

Ante 2025

**XXXII Corso Nazionale di Aggiornamento Tecnici Emodialisi
Dialisi e Tecnologia**

“ Nuove Opportunità per Vecchi Avversari ”

28 - 29 - 30 aprile Hotel Corallo Riccione



Diabete mellito in dialisi: quale spazio per i nuovi farmaci

Francesca Viazzi



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Structure of Talk

- **SGLT2-inhibitors** in ESKD: possible mechanism and safety
- **SGLT2-inhibitors** in ESKD: CV and kidney outcomes
- **GLP1-RA** in ESKD: possible mechanism and safety
- **GLP1-RA** in ESKD: CV and kidney outcomes
- Randomized studies



Table. Key Changes in the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease*

Annals of Internal Medicine

CLINICAL GUIDELINE

Diabetes Management in Chronic Kidney Disease: Synopsis of the KDIGO 2022 Clinical Practice Guideline Update

SGLT2 inhibitors

The GFR threshold for the use of SGLT2 inhibitors has been lowered to ≥ 20 mL/min/1.73 m². This affects Recommendation 1.3.1 and Practice Point 1.3.6 in the updated guideline.

Recommendation 1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥ 20 ml/min per 1.73 m² with an SGLT2i (1A).

Practice Point 1.3.6: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m², unless it is not tolerated or kidney replacement therapy is initiated.

Annals of Internal Medicine

CLINICAL GUIDELINE

Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2024 Clinical Practice Guideline

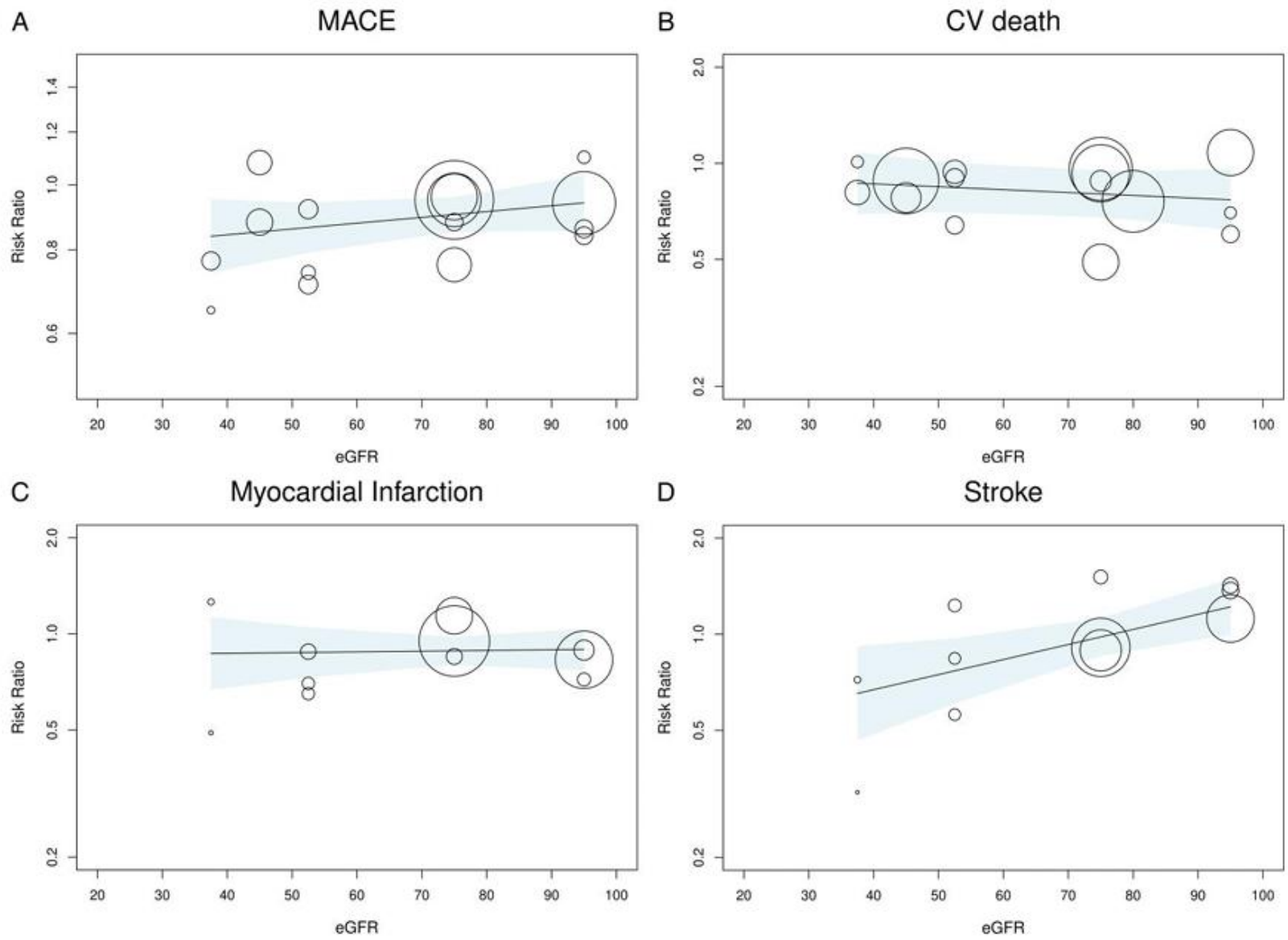
Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following (1A):

- eGFR ≥ 20 mL/min per 1.73 m² with urine ACR ≥ 200 mg/g (≥ 20 mg/mmol), or
- heart failure, irrespective of level of albuminuria.


Practice Point 3.7.3: SGLT2i initiation or use does not necessitate alteration of frequency of CKD monitoring and the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy.

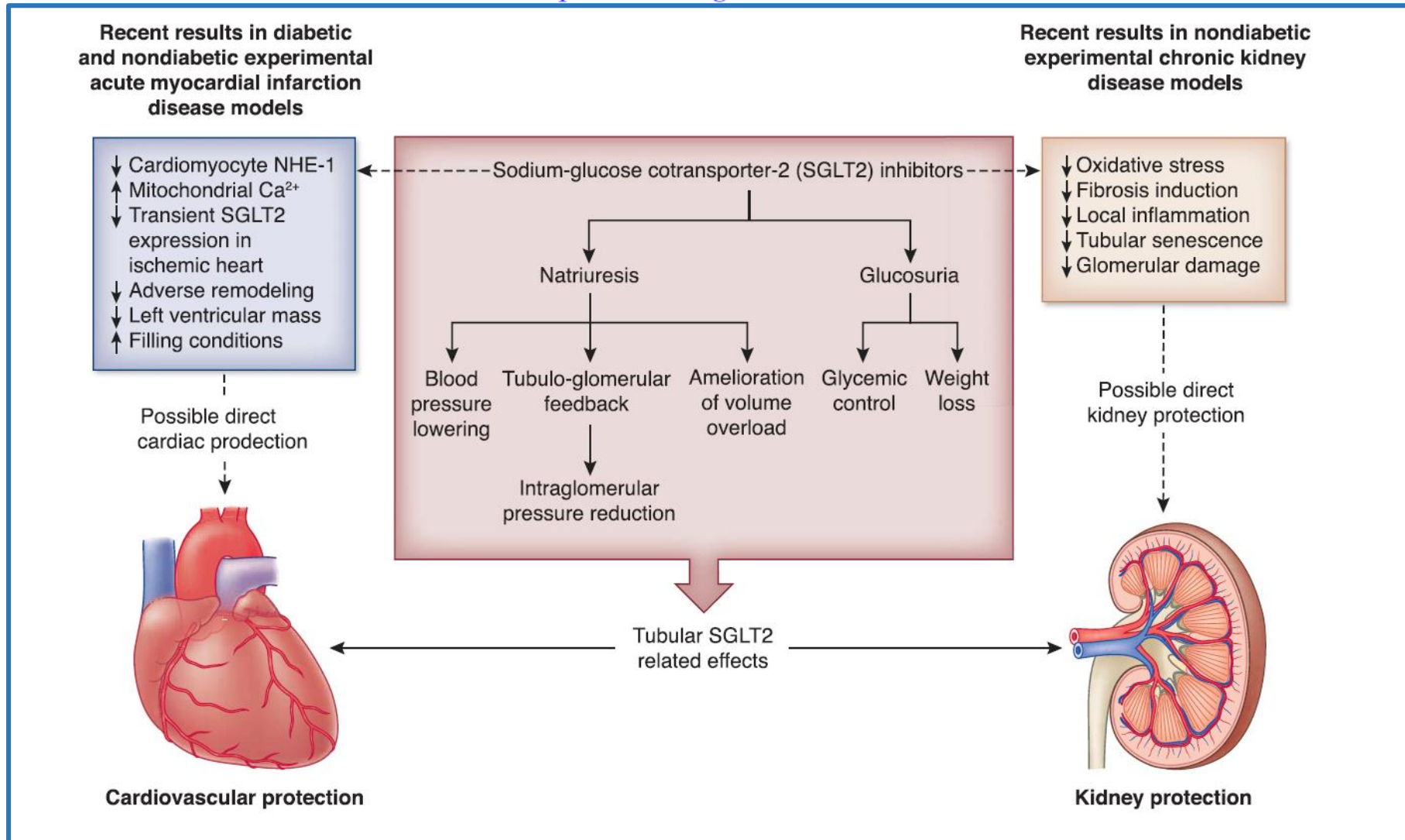
Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 mL/min per 1.73 m² with urine ACR < 200 mg/g (< 20 mg/mmol) with an SGLT2i (2B).

Differential effects of SGLT2-is on CV and renal outcomes according to renal function: a dose–response meta-analysis involving 10 randomized clinical trials and 71 553 individuals

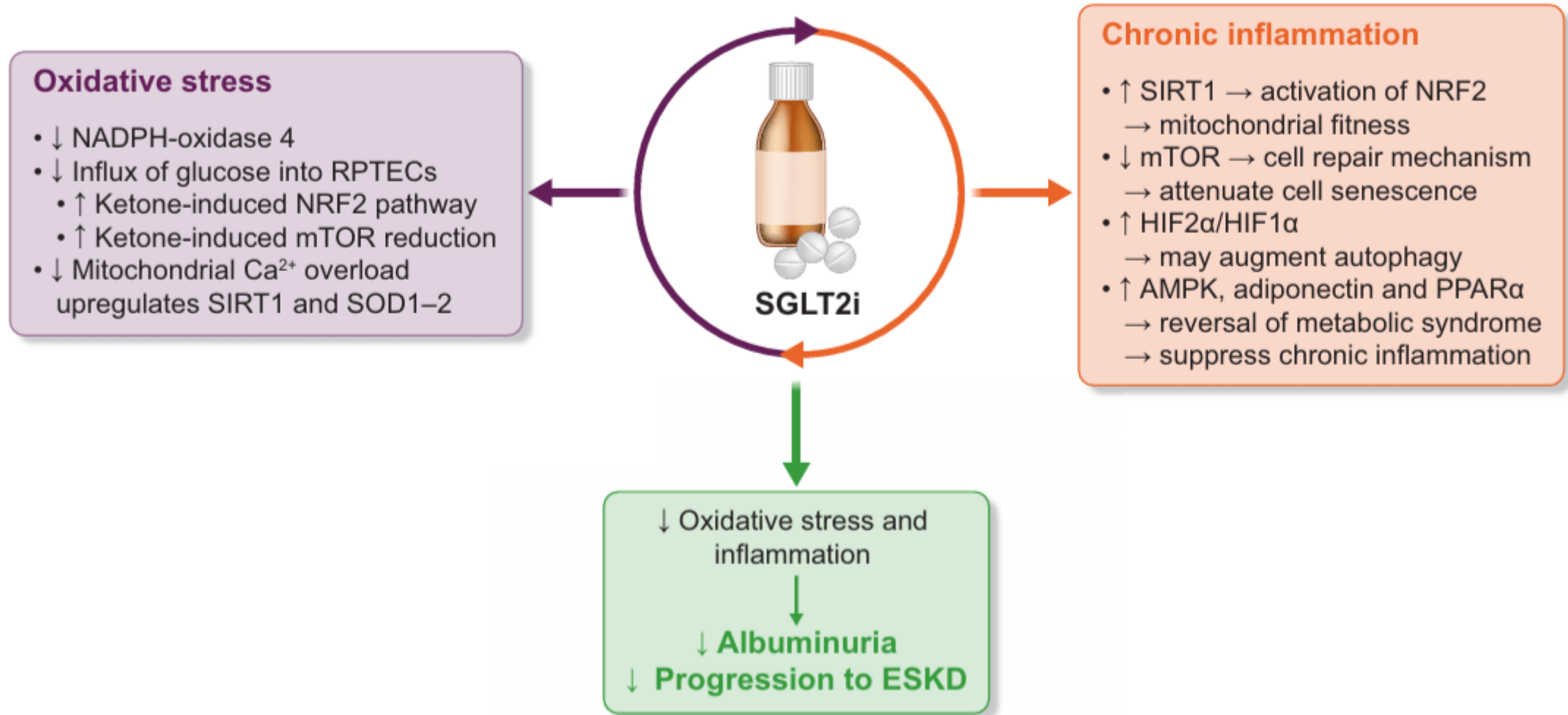


Will SGLT2 Inhibitors Be Effective and Safe in Patients with Severe CKD, Dialysis, or Kidney Transplantation

Hiddo J.L. Heerspink,¹ Stefan Berger ,² and Ron T. Gansevoort,² on behalf of the Renal Life Cycle Trial Investigators*
CJASN 18: 1500–1502, 2023. doi: <https://doi.org/10.2215/CJN.0000000000000221>



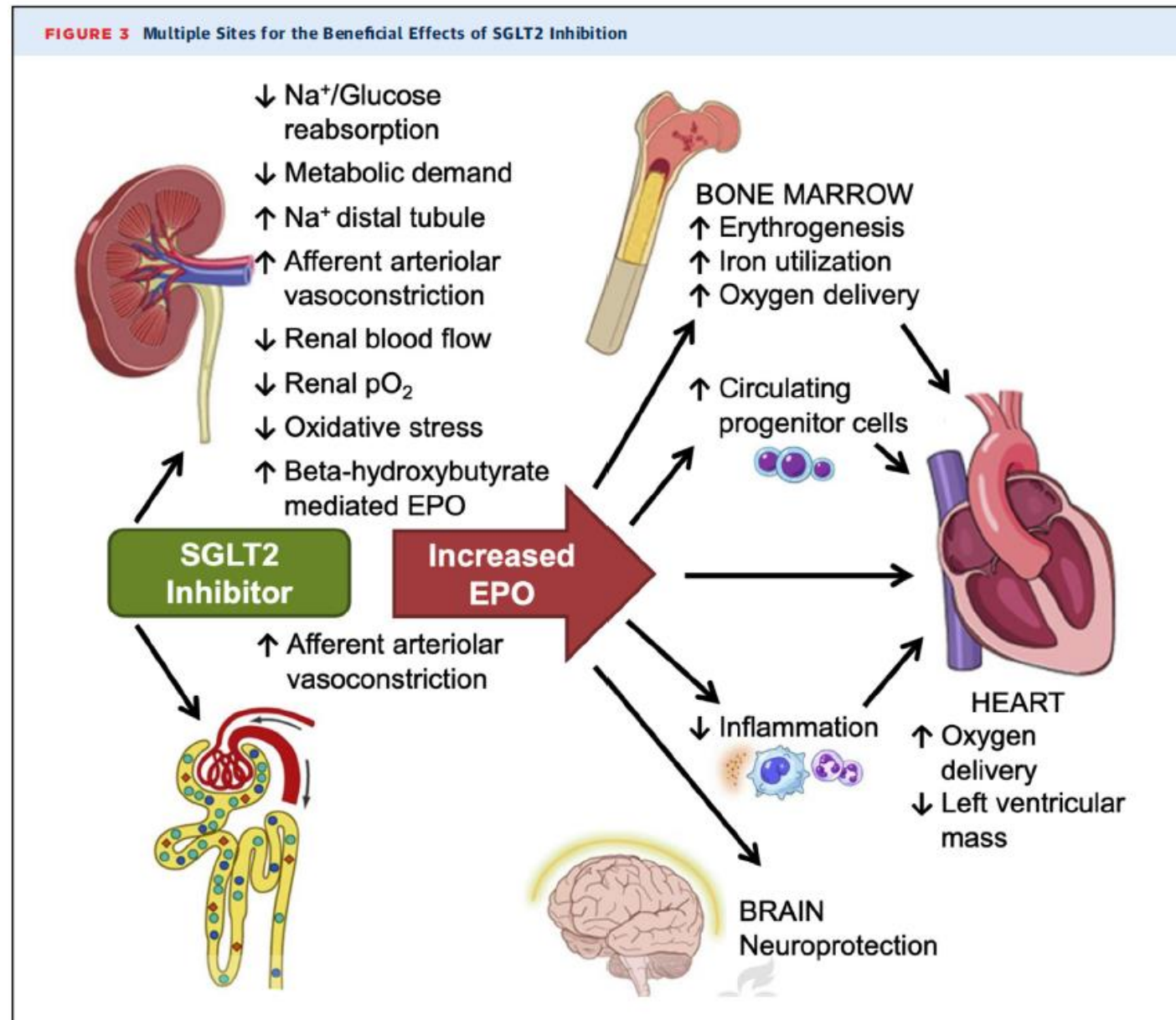
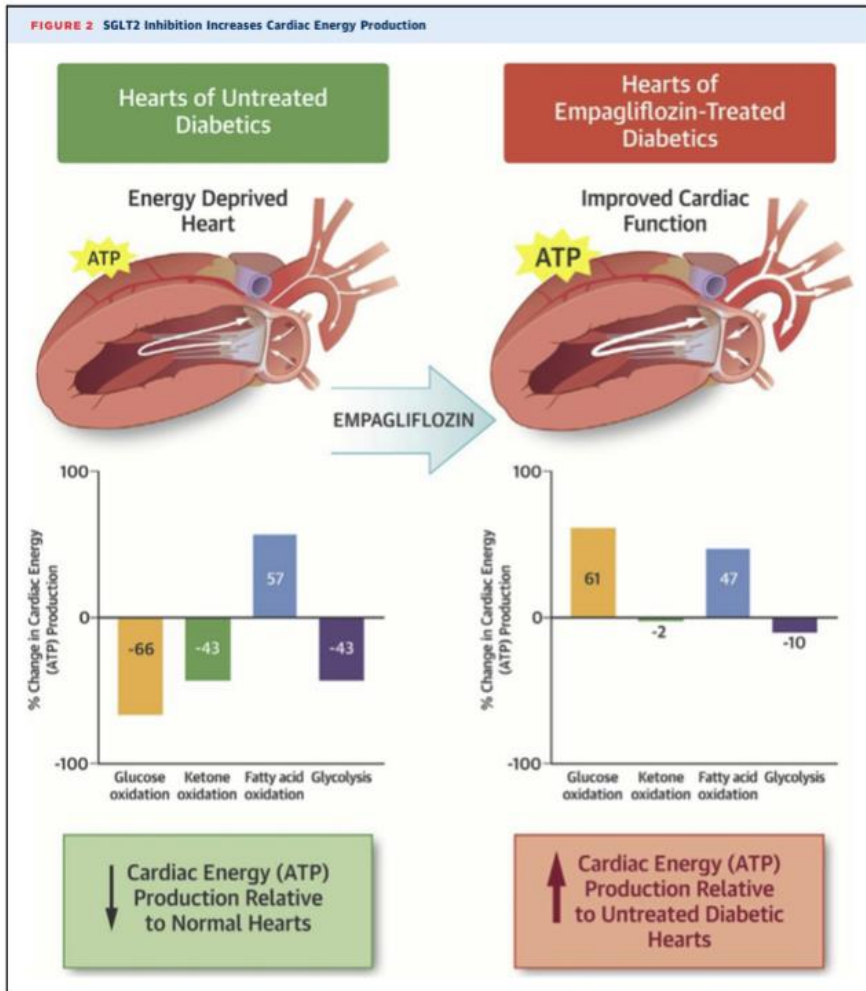
SGLT2 inhibition to target kidney aging



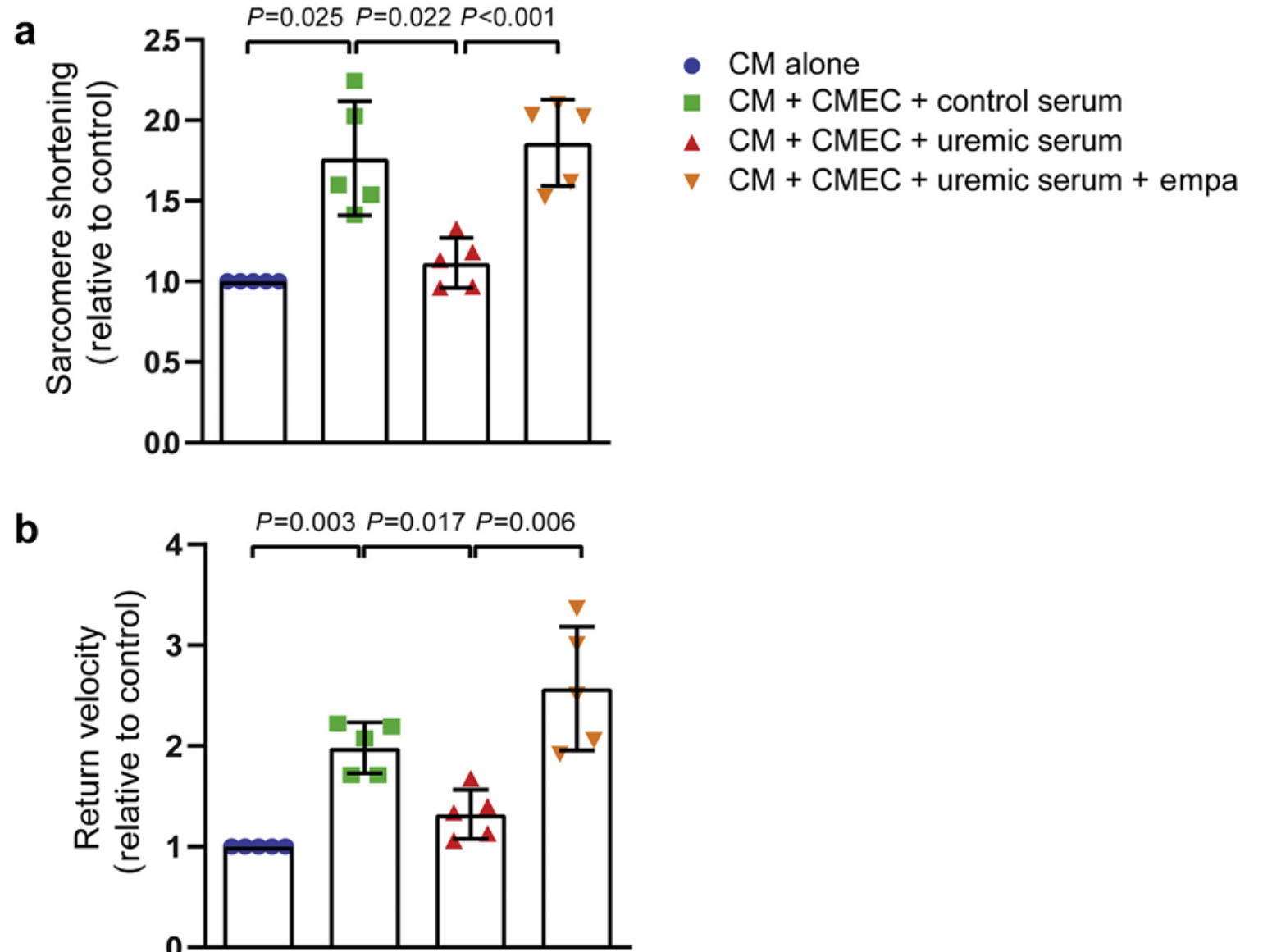
Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) -is A State-of-the-Art Review

Gary D. Lopaschuk, PHD,^a Subodh Verma, MD, PHD^b

JACC 2020

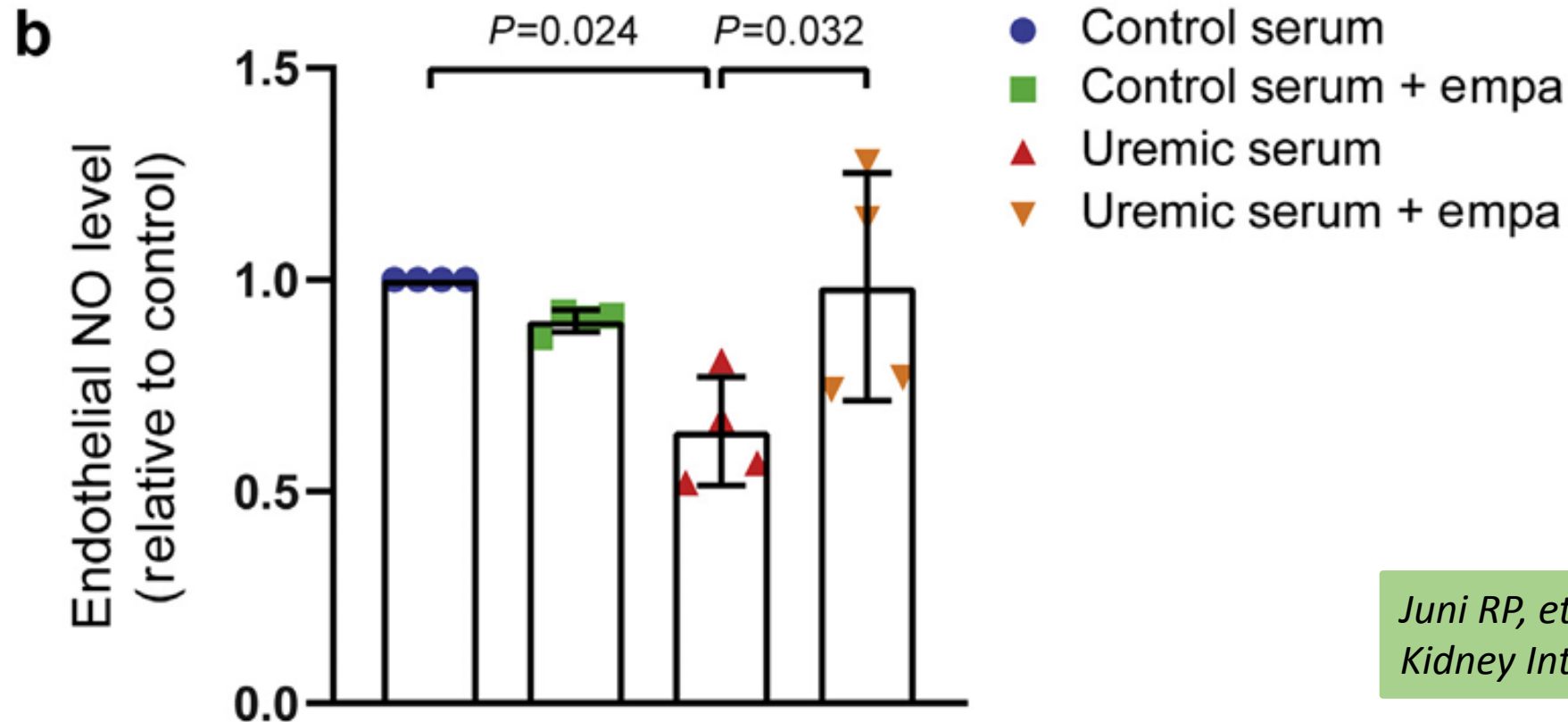


Empagliflozin restores UREMIC SERUM –induced impairment of endothelial regulation of cardiomyocyte relaxation and contraction



Empagliflozin restores UREMIC SERUM –induced impairment of endothelial regulation of cardiomyocyte relaxation and contraction

Empagliflozin alleviates uremic serum–induced mitochondrial oxidative damage, restoring the endothelium ability to enhance NO in cardiomyocytes



Juni RP, et al.,
Kidney International (2021) 99, 1088–1101

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

Methods



Prospective, single-center, open-label trial



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



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

Sampling protocol



1st dose
Day 1

Dapagliflozin 10 mg given before dialysis
Blood and dialysate samples after ingestion



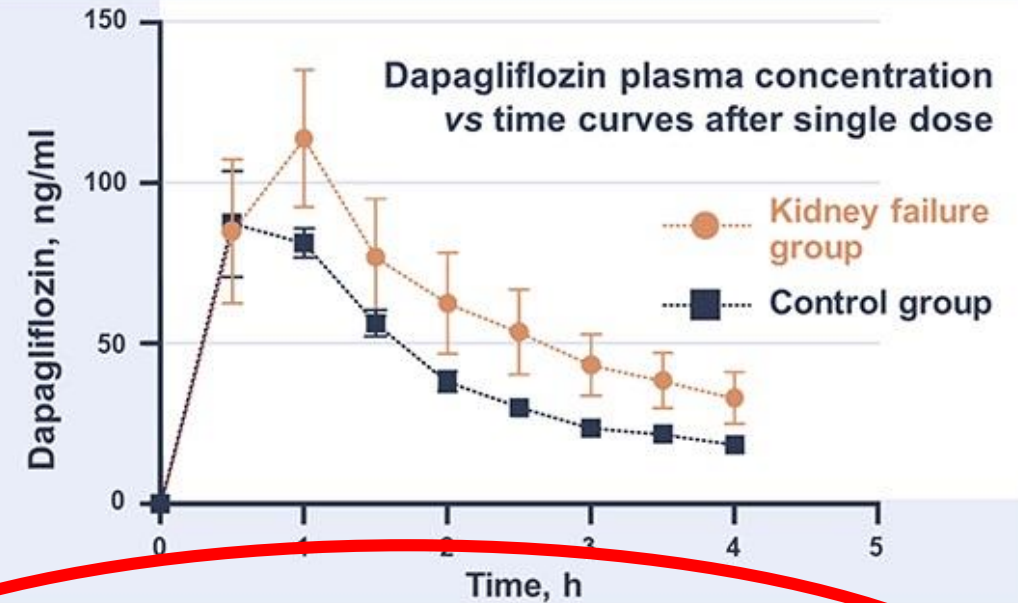
2nd dose
48 h later

Dapagliflozin 10 mg given before dialysis
Blood samples before ingestion



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

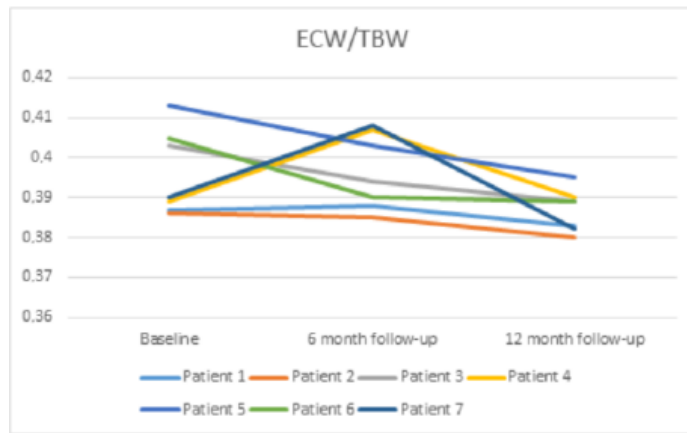


No serious adverse events reported

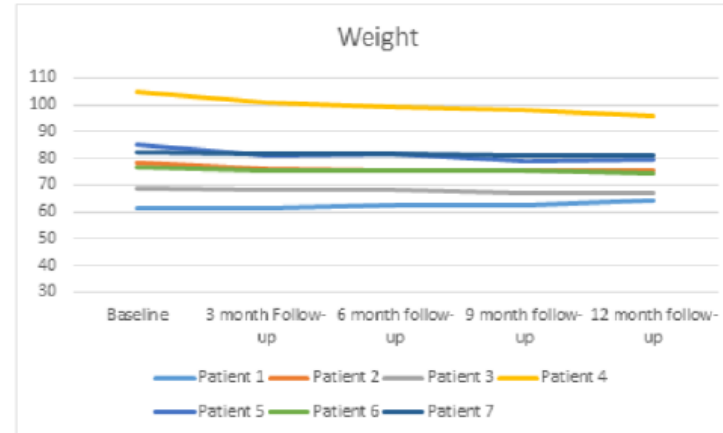
Conclusions: In individuals with kidney failure on dialysis, dapagliflozin was well-tolerated, was slightly dialyzable, and had nonaccumulating favorable pharmacokinetic properties.

Joaquim Barreto, Cynthia Borges, Tais Betoni Rodrigues, et al.
Pharmacokinetic Properties of Dapagliflozin in Hemodialysis and Peritoneal Dialysis Patients. CJASN doi: 10.2215/CJN.000000000000196.
Visual Abstract by Corina-Gabriela Teodosiu, MD

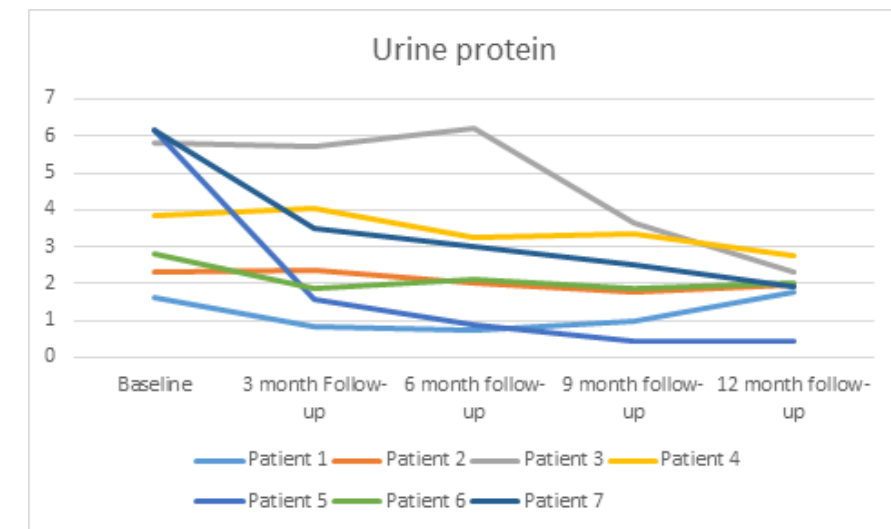
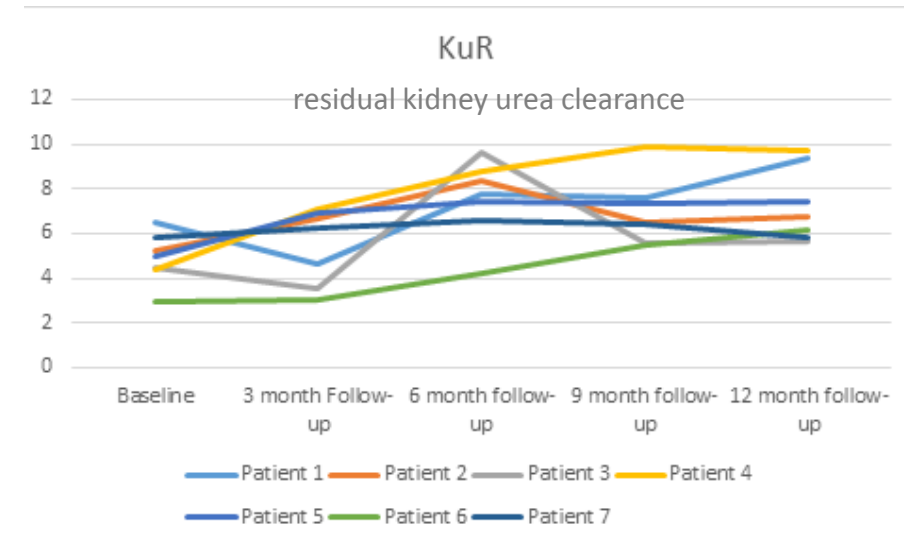
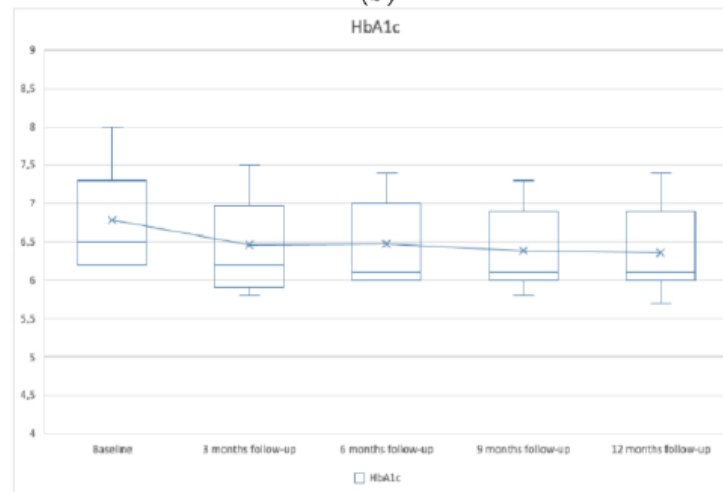
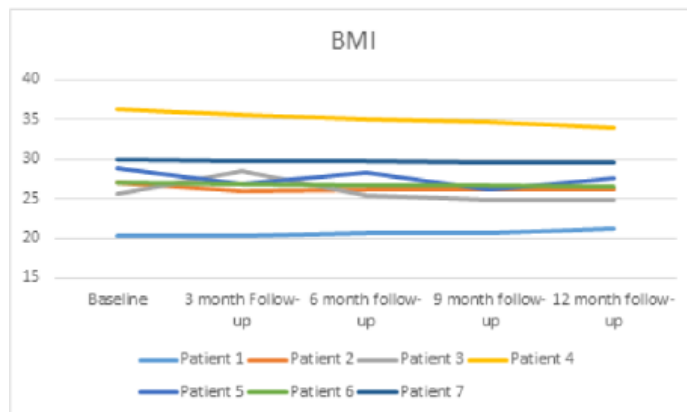
Efficacy and Safety of the Use of SGLT2 Inhibitors in Patients on Incremental Hemodialysis: Maximizing Residual Renal Function, Is There a Role for SGLT2 Inhibitors?



(a)

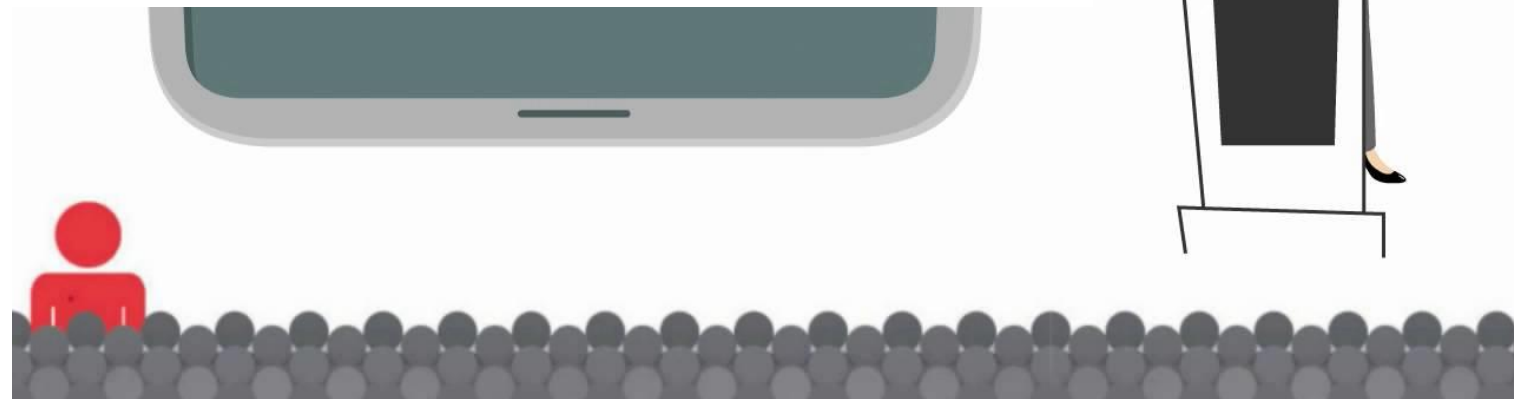


(b)



Structure of Talk

- **SGLT2-inhibitors** in ESKD: possible mechanism and safety
- **SGLT2-inhibitors** in ESKD: CV and kidney outcomes



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

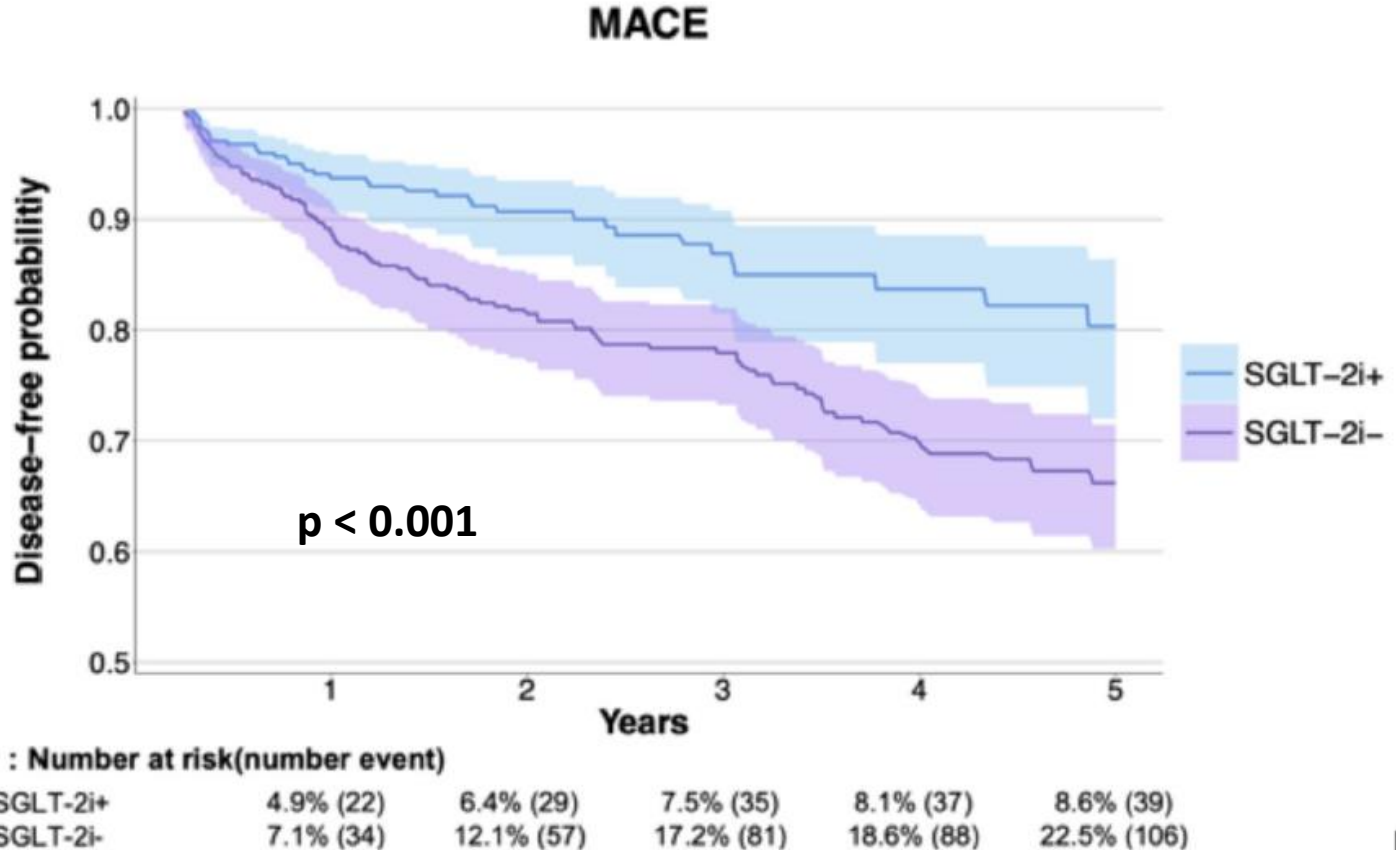
TriNetX Research Network database between 2012 and 2024

(B) MACE

49,762 ptz with T2DM who initiated dialysis
 1.57% of ptz utilized SGLT-2is within 3 months after dialysis.
771 SGLT-2i users (age 63.3) were matched with 771 non-users
 Median follow-up of 2.0 (IQR 0.3–3.9) years

SGLT-2i users were more likely to become dialysis-free 90 days after the index date (aHR = 0.49, p < 0.001).

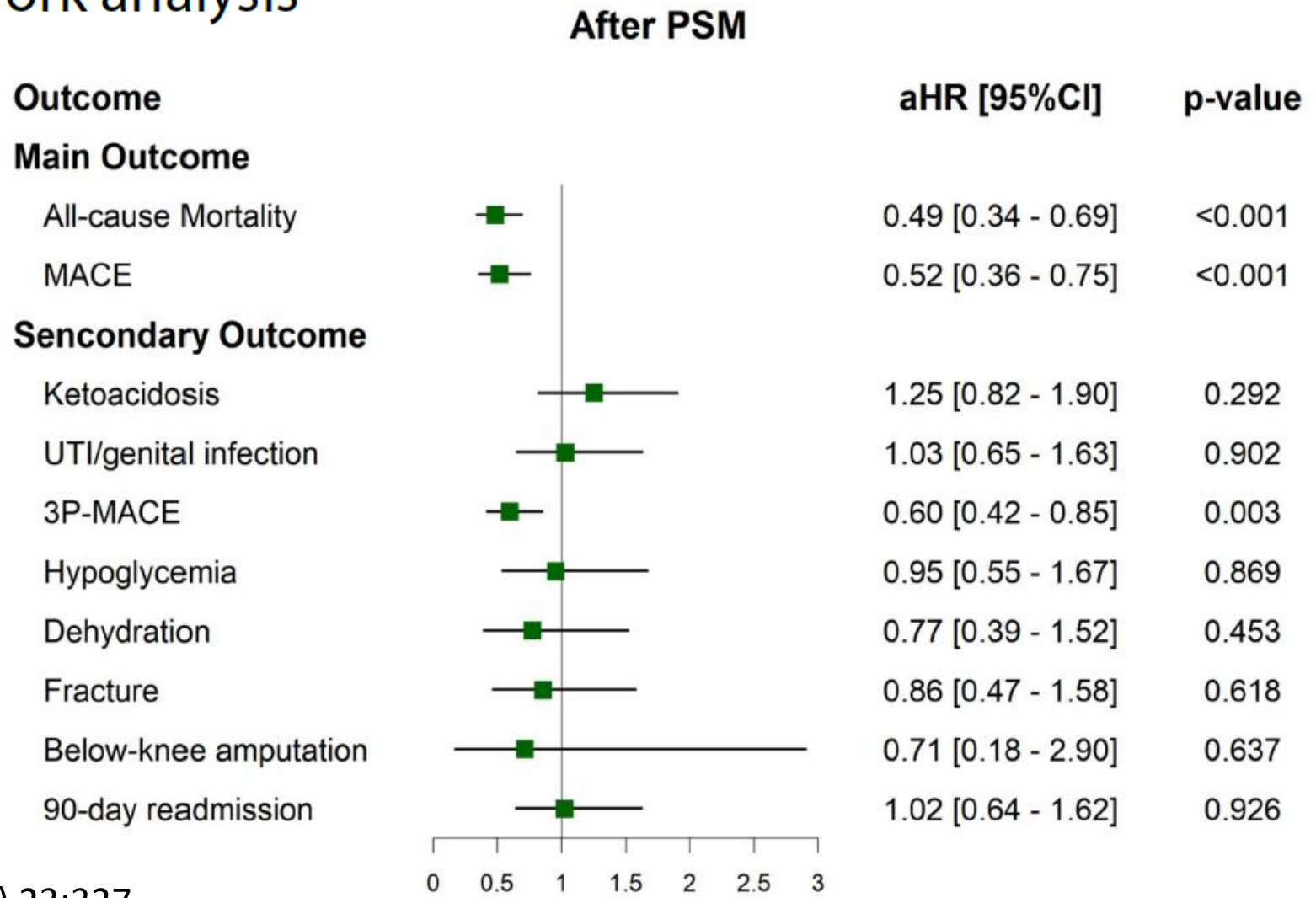
All Cause Mortality aHR = 0.49, p < 0.001
MACE aHR = 0.52, p < 0.001

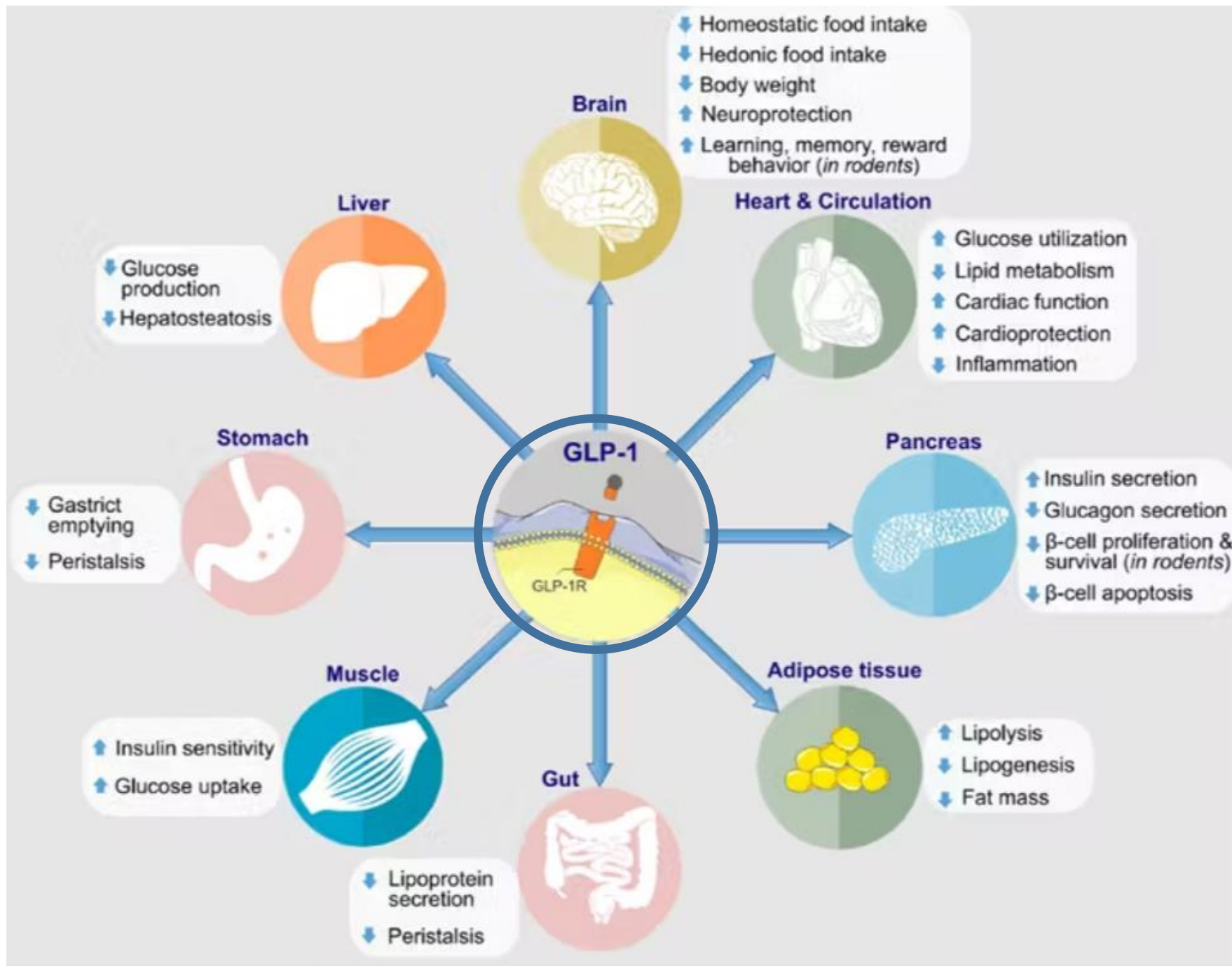


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Improved glycemic control with once-weekly dulaglutide in addition to insulin therapy in **15 T2DM ptz on HD** evaluated by continuous glucose monitoring

The main findings of the present study showed that **dulaglutide** may improve **glycemic control** and **glycemic excursion** and allow a significant **reduction in total daily dose of insulin** with no increased risk of hypoglycemia, leading to a **reduction in dryweight**, in patients with T2DM on HD.

The incidence of **asymptomatic hypoglycemia** detected by CGM tended **to be lower on HD days**.

Furthermore, administering dulaglutide once weekly after HD sessions led to a high **adherence rate**, and the drug was well tolerated.

Safety and Efficacy of GLP-1 Receptor Agonists in Type 2 DM with Advanced and End-Stage Kidney Disease: A Systematic Review and Meta-Analysis

Krisanapan P et al., Diseases 2024, 12, 14

Table 1. Characteristics of included studies.

Author (Year)	Terawaki et al. [23] (2013)	Hiramatsu et al. [21] (2015)	Idorn et al. [22] (2016)	Kondo et al. [34] (2017)	Yajima et al. [1] (2018)	Yajima et al. [2] (2018)	Hirose et al. [33] (2021)	Chen et al. [32] (2022)
Study type	Crossover controlled trial	Non-randomized controlled study	Randomized controlled trial	Retrospective cohort	Non-randomized controlled study	Non-randomized controlled study	Retrospective cohort	Retrospective cohort
Site	Japan, single center	Japan, single center	Denmark, multicenter	Japan, single center	Japan, single center	Japan, single center	Japan, national database	Taiwan, national database
GLP-1RA name	Liraglutide	Liraglutide	Liraglutide	Liraglutide	Dulaglutide	Dulaglutide	61.5% Dulaglutide, 36.5% Liraglutide, 2% Lixisenatide	N/A
GLP-1RA dosage	0.3 mg daily	0.6–0.9 mg daily	Titrate to a maximum dose of 1.8 mg daily	0.3–0.9 mg daily	0.75 mg weekly	0.75 mg weekly	N/A	N/A
Use of GLP-1RA	Single therapy	Single therapy	Add on therapy	Single therapy	Add on therapy	Add on therapy	Both single and add on therapy	Both single and add on therapy
Concomitant insulin used with GLP-1RA, %	0	0	80	0	100	100	34.1	16.3
Control	Vildagliptin, alogliptin, and insulin	Standard therapy	Placebo	None	Teneligliptin	Insulin	None	DPP-4i
Total N	10	30	24 ^a (20 ^b)	5	21	15	255	27,279
GLP1-RA	10	15	14 ^a (10 ^b)	5	11	15	255	701
Control	10	15	10	0	10	15	0	26,578
Male, n (%)	7 (70.0)	22 (73.3)	17 (85.0)	4 (80.0)	16 (76.2)	13 (86.7)	167 (65.5)	14,789 (54.2)
Age, year	62.9B ± 4.3	67.6 ± 7.0	67.1 ± 3.8	67.8 ± 4.3	68 (61, 72) ^c	72 (66, 79) ^c	66.5 ± 11.6	64.8 ± 13.0
Body mass index, kg/m ²	23.0 ± 1.5	24.8 ± 3.9	31.6 ± 2.4	23.2 ± 1.2	23.1 (21.6, 26.3) ^c	23.6 (22.9, 25.3) ^c	24.5 ± 5.1	N/A
Stage of advanced CKD	ESKD undergoing HD	ESKD undergoing PD	ESKD	ESKD undergoing HD	ESKD undergoing HD	ESKD undergoing HD	Stage 5 ND and ESKD	Stage 5 ND and ESKD
Duration of RRT	4.1 ± 1.1 years	10 ± 9.3 months	N/A	N/A	13.5 (3.7, 30.8) months ^c	12 (2, 82) months ^c	N/A	N/A
Duration of DM, years	25.4 ± 2.3	17.6 ± 12	14.2 ± 2.4	N/A	N/A	22 (18, 32) ^c	6.9 ± 6.9	N/A

Safety and Efficacy of GLP-1 Receptor Agonists in Type 2 DM with Advanced and End-Stage Kidney Disease: A Systematic Review and Meta-Analysis

Eight studies (five trials and three cohort studies)
27,639 patients

No difference was observed in **one-year mortality**.
There was **no** significant decrease in **SBP**.

GLP-1RAs significantly reduced **cardiothoracic ratio** (SMD of -1.2%; 95% CI -2.0, -0.4) and **pro-BNP** (SMD -335.9 pmol/L; 95% CI -438.9, -232.8). GLP-1RAs significantly reduced **mean blood glucose** (SMD -1.1 mg/dL; 95% CI -1.8, -0.3) and increased **weight loss** (SMD -2.2 kg; 95% CI -2.9, -1.5) with a potential benefit in cardiovascular outcomes.

In terms of **safety**, GLP-1RAs were associated with a **3.8- and 35.7-time higher risk of nausea and vomiting**, respectively, but were **not** significantly associated with a higher risk of **hypoglycemia**.

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- **SGLT2-inhibitors** in ESKD: possible mechanism and safety
- **SGLT2-inhibitors** in ESKD: CV and kidney outcomes
- **GLP1-RA** in ESKD: possible mechanism and safety
- **GLP1-RA** in ESKD: CV and kidney outcomes



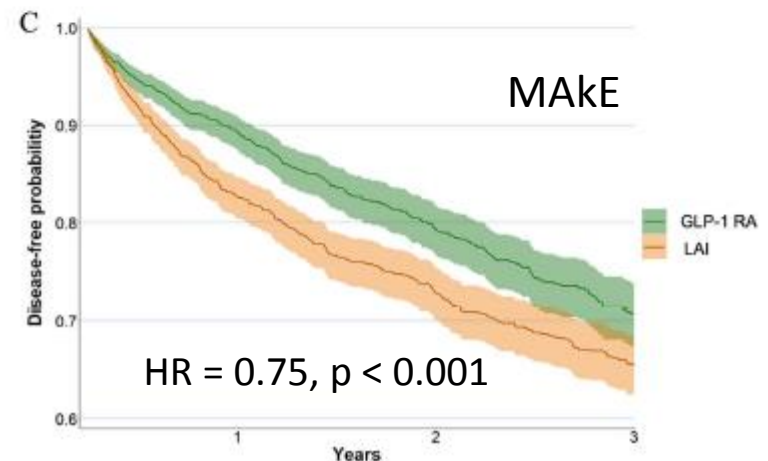
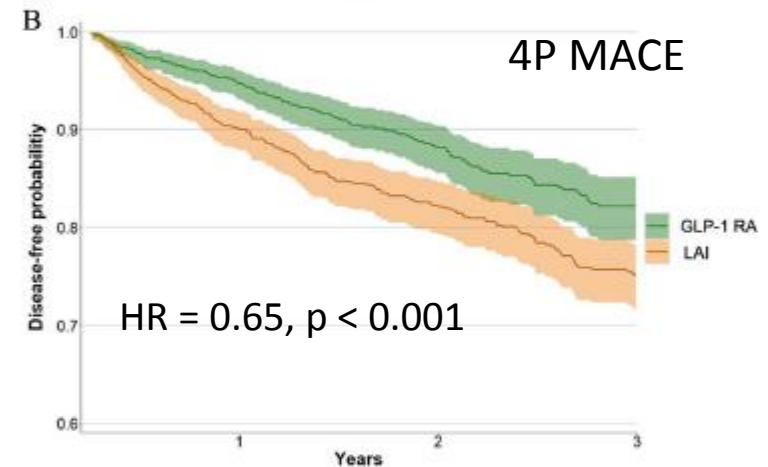
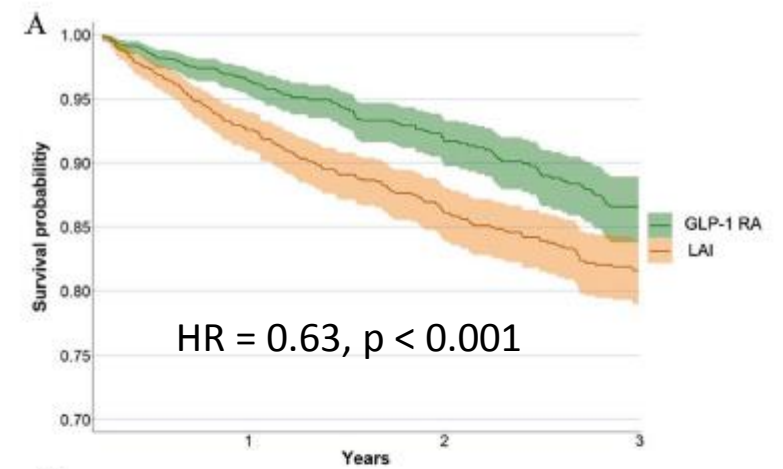
Mortality and cardiovascular events in diabetes mellitus patients at dialysis initiation treated with glucagon-like peptide-1 receptor agonists

82,041 ptz with T2D initializing dialysis,
 2.1% (n = 1685) patients were **GLP-1RAs users**
 1682 ptz in propensity-matched group, treated with **long-acting insulin (LAI)**
 Median follow-up of 1.4 years

Table 2 Incidence of outcomes among GLP-1 RA group compared to LAI control group after propensity score matching

Outcome	Patients with outcome		aHR (95%CI)	Log rank p-value	E value for HR	E value for lower bound of CI
	GLP-1RAs group	LAI group				
Primary outcome						
Mortality	6.5% (110/1682)	11.0% (185/1682)	0.63 (0.50–0.80)	<0.001	2.54	3.41
Secondary outcome						
4P-MACE	9.2% (115/1253)	14.8% (182/1229)	0.65 (0.51–0.82)	<0.001	2.47	3.33
MAKE	16.1% (270/1682)	21.6% (364/1682)	0.75 (0.64–0.87)	<0.001	1.75	2.07

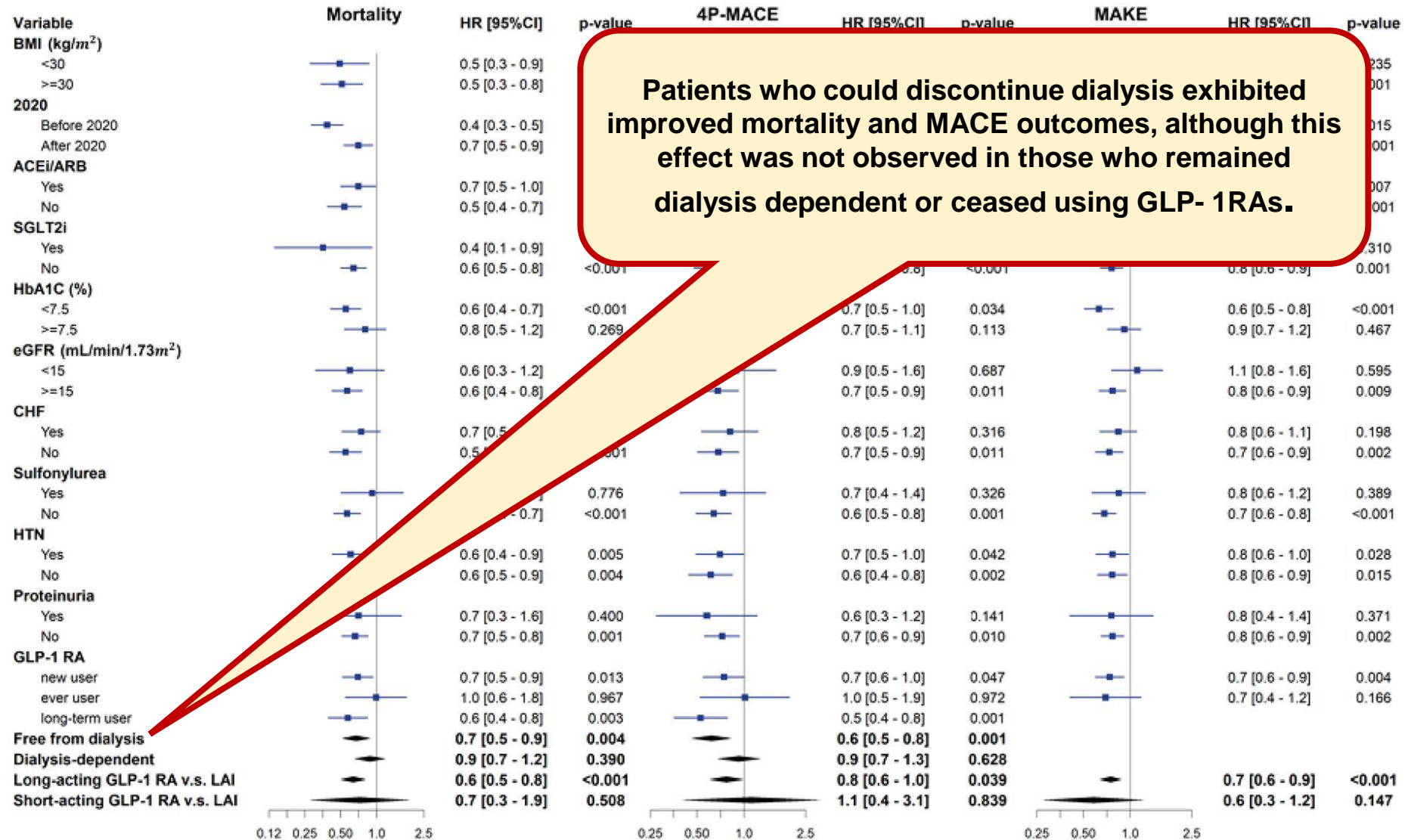
aHR adjusted hazard ratio, GLP-1RAs glucagon-like peptide-1 receptor agonists, LAI long-acting insulin, 4P-MACE four-point major adverse cardiovascular major adverse kidney event



**TriNetX Research
 Network database**

Mortality and cardiovascular events in diabetes mellitus patients at dialysis initiation treated with glucagon-like peptide-1 receptor agonists

82,041 ptz with T2D initializing dialysis,
 2.1% (n = 1685) patients were GLP-1RAs users
 1682 ptz in propensity-matched group, treated with LAI
 Median follow-up of 1.4 years



Patients who could discontinue dialysis exhibited improved mortality and MACE outcomes, although this effect was not observed in those who remained dialysis dependent or ceased using GLP-1RAs.



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- Randomized studies





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GLP1-RA in Dialysis

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None Selected



	Study Title	NCT Number	Status	Conditions	Interventions
1	Reduction of Peritoneal Glucose Uptake With Use of SGLT2 in Humans Undergoing Peritoneal Dialysis Treatment	NCT05250752	Unknown status *	<ul style="list-style-type: none"> •End Stage Renal Disease •Peritoneal Dialysis Complication 	Dapagliflozin 10 MG [Farxiga]
2	Effect of Canagliflozin on Ultrafiltration & Fibrosis in Patients on Peritoneal Dialysis	NCT06913647	Not yet recruiting	<ul style="list-style-type: none"> •ESRD •CKD (Chronic Kidney Disease) Stage 5D 	Canagliflozin 300 MG
3	meChANisms and sAfeTy of SGLT2 Inhibition in peRitoneal dialYsis	NCT05715814	Recruiting	<ul style="list-style-type: none"> •Peritoneal Dialysis Complication •End Stage Kidney Disease •Sodium-glucose Co-transporter-2 Inhibitors 	Empagliflozin 25 MG
4	Canagliflozin in Advanced Renal Disease With MRI Endpoints	NCT06182839	Recruiting	<ul style="list-style-type: none"> •ESRD, CKD Stage 4, CKD Stage 5 	Canagliflozin 300Mg Tab •Drug: Placebo
5	Empagliflozin on Residual Kidney Function in Incident Peritoneal Dialysis Patients	NCT06483074	Recruiting	<ul style="list-style-type: none"> •End Stage Renal Disease on Dialysis •Peritoneal Dialysis Complication •Sodium-glucose Cotransporter-2 Inhibitor 	Empagliflozin 10 MG
6	The Effect of Dapagliflozin on Ultrafiltration Among Peritoneal Dialysis Patients	NCT04923295	Completed	<ul style="list-style-type: none"> •Peritoneal Dialysis Complication •Ultrafiltration Failure 	Dapagliflozin 10Mg Tab
7	Effect of Empagliflozin on Peritoneal and Kidney Function in End Stage Renal Disease	NCT05671991	Recruiting	<ul style="list-style-type: none"> •End Stage Renal Disease on Dialysis 	Empagliflozin 25 mg vs Placebo •Drug: Empagliflozin 10 MG
8	Dapagliflozin Delays the Loss of Renal Function in Peritoneal Dialysis Patients	NCT06398977	Recruiting	<ul style="list-style-type: none"> •Peritoneal Dialysis Complication •Renal Function Aggravated •Sodium-glucose Co-transporter-2 Inhibitors 	Dapagliflozin
9	Pharmacokinetics and Dialyzability of Dapagliflozin in Dialysis Patients	NCT05343078	Completed	<ul style="list-style-type: none"> •End-stage Renal Disease 	Dapagliflozin 10Mg Tab

Study Title	NCT Number	Status	Conditions	Interventions
Safety, Tolerability, and Feasibility of Empagliflozin Therapy in Dialysis-dependent ESKD	NCT05614115	Recruiting	<ul style="list-style-type: none"> •End-stage Kidney Disease •Kidney Disease, Chronic •Dialysis 	<ul style="list-style-type: none"> •Drug: Empagliflozin •Other: Placebo
Effect of Empagliflozin on Peritoneal and Kidney Function in End Stage Renal Disease	NCT05671991	Recruiting	<ul style="list-style-type: none"> •End Stage Renal Disease on Dialysis 	<ul style="list-style-type: none"> •Drug: Empagliflozin 25 mg vs Placebo •Drug: Empagliflozin 10 MG
Empagliflozin in Heart Failure Dialysis Patients	NCT05967156	Recruiting	<ul style="list-style-type: none"> •Heart Failure •Hemodialysis 	<ul style="list-style-type: none"> •Drug: Empagliflozin10Mg Tab
Pharmacokinetics and Dialyzability of Dapagliflozin in Dialysis Patients	NCT05343078	Completed	<ul style="list-style-type: none"> •End-stage Renal Disease 	<ul style="list-style-type: none"> •Drug: Dapagliflozin 10Mg Tab
The Efficacy and Safety of Dapagliflozin in Improving Heart Failure in Dialysis Patients	NCT06365541	Recruiting	<ul style="list-style-type: none"> •The Efficacy and Safety of Dapagliflozin in Improving Heart Failure in Dialysis Patients 	<ul style="list-style-type: none"> •Drug: Dapagliflozin
EMPAGliflozin in Heart Failure With PReserved Ejection Fraction and End Stage Renal Disease	NCT06249945	Recruiting	<ul style="list-style-type: none"> •Heart Failure With Preserved Ejection Fraction •End Stage Renal Disease on Dialysis 	<ul style="list-style-type: none"> •Drug: Empagliflozin 25 MG •Drug: Placebo
Empagliflozin in Heart Failure with Reduced Ejection Fraction and End Stage Renal Disease	NCT06249932	Recruiting	<ul style="list-style-type: none"> •Heart Failure with Reduced Ejection Fraction •End Stage Renal Disease on Dialysis 	<ul style="list-style-type: none"> •Drug: Empagliflozin 25 MG •Drug: Placebo
The RENAL LIFECYCLE Trial: A RCT to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients With Severe CKD	NCT05374291	Enrolling by invitation	<ul style="list-style-type: none"> •Kidney Disease, Chronic •Renal Transplant Failure •Heart Failure 	<ul style="list-style-type: none"> •Drug: Dapagliflozin 10 mg/day (oral) •Drug: Placebo

The RENAL LIFECYCLE Trial: A RCT to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients With Severe CKD

Europe and Australia.
composite end point of kidney failure,
heart failure hospitalization,
or all-cause mortality.

The trial aims to address the efficacy and safety of dapagliflozin 10 mg versus placebo in at least **1500 patients** with

- (1) An eGFR <25 ml/min per 1.73 m²
- (2) Dialysis patients with residual diuresis 500 ml/24-hour; or
- (3) Kidney transplant recipients with an eGFR <45 ml/min per 1.73 m²

Study Completion (Estimated) ⓘ

2027-01

Enrollment (Estimated) ⓘ

1500

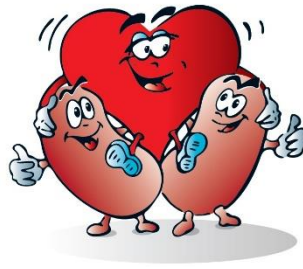
Study Type ⓘ

Interventional

Phase ⓘ

Phase 3

Take Home Messages



Both SGLT2-I and GLP1-RA seem to be safe in patients in Dialysis

Retrospective cohorts of DM patients at dialysis initiation showed a 50% decrease in CV and all cause mortality in SGLT2-i users

Retrospective cohorts of DM patients at dialysis initiation showed a 35% decrease in CV and all cause mortality in and a 25% reduction in the need to continue dialysis within 3 years in the GLP-1RAs group

Randomized controlled trials are warranted to study the effect on CV and Renal outcomes in patients in RRT