SGLT-2 e finerenone: come proteggere il rene

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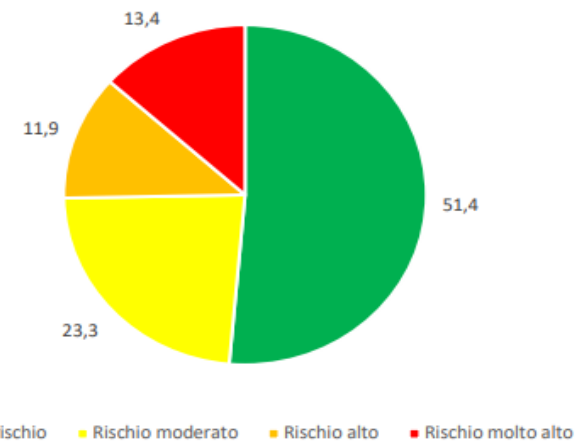
ASLNA 3 SUD

Andamento per classi di malattia renale (Classi KDIGO) (%)

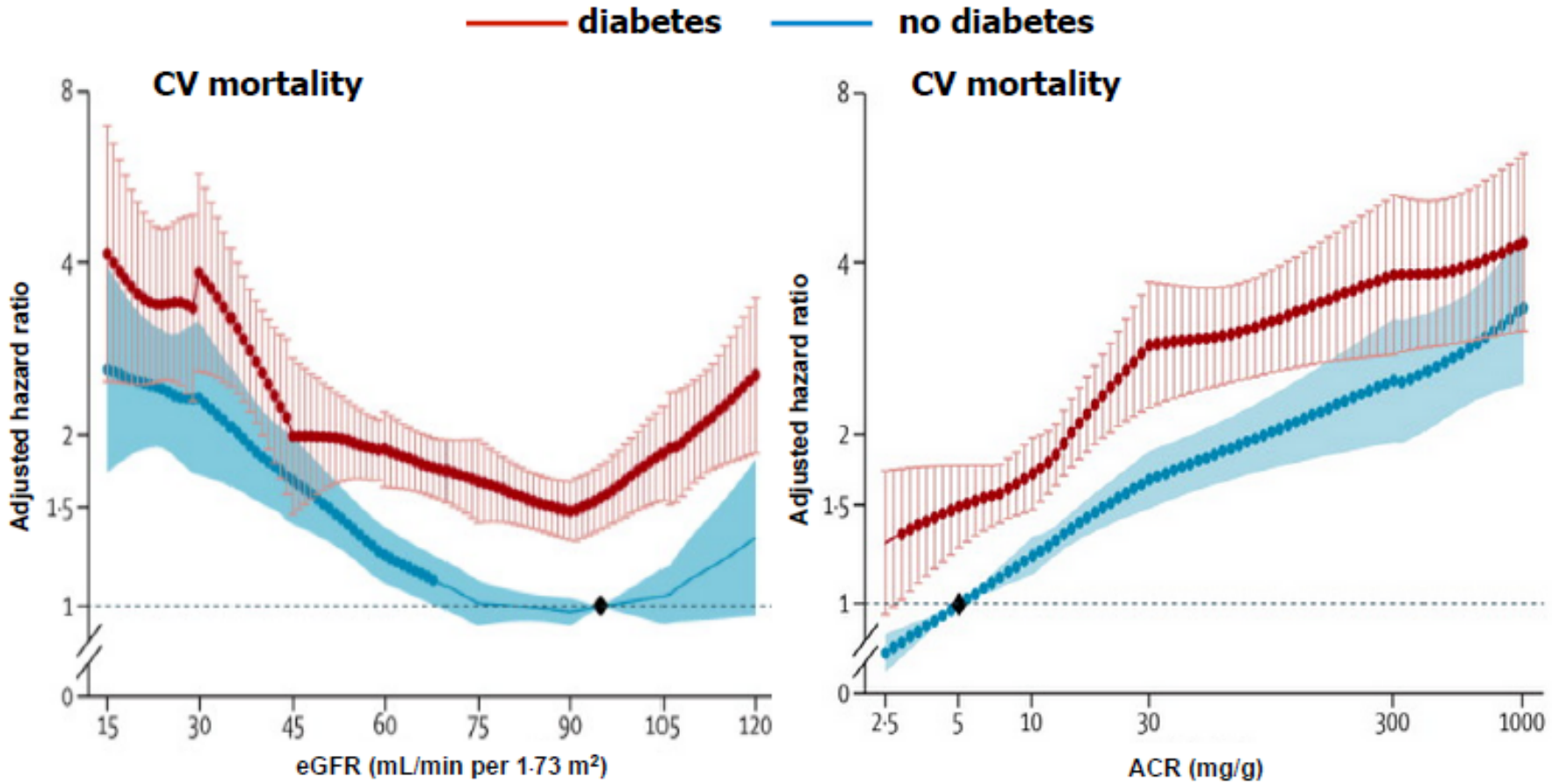
			Categorie di albuminuria persistente		
			A1	A2	A3
			Normale o lievemente aumentata	Moderatamente aumentata	Severamente aumentata
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
Categorie di eGFR (ml/min*1,73 m²)	Normale o elevato	≥90	19,6	5,1	1,0
	Lievemente diminuito	60-89	31,8	9,2	2,1
	Da lievemente a moderatamente diminuito	45-59	9,0	3,8	1,3
	Da moderatamente a severamente diminuito	30-44	5,0	2,9	1,4
	Severamente diminuito	15-29	1,3	1,1	1,0
	Insufficienza renale	<15	2,6	1,1	0,7

Annali AMD 2023

Andamento per classi di malattia renale (Classi KDIGO) (%)



Hazard ratio for CV mortality in the combined general and high-risk populations according to eGFR (CKD-EPI) and albuminuria in pts with and without diabetes (1.024.977 pts)

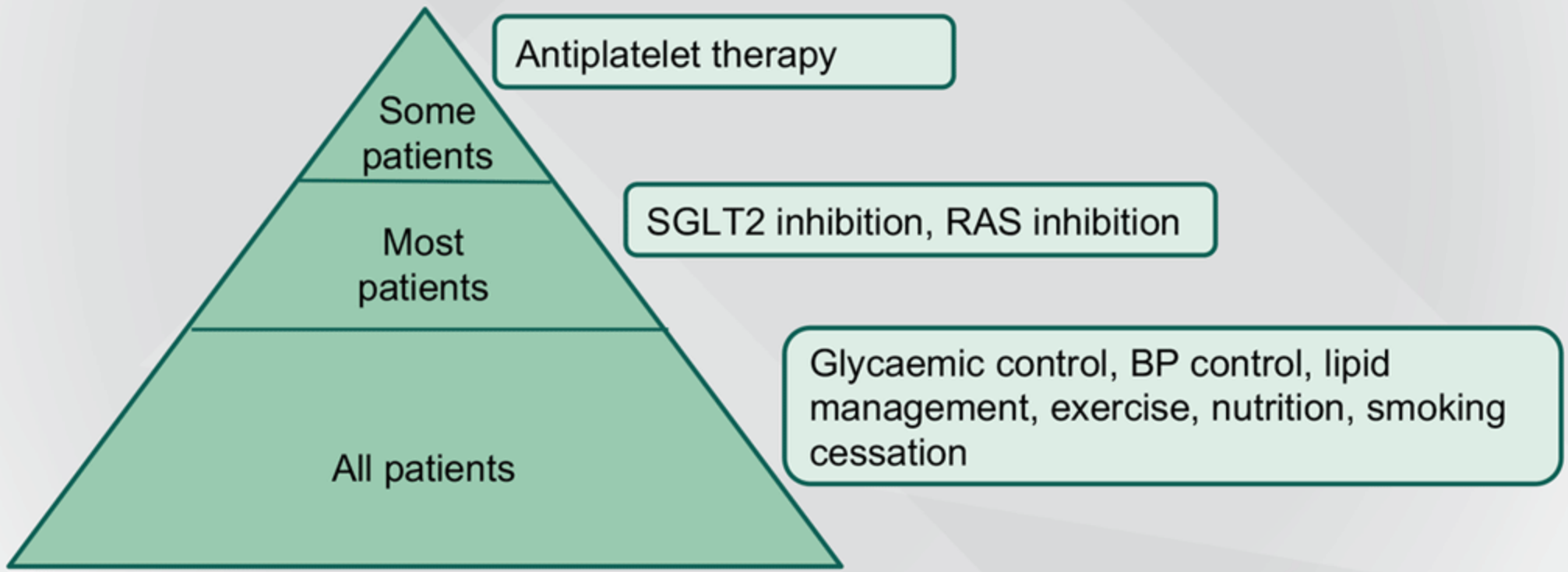


HR, according to eGFR and ACR, adjusted for each other, age, ethnic origin, race, CV disease, smoking, cholesterol, BMI.

from Fox CS et al for the CKD Prognosis Consortium, Lancet, 2012

KDIGO: Updated Comprehensive Care Strategy

For patients with T2DM and CKD:



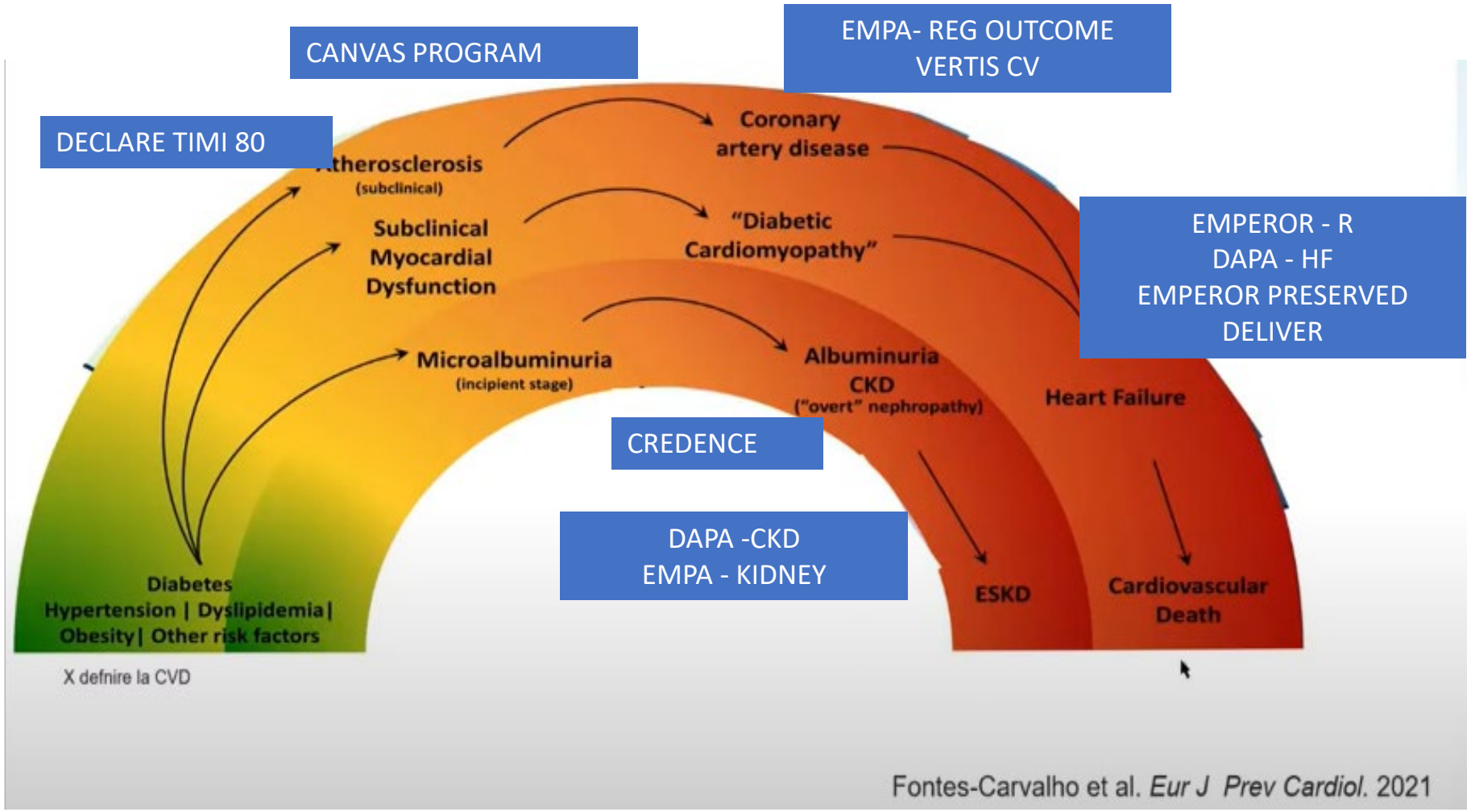
SGLT2 inib. CVOT trials: benefici renali

	Outcome compositi correlati renale	HR (IC 95%)
EMPA-REG OUTCOME[1] empagliflozin	**Raddoppio della creatinina, inizio della terapia renale sostitutiva o morte per cause renali**	**0,54 (0,40-0,75)** p < 0,001
Programma CANVAS[2] canagliflozin	Riduzione sostenuta del 40% di eGFR, terapia renale sostitutiva (dialisi o trapianto) o morte per cause renali	**0,60** (0,47 - 0,77) p < 0,001
DECLARE TIMI 58[3] dapagliflozin	Riduzione sostenuta ≥40% di eGFR a <60 ml/min/1,73 m^2 e/o nefropatia terminale e/o morte per cause renali o CV	**0,76** (0,67 - 0,87) p = ND
VERTIS CV[4] ertugliflozin	Morte per cause renali, dialisi/trapianto o raddoppio della creatinina vs basale	**0,81** (0,63 - 1,04) p = ND

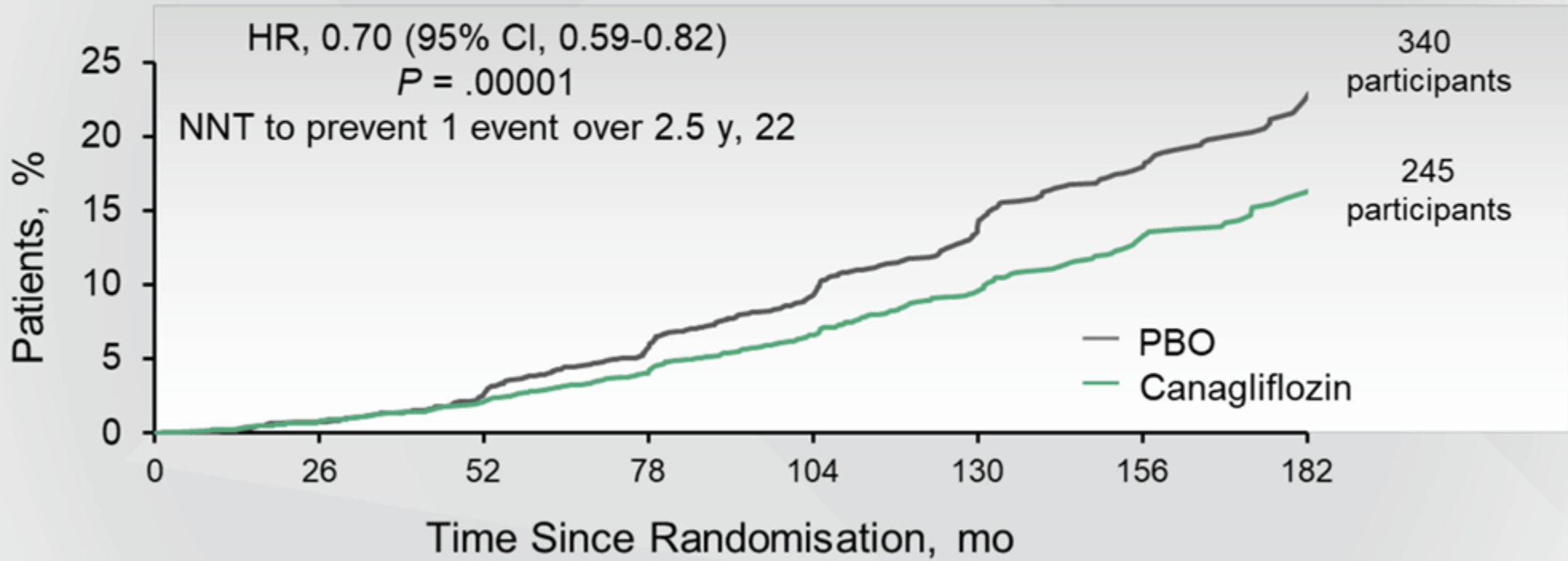
HR = hazard ratio; eGFR = velocita di filtrazione glomerulare stimata; CV = cardiovascolare. ND = non disponibile

1. Wanner C, Inzucchi SE, Lachin JM et al. EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016; 375 (4): 323-334.
2. Neal B et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377: 644-57.
3. Wiviott SD et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380: 347-57. 4. Cannon CP et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med 2020; 383: 1425-35.

PROTECTIVE EFFECTS OF SGLT-2 INHIBITORS ACROSS THE CARDIORENAL CONTINUUM



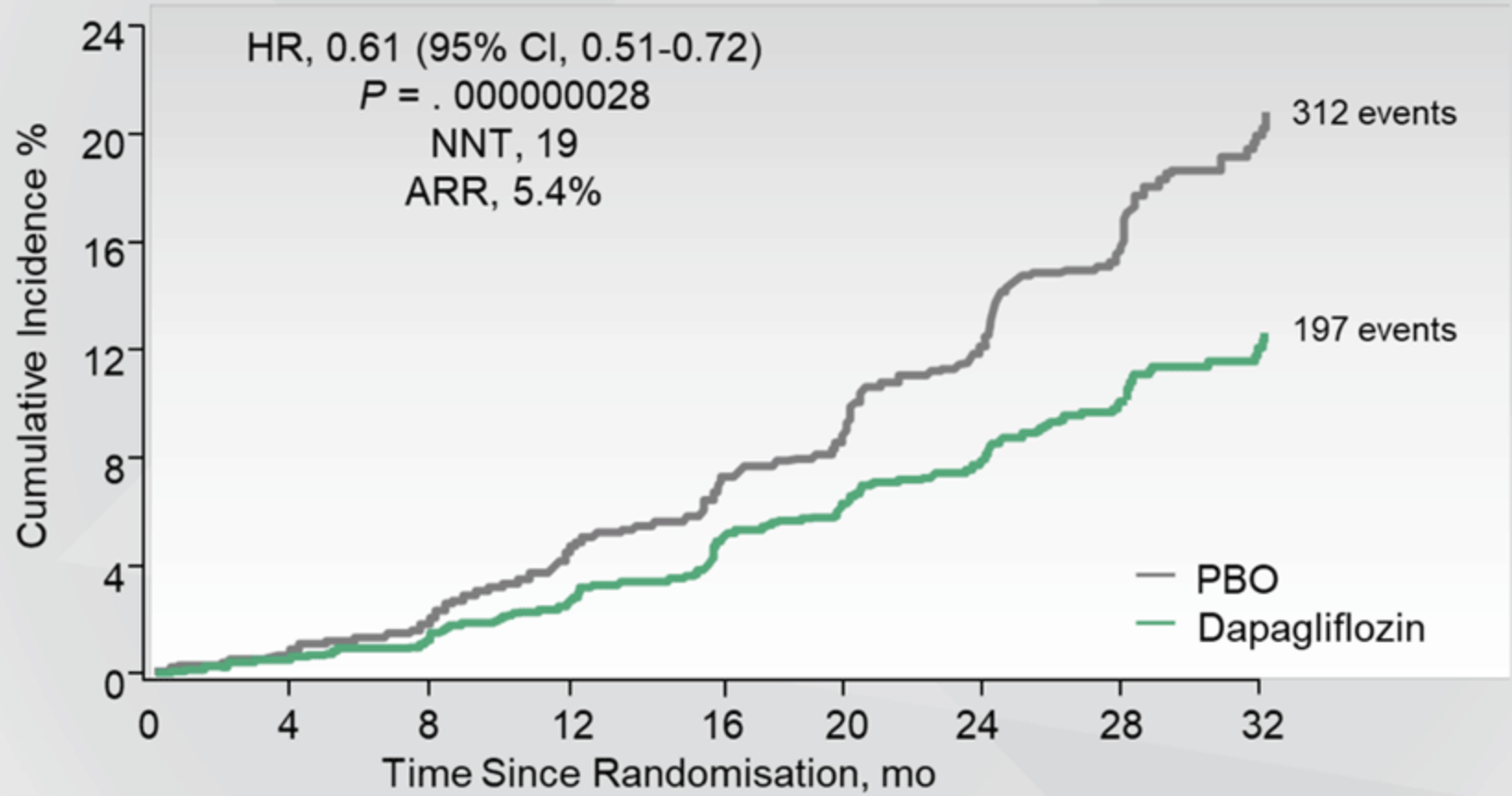
CREDENCE: ESRD, Doubling of sCr, Renal or CV Death



Patients (N = 4,401) with T2DM, eGFR 30-60 mL/min/1.73 m^2, and ACR >300 mg/g on RAS inhibitor.

https://www.nejm.org/doi/full/10.1056/NEJMoa1811744

DAPA-CKD: Sustained ≥50% eGFR Decline, ESRD, Renal or CV Death



Patients (N = 4,304) with T2DM (68%) or non-T2DM (32%), eGFR ≥25 and ≤75 mL/min.1.73 m², and ACR ≥200 mg/g on RAS inhibitor.

N Engl J Med 2020;383:1436-1446

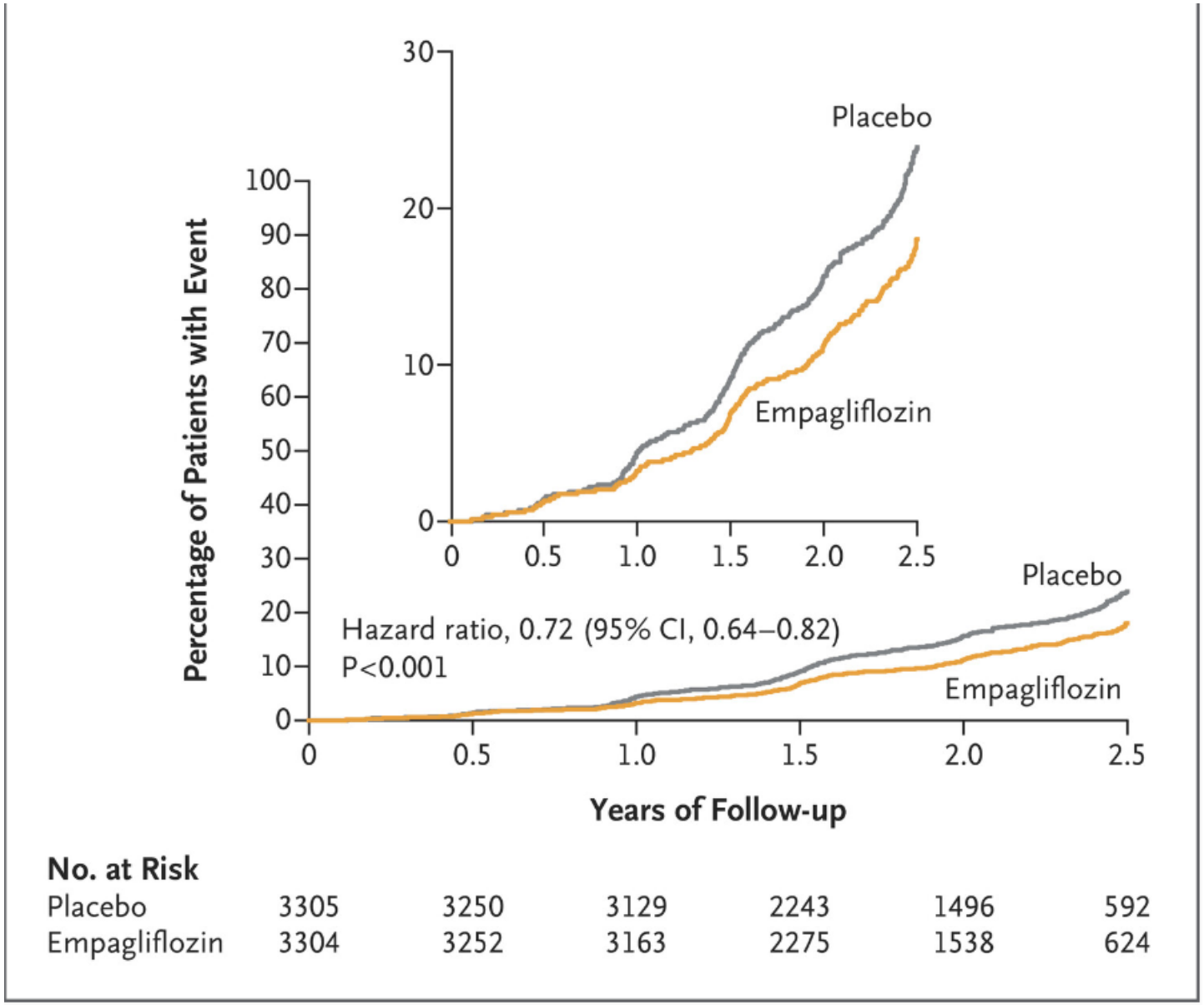
Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group

Published November 4, 2022
N Engl J Med 2023;388:117-127

First occurrence of progression of kidney disease or death from cardiovascular causes. Progression of kidney disease was defined as end-stage kidney disease (ESKD; the initiation of maintenance dialysis or receipt of a kidney transplant), a sustained decrease in the eGFR to less than 10 ml per minute per 1.73 m^2, a sustained decrease from baseline in the eGFR of at least 40%, or death from renal causes

Paz con e senza diabete
eGFR 20-45 ml/min/1.73 m2
o eGFR 45-90 ml/min/1.73 m2 e UACR ≥200mg/g



DARWIN-RENAL

L'obiettivo è stato quello **di confrontare gli esiti renali dei pazienti che avevano iniziato dapagliflozin rispetto ad altri farmaci ipoglicemizzanti**

Disegno

Studio retrospettivo multicentrico comparativo sull'efficacia, **sponsorizzato dalla Società Italiana di Diabetologia, e con il supporto non condizionante di AZ**, in **50 centri** specializzati nella cura del diabete in Italia.

Raccolta dati

La raccolta dei dati dei centri è avvenuta da febbraio 2021 a maggio 2022 utilizzando un software di estrazione automatizzata dei dati. Sono stati **estratti i dati sui pazienti che hanno iniziato nuovi farmaci ipoglicemizzanti (GLM) dal 01/01/2015 al 30/09/2020.**

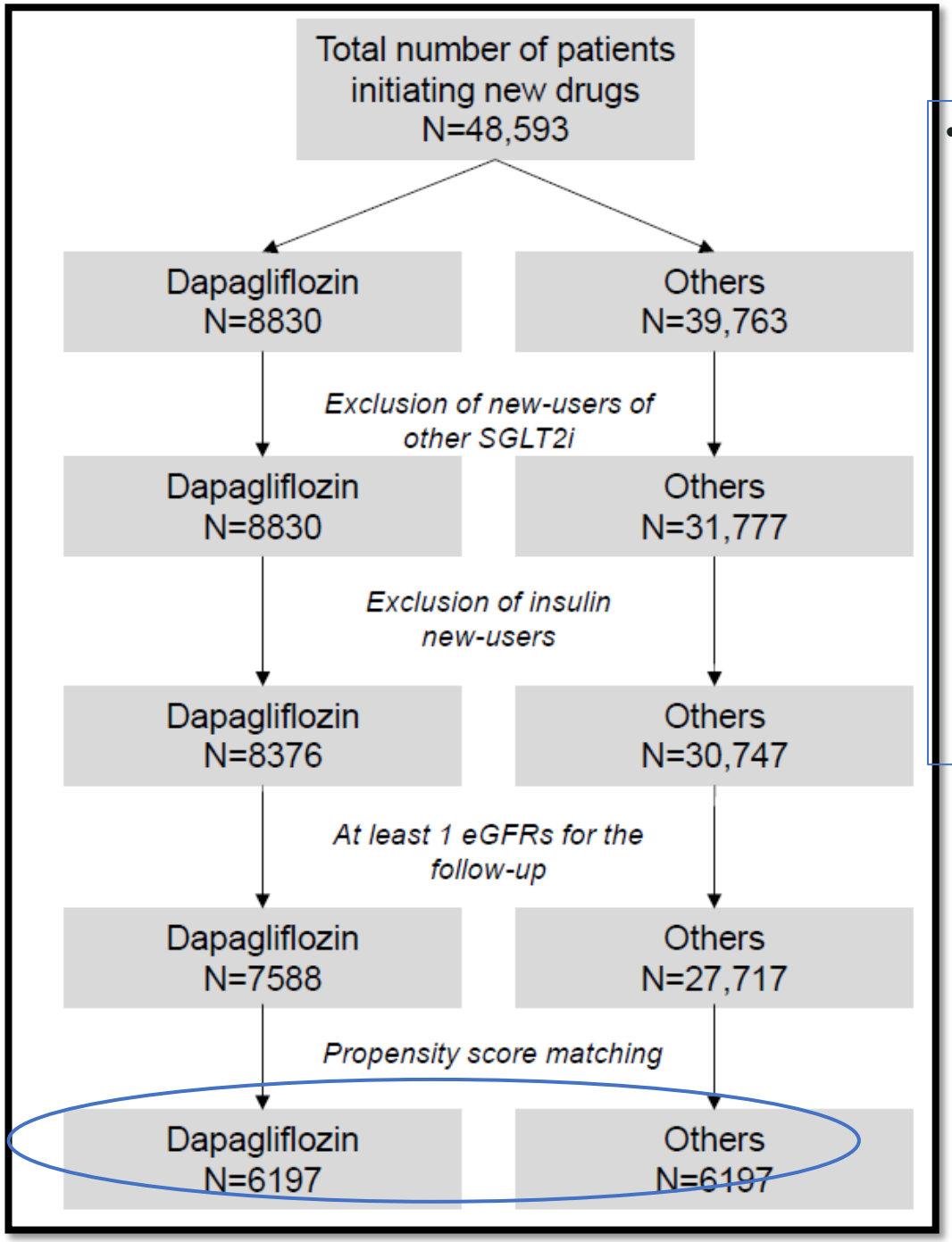
Popolazione

2 gruppi di pazienti:

- **pazienti che avevano iniziato il trattamento con dapagliflozin**.
- Il gruppo di **controllo era costituito da pazienti che avevano iniziato qualsiasi altro ipoglicemizzante, esclusa l'insulina e altri SGLT2i**. Tali farmaci di confronto includevano: 40% inibitori della DPP-4, 22% agonisti del recettore del GLP-1 (GLP-1RA), 16% sulfanilurea/glinidi (raggruppati insieme), 8% pioglitazone, 5.8% metformina e 4% acarbosio.

Fadini et al. The Lancet Regional Health –Europe 2024

Criteri di inclusione



- I pazienti potevano essere inclusi se avevano:
  - un'età compresa tra 18 e 80 anni
  - avevano diabete di tipo 2 da almeno un anno
  - avevano iniziato per la prima volta (come evidente dal database) il GLM di interesse
  - avevano informazioni disponibili sugli esiti renali (almeno un valore eGFR successivo alla data indice)

- I criteri di esclusione erano:
  - altre forme di diabete
  - età <18 o >80
  - terapia precedente con un altro SGLT2i nei 12 mesi precedenti alla data indice
  - CKD stadio V o dialisi

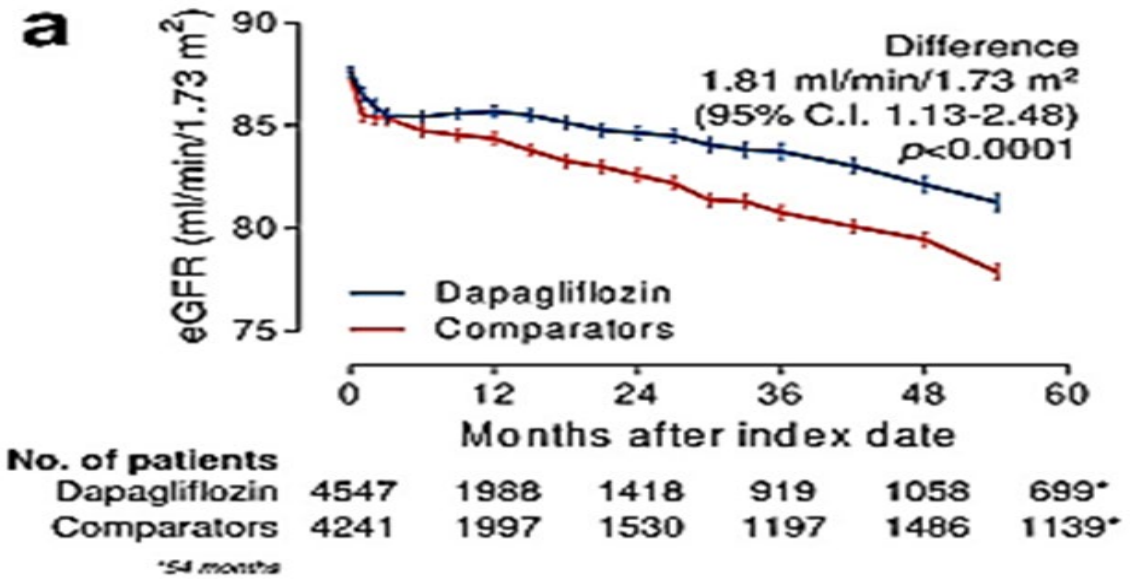
- In accordo a questi criteri di inclusione, sono stati identificati 7588 pazienti nel gruppo dapagliflozin e 27.717 pazienti nel gruppo di controllo.

- A causa del grado previsto di missing data e per garantire una valutazione omogenea dei due gruppi, è stato applicato il propensity score matching (PSM). Dopo il PSM, nell'analisi finale sono stati inclusi in media **6197 pazienti per gruppo.**

Endpoint Primario: Variazione in eGFR nel tempo

Tempo di osservazione dal basale a 54 mesi

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



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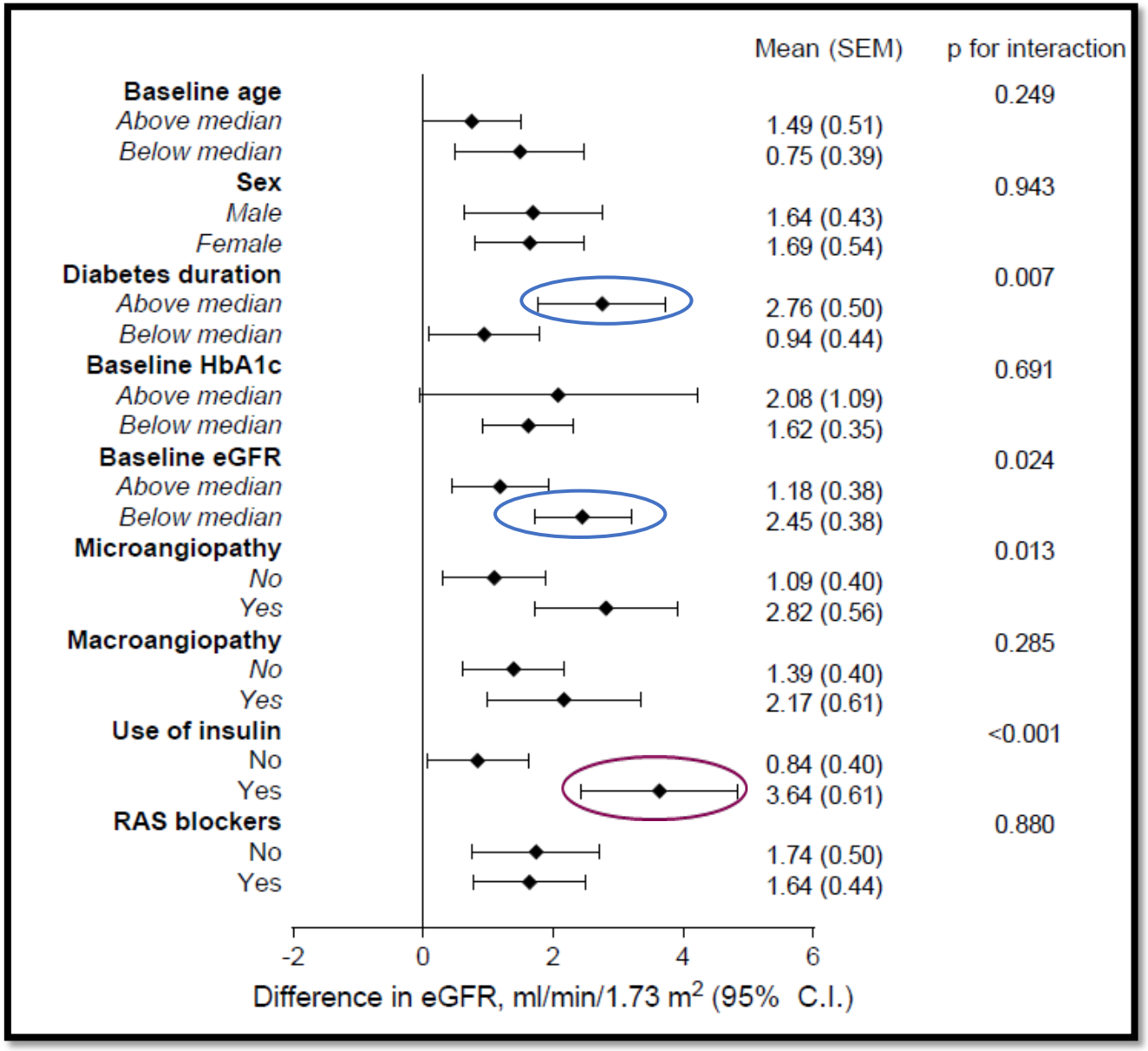
Analisi di sottogruppi



- Per l'endpoint primario, è stata eseguita **un'analisi di sottogruppi**, con i pazienti stratificati in base a caratteristiche basali pre-specificate. È stata calcolata la differenza media nella variazione dell'eGFR in ciascuno strato, insieme al rispettivo valore p per l'interazione.

Tutte le stime puntuali erano significativamente a favore di dapagliflozin e la maggior parte degli effetti nei vari strati erano statisticamente significativi.

- È stata riscontrato una **minore riduzione del declino dell'eGFR nel tempo con dapagliflozin** rispetto ai comparatori nei pazienti con:
  - durata del diabete più lunga
  - eGFR basale inferiore alla media
  - e che utilizzavano insulina

Fadini et al. The Lancet Regional Health –Europe 2024

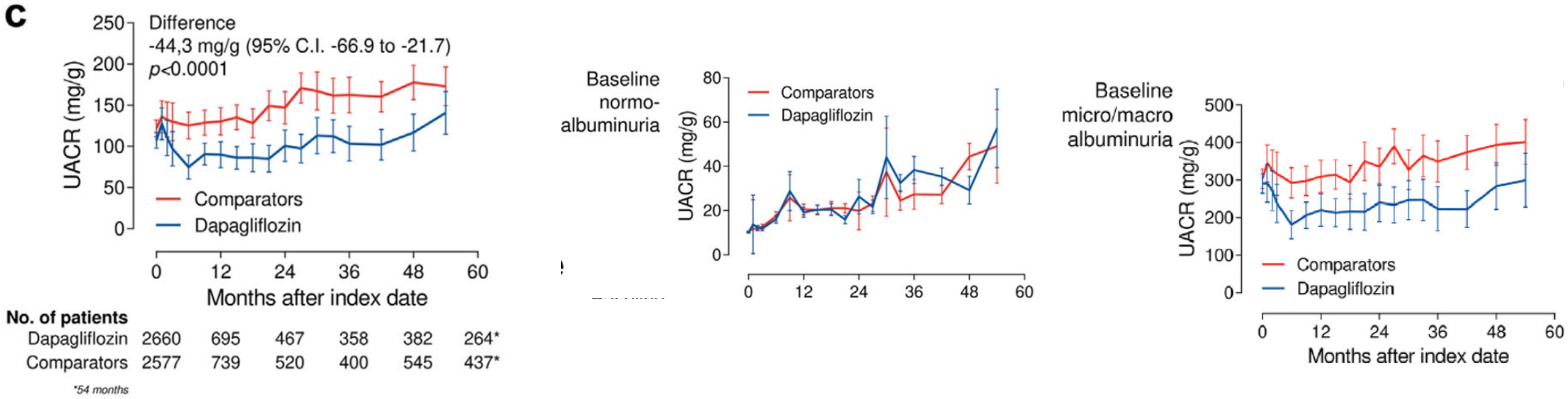
Endpoint Secondario: Variazione dell'albuminuria nel tempo

Tempo di osservazione dal basale a 54 mesi

L'UACR è diminuito significativamente nei nuovi utilizzatori di dapagliflozin entro i primi 6 mesi ed è rimasto più basso che nei nuovi users dei comparatori per l'intera osservazione. **La media aggiustata tra le differenze di gruppo era -44,3 mg/g** (IC 95% da -66,9 a -21,7; p < 0,0001)

Nei pazienti con **normoalbuminuria al basale**, la variazione dell'UACR nel tempo **non ha mostrato differenze tra i due i due gruppi**

L'effetto di dapagliflozin nell'intera popolazione è stato osservato in pazienti con micro- o macro-albuminuria basale. Tra i pazienti con **micro o macro albuminuria, il tasso di miglioramento della classe di albuminuria era significativamente maggiore con dapagliflozin** che con i comparatori



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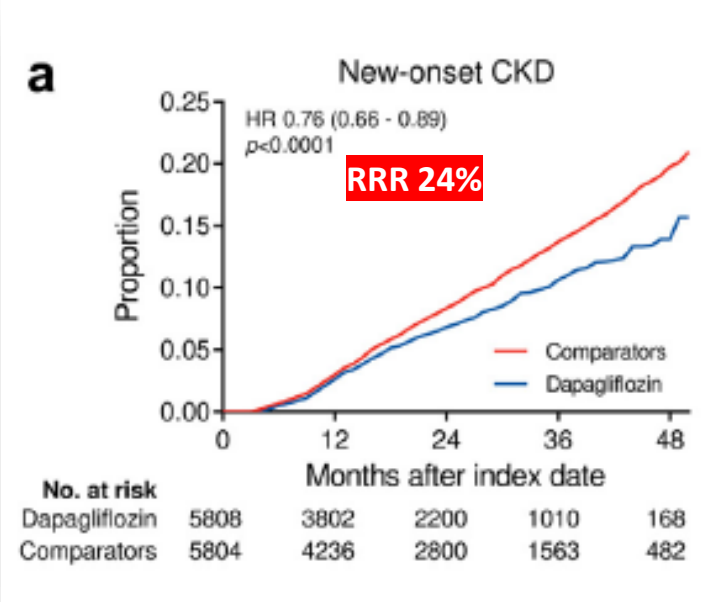
Endpoint Secondari Selezionati

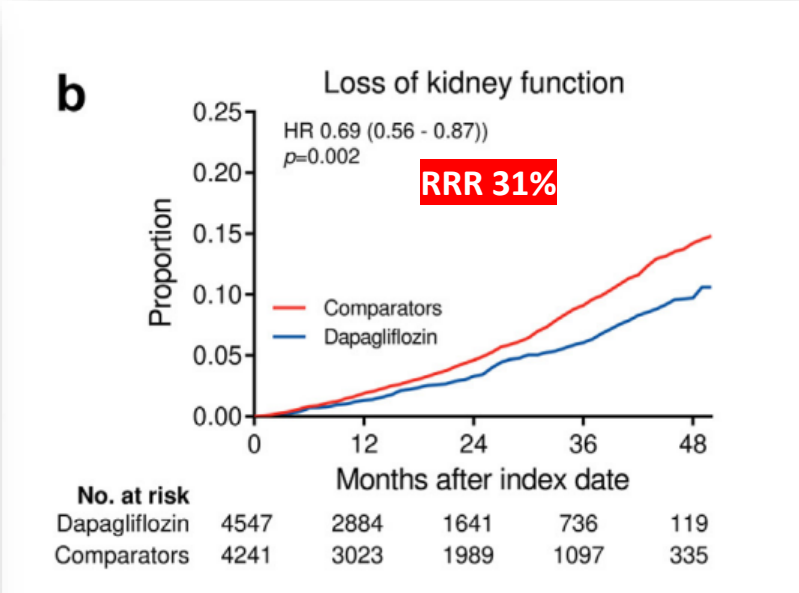
Nuova insorgenza di CKD



- 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)

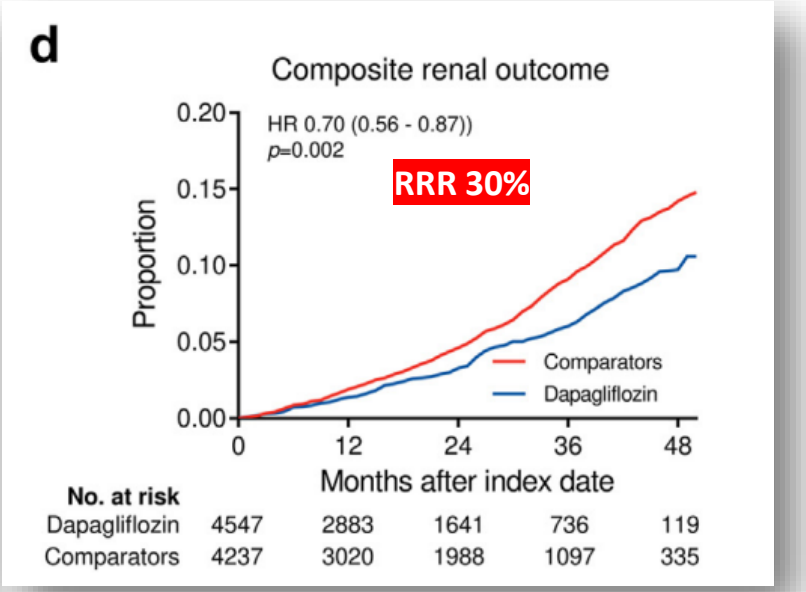
Perdita di funzionalità renale



- I nuovi utilizzatori di dapagliflozin avevano:

➢ **minore perdita della funzionalità renale**, definita come >40% di >57% di riduzione dell'eGFR, con rispettiva HR di 0,69 (I.C. 95% 0,56 - 0,87; p=0,002) e 0,65 (I.C. 95% 0,44 - 0,96; p=0,035)

Outcome renale composito



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

Potential Effects By Which SGLT-2 Inhibition Improves Renal Outcomes

SGLT-2 INHIBITION

Reduce Glomerular Pressure[1]
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity[3]
↓SNS activity[4]

Inflammation/Fibrosis Reductions[1,2]
↓Inflammatory markers
↓Fibrotic markers

Decreased Renal Workload and Hypoxia[1,2]
↓Solute transport
↓Oxygen demand
↑ Hematopoiesis

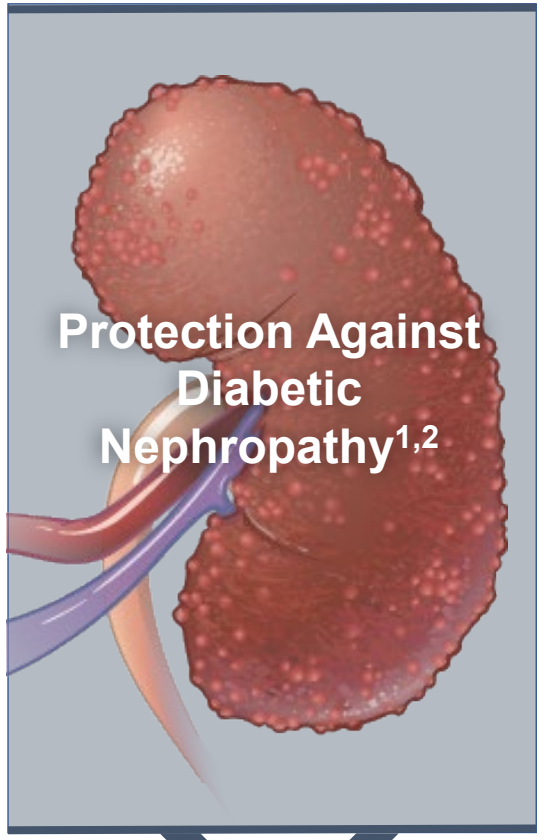
CLINICAL EFFECTS

Stabilization of eGFR[2]

↓Blood Pressure[1]

↓Tubular/Glomerular Injury[1,2]
↓Albuminuria

↓Renal Ischemic Injury[1]
↑Hb/hematocrit[2]



Preserved Renal Function[2]

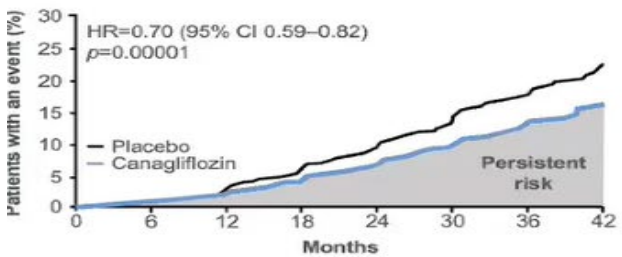
eGFR=estimated glomerular filtration rate; Hb=hemoglobin; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system.

1. Heerspink HJL et al. *Kidney Int*. 2018;94(1):26-39. 2. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 3. Shin SJ et al. *PLoS One*. 2016;11:e0165703. 4. Sano M. *J Cardiol*. 2018;71(5):471-476.

Limitations also exist in our current approaches to the management of CKD and T2D

Persistent risk of CKD progression in patients with T2D despite RASi and SGLT-2i

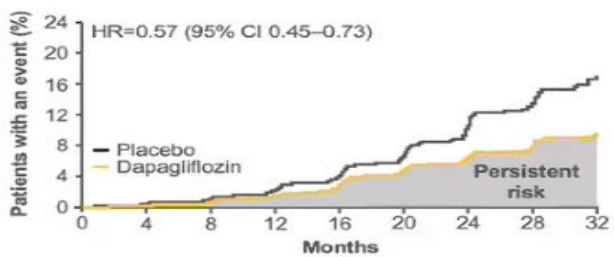
CREDENCE: Canagliflozin vs placebo[2]



Median UACR: 927 mg/g

Primary composite outcome: Kidney failure, doubling of SCr or death from kidney/CV causes

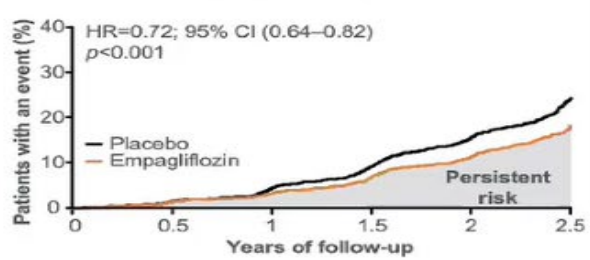
DAPA-CKD: Dapagliflozin vs placebo[3]



Median UACR: 949 mg/g

Secondary composite kidney outcome: Sustained ≥50% eGFR decline, ESKD or kidney-related death

EMPA-KIDNEY: Empagliflozin vs placebo[4]

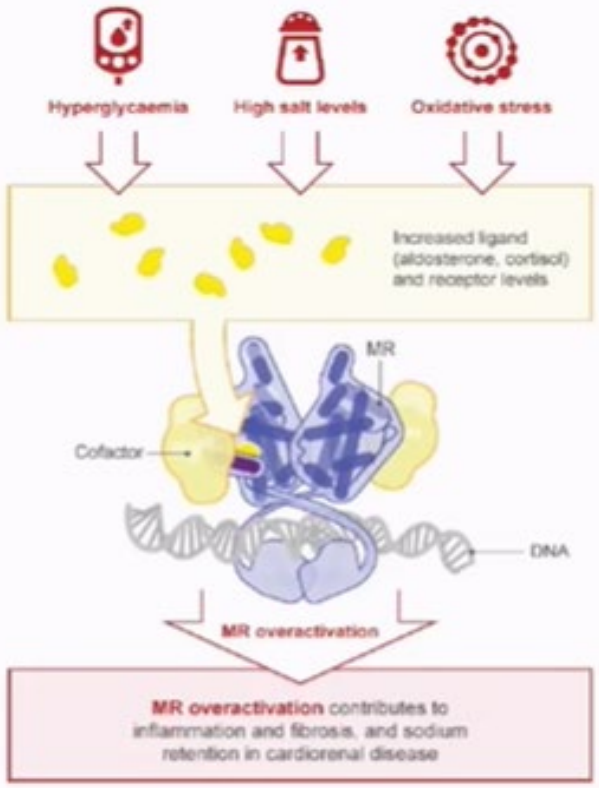


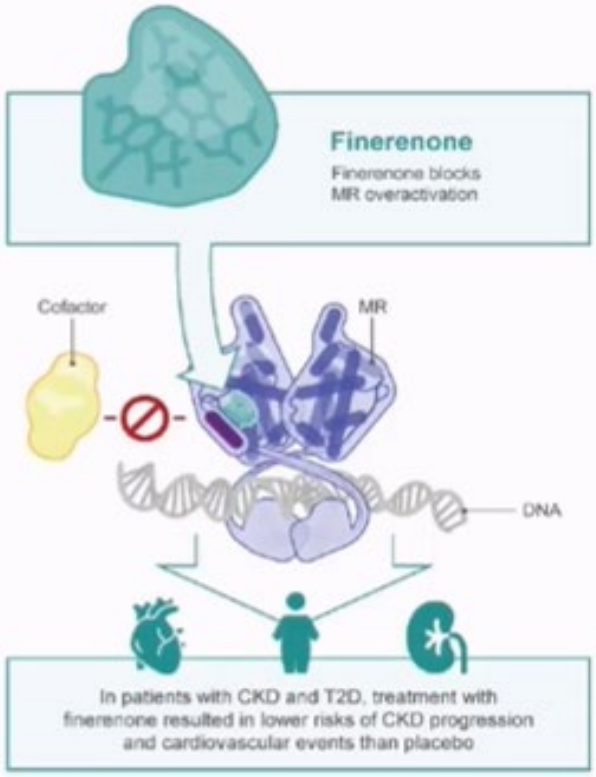
Median UACR: 329 mg/g

Primary heart and kidney outcomes: Sustained ≥40% decline in eGFR; sustained decline in eGFR to <10 ml/min/1.73 m², ESKD or kidney-related/CV death

1. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184; 2. Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306; 3. Wheeler DC, *et al. Lancet Diabetes Endocrinol* 2021;9:22–31; 4. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117–127

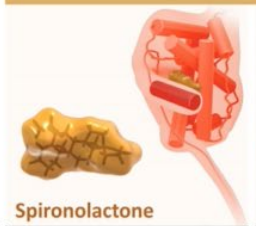
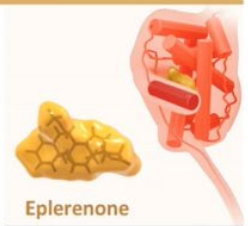
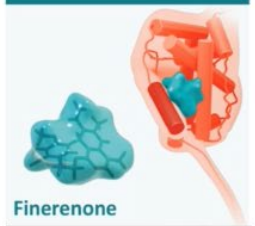
Proposed mode of action and pharmacology of finerenone





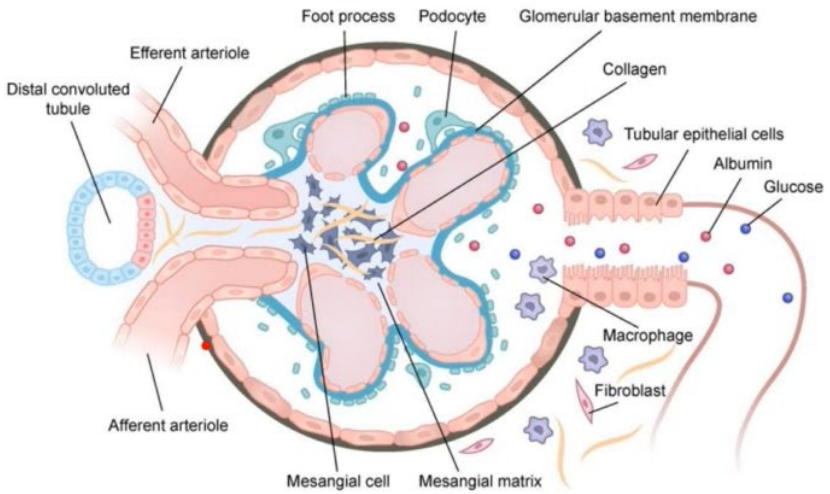
Lerma EV, Exp Rev Clin Pharmacol 2022

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	+++	++	+

Kintscher U et al. Br J Pharmacol. 2022 Jul;179(13):3220-3234.

Renal protection with non-steroidal mineralocorticoid receptor antagonist



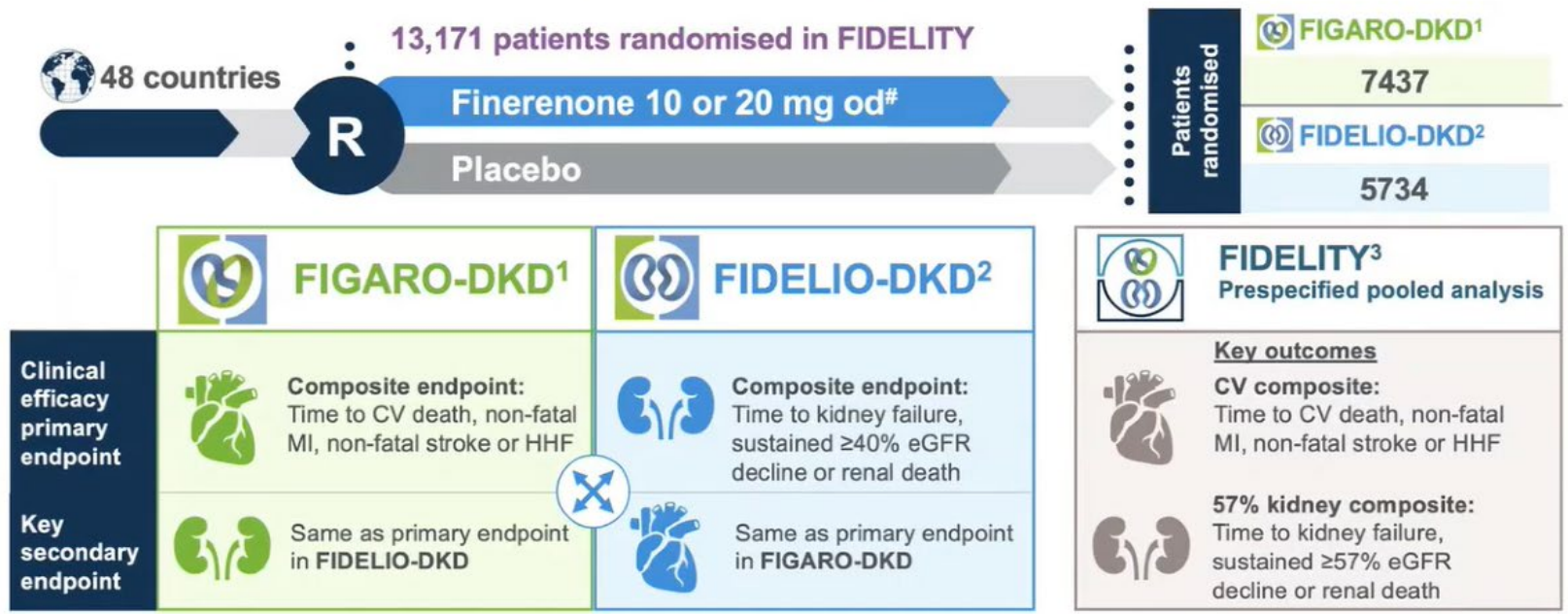
Glomerular hypertrophy and sclerosis
Thickening of GBM
Podocytopathy
Mesangial cell hypertrophy
Mesangial expansion
Albuminuria
Macrophage infiltration
Collagen deposition
Atrophy of tubular epithelial cells

Finerenone

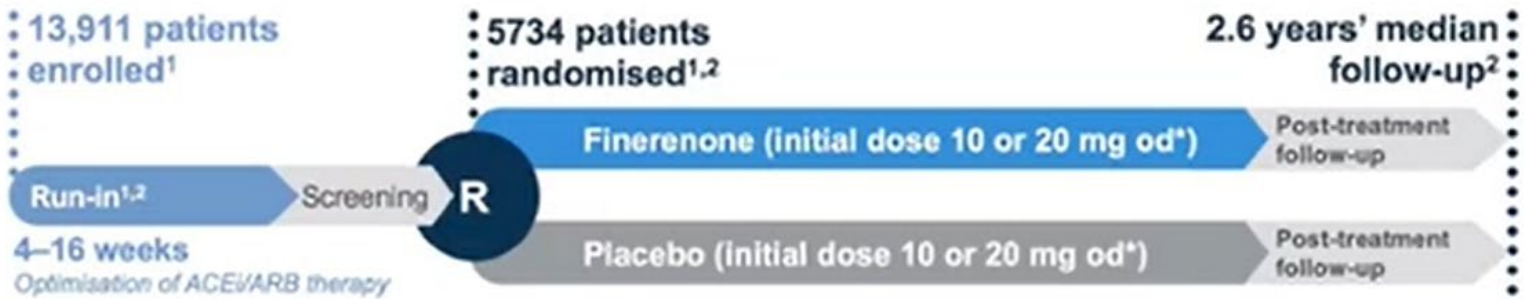
Proinflammatory and profibrotic factors
- ROS
- TNF-α
- IL-1β
- CCL-2 (MCP-1)
- TGF-β
- PAI-1
- CTGF

Kim DL et al. Endocrinol Metab (Seoul). 2023 Feb;38(1):43-55.

FIGARO-DKD and FIDELIO-DKD investigated the effects of finerenone on kidney and CV outcomes in over 13,000 patients with CKD and T2D



FIDELIO-DKD was a double-blind, randomised, placebo-controlled trial



Key endpoints[1,2]

1. Kidney composite

Time to kidney failure,[#] sustained ≥40% decrease in eGFR from baseline,[‡] or renal death

2. CV composite

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

*Patients received an initial dose of study drug of 10 mg od or 20 od based on an eGFR at the screening visit of 25–<60 or ≥60 ml/min/1.73 m², respectively. Up-titration of study drug from 10 to 20 mg od was encourage from month 1 provided serum potassium ≤4.8 mmol/l and was eGFR stable; down-titration of study drug from 20 to 10 mg od was permitted at any time after start of treatment; #ESKD or sustained eGFR <15 ml/min/1.73 m²; ‡confirmed by two eGFR measurements ≥4 weeks apart

1. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 2. Bakris GL, *et al. N Engl J Med* 2020; doi: 10.1056/NEJMoa2025845

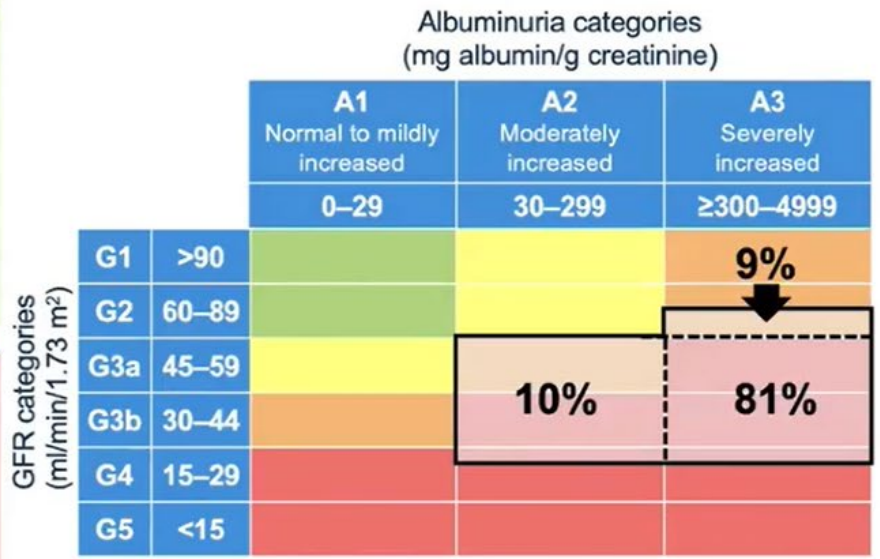
FIDELIO-DKD included a broad patient population across early-to-late disease stages of CKD in T2D

Inclusion criteria[1,2]

- T2D and CKD, defined as **either:**
  - UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m² *# **or**
  - UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m² *
- Treated with either an ACEi or an ARB at maximal tolerated dose
- [K⁺] ≤4.8 mmol/l

Key exclusion criteria[1,2]

- HFrEF with NYHA class II–IV
- Other kidney disease‡
- Uncontrolled arterial hypertension§
- Dialysis for acute kidney failure or kidney transplant

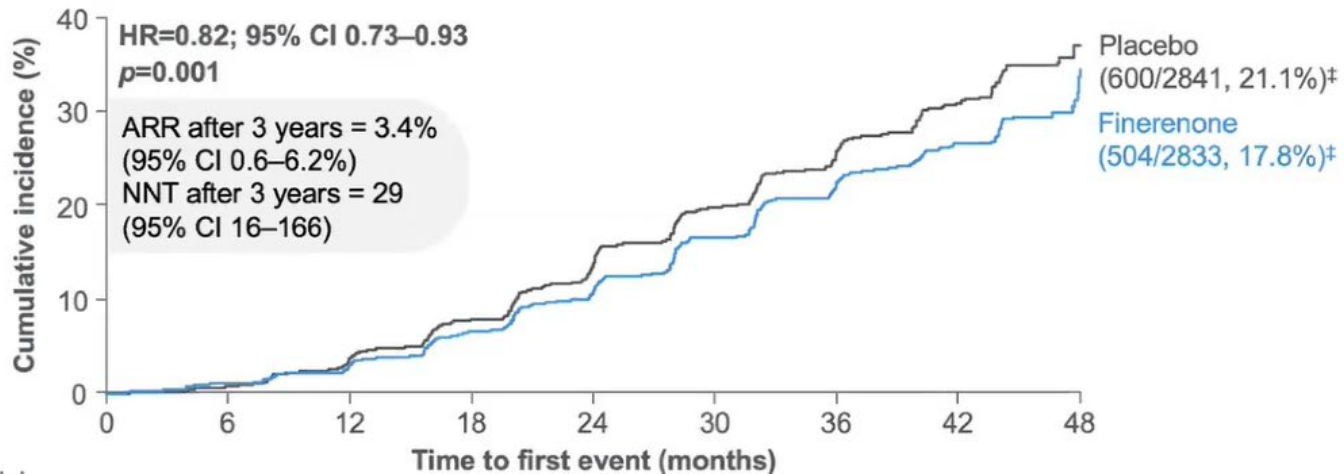


*Two recruitment caps were prespecified and closed per region; (1) the randomisation of patients with moderately increased albuminuria and diabetic retinopathy was restricted to ~10% of all randomised patients; and (2) the randomisation of patients with severely increased albuminuria and eGFR 60–75 ml/min/1.73 m² was restricted to ~10% of all patients randomised with severely increased albuminuria; #And a history of diabetic retinopathy; ‡Known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis; §Mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit

1. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 2. Bakris GL, *et al. N Engl J Med* 2020; doi: 10.1056/NEJMoa2025845

Finerenone significantly reduced the risk of the primary composite kidney endpoint vs placebo

Time to kidney failure*, sustained ≥40% decrease in eGFR from baseline#, or renal death



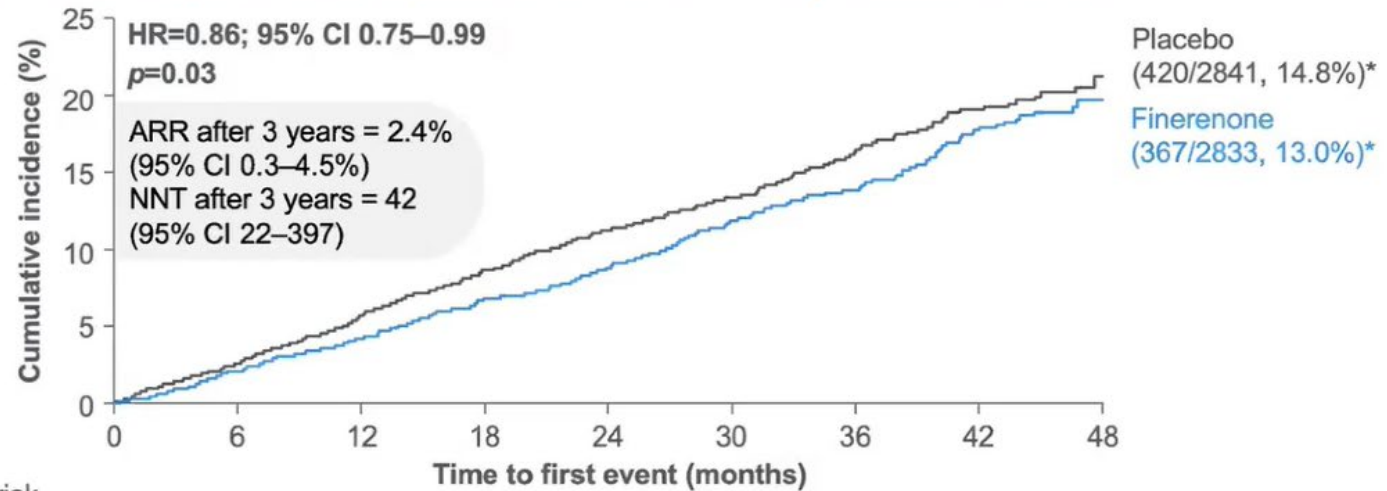
No. at risk					
Finerenone	2833	2607	1808	787	83
Placebo	2841	2586	1758	792	82

*ESKD or an eGFR <15 ml/min/1.73 m²; #sustained over ≥4 weeks; ‡over a median follow-up of 2.6 years

Bakris GL, *et al. N Engl J Med* 2020; doi: 10.1056/NEJMoa2025845

Finerenone significantly reduced the risk of the key secondary CV endpoint vs placebo

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



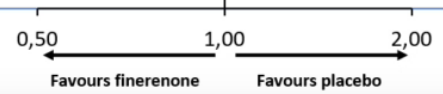
No. at risk					
Finerenone	2833	2688	2017	984	111
Placebo	2841	2653	1969	951	115

*over a median follow-up of 2.6 years

Bakris GL, *et al. N Engl J Med* 2020; doi: 10.1056/NEJMoa2025845

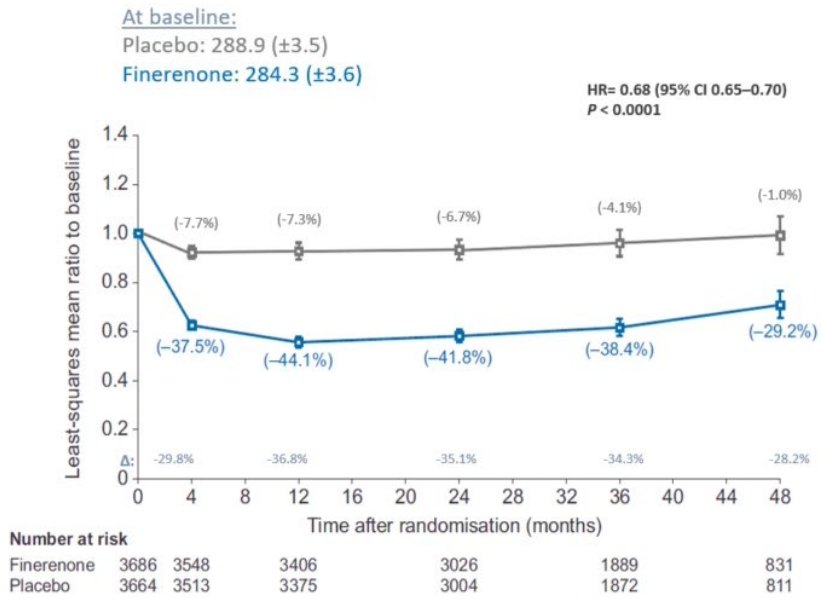
Efficacy outcomes

Endpoint	Finerenone (n=2833)		Placebo (n=2841)		Hazard ratio (95% CI)	*p*-value
	n (%)	n per 100 PY	n (%)	n per 100 PY		
Primary composite kidney endpoint	504 (17.8)	7.59	600 (21.1)	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	2.99	235 (8.3)	3.39	0.87 (0.72–1.05)	–
End-stage kidney disease	119 (4.2)	1.60	139 (4.9)	1.87	0.86 (0.67–1.10)	–
Sustained* decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	2.40	199 (7.0)	2.87	0.82 (0.67–1.01)	–
Sustained* ≥40% decrease in eGFR from baseline	479 (16.9)	7.21	577 (20.3)	8.73	0.81 (0.72–0.92)	–
Renal death	2 (<0.1)	–	2 (<0.1)	–	–	–

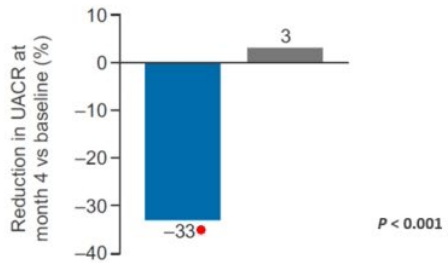


Bakris GL, N Engl J Med 2020

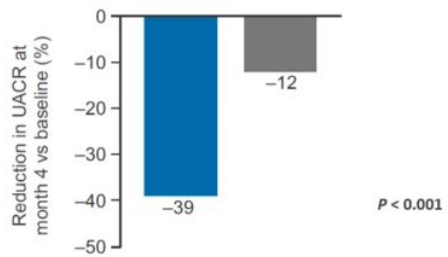
Finerenone and UACR



Change at month 4 for population with UACR 30 - <300 mg/g



Change at month 4 for population with UACR >300 mg/g

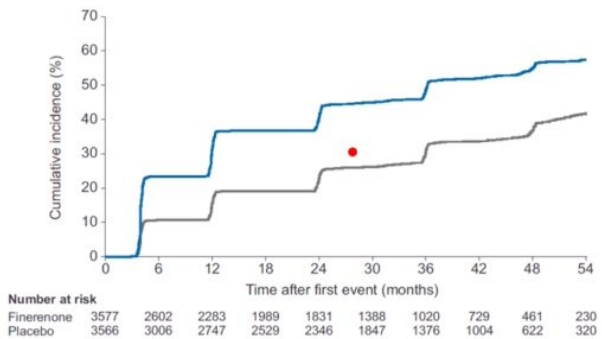


Ruilope ML, Nephrol Dial Transplant 2022

Finerenone significantly improves albuminuria regression and reduces albuminuria worsening

Albuminuria regression*

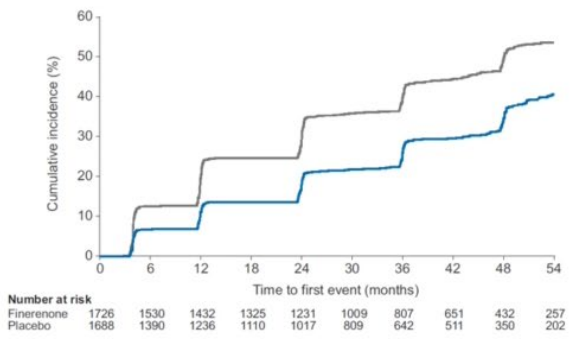
n. albuminuria regression/population
Placebo: 1106/3566
Finerenone: 1710/3577



HR= 1.82; (95% CI 1.69–1.96)
***P* < 0.0001**

Albuminuria progression**

n. albuminuria regression/population
Placebo: 720/1688
Finerenone: 525/1726



HR= 0.59; (95% CI 0.53–0.66)
***P* < 0.0001**

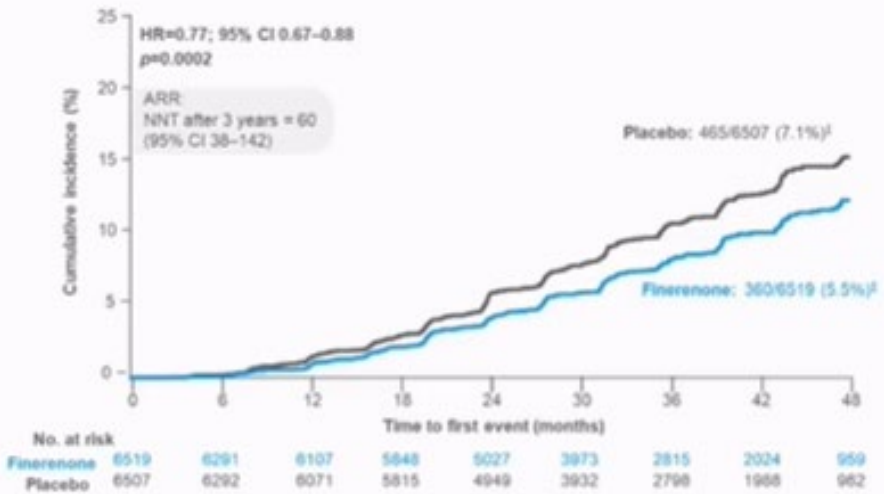
* Changed from severely increased to moderately increased albuminuria, or moderately increased to normal albuminuria, accompanied by a UACR decrease from baseline of >30%; ** UACR level of ≥ 300mg/g that was accompanied by a ≥ 30% increase in UACR from baseline

Ruilope ML, Nephrol Dial Transplant 2022

Outcome credence like

Finerenone and risk of the renal composite outcome

Time to kidney failure, sustained ≥57% decrease in eGFR from baseline, or renal death



Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
≥57% eGFR kidney composite outcome	360 (5.5)	465 (7.1)	0.77 (0.67–0.88)	0.0002
Kidney failure[a]	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESKD	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040[§]
Sustained[b] decrease in eGFR to <15 ml/min/1.73 m²	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026[§]
Sustained[a] ≥57% decrease in eGFR from baseline	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death[c]	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	0.459

0.50 1.00 2.00
Favours finerenone Favours placebo

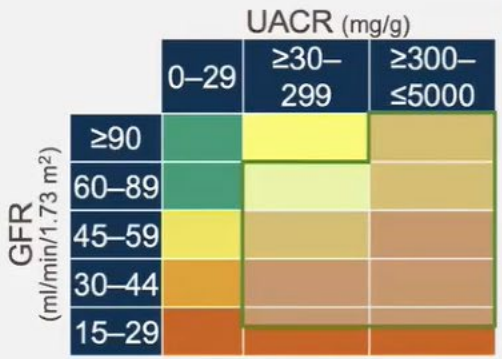
NNT 60 for 3 yrs

Agarwal R, Eur Heart J 2021

FIDELITY is a large, prespecified individual patient data analysis of FIDELIO-DKD and FIGARO-DKD

Key eligibility criteria

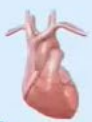
- ✓ T2D
- ✓ CKD
- ✓ On single RASi
- ✓ Serum [K^+] ≤4.8 mmol/l
- ✗ Symptomatic HFrEF



Key outcomes

CV composite

Time to CV death, non-fatal MI, non-fatal stroke or HHF



57% eGFR kidney composite

Time to kidney failure,# sustained ≥57% decrease in eGFR from baseline, or renal death

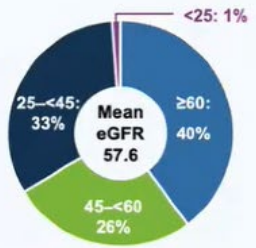
For prescribing information please refer to the SmPC of the product applicable in your country
[K^+], potassium concentration; MI, myocardial infarction; od, once daily; R, randomisation; SmPC, summary of product characteristics
Agarwal R, *et al. Eur Heart J* 2022;43:474–484

FIDELITY

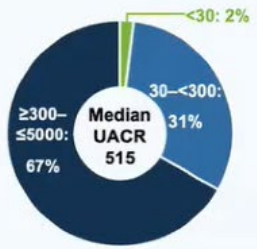
FIDELITY included patients with T2D across the spectrum of CKD severity, treated with a maximum tolerated dose of RASi

40% of patients had albuminuric CKD with preserved kidney function (eGFR ≥60 ml/min/1.73 m²)

Baseline eGFR (ml/min/1.73 m²)



Baseline UACR (mg/g)



Mean age: 65 years

99.8% of patients were treated with a **maximum tolerated dose of an ACEi or ARB**

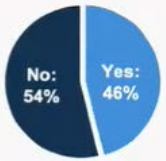
Blood pressure at baseline
137/76 mmHg

Medications (%)

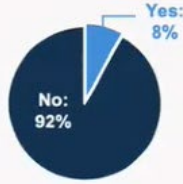
CV medications	
RASi	99.8
Diuretics	52
Glucose-lowering therapies	
Metformin	58
Insulin	59
GLP-1RAs	7.2
SGLT-2is	6.7

Disease history (%)

History of CV disease



History of HF



ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; GLP-1RA, glucagon-like peptide-1 receptor agonist

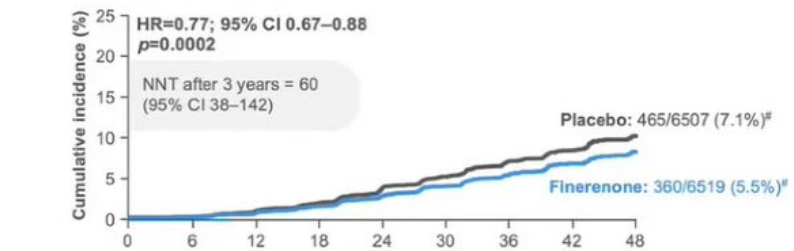
Agarwal R, *et al. Eur Heart J* 2022;43:474–484

FIDELITY

The FIDELITY primary analysis showed significant risk reductions in CV and kidney outcomes with finerenone

Kidney composite

Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or kidney-related death

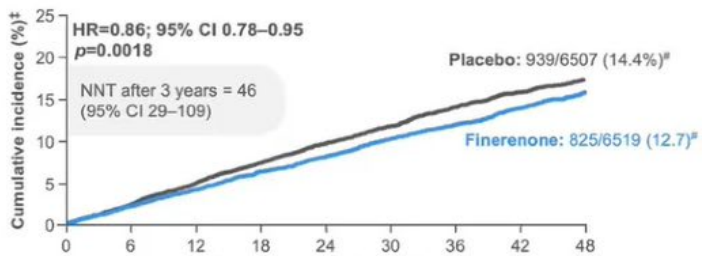


No. at risk									
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962

23% reduced **risk of CKD progression*** versus placebo (HR=0.77; 95% CI 0.67–0.88)

CV composite

Time to CV death, non-fatal MI, non-fatal stroke or HHF



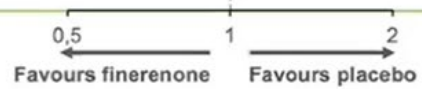
No. at risk§									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

14% reduced **risk of CV morbidity and mortality** versus placebo (HR=0.86; 95% CI 0.78–0.95)

Agarwal R, et al. Eur Heart J 2022

Finerenone had consistent effects on the components of the kidney composite outcome

Outcome	Finerenone (n=6519)		Placebo (n=6507)		HR (95% CI)	*p*-value
	n (%)	n per 100 PY	n (%)	n per 100 PY		
≥57% eGFR kidney composite outcome	**360 (5.5)**	**1.96**	**465 (7.1)**	**2.55**	**0.77 (0.67–0.88)**	**0.0002**
Kidney failure*	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
ESKD	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040#
Sustained‡ decrease in eGFR to <15 ml/min/1.73 m²	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026#
Sustained# ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	1.98	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)§	–



Agarwal R, et al. Eur J Heart 2022

New published ADA - KDIGO Consensus on "Diabetes Management in Chronic Kidney Disease" recommend Finerenone in all albuminuric patients with eGFR≥25 and normal potassium

A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2D, eGFR ≥25 mL/min/1.73m^2, normal serum potassium concentration, and albuminuria (albumin-to-creatinine ratio [ACR] ≥30 mg/g) despite maximum tolerated dose of renin-angiotensin system (RAS) inhibitor.

De Boer HI, Diabetes Care 2022

Key points

- The advent of novel kidney-protective drugs provides new therapeutic options for DKD but…….
  - increases the complexity of treatment decisions for caregivers.

- **Combining drugs**:
  - may enhance their kidney protective efficacy
  - could potentially reduce the risk of adverse effects that are associated with specific drug classes

- An important goal for the future pharmacological management of DKD is to individualize treatment:
  - optimal drug combinations based on
    - the underlying pathophysiology
    - guided by tissue or serum biomarkers.

Daniël H. van Raalte et al , Nature Rev.Neph. 2024

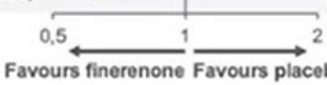
In FIDELITY, the effect of finerenone on UACR reduction was similar in patients treated with or without an SGLT-2i at baseline

- **SGLT-2i use at baseline**

877 (6.7%) patients on an SGLT-2i

- **Reduction in UACR with finerenone vs placebo at month 4**

	Finerenone, n at baseline (gMean, mg/g)	Placebo, n at baseline (gMean, mg/g)	Ratio of LS means (95% CI)	$p_{interaction}$
No SGLT-2i	6079 (449)	6065 (459)	0.69 (0.67–0.71)	0.17
SGLT-2i	438 (393)	439 (398)	0.63 (0.57–0.70)	

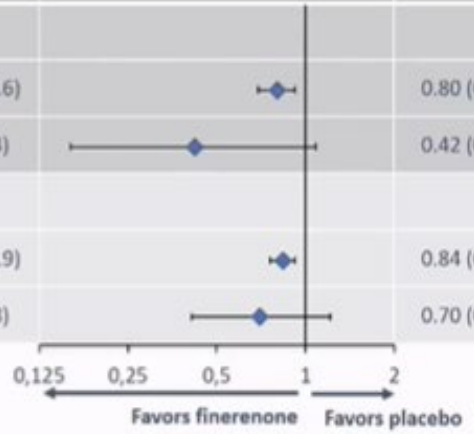


Although non-significant, the **larger UACR reduction** observed in **patients treated with finerenone in combination with SGLT-2is** (37%) vs those treated with finerenone alone (31%) suggests a **potential synergistic effect**

Rossing P, et al. Diabetes Care 2022

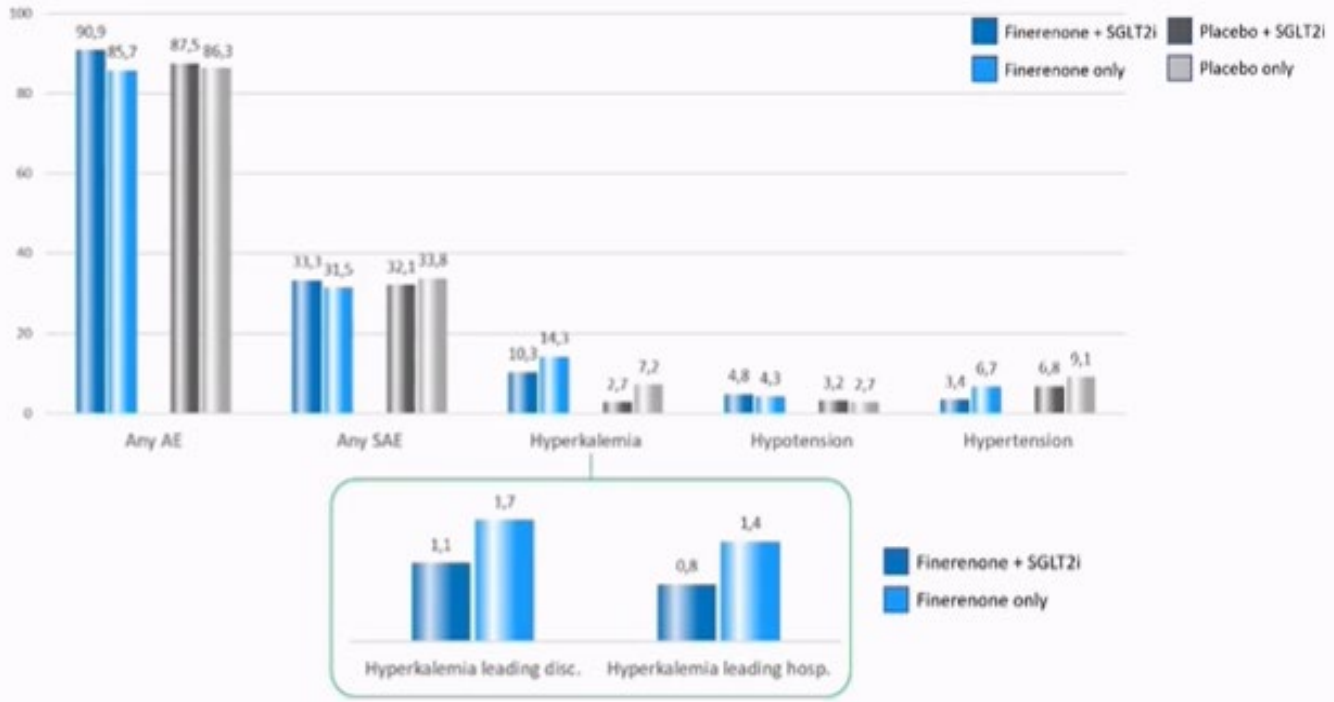
Benefits of finerenone on cardiorenal outcomes in T2D with CKD are observed irrespective of SGLT2i use

Endpoint	Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	Hazard ratio (95% CI)	Adjusted HR (95% CI)*	*p*-value for interaction
eGFR 57% kidney composite[a]					
Baseline SGLT-2i NO	351/6081 (2.1)	448/6068 (2.6)		0.80 (0.69–0.92)	0.29
Baseline SGLT-2i YES	9/438 (0.7)	17/439 (1.4)		0.42 (0.16–1.08)	
eGFR 40% kidney composite[a]					
Baseline SGLT-2i NO	818/6081 (5.0)	961/6068 (5.9)		0.84 (0.76–0.92)	0.59
Baseline SGLT-2i YES	36/438 (2.9)	34/439 (2.8)		0.70 (0.41–1.21)	



Rossing P, Diabetes Care 2022

Hyperkalemia incidence and relationship with SGLT2i



Rossing P, Diabetes Care 2022

AACE guidelines provides "Practice Points" to better manage finerenone

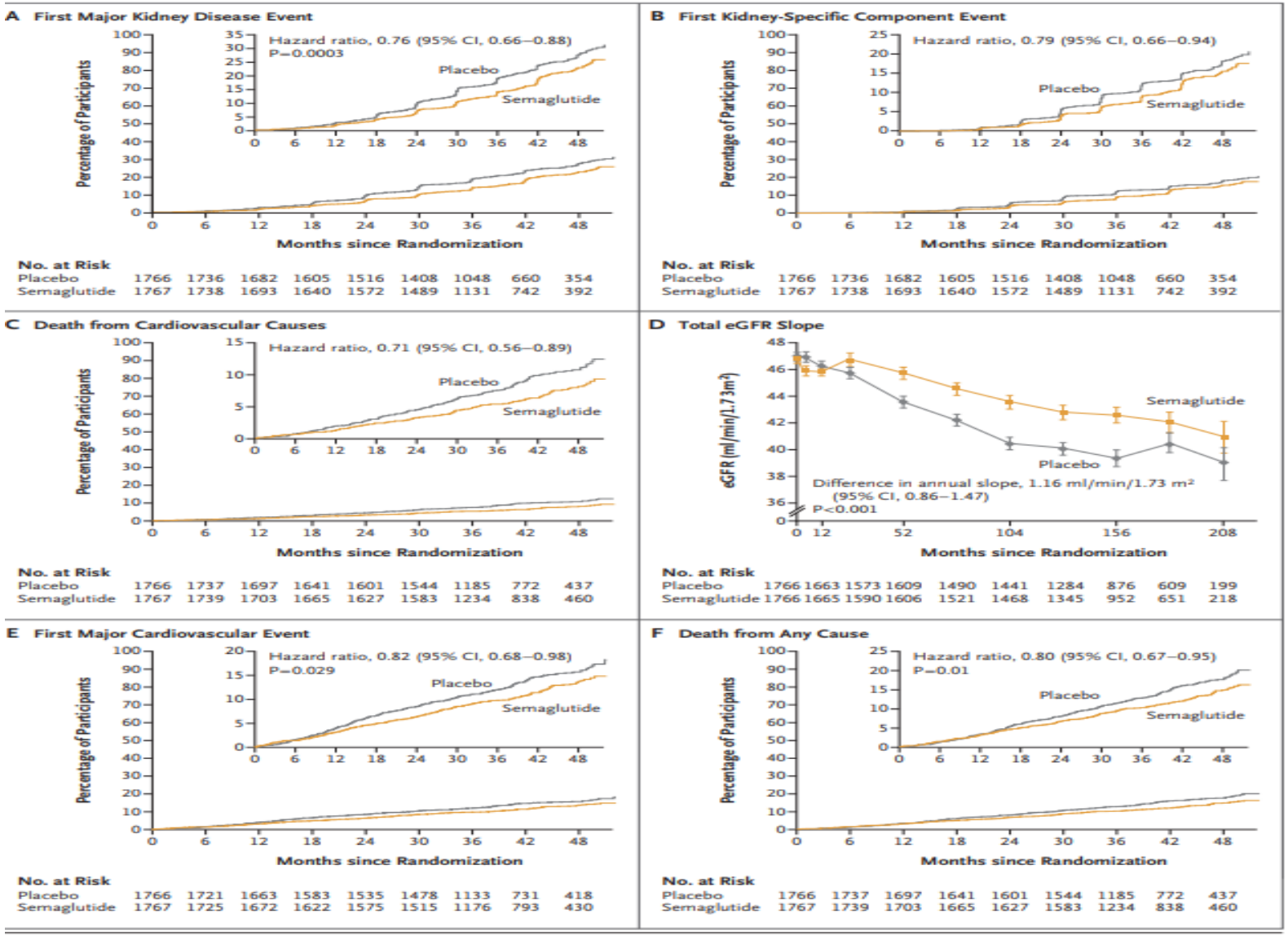
- Serum potassium levels and eGFR should be monitored within 2 to 4 weeks after initiating an ACE inhibitor, an ARB, an SGLT2i, finerenone, or with changes in these medications.

- Finerenone can be used for persistent albuminuria in addition to an ACE inhibitor or an ARB and SGLT2i, or in people with CKD in DM who cannot take an SGLT2i.

Mitigation of Side Effects for Newer Agents to Treat Diabetic Kidney Disease

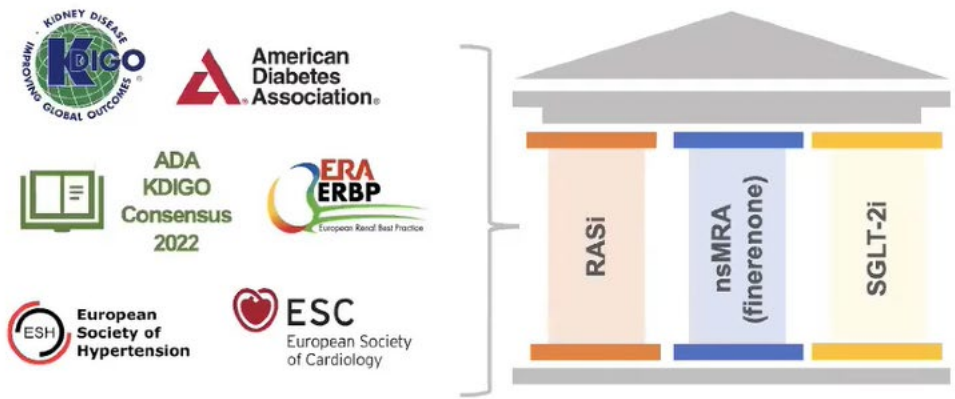
Side effects	Mitigation strategies
SGLT2 inhibitors	
Genital mycotic infections	◦ Hygiene, topical antifungals
Volume depletion	◦ Proactive dose reduction of diuretics in persons at risk for hypovolemia ◦ Hold SGLT2is during GI illness (nausea, vomiting, diarrhea) ◦ Improve glucose control to reduce glucosuria
Ketoacidosis	◦ Educate persons with DM on early recognition ◦ "STOP DKA" protocol (stop SGLT2i, test for ketones, maintain fluid and carbohydrate intake, use maintenance and supplemental insulin)
Hypoglycemia	◦ Adjustment of background antihyperglycemic agents
GLP-1 receptor agonists	
Nausea/vomiting/diarrhea	◦ Patient education on tolerability and symptom recognition ◦ Start at lowest dose and titrate slowly
Hypoglycemia	◦ Adjustment of background antihyperglycemic agents
Finerenone	
Hyperkalemia	◦ Dietary restriction of potassium ◦ Thiazide or loop diuretics ◦ SGLT2i ◦ Potassium-binding agents (patiromer or sodium zirconium cyclosilicate)

E riguardo i glp1 ???



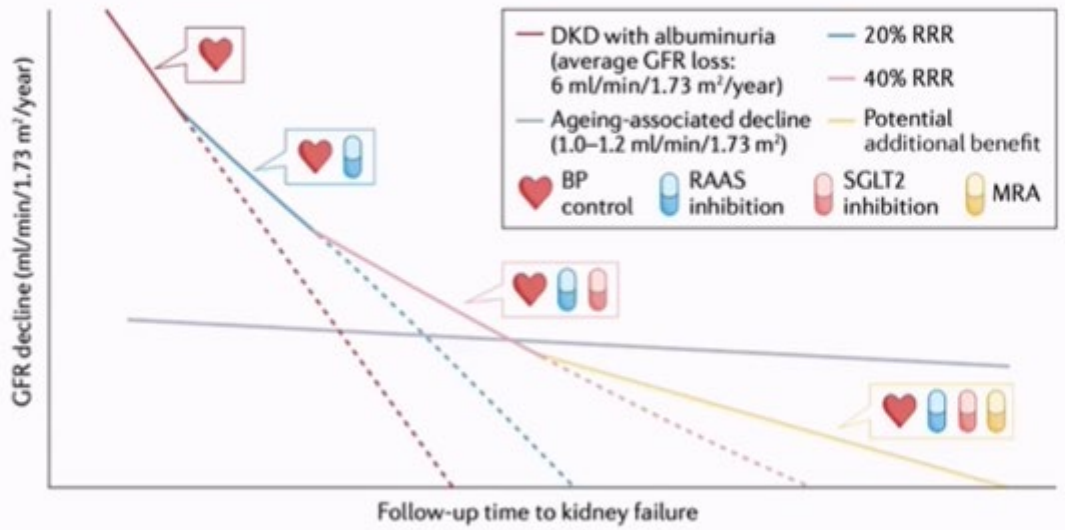
N Engl J Med 2024;391:109-121

Clinical guidelines for the management of CKD in T2D recommend a combination of drug therapies to optimally reduce risks, with Finerenone proposed as a core treatment pillar

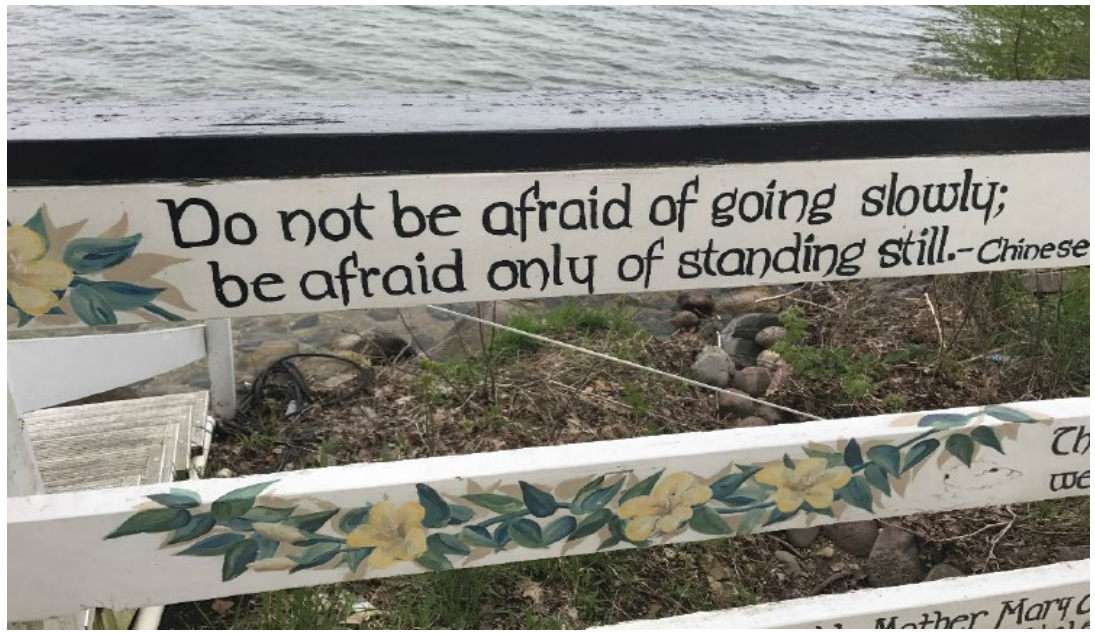


1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2022;102(5S):S1–S128; 2. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202;

Expanding the therapeutic options for patients with CKD and T2D



Fioretto P, Pontremoli R Nat Rev Nephrol 2022



Grazie per l'attenzione