Lo Studio FIGARO

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Disclosures

Grant: Sankyo, sanofi (University of Pisa)

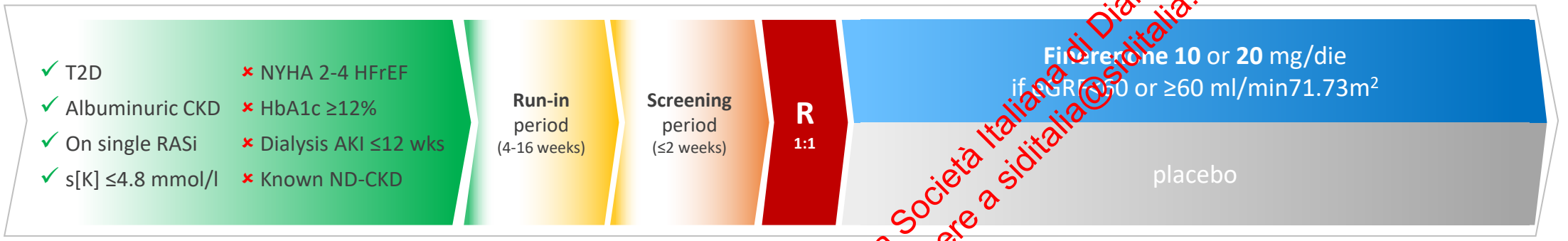
Advisory Board: Bayer, Novo, Sankyo

Talks: Lilly, Novo, sanofi, Boehringer Ingelheim

Agenda

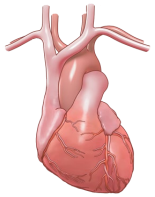
- The FIGARO Study
- The FIDELITY analysis
- Impact on Guidelines

FIGARO-DKD study design



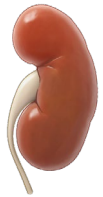
	UACR mg/g	eGFR mL/min/1.73m²
Microalbuminuric population:	≥30, <300	≥25, <90
Macroalbuminuric population:	≥300, ≤5000	≥60

Key endpoints



PRIMARY

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



KEY SECONDARY

Time to kidney failure (initiation of chronic dialysis for ≥90 days, kidney transplantation or sustained eGFR <15 ml/min/1.73 m²), **sustained ≥40% decrease in eGFR from baseline, or renal death**

Pitt B, N Engl J Med 2021

FIGARO-DKD enrolled population

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	0.2%	2.7%	14.9%
	G2	Mildly decreased	60–89	0.7%	13.4%	29.8%
	G3a	Mildly to moderately decreased	45–59	1.0%	15.3%	4.6%
	G3b	Moderately to severely decreased	30–44	0.8%	12.8%	1.2%
	G4	Severely decreased	15–29	0.2%	2.3%	0.2%
	G5	Kidney failure	<15			

Total by KDIGO risk	
Low risk:	0.8%
Moderate risk:	17.1%
High risk:	60.9%
Very high risk:	21.1%

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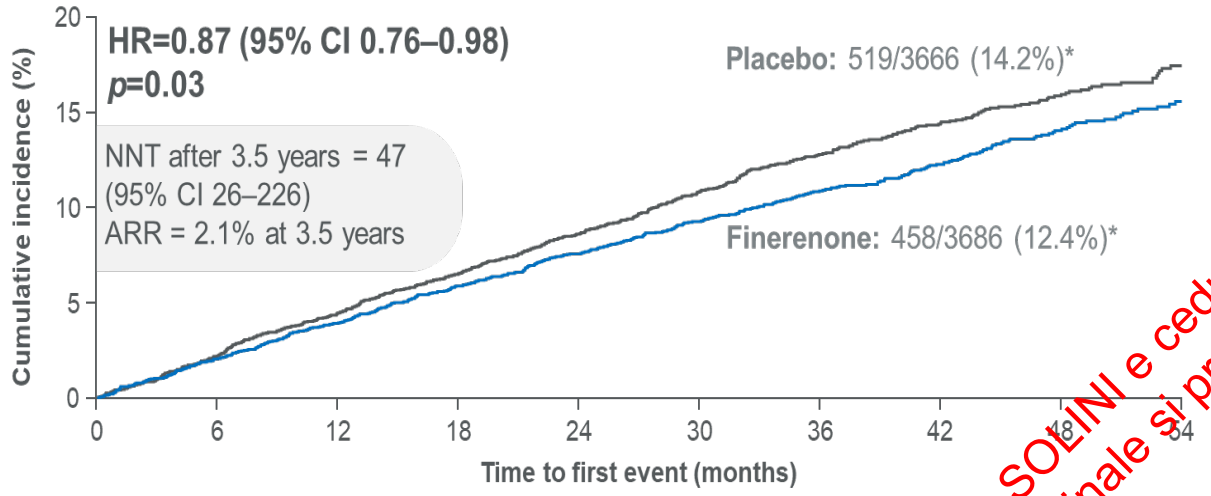
FIGARO-DKD patients characteristics

Selected baseline characteristics (mean age: 64.1 yrs)		Finerenone (n=3686)	Placebo(n=3666)
Mean eGFR, ml/min/1.73 m^2, ± SD		67.6±21.7	68.0±21.7
eGFR at baseline, ml/min/1.73 m^2, n (%)	<25	15 (0.4)	12 (0.3)
	25–<45	641 (17.4)	610 (16.6)
	45–<60	745 (20.2)	789 (21.5)
	≥60	2285 (62.0)	2254 (61.5)
Median UACR, mg/g, (IQR)		308 (105–749)	315 (111–731)
UACR at baseline, mg/g, n (%)	<30	1851 (50.2)	1878 (51.2)
	30–<300	1726 (46.8)	1688 (46.0)
	≥300	109 (3.0)	98 (2.7)
Mean HbA1c, %, ± SD		7.7±1.4	7.7±1.4
Mean systolic blood pressure, mmHg, ± SD		135.8±14.0	135.7±14.1
Mean duration of T2D, years, ± SD		14.5±8.6	14.4±8.4
History of CV disease, n (%)		**1676 (45.5)**	**1654 (45.1)**
ACE inhibitor, n (%)		1576 (42.8)	1561 (42.6)
ARB, n (%)		2108 (57.2)	2104 (57.4)
Mean serum potassium, mmol/l		4.33±0.43	4.33±0.43
Insulin, n (%)		2023 (54.9)	1970 (53.7)
GLP-1RA, n (%)		308 (8.4)	242 (6.6)
SGLT2 inhibitor, n (%)		314 (8.5)	304 (8.3)
SGLT2 inhibitor post-baseline, n (%)		580 (15.7)	578 (15.8)

Pitt B, N Engl J Med 2021

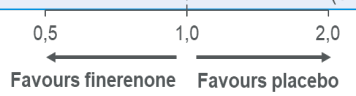
Finerenone and primary CV outcome



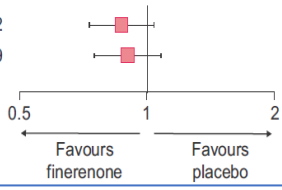
No. at risk									
Finerenone	3686	3600	3517	3427	3320	2781	2184	1093	598
Placebo	3666	3577	3479	3389	3267	2730	2125	1076	585

median of 3.4 years of follow-up

Outcome	Finerenone (n=3686) n (%)	Finerenone (n=3686) n/100 PY	Placebo (n=3666) n (%)	Placebo (n=3666) n/100 PY	HR (95% CI)	p-value
Primary composite CV outcome*	458 (12.4)	3.87	519 (14.2)	4.45	0.87 (0.76–0.98)	0.03
CV death	194 (5.3)	1.56	214 (5.8)	1.74	0.90 (0.74–1.09)	–
Non-fatal MI	103 (2.8)	0.85	102 (2.8)	0.85	0.99 (0.76–1.31)	–
Non-fatal stroke	108 (2.9)	0.89	111 (3.0)	0.92	0.97 (0.74–1.26)	–
Hospitalisation for HF	117 (3.2)	0.96	163 (4.4)	1.36	0.71 (0.56–0.90)	–



Outcome	Finerenone n/N	Placebo n/N	Finerenone n/100 PY	Placebo n/100 PY	Hazard ratio (95% CI)	$P_{interaction}$
CV composite						
UACR 30–<300 mg/g	226/1726 (13.1)	251/1688 (14.9)	3.88	4.42	0.87 (0.73–1.04)	0.60
UACR ≥300 mg/g	222/1851 (12.0)	254/1878 (13.5)	3.94	4.49	0.90 (0.75–1.08)	

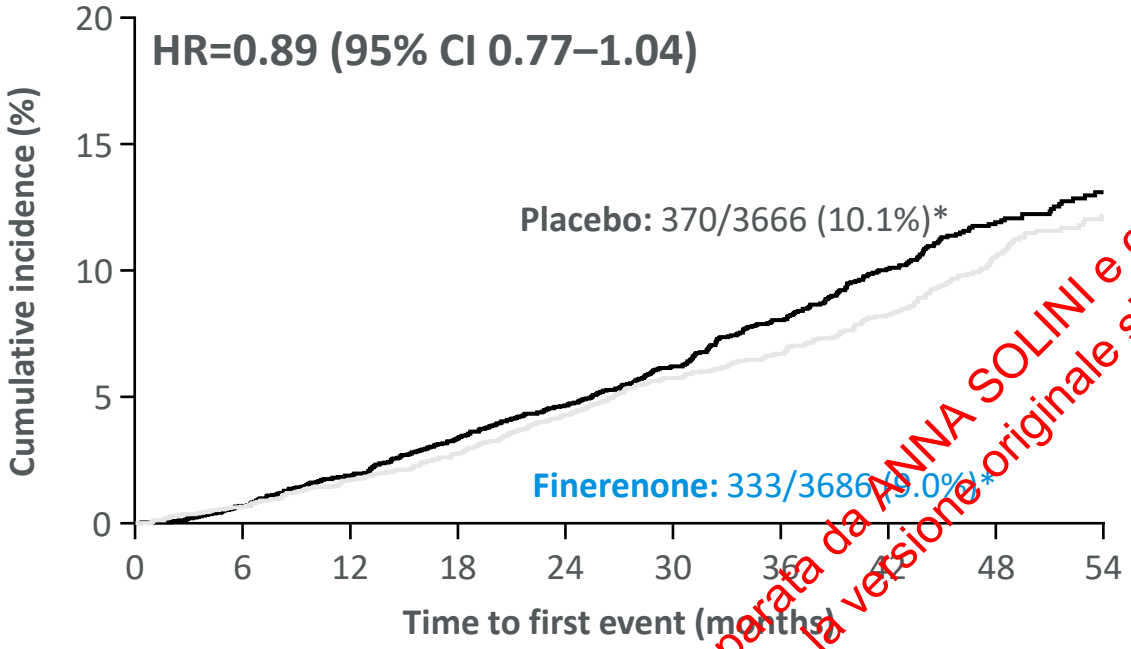


*Composite of CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF

Pitt B, N Engl J Med 2021; Ruilope LM, Nephrol Dial Transplant 2022

Death from any cause and hospitalisation for any cause

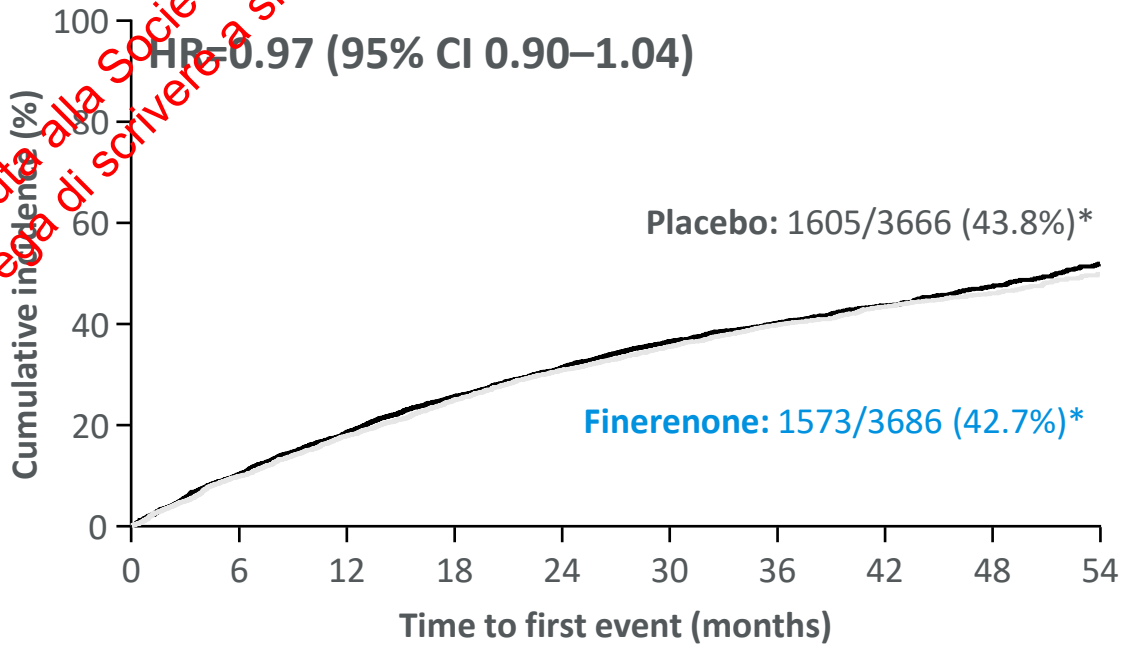
Death from any cause



No. at risk

3686	3661	3620	3581	3505	2968	2358	1858	1187	653
3666	3639	3593	3539	3469	2938	2315	1820	1177	647

Hospitalisation for any cause



No. at risk

3686	3306	3003	2730	2483	1956	1457	1116	678	350
3666	3277	2960	2684	2442	1935	1438	1090	682	337

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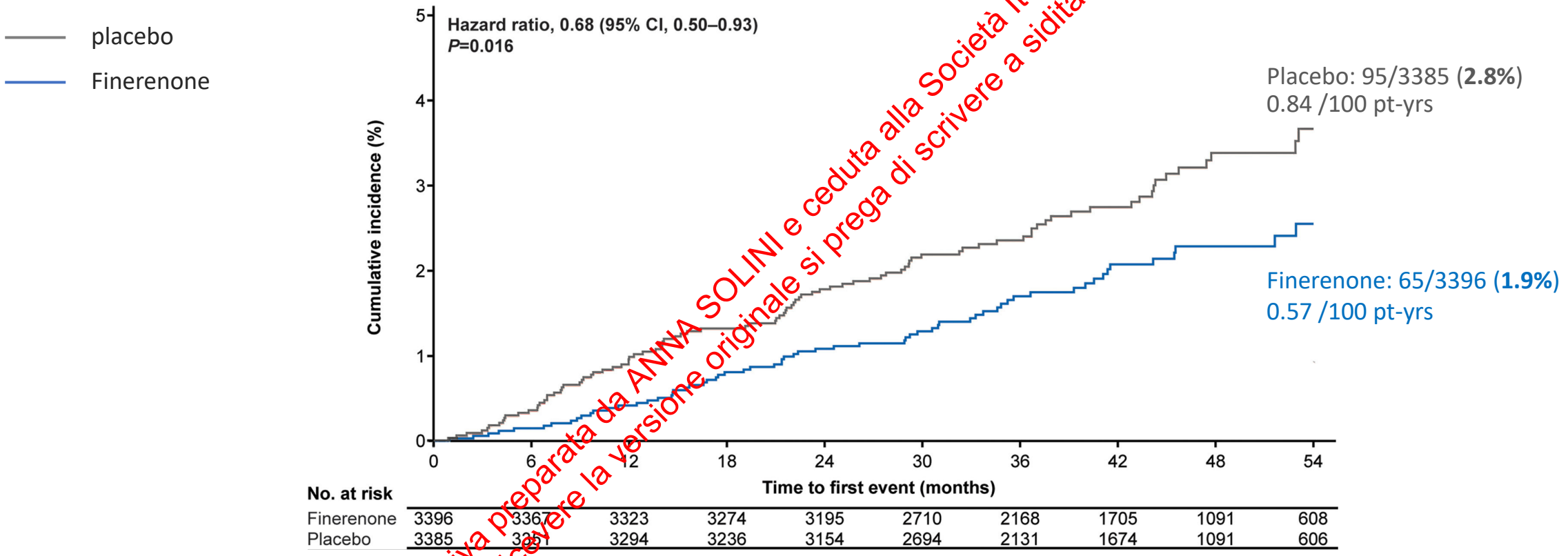
Finerenone and new-onset HF

Time to new-onset HF (defined as the first hospitalization for HF in patients without a history of HF at baseline)

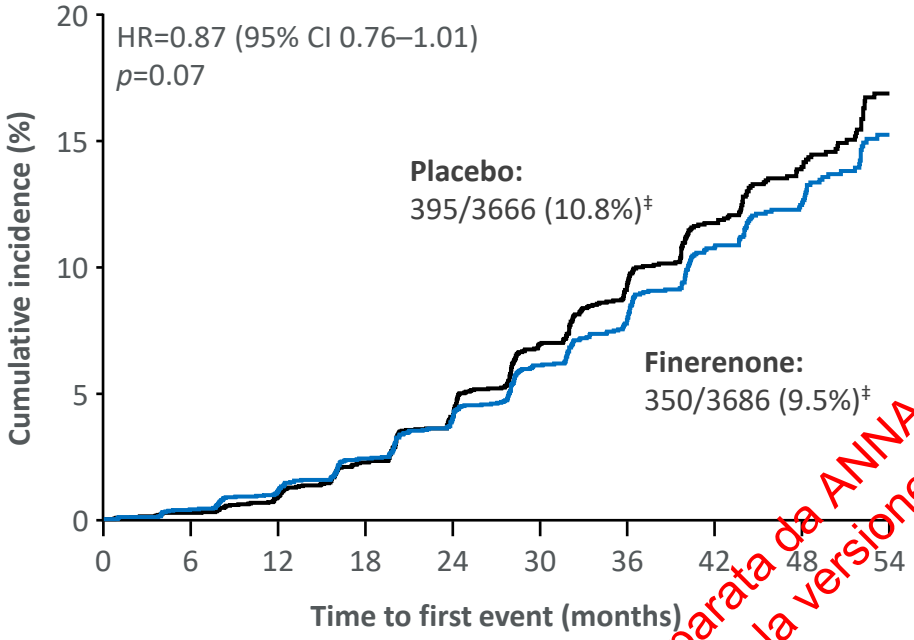


Filippatos et al., Circulation 2022; 145:437-447; doi: 10.1161/CIRCULATIONAHA.121.057983

Finerenone and secondary and exploratory additional composite kidney outcomes

Secondary kidney composite outcome

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

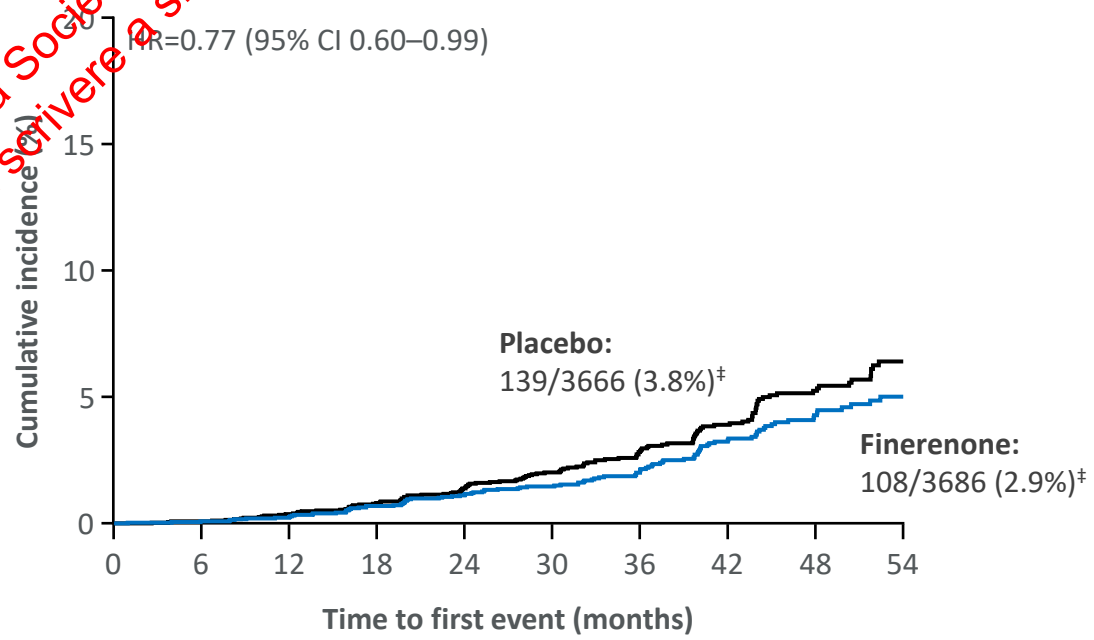


No. at risk

Finerenone	3686	3550	3445	3301	3131	2540	1940	1481	908	480
Placebo	3666	3546	3436	3282	3096	2502	1933	1443	907	485

Exploratory, additional kidney outcome

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



No. at risk

Finerenone	3686	3559	3474	3356	3218	2651	2047	1582	973	522
Placebo	3666	3552	3452	3325	3178	2615	2039	1538	970	520

*ESKD or an eGFR <15 ml/min/1.73 m^2; #events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; ‡number of patients with an event over a median of 3.4 years of follow-up

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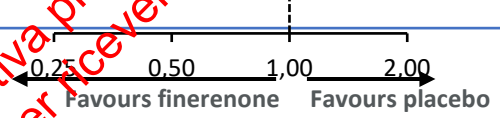
Secondary and exploratory additional composite kidney outcomes

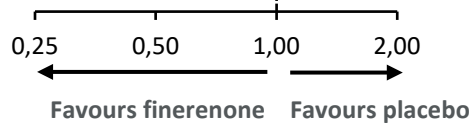
Components of the secondary kidney composite

Outcome	Finerenone (n=3686)		Placebo (n=3666)		HR (95% CI)
	n (%)	n/100 PY	n (%)	n/100 PY	
Secondary kidney outcome	350 (9.5)	3.15	395 (10.8)	3.58	0.87 (0.76–1.01)
Kidney failure*	46 (1.2)	0.40	62 (1.7)	0.54	0.72 (0.49–1.05)
ESKD	32 (0.9)	0.26	49 (1.3)	0.40	0.64 (0.41–<1.00‡)
Sustained# decrease in eGFR to <15 ml/min/1.73 m^2	28 (0.8)	0.24	38 (1.0)	0.33	0.71 (0.43–1.16)
Sustained# ≥40% decrease in eGFR	338 (9.2)	3.04	385 (10.5)	3.49	0.87 (0.75–1.00)
Renal death	0	–	2 (<0.1)	–	–



Components of the exploratory Additional kidney composite

	Finerenone (n=3686)	Placebo (n=3666)	HR (95% CI)
Secondary kidney composite	108 (2.9)	139 (3.8)	0.77 (0.60–0.99)
Kidney failure*	46 (1.2)	62 (1.7)	0.72 (0.49–1.05)
Sustained# ≥57% decrease in eGFR	90 (2.4)	116 (3.2)	0.76 (0.58–1.00)
Renal death	0	2 (<0.1)	–



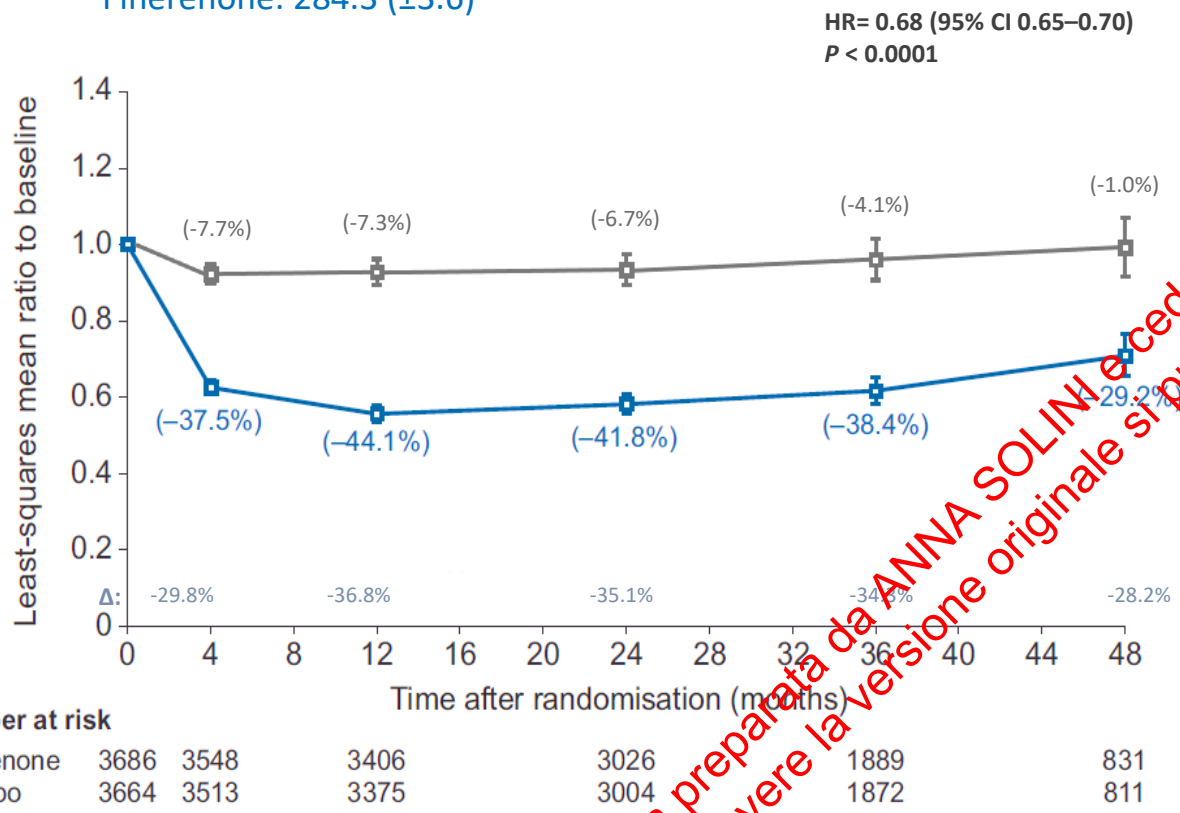
A 57% decrease in eGFR from baseline is equivalent to doubling of serum creatinine

p-values are not reported for components of composite outcomes.
*Kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 ml/min/1.73 m^2; #from baseline and confirmed by two eGFR measurements ≥4 weeks apart; ‡higher CI = 0.995

Pitt B, N Engl J Med 2021

Finerenone and UACR

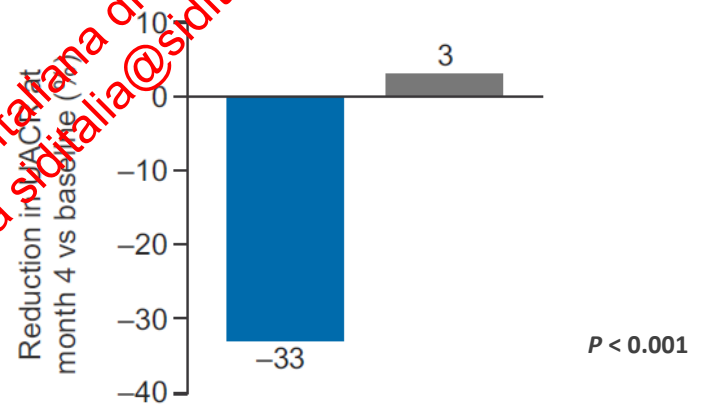
At baseline:
Placebo: 288.9 (±3.5)
Finerenone: 284.3 (±3.6)



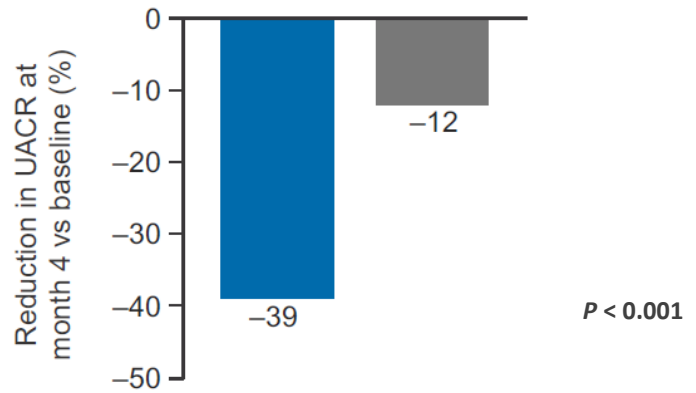
Number at risk

Finerenone	3686	3548	3406	3026	1889	831
Placebo	3664	3513	3375	3004	1872	811

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



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

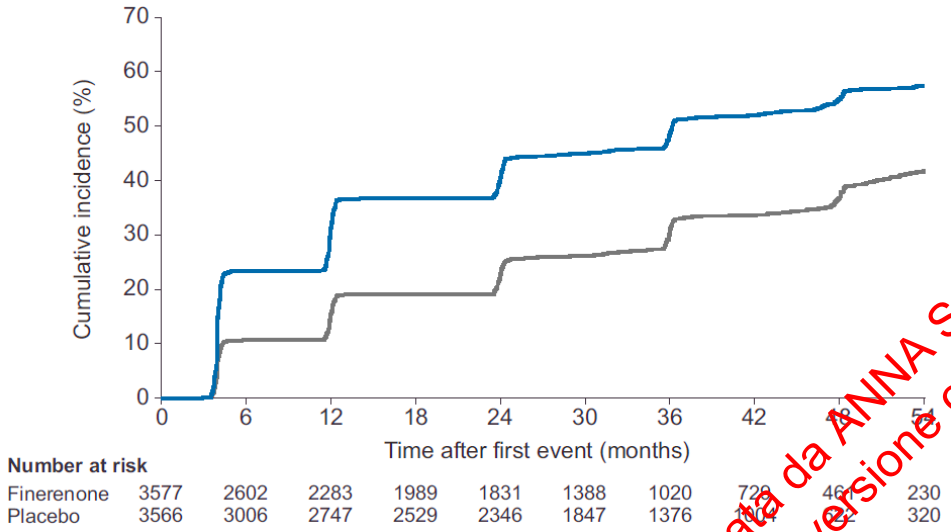


Ruilope ML, Nephrol Dial Transplant 2022

Finerenone significantly improves albuminuria regression and reduces albuminuria worsening

Albuminuria regression*

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

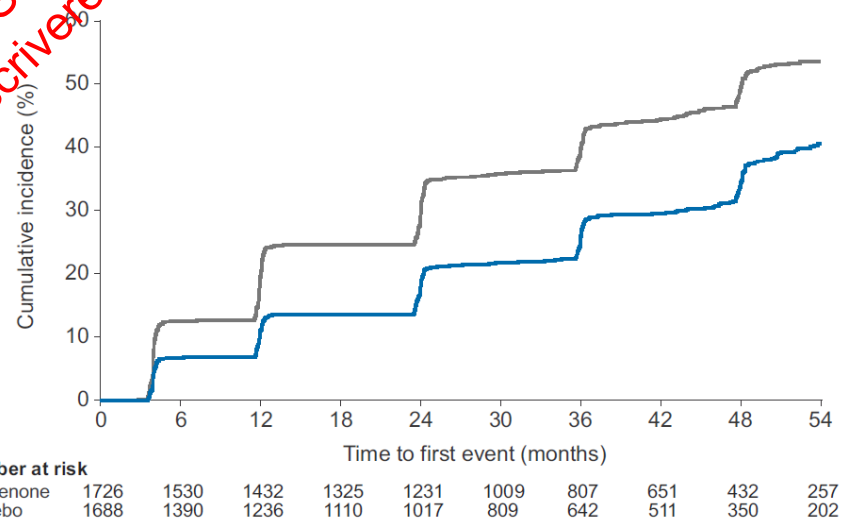


Number at risk										
Finerenone	3577	2602	2283	1989	1831	1388	1020	729	461	230
Placebo	3566	3006	2747	2529	2346	1847	1376	1004	642	320

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

Albuminuria progression**

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



Number at risk										
Finerenone	1726	1530	1432	1325	1231	1009	807	651	432	257
Placebo	1688	1390	1236	1110	1017	809	642	511	350	202

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

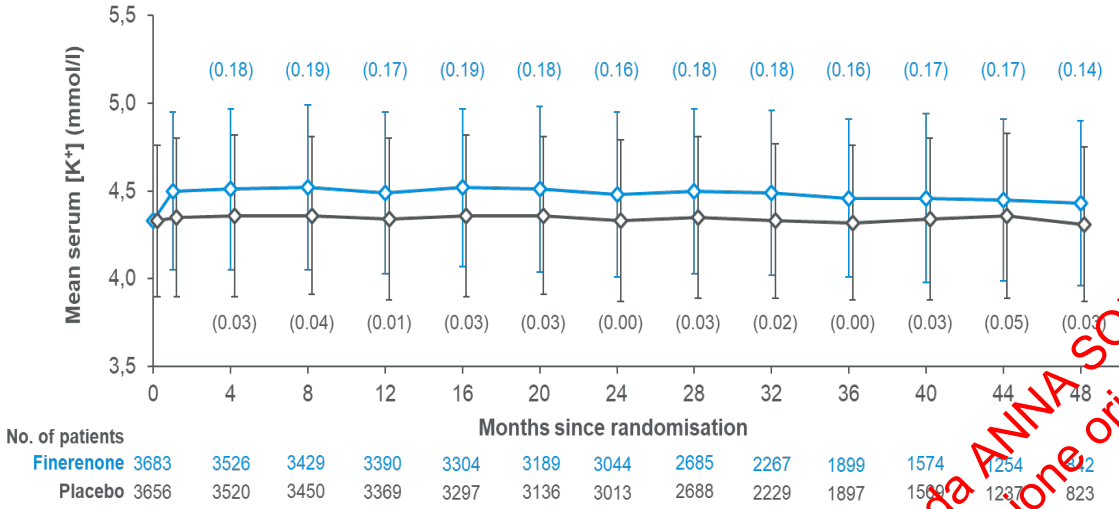
* Changed from severely increased to moderately increased albuminuria, or moderately increased to normal albuminuria, accompanied by a UACR decrease from baseline of >30%; ** UACR level of ≥ 300mg/g that was accompanied by a ≥ 30% increase in UACR from baseline

Ruilope ML, Nephrol Dial Transplant 2022

Other effects

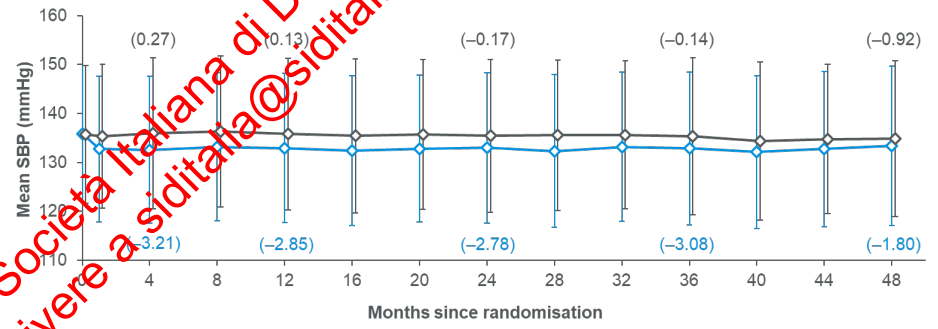
Mean serum potassium (mmol/L)

At baseline:
Placebo: 4.33 (±0.43)
Finerenone: 4.33 (±0.43)



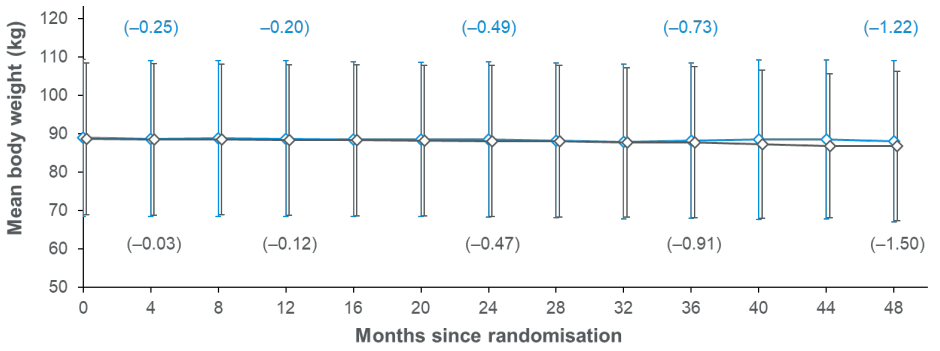
Maximum mean difference in serum potassium between groups= **0.16 mmol/l** at month 16

SBP

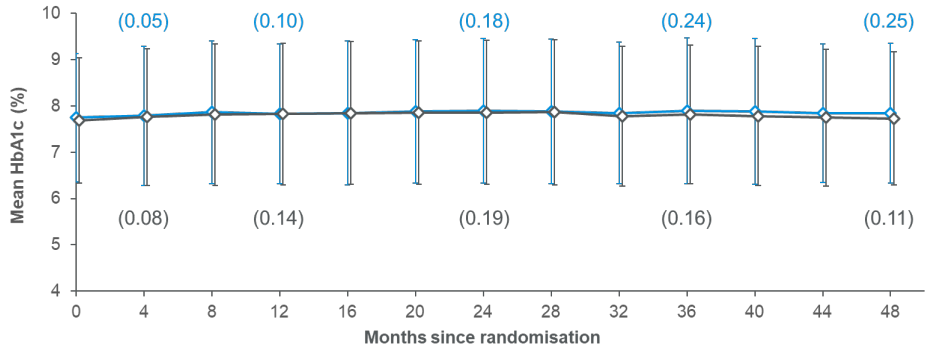


Maximum mean difference in blood pressure between groups= -**3.5 mmHg** at month 4

Body weight



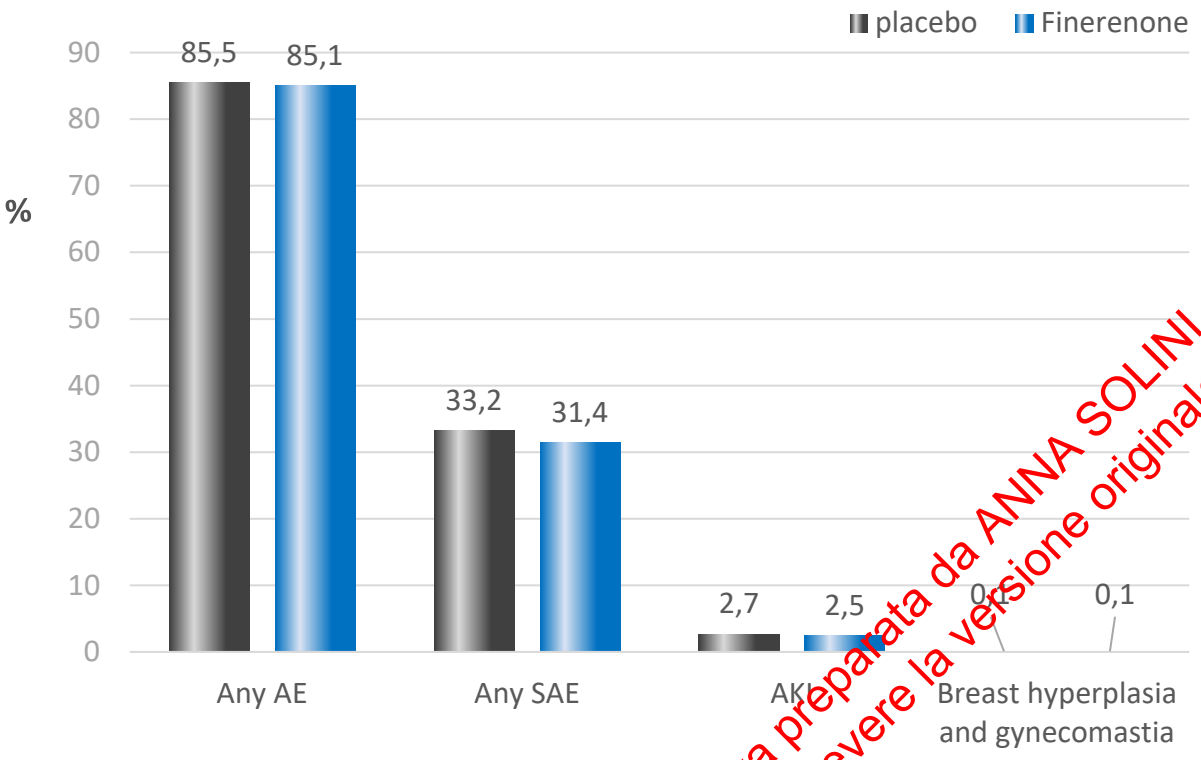
HbA1c



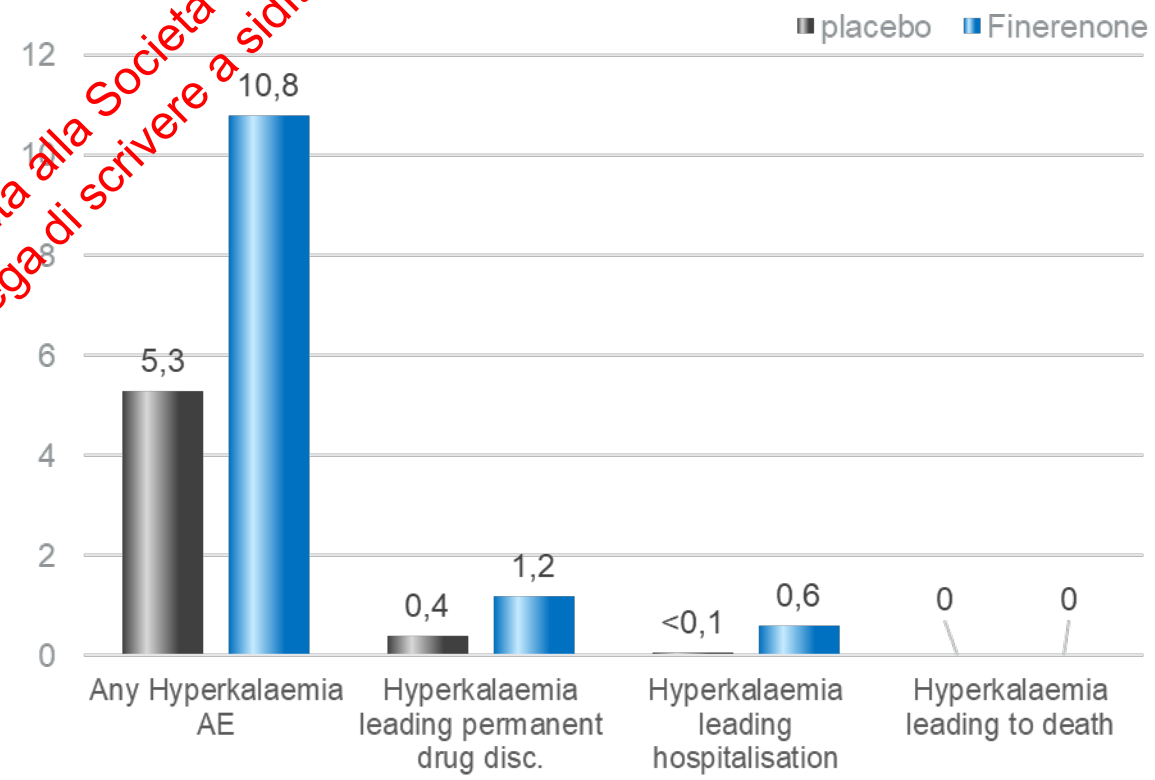
Pitt B, N Engl J Med 2021

AE and SAE and hyperkalaemia events

Patients with a serious and non-serious Adverse Events (%)



Patients with a treatment-emergent Hyperkalaemia AE (%)



Pitt B, N Engl J Med 2021

Agenda

- The FIGARO Study
- The FIDELITY analysis

FIDELITY: FIDELIO & FIGARO pooled analysis

FIDELIO-DKD

Population: 5.734
Median Follow-up: 2.6 years

UACR mg/g	**eGFR** mL/min/1.73m^2
≥30, <300	≥25, <60 + retinopathy
≥300, ≤5000	≥25, <75

+

FIGARO-DKD

Population: 7.437
Median Follow-up: 3.4 years

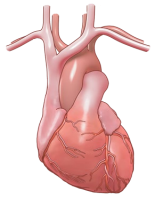
UACR mg/g	**eGFR** mL/min/1.73m^2
≥30, <300	≥25, <90
≥300, ≤5000	≥60

FIDELITY

- ✓ T2D
- ✓ Albuminuric CKD
- ✓ On single RASi
- ✓ s[K] ≤4.8 mmol/l
- ✗ NYHA 2-4 HFrEF
- ✗ HbA1c ≥12%
- ✗ Dialysis AKI ≤12 wks
- ✗ Known ND-CKD

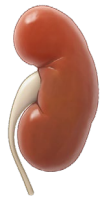
Run-in period (4-16 weeks) → **Screening** period (≤2 weeks) → **R** 1:1

- **Finerenone** 10 or 20 mg/die if eGRF<60 or ≥60 ml/min71.73m^2
- placebo



PRIMARY

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



KEY SECONDARY

Time to kidney failure (initiation of chronic dialysis for ≥90 days, kidney transplantation or sustained eGFR <15 ml/min/1.73 m^2), **sustained ≥57% decrease in eGFR from baseline, or renal death**

Bakris G, N Engl J Med 2020; Pitt B, N Engl J Med 2021

FIDELITY Pooled Analysis

FIDELIO-DKD

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	≥90				
G2	Mildly decreased	60–89				10%
G3a	Mildly to moderately decreased	45–59			4%	75%
G3b	Moderately to severely decreased	30–44			6%	
G4	Severely decreased	15–29				
G5	Kidney failure	<15				

30≤UACR<300 mg/g and **25≤eGFR<60** mL/min/1.73m² and history of **diabetic retinopathy**

or

300≤UACR≤5000 mg/g and **25≤eGFR<75** mL/min/1.73m²

+

FIGARO-DKD

Persistent albuminuria categories Description and range		
A1	A2	A3
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
		45%
	13%	
	15%	
	13%	

30≤UACR<300 mg/g and **25≤eGFR<90** mL/min/1.73m²

or

300≤UACR≤5000 mg/g and **eGFR≥60** mL/min/1.73m²

=

FIDELITY
(FIDELIO-DKD + FIGARO-DKD pooled)

Persistent albuminuria categories Description and range		
A1	A2	A3
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol

1. KDIGO. Kidney Int 2020; 2. Ruilope LM, Am J Nephrol 2019; 3. Bakris G, Am J Nephrol 2019; 4. Agarwal R, Eur Heart J 2021

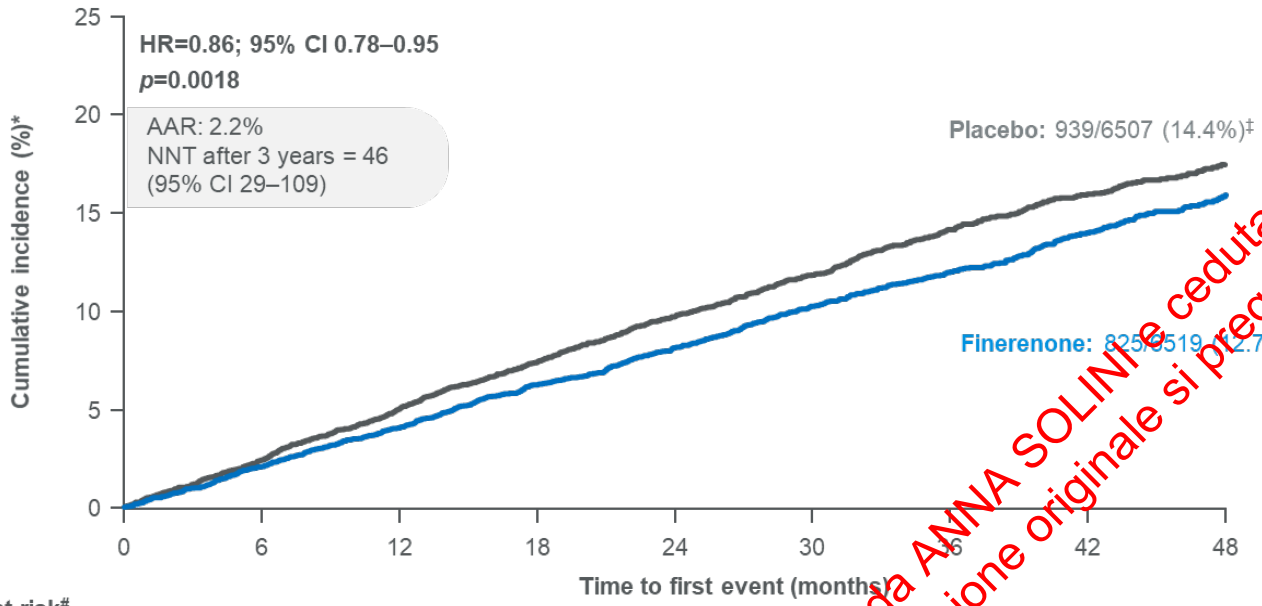
FIDELITY-DKD patients main characteristics

Selected baseline characteristics (mean age: 64.8 yrs)		Finerenone (n=6519)	Placebo(n=6507)
Mean eGFR, ml/min/1.73 m^2, ± SD		57.5±21.6	57.7±21.8
eGFR at baseline, ml/min/1.73 m^2, n (%)	<25	81 (1.2)	81 (1.2)
	25–<45	2117 (32.5)	2115 (32.5)
	45–<60	1717 (26.3)	1717 (26.4)
	≥60	2603 (39.9)	2592 (39.8)
Median UACR, mg/g, (IQR)		514 (198–1129)	515 (198–1163)
UACR at baseline, mg/g, n (%)	<30	120 (1.8)	110 (1.4)
	30–<300	2076 (31.8)	2023 (31.1)
	≥300	4321 (66.3)	4371 (67.2)
Serum potassium, mmol/L		4.35±0.44	4.35±0.44
Mean HbA1c, %, ± SD		7.7±1.4	7.7±1.4
Mean systolic blood pressure, mmHg, ± SD		136.8±14.2	136.7±14.3
Mean duration of T2D, years, ± SD		15.4±8.7	15.4±8.7
History of CV disease, n (%)		**2979 (45.7)**	**2956 (45.4)**
ACE inhibitor, n (%)		2526 (38.7)	2553 (39.2)
ARB, n (%)		3987 (61.2)	3950 (60.7)
Mean serum potassium, mmol/l		4.35±0.44	4.35±0.44
Insulin, n (%)		3866 (59.3)	3764 (57.8)
GLP-1RA, n (%)		497 (7.6)	447 (6.9)
SGLT-2 inhibitor, n (%)		438 (6.7)	439 (6.7)

Agarwal R, Eur Heart J 2021

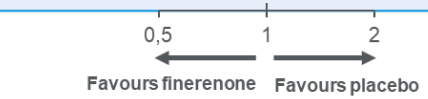
Effect on the CV composite outcome

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



median of 3.0 years of follow-up

Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	Hazard ratio (95% CI)	p-value
Composite CV outcome§	**825 (12.7)**	**939 (14.4)**	**0.86 (0.78–0.95)**	**0.0018**
CV death	322 (4.9)	364 (5.6)	0.88 (0.76–1.02)	0.0922
Non-fatal MI	173 (2.7)	189 (2.8)	0.91 (0.74–1.12)	0.3601
Non-fatal stroke	198 (3.0)	198 (3.0)	0.99 (0.82–1.21)	0.9460
Hospitalisation for HF	256 (3.9)	325 (5.0)	0.78 (0.66–0.92)	0.0030

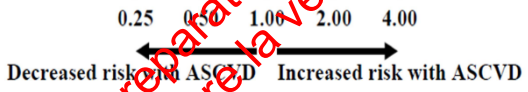


Agarwal R, Eur Heart J 2021

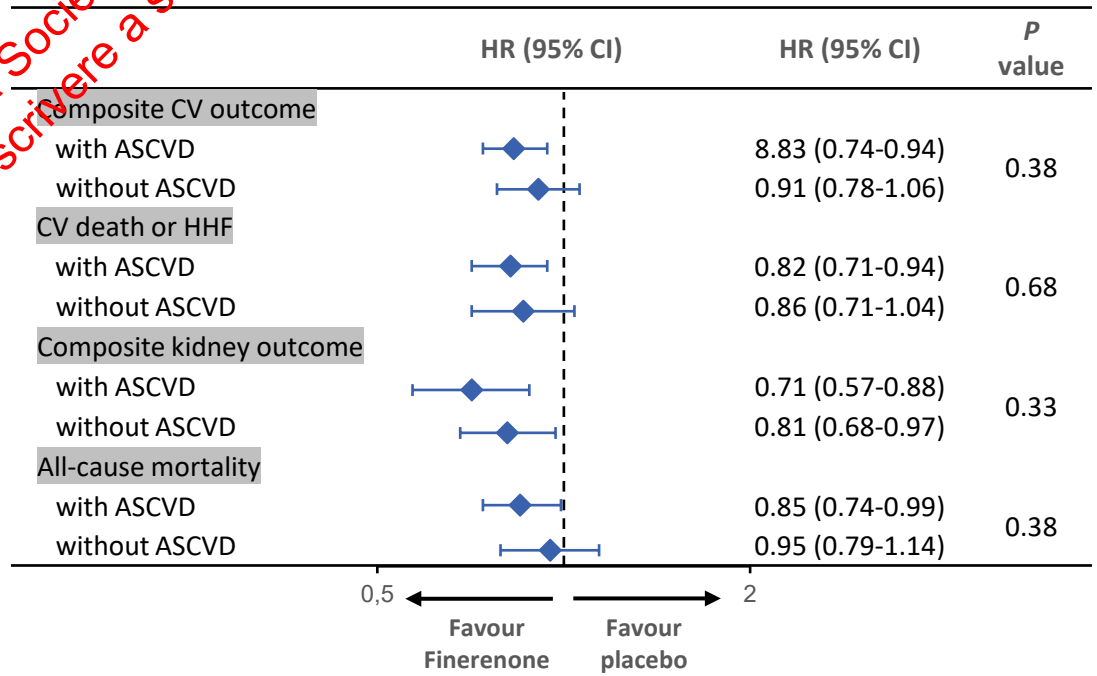
Finerenone and CV endpoints according to the presence of ASCVD history at baseline

Overall population

Outcome	History of ASCVD: Yes (*n* = 5935) *n* (%)	Yes (*n* = 5935) *n* per 100 PY	No (*n* = 7091) *n* (%)	No (*n* = 7091) *n* per 100 PY	Hazard ratio (95% CI)
Composite CV outcome	1106 (18.6)	6.90	658 (9.3)	3.03	2.09 (1.89–2.30)
CV death or HHF	753 (12.7)	4.51	426 (6.0)	1.92	2.13 (1.88–2.40)
Composite kidney outcome	328 (5.5)	2.07	497 (7.0)	2.40	0.96 (0.83–1.10)
All-cause mortality	695 (11.7)	4.03	471 (6.6)	2.09	1.72 (1.52–1.94)



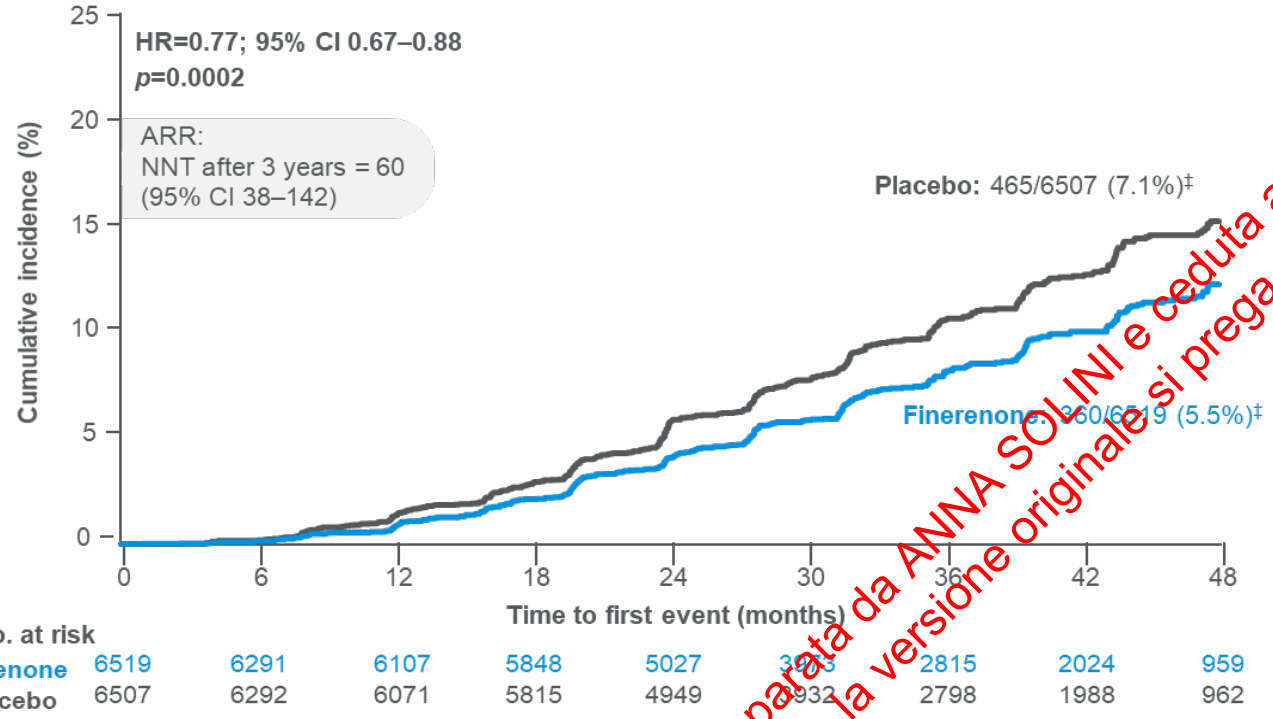
Finerenone vs placebo in T2D and CKD population with or without ASCVD



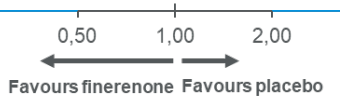
Filippatos G, EHJ Cardiovasc Pharmacother 2022

Finerenone and risk of the renal composite outcome

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



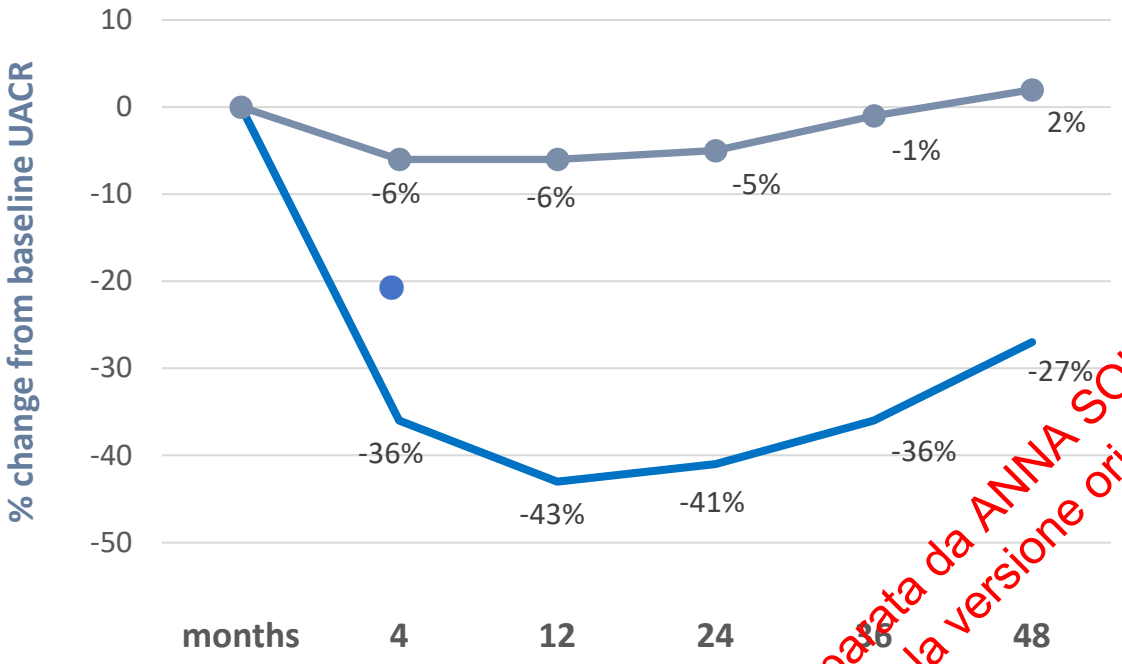
Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	*p*-value
≥57% eGFR kidney composite outcome	**360 (5.5)**	**465 (7.1)**	**0.77 (0.67–0.88)**	**0.0002**
Kidney failure*	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESKD	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040¶
Sustained# decrease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



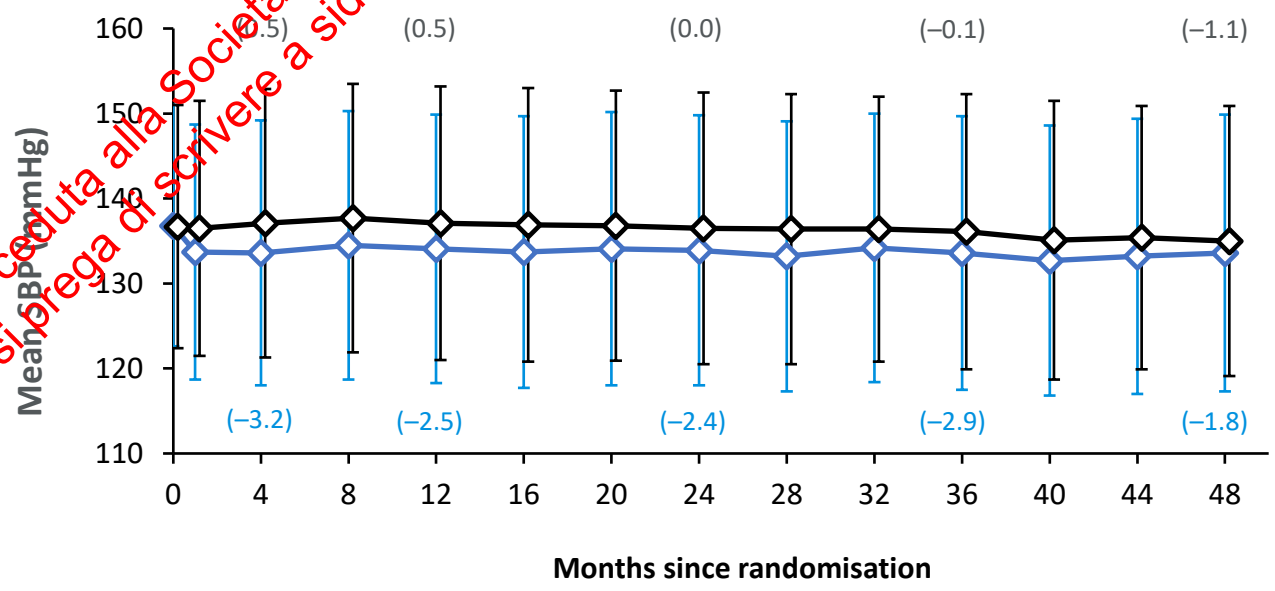
Agarwal R, Eur Heart J 2021

Finerenone and UACR

Urine Albumine-Creatinine ratio



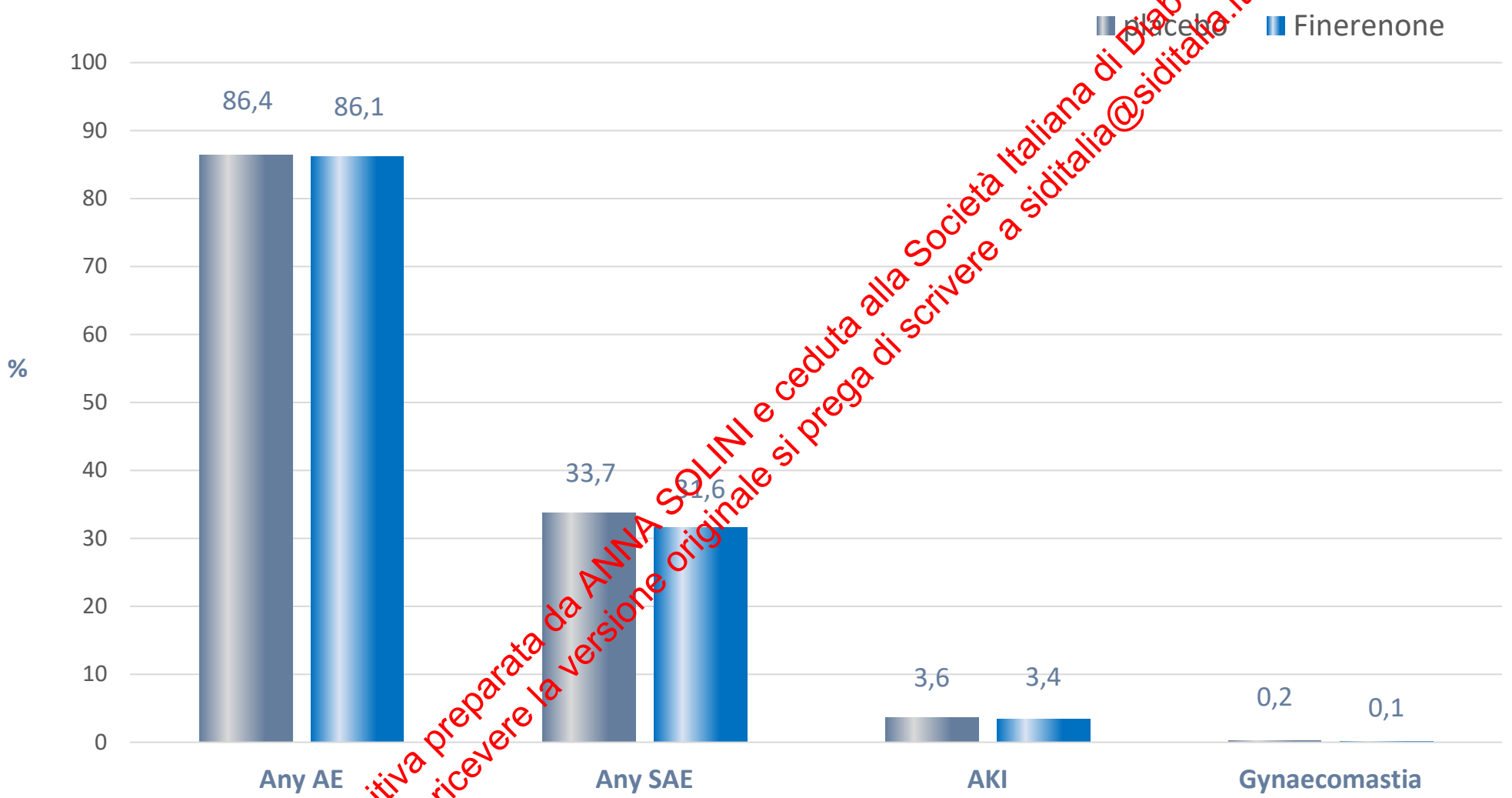
Systolic Blood Pressure



Patients (n):						
Finerenone	6509	6324	6070	5001	2842	926
Placebo	6489	6310	6057	4968	2814	901

Agarwal R, Eur Heart J 2021

Safety (pooled analysis)

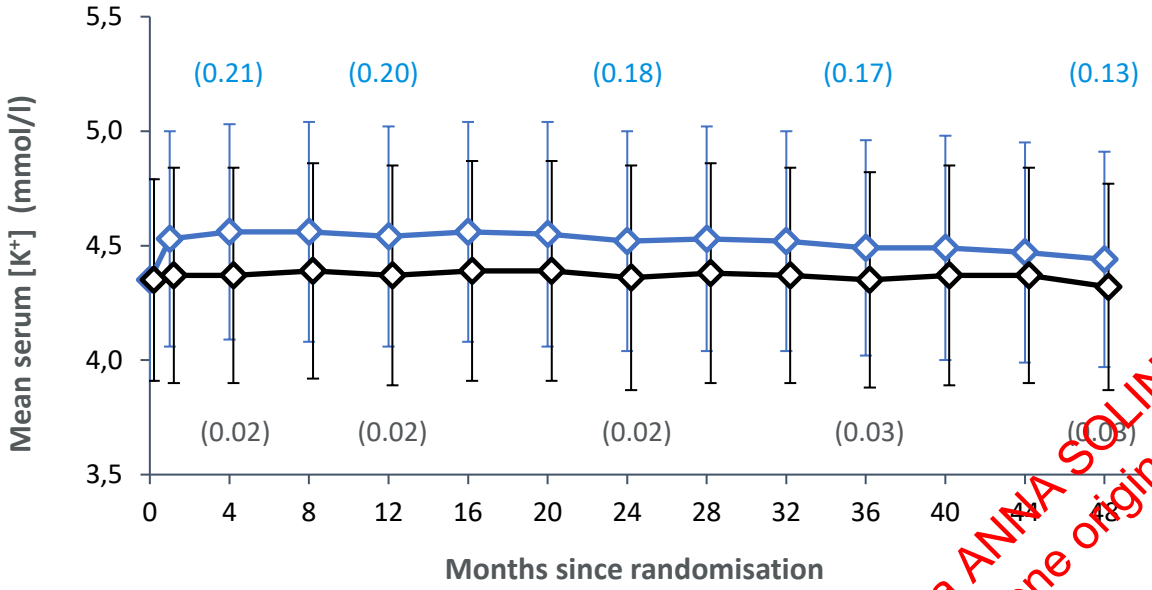


Agarwal R, Eur Heart J 2021

Serum potassium levels and hyperkalaemia in FIDELITY pooled analysis

Mean serum potassium (mmol/L)

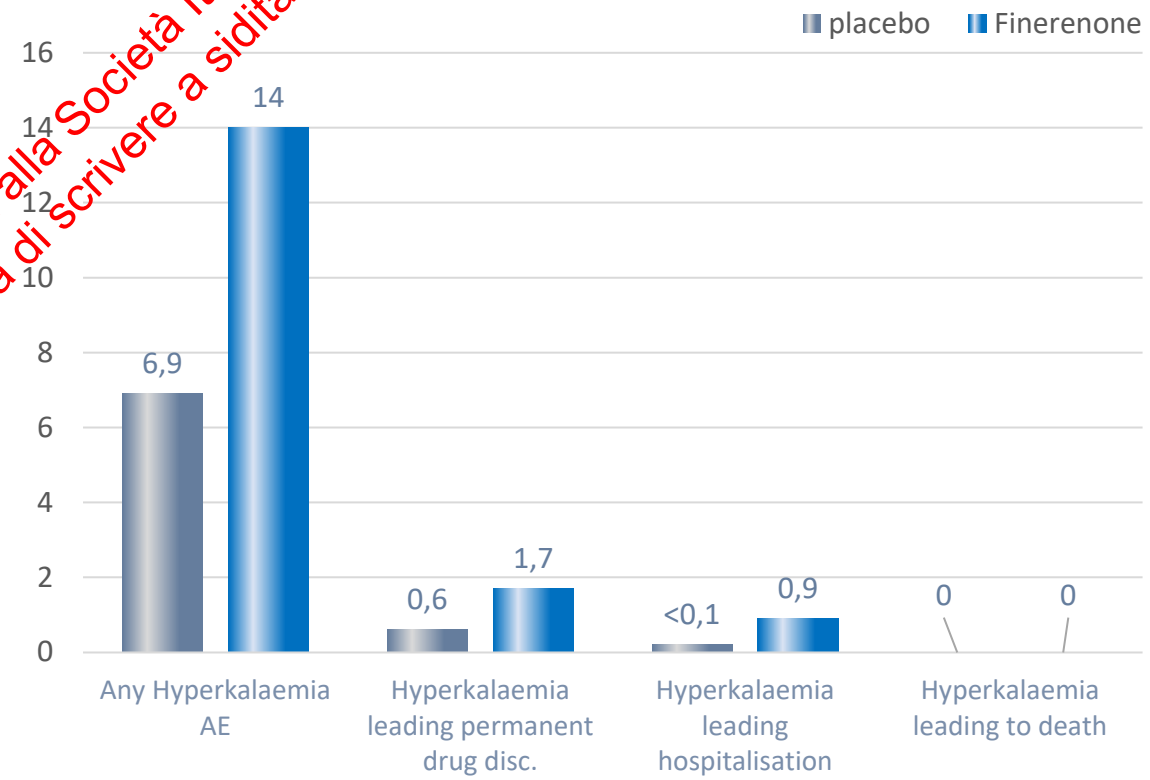
At baseline:
Placebo: 4.35 (±0.44)
Finerenone: 4.35 (±0.44)



Patients (n):						
Finerenone	6510	6234	5990	4916	2781	912
Placebo	6487	6229	5965	4878	2764	887

After 4th month, maximum mean difference in serum potassium between groups was about = **-0.19 mmol/l**

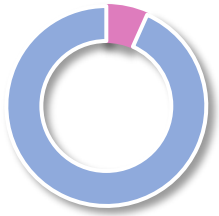
Patients with a treatment-emergent Hyperkalaemia AE (%)



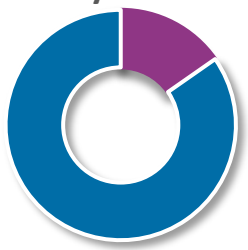
Agarwal R, Eur Heart J 2021

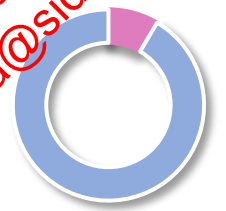
Finerenone reduced primary and secondary outcomes irrespective of SGLT2i use

6.7% (877) of patients use SGLT-2i at baseline



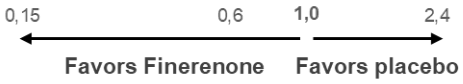
15.3% (1,990) of patients received SGLT-2i at any time during study period





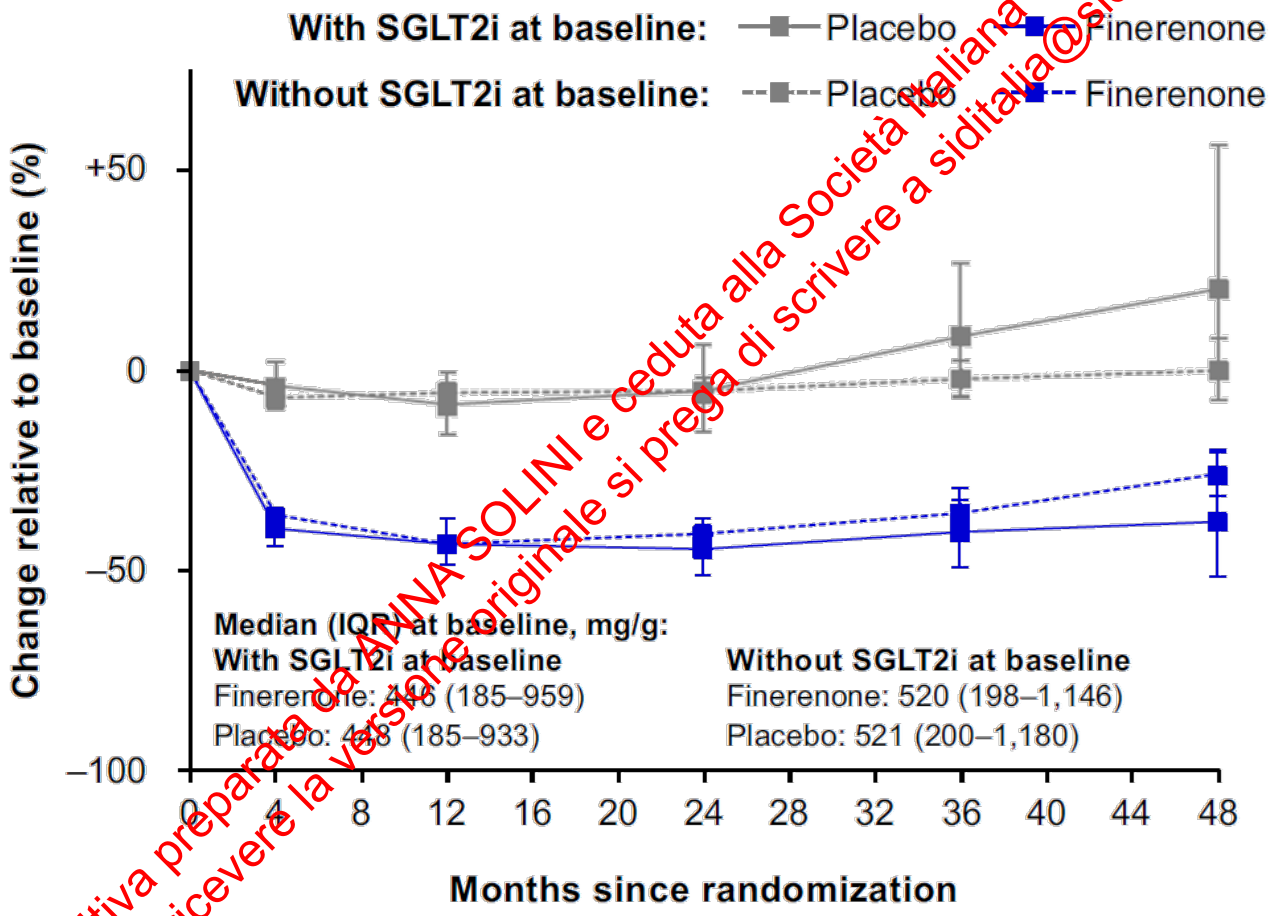
8.5% (1,113) of patients started SGLT-2i during on-treatment period

	Finerenone n/N (%)	Finerenone n/100 PY	Placebo n/N (%)	Placebo n/100 PY	HR (95% CI)	HR (95% CI)	P_{int} value
Cardiovascular Composite outcome							
At baseline							
SGLT2i	39/438 (8.9)	2.95	52/439 (11.8)	4.08		0.67 (0.42-1.07)‡	0.46†
No SGLT2i	786/6081 (12.9)	4.44	887/6068 (14.6)	5.08		0.87 (0.79-0.96)‡	
At any time*							
SGLT2i	41	2.40	58	3.20		0.77 (0.51-1.15)§	0.77§
No SGLT2i	579	3.83	700	4.69		0.82 (0.73-0.91)§	
Kidney Composite outcome							
At baseline							
SGLT2i	9/438 (2.1)	0.70	17/439 (3.9)	1.37		0.42 (0.16-1.08)‡	0.29†
No SGLT2i	351/6081 (5.8)	2.06	448/6068 (7.4)	2.64		0.80 (0.69-0.92)‡	
At any time*							
SGLT2i	11	0.63	13	0.70		0.92 (0.41-2.8)§	0.50§
No SGLT2i	213	1.40	312	2.06		0.69 (0.58-0.83)§	



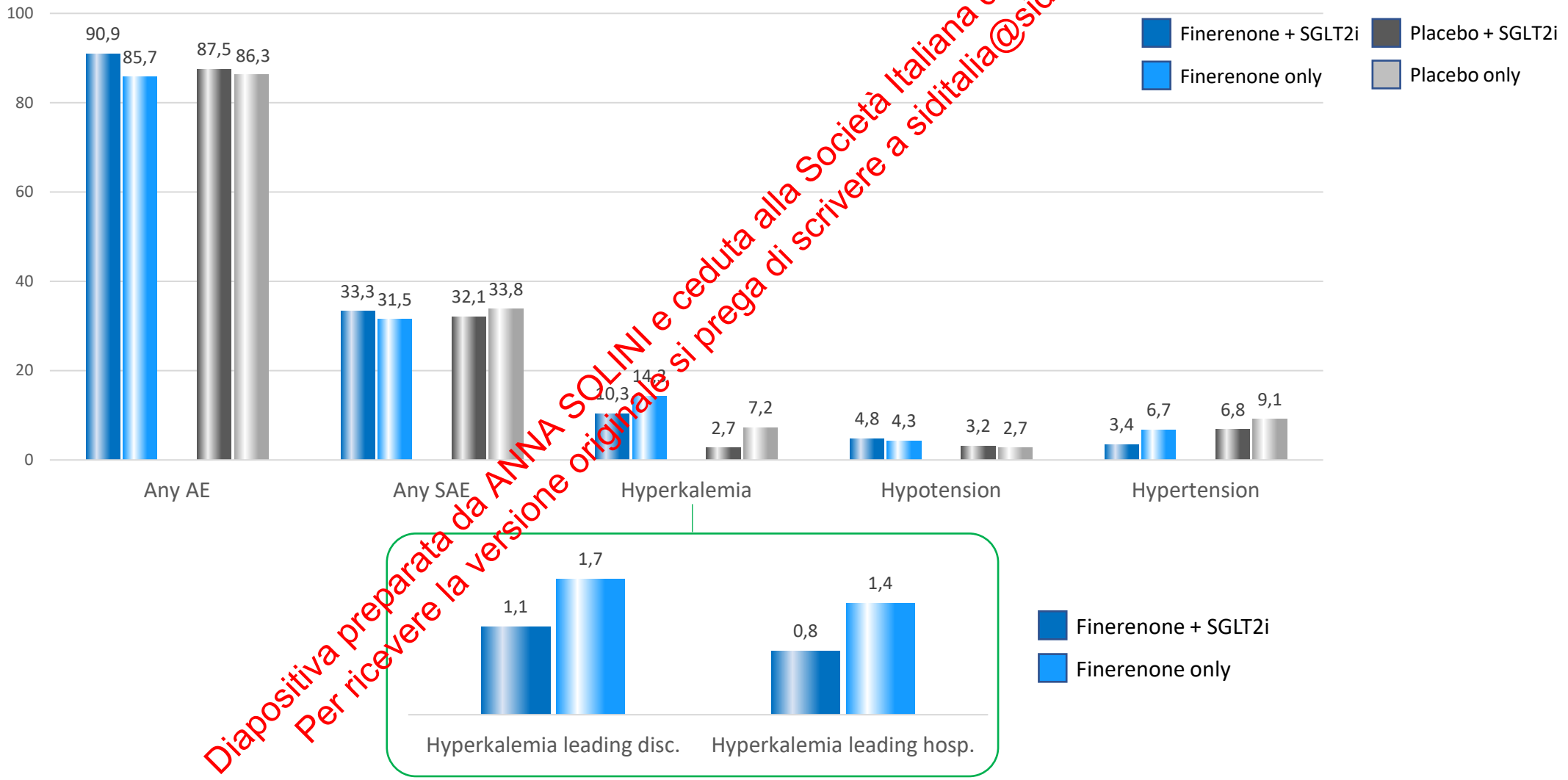
Rossing P, Diabetes Care 2022

Finerenone and UACR in patients with CKD and T2D: relationship with SGLT2i



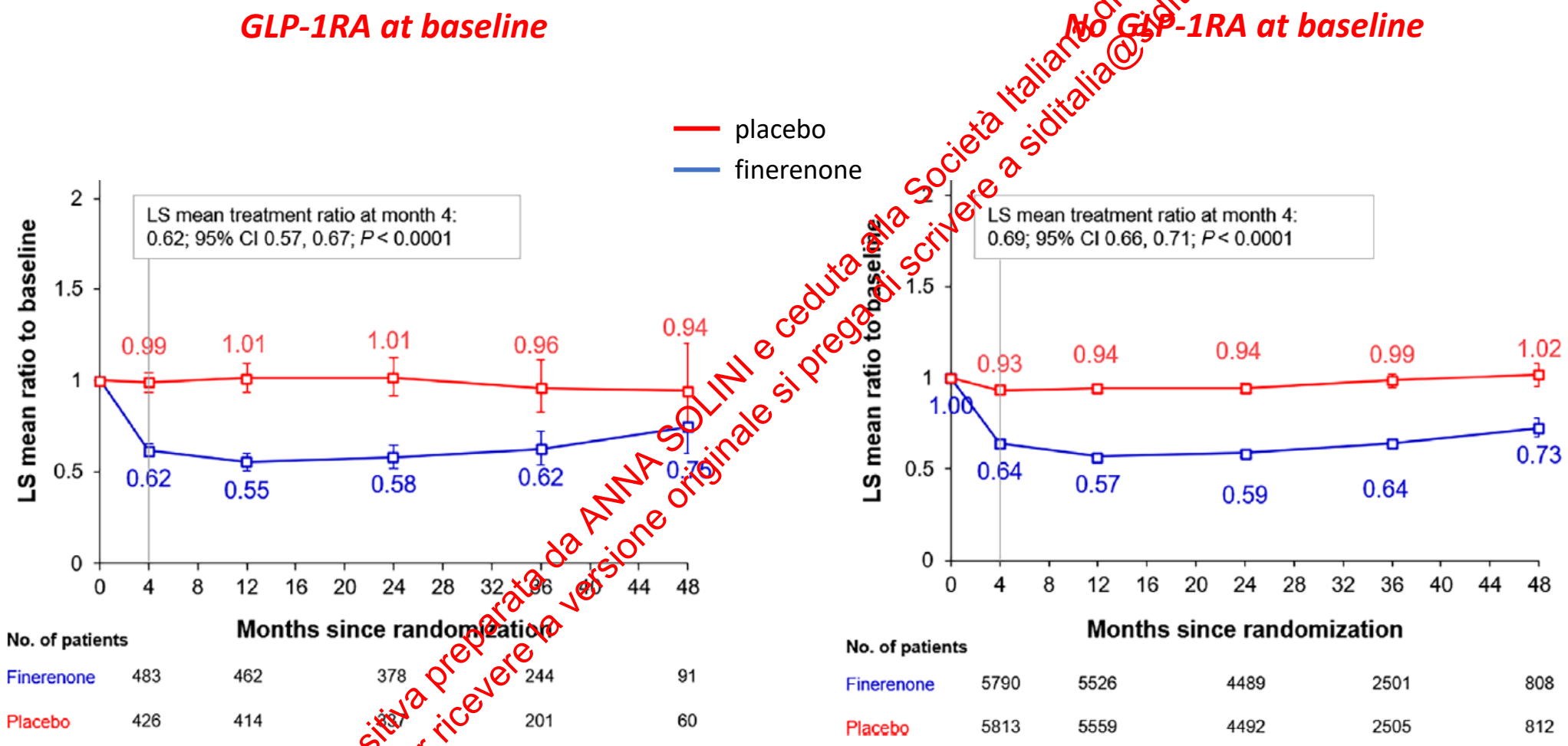
Rossing P, Diabetes Care 2022

Hyperkalemia incidence and relationship with SGLT2i



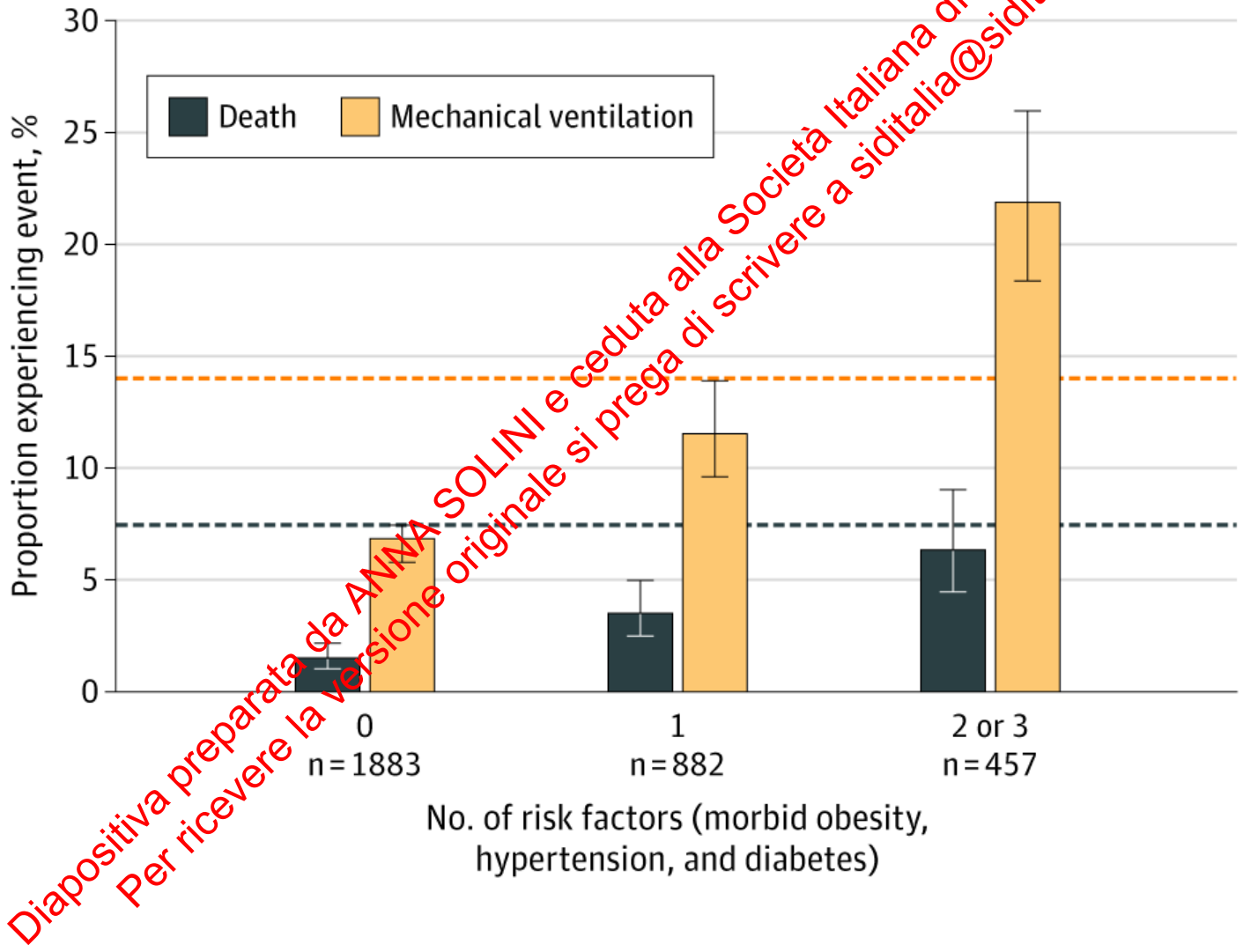
Rossing P, Diabetes Care 2022

Finerenone and UACR in patients with CKD and T2D: relationship with GLP1-RA



Rossing P, Diabetes Care 2022

Obesity, hypertension and diabetes are major risk factors for COVID-19 morbidity and mortality

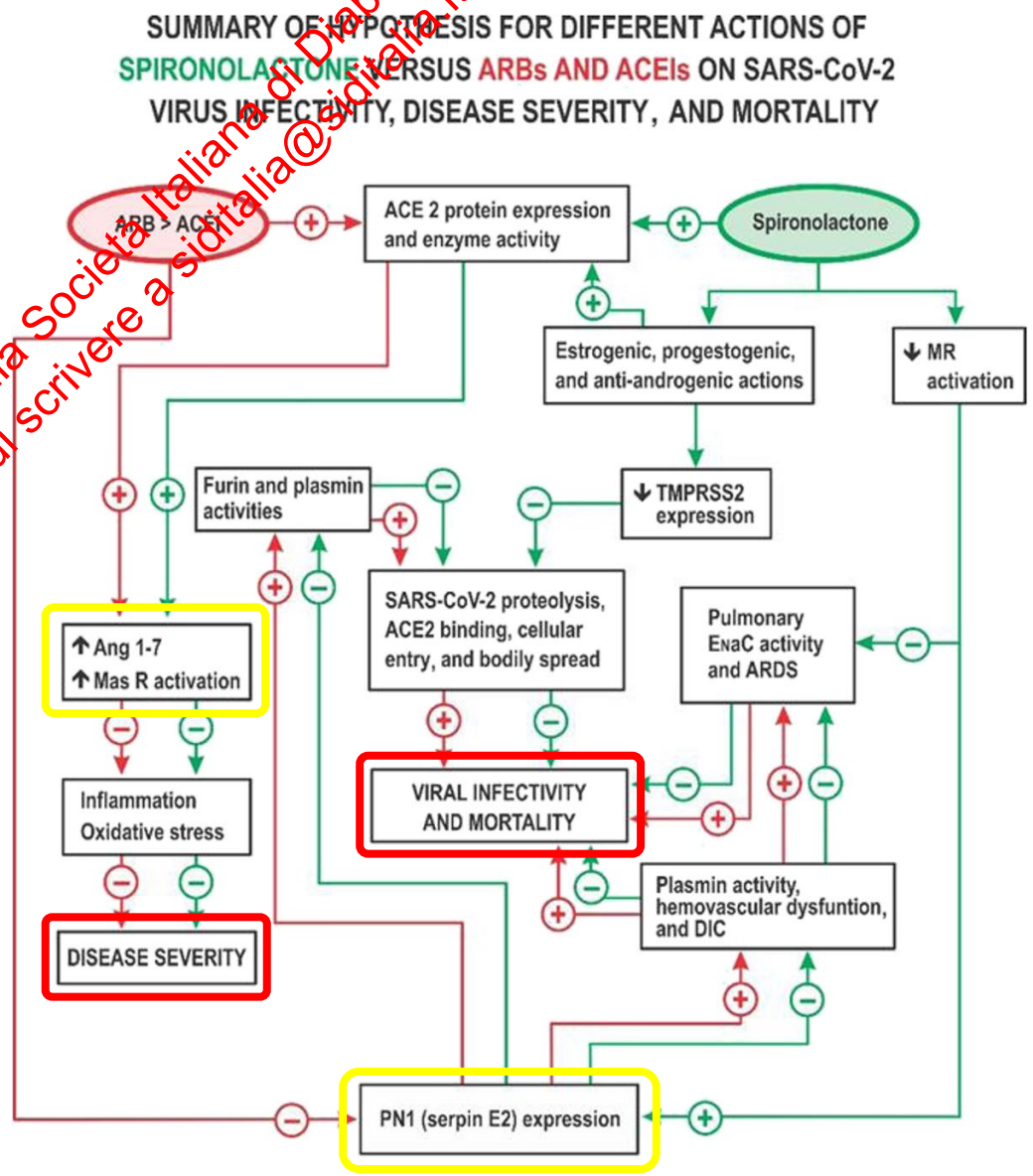


Cunningham JW, JAMA Intern Med 2020

Mineralocorticoid receptor antagonism could be useful in treating COVID-19 morbidity

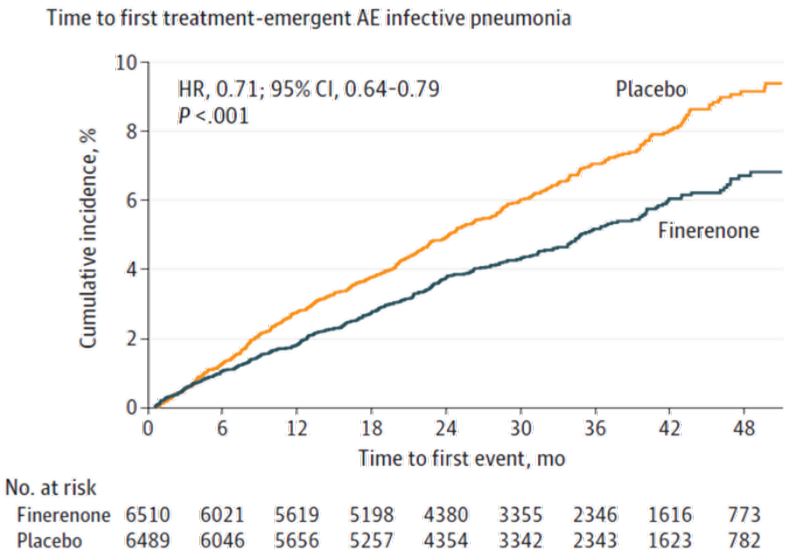
Although ACE2 is the functional host receptor for the SARS-CoV-2 spike protein, it has been demonstrated to be associated with protection against lung injury caused by acute respiratory distress syndromes, probably inducing several pathways including the production of angiotensin 1-7 that acts on the Mas receptor to reduce inflammation and preserve organ function

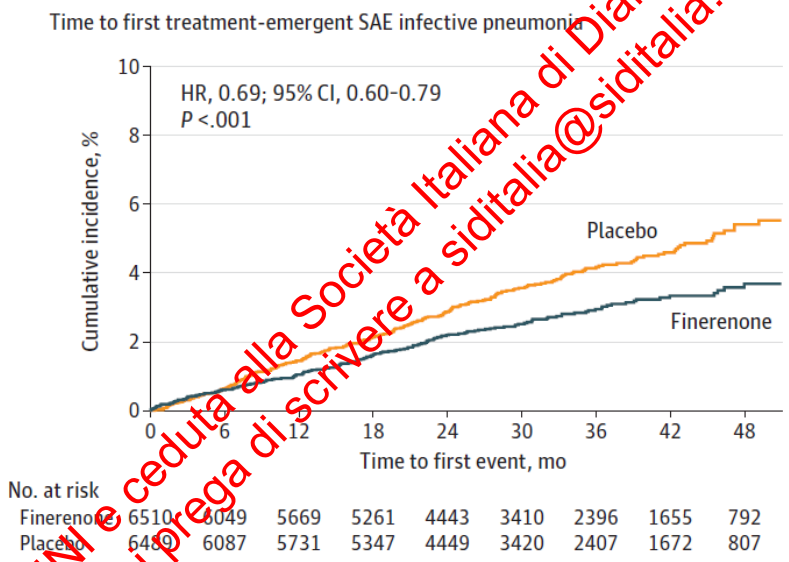
MRAs increase ACE2 expression and therefore production of angiotensin 1-7 and moreover, blocking MR receptor, increase the protease nexin-1 (PN1) expression. Activation of these pathways may result in a beneficial effect for COVID-19 patients on both disease severity and viral severity and mortality.



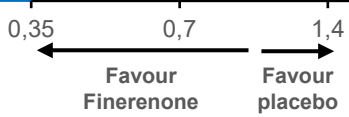
Pitt B, JAMA Net Open 2022

Finerenone reduces significantly treatment-emergent pneumonia and COVID-19 adverse events





	Finerenone		Placebo		HR (95% CI)	HR (95% CI)	*P* value
	Events (%)	Events/100 PY	Events	Events/100 PY			
Pneumonia							
AE	307/6510 (4.7)	1.88	434/6489 (6.7)	2.64		0,71 (0.64-0.79)	<0.001
SAE	171/6510 (2.6)	1.03	250/6489 (3.9)	1.50		0,69 (0.60-0.79)	<0.001
Fatal AE	10/6510 (0.2)	0.06	13/6489 (0.2)	0.08		0,78 (0.44-1.40)	0.41
COVID-19							
AE	86/6510 (1.3)	0.43	118/6489 (1.8)	0.59		0.73 (0.60-0.89)	0.002
SAE	38/6510 (0.6)	0.19	61/6489 (0.9)	0.30		0.63 (0.47-0.83)	0.001
Fatel SAE	14/6510 (0.2)	0.07	19/6489 (0.3)	0.09		0.74 (0.46-1.21)	0.23



Less than 0.1% of patients withdrawn drug in treatment-emergent Pneumonia and COVID-19 AE

Pitt B, JAMA Net Open 2022

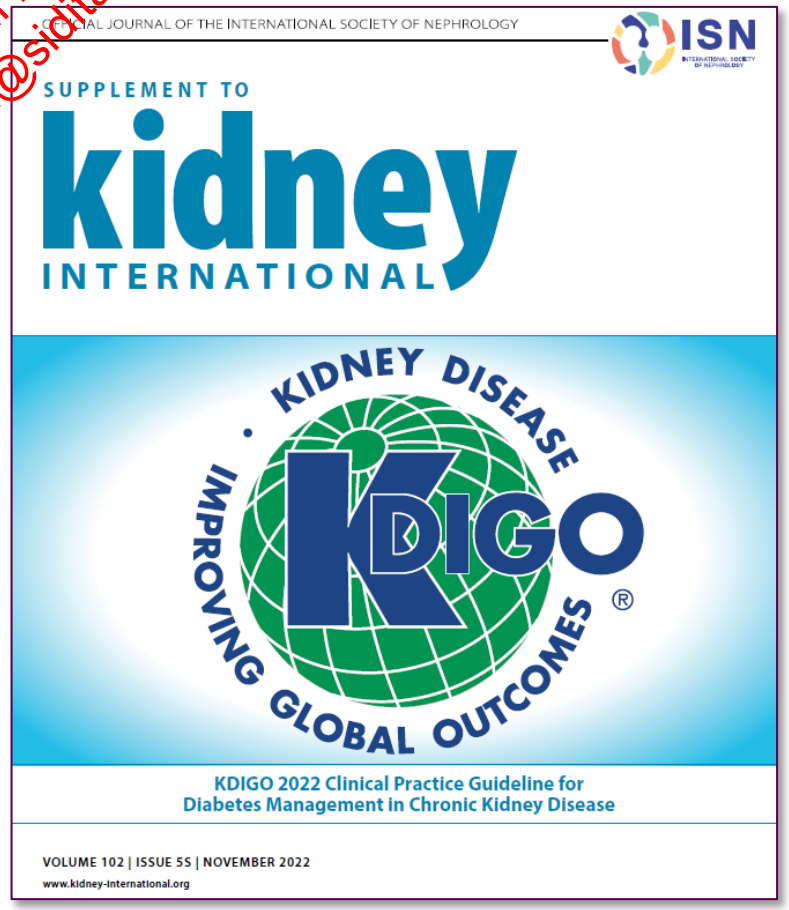
Agenda

- The FIGARO Study
- The FIDELITY analysis
- Impact on Guidelines

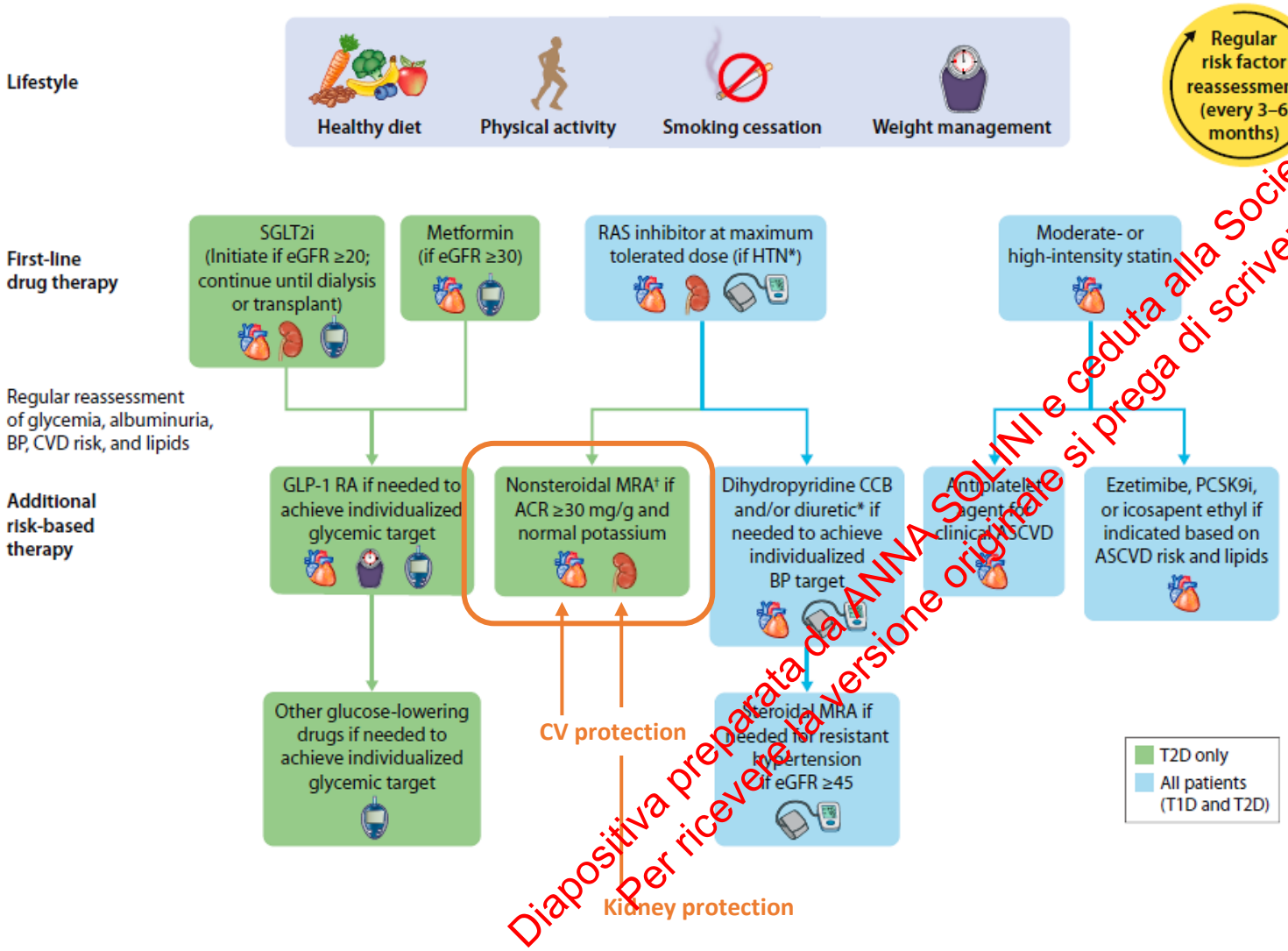
Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

Ian H. de Boer,[1] Kamlesh Khunti,[2] Tami Sadusky,[3] Katherine R. Tuttle,[4] Joshua J. Neumiller,[5] Connie M. Rhee,[6] Sylvia E. Rosas,[7] Peter Rossing,[8,9] and George Bakris[10]

https://doi.org/10.2337/dci22-0027



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

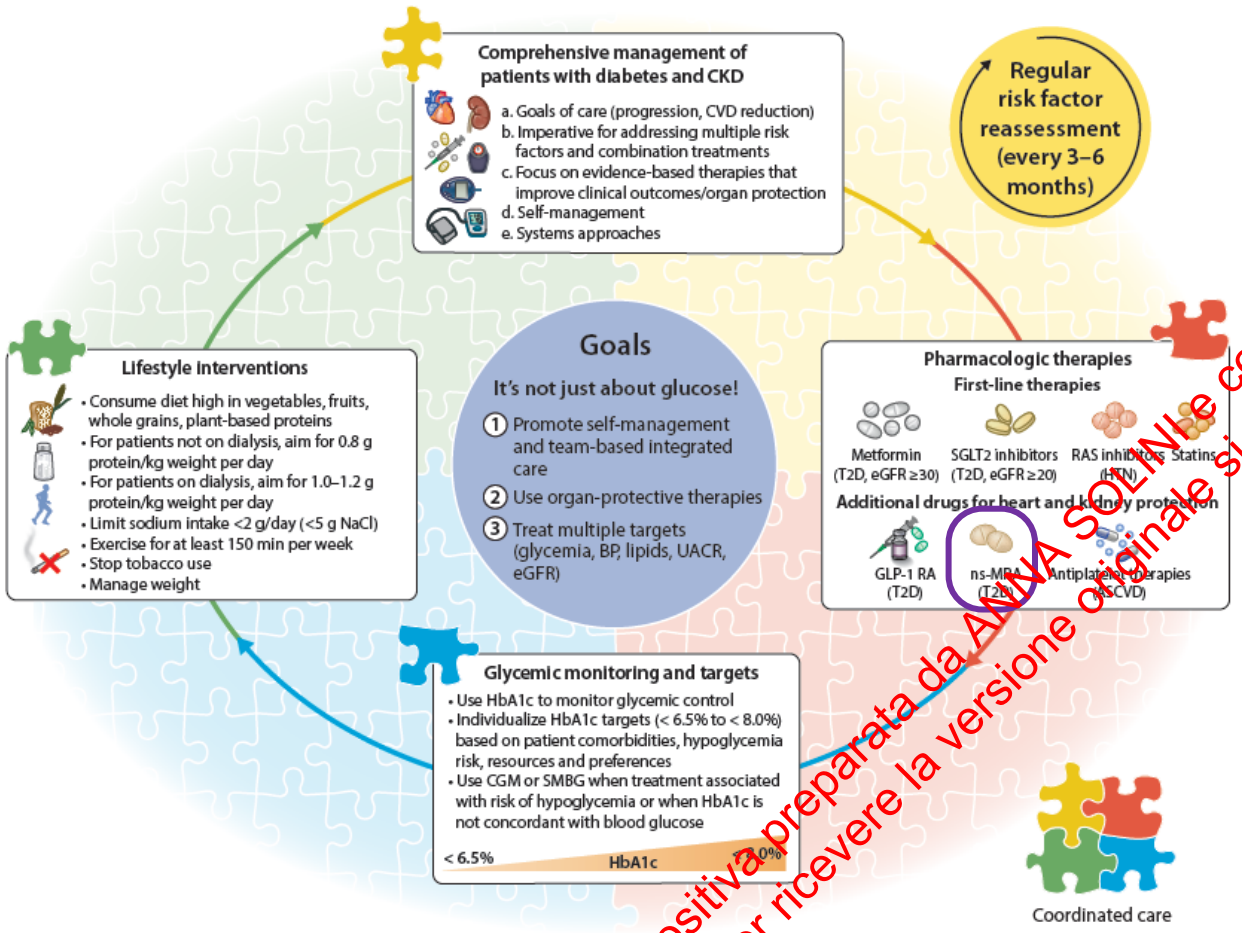


A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2D, eGFR ≥25 mL/min/1.73m^2, normal serum potassium concentration, and albuminuria (albumin-to-creatinine ratio [ACR] ≥30 mg/g) despite maximum tolerated dose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

De Boer HI, Diabetes Care 2022

New published KDIGO Clinical Practice Guidelines on "Diabetes Management in Chronic Kidney Disease" recommend Finerenone in all albuminuric patients with eGFR≥25 and normal potassium

Therapeutical approach for improving outcomes in patients with diabetes and CKD



*ACEi or ARB should be first-line therapy for hypertension when albuminuria is present, otherwise dihydropyridine CCB or diuretic can also be considered; all three classes often needed to attain BP targets

Guidelines include data from FIDELIO-DKD, FIGARO-DKD trials, and FIDELITY pooled-analysis

Recommendation 1.4.1 – 2A

We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with **T2D**, an **eGFR ≥25** ml/min per 1.73 m^2, **normal serum potassium** concentration, and **albuminuria** (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor.

"This recommendation places a high value on the high-quality evidence, from […] FIDELIOD-DKD and […] FIGARO-DKD, that finerenone, on top of ACEi or ARB treatment, slows progressive loss of eGFR and decreases the risk of a cardiovascular event among people with T2D and albuminuria. It places a relatively lower value on the lack of definitive data regarding adding nonsteroidal MRA to SGLT2i (current standard of care), the risk of hyperkalemia and monitoring of potassium during nonsteroidal MRA treatment, and the lack of observational data evaluating benefits and risks outside of the clinical trial setting.
In the judgment of the Work Group, the majority of well-informed patients addressed by the recommendation would want to receive treatment with a nonsteroidal MRA, but many would not."

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, Kidney Int 2022

Top 10 Takeaways for Clinicians from the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD

8

Non-steroidal mineralocorticoid antagonists (ns-MRA)

ns-MRA reduce risks of CKD progression and cardiovascular events for people with T2D and residual albuminuria. They are suggested for patients with T2D, urine ACR ≥30 mg/g, and normal serum potassium on other standard of care therapies. Serum potassium and creatinine should be monitored.

Top 10 Takeaways for Patients from the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD

8

Non-steroidal mineralocorticoid antagonists (ns-MRA)

ns-MRA reduce risks of CKD progression and cardiovascular events for people with T2D and residual albuminuria despite other treatments. They are suggested for patients with T2D, urine ACR ≥30 mg/g, and normal serum potassium on other standard of care therapies.

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, Kidney Int 2022

Summary of Recommendations of Finerenone use in DKD disease

Scientific Society	Year	Recommendation	Grade
American Diabetes Association	2022	In patients with chronic kidney disease who are at increased risk for cardiovascular events or chronic kidney disease progression or are unable to use a sodium–glucose cotransporter 2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended to reduce chronic kidney disease progression and cardiovascular events [recommendation 11.3c]	A
American Diabetes Association & KDIGO consensus	2022	A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2D, eGFR ≥25 mL/min/1.73m2, normal serum potassium concentration, and albuminuria (albumin-to-creatinine ratio [ACR] ≥30 mg/g) despite maximum tolerated dose of renin-angiotensin system (RAS) inhibitor	-
KDIGO	2022	We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor [recommendation 1.4.1]	2A
AACE American Association of Clinical Endocrinology	2022	A non-steroidal mineralocorticoid receptor antagonist (finerenone) with proven kidney and CVD benefit is recommended for persons with T2D, an eGFR ≥25 mL/min/1.73 m2, normal serum potassium concentration, and albuminuria (ACR ≥30 mg/g) despite a maximum tolerated dose of a renin-angiotensin system inhibitor [recommendation 6.6]	1A

1. American Diabetes Association Professional Practice Committee, Diabetes Care 2022;45(1); https://doi.org/10.2337/dc22-S011; 2. De Boer HI et al., Diabetes Care 2022; DOI: 10.2337/dci22-0027; 3. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, Kidney Int 2022; 102(55); 4. Blonde L et al., Endocrine Practice 2022, in press; https://doi.org/10.1016/j.eprac.2022.08.002

AACE guidelines provides "Practice Points" to better manage Finerenone

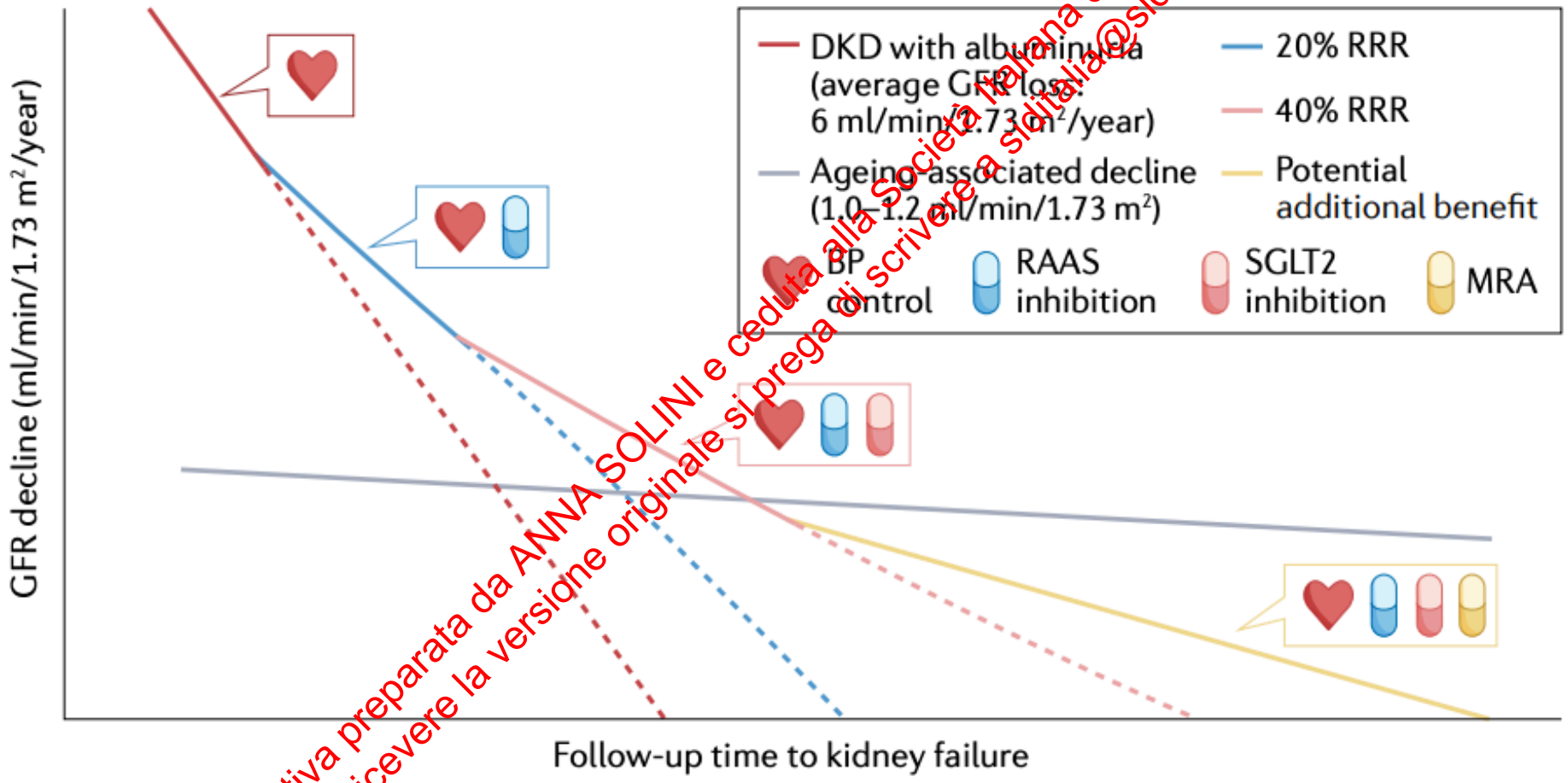
- Serum potassium levels and eGFR should be monitored within 2 to 4 weeks after initiating an ACE inhibitor, an ARB, an SGLT2i, finerenone, or with changes in these medications.

- 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)

Expanding the therapeutic options for patients with CKD and T2D



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