UTIC CLUB | ANMCO
CRITICAL CARE COMMUNITY

Valore prognostico di eGFR e UARC, corretto inquadramento del profilo di rischio del paziente ASCVD, ruolo degli SGLT2i

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Disclosures

Lectures for

Boheringer Ingelheim, AstraZeneca, Daiichi, Bayer, Amgen, Pfizer, PIAM, Menarini, Bayer, Sanofi, Neopharmed, Servier, Sandoz, Eli Lilly, Novonordisk

Agenda

Diagnosi
& Epidemiologia

Prognosi
Cardiovascolare e Renale

Stratificazione
del Rischio
ASCVD

Ruolo degli
SGLT2i

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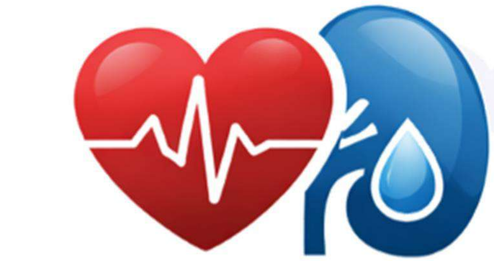

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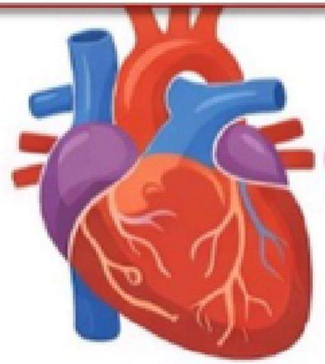
Prevalenza Globale

850 Milioni

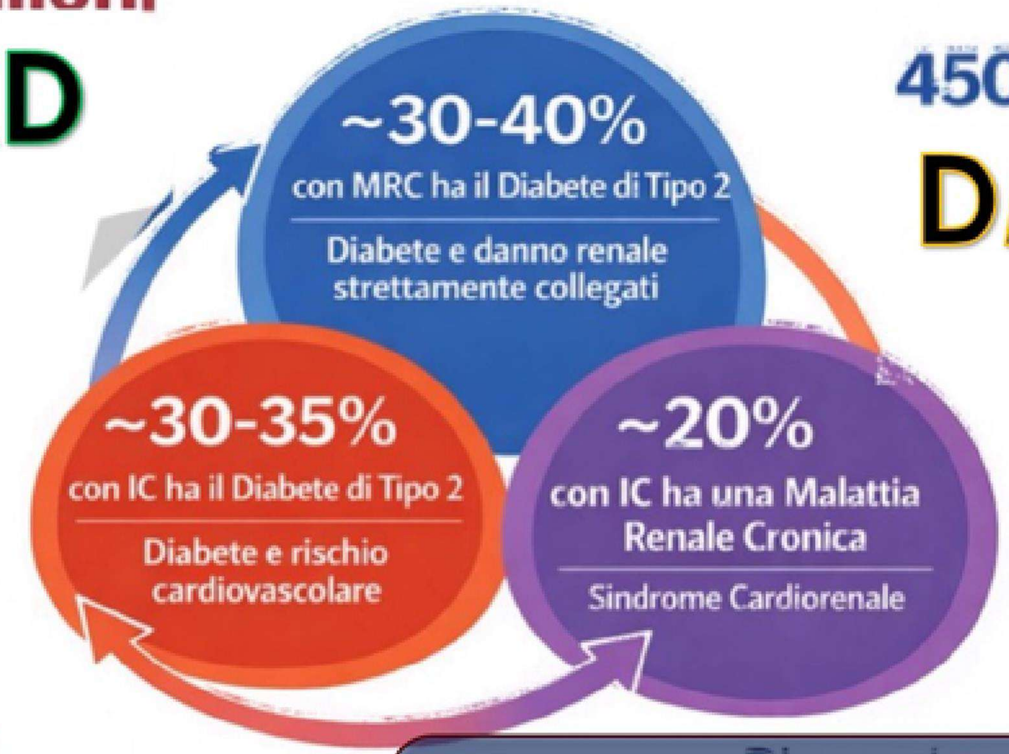
CKD

Entro il 2040 la CKD diventerà la 5° causa di morte a livello globale, con un aumento del 100% degli anni di vita persi rispetto al 2016



60 Milioni

HF



450 Milioni

DM

DIAGNOSI PRECOCE
STRATEGIE TERAPEUTICHE INTEGRATE
GESTIONE MULTIDISCIPLINARE

Herrington W G et al *Lancet* 2026; 407: 90–104

Diagnosi CKD

Early-stage CKD is usually asymptomatic requiring laboratory tests for detection

eGFR
Blood sample

Indicative of CKD

eGFR < 60ml/min/1.73m²

Indicates kidney function loss

eGFR > 60ml/min/1.73m²

UACR ≥ 30 mg/g

Indicates kidney damage

UACR
Random spot urine sample

Validated subsequently with first-morning void sample

EITHER value indicative of CKD present for ≥3 months

CKD diagnosed

EDUCATE
SCREEN
TREAT

Consider initiation of treatment at first presentation if CKD is deemed likely due to presence of other clinical indicators

Diagnosi CKD

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eGFR
Blood sample

Indicative of CKD

eGFR < 60ml/min/1.73m²

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UACR
Random spot urine sample

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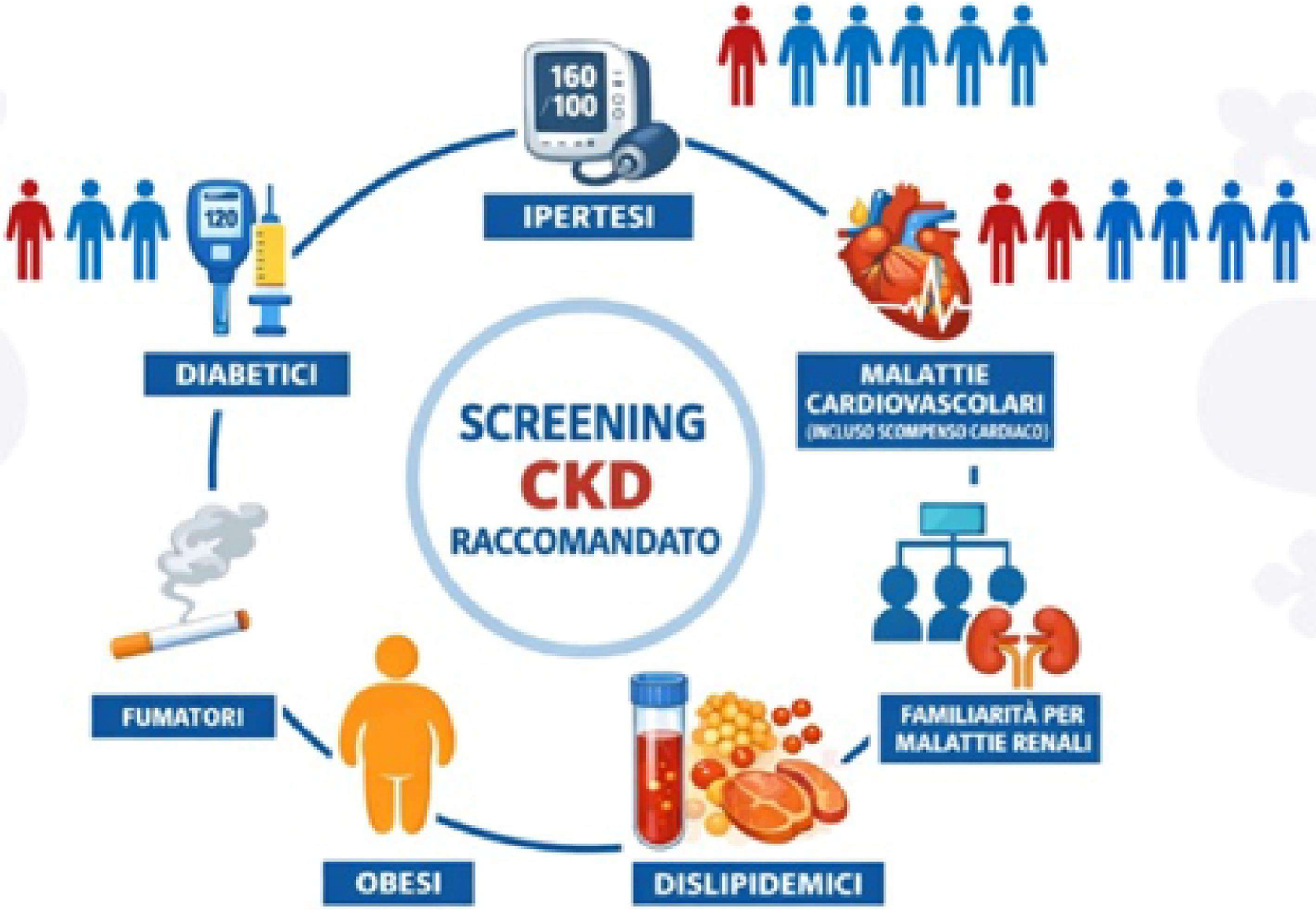

ISN-KDIGO Early CKD Screening. 2022. Trevisan R et al. J Am Soc Nephrol 2006; Kazancioglu R. Kidney Int Suppl 2013; National Kidney Foundation. Aging and Kidney Disease. 2022. Jo W et al. PLoS One 2020; Menon V et al. Kidney International 2005

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KDIGO: classification and prognosis of CKD

Increased risk of complications by chronic kidney disease stage relative to a healthy population

eGFR category		Persistent albuminuria category					
		Normal or mildly increased A1 <30 mg/g <3 mg/mmol		Moderately increased A2 30–300 mg/g 3–30 mg/mmol		Severely increased A3 >300mg/g >30 mg/mmol	
Normal or high	G1 (≥90 mL/min per 1·73 m²)	Screen 1		1·3 1·5	1·5 2·4	1·7 2·6	2·5 7·2
Mildly decreased	G2 (60–89 mL/min per 1·73 m²)	Screen 1		1·0 1·4	1·2 4·7	1·3 2·2	1·9 13·4
Mildly to moderately decreased	G3a (45–59 mL/min per 1·73 m²)	0·9 1·2	1·1 6·4	1·2 1·6	1·5 11·4	1·5 2·5	2·2 28·2
Moderately to severely decreased	G3b (30–44 mL/min per 1·73 m²)	1·1 1·5	1·4 14·8	1·3 1·8	1·8 23·3	1·8 2·8	2·6 47·7
Severely decreased	G4 (15–29 mL/min per 1·73 m²)	1·5 2·1	2·0 40·8	1·7 2·3	2·2 51·3	2·3 3·6	3·4 84·1
Kidney failure	G5 (<15 mL/min per 1·73 m²)	2·4 4·1	3·2 78·3	2·7 4·1	3·5 94·5	3·1 5·2	4·7 97·7

- 0.04/1000 patient-yrs
- x5
- x20
- x150

A All-cause Death or H

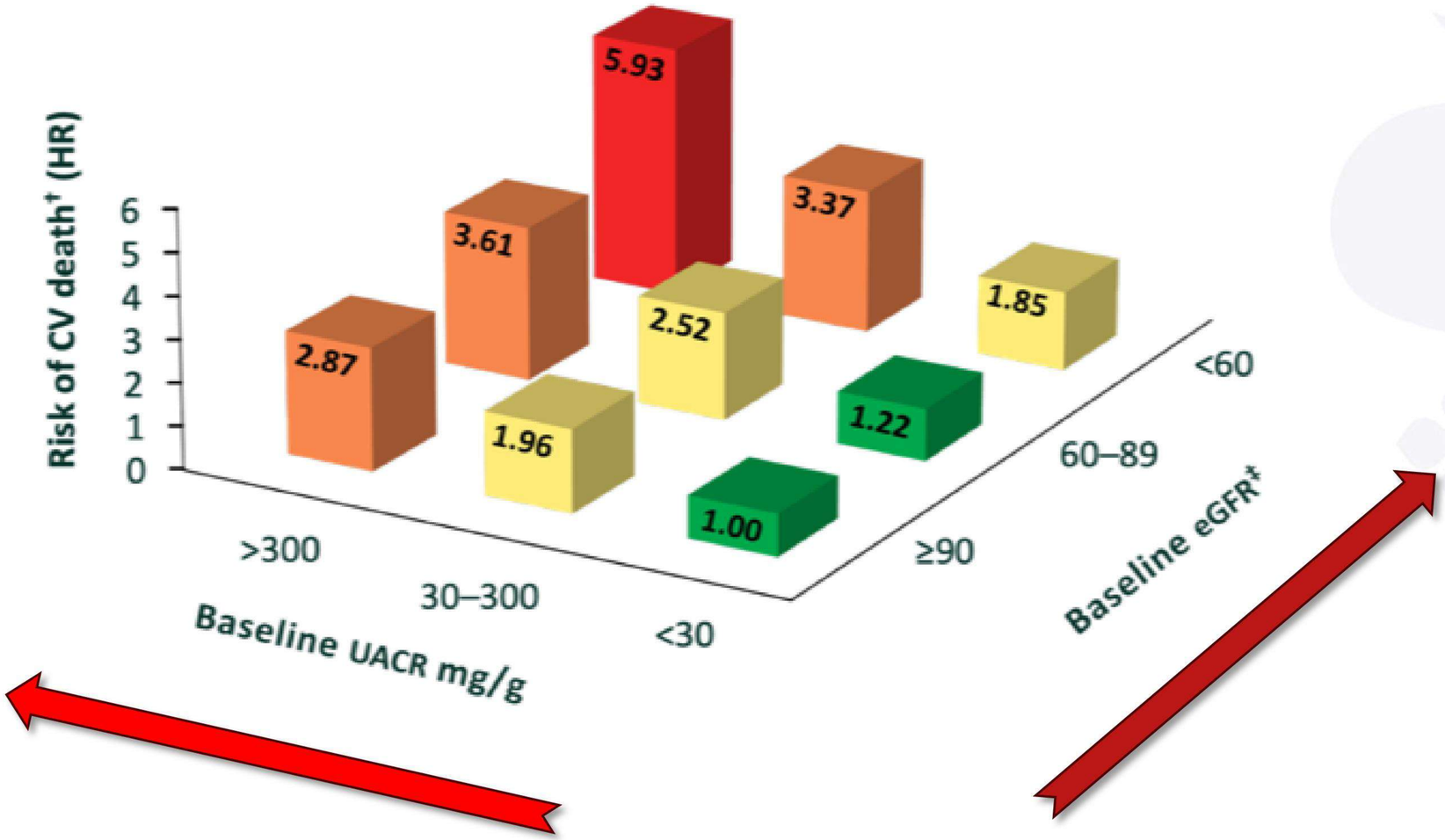
B ASCVD: MI, Stroke, PAD

C CV Death, HF, AF

D Replacement Tx or AKI

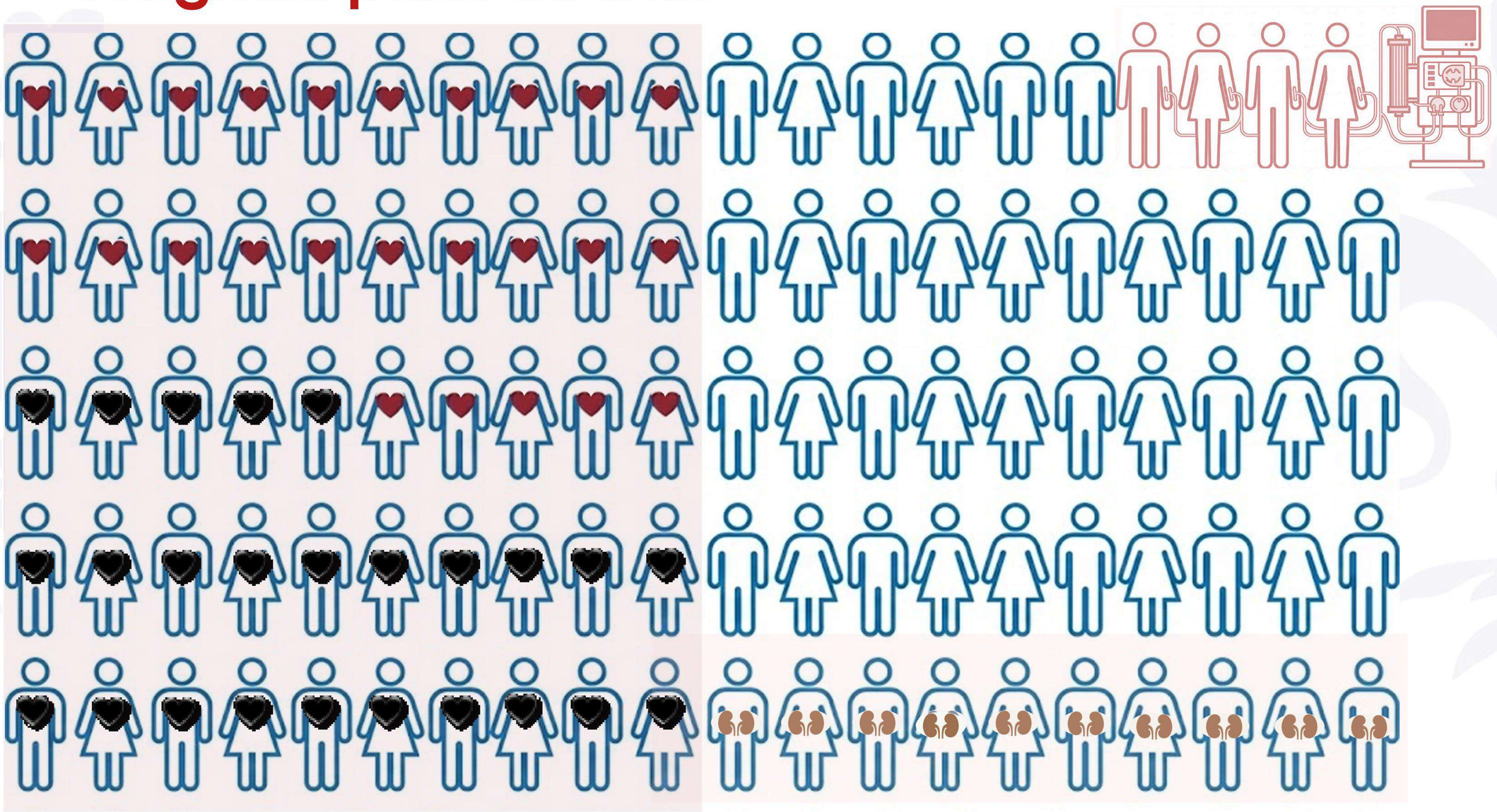
KDIGO 2024 clinical practice guideline. *Kidney Int* 2024;105:S117–314

Reduced eGFR and increased albuminuria are *independently* associated with increased risk of CV death



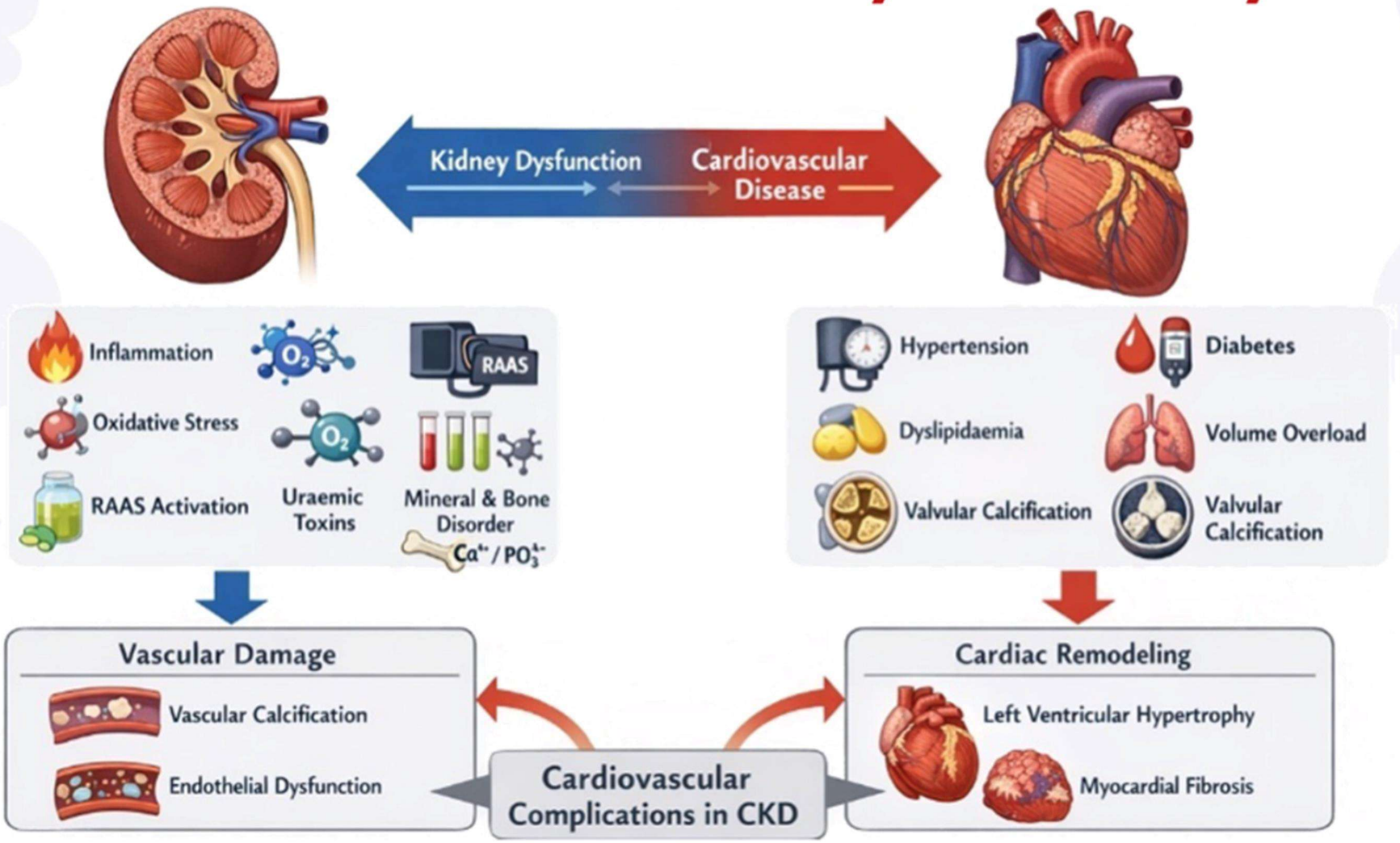
Adapted from Ninomiya T et al. J Am Soc Nephrol 2009;20:1813

Prognosi pazienti CKD



Foley RN *et al. J Am Soc Nephrol.* 2005;16:489
Dalrymple L, et al. J Gen Intern Med. 2011;26:379-385.

Cross Talk between Kidney and CV System



Sarafidis PA et al. J Cardiometab Syndr 2006;1:58; Ronco C. Contrib Nephrol 2010;164:33; Banerjee S and Panas R. Hellenic J Cardiol 2017;58:342; Leon BM and Maddox TM. World J Diabetes 2015;6:1246; Dzau VJ et al. Circulation 2006;114:2850

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Come abbiamo pensato il rene nel pz CV *sino ad oggi*

- ***Renism (nichilismo terapeutico)***

-Pratica di limitare terapie/procedure efficaci (CVG, MRA) per timore iperk e declino eGFR

-Associata a esiti clinici avversi in pz con CVD + CKD

-Obiettivo clinico: massimizzare GDMT anticipando e gestendo proattivamente gli effetti collaterali renali ed iperK piuttosto che evitare terapie

- ***Astensione terapeutica***

Classe Farmacologica	GFR 30-60	GFR <30	GFR <15 / Dialisi
DOAC	Dose ridotta (monitorare)	Dose ridotta, Dabi controindicato	Controindicati
Fondaparinux	Dose ridotta/cautela	Controindicato	Controindicato
Levosimendan	Cautela/possibile	Controindicato (dati limitati)	Controindicato
Sacubitril/valsartan	Cautela, monitorare	Evitare (possibile continuazione)	Controindicato
ACE-Inibitori/Sartani	Cautela, monitorare K+/renale	Cautela (no stenosi bilaterale)	Cautela
Vericiguat	Uso possibile	Possibile (non <15)	Non raccomandato
SGLT2i		Non iniziare; continua se in uso	Controindicato

CKD for cardiovascular risk estimation

No previous cardiovascular disease or type 2 diabetes

SCORE2

(Europe)
<70 years

SCORE2-OP

(Europe)
≥70 years

SCORE2-Diabetes

(Europe)
Type 2 Diabetes

SCORE2 is recommended in apparently healthy people <70 years of age without established ASCVD, DM, CKD, genetic/rare lipid or BP disorders for estimation of 10-year fatal and non-fatal CVD risk.[2] [c]	I	B
SCORE2-OP is recommended in apparently healthy people ≥70 years of age without established ASCVD, DM, CKD, genetic/rare lipid or BP disorders for estimation of 10-year fatal and non-fatal CVD risk.[3] [c]	I	B

In patients with T2DM without symptomatic ASCVD or severe TOD,[c] it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes.[d,50]	I	B

Chronic Kidney Disease Prognosis Consortium:
CKD measures improved CVD risk prediction beyond SCORE2 and SCORE2-OP

In validation datasets	SCORE2 population (age 40-69, no diabetes	SCORE2-OP population (age 70+, no diabetes)
CKD Stages	Risk ratio of CKD Add-on (eGFR+ACR) to SCORE2	Risk ratio of CKD Add-on (eGFR+ACR) to SCORE2-OP
Risk ratio, Median (IQI)		
No CKD	0.98 (0.97, 1.00)	0.97 (0.93, 0.99)
CKD at moderate risk	1.29 (1.24, 1.30)	1.15 (1.11, 1.17)
CKD at high risk	1.70 (1.63, 1.74)	1.29 (1.23, 1.34)
CKD at very high risk	2.78 (2.59, 3.05)	1.60 (1.38, 1.65)
Overall	1.03 (1.00, 1.07)	1.04 (0.99, 1.07)

Matsushita et al. Eur J Prev Cardiol. 2023

SCORE2 Variables

Age (40-85yrs)	65
Gender	Male
Systolic Blood Pressure (mmHg)	135
Total Cholesterol (mg/dL) click on units to change between mg/dL and mmol/L	180
HDL Cholesterol (mg/dL) click on units to change between mg/dL and mmol/L	35
Smoking Status	Not Current Smoker
Diabetes	No

Kidney Measures

eGFR (estimated glomerular filtration rate) (mL/min/1.73m²)	35
Urine Albumin to Creatinine Ratio (mg/g) click on units to change between mg/g and mg/mmol	40

Convert Urine Protein-Creatinine to Albumin-Creatinine

SCORE2 Cardiovascular Risk with eGFR & ACR

Who is it for?

Everyone

What does it predict?

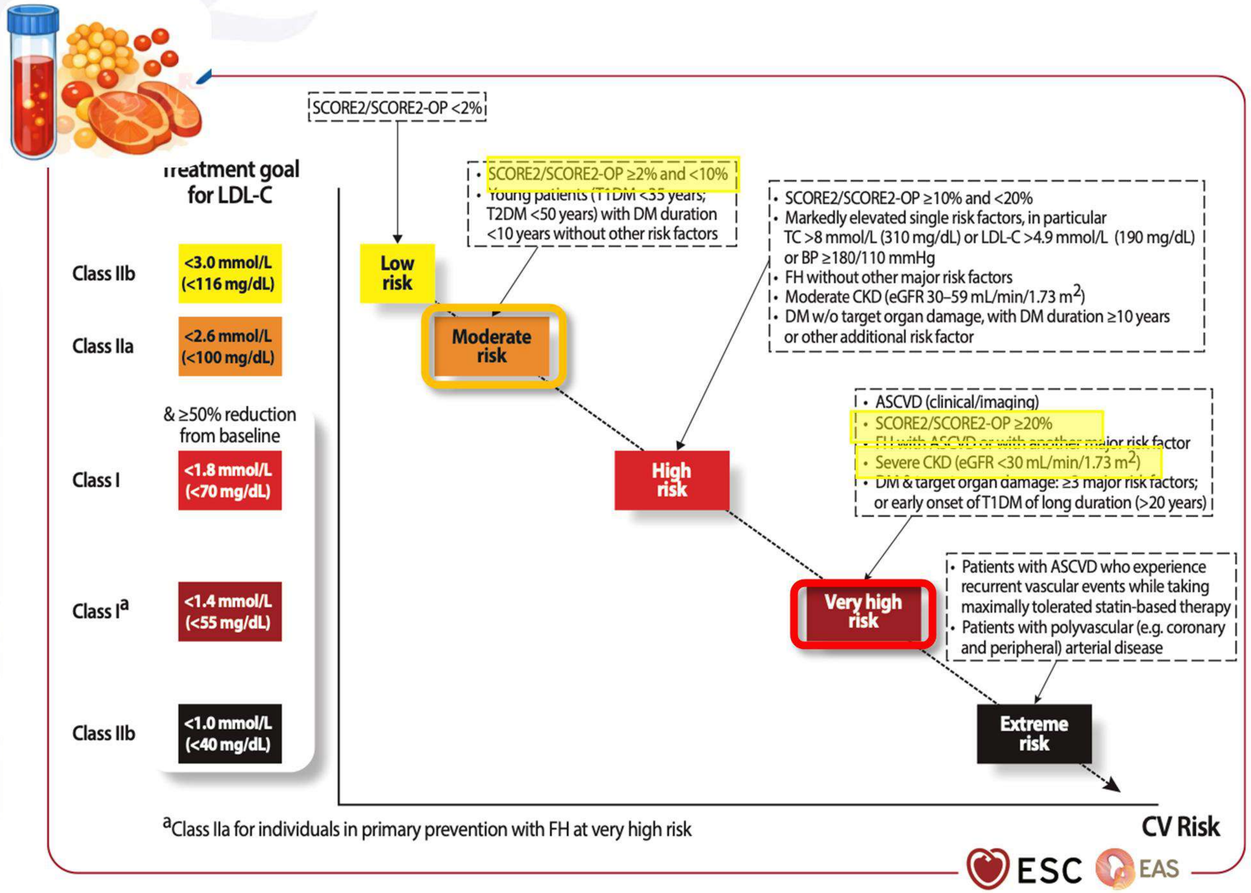
10-yr risk of myocardial infarction, stroke, and CVD mortality

Medium risk countries

Original SCORE2	Original SCORE2 **+ CKD Add-on**
9.9%	21.0%

https://ckdpcrisk.org

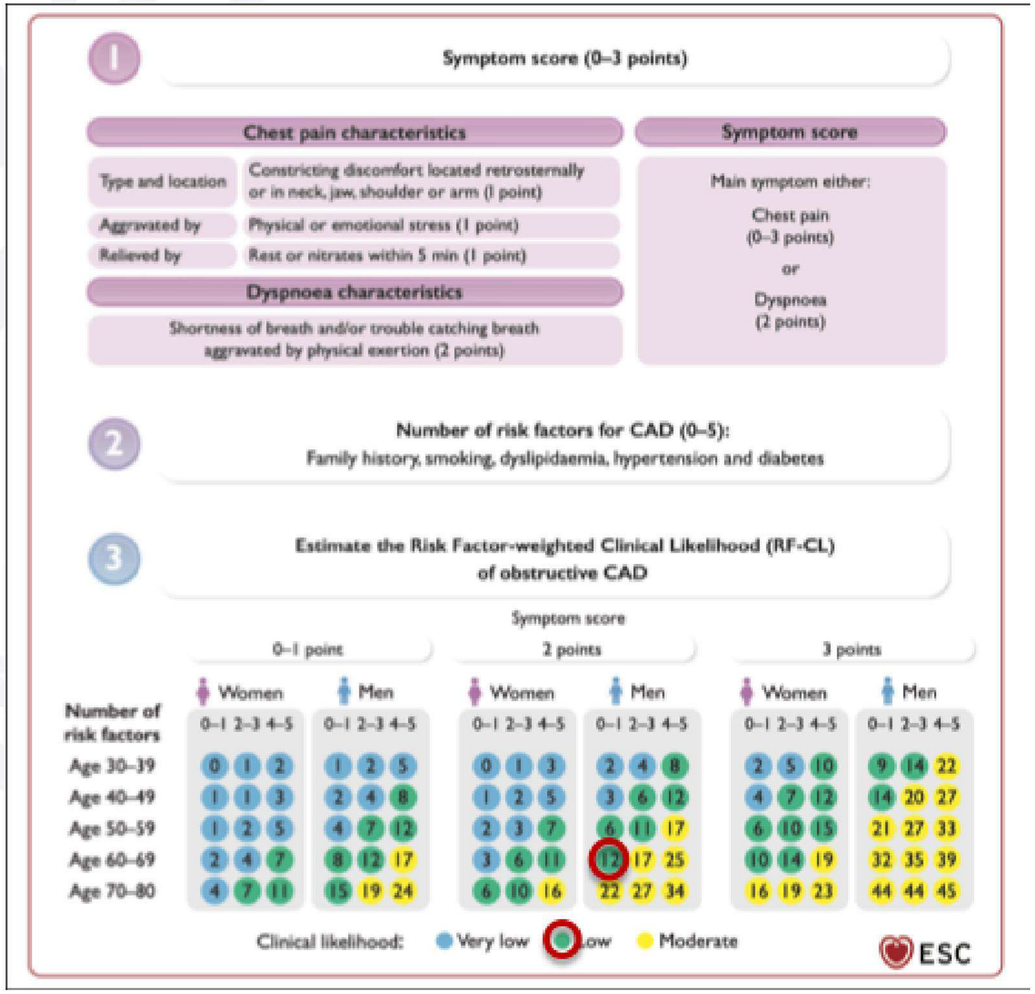
Target terapeutici alla luce della CKD

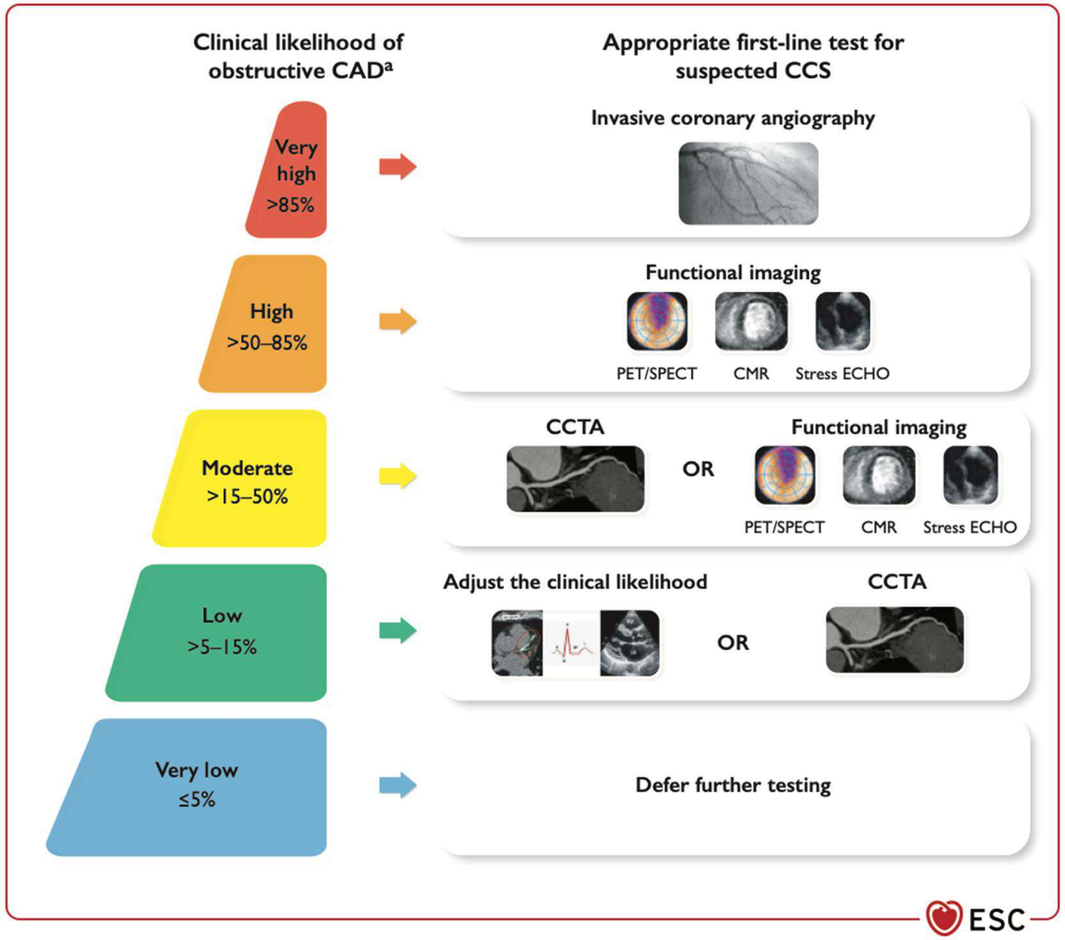


In adults with moderate-to-severe CKD who are receiving BP-lowering drugs and who have eGFR >30 mL/min/1.73 m^2, it is recommended to target systolic BP to 120–129 mmHg, if tolerated. Individualized BP targets are recommended for those with lower eGFR or renal transplantation.[274,779]	I	A
In hypertensive patients with CKD and eGFR >20 mL/min/1.73 m^2, SGLT2 inhibitors are recommended to improve outcomes in the context of their modest BP-lowering properties.[776,777]	I	A
ACE inhibitors or ARBs are more effective at reducing albuminuria than other BP-lowering agents and should be considered as part of the treatment strategy for patients with hypertension and microalbuminuria or proteinuria.[780–782]	IIa	B

Recommendation 3.4.1: We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement *(2B)*.

Appropriatezza diagnostica alla luce della CKD





ESC Guidelines European Heart Journal (2024) 45, 3415–3537

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CKD + Diabetes

CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)

Study Population

Randomized Control Trial (N = 4401)

63 years

HbA1c = 8.3%

Alb/Cr = 927 mg/g

eGFR = 56.2

Primary Outcome

61 per 1000 patient years

Placebo

Composite of ESRD, doubling of serum Cr, renal or CV death

HR = 0.70
(CI, 0.59 to 0.82)

Canagliflozin

43 per 1000 patient years

Renal-Specific Outcome

ESRD, 2 x serum creatinine, death from renal cause

HR = 0.66
CI 0.53 to 0.81

Cardiovascular Outcome

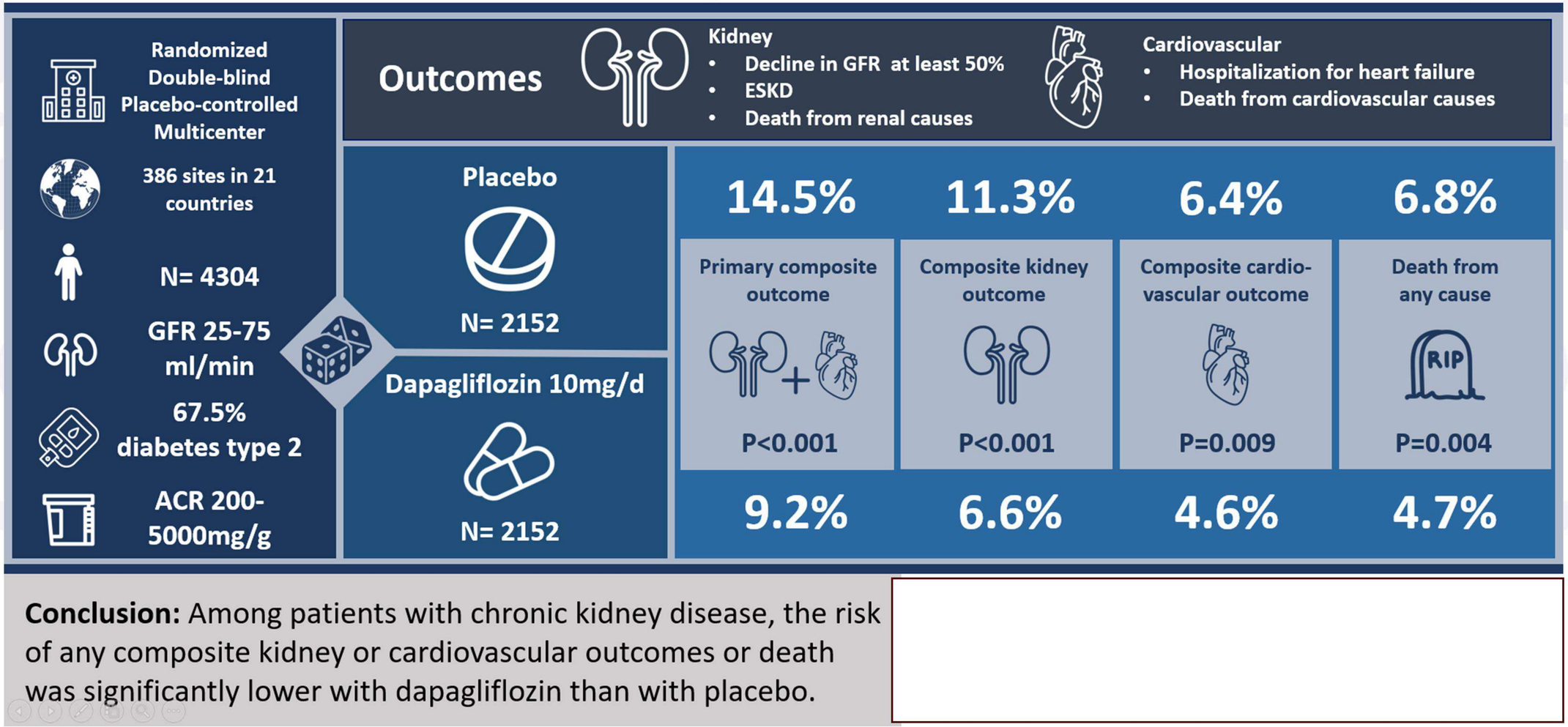
Cardiovascular death, myocardial infarction, or stroke

HR = 0.80
CI 0.67 to 0.95

Conclusion: In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group.

Perkovic V et al NEJM 2019

CKD +/- Diabetes
DAPA-CKD trial



Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

Heerspink HJL et al NEJM 2020

CKD +/- Diabetes
EMPA-KIDNEY trial

Population: Designed to assess the effects of empagliflozin in a broad range of patients (~6000) with chronic kidney disease (CKD) at risk of progression, including many patients without diabetes, and patients with low levels of proteinuria

Trial design

EMPA-KIDNEY

Evidence of CKD at risk of kidney disease progression

- Empagliflozin 10 mg once daily + standard of care†
- Placebo once daily + standard of care†

Event driven: 1070 primary outcomes: 90% power at p<0.05 to detect an 18% relative risk reduction

Composite primary outcome

Kidney disease progression OR **CV death**

Kidney function loss defined as:
- Sustained reduction of ≥40% eGFR decline
- Sustained eGFR <10 ml/min/1.73 m^2

End-stage kidney disease
- Defined as initiation of chronic dialysis or kidney transplant

Renal death

Key secondary outcomes‡

- All-cause hospitalization
- First occurrence of hospitalization for heart failure or CV death
- All-cause mortality

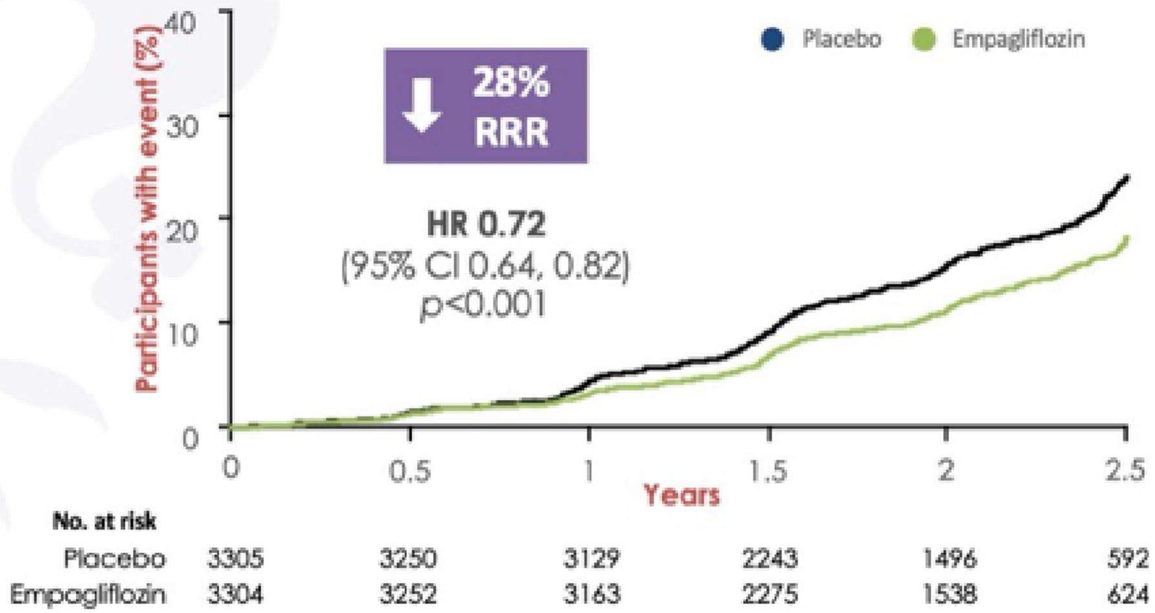
*Between 15 May 2019 and 16 April 2021, **6609** patients were randomized; †Guideline-directed medical therapy; ‡Other outcomes prespecifie

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate

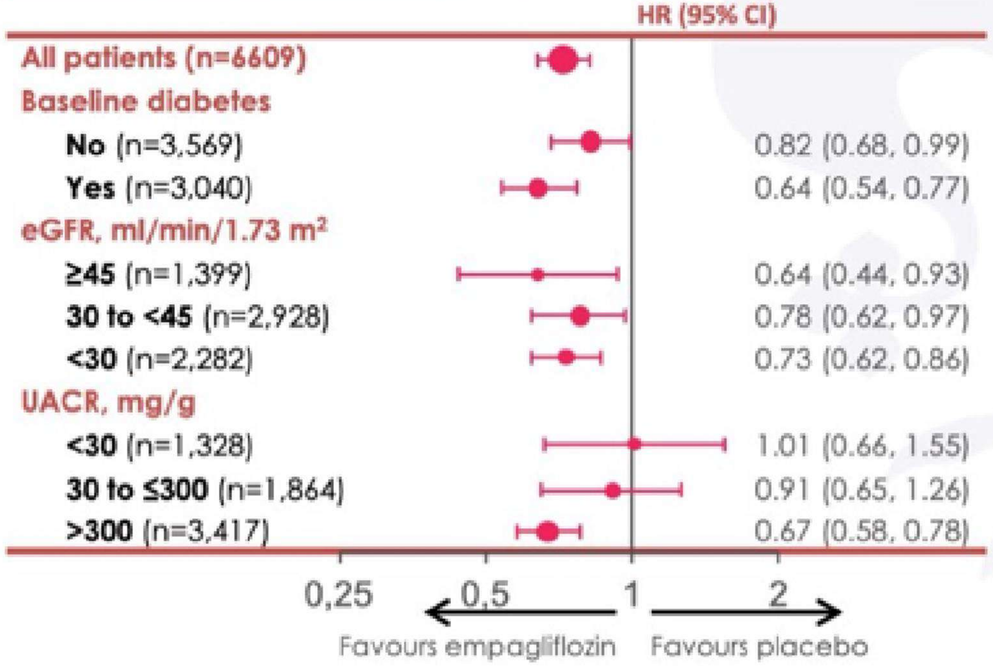
The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; DOI: 10.1056/NEJMoa2204233

CKD +/- Diabetes
EMPA-KIDNEY trial

Empagliflozin reduced the risk of the primary outcome of CV death or kidney disease progression†[1]



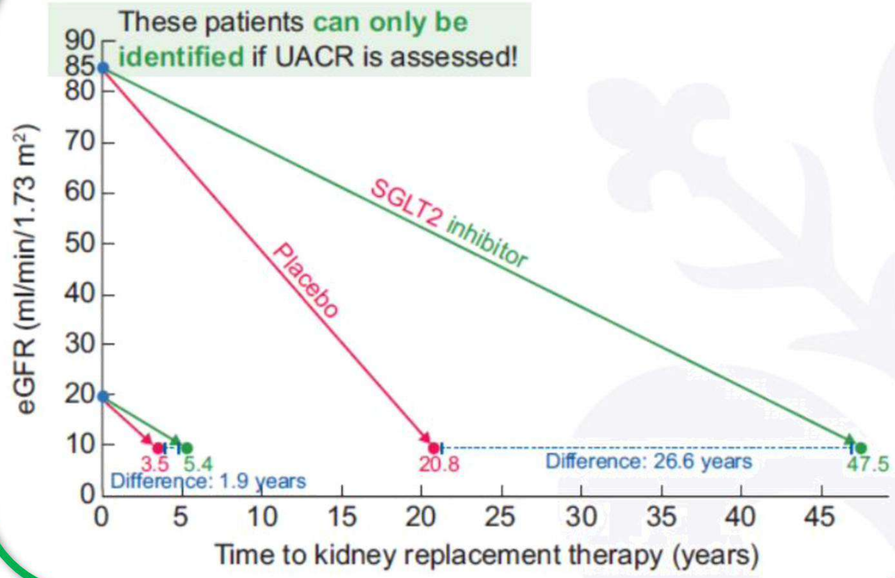
Relative reduction in risk of CV death or kidney disease progression*[1]

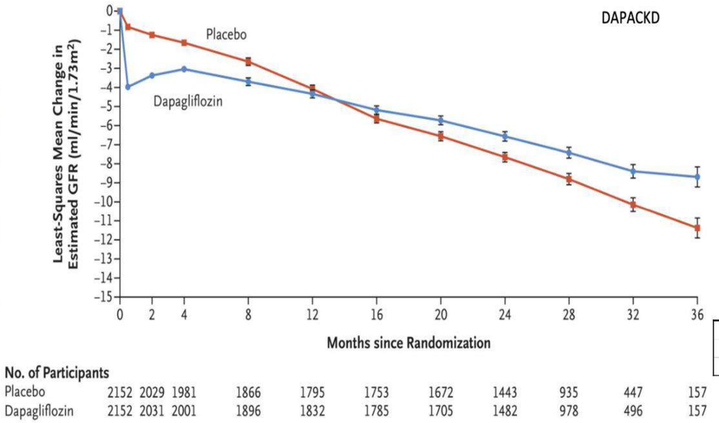


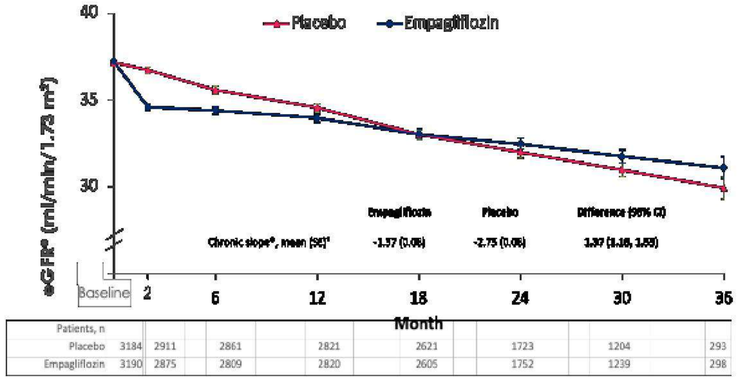
EMPA-KIDNEY Collaborative Group. N Engl J Med 2023;388:117

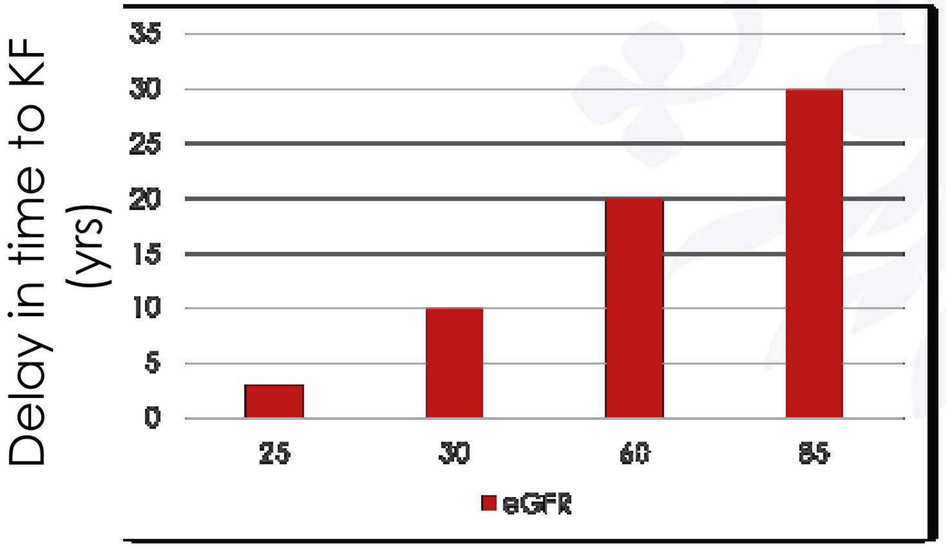
SGLT2i effect on Slope GFR

Study	Population: Number Age (years) HF (%); Diabetes (%)	Mean GFR	Median UACR	Mean Follow-up	Groups	Slope GFR Chronic phase Days	Mean changes (95%CI)
DAPA-CKD	4304 61.8±12.1 11; 68	43	949	2.4	Dapa	15-1085	−1.67±0.11
					Plac		−3.59±0.11
EMPA-KIDNEY	6609 63.9±13.9 n.a.; 46	37	329	2.0	Empa	60-1085	−1.37±0.08
					Plac		−2.16±0.08



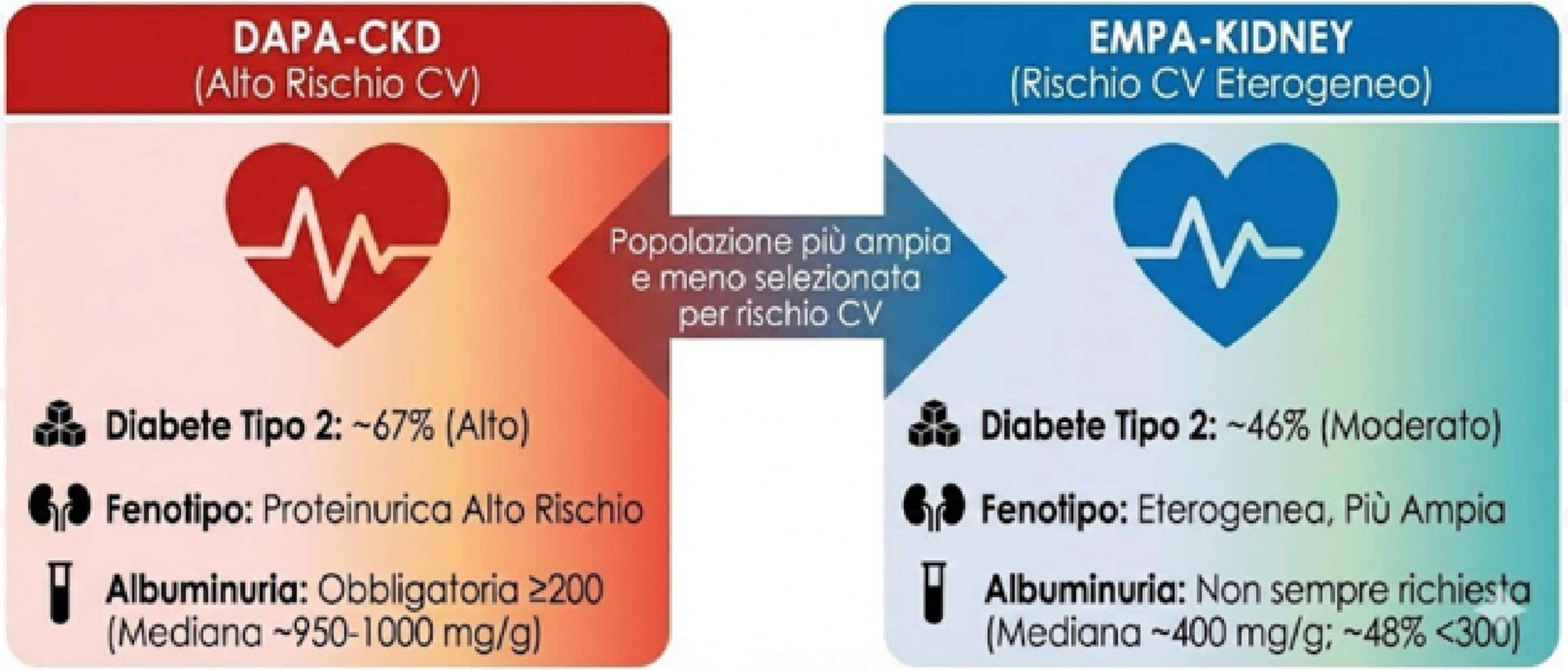






	DAPA-CKD (Dapagliflozin)	EMPA-KIDNEY (Empagliflozin)
Farmaco	Dapagliflozin	Empagliflozin
Numero pazienti	4,304	6,609
Età media	~61-62	~63-64
Diabete tipo 2	~67%	~46%
eGFR medio	~43	~37
Range eGFR	25-75	20-<45 or 45-<90+≥200
Albuminuria (UACR)	≥200/~950-1000 mg/g	Non sempre/~400 mg/g
Albuminuria bassa (<300)	Rara	~48%
Fenotipo prevalente	Proteinurica Alto Rischio	Eterogenea Più Ampia
Endpoint primario	≥50% declino/ESKD/Morte Renale o CV	≥40% declino/<10 ml/min/ESKD/ Morte Renale o CV

CV Risk Profile: DAPA-CKD vs EMPA-KIDNEY



EMPOWER program kidney outcomes

	EMPA-REG OUTCOME[1–4] N=7020	EMPEROR-R[5,6] N=3730	EMPEROR-P[7] N=5988	EMPA-KIDNEY[10] N=6609
Patient population	**T2D + high CV risk** 32% kidney disease	**HFrEF** 53% CKD	**HFpEF** 50% eGFR <60 ml/min/1.73 m²	**CKD 46% diabetes; 27% CVD**
Mean, ml/min/1.73 m²	74	62	61	**37**
Median, mg/g	18	36/15 CKD/no CKD	NR	**331/327 Empa/Pbo**
Kidney composite outcomes	Incident or worsening nephropathy, RRR vs Pbo ↓39%	Kidney composite†, RRR vs Pbo ↓50%	Kidney composite†, similar (HR vs Pbo 0.95)	**Kidney disease progression or CV death‡, RRR vs Pbo ↓28%**
Long-term kidney function, slope diff. to placebo ml/min/1.73 m²	+1.68[11]	+1.73	+1.36	**+1.37**
Kidney safety	AKI/acute kidney failure, reduced	Acute kidney failure, similar rate	Acute kidney failure, similar rate	**AKI, RRR vs Pbo ↓22%**

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. Circulation.* 2018;137:119; 3. Tye SC *et al. Front Pharmacol* 2021;12:786706; 4. Wanner C *et al. N Engl J Med* 2016;375:323; 5. Zannad F *et al. Circulation* 2021;143:310; 6. Packer M, *et al. N Engl J Med* 2020;383:1413; 7. Anker S *et al. N Engl J Med* 2021;385;1451; 8. Voors AA *et al. Nature Med* 2022;28:568; 9. Patorno E *et al. Diabetes Obes Metab* 2022;24:442; 10. EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117; 11. Wanner C *et al. J Am Soc Nephrol* 2018;29:2755

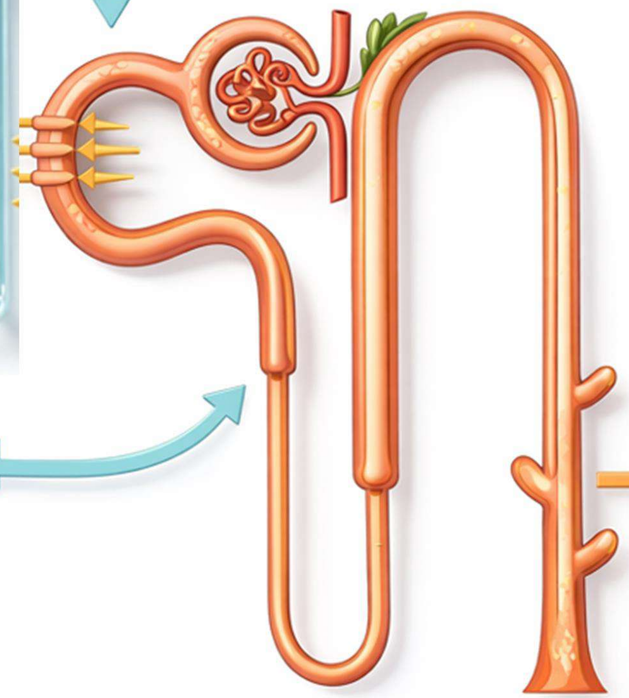
Effetti nefroprotettivi SGLT2i

RIDUZIONE SOVRACCARICO TUBULARE E IPOSSIA

- Riduzione riassorbimento sodio e glucosio
- Meno sovraccarico tubulare
- Migliora ipossia renale
- Migliora integrità tubulare

EFFETTI ANTINFIAMMATORI & ANTIFIBROTICI

- Benefici su marcatori antinfiammatori
- Benefici su marcatori antiossidanti
- Benefici su marcatori antifibrotici



RIDUZIONE PRESSIONE INTRAGLOMERULARE & PROTEINURIA

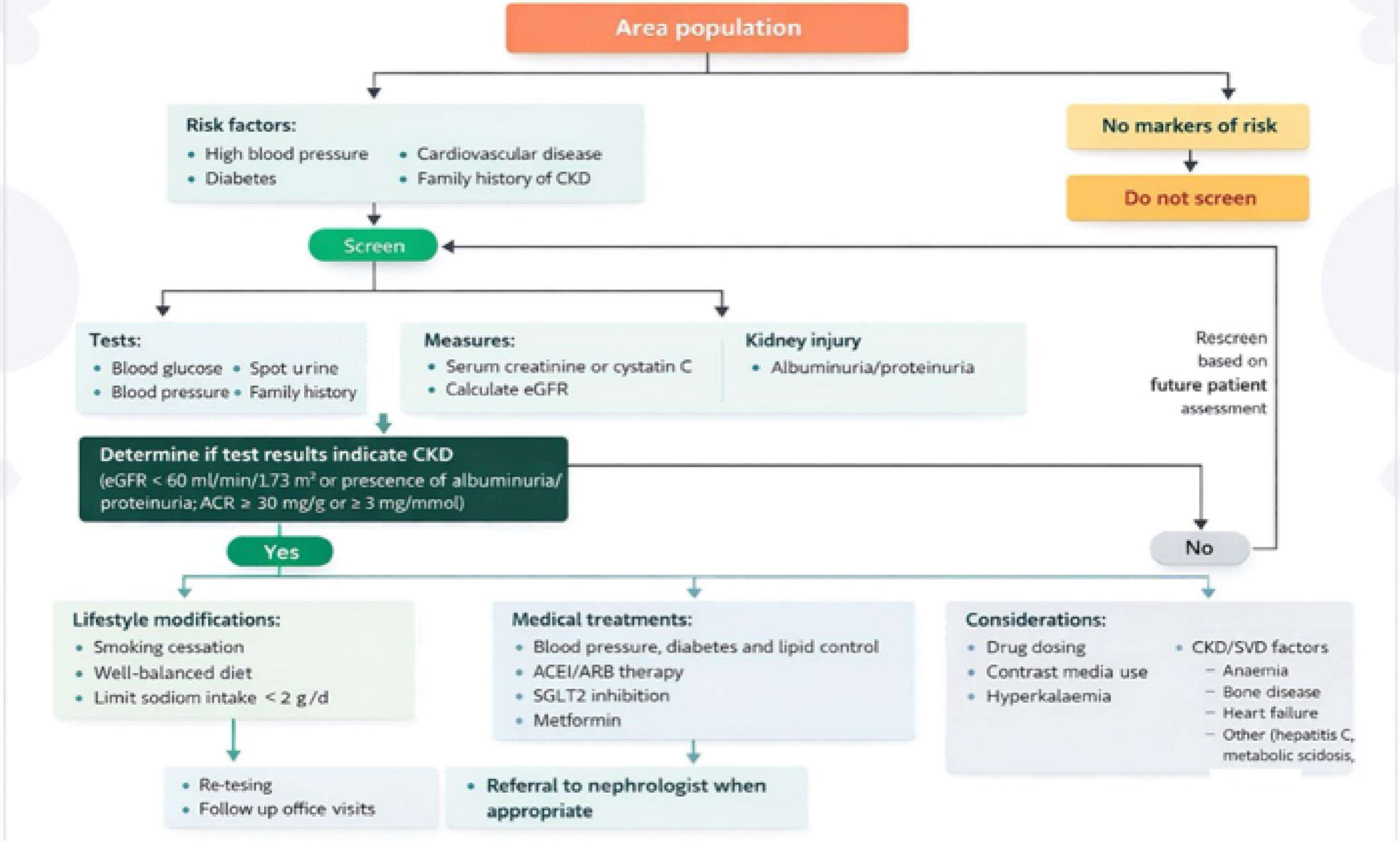
- Secrezione distale di sodio
- Feedback tubuloglomerulare
- Riduce iperfiltrazione

- Meno Pressione intraglomerulare
- Meno Proteinuria

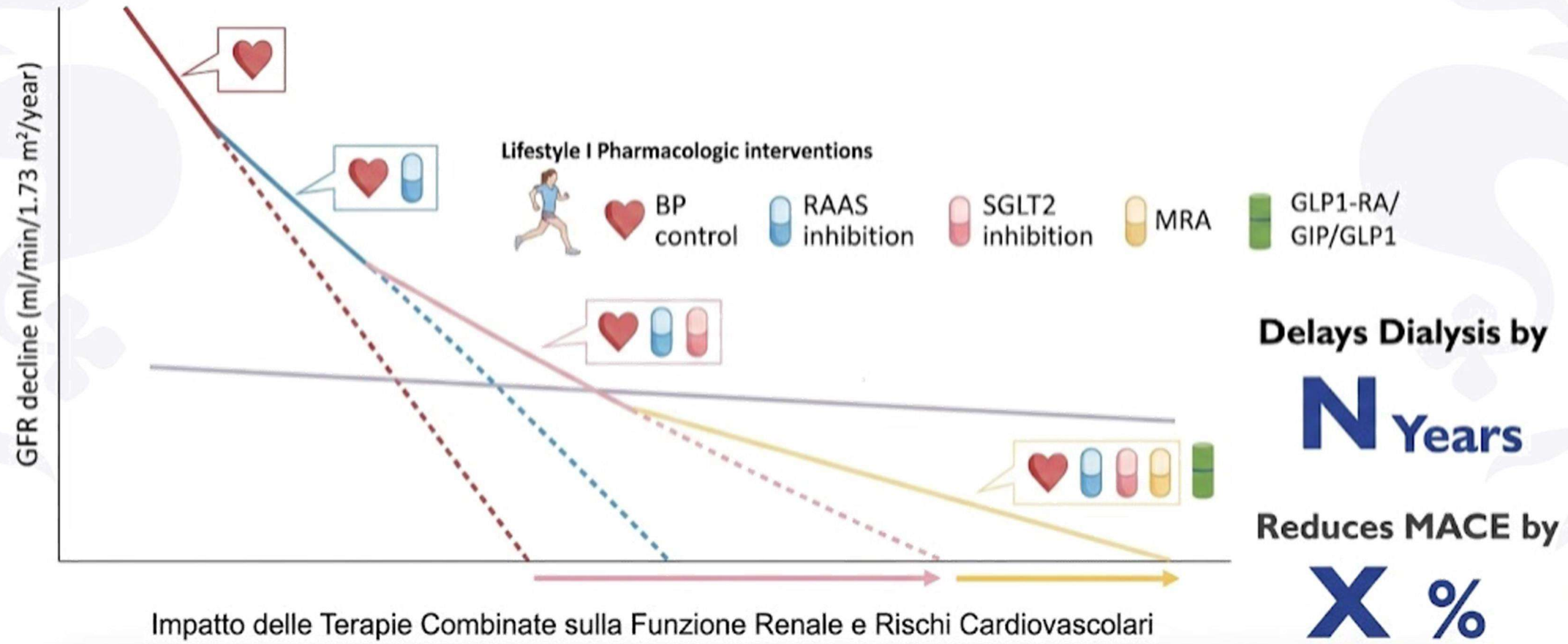
RIDUZIONE PESO CORPOREO & ACIDO URICO

- Riduzione peso corporeo e tessuto adiposo
- Riduzione acido urico
- Migliora funzione endoteliale

Holistic approach to CKD and risk modification



Multifactorial intervention to change the course of CKD



SGLT2i *disease modifyng therapy for:*

DM

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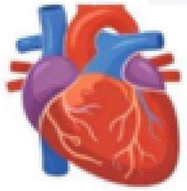
"A **SGLT2 inhibitor** (canagliflozin, empagliflozin, or dapagliflozin) is **recommended in patients with T2D and CKD** with an **eGFR ≥20 ml/min/1.73 m²** to reduce the risk of CVD and kidney failure(1A)."*‡[3]



HF

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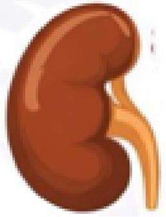
A **SGLT2i** (empaglifozin, dapaglifozin) is recommended **in patients with HF** with an eGFR > 20ml/min/1.73 m² (empa), > 25 (dapa), regardless of LVEF to reduce the risk of HHF and CV death (1A)



CKD

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

- "We recommend treating **patients with T2D, CKD,** and an **eGFR ≥20 ml/min/1.73 m²** with an **SGLT2 inhibitor** (1A)."*†[1,2]

@Closing Remarks (1)

- La CKD và cercata (medicina preventiva/proattiva/di iniziativa)
- Tutti i pz CV o a rischio (diabetici, ipertesi, dislipidemici, obesi, etc) vanno screenati (dosaggio eGFR + uARC)
- eGFR e uARC sono FdR *indipendenti* e *sottostimati* di eventi CV
- La probabilità dei pz CKD di avere un evento CV è molto più alta di quella di andare incontro a eventi avversi renali, compresa la dialisi
- Riconoscere e stadiare CKD migliora la stratificazione del rischio CV consente un migliore management di questi pz
  (target terapeutici, iter diagnostico-terapeutici)

@Closing Remarks (2)

- Gli SGLTi sono in grado di rendere la CKD un FdR *modificabile*
- Riducono significativamente eventi renali e CV e sono in grado di rallentare la progressione eGFR indipendentemente da diabete, grado di disfunzione renale e per empa da presenza o meno di proteinuria
- Alla luce degli effetti degli SGLT2i bisogna ripensare la CKD (da fdr di nichilismo/inerzia terapeutica a target farmacologico azionabile)
- Se precocemente cercata, diagnosticata e tempestivamente trattata la CKD può consentire di cambiare la storia naturale dei pz CV
- Occorre uno switch-mode da approccio a silos a visione integrata