LO STUDIO FIDELIO

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Dichiarazione dei conflitti d'interesse

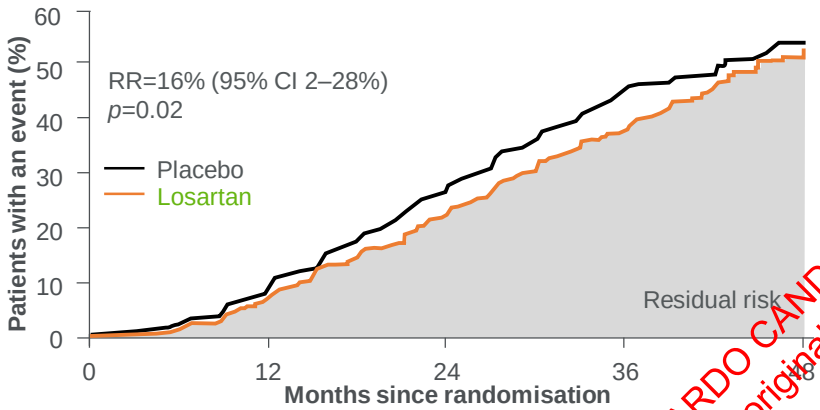
Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

•**Advisory Board Membership and Consultancy**: Boehringer Ingelheim, Eli-Lilly, Mundipharma Pharmaceutica, Novo Nordisk, Astra-Zeneca, Sanofi-Aventis, Roche Diabetes Care.

•**Lectures**: Astra Zeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Sanofi-Aventis, Mundipharma Pharmaceutica, Abbott, MSD, Neopharmed Gentili, Menarini, Essex Italia, Ascensia Diabetes.

Despite SoC therapies, patients with CKD and T2D are at high risk of CKD progression

RENAAL: Losartan vs placebo[1]



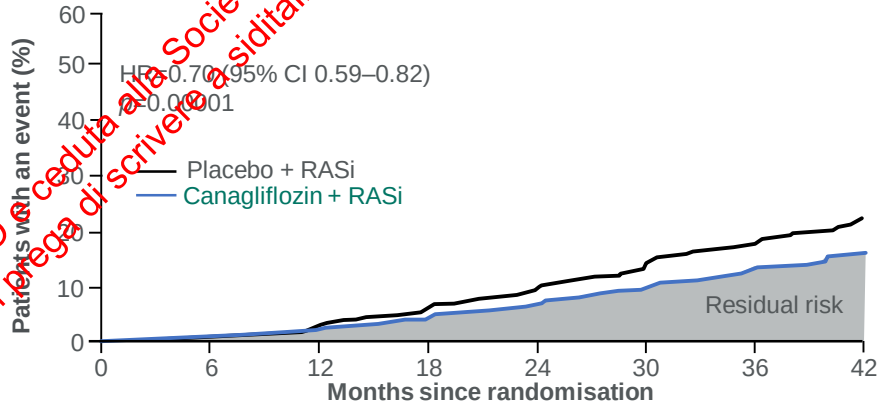
No. at risk

762	689	554	295	36
751	692	583	329	52

Patients with severely increased albuminuria: 100%
Median UACR: 1249 mg/g

Primary composite outcome:
Doubling of SCr, kidney failure* or all-cause death

CREDENCE: Canagliflozin vs placebo[2]



No. at risk

2199	2178	2132	2047	1725	1129	621	170
2202	2181	2145	2081	1786	1211	646	196

Patients with moderately increased albuminuria: 11%
Patients with severely increased albuminuria: 88%
Median UACR: 927 mg/g

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

1. Brenner BM, *et al. N Engl J Med* 2001;345:861–869; 2. Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306

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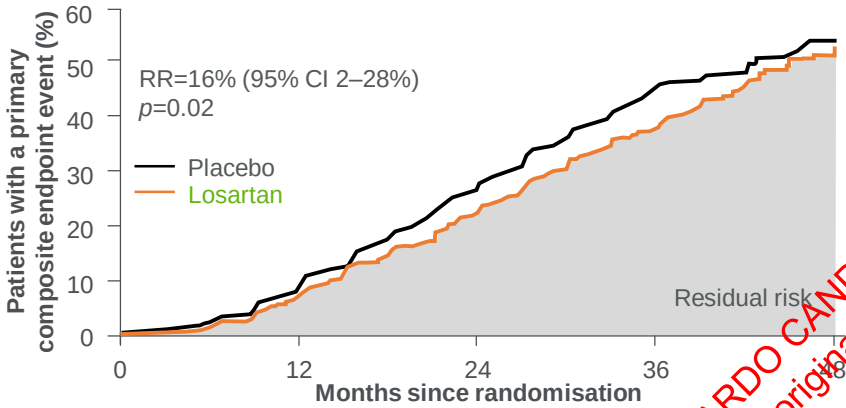

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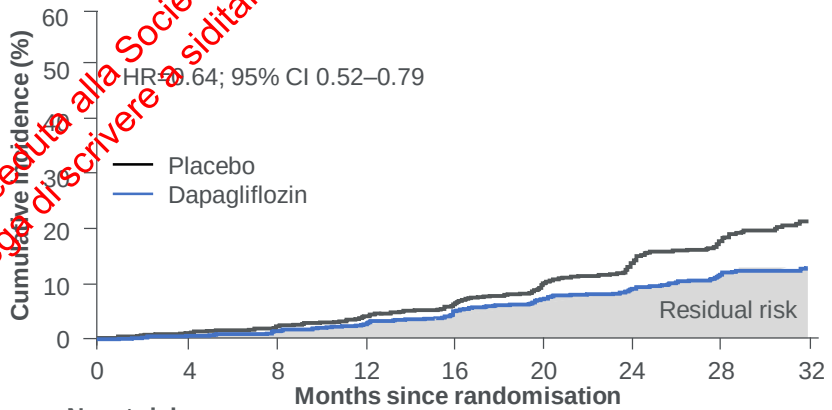
DAPA-CKD:#‡ Dapagliflozin vs placebo[2]



No. at risk

1455	1383	1349	1307	1262	1155	910	580	215
1451	1360	1321	1275	1224	1130	868	545	190

Patients with severely increased albuminuria: 89.7%[3]
Median UACR: 949 mg/g[3]

Primary composite outcome:
Sustained ≥50% eGFR decline, ESKD or death from kidney or CV causes

1. Brenner BM, *et al. N Engl J Med* 2001;345:861–869; 2. Wheeler DC, *et al. Lancet Diabetes Endocrinol* 2021;9:22–31; 3. Wheeler DC, *et al. Nephrol Dial Transplant* 2020;35:1700–1711

FIDELIO-DKD objective

To assess the effects of finerenone to slow CKD progression and reduce CV morbidity and mortality in patients with CKD and T2D[1,2]

1. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 2. Bakris GL, *et al. N Engl J Med 2020;383:2219-29*

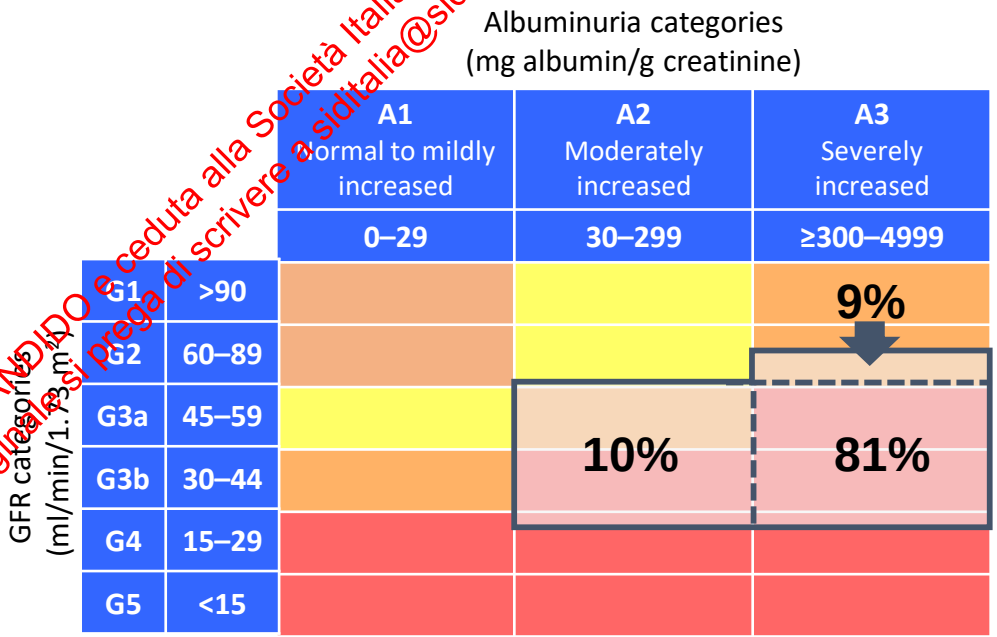
FIDELIO-DKD included a broad patient population across early-to-late disease stages of CKD in T2D

Inclusion criteria[1,2]

- T2D and CKD, defined as **either:**
  - UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m^2 *# **or**
  - UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m^2 *
- 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 m^2 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;383:2219-29

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

13,911 patients enrolled[1]

Run-in[1,2] — Screening

4–16 weeks

Optimisation of ACEi/ARB therapy

R

5734 patients randomised[1,2]

- Finerenone (initial dose 10 or 20 mg od*) → Post-treatment follow-up
- Placebo (initial dose 10 or 20 mg od*) → Post-treatment follow-up

2.6 years' median follow-up[2]

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 m^2, respectively. Up-titration of study drug from 10 to 20 mg od was encouraged 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 m^2; [‡]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;383:2219-29

Patients had well-controlled diabetes, with the majority receiving insulin and ~5% an SGLT-2 inhibitor

Selected baseline characteristic	Finerenone (n=2833)	Placebo (n=2841)
Mean age at enrolment, years	65.4	65.7
Male, n (%)	1953 (68.9)	2030 (71.5)
Mean duration of T2D, years	16.6	16.6
Mean HbA1c, %,	7.7	7.7
Glucose-lowering therapies, n (%)	2747 (97.0)	2777 (97.7)
Insulin, n (%)	1843 (65.1)	1794 (63.1)
SGLT-2 inhibitor, n (%)	124 (4.4)	135 (4.8)
GLP-1RA, n (%)	189 (6.7)	205 (7.2)
SGLT-2 inhibitor initiated post-baseline	186 (6.6)	216 (7.6)

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

Patients had advanced CKD

Selected baseline characteristic		Finerenone (n=2833)	Placebo (n=2841)
Mean eGFR, ml/min/1.73 m^2		44.4	44.3
eGFR at baseline, ml/min/1.73 m^2, n (%)	<25	66 (2.3)	69 (2.4)
	25–<45	1476 (52.1)	1505 (53.0)
	45–<60	972 (34.3)	928 (32.7)
	≥60	318 (11.2)	338 (11.9)
Median UACR, mg/g, (IQR)		833 (441–1628)	867 (453–1645)
UACR at baseline, mg/g, n (%)*	30–<300	350 (12.4)	335 (11.8)
	≥300	2470 (87.2)	2493 (87.8)
Mean serum potassium, mmol/l		4. 4	4.4
ACE inhibitor, n (%)		950 (33.5)	992 (34.9)
ARB, n (%)		1879 (66.3)	1846 (65.0)

*0.4% of patients in both groups had a UACR <30 mg/g at baseline

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

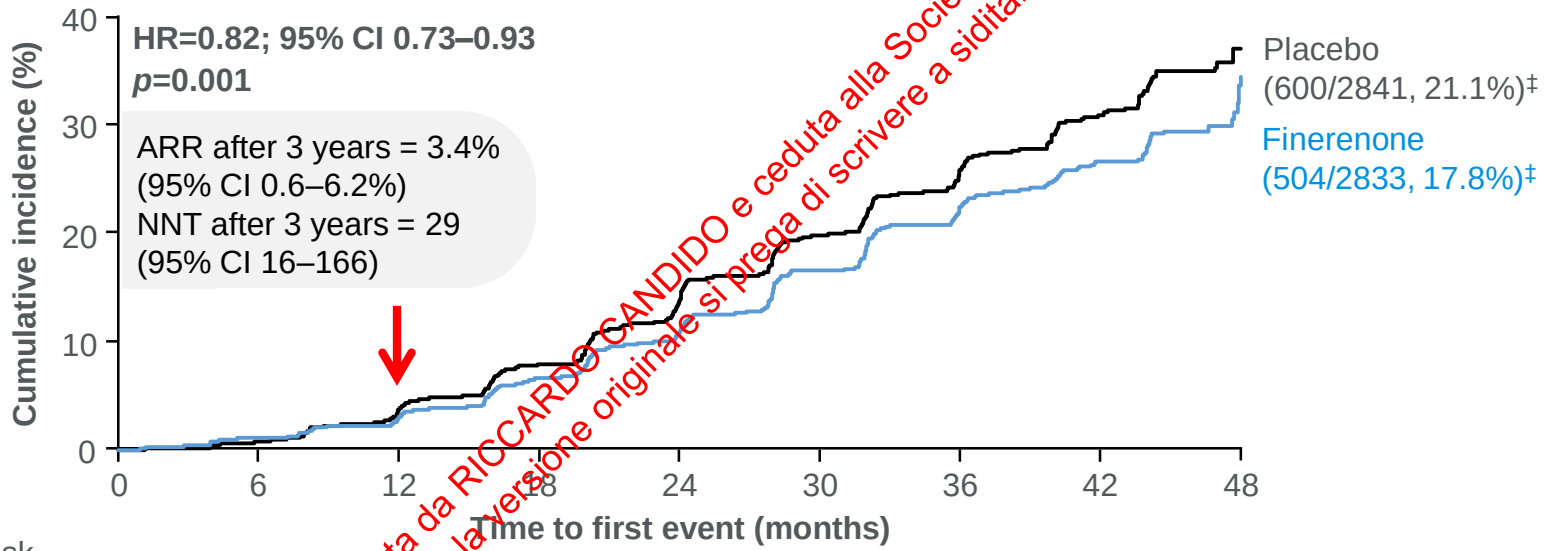
Patients had well-controlled blood pressure, and almost half had a history of CV disease

Selected baseline characteristic	Finerenone (n=2833)	Placebo (n=2841)
Mean SBP, mmHg	138.1	138.0
Medical history, n (%)		
Hypertension	2737 (96.6)	2768 (97.4)
Cardiovascular disease	1303 (46.0)	1302 (45.8)
Heart failure	195 (6.9)	241 (8.5)
Cardiovascular medication, n (%)		
Beta blocker	1462 (51.6)	1506 (53.0)
Calcium channel blocker	1773 (62.6)	1812 (63.8)
Diuretic	1577 (55.7)	1637 (57.6)
Statin	2105 (74.3)	2110 (74.3)
Platelet aggregation inhibitor	1633 (57.6)	1595 (56.1)

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

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

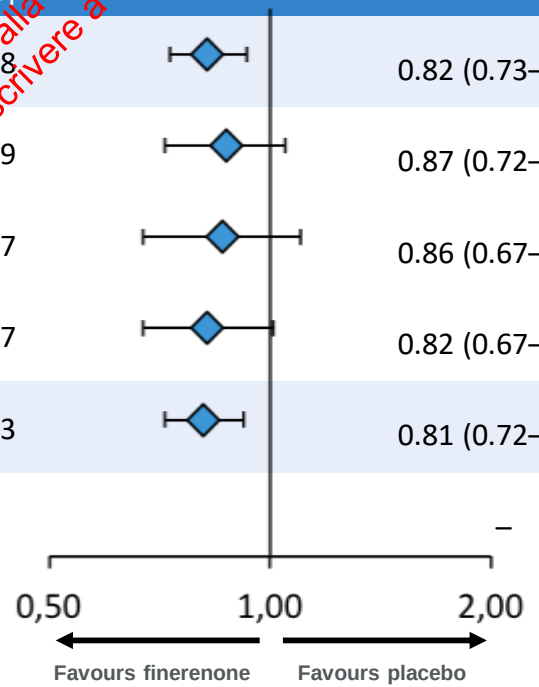


*ESKD or an eGFR <15 ml/min/1.73 m^2; #sustained over ≥4 weeks; ‡over a median follow-up of 2.6 years

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

Finerenone had consistent effects on the components of the primary endpoint

Endpoint	Finerenone (n=2833) n (%)	Finerenone (n=2833) n per 100 PY	Placebo (n=2841) n (%)	Placebo (n=2841) n per 100 PY	Hazard ratio (95% CI)	*p*-value
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)	–	–	–

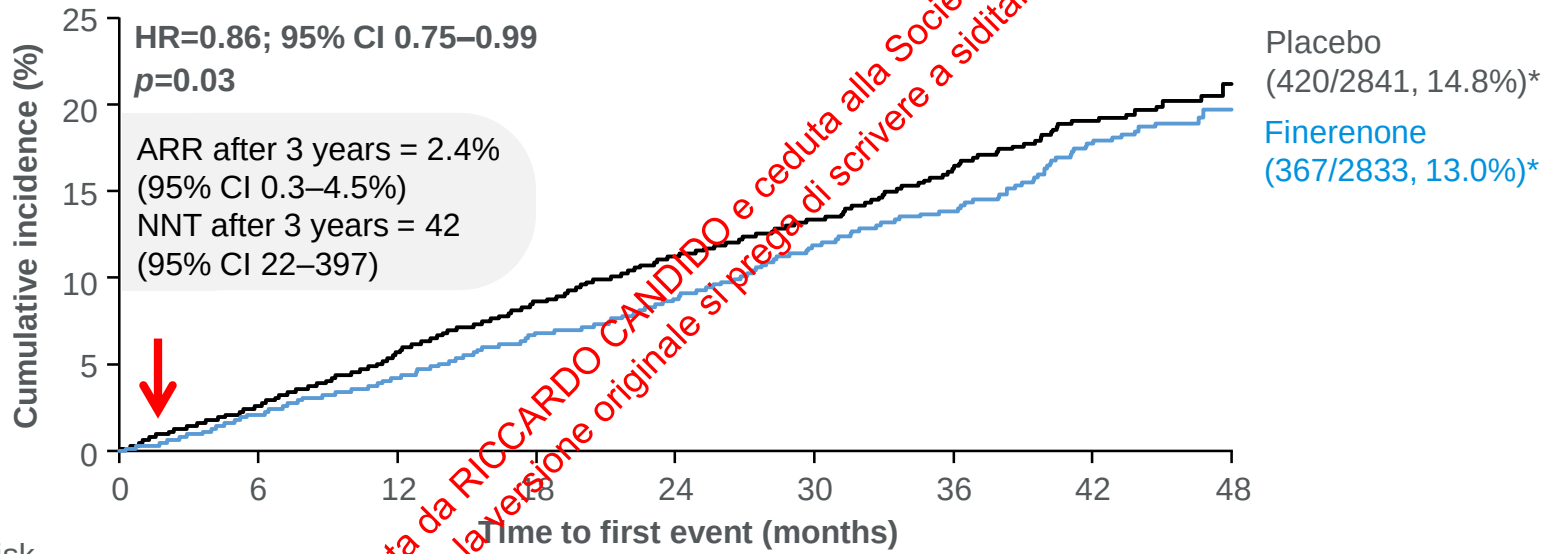


n refers to number of patients with an event
*Confirmed by two eGFR measurements ≥4 weeks apart

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

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



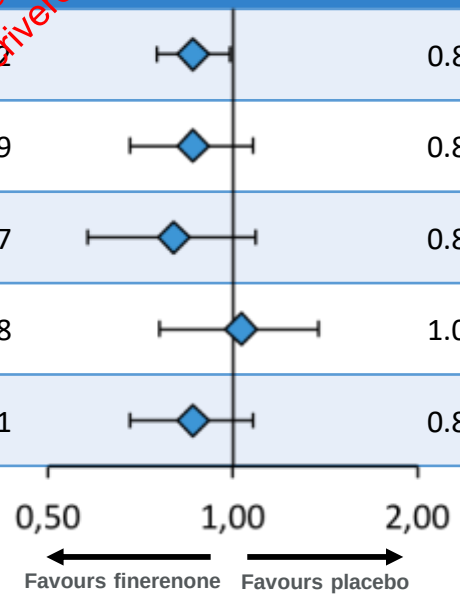
No. at risk					
Finerenone	2833	2688	2017	984	111
Placebo	2841	2653	1969	951	115

*over a median follow-up of 2.6 years

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

Finerenone had consistent effects on cardiovascular death, myocardial infarction and hospitalisation for heart failure

Endpoint	Finerenone (n=2833)		Placebo (n=2841)		Hazard ratio (95% CI)	*p*-value
	n (%)	n per 100 PY	n (%)	n per 100 PY		
Key secondary cardiovascular composite endpoint	367 (13.0)	5.11	420 (14.8)	5.92	0.86 (0.75–0.99)	0.03
Cardiovascular death	128 (4.5)	1.69	150 (5.3)	1.99	0.86 (0.68–1.08)	–
Non-fatal MI	70 (2.5)	0.94	87 (3.1)	1.17	0.80 (0.58–1.09)	–
Non-fatal stroke	90 (3.2)	1.21	87 (3.1)	1.18	1.03 (0.76–1.38)	–
Hospitalisation for HF	139 (4.9)	1.89	162 (5.7)	2.21	0.86 (0.68–1.08)	–

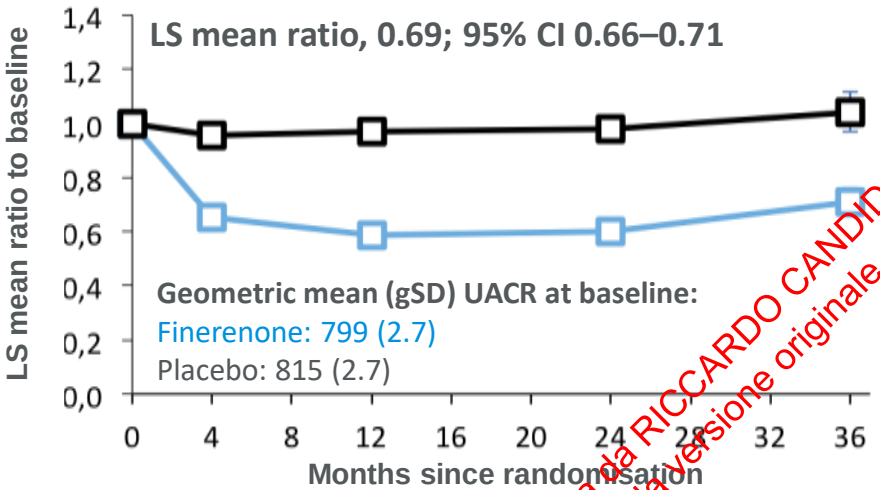


n refers to number of patients with an event

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

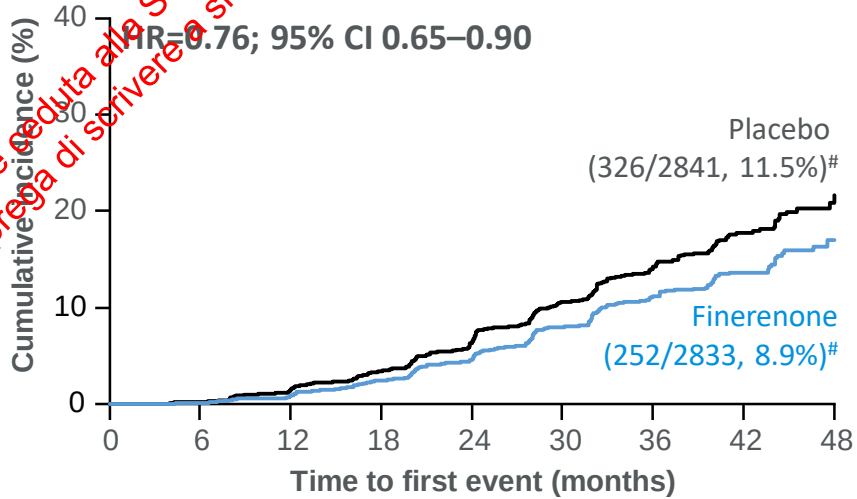
Effects of finerenone on prespecified secondary kidney endpoints support the primary endpoint results

Change in UACR



No. of patients				
Finerenone 2831	2582	2441	856	
Placebo 2840	2598	1825	834	

Secondary kidney composite endpoint*



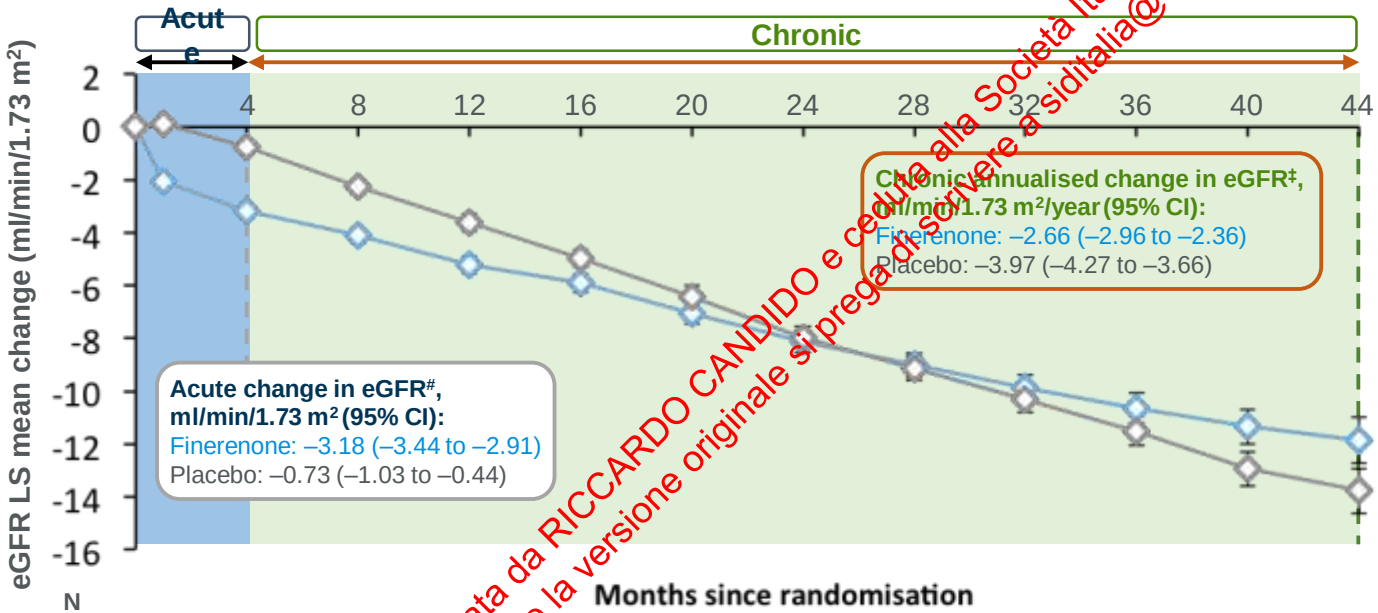
No. at risk					
2833	2655	1915	883	101
2841	2636	1887	873	98

p-values for prespecified hierarchical outcomes below the key secondary outcome are not reported because of *N Eng J Med* guidelines for statistical reporting

*Composite of time to first onset of kidney failure, sustained ≥57% decrease in eGFR from baseline (confirmed by two eGFR measurements ≥4 weeks apart), or renal death; #over a median follow-up of 2.6 years

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

The acute effect of finerenone is a drop in eGFR but the long-term effect is a slowing of eGFR decline*



Mean eGFR at baseline (ml/min/1.73 m²):
Finerenone = 44.4±12.5
Placebo = 44.3±12.6

*Mixed model analysis of eGFR over time. Full analysis set; #LS mean change in eGFR slope from baseline to month 4; ‡LS mean change in eGFR slope from month 4 to the permanent discontinuation or end-of-study visit

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

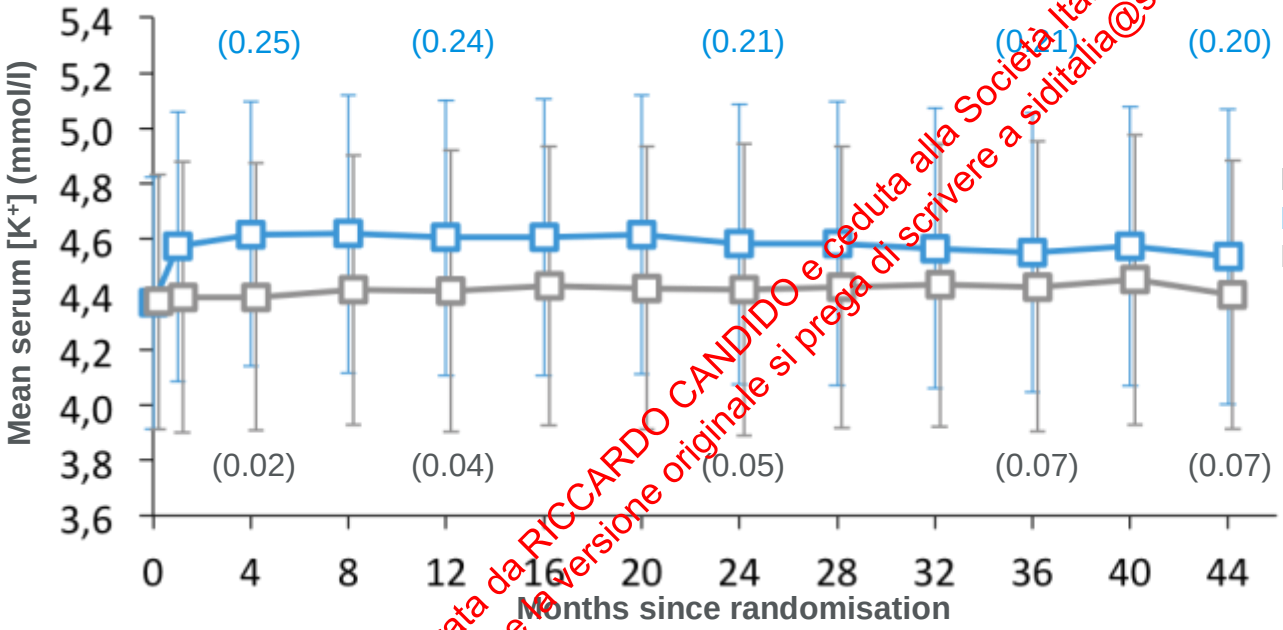
Overall, treatment-emergent adverse events were not more frequent with finerenone

Treatment-emergent adverse events, n (%)	Finerenone (n=2827)	Placebo (n=2831)
Overall events		
Any AE	2468 (87.3)	2478 (87.5)
Any SAE	902 (31.9)	971 (34.3)
Events related to study drug		
Any study drug-related AE	646 (22.9)	449 (15.9)
Any study drug-related SAE	48 (1.7)	34 (1.2)
Events leading to treatment discontinuation		
Any AE leading to discontinuation of study drug	207 (7.3)	168 (5.9)
Any SAE leading to discontinuation of study drug	75 (2.7)	78 (2.8)

AE, adverse event; SAE, serious adverse event

Bakris GL *et al*. *N Engl J Med 2020;383:2219-29*

Finerenone had a predictable impact on serum potassium



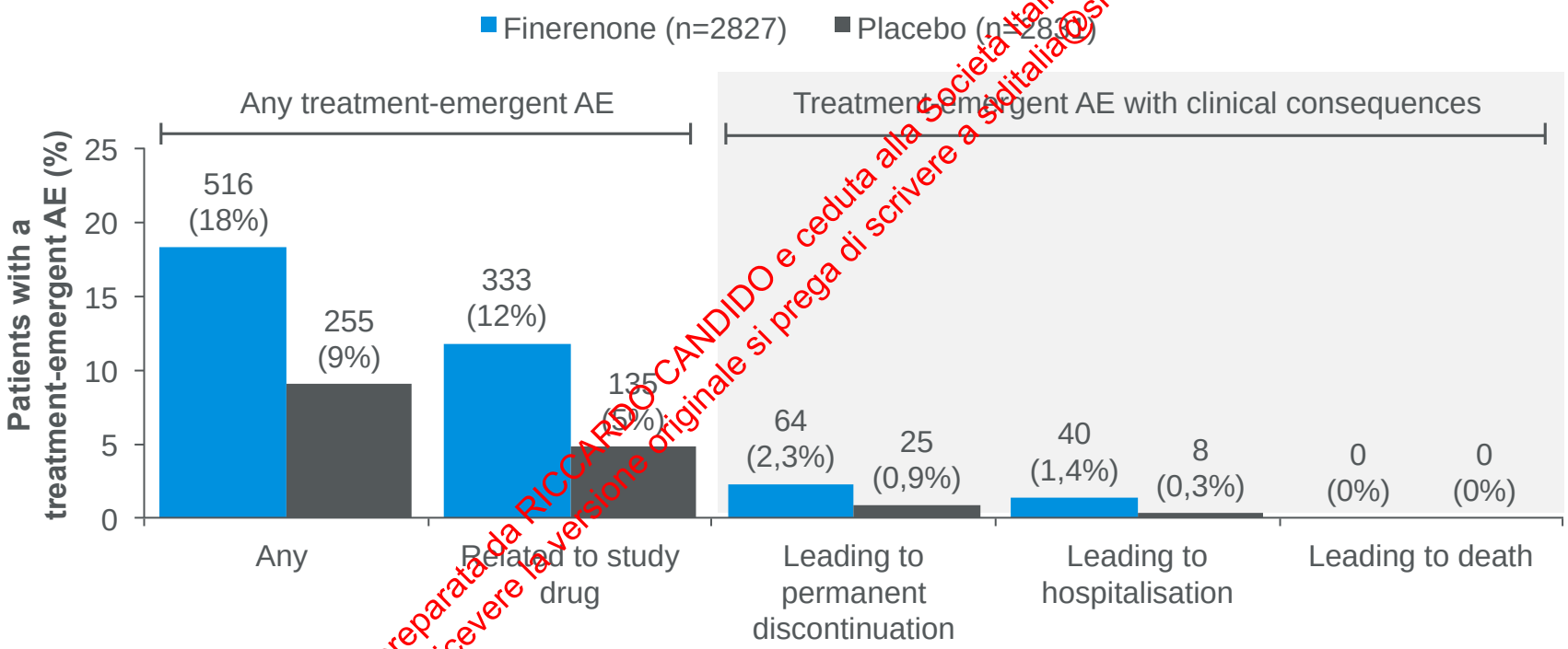
Mean baseline serum [K⁺]
Finerenone: 4.37±0.46
Placebo: 4.37±0.46

Maximum mean difference in serum potassium between groups = 0.23 mmol/l at month 4

Numbers in parentheses show change from baseline; error bars show standard deviation

Bakris GL *et al*. *N Engl J Med 2020;383:2219-29*

The incidences of treatment discontinuation and hospitalisation due to hyperkalaemia were low



*Investigator-reported AEs using the MedDRA preferred terms 'hyperkalemia' and 'blood potassium increased'

Bakris GL *et al*. *N Engl J Med 2020;383:2219-29*

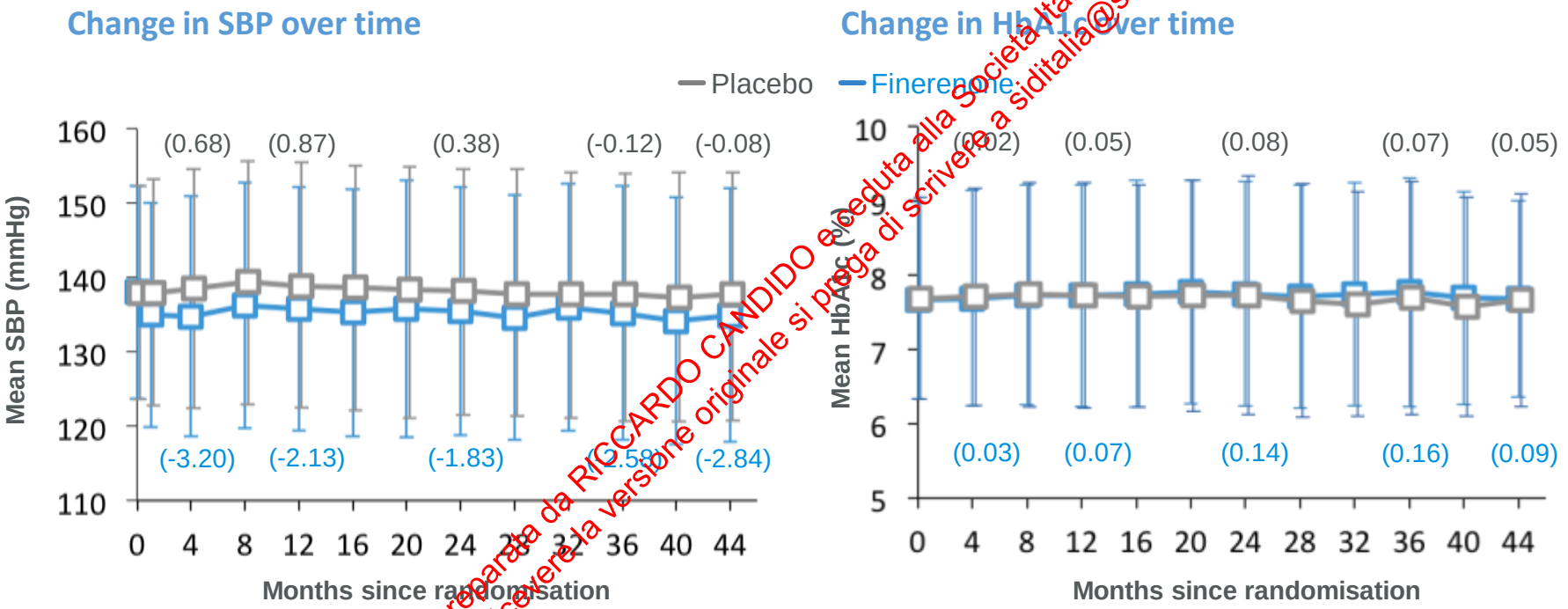
Gynaecomastia and acute kidney injury or acute renal failure were balanced between groups

Treatment-emergent adverse events, n (%)	Finerenone (N=2827)	Placebo (N=2831)
Reproductive system and breast disorders		
Breast hyperplasia	0	3 (0.1)
Gynaecomastia	6 (0.2)	6 (0.2)
Kidney-related AEs		
Acute kidney injury	129 (4.6)	136 (4.8)
Hospitalisation due to acute kidney injury	53 (1.9)	47 (1.7)
Treatment discontinuation due to acute kidney injury	5 (0.2)	7 (0.2)
Hospitalisation due to acute renal failure*	70 (2.5)	71 (2.5)
Treatment discontinuation due to acute renal failure*	31 (1.1)	36 (1.3)

*Standardised MedDRA Query term 'acute renal failure'

Bakris GL *et al*. *N Engl J Med 2020;383:2219-29*

Finerenone had modest effects on blood pressure and did not affect blood glucose



Numbers in parentheses show change from baseline; error bars show standard deviation

Bakris GL *et al*. *N Engl J Med 2020;383:2219-29*

Summary

A first in CKD in T2D

First positive **long-term phase III trial** to investigate the effects of a **novel nonsteroidal selective MRA** in a **broad patient population** with **advanced CKD and T2D**[1]

Finerenone has **benefits** on clinically important **kidney* and CV outcomes**[#1]

Novel MoA

Kidney* and CV benefits[#] of finerenone obtained on a **background of optimised RAS blockade and well-controlled HbA1c and blood pressure**[1]

Preclinical evidence suggests effects of finerenone driven by **inflamination and fibrosis**[2]

Favourable–benefit risk

Overall **treatment-emergent AEs and SAEs were similar** with finerenone and placebo[1]

Low incidence of **hyperkalaemia** resulting in **permanent treatment discontinuation**[1]

*Time to first onset of kidney failure, sustained ≥40% decrease in eGFR from baseline (confirmed by two eGFR measurements ≥4 weeks apart), or renal death; [#]time to first onset of CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF

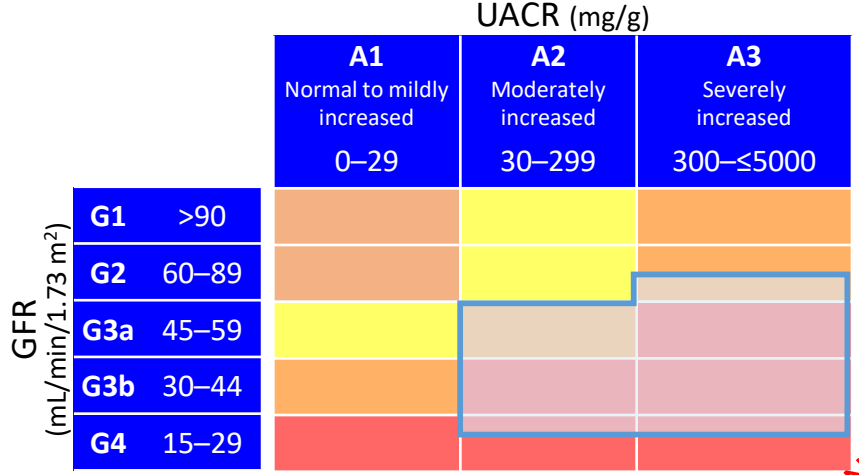
1. Bakris GL, *et al. N Engl J Med 2020;383:2219-29.* 2. Agarwal R, *et al. Eur Heart J 2021;42(2):152-161*

Nephrol Dial Transplant (2022) 37: 1261–1269
https://doi.org/10.1093/ndt/gfab336
Advance Access publication date 25 November 2021

Effects of canagliflozin versus finerenone on cardiorenal outcomes: exploratory *post hoc* analyses from FIDELIO-DKD compared to reported CREDENCE results

Rajiv Agarwal[1], Stefan D. Anker[2], Gerasimos Filippatos[3], Bertram Pitt[4], Peter Rossing[5,6], Luis M. Ruilope[7,8,9], John Boletis[10], Robert Toto[11], Guillermo E. Umpierrez[12], Christoph Wanner[13], Takashi Wada[14], Charlie Scott[15], Amer Joseph[16], Ike Ogbaa[17], Luke Roberts[18], Markus F. Scheerer[19] and George L. Bakris[20]; on behalf of the FIDELIO-DKD investigators

FIDELIO-DKD and CREDENCE: Inclusion/exclusion criteria



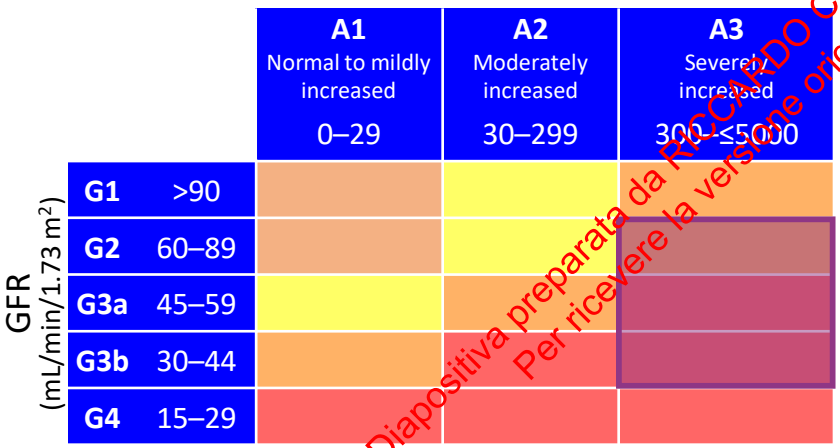
CKD inclusion criteria

FIDELIO-DKD

Key exclusion criteria

- Non-diabetic HD, including clinically relevant renal artery stenosis
- HbA1c >12%
- Uncontrolled arterial hypertension (Mean sitting SBP ≥170 mm Hg or mean sitting DBP ≥110 mm Hg at the run-in visit or mean sitting SBP ≥160 mm Hg)
- Symptomatic HFrEF (class II–IV NYHA)
- Serum [K^+] >4.8 mmol/L

Bakris GB,. *et al N Engl J Med* 2020;383:2219–2229



CREDENCE

Key exclusion criteria

- Non-diabetic kidney disease
- Uncontrolled arterial hypertension (SBP ≥180 and/or diastolic BP ≥100 mmHg by week–2)
- Class IV NYHA HF
- MRA treatment at baseline
- Serum [K^+] >5.5 mmol/L

Perkovic V, et al. N Engl J Med 2019;380:2295–2306

FIDELIO-DKD and CREDENCE: Endpoint definitions

Kidney-specific composite endpoint

Kidney failure
- Chronic dialysis for ≥90 days
- Kidney transplant
- Sustained eGFR <15 mL/min/1.73 m^2

Sustained **≥40% decrease** in eGFR from baseline

Renal death

Bakris GB,. *et al N Engl J Med* 2020;383:2219–2229

Cardiorenal composite endpoint

ESKD
- Chronic dialysis for ≥30 days
- Kidney transplant
- Sustained eGFR <15 mL/min/1.73 m^2

Sustained **≥57% decrease** in eGFR from baseline

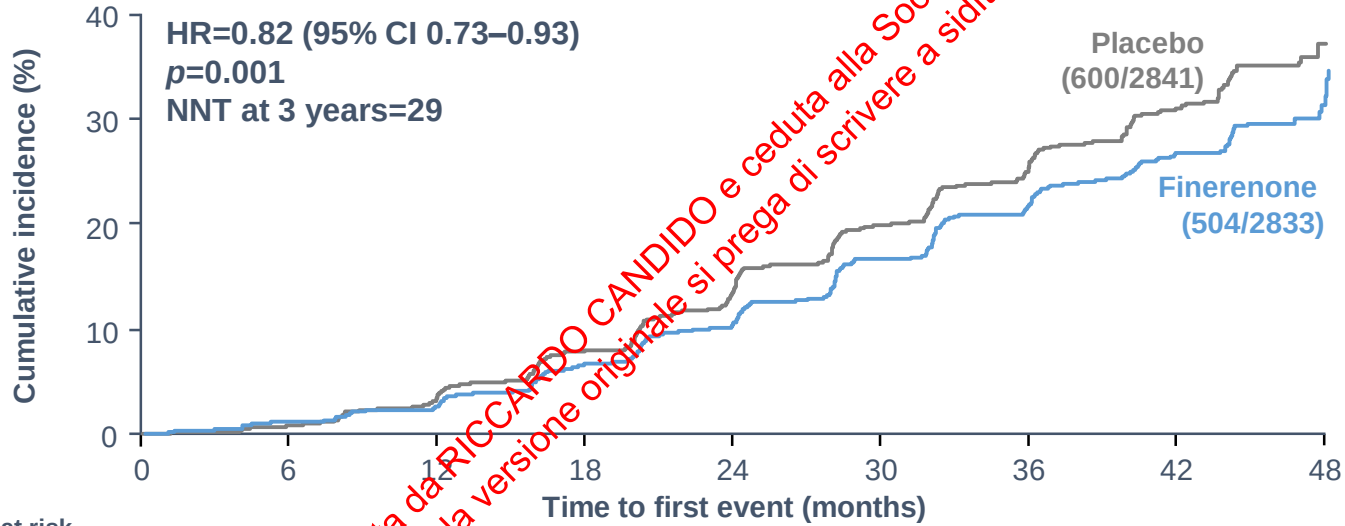
Renal death

CV death

Perkovic V, et al. N Engl J Med 2019;380:2295–2306

In FIDELIO-DKD, finerenone significantly reduced the risk of the composite kidney outcome by 18%

FIDELIO-DKD primary endpoint (kidney-specific composite incl. ≥40% decrease in eGFR)*

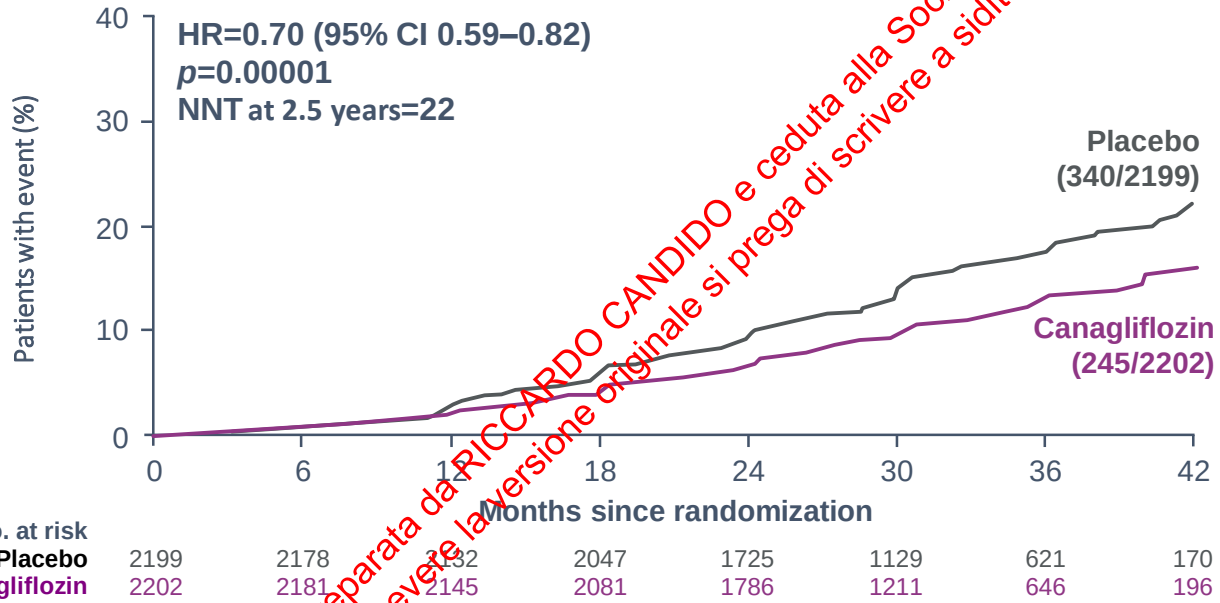


*Composite of kidney failure (ESKD or an eGFR <15 mL/min/1.73 m^2), sustained ≥40% decrease in eGFR from baseline, or renal death.
CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio

Bakris GL *et al. N Engl J Med 2020;383:2219-29*

In CREDENCE, canagliflozin significantly reduced the risk of cardiorenal composite endpoint by 30%

CREDENCE primary endpoint (cardiorenal composite incl. ≥57% decrease in eGFR + CV death)*



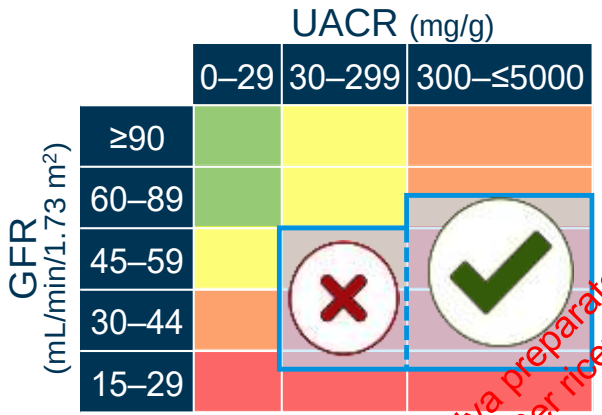
*Composite of ESKD, doubling of serum creatinine (sustained for ≥30 days) or renal/CV death. ESKD was defined as dialysis for ≥30 days, kidney transplantation, eGFR of <15 mL/min/1.73 m^2 for ≥30 days

Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306

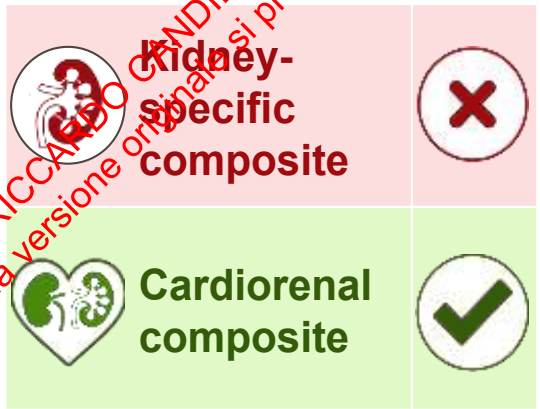
Analysis aims and design

To assess how differences in trial design between FIDELIO-DKD and CREDENCE influence relative treatment effects

Equivalent CKD inclusion criteria



Equivalent endpoints

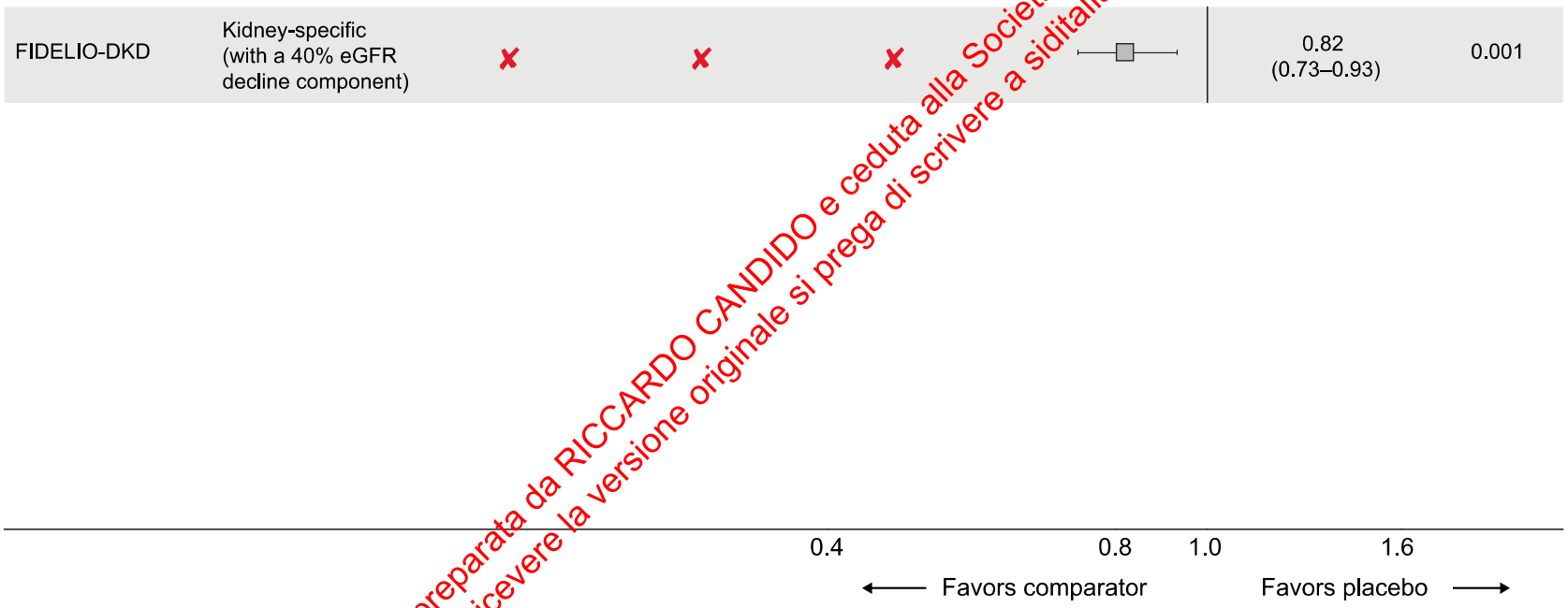


Matched HF incidence

Agarwal R *et al*. *Nephrol Dial Transplant 2022; 37: 1261–1269*

When key differences in trial design are accounted for, FIDELIO-DKD and CREDENCE demonstrate cardiorenal benefits of similar magnitude

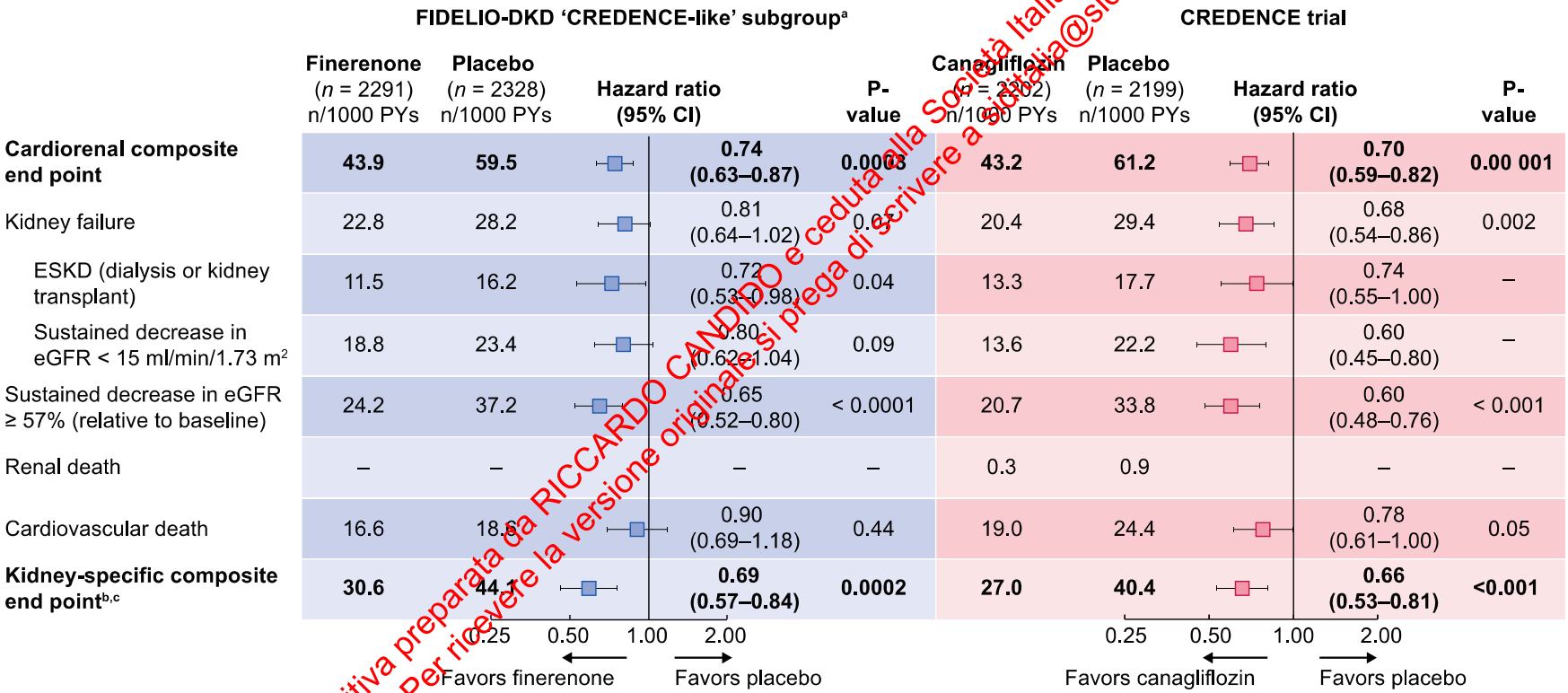
Dataset	Composite endpoint	Equivalent endpoints?	Equivalent CKD eligibility criteria?	Matched HF incidence?	Hazard ratio (95% CI)	*P*-value
FIDELIO-DKD	Kidney-specific (with a 40% eGFR decline component)	✘	✘	✘	0.82 (0.73–0.93)	0.001



*Patients with an eGFR >75 mL/min/1.73 m^2 were ineligible for FIDELIO-DKD; #*p*-value unavailable as this was an inflation analysis

Agarwal R *et al*. *Nephrol Dial Transplant 2022; 37: 1261–1269*

In the FIDELIO-DKD CREDENCE-like subgroup, finerenone reduced the risk of the cardiorenal outcome by 26% vs placebo



Agarwal R *et al*. *Nephrol Dial Transplant 2022; 37: 1261–1269*

Patients treated with SGLT-2i at baseline had higher eGFR and HbA1c, and lower median UACR and SBP than those without

Patient characteristic*	No SGLT-2i (n=5415)	SGLT-2i (n=259)
Age, years	66±9	63±10
Race, White	3412 (63)	180 (70)
Black/AA	255 (5)	9 (4)
Asian	1382 (26)	58 (22)
Sex, male	3795 (70)	188 (73)
SBP, mmHg	138±14[#]	135±14
BMI, kg/m^2	31±6[‡]	32±6
Duration of diabetes, years	17±9[§]	17±9
HbA1c	7.7±1.5[§]	8.0±1.2
eGFR, mL/min/1.73 m^2	44±13[¶]	51±12
Serum potassium, mmol/L	4.4±0.5[¶]	4.3±0.4
UACR, mg/g, median (IQR)	866 (456–1653)[**]	619 (370–1258)
History of CV disease	2488 (46)	117 (45)

Medication use, n (%)	No SGLT-2i (n=5415)	SGLT-2i (n=259)
ACEi	1865 (34)	77 (30)
ARB	3543 (65)	182 (70)
Diuretics	3069 (57)	145 (56)
Statins	3992 (74)	223 (86)
Potassium-lowering agents	131 (2)	5 (2)
Glucose-lowering therapies	5265 (97)	259 (100)
Insulin and analogues	3464 (64)	173 (67)
GLP-1RA	346 (6)	48 (19)

At baseline, 259 (4.6%) patients were receiving SGLT-2i. After the study start, SGLT-2i was initiated as a new medication in 328 (5.8%) patients

*Values are n (%) or mean ± SD unless otherwise stated. Symbols indicate data missing for the stated number of patients: [#]n=5; [‡]n=17; [§]n=11; [¶]n=2; **n=3

AA, African American; BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; SD, standard deviation

Rossing P *et al. Kidney Int Rep 2022; 7: 36–45*

Kidney benefit was consistent irrespective of SGLT-2i use at baseline and during the trial[1]

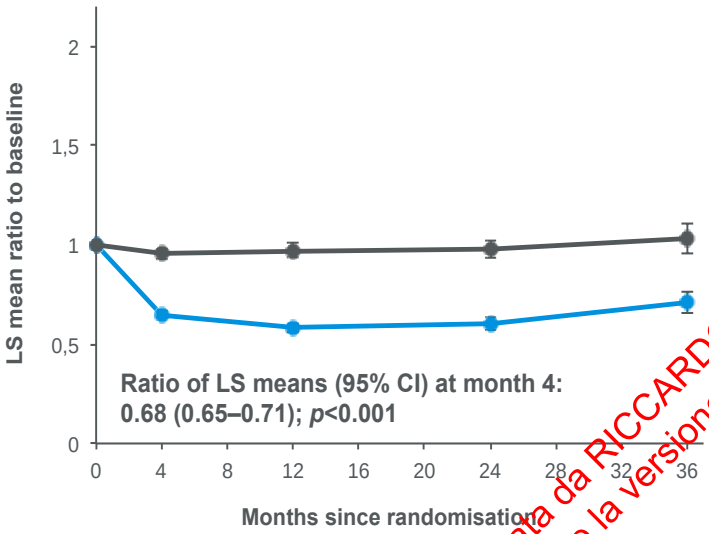
Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)*	*p*-interaction*
Primary composite kidney outcome#				
Overall FIDELIO-DKD population[2]	504/2833 (17.8)	600/2841 (21.1)	0.82 (0.73–0.93)	
No SGLT-2i at baseline	490/2709 (18.1)	590/2706 (21.8)	0.82 (0.72–0.92)	0.21
SGLT-2i at baseline	14/124 (11.3)	10/135 (7.4)	1.38 (0.61–3.10)	
Secondary composite kidney outcome‡				
Overall FIDELIO-DKD population[2]	252/2833 (8.9)	326/2841 (11.5)	0.76 (0.65–0.90)	
No SGLT-2i at baseline	249/2709 (9.2)	320/2706 (11.8)	0.77 (0.65–0.91)	0.54
SGLT-2i at baseline	3/124 (2.4)	6/135 (4.4)	0.50 (0.12–1.99)	

Finerenone benefit for the primary kidney outcome was also consistent regardless of SGLT-2i use at any time (*p*-value for interaction 0.83) §

1. Rossing P *et al. Kidney Int Rep 2022; 7: 36–45*
2. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229

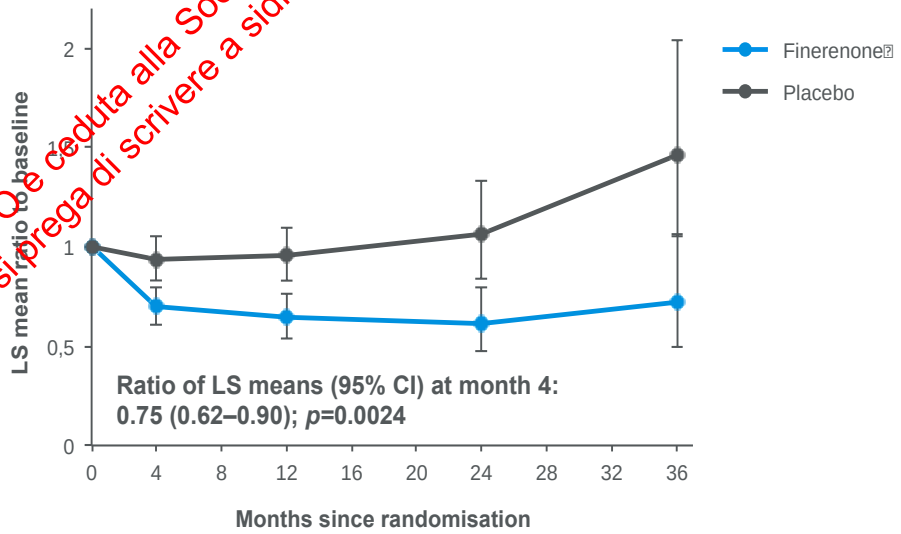
The change in UACR from baseline to month 4 was consistent irrespective of SGLT-2i use at baseline

Without SGLT-2i



No. of patients				
Finerenone	2604	2465	1766	818
Placebo	2597	2471	1742	798

Wit SGLT-2i

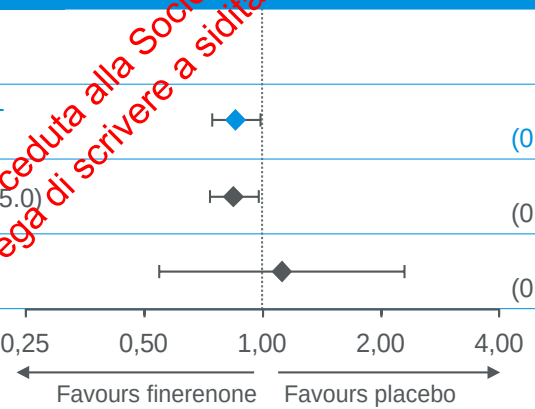


No. of patients				
Finerenone	121	117	72	38
Placebo	129	127	83	36

Rossing P *et al. Kidney Int Rep 2022; 7: 36–45*

CV benefit was consistent irrespective of SGLT-2i use at baseline and during the trial[1]

Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)*	*p*-interaction*
Key secondary composite CV# outcome				
Overall FIDELIO-DKD population[2]	367/2833 (13.0)	420/2841 (14.8)	0.86 (0.75–0.99)	
No SGLT-2i at baseline	352/2709 (13.0)	405/2706 (15.0)	0.85 (0.74–0.98)	0.46
SGLT-2i at baseline	15/124 (12.1)	15/135 (11.1)	1.12 (0.55–2.30)	



Finerenone benefit for the key secondary CV outcome was also consistent regardless of SGLT-2i use at any time (*p*-value for interaction 0.26)‡

*Hazard ratios (95% CI) and interaction *p*-values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup, and a subgroup by treatment interaction term as fixed effects; #secondary composite CV outcome included the number of patients with CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure[1]; ‡Cox proportional hazards model after forward selection (including the following variables: history of CV disease, diuretics use at baseline, age at run-in, baseline HbA1c, baseline C-reactive protein, baseline serum creatinine, baseline serum albumin, and baseline systolic blood pressure) was also used to determine the effect of SGLT-2i use at any time during the trial, including SGLT-2i use as a time-dependent covariate

1. Rossing P *et al. Kidney Int Rep 2022; 7: 36–45*. 2. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229

Overall safety outcomes were consistent, with treatment-emergent hyperkalaemia-related events lower in patients with SGLT-2i use at baseline compared with those without

Treatment-emergent AE, n (%)	No SGLT-2i at baseline		SGLT-2i at baseline	
	Finerenone (n=2703)	Placebo (n=2696)	Finerenone (n=124)	Placebo (n=135)
Any AE	2355 (87.1)	2351 (87.6)	113 (91.1)	117 (86.7)
Related to study drug	621 (23.0)	434 (16.1)	25 (20.2)	15 (11.1)
Leading to permanent discontinuation	202 (7.5)	161 (6.0)	5 (4.0)	7 (5.2)
Any SAE	863 (31.9)	931 (34.5)	39 (31.5)	40 (29.6)
Related to study drug	47 (1.7)	34 (1.3)	1 (0.8)	0 (0.0)
Leading to permanent discontinuation	71 (2.6)	77 (2.9)	4 (3.2)	1 (0.7)
AE with outcome death	30 (1.1)	49 (1.8)	1 (0.8)	2 (1.5)
Treatment-emergent hyperkalaemia AE, n (%)				
Any AE	506 (18.7)	251 (9.3)	10 (8.1)	4 (3.0)
Related to study drug	328 (12.1)	132 (4.9)	5 (4.0)	3 (2.2)
Leading to permanent discontinuation	63 (2.3)	24 (0.9)	1 (0.8)	1 (0.7)
Treatment-emergent AEs of interest by system organ class (>5% patients)				
Hypertension	205 (7.6)	262 (9.7)	7 (5.6)	11 (8.1)
Hypoglycemia	147 (5.4)	187 (6.9)	4 (3.2)	7 (5.2)

AE, adverse event; GLP-1RA, glucagon-like peptide-1 receptor agonist; SAE, serious adverse event; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Rossing P *et al. Kidney Int Rep 2022; 7: 36–45*

Received: 9 July 2021 | Revised: 13 September 2021 | Accepted: 21 September 2021 Diabetes Obes Metab. 2022;24:125–134
DOI: 10.1111/dom.14558

ORIGINAL ARTICLE

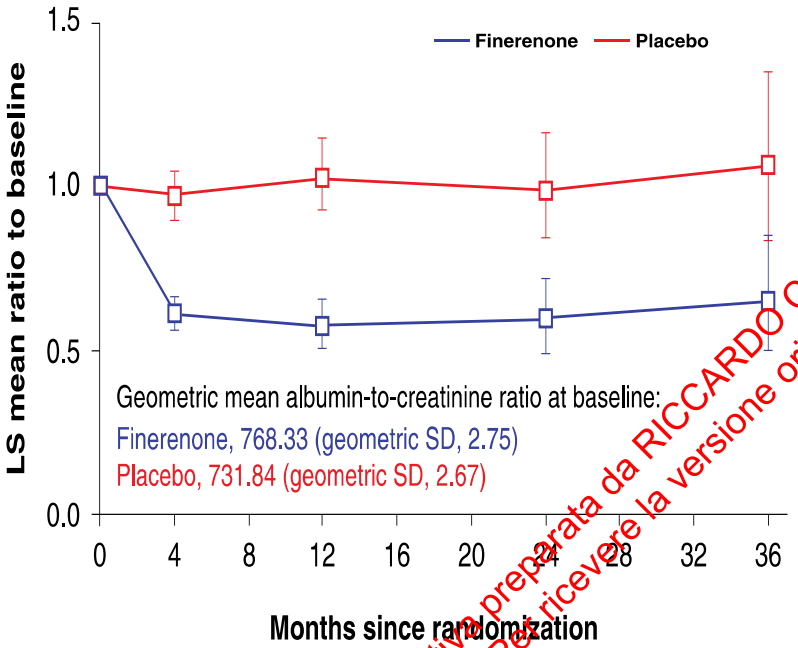
WILEY

Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: A subgroup analysis from the FIDELIO-DKD trial

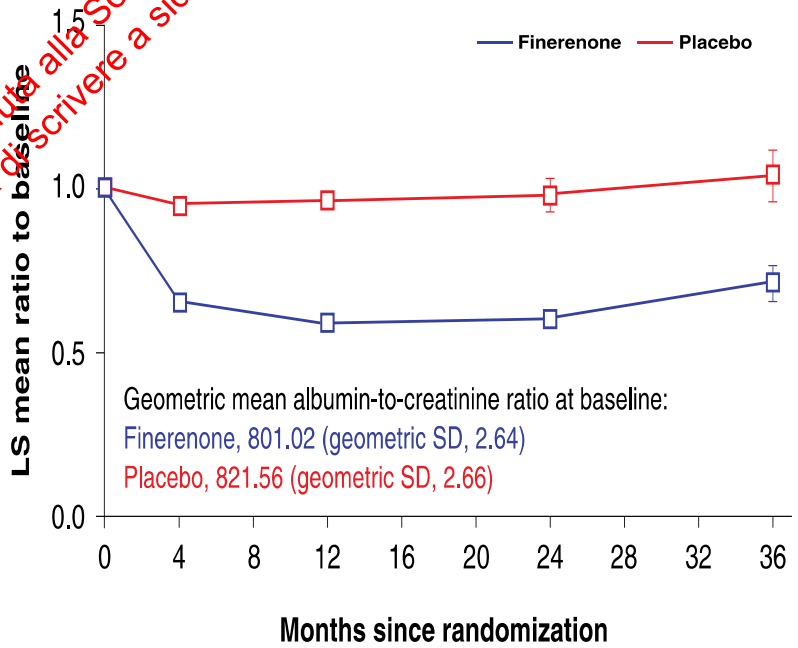
Peter Rossing MD[1,2] | Rajiv Agarwal MD[3] | Stefan D. Anker MD[4] | Gerasimos Filippatos MD[5] | Bertram Pitt MD[6] | Luis M. Ruilope MD[7,8,9] | Aslam Amod MD[10] | Michel Marre MD[11] | Amer Joseph MBBS[12] | Andrea Lage MD[13] | Charlie Scott MSc[14] | George L. Bakris MD[15] | on behalf of the FIDELIO-DKD Investigators

Effect on albuminuria over time by baseline GLP-1RA use

With GLP-1RA at baseline



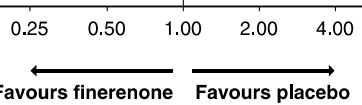
Without GLP-1RA at baseline



Rossing P et al. Diabetes Obes Metab. 2022;24:125–134

Primary and secondary composite outcomes by baseline GLP-1RA use

Outcome	Finerenone		Placebo		Hazard ratio (95% CI)†	$P_{interaction}$‡
	n/N (%)	n per 100 PY	n/N (%)	n per 100 PY		
Primary composite kidney outcome						0.15
GLP-1RA at baseline	32/189 (16.9)	7.03	32/205 (15.6)	6.29	1.17 (0.71, 1.90)	
No GLP-1RA at baseline	472/2644 (17.9)	7.63	568/2636 (21.5)	9.32	0.80 (0.71, 0.91)	
Secondary composite kidney outcome						0.33
GLP-1RA at baseline	18/189 (9.5)	3.82	20/205 (9.8)	3.80	1.04 (0.55, 1.96)	
No GLP-1RA at baseline	234/2644 (8.9)	3.63	306/2636 (11.6)	4.81	0.75 (0.63, 0.88)	
Secondary composite CV outcome						0.51
GLP-1RA at baseline	27/189 (14.3)	5.54	28/205 (13.7)	5.20	1.02 (0.60, 1.74)	
No GLP-1RA at baseline	340/2644 (12.9)	5.07	392/2636 (14.9)	5.98	0.85 (0.73, 0.98)	



Rossing P et al. Diabetes Obes Metab. 2022;24:125–134

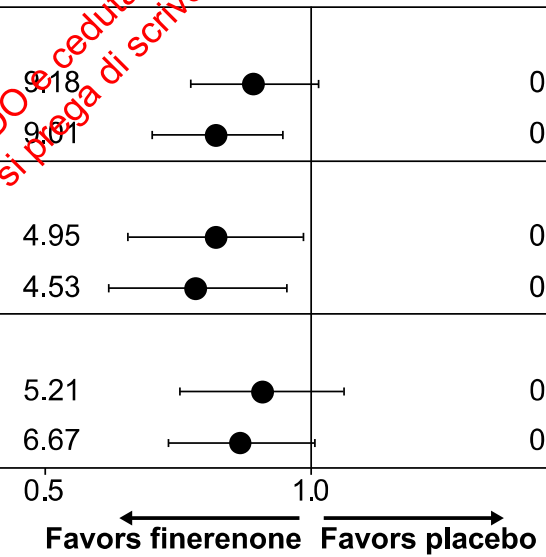
Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes According to Baseline HbA_{1c} and Insulin Use: An Analysis From the FIDELIO-DKD Study

*Peter Rossing,[1,2] Ellen Burgess,[3] Rajiv Agarwal,[4] Stefan D. Anker,[5] Gerasimos Filippatos,[6] Bertram Pitt,[7] Luis M. Ruilope,[8–10] Pieter Gillard,[11] Richard J. MacIsaac,[12] Julio Wainstein,[13,14] Amer Joseph,[15] Meike Brinker,[15] Lothar Roessig,[15] Charlie Scott,[16] and George L. Bakris,[17] on behalf of the FIDELIO-DKD Investigators**

Diabetes Care 2022;45:888–897 | https://doi.org/10.2337/dc21-1944

Finerenone in Patients With CKD and Type 2 Diabetes According to Baseline HbA1c

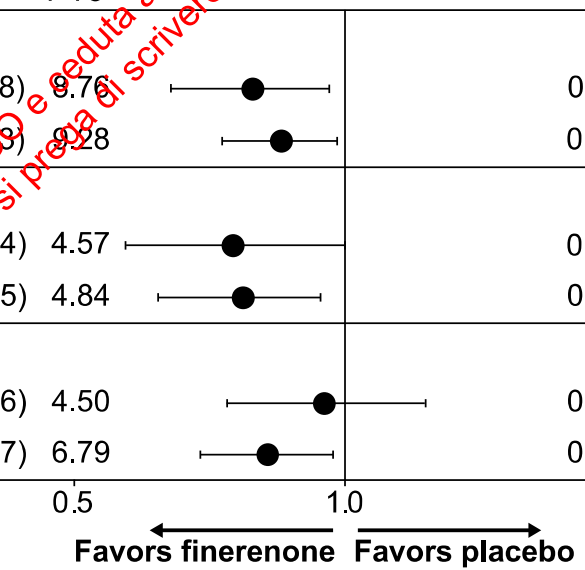
Outcome by baseline HbA_{1c}	Finerenone (N=2826) n/N (%)	Finerenone (N=2826) n/100 PYs	Placebo (N=2837) n/N (%)	Placebo (N=2837) n/100 PYs	Hazard ratio (95% CI)	*P* for interaction
Primary composite kidney outcome						
HbA1c <7.5%	260/1384 (18.8)	7.92	304/1410 (21.6)	9.18	0.86 (0.73–1.02)	0.41
HbA1c ≥7.5%	243/1442 (16.9)	7.27	296/1427 (20.7)	9.01	0.78 (0.66–0.93)	
Secondary composite kidney outcome						
HbA1c <7.5%	129/1384 (9.3)	3.77	171/1410 (12.1)	4.95	0.78 (0.62–0.98)	0.80
HbA1c ≥7.5%	122/1442 (8.5)	3.50	155/1427 (10.9)	4.53	0.74 (0.59–0.94)	
Key secondary composite CV outcome						
HbA1c <7.5%	164/1384 (11.8)	4.80	187/1410 (13.3)	5.21	0.88 (0.71–1.09)	0.70
HbA1c ≥7.5%	201/1442 (13.9)	5.58	233/1427 (16.3)	6.67	0.83 (0.69–1.01)	



Rossing P et al. Diabetes Care 2022;45:888–897

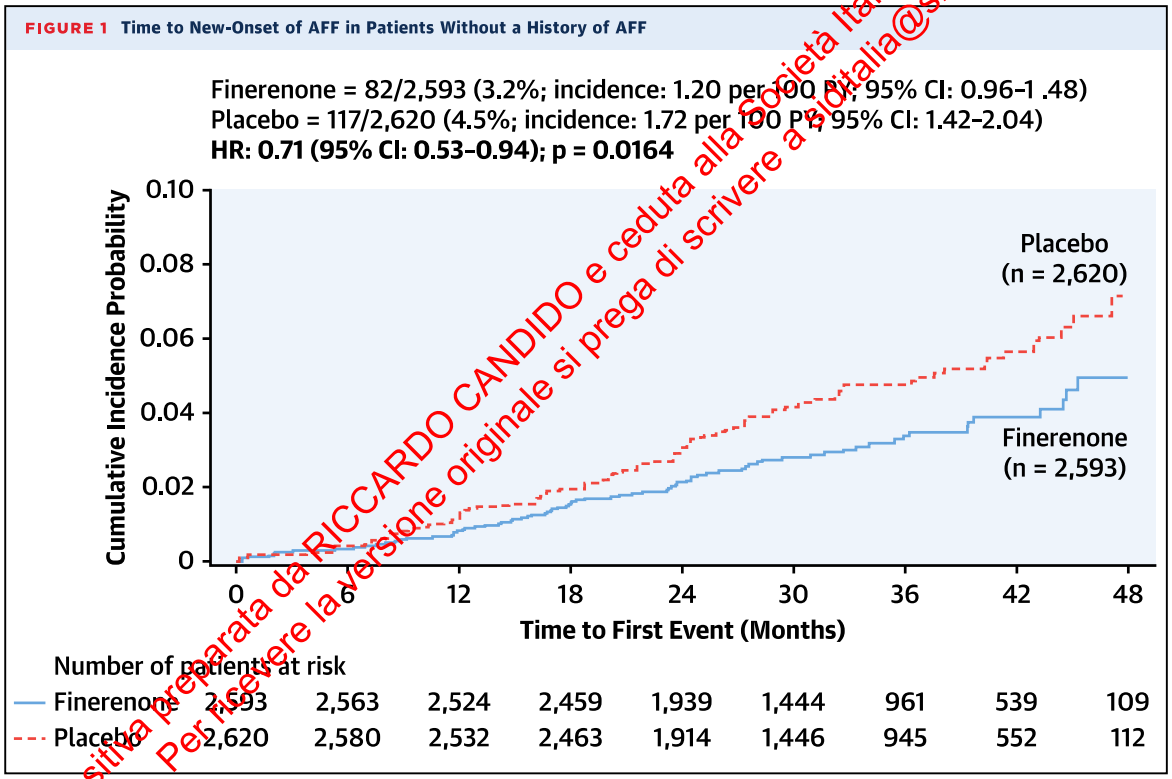
Finerenone in Patients With CKD and Type 2 Diabetes According to Insulin Use

Outcome by baseline insulin use	Finerenone (N=2833) n/N (%)	Finerenone (N=2833) n/100 PYs	Placebo (N=2841) n/N (%)	Placebo (N=2841) n/100 PYs	Hazard ratio (95% CI)	*P* for interaction
Primary composite kidney outcome						
No insulin at baseline	172/990 (17.4)	7.14	218/1047 (20.8)	8.76	0.79 (0.64–0.96)	0.56
Insulin at baseline	332/1843 (18.0)	7.85	382/1794 (21.3)	9.28	0.85 (0.73–0.98)	
Secondary composite kidney outcome						
No insulin at baseline	86/990 (8.7)	3.44	119/1047 (11.4)	4.57	0.75 (0.57–1.00)	0.93
Insulin at baseline	166/1843 (9.0)	3.76	207/1794 (11.5)	4.84	0.74 (0.59–0.94)	
Key secondary composite CV outcome						
No insulin at baseline	112/990 (11.3)	4.31	121/1047 (11.6)	4.50	0.88 (0.71–1.09)	0.70
Insulin at baseline	255/1843 (13.8)	5.56	299/1794 (16.7)	6.79	0.83 (0.69–1.01)	



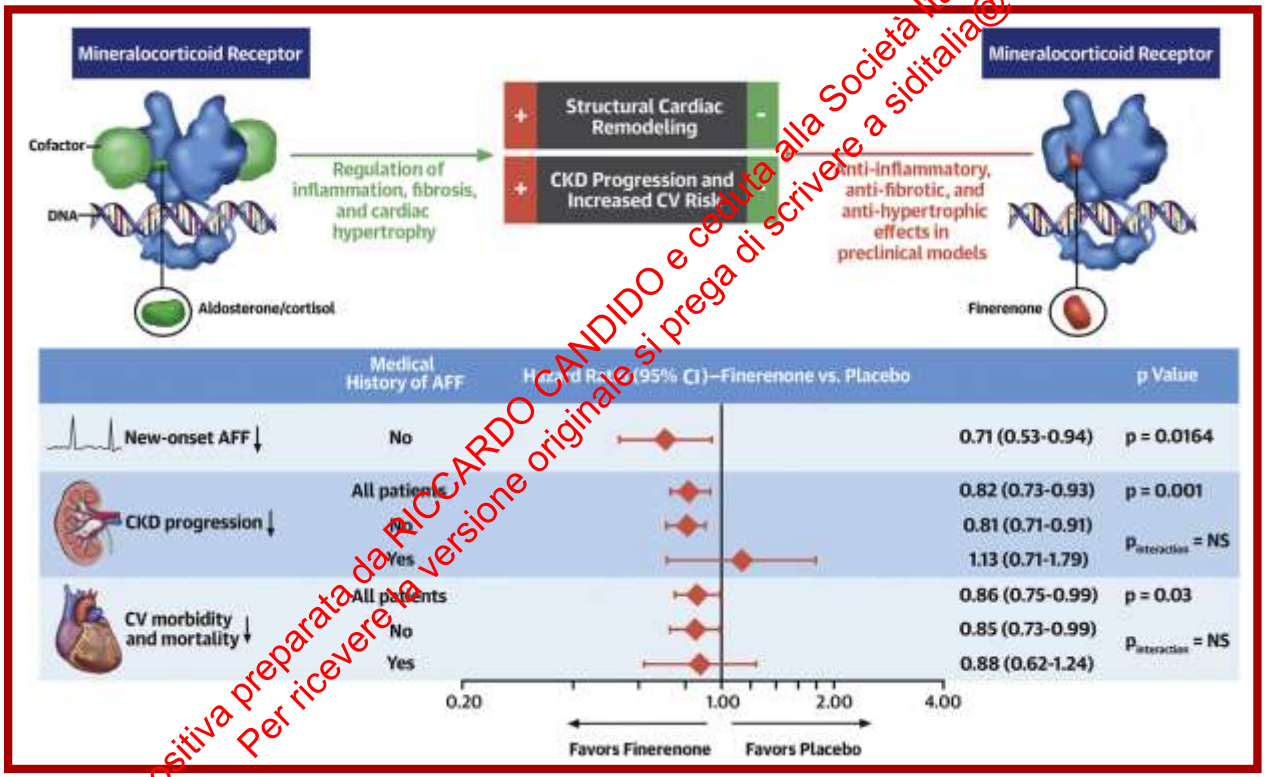
Rossing P et al. Diabetes Care 2022;45:888–897

Finerenone Reduces New-Onset Atrial Fibrillation in Patients With CKD and Type 2 Diabetes



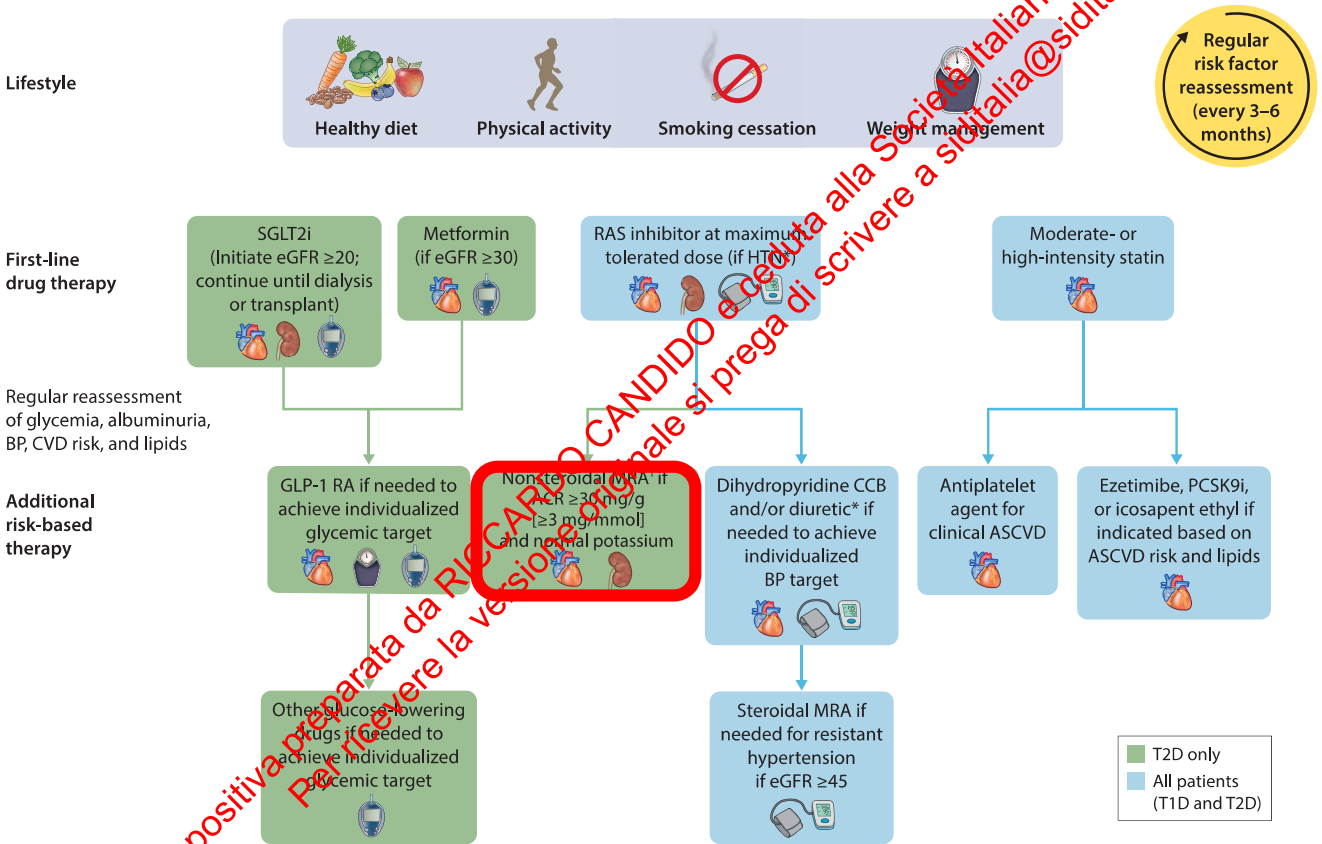
Filippatos G et al. J Am Coll Cardiol 2021;78:142–52

New-Onset AFF and Cardiorenal Outcomes by AFF History in FIDELIO-DKD



Filippatos G et al. J Am Coll Cardiol 2021;78:142–52

KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE



Kidney International (2022) 102 (Suppl 5S), S1–S127