

CONGRESSO REGIONALE

SID-AMD

LAZIO

DIABETOLOGIA 2024:
NUOVI SCENARI CLINICI
E PROSPETTIVE TERAPEUTICHE



ROMA, 29-30 NOVEMBRE 2024

UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA

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 CVD⁵⁻¹⁴

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}

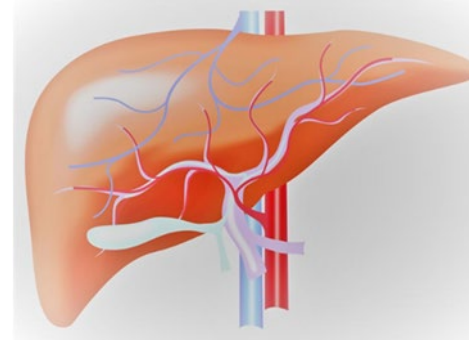


1. Häring H-U et al. Diabetes Care 2014;37:1650 2. Lavelle-Gonzalez FJ et al. Diabetologia 2013;56:2582 3. Bailey CJ et al. Lancet 2010;375:2223 4. Rosenstock J et al. Diabetes Obes Metab 2018;20:520 5. McGuire DK et al. JAMA Cardiol 2021;6:148 6. Neal B et al. N Engl J Med 2017;377:644 7. Radholm K 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%.

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

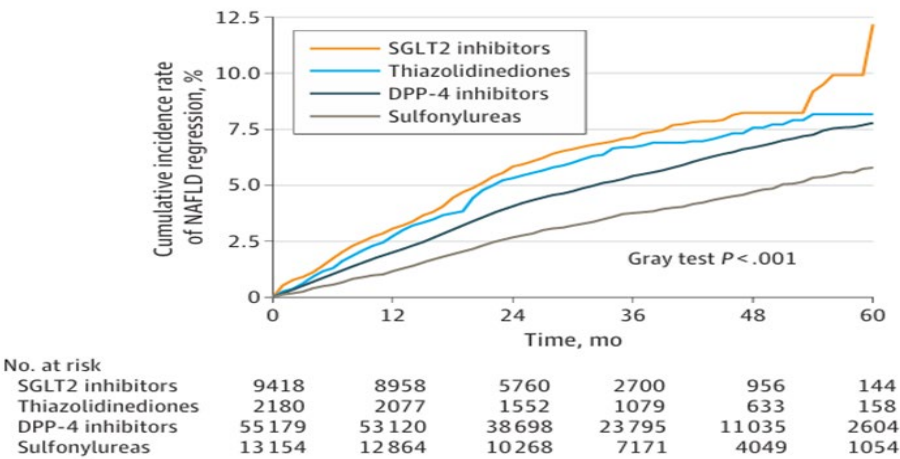
Retrospective non randomized interventional cohort study (80178 patients) to investigate which OAD is associated with the best patient outcomes in NAFLD and type 2 diabetes (T2D)

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

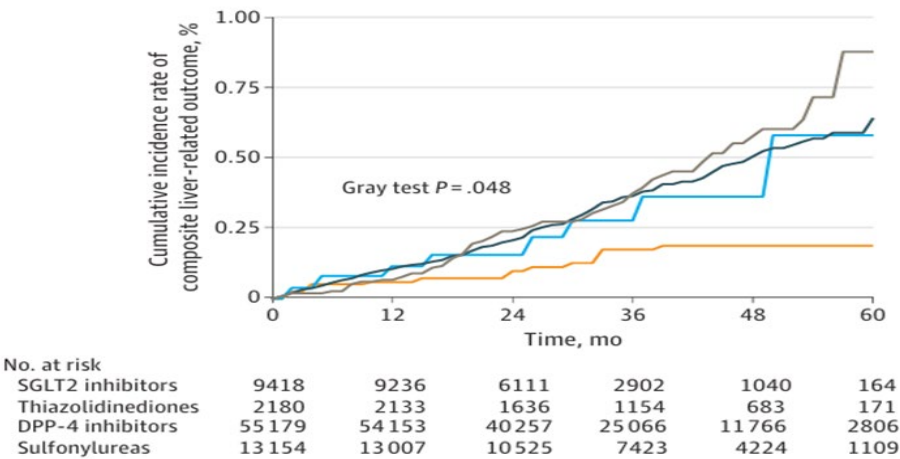
The secondary end point² was **Composite liver-related outcome** (defined as liver-related hospitalization, liver-related mortality, liver transplant, and hepatocellular carcinoma) .

Weighted Cumulative Incidence Function According to Oral Antidiabetic Drug Class

A NAFLD regression



B Liver-related outcomes





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

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



Mohammad Shafi Kuchay,² 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 Mithal¹

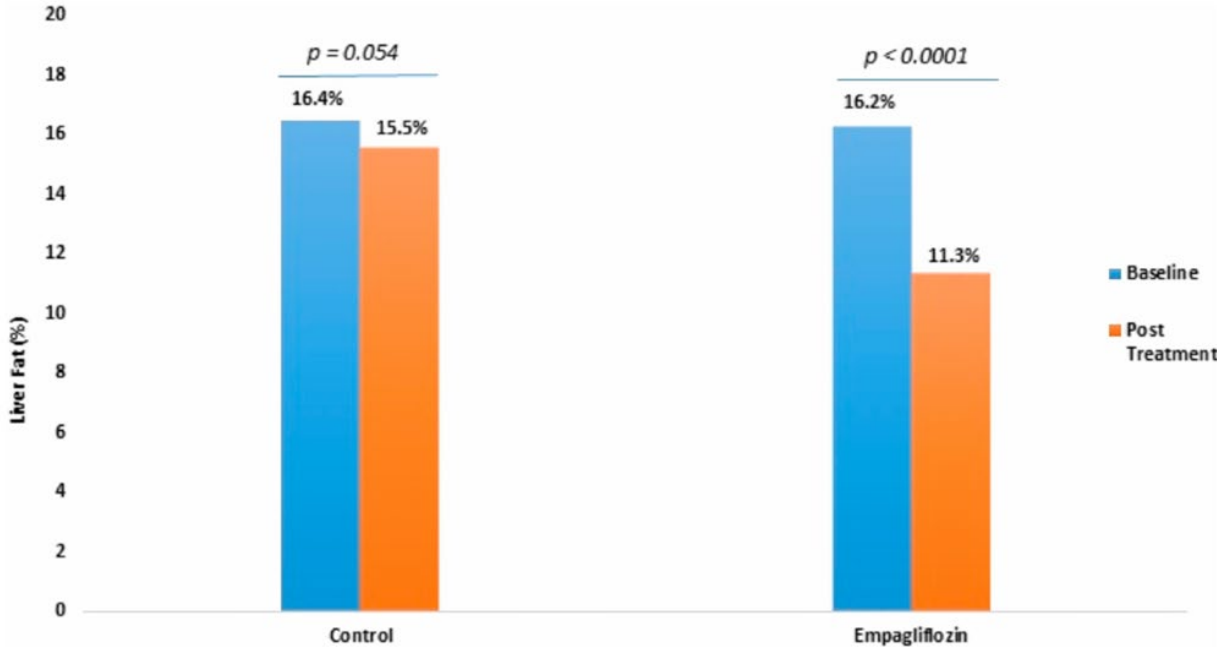
50 pazienti con diabete di tipo 2 e NAFLD sono stati assegnati in modo casuale al gruppo empagliflozin (empagliflozin 10 mg al giorno) o al gruppo di controllo .

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

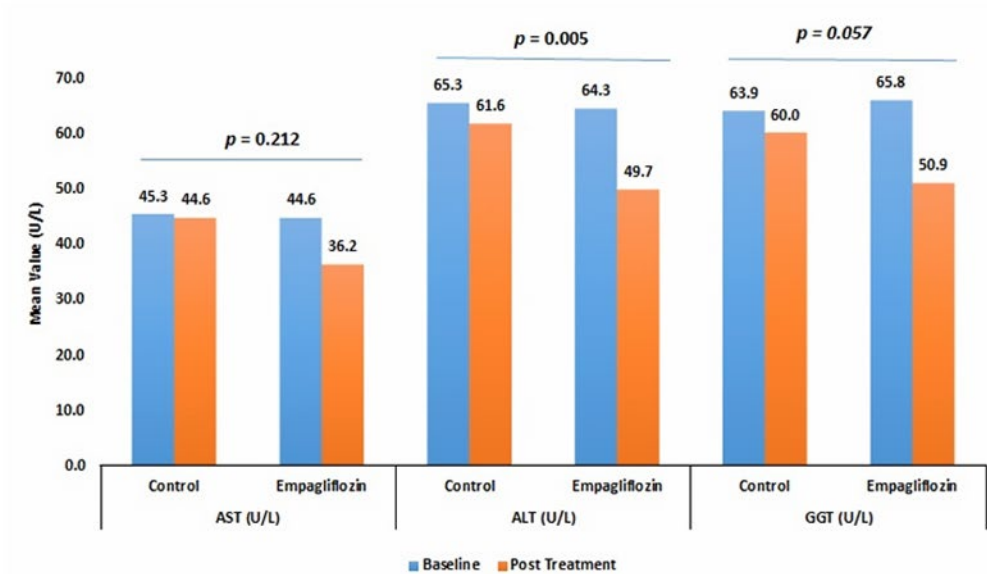
L'outcomes secondari erano la variazione dei livelli sierici di AST, ALT e GGT.

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



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.

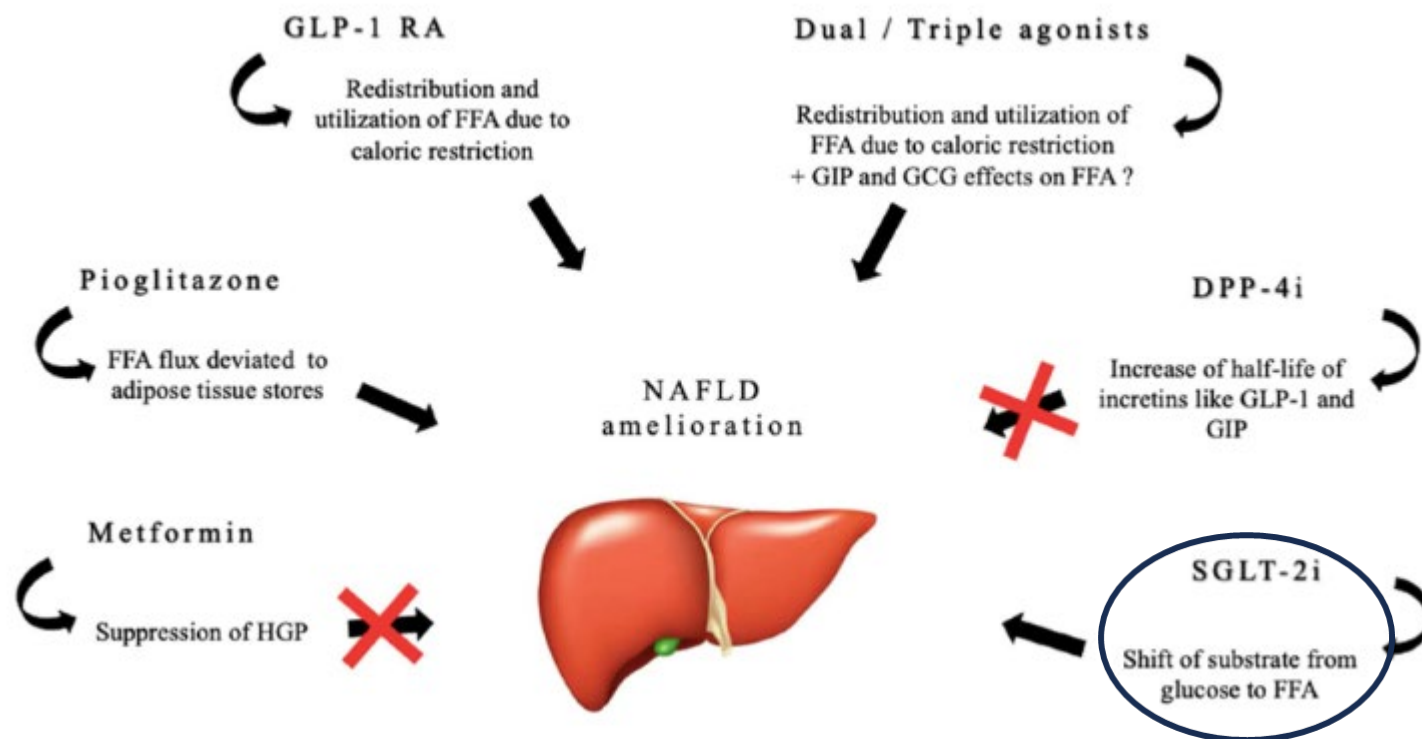
Comparison among the grades of fatty liver at initial assessment and after 24 weeks of interventional treatment in NAFLD patients

	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.

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

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

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

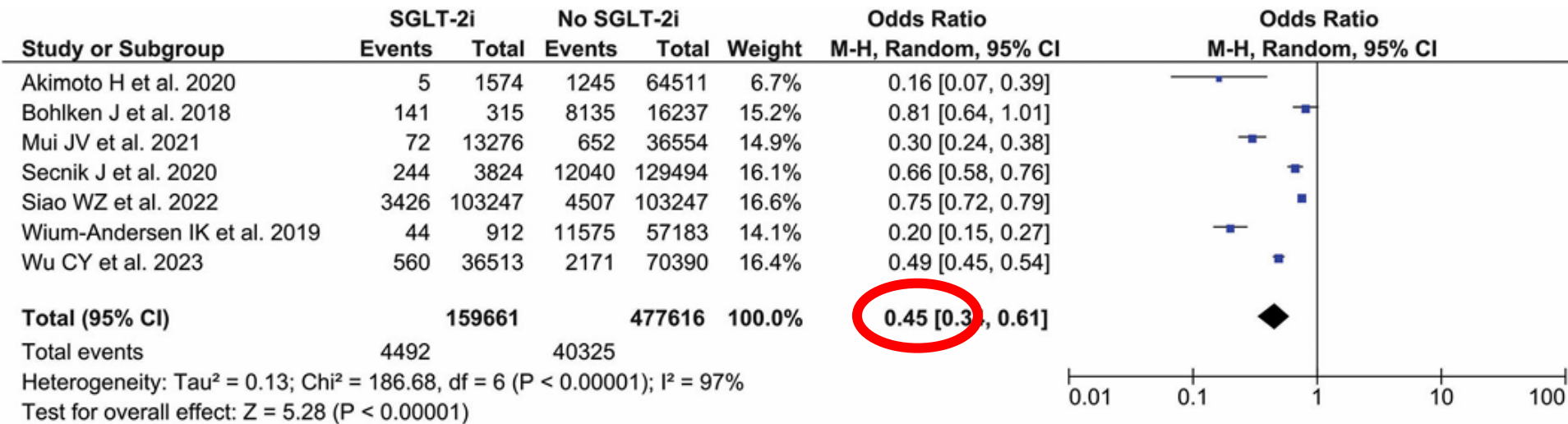
Type of dementia	No. studies pooled	Pooled estimate		Level of significance of pooled RR	Tests of heterogeneity			Tests of publication bias
		RR	95% CI	P	Q value (d.f.)	P-value	I ² (%)	Egger's P
All type dementia	20	1.73	1.65–1.82	<0.001	76.5 (22)	<0.01	71.25	0.12
Alzheimer's disease	20	1.56	1.41–1.73	<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

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.



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 Kang⁴

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.

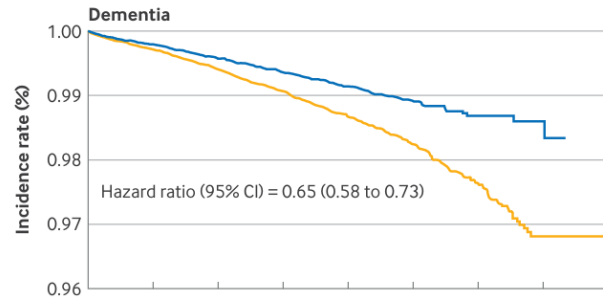
110.885 propensity score matched pairs of adults with type 2 diabetes aged 40-69 years who were **initiators** of either an SGLT-2 inhibitor or a DPP-4 inhibitor (**free of known dementia** and followed-up for a mean 670 days)

The primary outcome was new onset dementia.

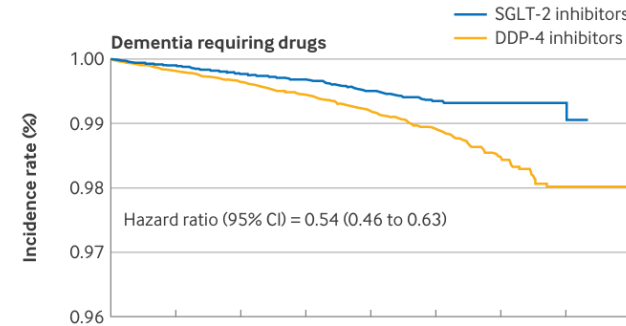
Secondary outcomes were dementia requiring drug treatment and individual types of dementia, including Alzheimer's disease and vascular dementia.

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

-35%



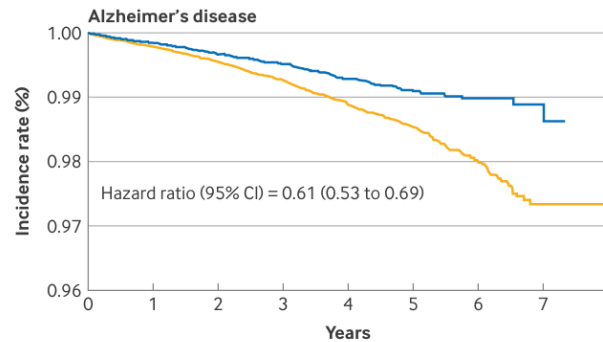
DDP-4 inhibitors	110 885	64 159	44 452	29 171	18 856	10 149	4 122	878	2
SGLT-2 inhibitors	110 885	56 999	36 536	22 355	13 561	6 827	2 587	289	0



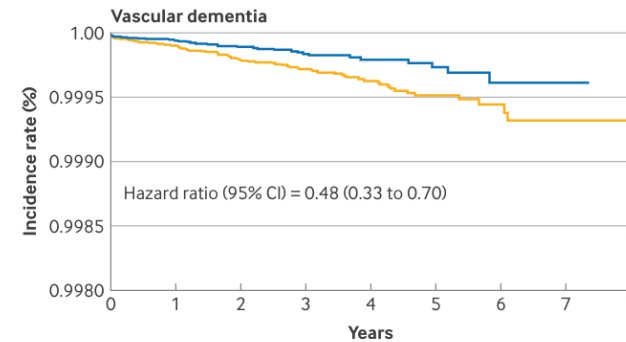
DDP-4 inhibitors	110 885	64 213	44 544	29 273	18 942	10 216	4 156	888	2
SGLT-2 inhibitors	110 885	57 053	36 592	22 414	13 593	6 844	2 596	391	0

- 46%

- 39%



No at risk									
DDP-4 inhibitors	110 885	64 195	44 452	29 171	18 856	10 149	4 122	878	2
SGLT-2 inhibitors	110 885	57 026	36 536	22 355	13 561	6 827	2 587	289	0



No at risk									
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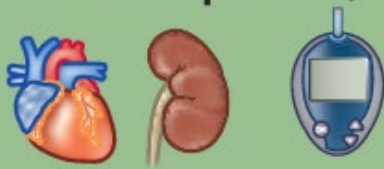
- 52%

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

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/1.73m²**
- **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 m² with UACR ≥ 200 mg/g)

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

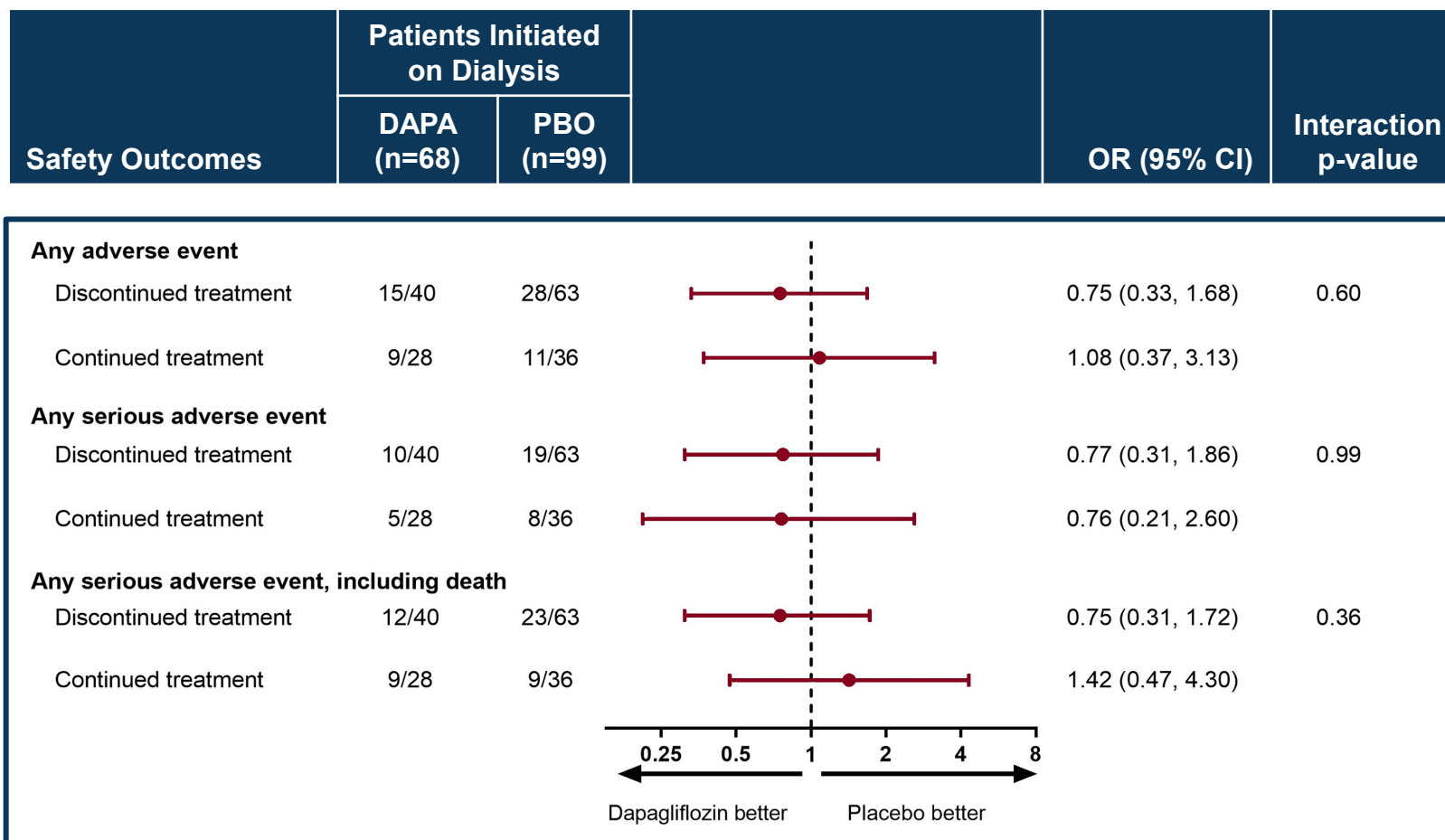
...in contrast to most other trials, participants who reached dialysis were allowed to continue study medication with dapagliflozin or placebo

During median 2.4 years follow-up, 68/2152 (3.2%) and 99/2152 (4.6%) participants in the dapagliflozin 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.

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



^aChronic 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.

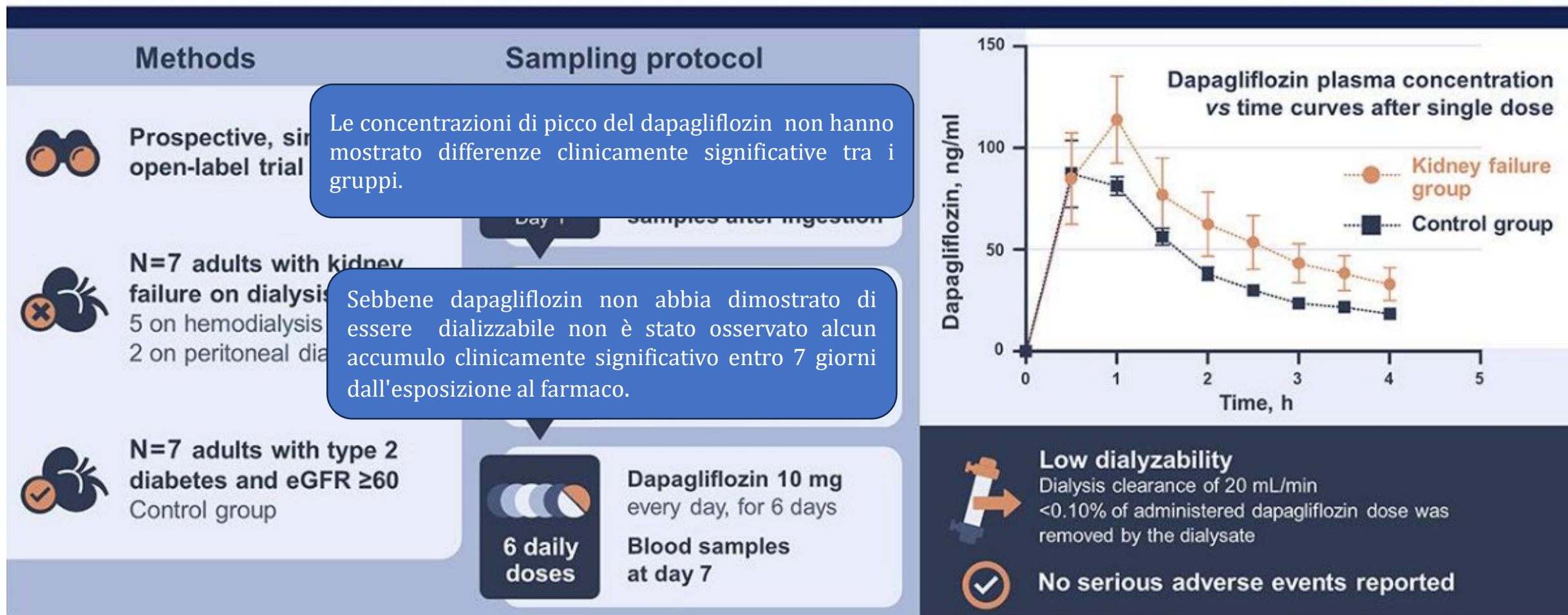
Pharmacokinetic Properties of Dapagliflozin in Hemodialysis and Peritoneal Dialysis Patients

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?



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



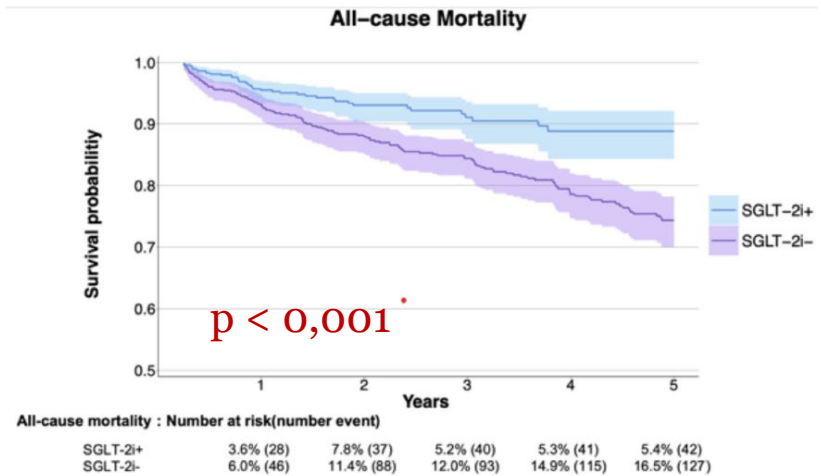
Chung-An Wang¹, Li-Chun Lin², Jui-Yi Chen^{3,4}, Wei-Jie Wang^{5,6} and Vin-Cent Wu^{7,8,9*}

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.

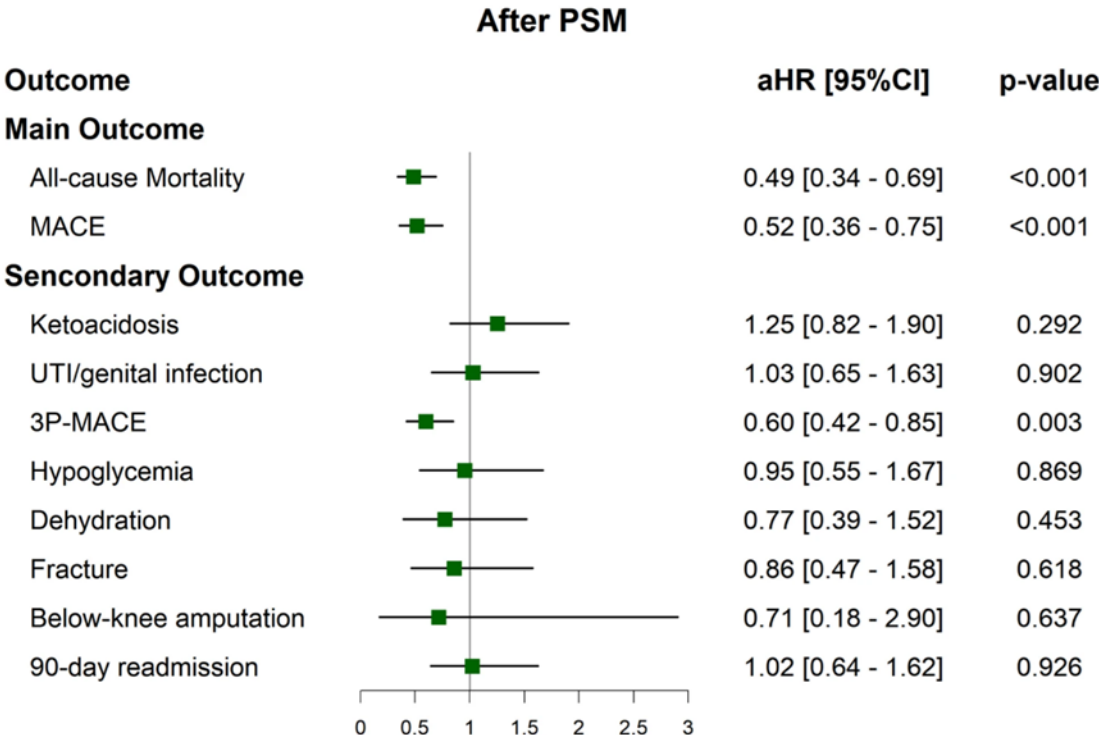
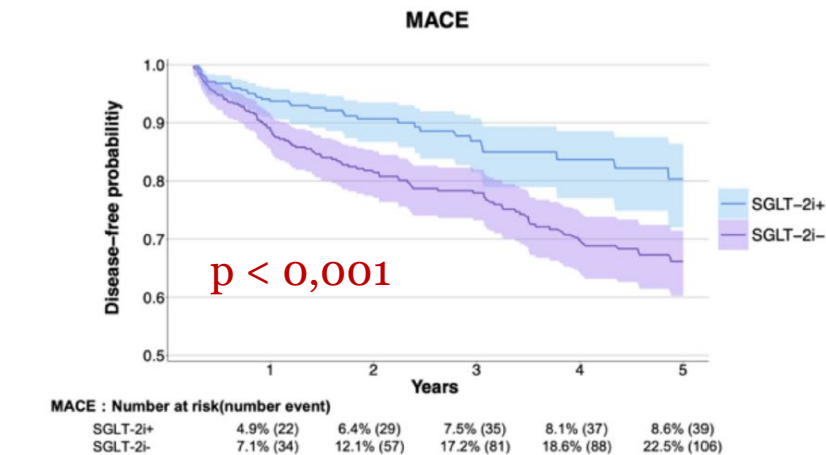
I pazienti sono stati classificati come utilizzatori di SGLT2i se avevano ricevuto una prescrizione per un SGLT2i entro 3 mesi dall'inizio della dialisi

Follow-up medio di 2,0 anni

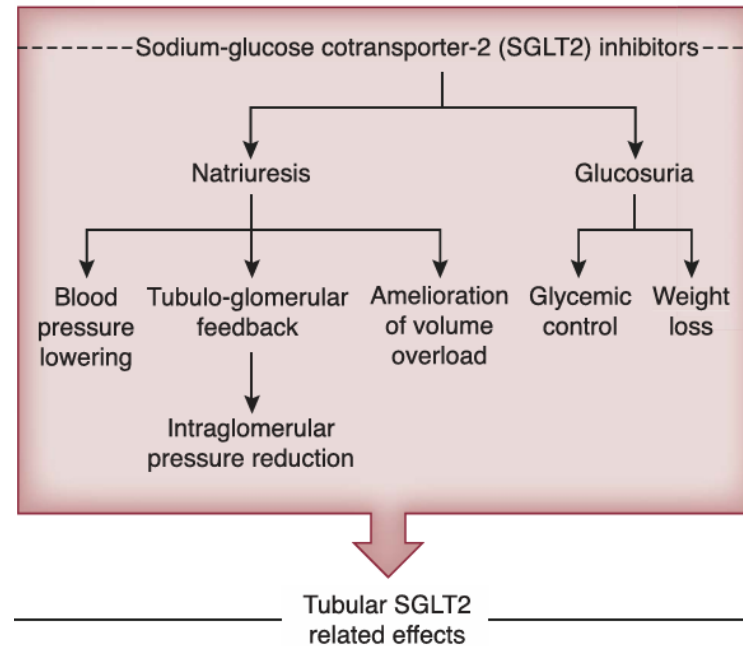
(A) All-cause Mortality



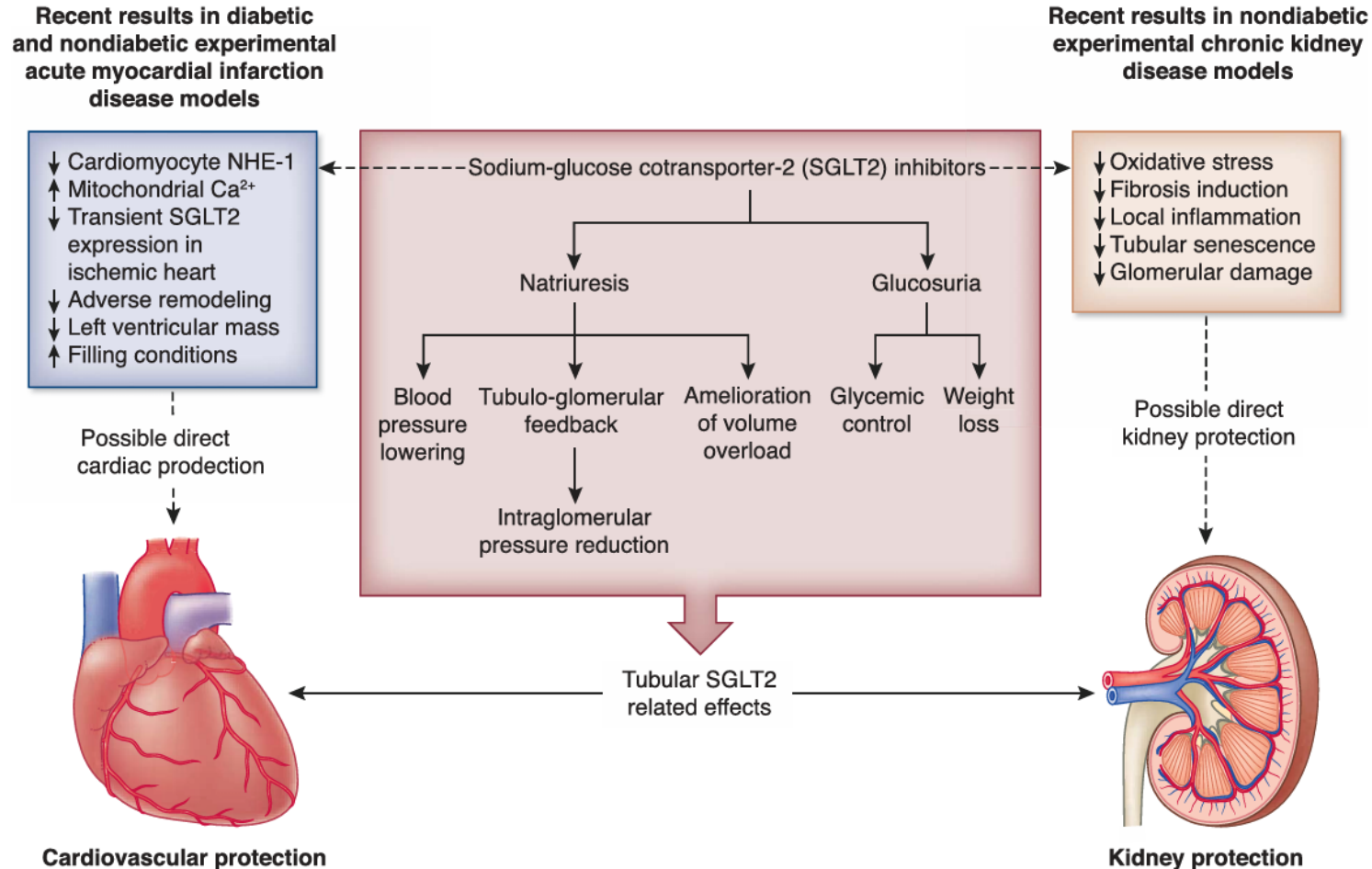
(B) MACE



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



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



grazie