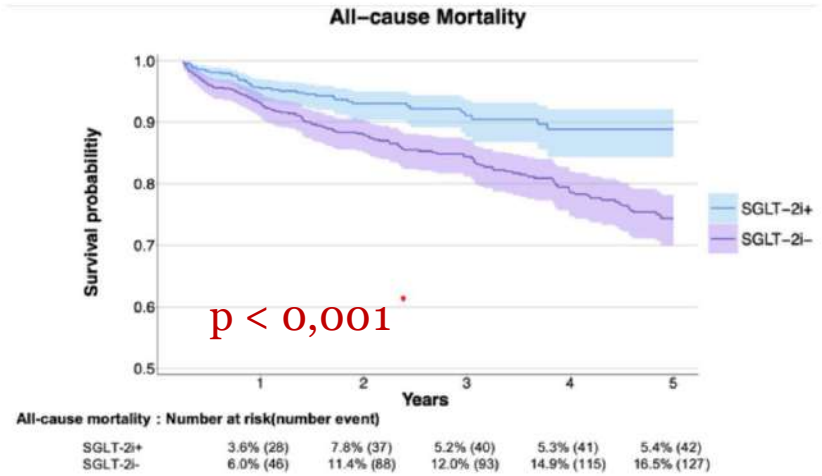
L'obiettivo di questo studio di RW è studiare l'associazione tra SGLT-2i e gli outcomes di mortalità e CV nei pazienti con diabete di tipo 2 all'inizio della dialisi.

I pazienti sono stati classificati come utilizzatori di SGLT2i se avevano ricevuto una prescrizione per un SGLT2i entro 3 mesi dall'inizio della dialisi

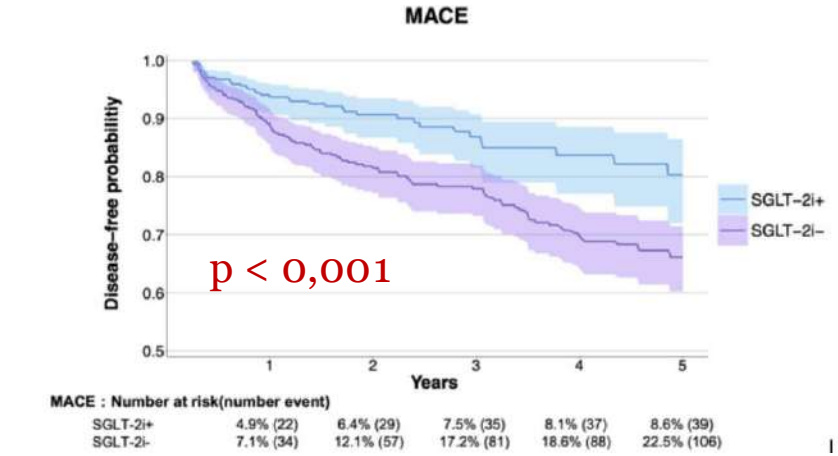
Wang et al. Cardiovascular Diabetology (2024) 23:327

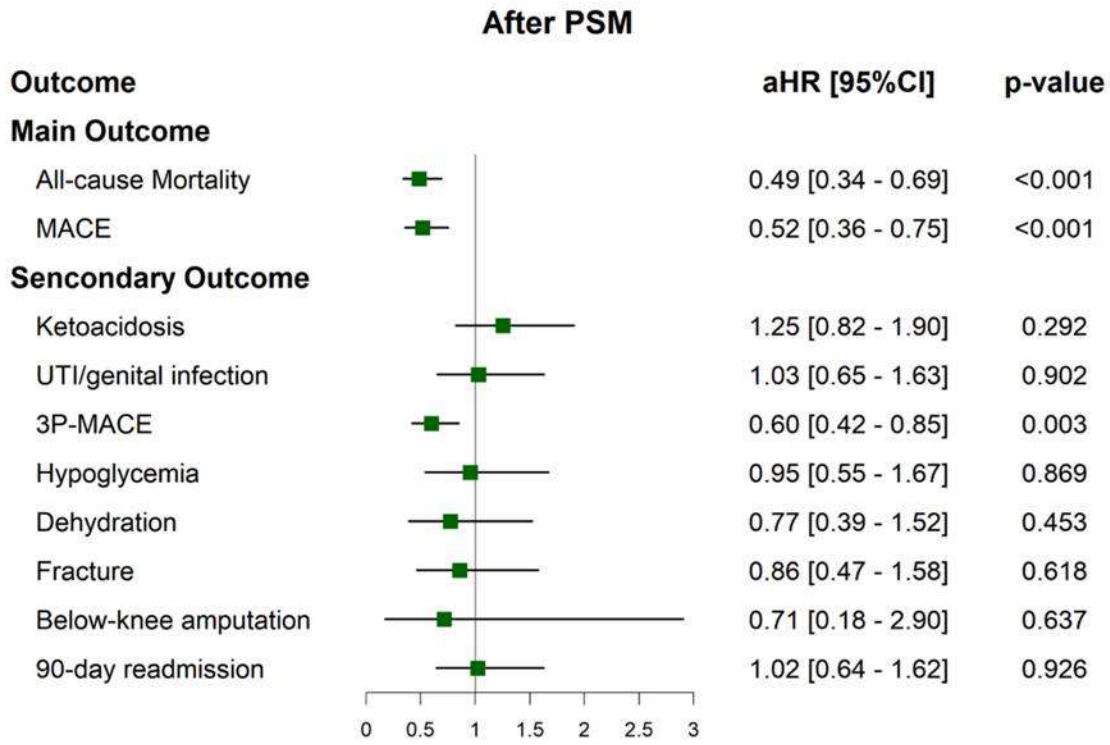
Follow-up medio di 2,0 anni

(A) All-cause Mortality



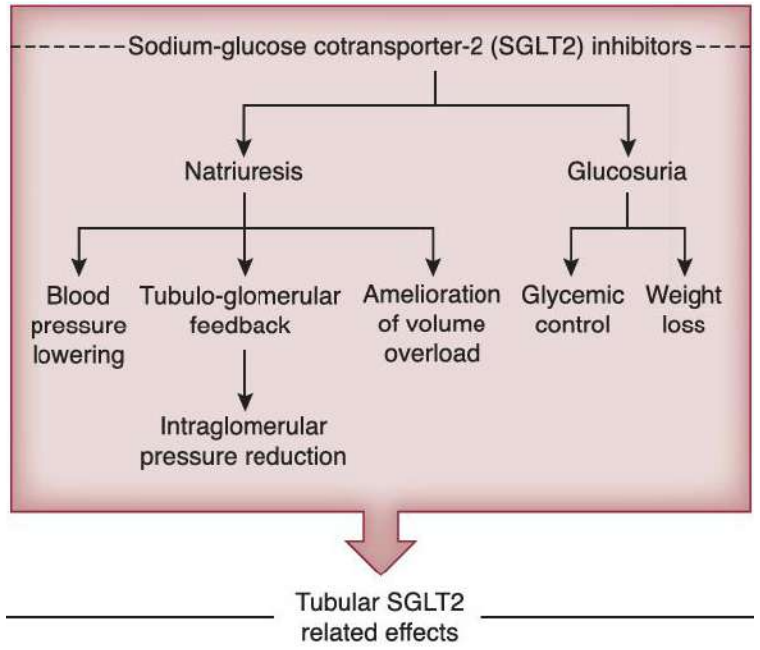
(B) MACE





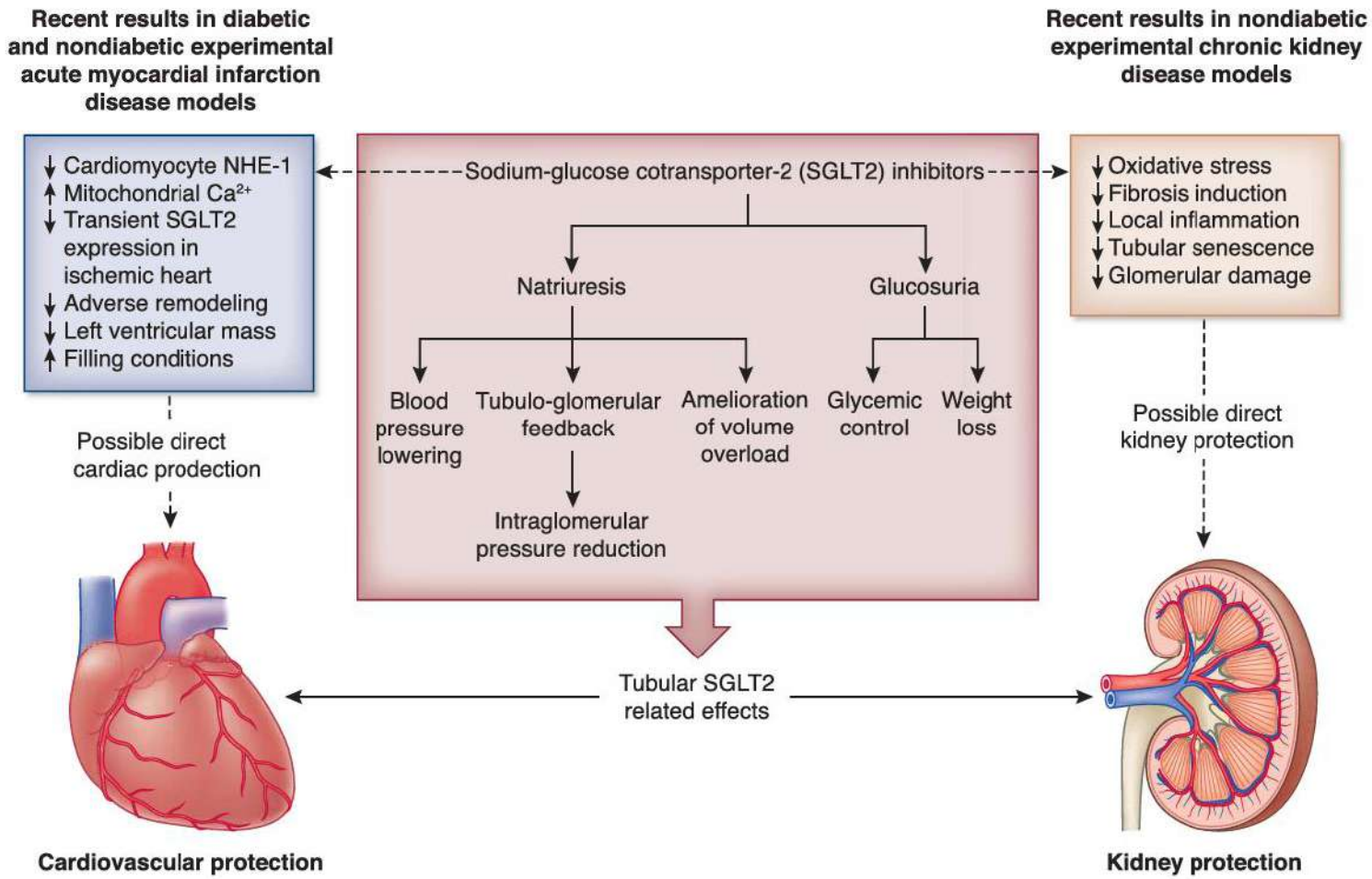
Wang et al. Cardiovascular Diabetology (2024) 23:327

Come è possibile che l'efficacia degli inibitori SGLT2 persista nei pazienti con funzionalità renale gravemente compromessa o sottoposti a dialisi?



CJASN 18: 1500–1502, 2023.

Come è possibile che l'efficacia degli inibitori SGLT2 persista nei pazienti con funzionalità renale gravemente compromessa o sottoposti a dialisi?



CJASN 18: 1500–1502, 2023.

grazie