

IL CONTINUUM CARDIO-NEFRO-METABOLICO

**Effetto del trattamento precoce con
SGLT-2 inibitori nel paziente
con sindrome cardiorenale**

Iacoviello Massimo



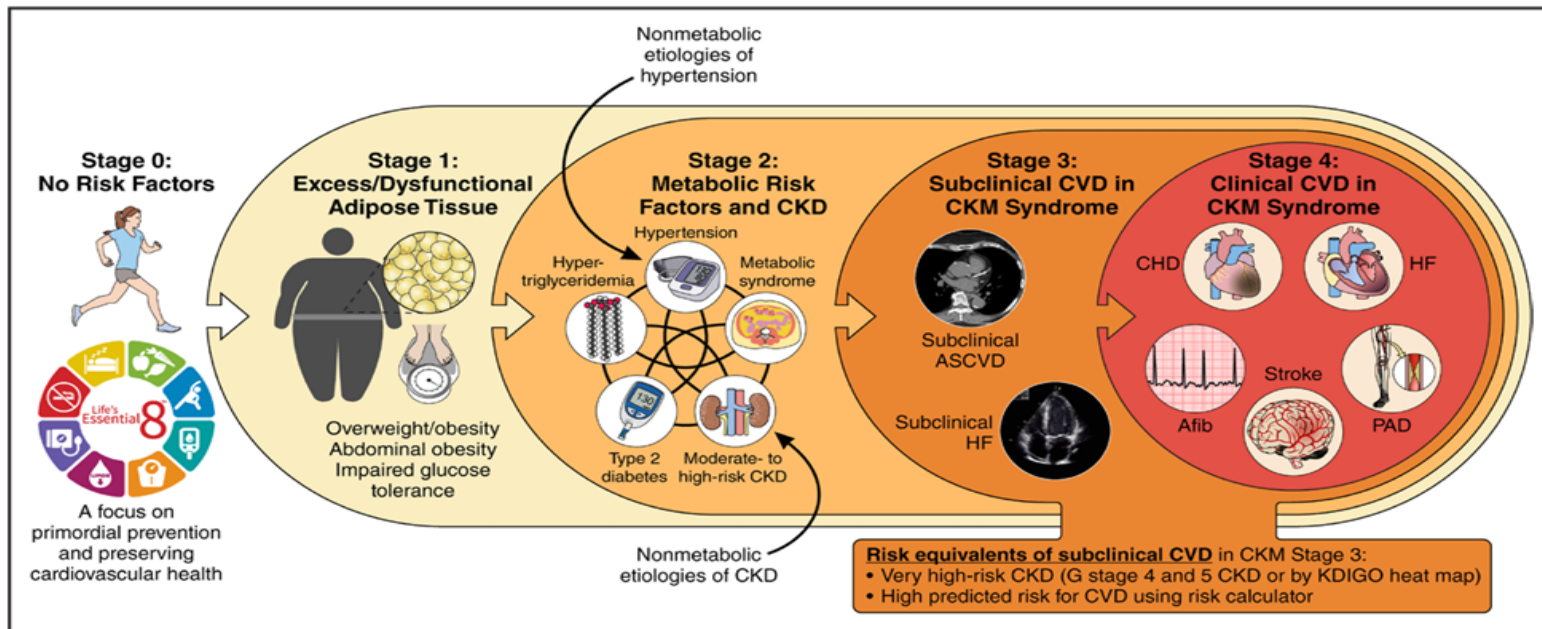
Disclosure

Ai sensi dell'art. 4.5 su “Docenti e moderatori dell'evento”, pag. 8 del Manuale Nazionale di Accreditamento per l'erogazione di eventi ECM del 06/12/2018, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Fee for consultancy services and Advisory Board: Novo Nordisk, Eli Lilly, Boehringer Ingelheim
- Speaker fees: Astra, Boehringer Ingelheim, Eli Lilly, Bruno, Novartis, Novo Nordisk

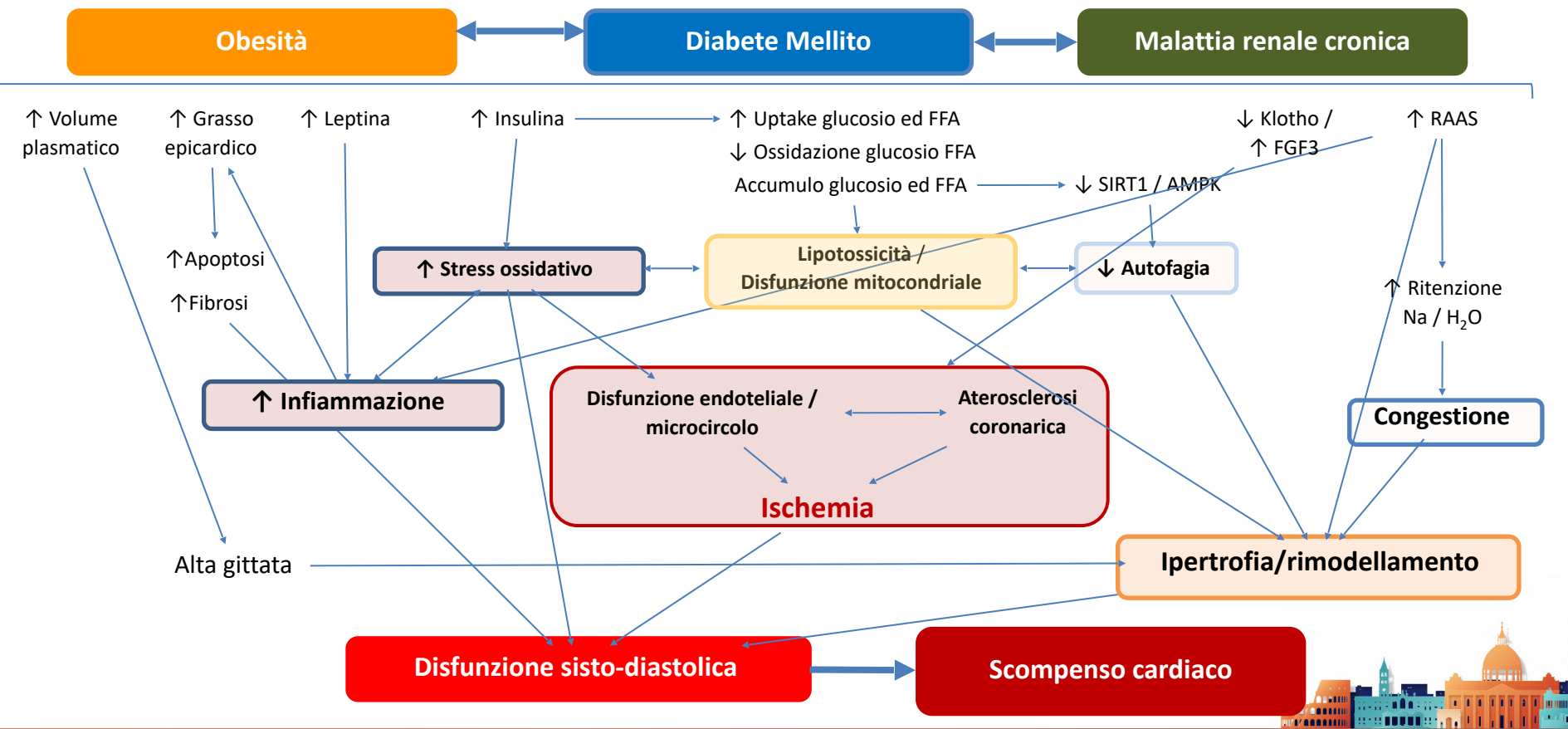


SGLT2i first nel continuum cardiorenale e metabolico



Ndumele CE. et al. Circulation. 2023;148:1606–1635





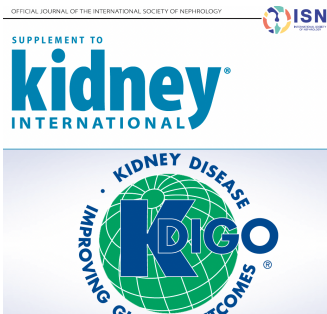


Table 1 | Criteria for chronic kidney disease (either of the following present for a minimum of 3 months)

Markers of kidney damage (1 or more)	Albuminuria (ACR ≥ 30 mg/g [≥ 3 mg/mmol]) Urine sediment abnormalities Persistent hematuria Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR < 60 ml/min per 1.73 m² (GFR categories G3a–G5)

ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate.



CKD is classified based on:

- Cause (C)
- GFR (G)
- Albuminuria (A)

				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥ 300 mg/g ≥ 30 mg/mmol
GFR categories (mL/min/1.73 m ²)	Description and range					
	G1	Normal or high	≥ 90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	< 15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

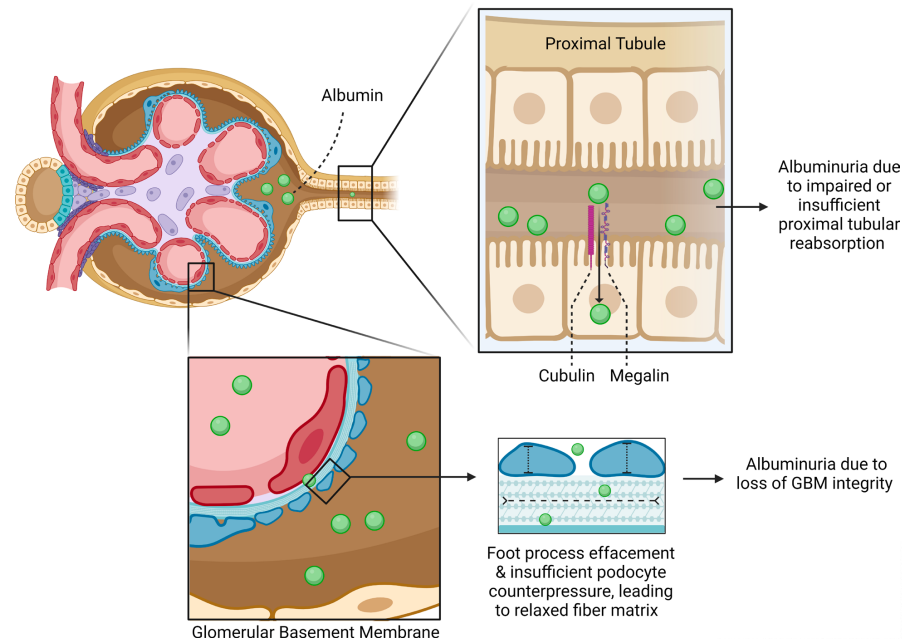
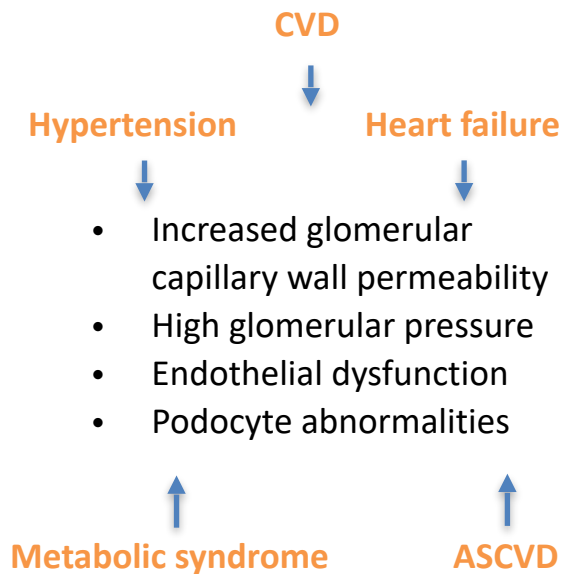
Low risk (if no other markers of kidney disease, no CKD)

Moderately increased risk

High risk

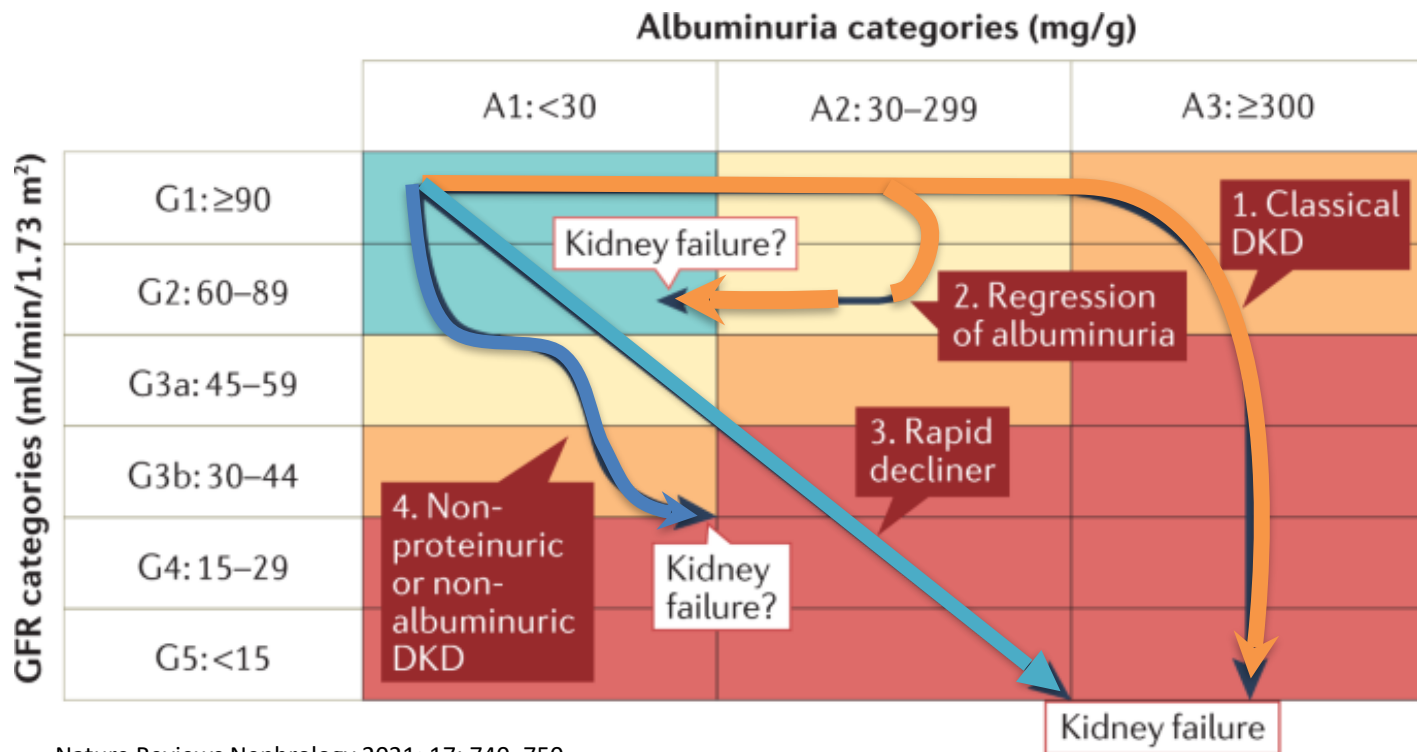
Very high risk

Il background fisiopatologico della albuminuria



Claudel and Verma. Circulation. 2025;151:716–732.





Nature Reviews Nephrology 2021; 17: 740–750



Risk of cardiovascular death according to KDIGO

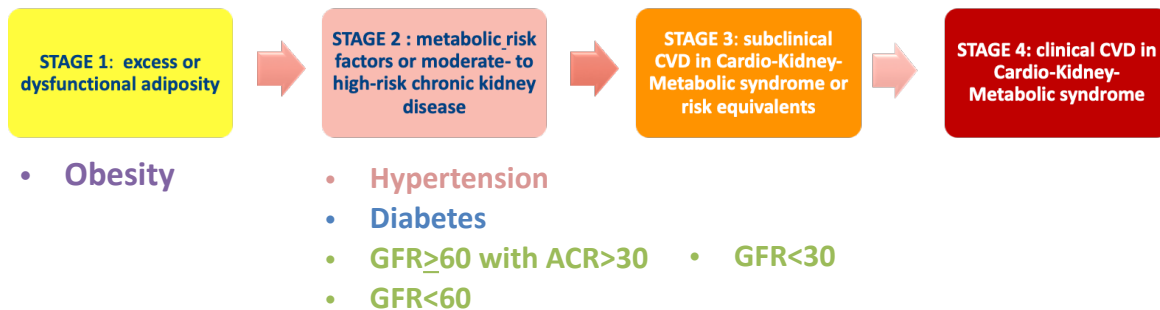
		Albuminuria categories (mg/g)			
		A1		A2	A3
		<10 mg/g	10-29 mg/g	30-299 mg/g	≥300 mg/g
G1	≥105	0.93 (0.74–1.16)	1.33 (1.04–1.72)	2.46 (1.88–3.23)	2.69 (1.36–5.32)
	90–104	1 (reference)	1.63 (1.20–2.19)	1.82 (1.36–2.45)	4.77 (3.16–7.22)
G2	75–89	1.03 (0.85–1.24)	1.48 (1.23–1.78)	1.73 (1.29–2.32)	4.01 (2.62–6.14)
	60–74	1.09 (0.92–1.29)	1.58 (1.31–1.91)	2.18 (1.58–3.02)	4.23 (2.95–6.06)
G3a	45–59	1.52 (1.18–1.97)	2.38 (1.91–2.96)	3.13 (2.32–4.22)	4.97 (3.70–6.66)
G3b	30–44	2.40 (1.80–3.21)	3.07 (1.73–5.44)	4.12 (2.84–5.98)	6.10 (4.08–9.10)
G4	15–29	13.51 (4.89–37.35)	7.99 (1.95–32.81)	5.60 (3.66–8.57)	9.49 (4.97–18.10)
G5	<15				

Nature Reviews Nephrology 2022, 18: 696–707



Holistic approach

Critical need for early identification and stratification of CKM stages, fostering an interdisciplinary approach that bridges specialties and ensures comprehensive care



• Metabolic risk

- Glycemia – Hb1Ac
- Adiposopathy
- Lipidic profile
- SCORE2-Diabetes

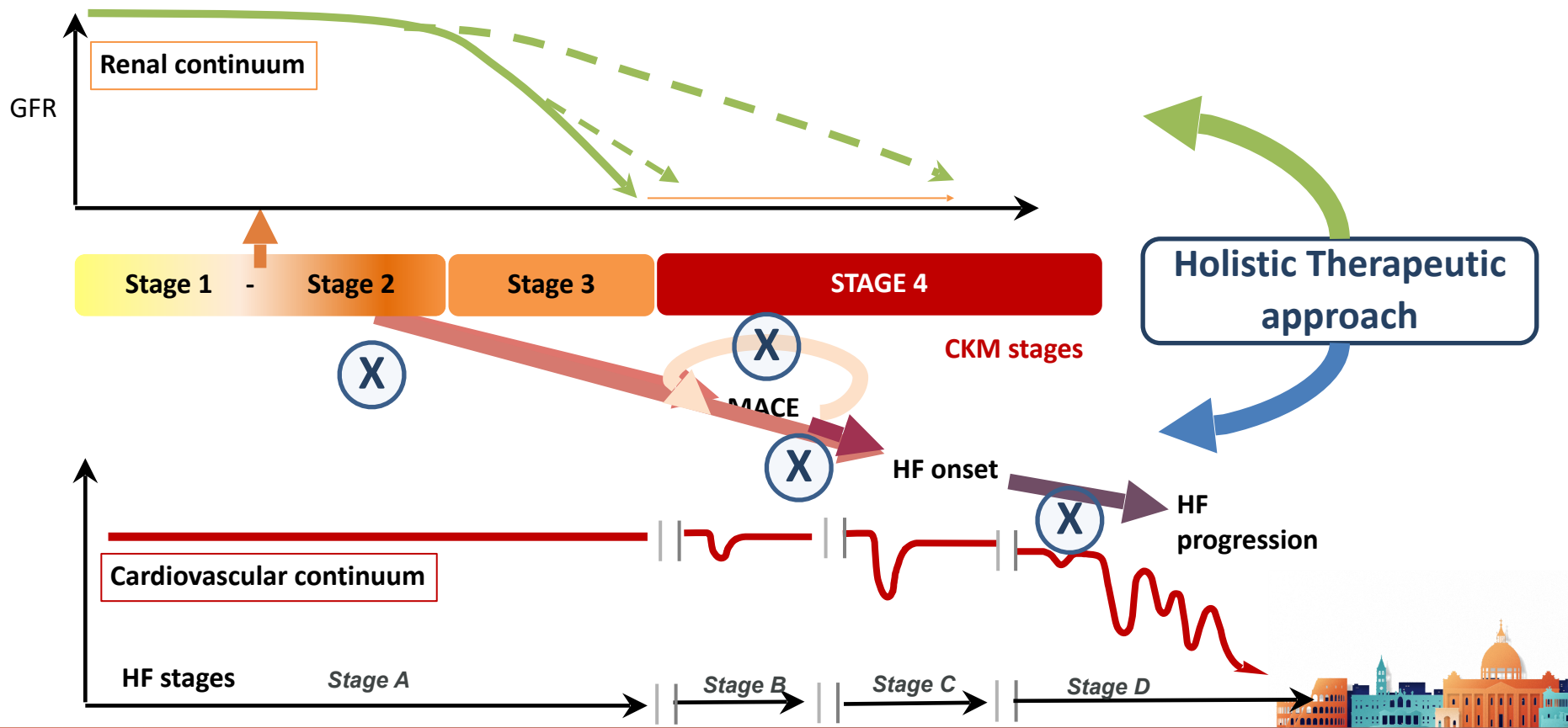
• Renal function

- GFR/ACR

• Cardiovascular profile

- Arterial pressure
- ECG
- NT-proBNP
- Echocardiography
- Echo-Doppler peripheral arteries

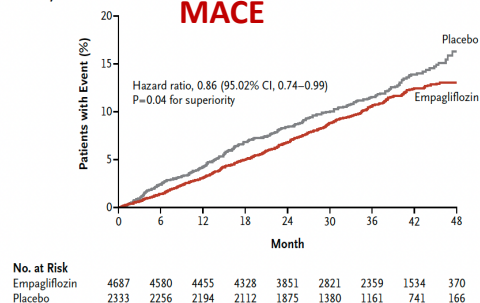




EMPAREG-outcome

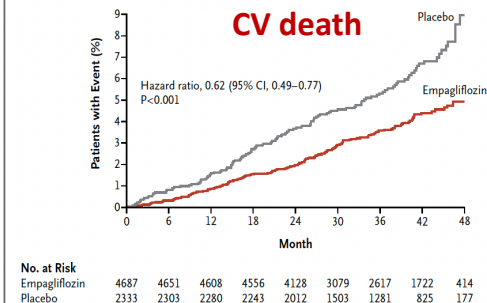
A Primary Outcome

MACE



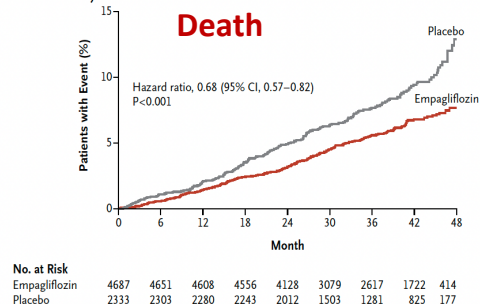
B Death from Cardiovascular Causes

CV death



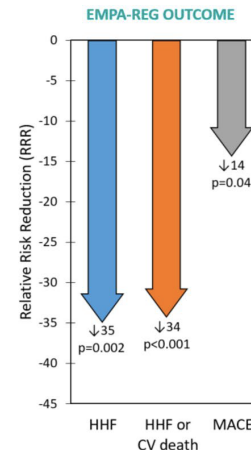
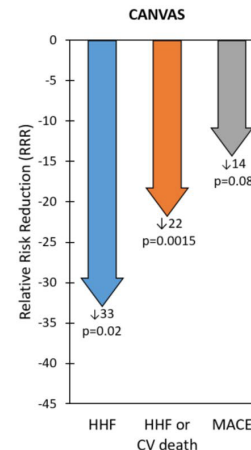
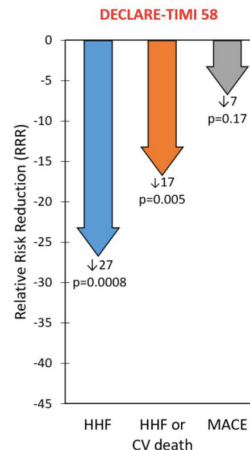
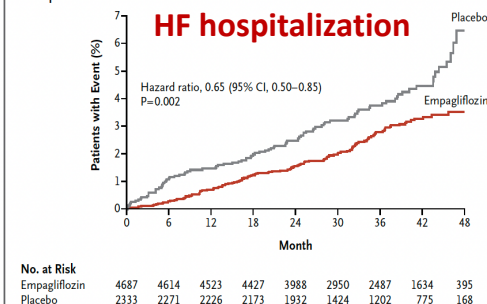
C Death from Any Cause

Death



D Hospitalization for Heart Failure

HF hospitalization



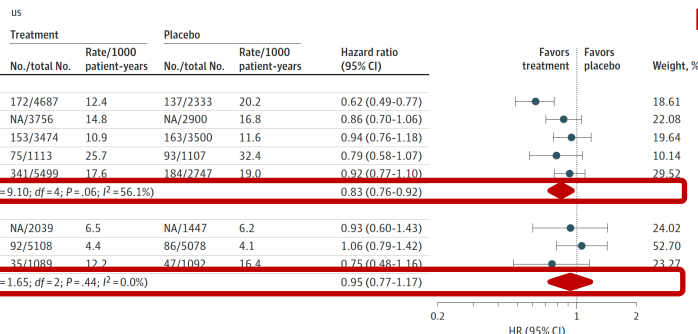
Kluger et al. Cardiovasc Diabetol 2019

N Engl J Med 2015;373:2117-28.

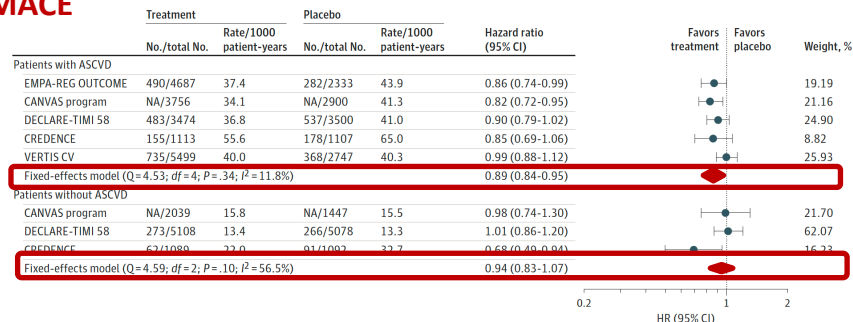


SGLT2i nel paziente con Diabete Mellito di Tipo 2

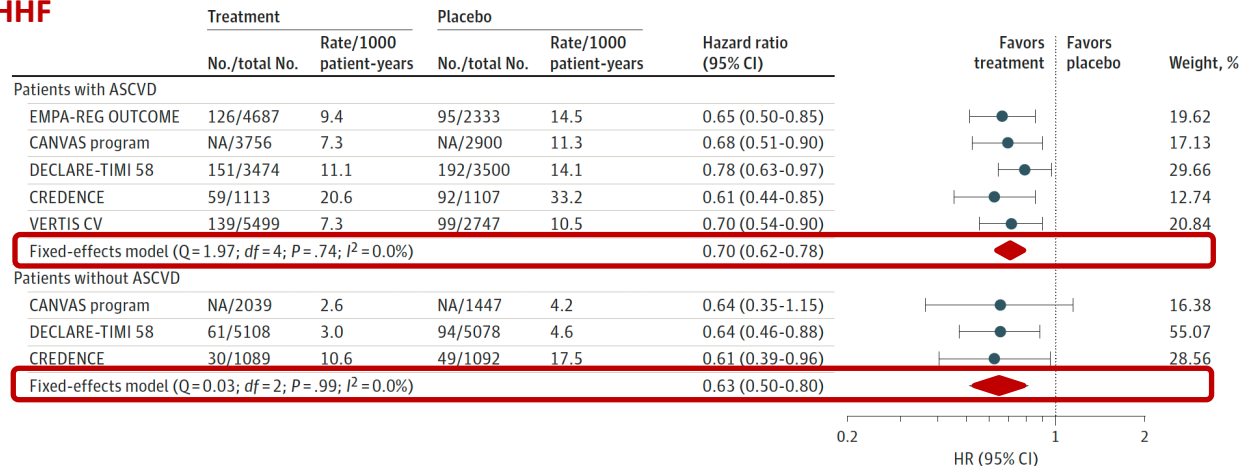
CV Death



MACE



HHF



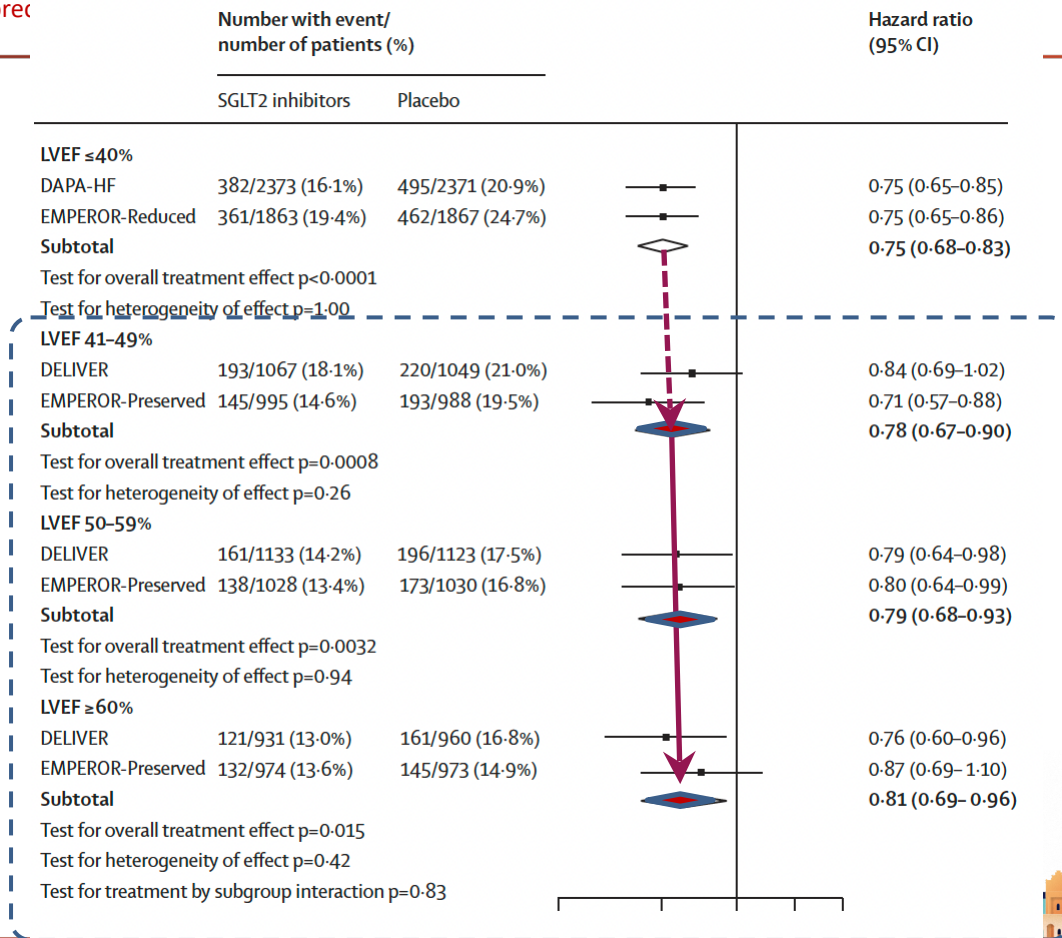
JAMA Cardiol. 2021;6:148-158

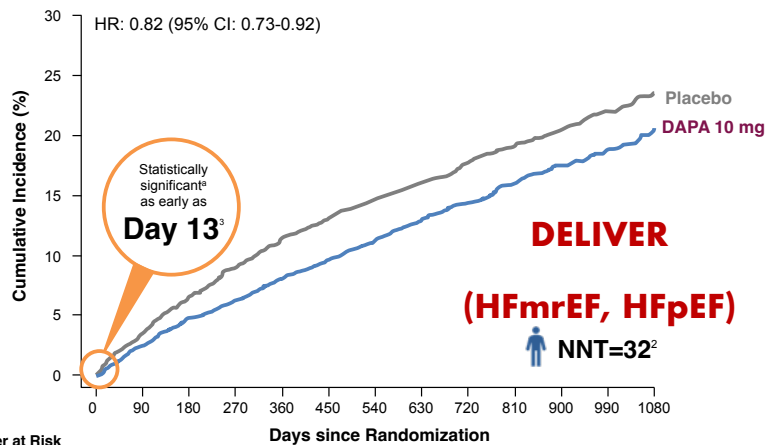
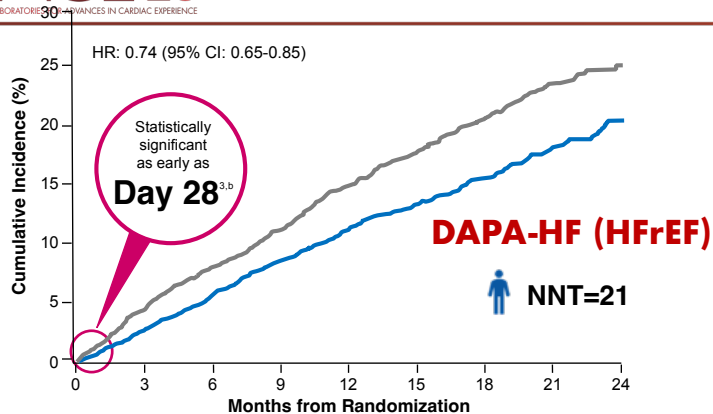
Metanalisi:

EMPEROR-preserved /

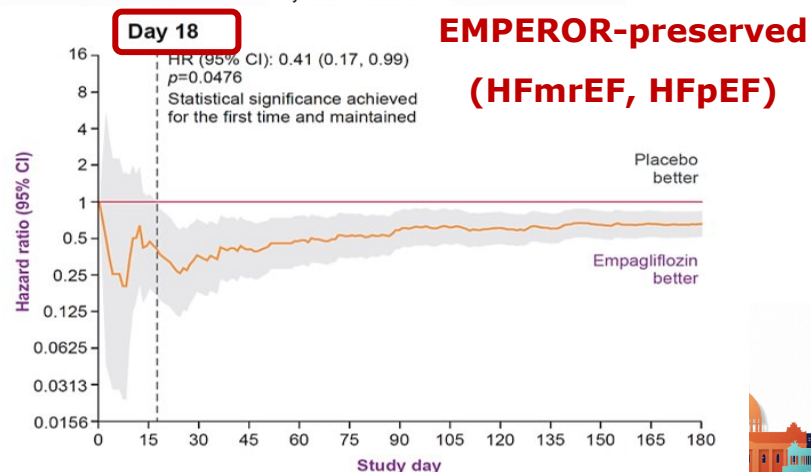
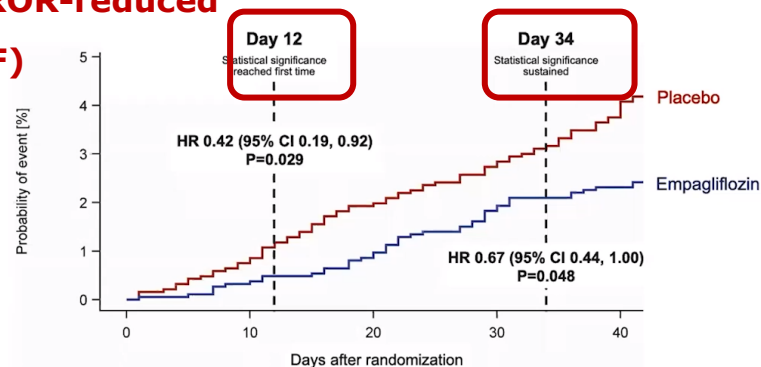
DELIVER

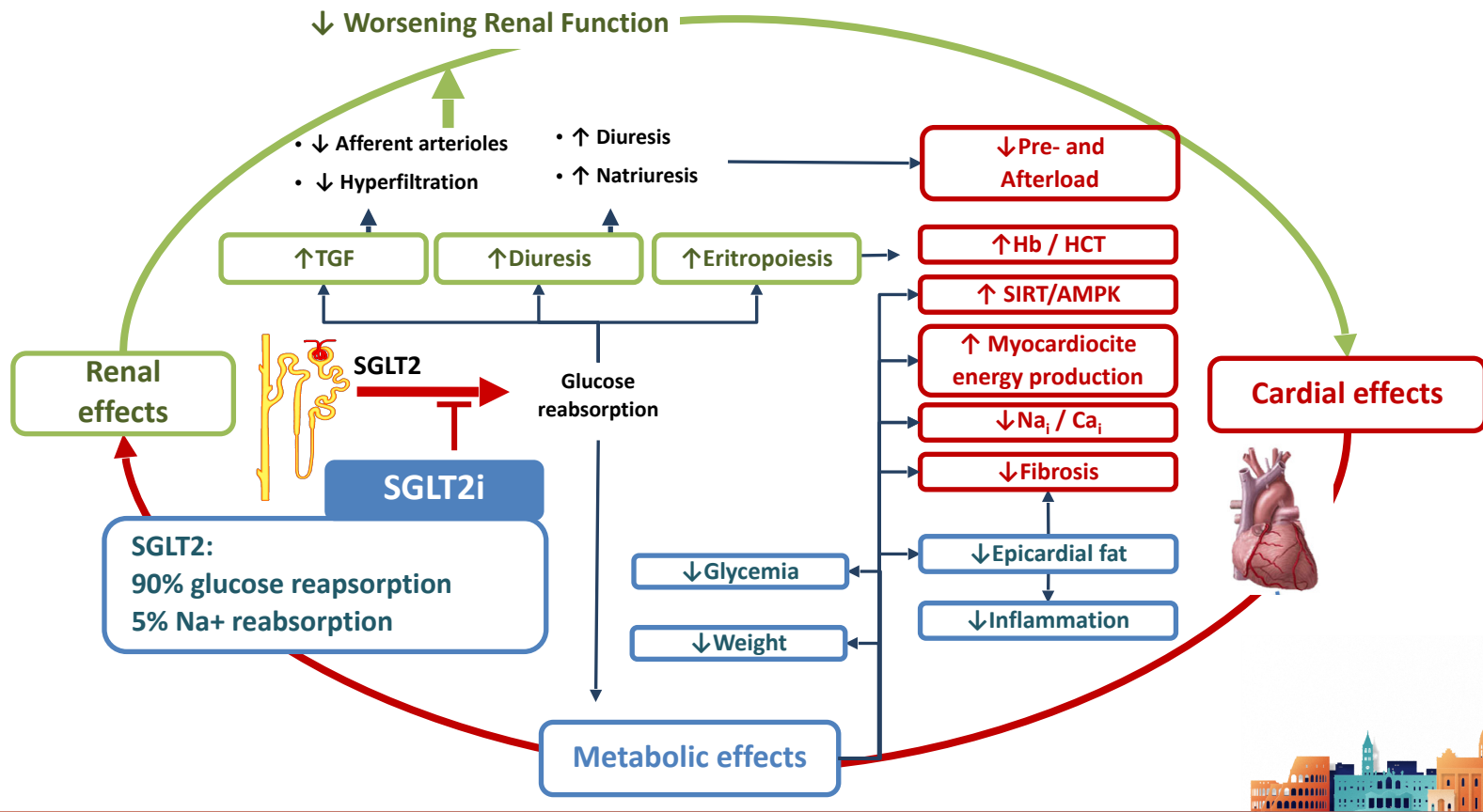
Vaduganathan et al. Lancet 2022

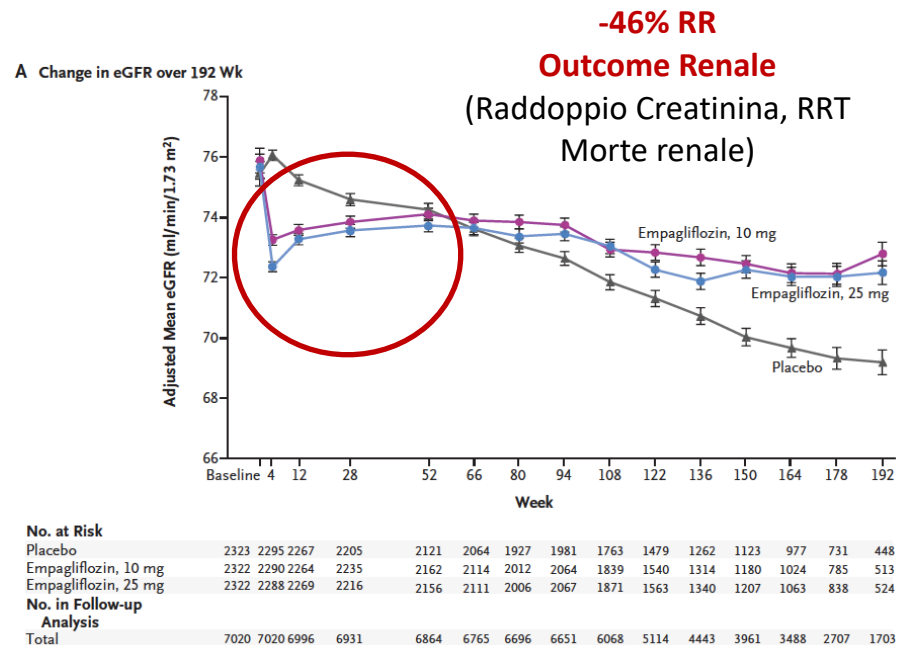




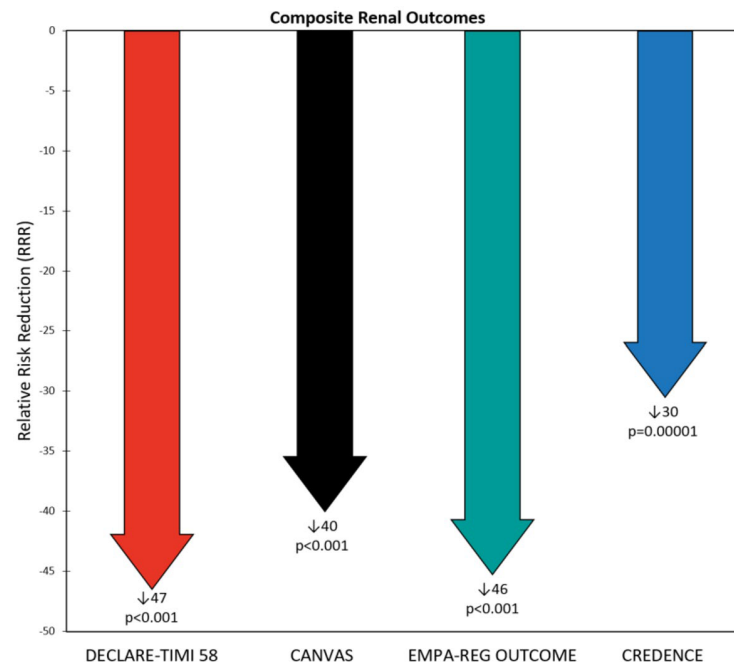
EMPEROR-reduced (HFrEF)







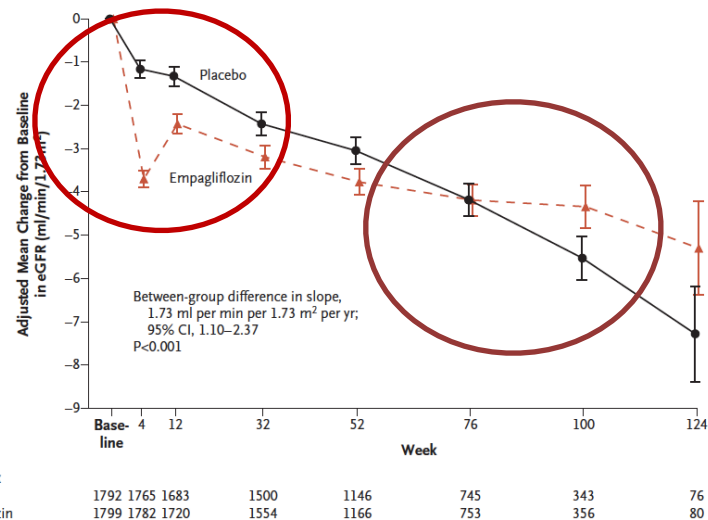
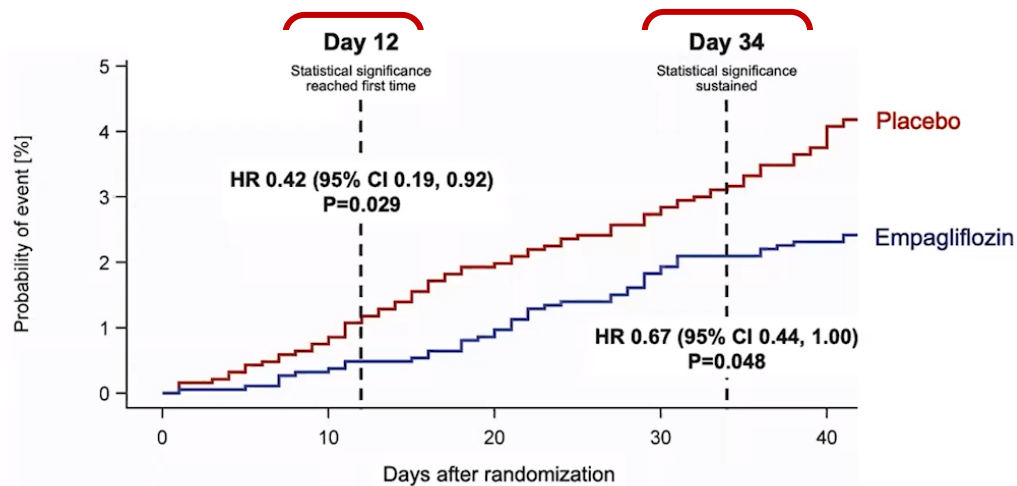
N Engl J Med 2016;375:323-34.



Kluger et al. Cardiovasc Diabetol 2019



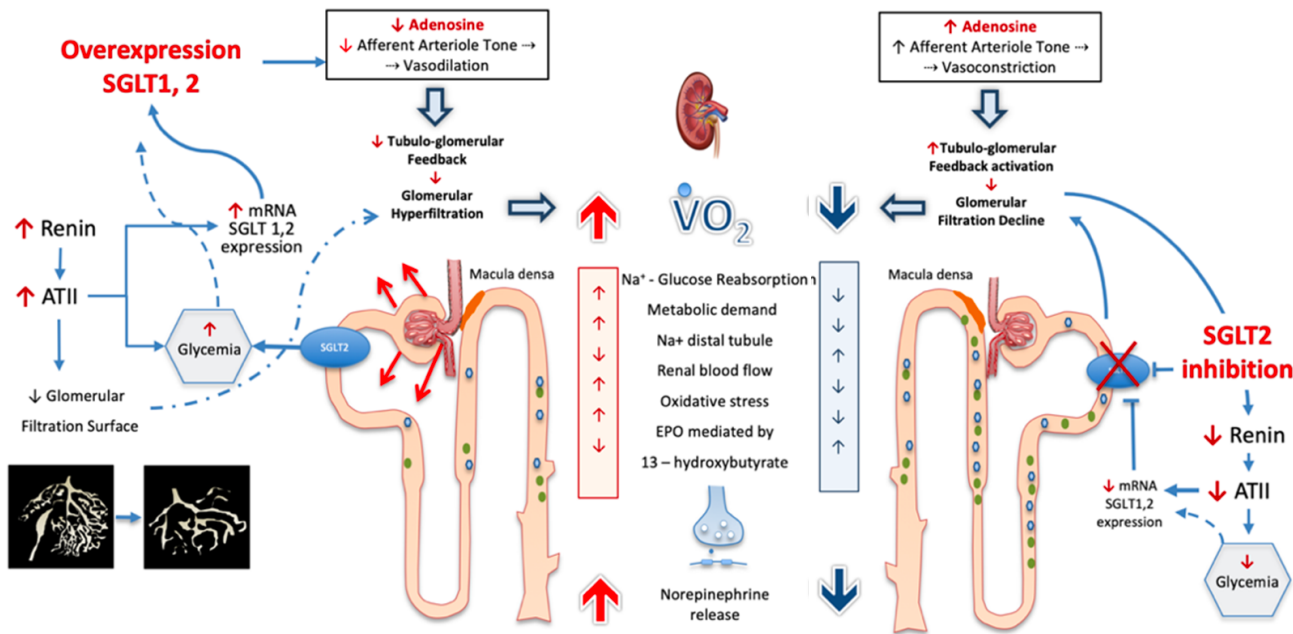
EMPEROR-reduced (HFrEF)



Packer M et al. NEJM 2020



SGLT2i and renal protection



Gronda, E.; Vanoli, E.; Iacoviello, M.; Caldarola, P.; Gabrielli, D.; Tavazzi, L. Int. J. Mol. Sci. 2022, 23, 11987.



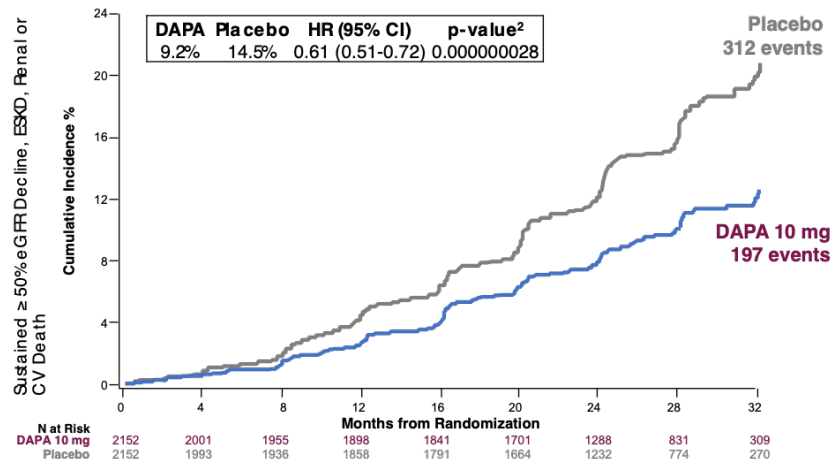
			Albuminuria (mg/g)		
			A1	A2	A3
			Normale o lievemente aumentata	Moderatamente aumentata	Severamente aumentata
			<30	30-300	>300
eGFR (mL/min/1.73 m ²)	G1	≥90			
	G2	60-89			
	G3a	45-59			
	G3b	30-44			
	G4	15-29			
	G5	<15			

CREDENCE
Pazienti con Diabete e eGFR da ≥ 30 e 90 mL/min/1.73m² e ACR da 300 a 5000 mg/g

DAPA-CKD
Pazienti con e senza Diabete e eGFR da ≥ 25 e ≤75 mL/min/1.73m² e ACR ≥200 mg/g

EMPA-KIDNEY
Pazienti con e senza Diabete e eGFR da ≥ 45 e 90 mL/min/1.73m² e ACR ≥200 mg/g o eGFR da ≥20 a <45 mL/min/1.73m²





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 ≥ 24 weeks
- With and without T2D

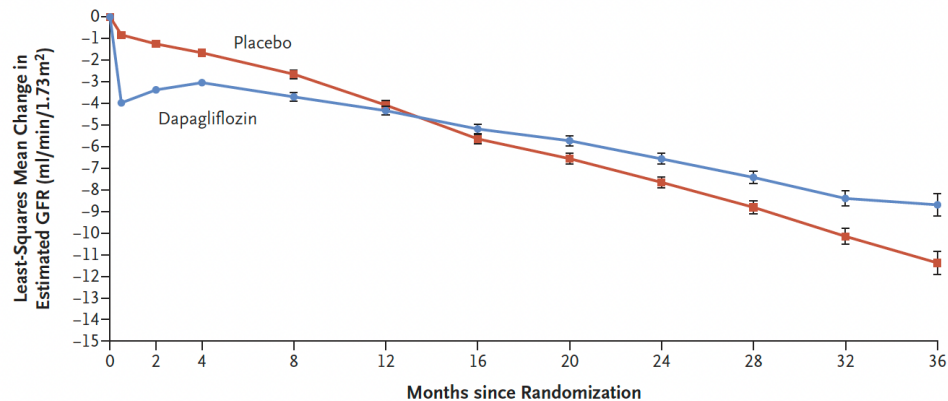
Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤ 6 months prior to enrollment

DAPA-CKD

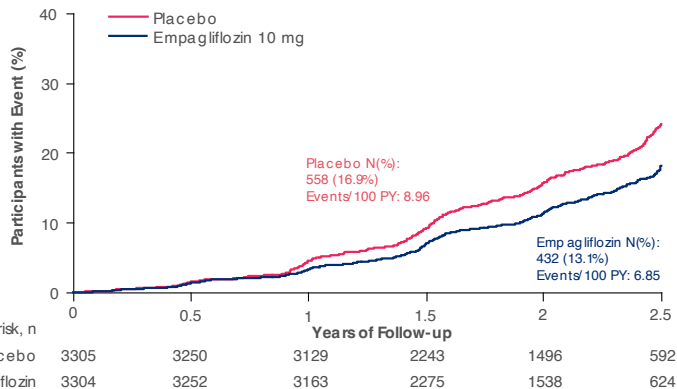
Heerspink HJL et al. Online ahead of print. *N Engl J Med.* 2020; ;

Composite of sustained $\geq 50\%$ eGFR decline, ESKD^a, renal or CV death



No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157



HR 0.72
(95% CI 0.64, 0.82)
P < 0.001

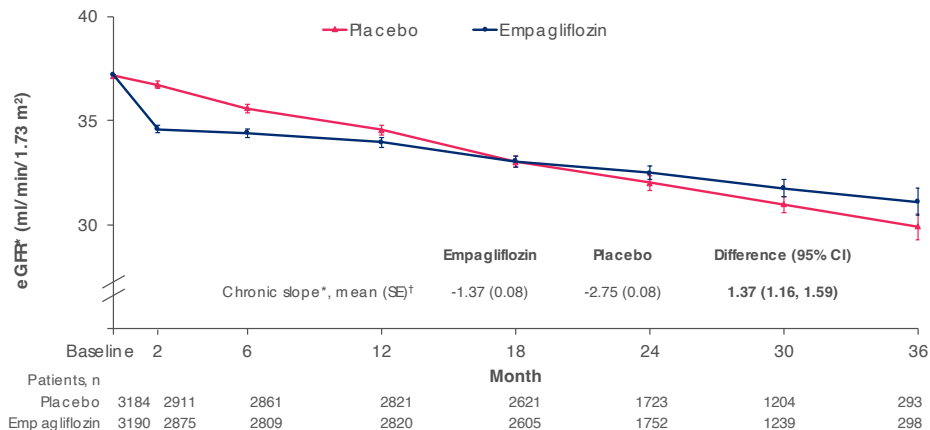
ARR
28%

NNT=28*

EMPA-KIDNEY

The EMPA-KIDNEY Collaborative Group. N Engl J Med
2022

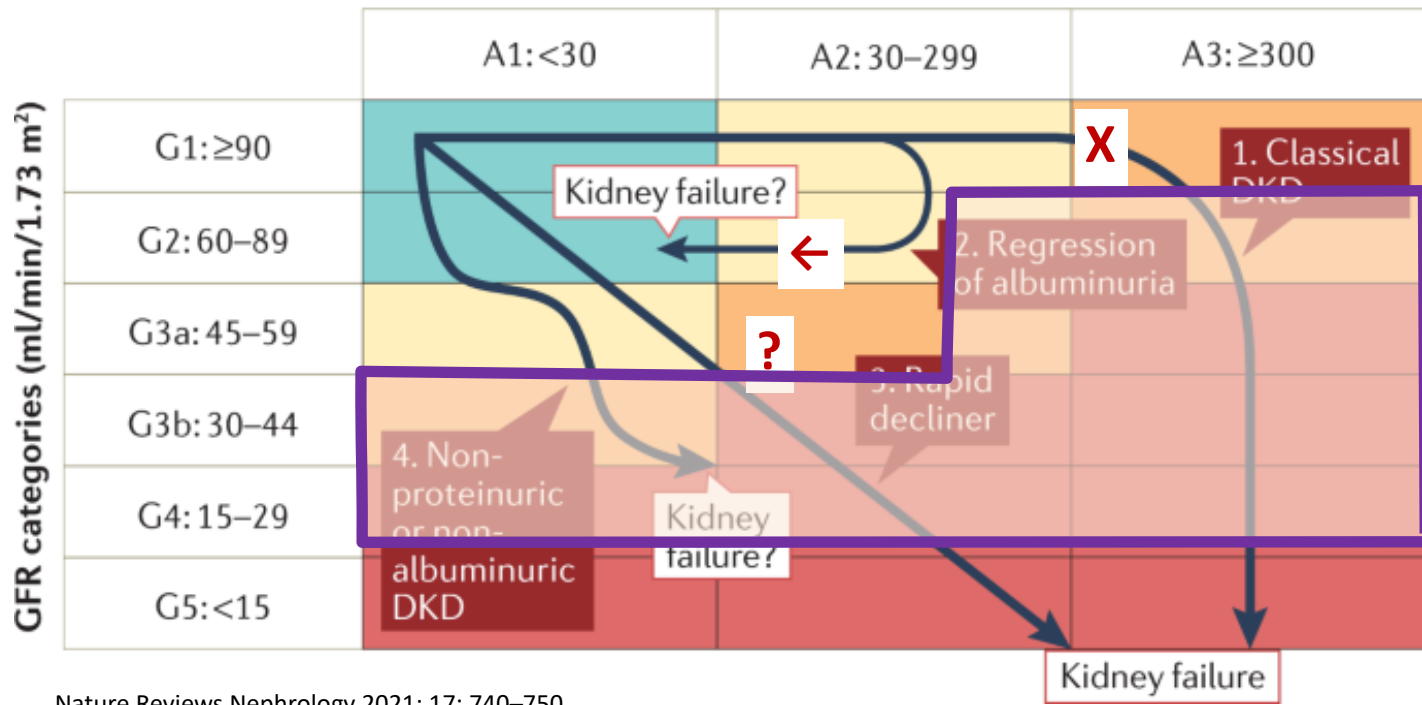
Composite of sustained $\geq 40\%$ eGFR decline, stable GFR <10 ml/min/1.73 m², ESKD^a, renal or CV death



- Key Inclusion Criteria**
- Age ≥ 18 years
 - eGFR ≥ 45 to <90 ml/min/1.73 m² with UACR A2–A3 (≥ 200 mg/g) , or
 - eGFR ≥ 20 to <45 ml/min/1.73 m²
 - ACEi or ARB unless tolerated or not indicated
 - With and without T2D

- Key Exclusion Criteria**
- T1D
 - T2D and prior atherosclerotic CV disease with eGFR >60 ml/min/1.73 m²
 - Receiving dual RAS-inhibition (two of ACEi, ARB, DRI)
 - Maintenance dialysis, functioning kidney transplant or scheduled living donor transplant
 - Polycystic kidney disease

Albuminuria categories (mg/g)

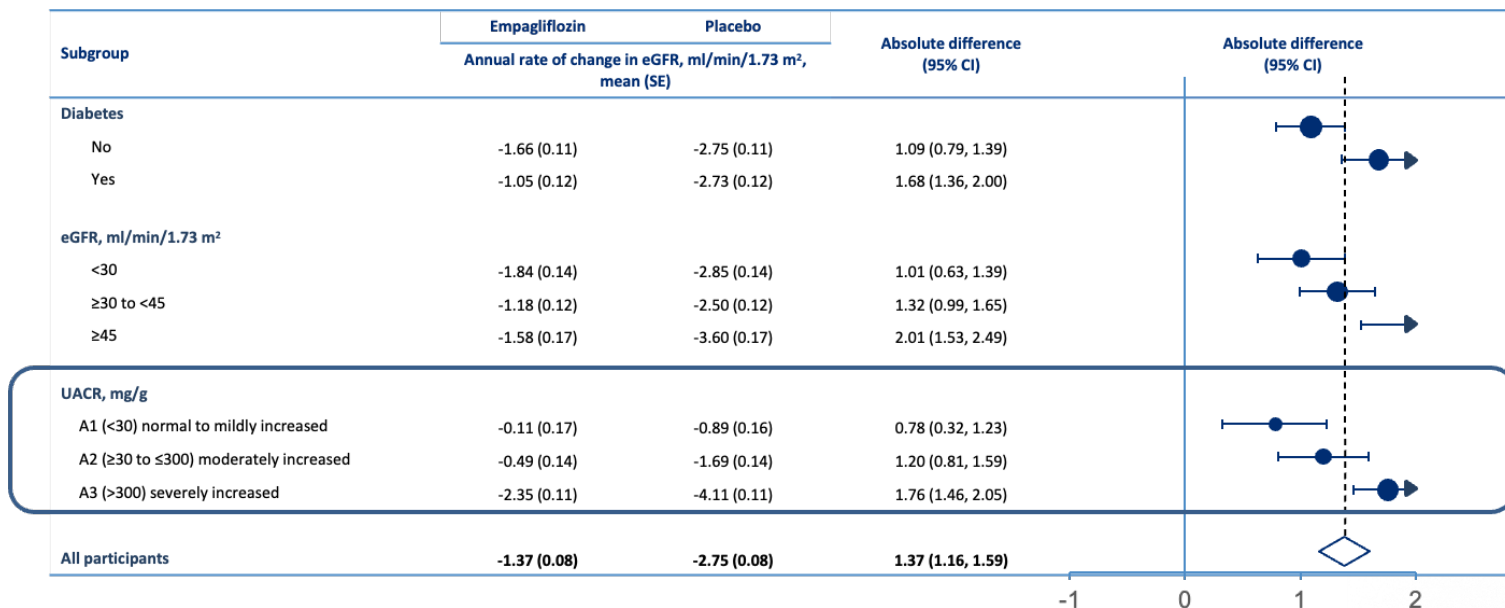


EMPA-KIDNEY
Pazienti con e senza Diabete e
eGFR da ≥ 45 e 90 ml/min/
1.73m²
e ACR ≥ 200 mg/g
o
eGFR da ≥ 20 a <45 ml/min/
1.73m²

Nature Reviews Nephrology 2021; 17: 740–750



EMPA-KIDNEY



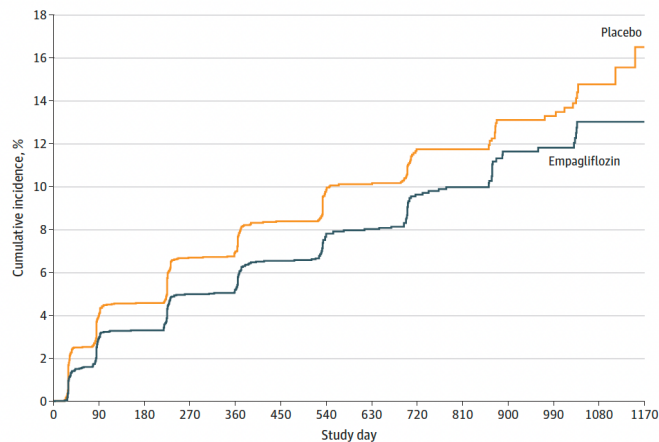
*Mean annual rates of change in eGFR from 2 months to the final follow-up visit ('chronic slopes') by treatment allocation were estimated using shared parameter models eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

The EMPA-KIDNEY Collaborative Group. N Engl J Med 2023;388:117



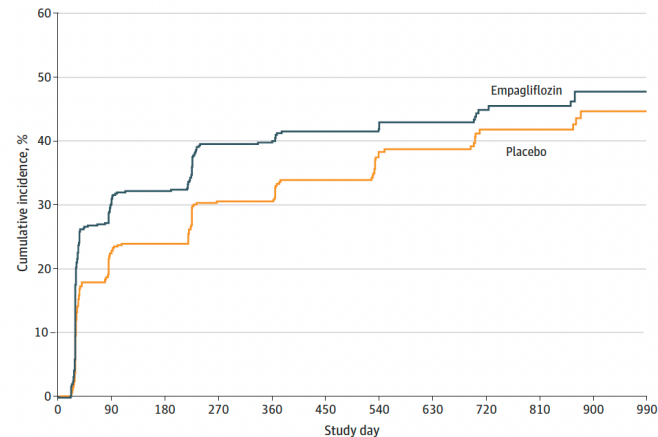
SGLT2i ed albuminuria: EMPEROR pooled

A Normal or microalbuminuria



No. at risk														
Placebo	4336	3711	3595	3098	2993	2240	1586	1412	871	794	436	364	108	64
Empagliflozin	4312	3776	3684	3145	3027	2283	1635	1455	910	816	441	374	110	77

B Macroalbuminuria



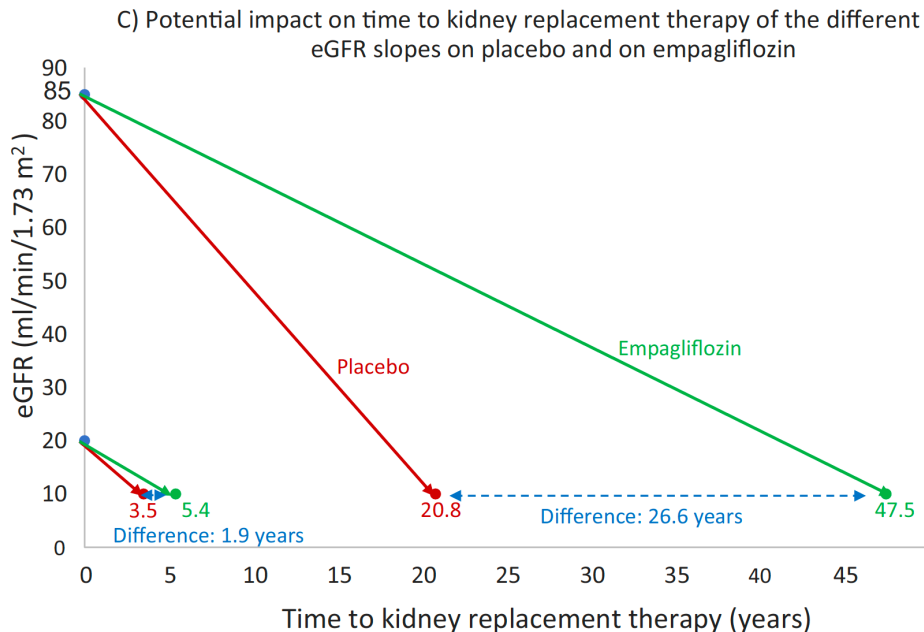
No. at risk	500	342	323	244	231	168	110	99	64	57	30	26
Placebo	500	342	323	244	231	168	110	99	64	57	30	26
Empagliflozin	525	321	297	223	219	159	117	98	61	54	30	25

JAMA Cardiol. 2022;7(11):1148-1159.



La protezione renale: l'importanza di un'introduzione precoce di SGLT2i

EMPA-KIDNEY



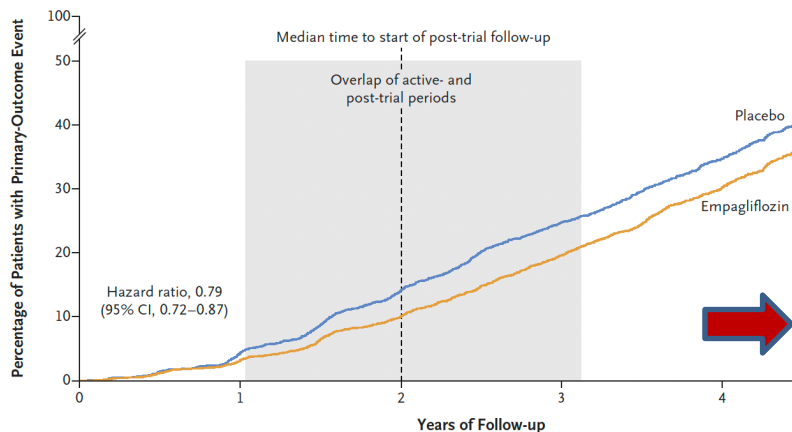
Fernandez-Fernandez et al.
Clinical Kidney Journal 2023;16:1187–1198



EMPA-KIDNEY: post-trial follow-up

L'introduzione precoce di SGLT2i migliora l'outcome renale e cardiovascolare

A Primary-Outcome Events for Combined Active and Post-Trial Periods

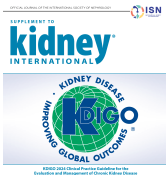


No. at Risk					
Placebo	3305	3131	2484	1874	905
Empagliflozin	3304	3170	2596	2014	977
Absolute benefit		12±5	41±8	52±11	45±14

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)
	Patients with Event no. (%)	Rate no. of events/ 100 patient-yr	Patients with Event no. (%)	Rate no. of events/ 100 patient-yr	
Primary outcome					
Progression of kidney disease or death from cardiovascular causes	865 (26.2)	8.4	1001 (30.3)	10.0	0.79 (0.72–0.87)
Secondary outcome					
Kidney disease progression	778 (23.5)	7.5	897 (27.1)	9.0	0.79 (0.72–0.87)
Death from any cause or end-stage kidney disease	559 (16.9)	5.1	648 (19.6)	6.1	0.81 (0.72–0.90)
End-stage kidney disease	296 (9.0)	2.7	372 (11.3)	3.5	0.74 (0.64–0.87)
Tertiary outcome					
Death from any cause	301 (9.1)	2.7	336 (10.2)	3.0	0.86 (0.74–1.01)
Death from cardiovascular cause	126 (3.8)	1.1	162 (4.9)	1.5	0.75 (0.59–0.95)

N Engl J Med 2025;392:777-87.





Guidelines

- T2DM, CKD and $GFR \geq 20$
- CKD and $GFR \geq 20 / ACR \geq 200 \text{ mg/g}$
- CKD and GFR_{20-45}
- CKD and HF with $GFR \geq 20$



Guidelines

- T2DM
- CKD
- HFrEF, HFmrEF, HFpEF, HFimpEF

SGLT2i recommendation

