

DIABETE OGGI

**prevenzione e cura al centro
del cambiamento**

Nuove opzioni terapeutiche nella malattia renale diabetica

Martina Vitale

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Azienda Ospedaliera Sant'Andrea, Roma*

Latina, 7 giugno 2025

La dott.ssa Martina Vitale dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

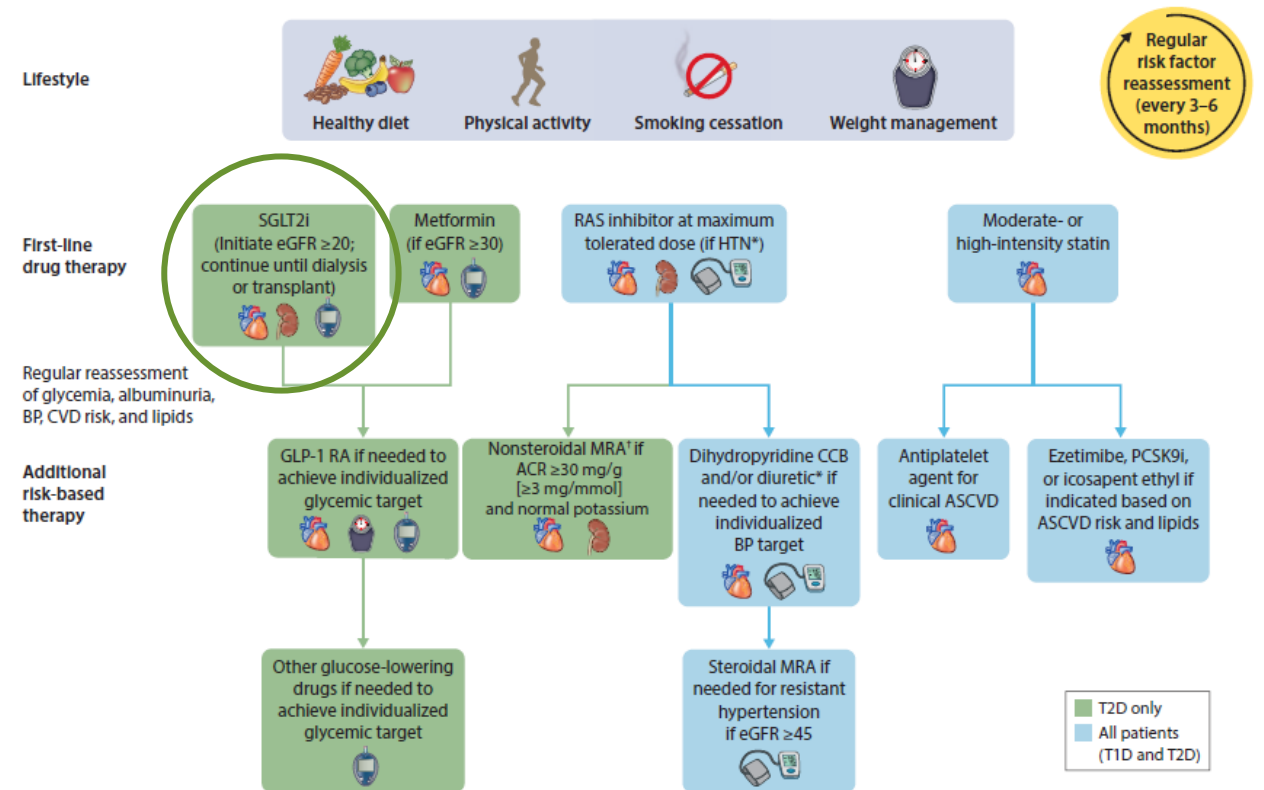
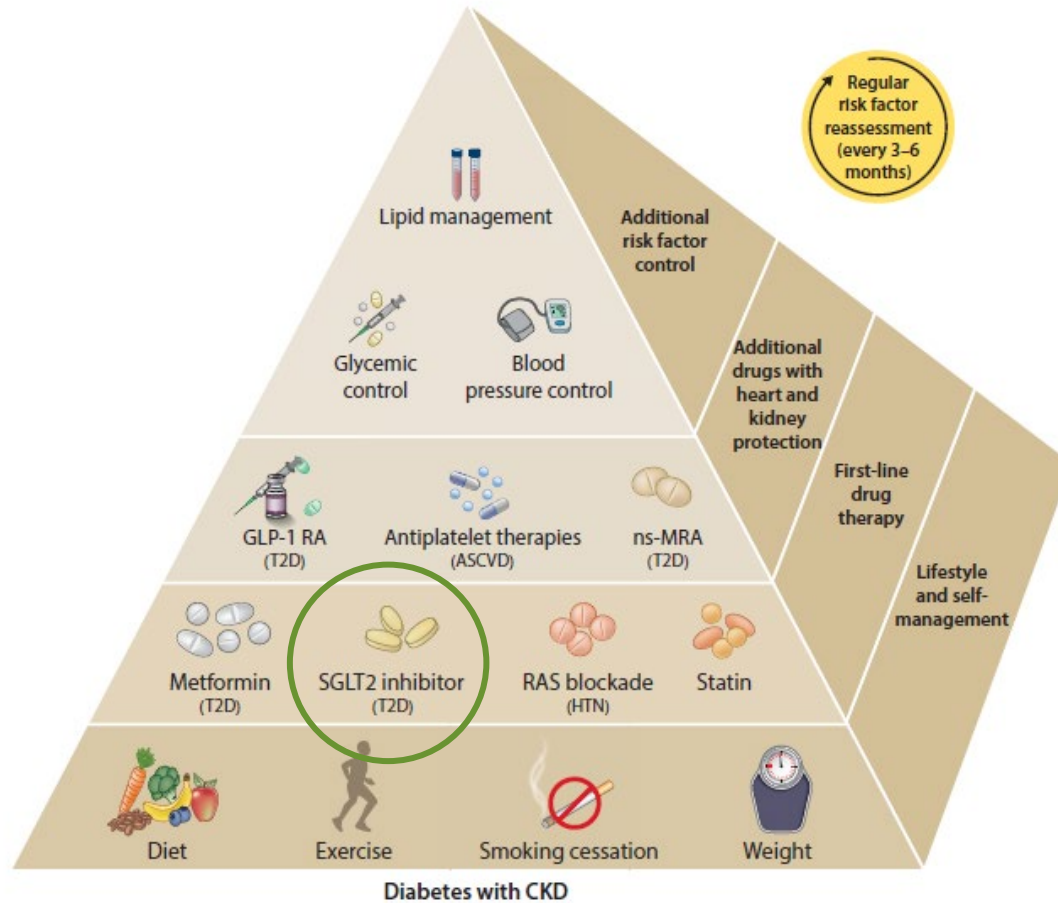
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

AGENDA

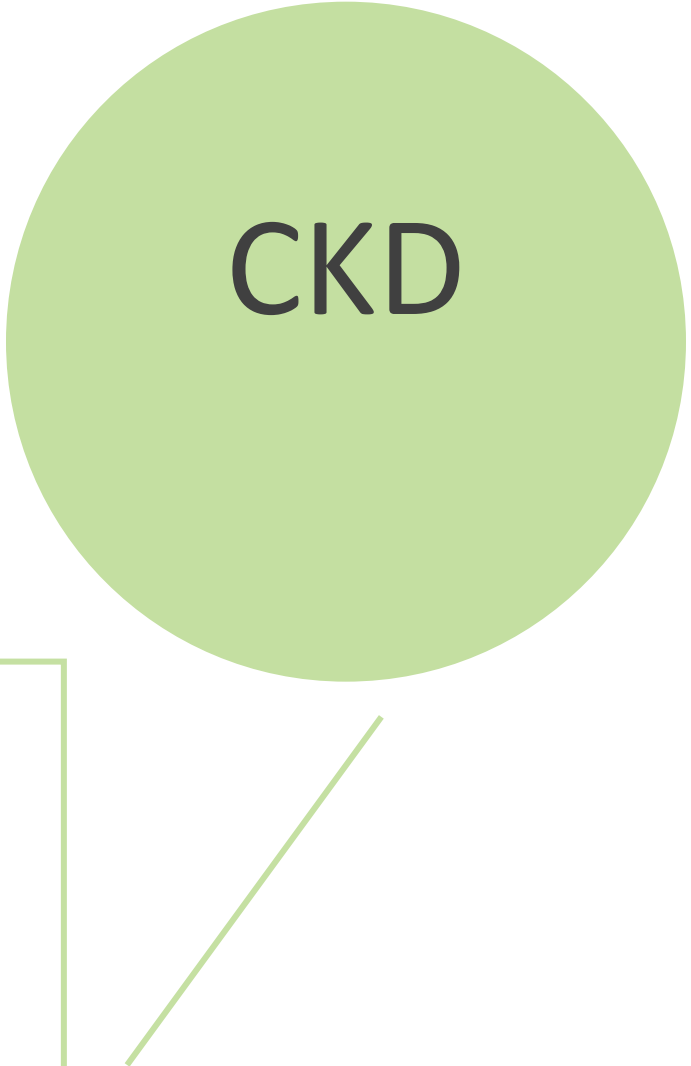
- 1 "vecchie" molecole, vecchie e **nuove** evidenze – SGLT2-i
- 2 "vecchie" molecole, **nuove** evidenze – GLP1-RA
- 3 **nuove** molecole - Finerenone



CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE



CKD TRIALS WITH SGLT2-i



CKD

CREDENCE (*canagliflozin*)
DAPA-CKD (*dapagliflozin*)
EMPA-KIDNEY (*empagliflozin*)

Inclusion Criteria:

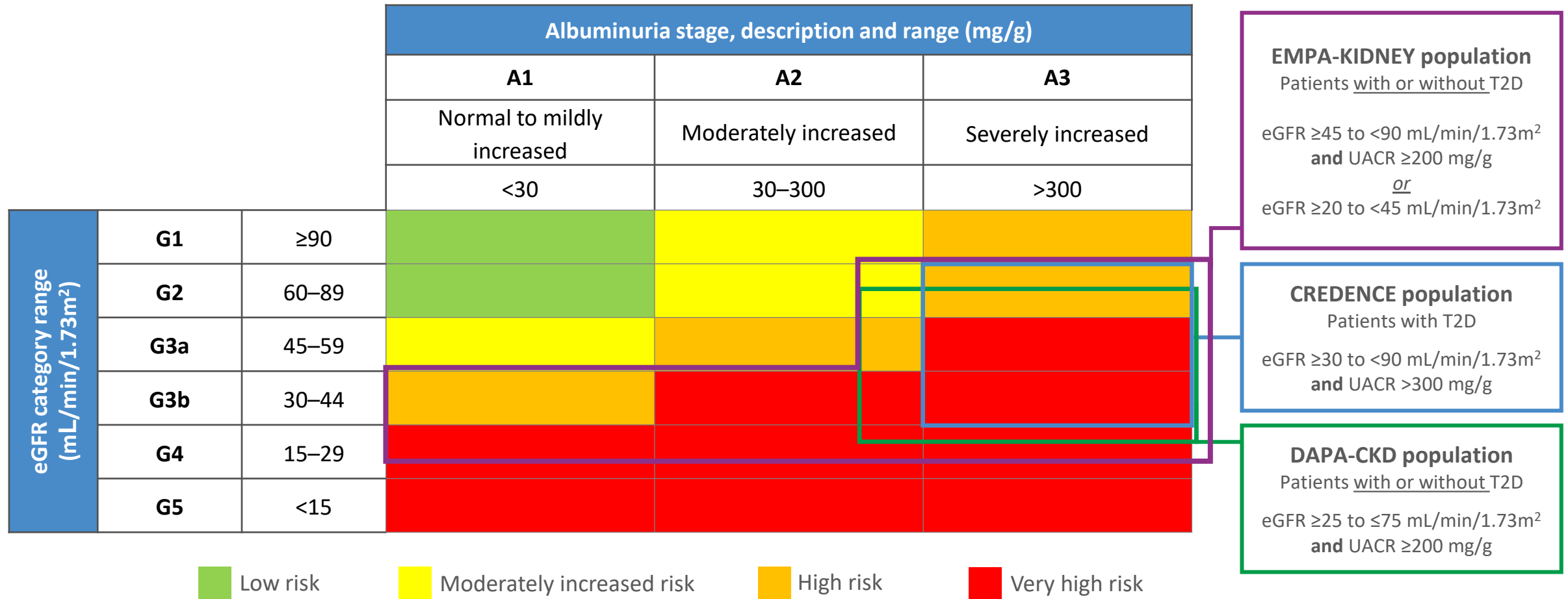
- With or w/o T2DM
- ↓eGFR and ↑ UACR or ↓eGFR

Primary outcome: renal composite

CKD TRIALS WITH SGLT2-i

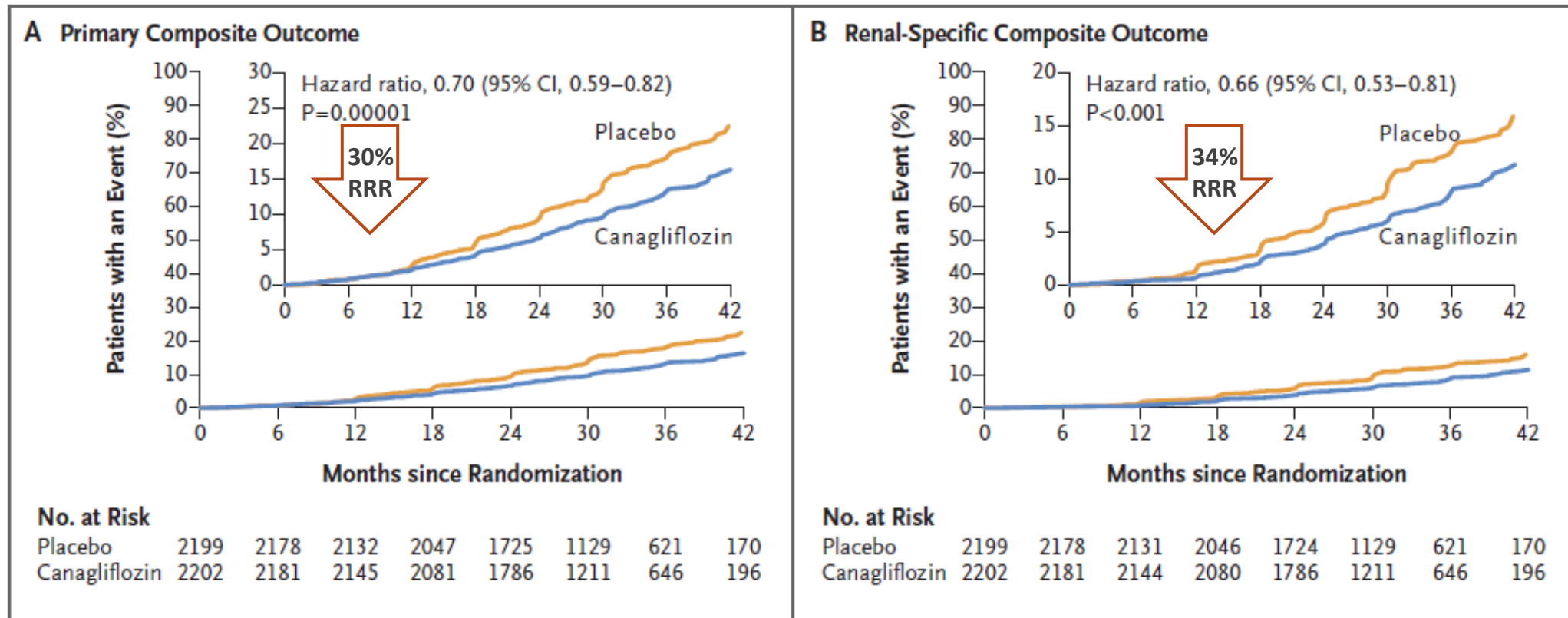
Trial	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Drug	Canagliflozin	Dapagliflozin	Empagliflozin
Participants, n (active drug/placebo)	4,401 (2,202/2,199)	4,304 (2,152/2,152)	6,609 (3,304/3,305)
Median follow-up, years	2.6	2.4	2.0
T2DM	100%	67.5%	46.0%
eGFR (ml/min/1.73m²) (active drug/placebo)	56.3/56.0	43.2/43.0	37.4/37.3
Renal function at baseline			
Normal (eGFR ≥90)	4.8%	-	-
Mild impairment (eGFR 60-89)	35.4%	10.5%	21.2% (>45)
Moderate impairment (eGFR 30-59)	55.9%	75.0%	44.3% (30-45)
Severe impairment (eGFR<30)	3.9%	14.5%	34.5%
Albuminuria at baseline			
Normoalbuminuria	0.7%	-	20.1%
Microalbuminuria	11.3%	10.3%	28.2%
Macroalbuminuria	88.0%	89.7 %	51.7%

CKD TRIALS WITH SGLT2-i



CKD TRIALS WITH SGLT2-i

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

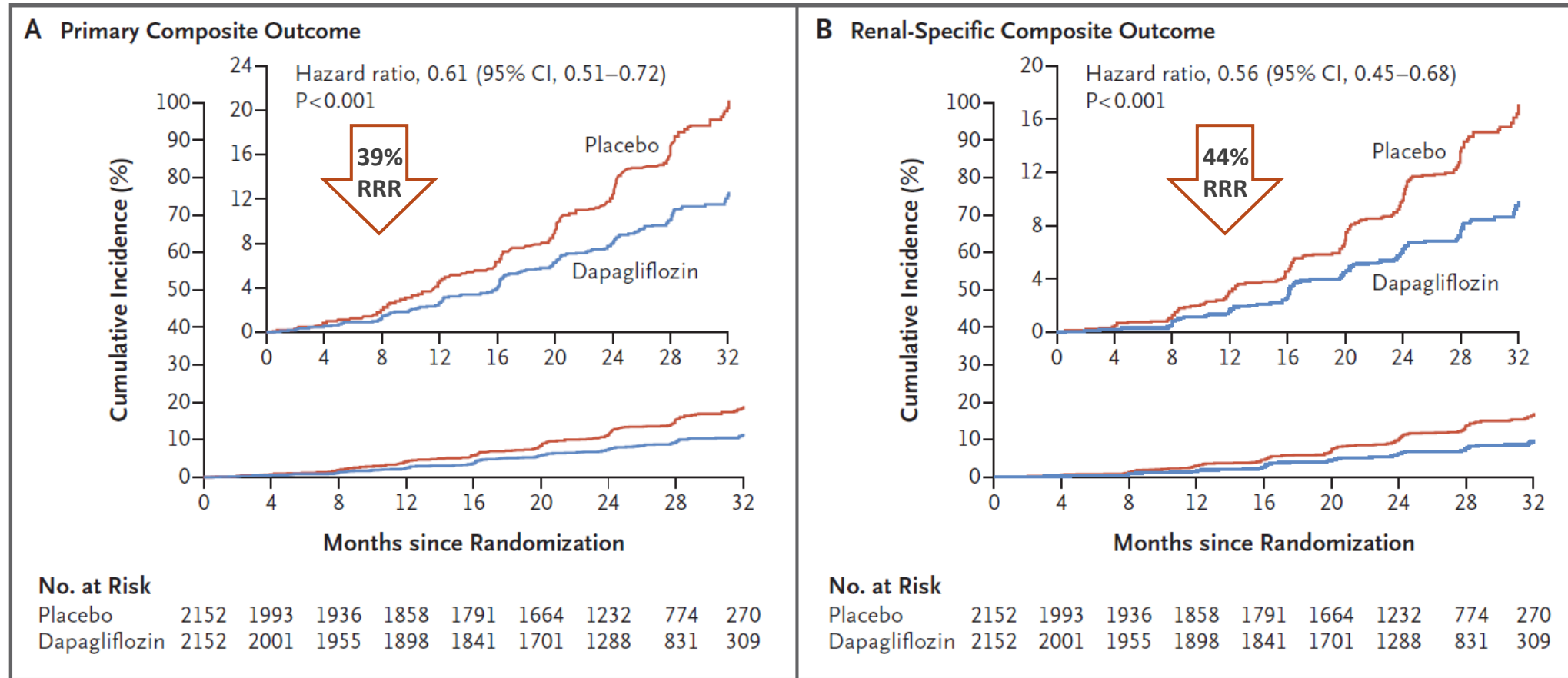


Doubling of serum creatinine level, ESRD, or death from renal or cardiovascular causes

Doubling of serum creatinine level, ESRD, or renal death

CKD TRIALS WITH SGLT2-i

Dapagliflozin in Patients with Chronic Kidney Disease



Sustained decline in eGFR $\geq 50\%$, ESRD, or death from renal or cardiovascular causes

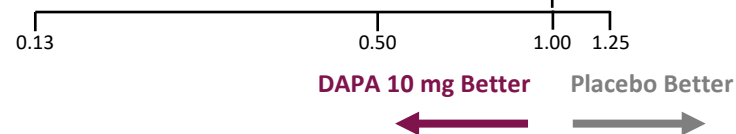
Sustained decline in eGFR $\geq 50\%$, ESRD, or death from renal causes

CKD TRIALS WITH SGLT2-i

Dapagliflozin in Patients with Chronic Kidney Disease

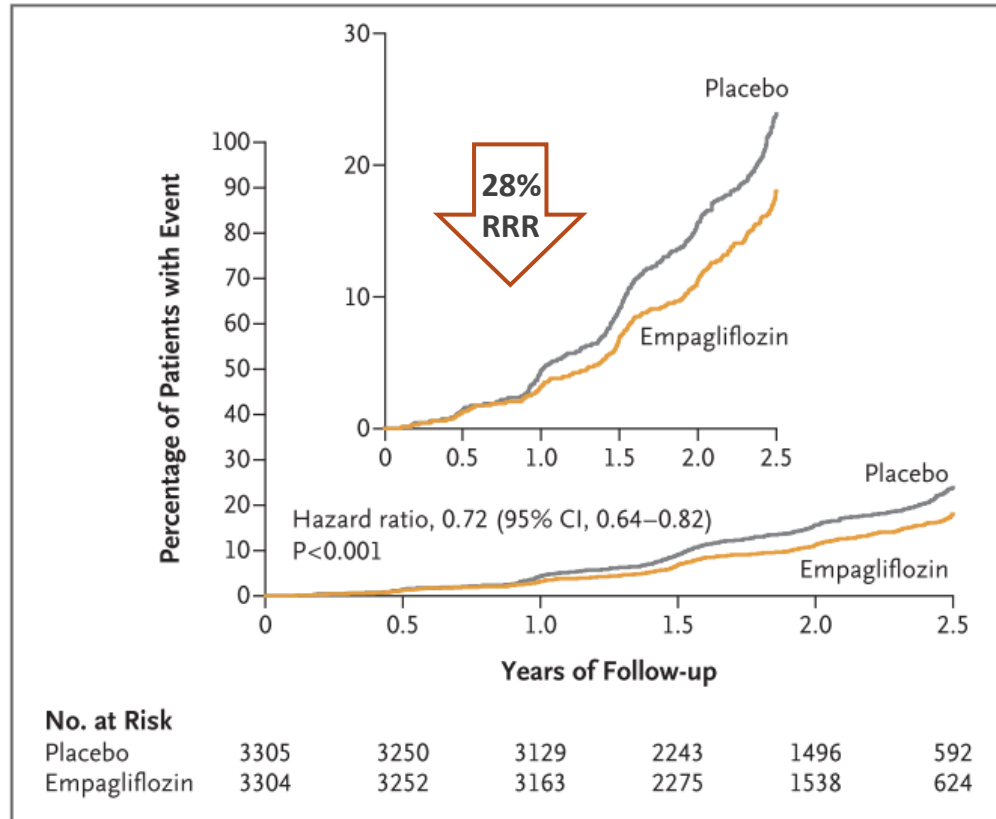


	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					
Yes	152	229	0.64	(0.52, 0.79)	0.24
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					
≤1000	44	84	0.54	(0.37, 0.77)	0.52
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					
<45	152	217	0.63	(0.51, 0.78)	0.22
≥45	45	95	0.49	(0.34, 0.69)	

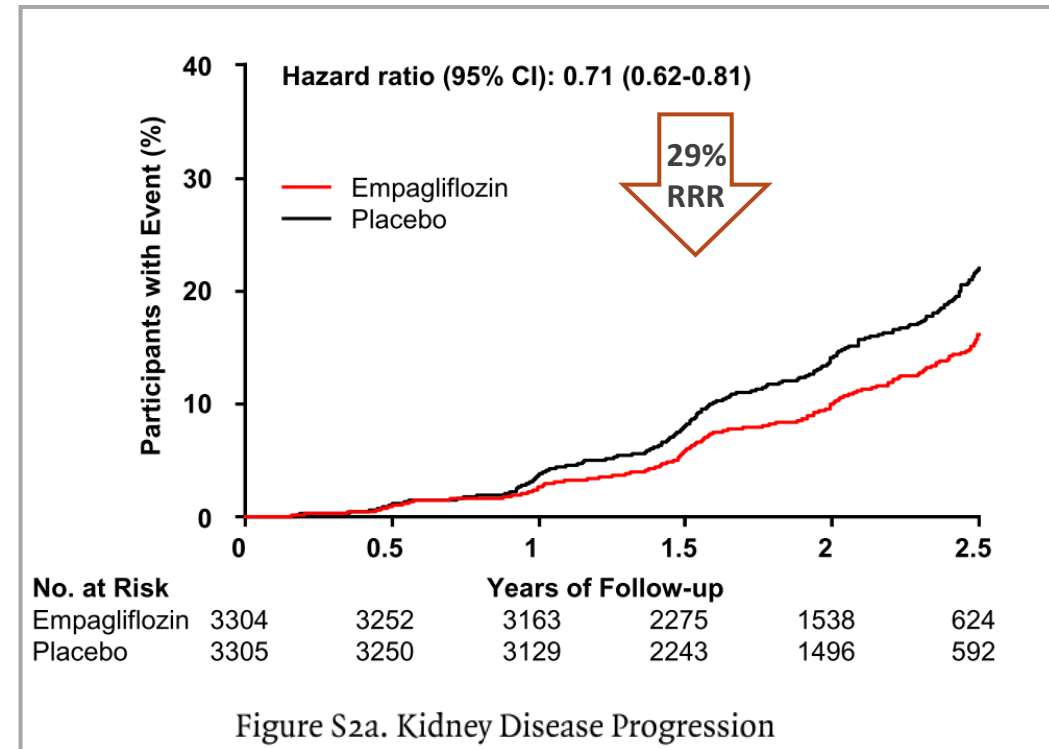


CKD TRIALS WITH SGLT2-i

Empagliflozin in Patients with Chronic Kidney Disease



Sustained decline in eGFR $\geq 40\%$, ESRD, or death from renal or cardiovascular causes



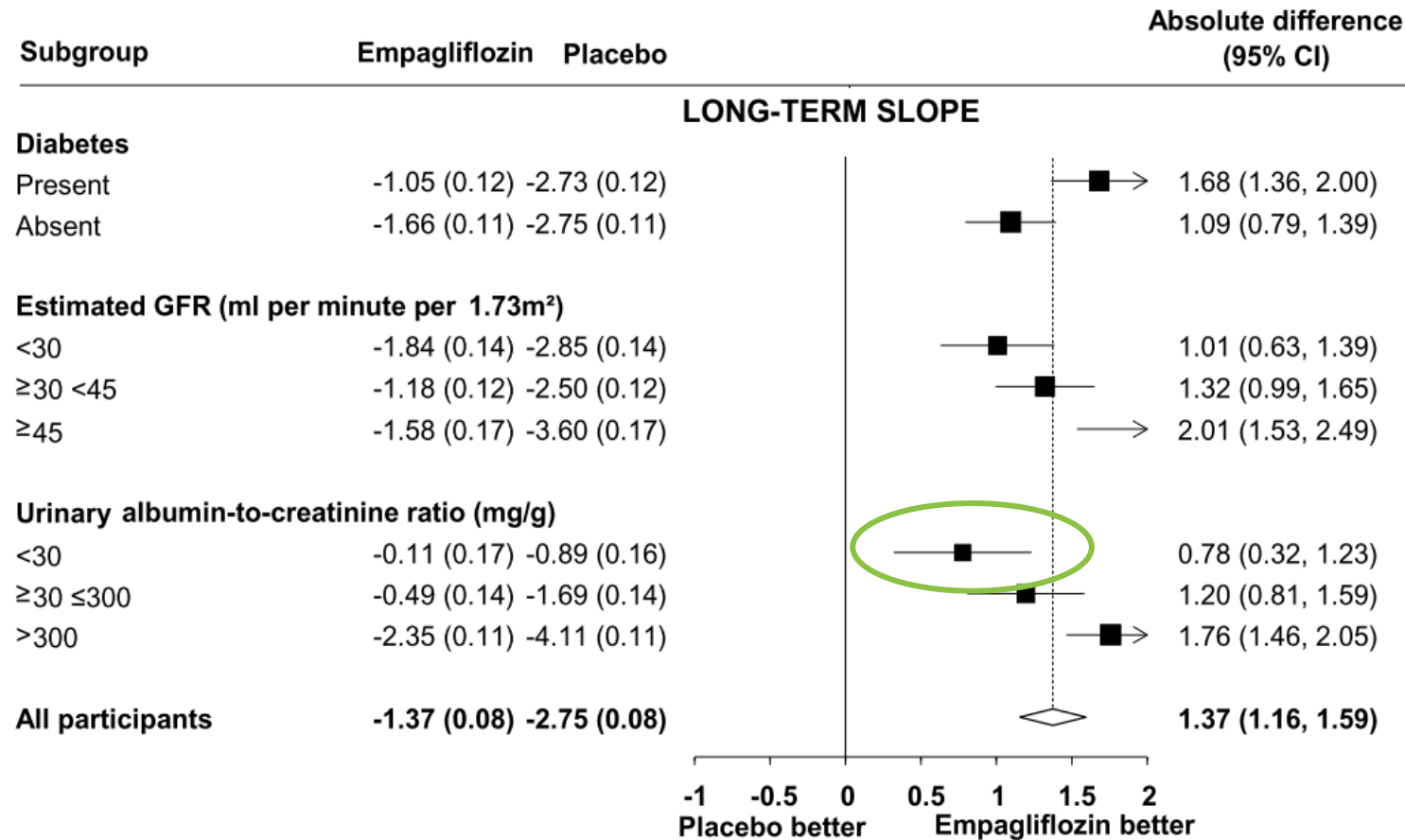
Sustained decline in eGFR $\geq 40\%$, ESRD, or death from renal causes

CKD TRIALS WITH SGLT2-i

Empagliflozin in Patients with Chronic Kidney Disease



Mean annual rate of change in estimated GFR
(ml per minute per 1.73m² per year)



CKD TRIALS WITH SGLT2-i

Key outcomes of SGLT2-I trials



	(n=4401)	(n=4304)	(n=6609)
Primary Composite Outcome (Progression of kidney disease or CV death)	HR 0.70 (95% CI, 0.59-0.82)	HR 0.61 (95% CI, 0.51-0.72)	HR 0.72 (95% CI, 0.64-0.82)
Progression of kidney disease	HR 0.66 (95% CI, 0.53-0.81)	HR 0.56 (95% CI, 0.45-0.68)	HR 0.71 (95% CI, 0.62-0.81)
Composite of CV death or HHF	HR 0.69 (95% CI, 0.57-0.83)	HR 0.71 (95% CI, 0.55-0.92)	HR 0.84 (95% CI, 0.67-1.07)
Hospitalization for any cause	-	-	HR 0.86 (95% CI, 0.78-0.95)
Death for any cause	HR 0.83 (95% CI, 0.68-1.02)	HR 0.69 (95% CI, 0.53-0.88)	HR 0.87 (95% CI, 0.70-1.08)
ESKD or CV death	HR 0.73 (95% CI, 0.61-0.87)	-	HR 0.73 (95% CI, 0.59-0.89)
ESKD	HR 0.68 (95% CI, 0.54-0.86)	HR 0.64 (95% CI, 0.50-0.82)	-
CV death	HR 0.78 (95% CI, 0.61-1.00)	HR 0.81 (95% CI, 0.58-1.12)	HR 0.84 (95% CI, 0.60-1.19)

Perkovic V et al. N Engl J Med 2019;380:2295-306.; Heerspink HJL et al. N Engl J Med. 2020 Oct 8;383(15):1436-1446.;

Herrington WG et al. N Engl J Med. 2023 Jan 12;388(2):117-127.

Long-term benefits of dapagliflozin on renal outcomes of type 2 diabetes under routine care: a comparative effectiveness study on propensity score matched cohorts at low renal risk



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DARWIN-Renal Study Investigators



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^cDepartment of Information Engineering, University of Padova, 35100 Padua, Italy

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Long-term benefits of **Dapagliflozin** on renal outcomes of type 2 diabetes under routine care:
a comparative effectiveness study on propensity score matched cohorts at low renal risk

DARWIN-
Renal

Obiettivo

Dimostrare l'efficacia a lungo termine di dapagliflozin su esiti renali multipli e sull'albuminuria nei pazienti con diabete di tipo 2 e basso rischio renale

Studio multicentrico **retrospettivo** comparativo di efficacia, condotto dalla **Società Italiana di Diabetologia** in 50 centri specializzati nella cura del diabete in Italia

Dal **gennaio 2015** al **settembre 2022**, i dati clinici sono stati estratti dalle cartelle cliniche elettroniche

- Pazienti avviati a **dapagliflozin**
- Pazienti avviati a **qualsiasi altro farmaco ipoglicemizzante**

I farmaci di confronto comprendevano:
*DPP-4i (40%), GLP-1RA (22.3%),
sulfoniluree/glinidi (16.1%),
pioglitazone (8%), metformina (5.8%),
acarbosio (4%)*

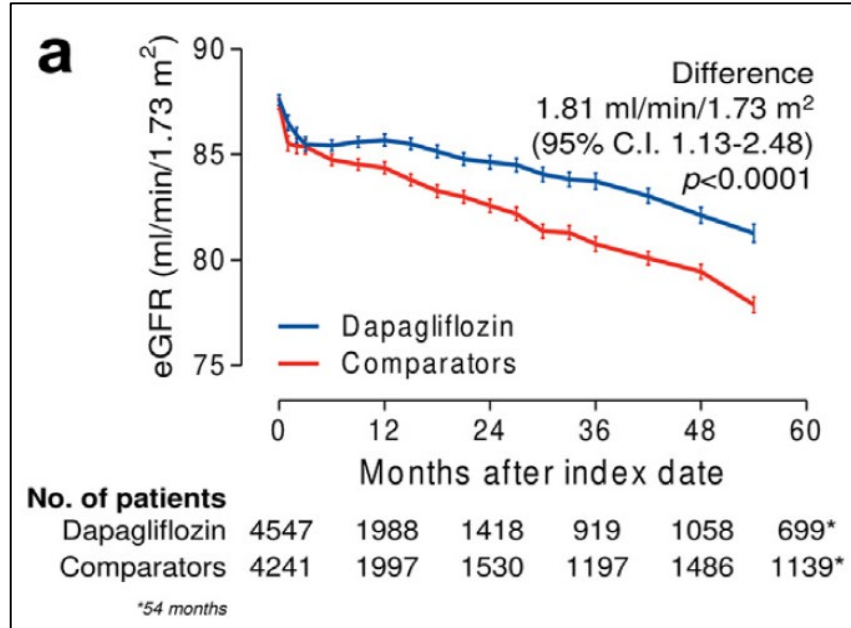
CKD TRIALS WITH SGLT2-i

Trial	CREDENCE	DAPA-CKD	EMPA-KIDNEY	DARWIN-Renal
Drug	Canagliflozin	Dapagliflozin	Empagliflozin	Dapagliflozin
Participants, n (active drug/placebo)	4,401 (2,202/2,199)	4,304 (2,152/2,152)	6,609 (3,304/3,305)	12,400 (6,200/6,200)
Median follow-up, years	2.6	2.4	2.0	2.5
T2DM	100%	67.5%	46.0%	100%
eGFR (ml/min/1.73m ²) (active drug/placebo)	56.3/56.0	43.2/43.0	37.4/37.3	87.7/87.4
Renal function at baseline				
Normal (eGFR ≥90)	4.8%	-	-	
Mild impairment (eGFR 60-89)	35.4%	10.5%	21.2%(>45)	93.6%(>60)
Moderate impairment (eGFR 30-59)	55.9%	75.0%	44.3% ⁽³⁰⁻⁴⁵⁾	6.4%(<60)
Severe impairment (eGFR<30)	3.9%	14.5%	34.5%	
Albuminuria at baseline				
Normoalbuminuria	0.7%	-	20.1%	85%(<30)
Microalbuminuria	11.3%	10.3%	28.2%	15%(>30)
Macroalbuminuria	88.0%	89.7%	51.7%	

CKD TRIALS WITH SGLT2-i

Long-term benefits of **Dapagliflozin** on renal outcomes of type 2 diabetes under routine care:
a comparative effectiveness study on propensity score matched cohorts at low renal risk

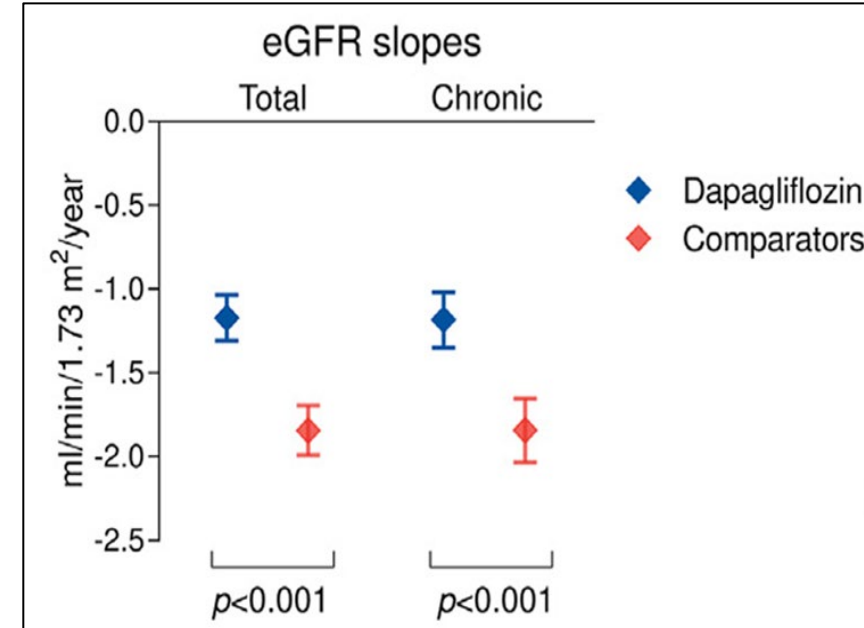
**DARWIN-
Renal**



Da un valore basale di 87,5 ml/min/1,73 m²,
**eGFR è diminuito significativamente meno tra i nuovi
utilizzatori di dapagliflozin**

che tra i nuovi utilizzatori di farmaci di confronto.

La **differenza era di 1,81 ml/min/ 1,73 m²**
(95% C.I. 1,13–2,48) a favore di dapagliflozin
($p < 0,0001$)



Il **declino medio totale per anno dell'eGFR** è stato
-1,17 ml/min/1,73 m²/anno (95% C.I. -1,03 to -1,31)
nel gruppo dapagliflozin e
-1,84 ml/min/ 1,73 m²/anno (95% C.I. -1,70 to -1,99)
nel gruppo di controllo.

La **differenza era di 0,67 ml/min/1,73 m²/anno**
(95% C.I. 0,47–0,88) ($p < 0,0001$)

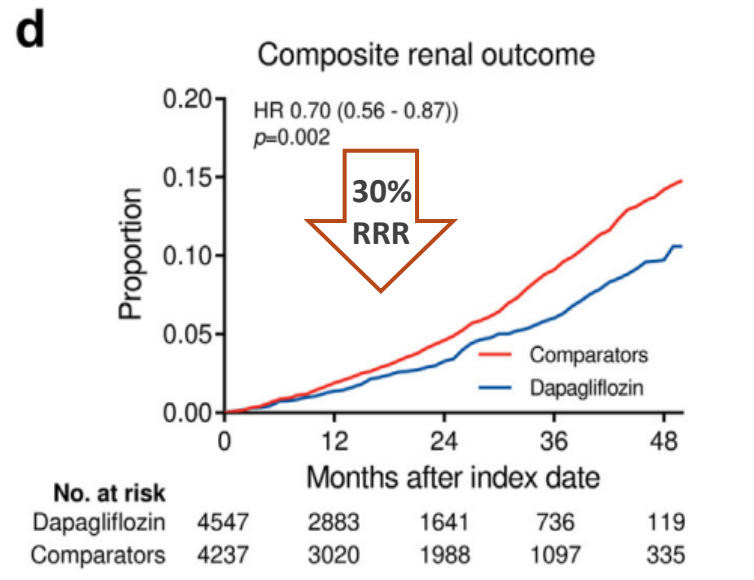
CKD TRIALS WITH SGLT2-i

DARWIN-
Renal

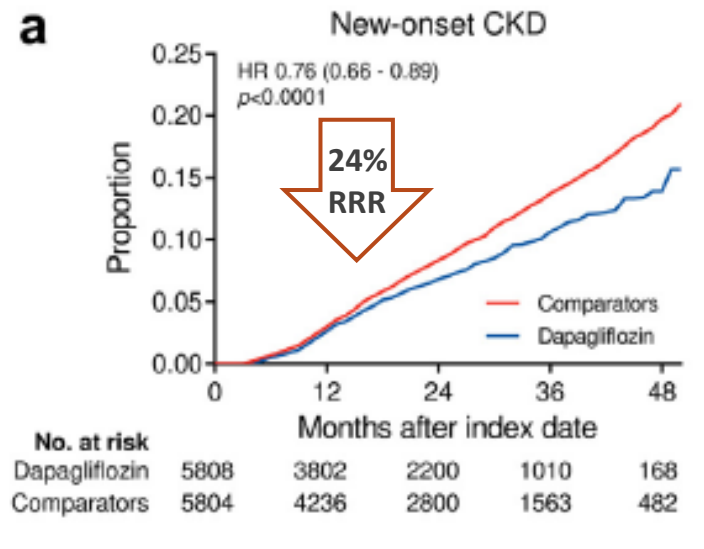
Outcome
renale
composito

Nuova
insorgenza di
CKD

Perdita di
funzionalità
renale

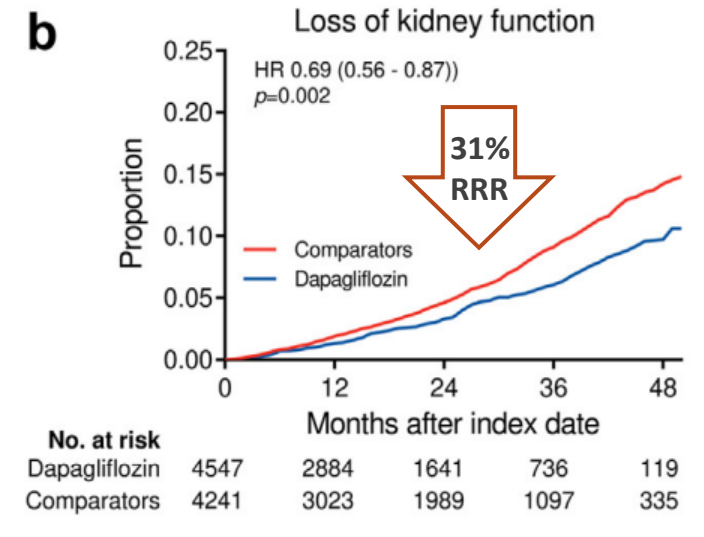


Endpoint renale composito (perdita del 40% della funzionalità renale, malattia renale allo stadio terminale o dialisi)
è risultato significativamente più basso nel gruppo dapagliflozin
(HR 0,70; 95% C.I. 0,56 - 0,87; $p=0,002$)



I nuovi utilizzatori di dapagliflozin avevano **un tasso più basso di nuova insorgenza di CKD**

(HR 0,76; 95% C.I. 0,66 - 0,89; $p<0,001$)



I nuovi utilizzatori di dapagliflozin avevano **minore perdita della funzionalità renale**, definita come >40% di riduzione dell'eGFR

(HR 0,69; 95% C.I. 0,56 - 0,87; $p=0,002$)

1

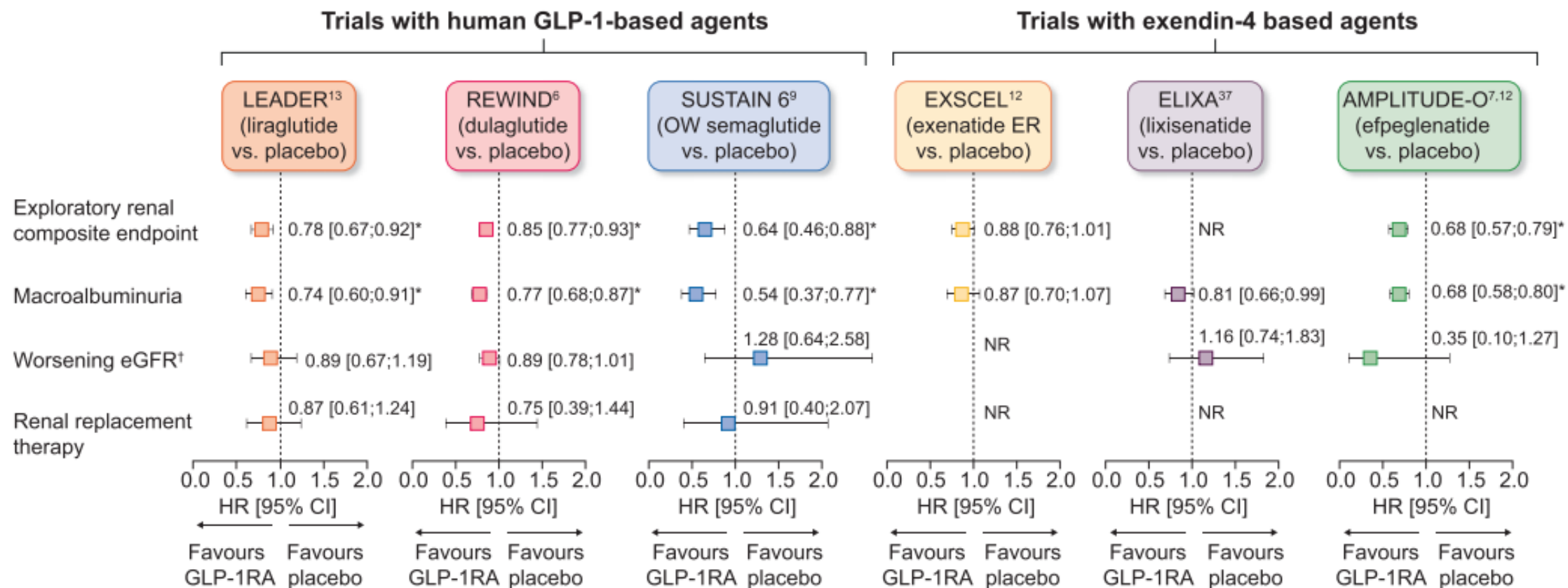
“vecchie” molecole, vecchie e **nuove** evidenze – SGLT2-i

- Le evidenze degli **RCT** dimostrano una significativa **protezione renale** da parte degli SGLT2-i nei pazienti con diabete tipo 2 e malattia renale cronica
- La protezione renale indotta dagli SGLT2-i è stata confermata in un’ampia gamma di pazienti, da quelli **macroalbuminurici**, a quelli con **fenotipo non-albuminurico**, fino a pazienti a basso rischio renale, in **prevenzione primaria**

AGENDA

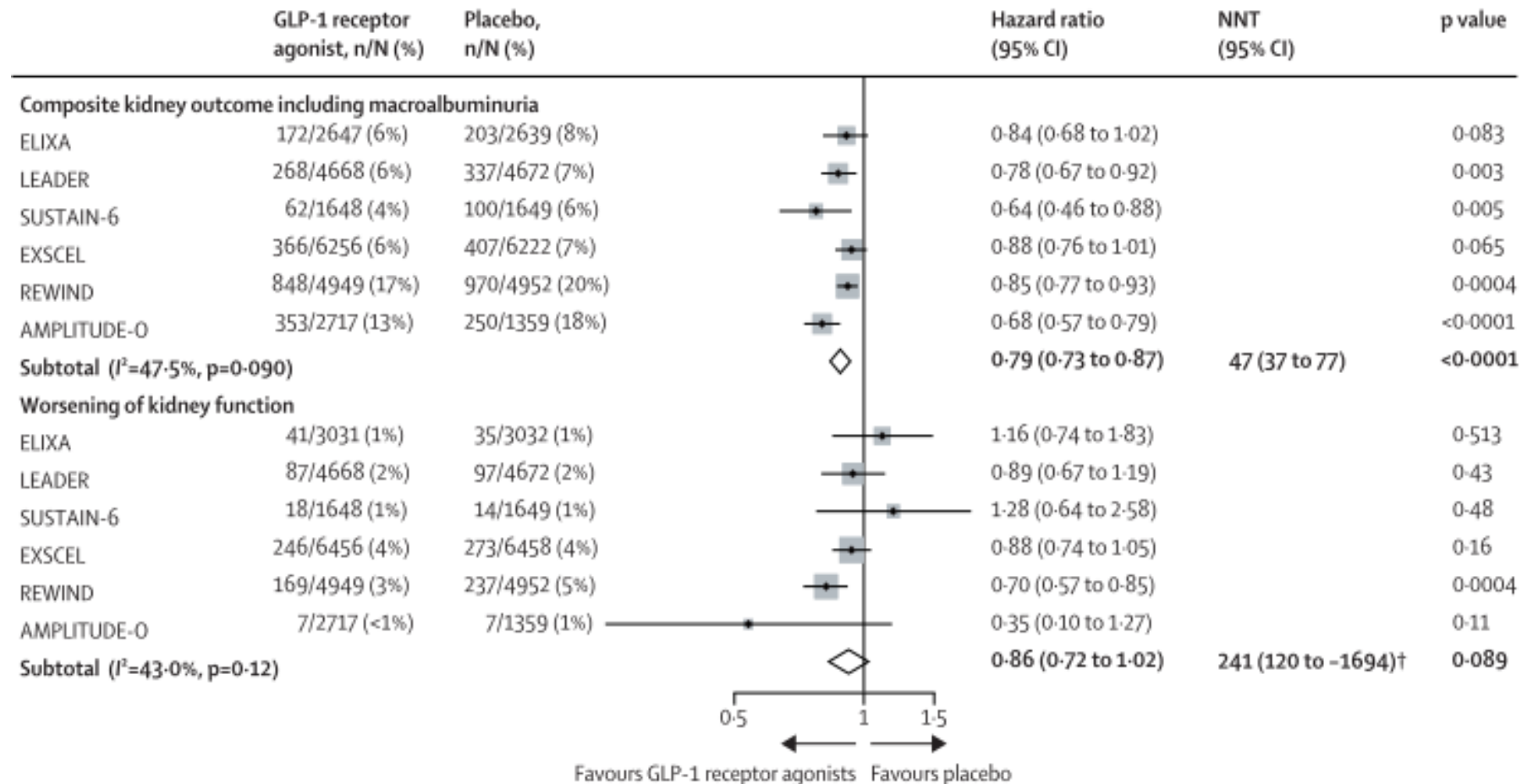
- 1 "vecchie" molecole, vecchie e **nuove** evidenze – SGLT2-i
- 2 "vecchie" molecole, **nuove** evidenze – GLP1-RA
- 3 **nuove** molecole - Finerenone

Exploratory kidney outcomes analyses from GLP-1 RA CVOTs



Exploratory kidney outcomes analyses from GLP-1 RA CVOTs

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes:
a systematic review and meta-analysis of randomised trials



THE FLOW TRIAL

Methods

Participants:



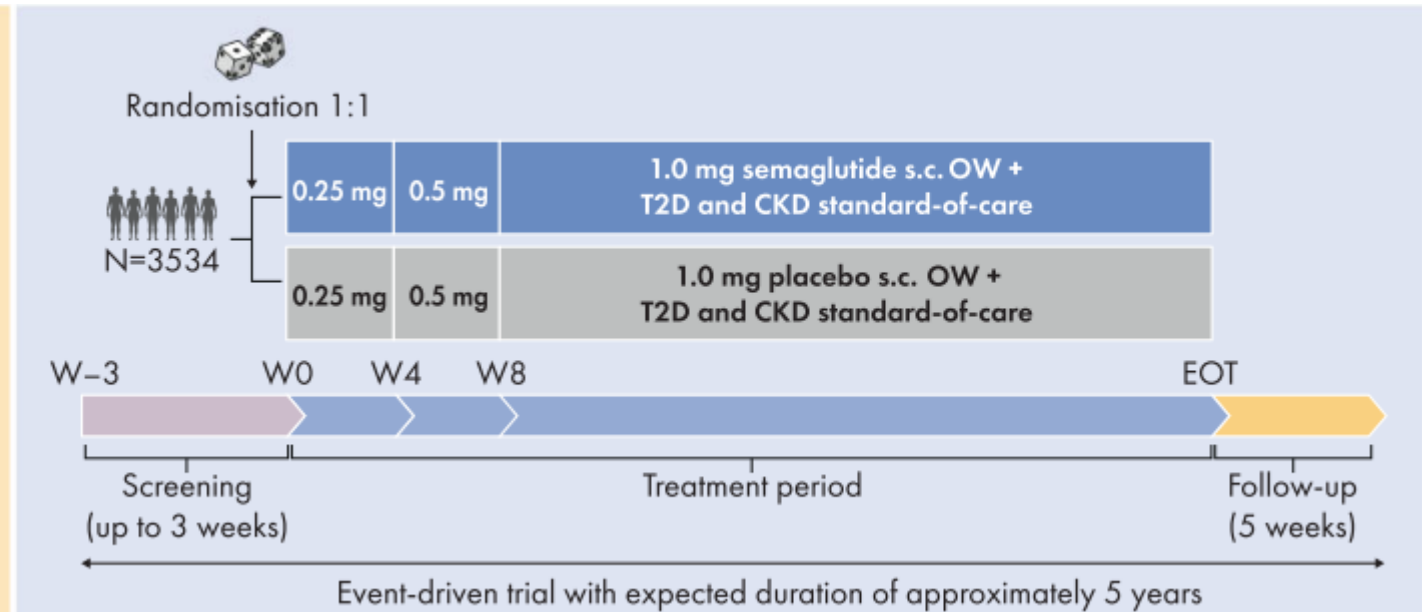
- Adults with T2D
- eGFR ≥ 50 to ≤ 75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥ 25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:



Time to first occurrence of:

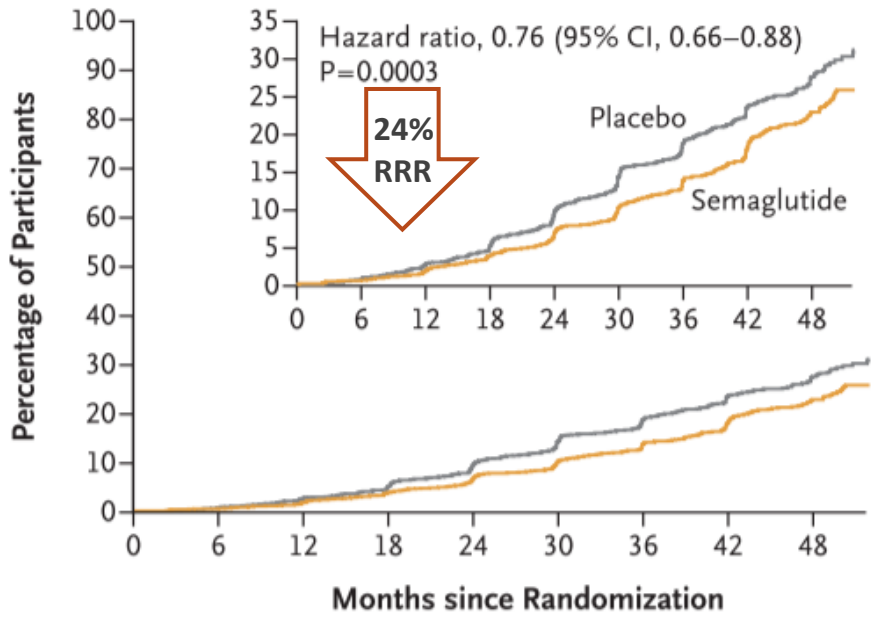
- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent $\geq 50\%$ reduction in eGFR; or
- Death from kidney or CV causes



		UACR categories (mg/g)		
		<30	≥ 30 – <300	≥ 300
eGFR categories (mL/min/1.73 m ²)	≥ 90	1 (<0.1)	7 (0.2)	23 (0.6)
	≥ 60 – <90	24 (0.7)	173 (4.9)	491 (13.9)
	≥ 45 – <60	37 (1.0)	324 (9.2)	694 (19.6)
	≥ 30 – <45	40 (1.1)	414 (11.7)	625 (25.6)
	≥ 15 – <30	7 (0.2)	37 (2.5)	306 (8.8)
	<15	NA	NA	NA

Low risk n=25 (0.7%) Moderate risk n=217 (6.1%) High risk n=878 (24.8%) Very high risk n=2,413 (68.2%)

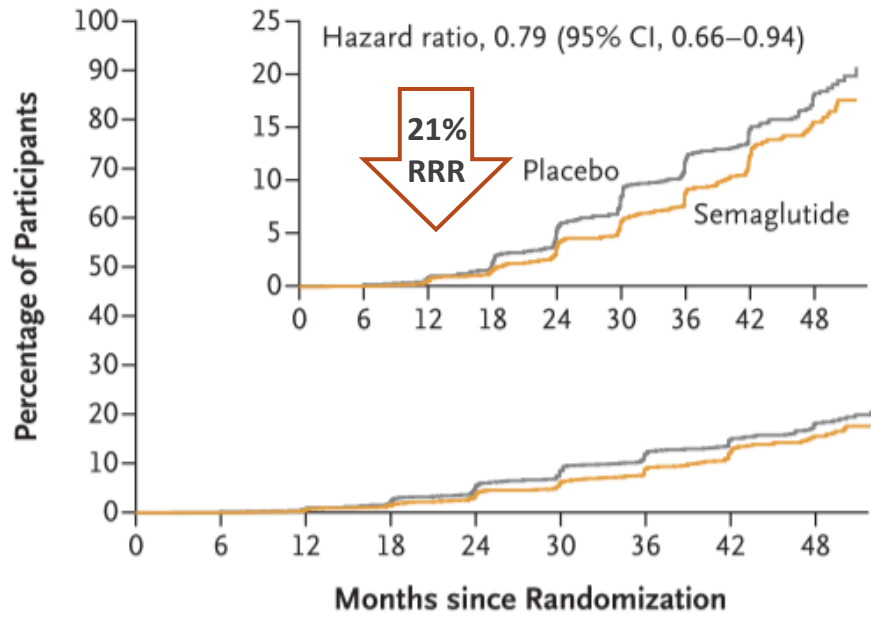
A First Major Kidney Disease Event



No. at Risk

Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

B First Kidney-Specific Component Event

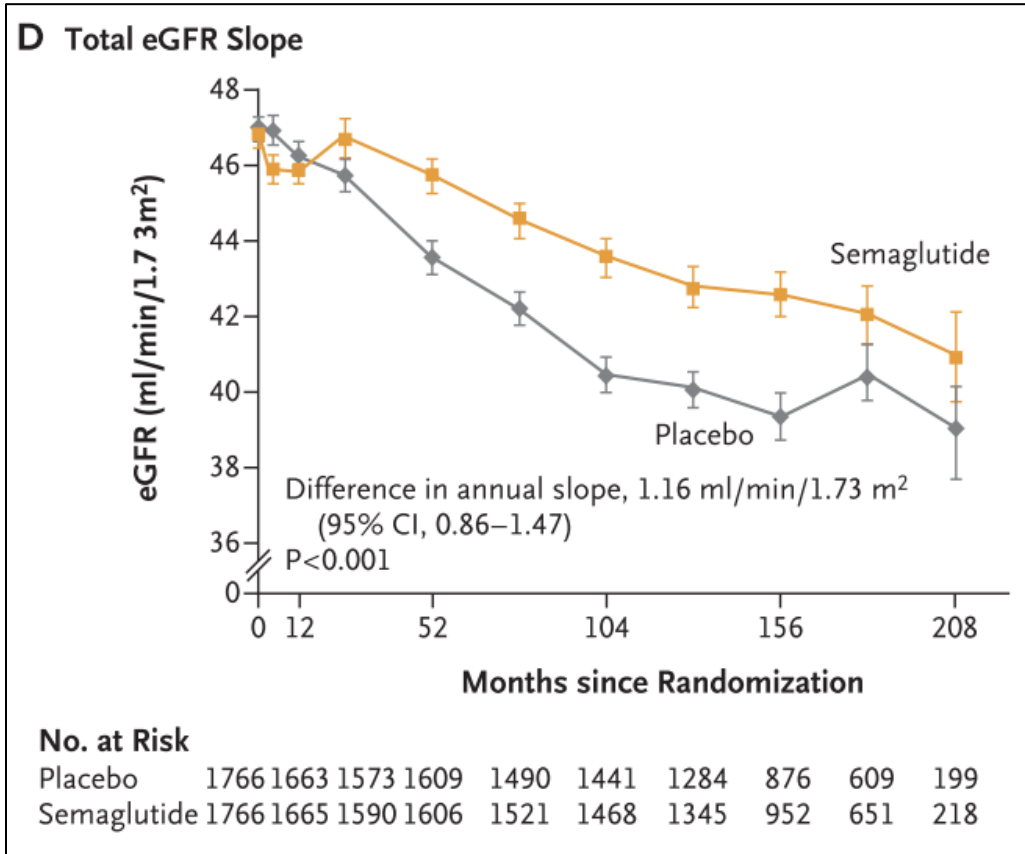


No. at Risk

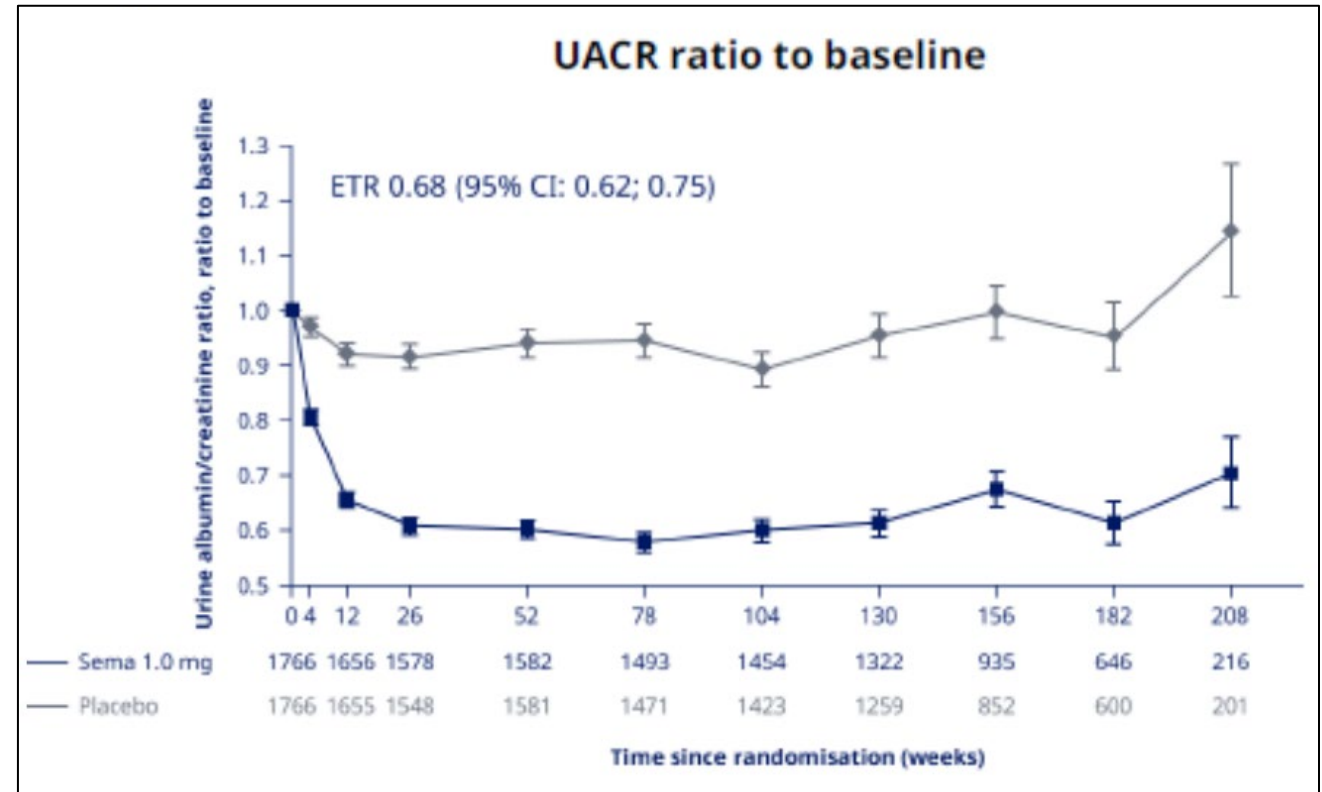
Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

persistent $\geq 50\%$ reduction in eGFR, ESRD, or death from renal or cardiovascular causes

persistent $\geq 50\%$ reduction in eGFR, ESRD, or death from renal causes



Semaglutide slower loss of kidney function
by a mean eGFR of **1.16 mL/min/1.73m²/year**



At 104 weeks, the UACR was reduced by **12%** in the placebo group vs. **40%** in the semaglutide group, for a between-group difference of **32%** (95% CI 25 – 38%)

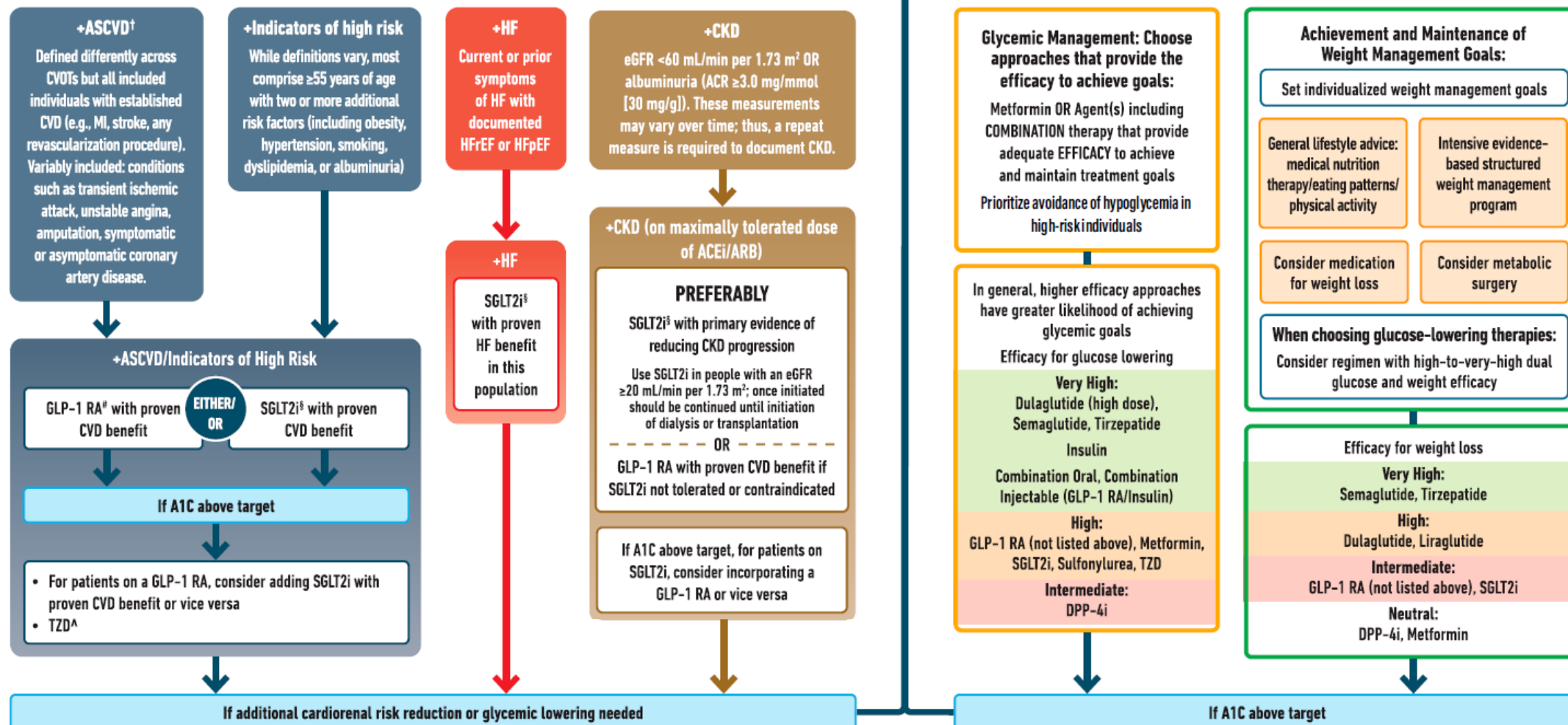
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

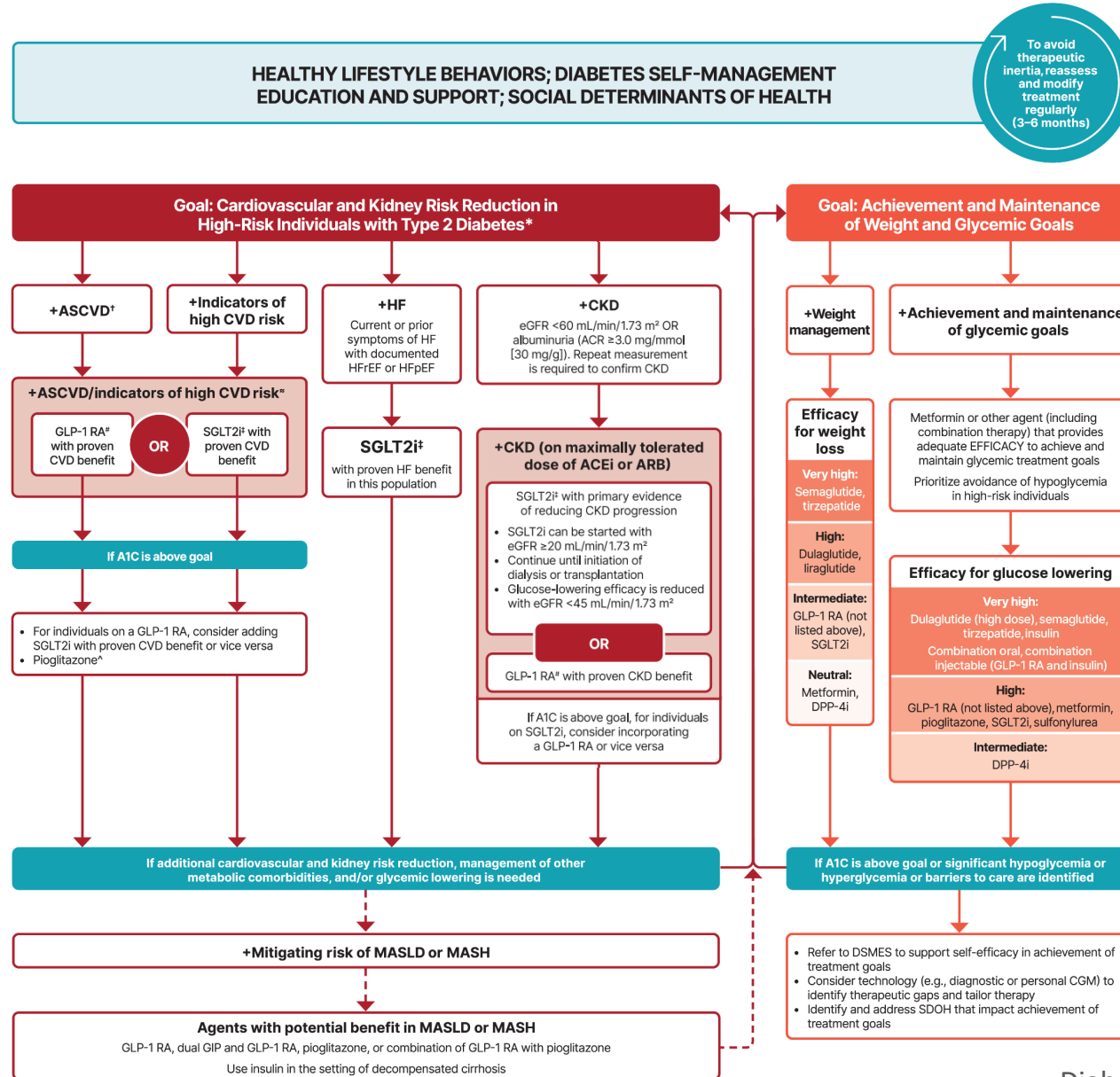


Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes (in addition to comprehensive CV risk management)*

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals



Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



2

"vecchie" molecole, **nuove** evidenze – GLP1-RA

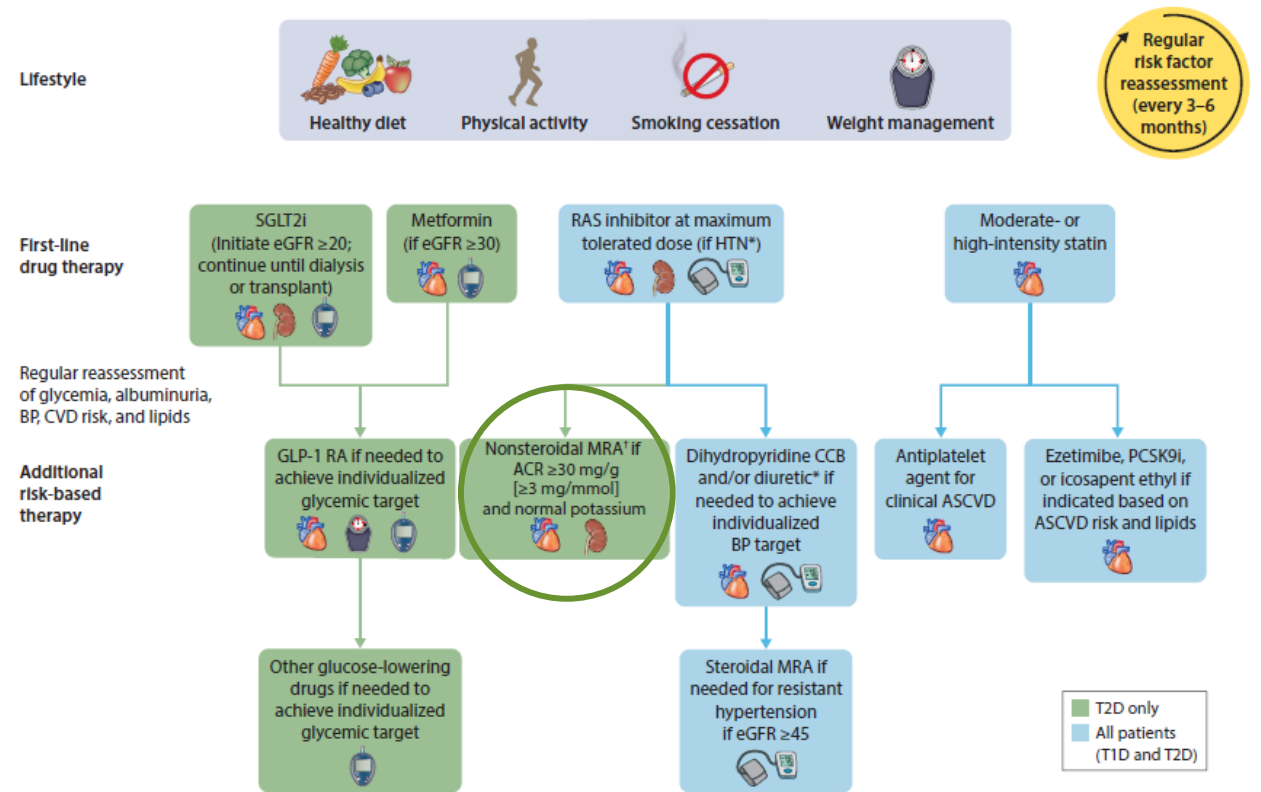
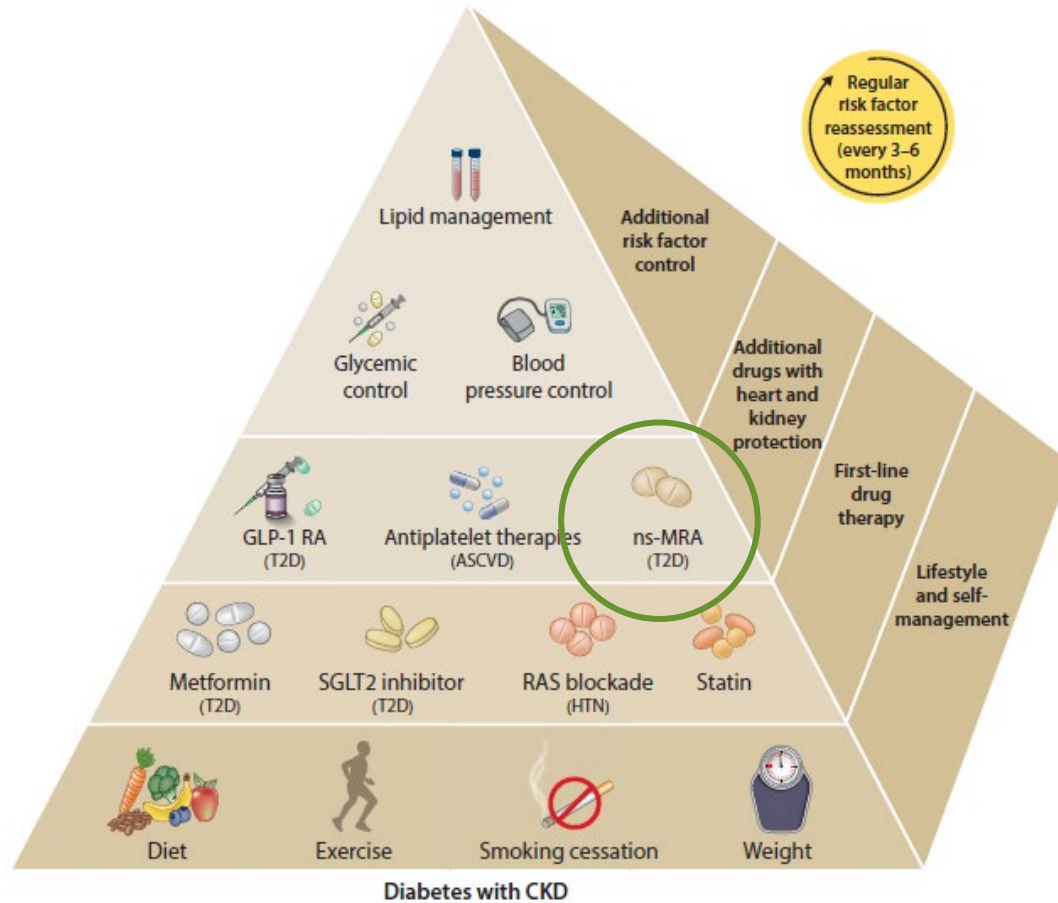
- Lo studio FLOW ha dimostrato che semaglutide **riduce il rischio di outcomes renali** in pazienti con diabete tipo 2 e malattia renale cronica

AGENDA

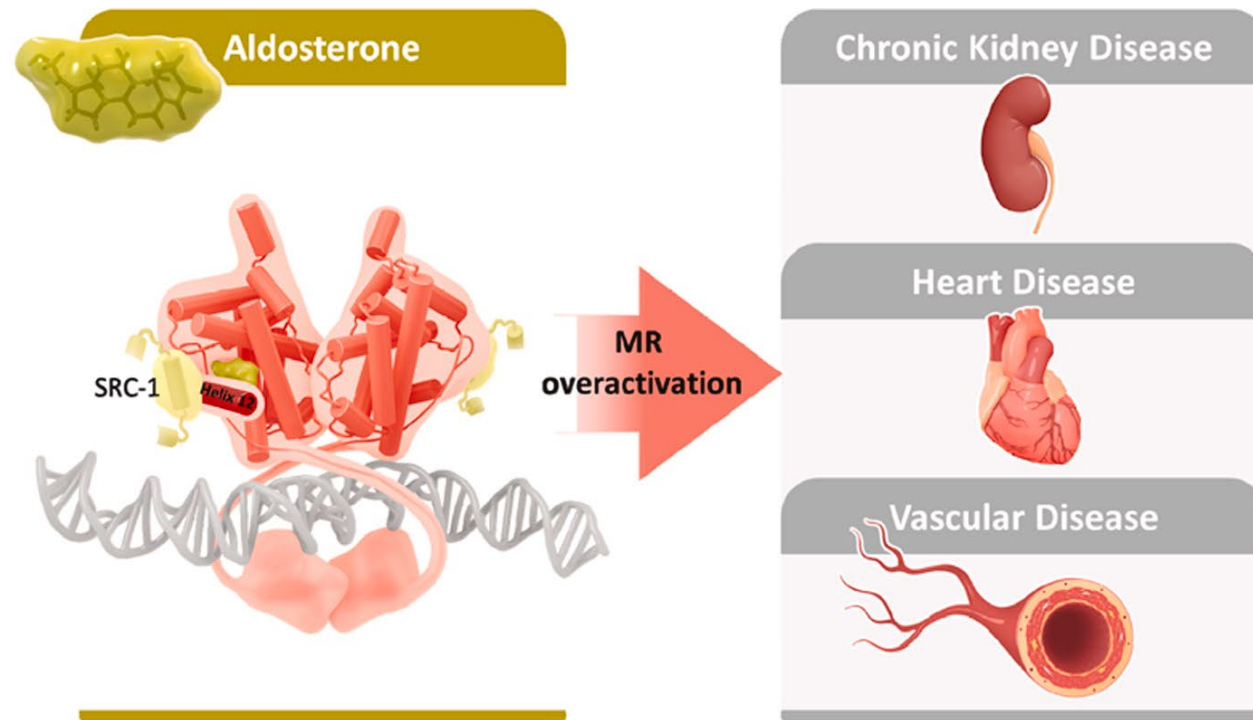
- 1 "vecchie" molecole, vecchie e **nuove** evidenze – SGLT2-i
- 2 "vecchie" molecole, **nuove** evidenze – GLP1-RA
- 3 **nuove** molecole - Finerenone



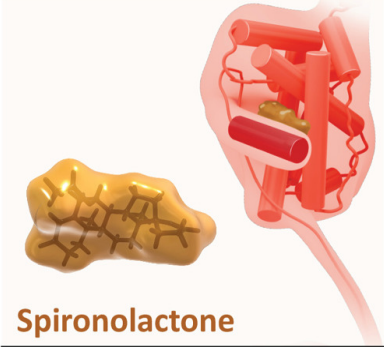
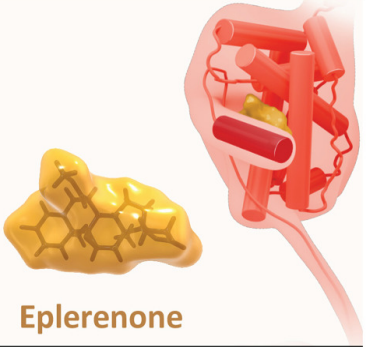
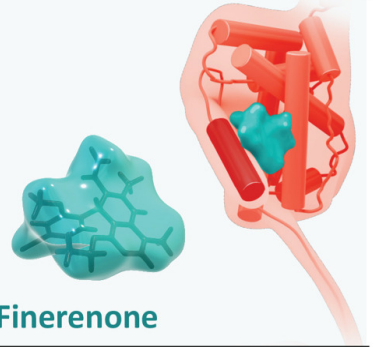
CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE



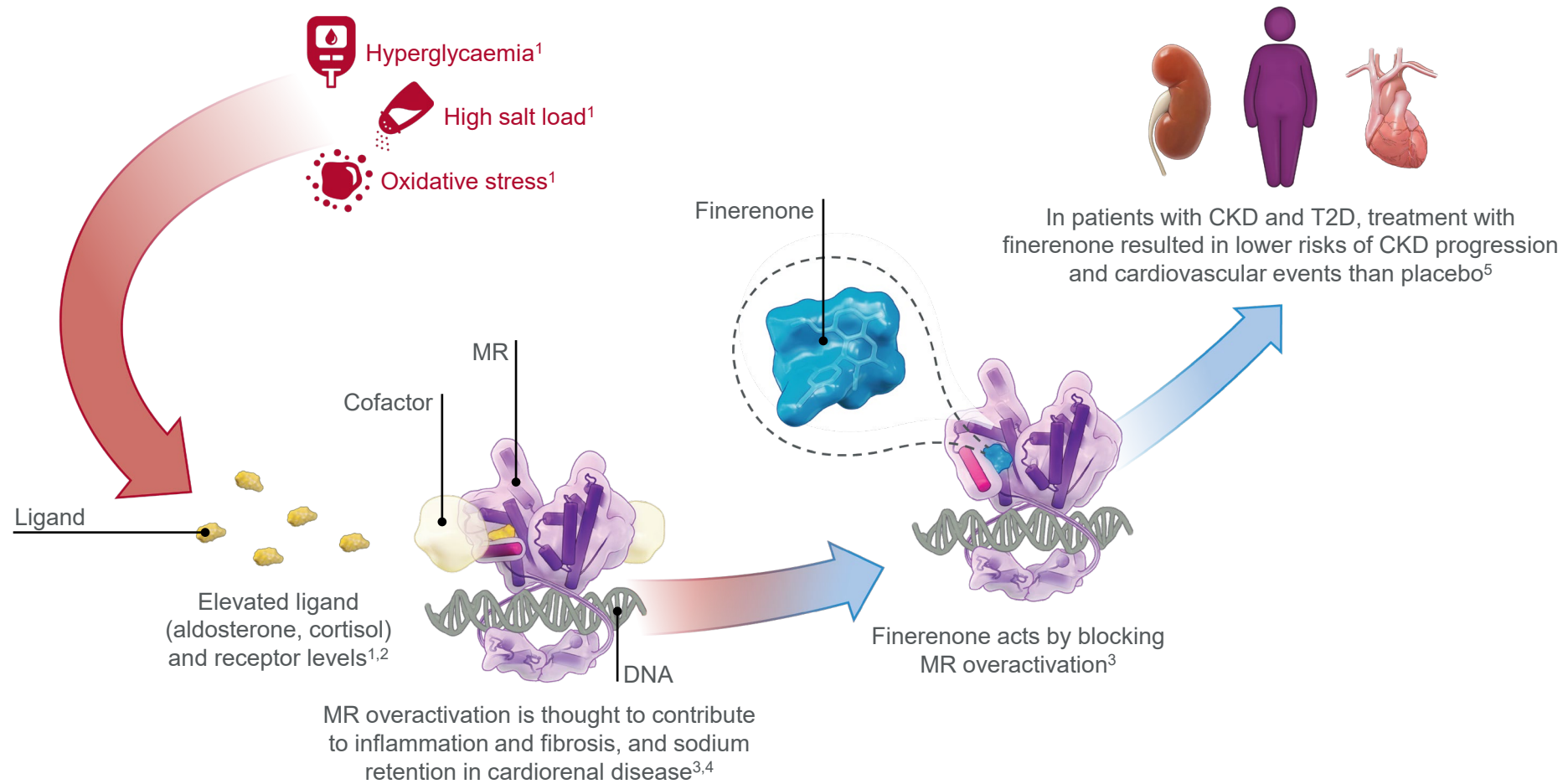
Non-steroidal mineralocorticoid receptor antagonist in cardiorenal disease



Pharmacokinetic and pharmacodynamic characteristics of MR antagonists

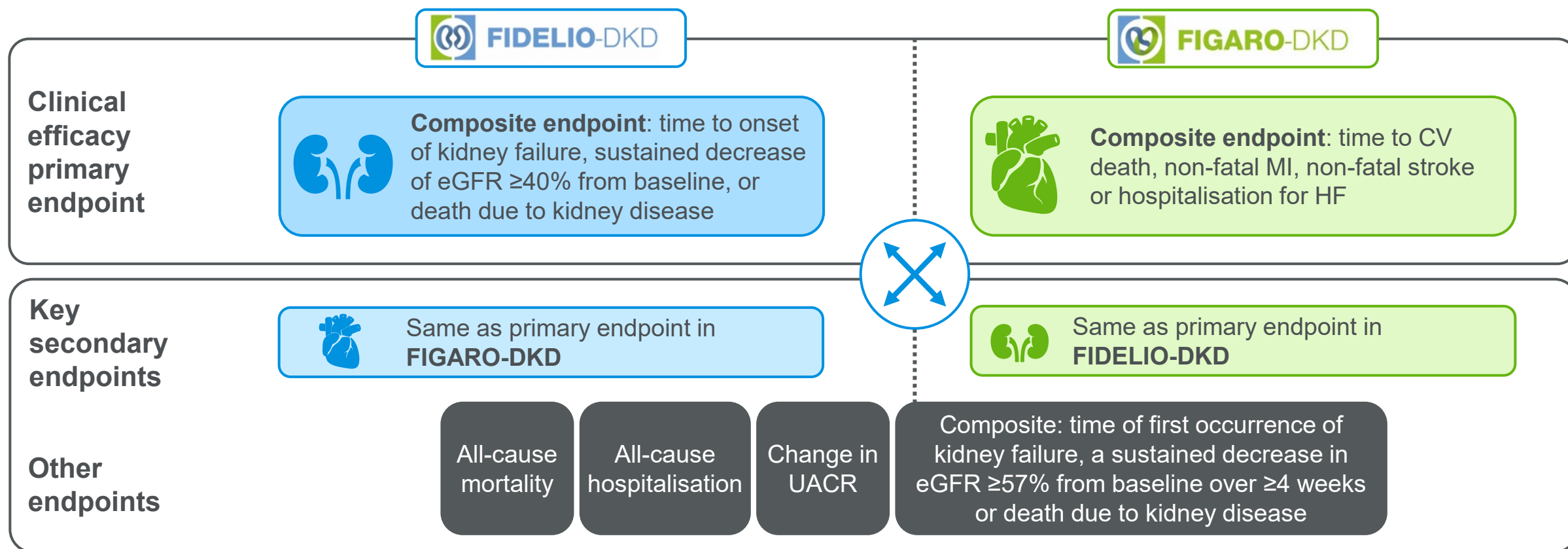
	Steroidal MRAs		Finerenone
			
	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	–
Sexual side effects	++	(+)	–
Half-life	>20 h**	4–6 h**	2–3 h*
Active metabolites	++	–	–
Effect on BP	+++	++	+

Non-steroidal mineralocorticoid receptor antagonist in cardiorenal disease

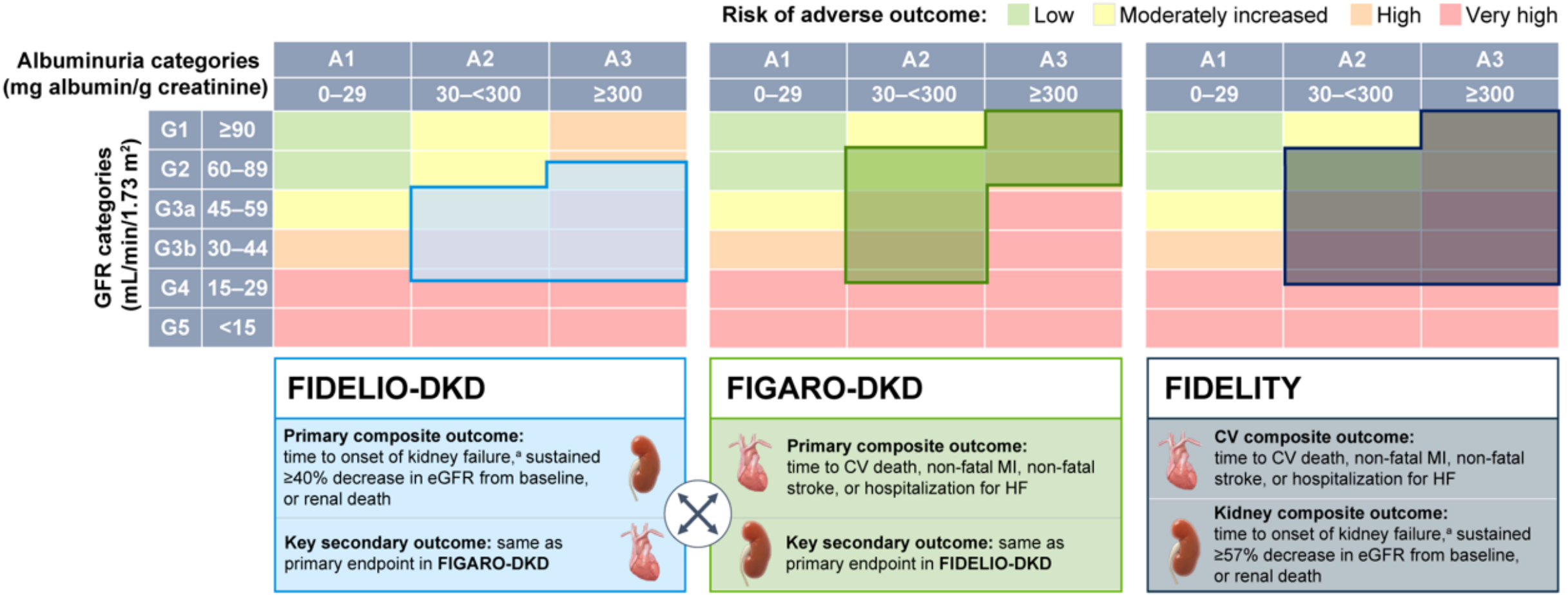


CKD TRIALS WITH FINERENONE

Two phase III trials with complementary kidney and CV endpoints



CKD TRIALS WITH FINERENONE



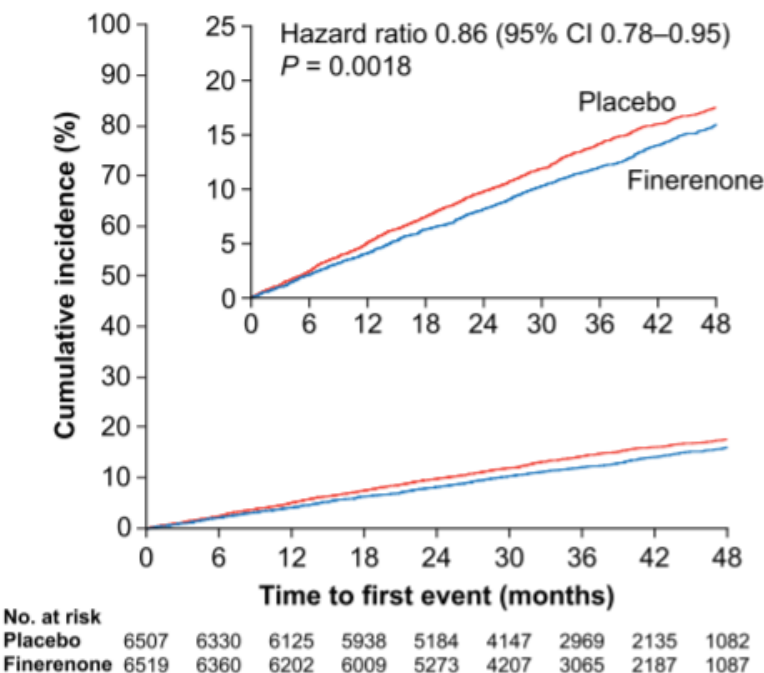
>13,000 patients across the disease continuum
of CKD and T2D (CKD stage 1–4) with
moderate-to-severely elevated albuminuria
(UACR ≥30 mg/g)

CKD TRIALS WITH FINERENONE



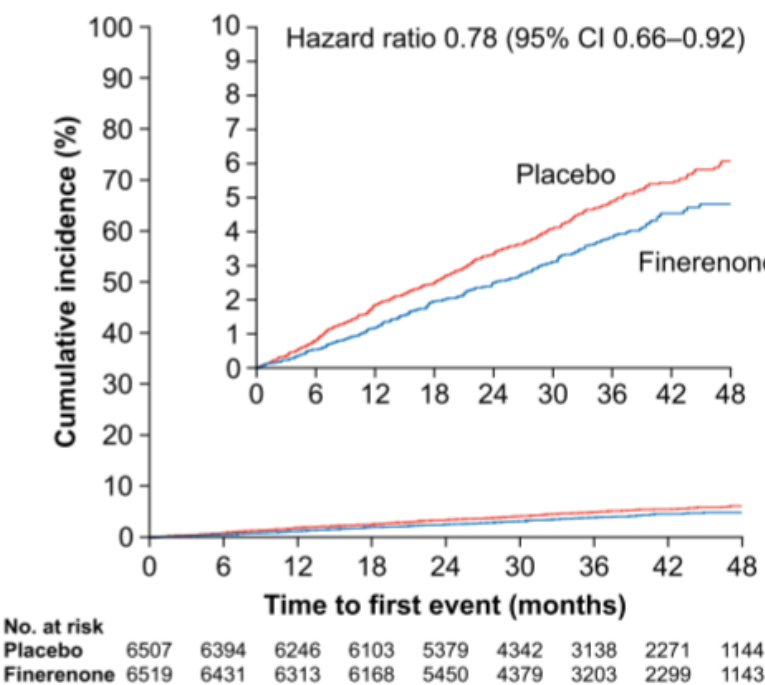
Cardiovascular and kidney outcomes with **Finerenone**
in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

A Composite cardiovascular outcome

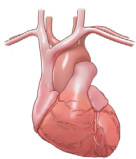


14%
RRR

D Hospitalization for heart failure



22%
RRR



PRIMARY CV ENDPOINT

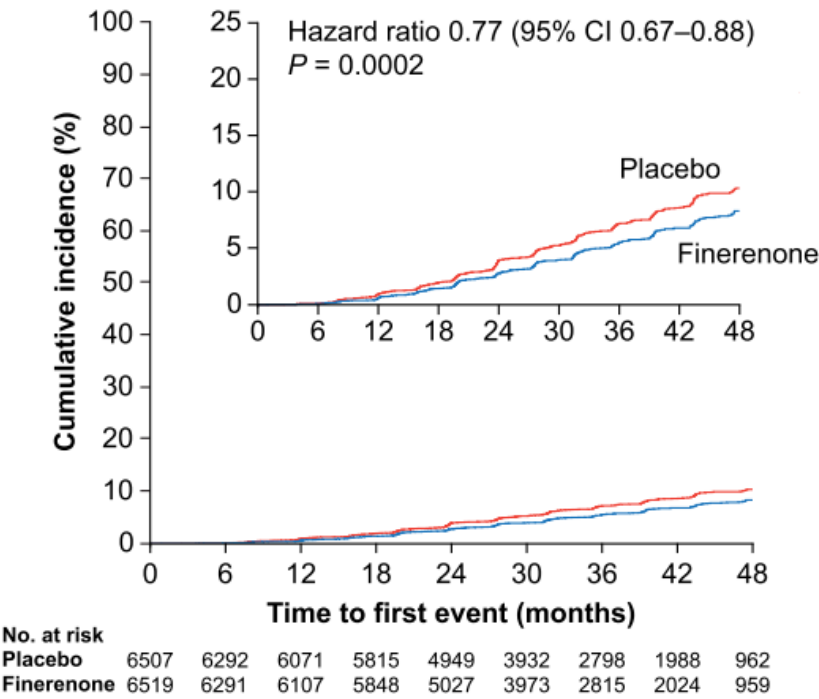
Time to CV death,
non-fatal MI, non-fatal stroke or
hospitalisation for HF

CKD TRIALS WITH FINERENONE

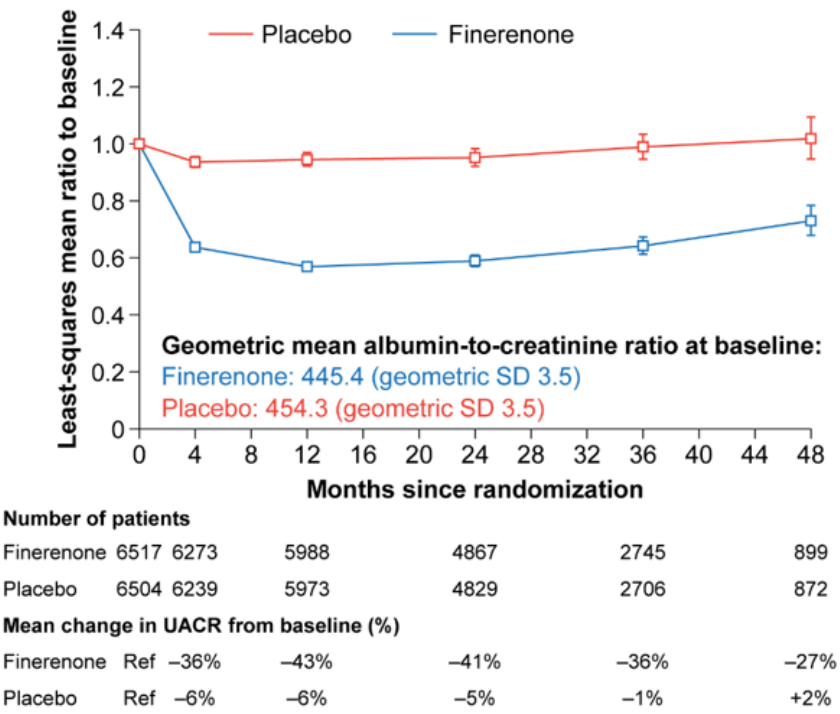


Cardiovascular and kidney outcomes with **Finerenone**
in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

B eGFR ≥57% composite kidney outcome



A Urine albumin-to-creatinine ratio



KEY SECONDARY KIDNEY ENDPOINT

Time to kidney failure,
sustained $\geq 57\%$ decrease in
from baseline or renal death

23%
RRR

UACR

ratio of LS mean change from baseline
0.68 (95% CI 0.66–0.70)

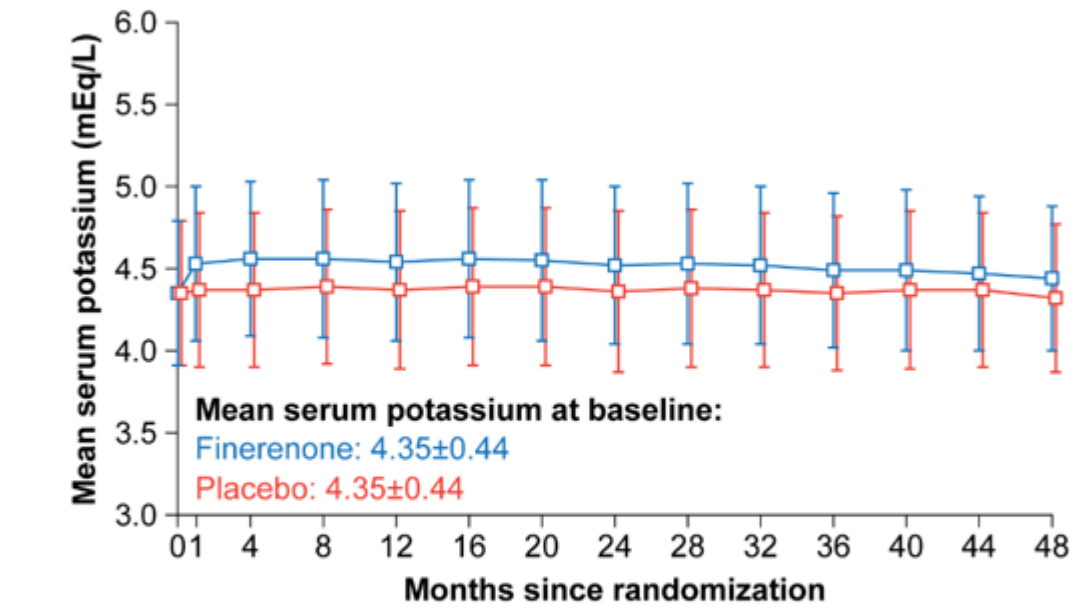
32%
RRR

CKD TRIALS WITH FINERENONE

Cardiovascular and kidney outcomes with **Finerenone**
in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis



B Mean serum potassium



Number of patients						
Finerenone	6510	6234	5990	4916	2781	912
Placebo	6487	6229	5965	4878	2759	887
Mean change in serum potassium from baseline (mEq/L)						
Finerenone	Ref	0.21	0.20	0.18	0.17	0.13
Placebo	Ref	0.02	0.02	0.02	0.03	0.03

Prescrizione – aspetti pratici



Indicazione ammessa alla rimborsabilità: *Kosovo* è indicato per il trattamento dei pazienti adulti con malattia renale (stadi 3 e 4 con albuminuria) associata a diabete mellito di tipo 2, in trattamento con ACEi/ARB alla massima dose tollerata e che presentino una delle seguenti condizioni:

- 1) controindicazione o intolleranza agli inibitori SGLT2;**
- 2) comprovata evidenza di persistente albuminuria e/o rapido declino funzionale renale (perdita di eGFR ≥ 3 mL/min/anno), nonostante il trattamento con inibitori SGLT2**

1. REGISTRARE I DATI DEL PAZIENTE

- a. Centro prescrittore
- b. Nome e cognome medico prescrittore
- c. Dati anagrafici del paziente
- d. ASL di residenza
- e. Nome e cognome dell'MMG
- f. Codice ASL MMG

2. REGISTRARE I DATI CLINICI PER L'ELEGGIBILITÀ DEL PAZIENTE

- a. eGFR $\geq 25 < 60$ mL/min/1,73 m²
- b. UACR ≥ 30 mg/g
- c. Potassio sierico ≤ 5 mmol/L
- d. T2D
- e. Trattamento stabile ACEi/ARBs da almeno 4 settimane
- f. SGLT2i sì vs no – specificare perché
- g. Trattamento concomitante con potenti inibitori CYP3A4 o MRA o diuretici risparmiatori di potassio
- h. Paziente affetto da Morbo di Addison
- i. Compromissione Funzionalità epatica

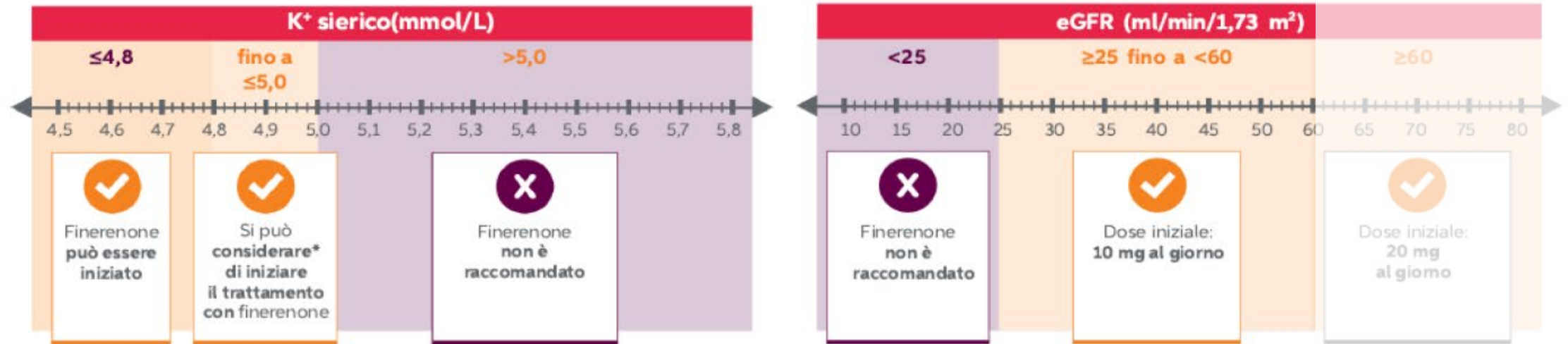
3. PIANO TERAPEUTICO

- a. Durata (6 mesi per la prima prescrizione)
- b. Posologia (10 mg)

Inizio del trattamento

È necessario misurare preventivamente il potassio sierico e la velocità di filtrazione glomerulare stimata (eGFR) per poter stabilire se il trattamento con finerenone possa essere iniziato e determinarne la dose iniziale.

Nei pazienti con eGFR <25 mL/min/1,73 m² il trattamento con finerenone non deve essere iniziato a causa di dati clinici limitati (vedere paragrafi 4,4 e 5,2).



Proseguimento del trattamento

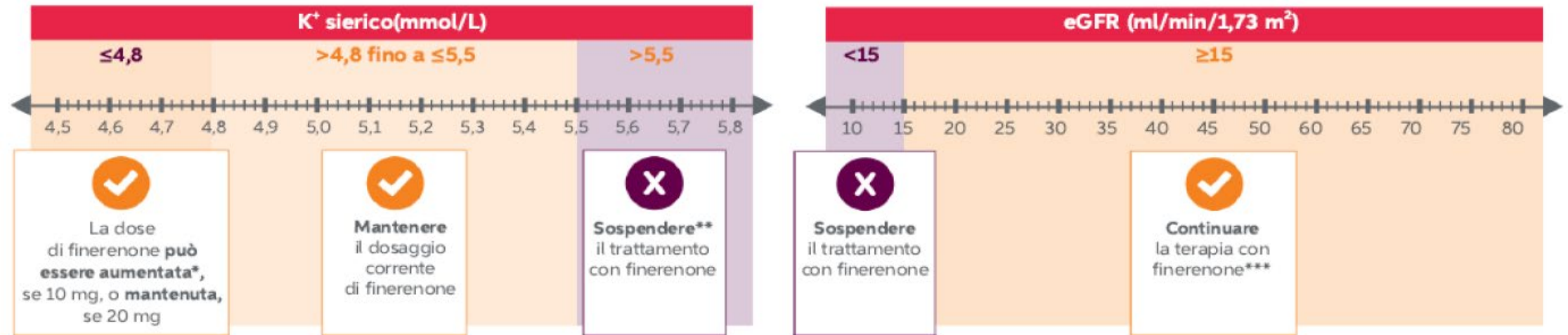
Potassio sierico ed eGFR devono essere nuovamente misurati **4 settimane dopo l'inizio o il riavvio del trattamento con finerenone o dopo un incremento della dose.**

Successivamente, il potassio sierico deve essere nuovamente misurato regolarmente e al bisogno in base alle caratteristiche del paziente e ai livelli di potassio sierico.

Nei pazienti con $\text{eGFR} \geq 15 \text{ mL/min/1,73 m}^2$, il trattamento con finerenone può essere proseguito con aggiustamenti della dose in base ai livelli di potassio sierico.

L'eGFR deve essere misurato **4 settimane dopo l'inizio del trattamento** per stabilire se la dose iniziale possa essere aumentata alla dose giornaliera raccomandata di 20 mg.

A causa di dati clinici limitati, il trattamento con finerenone deve essere interrotto nei pazienti con malattia renale giunta allo stadio terminale ($\text{eGFR} < 15 \text{ mL/min/1,73 m}^2$) (vedere paragrafo 4,4).



3

nuove molecole - Finerenone

- Finerenone riduce il rischio di progressione della malattia renale cronica e nei pazienti con diabete tipo 2 e albuminuria residua

TAKE HOME MESSAGE

Non steroidal MRA

RAS blockers
SGLT2-i



Haemodynamic

(Elevated BP and/or
intraglomerular pressure)



Metabolic

(poor glycaemic
control)

RAS blockers
SGLT2-i
GLP-1 RA

Non steroidal MRA



Inflammation and fibrosis

Glucose-lowering agents
SGLT2-i
GLP-1 RA

Tubulointerstitial
injury and
inflammation

Glomerulosclerosis

Mesangial
expansion

Glomerular
hypertrophy

Kidney fibrosis

CKD
PROGRESSION

TAKE HOME MESSAGE

The *four pillars* of cardiorenal protection
in people with CKD and T2D

