Basta con la DKD!

Finerenone

Roberto Pontremoli

Università degli Studi e IRCCS Ospedale Policlinico San Martino – Genova

Il sottoscritto Roberto PONTREMOLI

ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

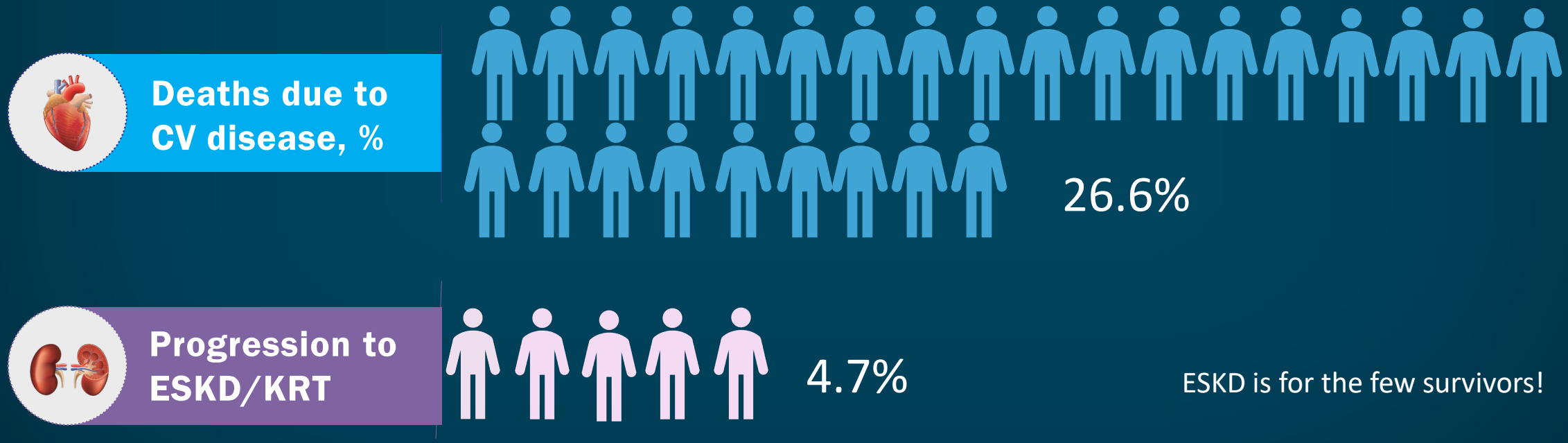
dichiara che

negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario

- ASTRAZENECA
- BAYER
- BOEHRINGER-INGELHEIM
- LILLY
- MENARINI
- MSD
- NOVARTIS
- NOVONORDISK
- RECORDATI

Presence of CKD Is Commonly Associated With the Development of Fatal CV Outcomes

- Older patients[a] with CKD are 6 times more likely to die of CV disease than to advance to ESKD and dialysis[b]



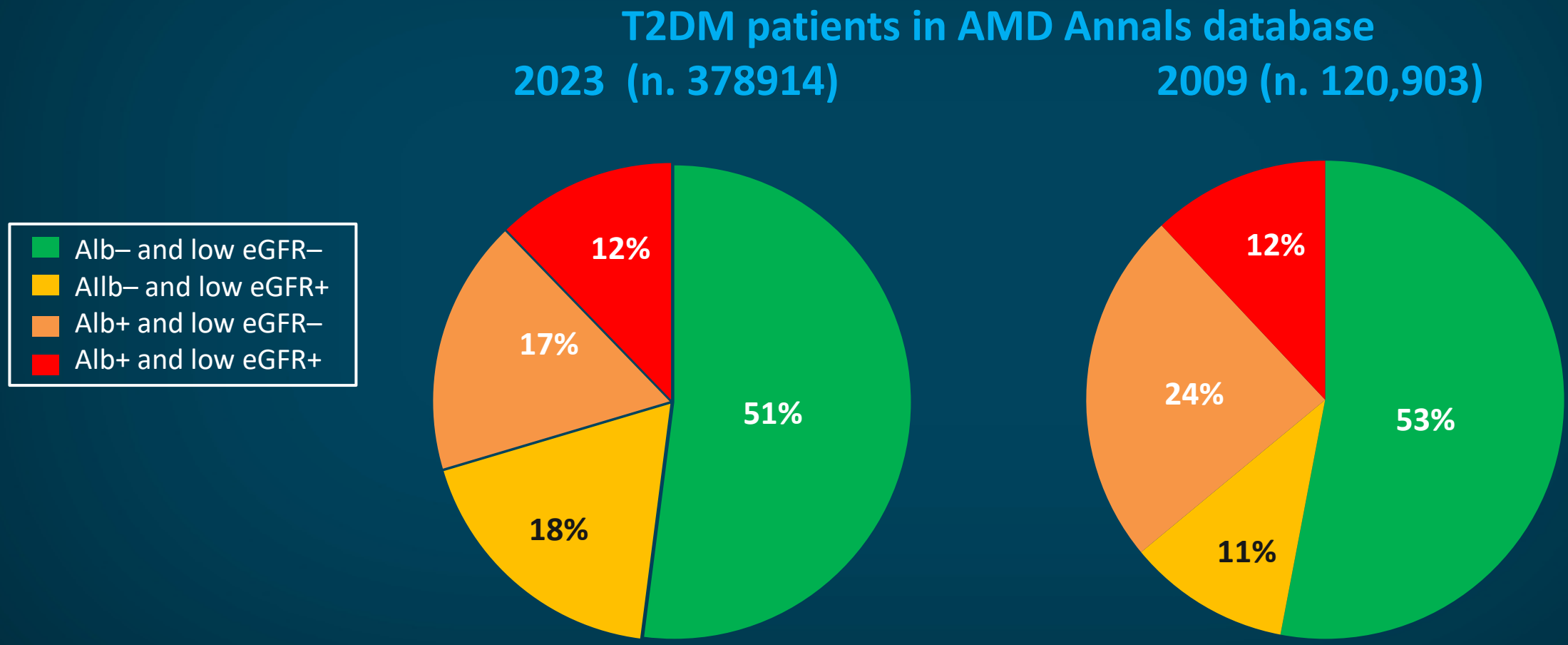
[a] ≥65 years of age. [b] During median 9.7 years of follow-up.
KRT = kidney replacement therapy.

Dalrymple L, et al. *J Gen Intern Med*. 2011;26:379-385.

Redefining Diabetic Kidney Disease:

Large-Scale Study Reveals Shifting Phenotypes, Declining Albuminuria, and Persistent eGFR-Based Risk

T2DM patients in AMD Annals database

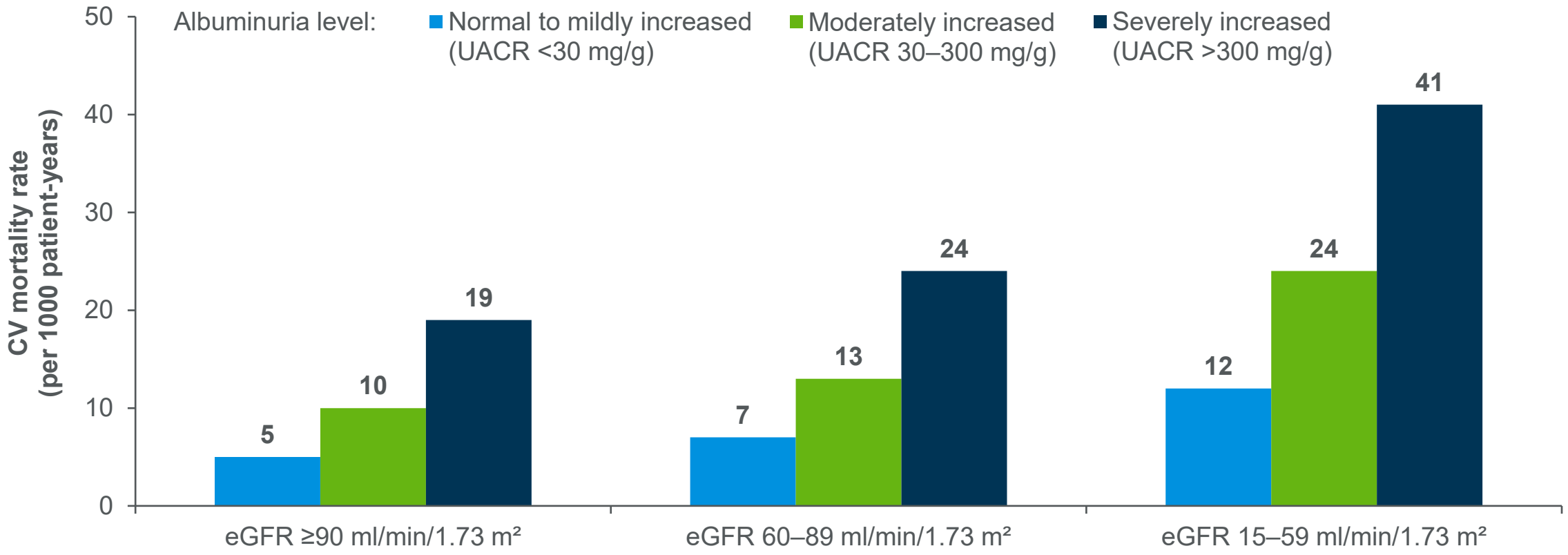


Alb– = normoalbuminuria; Alb+ = albuminuria; CV = cardiovascular; eGFR = estimated glomerular filtration rate.

De Cosmo S, et al. *Nephrol Dial Transplant*. 2014;29(3):657-662. De Cosmo S et al. 2025 submitted

Increasing albuminuria is associated with higher CV mortality risk across all eGFR categories

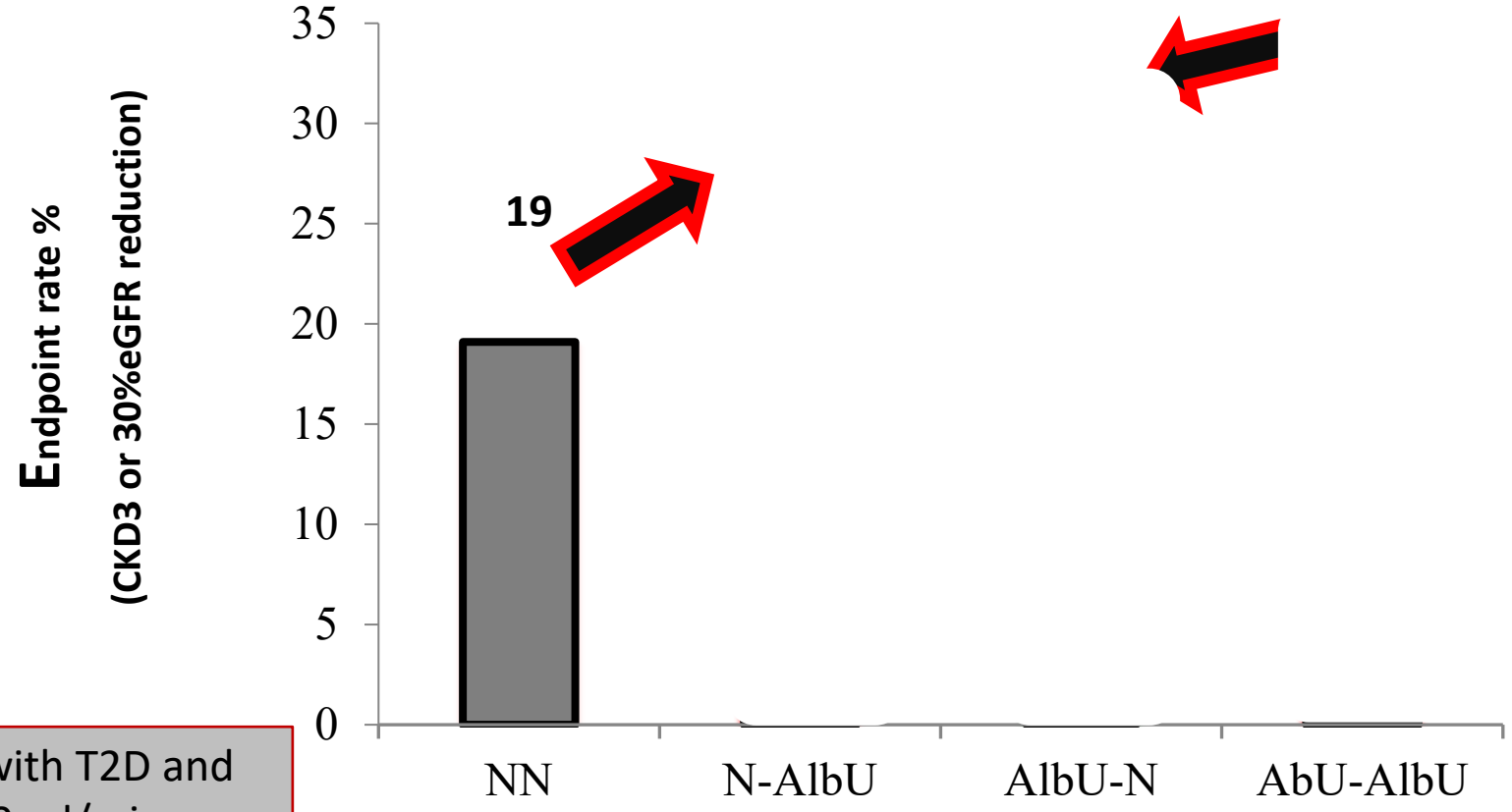
CV mortality by eGFR range and albuminuria for 14,586 adults, 1988–2000*



Astor BC, *et al. Am J Epidemiol* 2008;167:1226–1234

Changes in albuminuria and renal outcome in patients with type 2 diabetes and hypertension: a real-life observational study

Francesca Viazzi[a], Antonio Ceriello[b,c,d], Paola Fioretto[e], Carlo Giorda[f], Pietro Guida[g,h], Giuseppina Russo[i], Eulalia Greco[j], Salvatore De Cosmo[i], Roberto Pontremoli[a], the AMD-Annals Study Group*



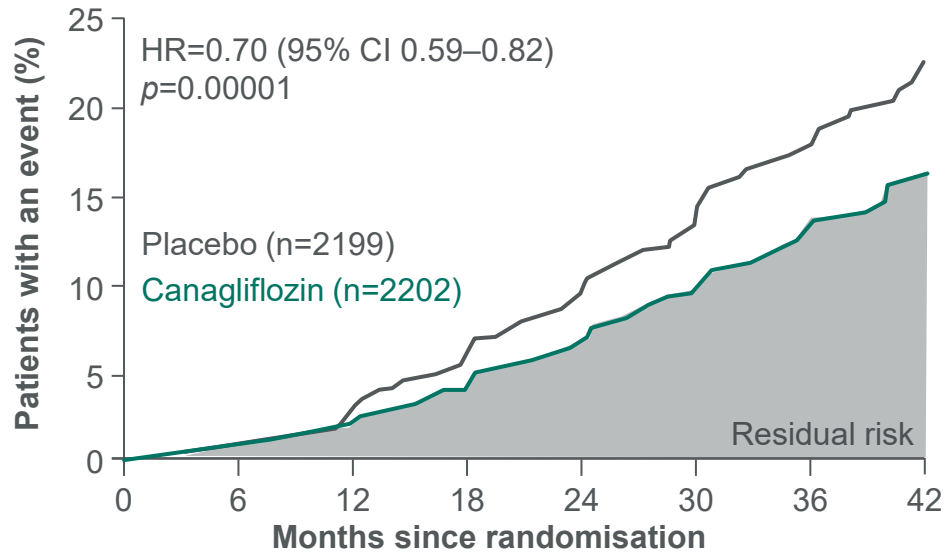
P<0.001 for all comparisons

- 12,611 ptz with T2D and HT eGFR >60 ml/min
- 4-years f-up

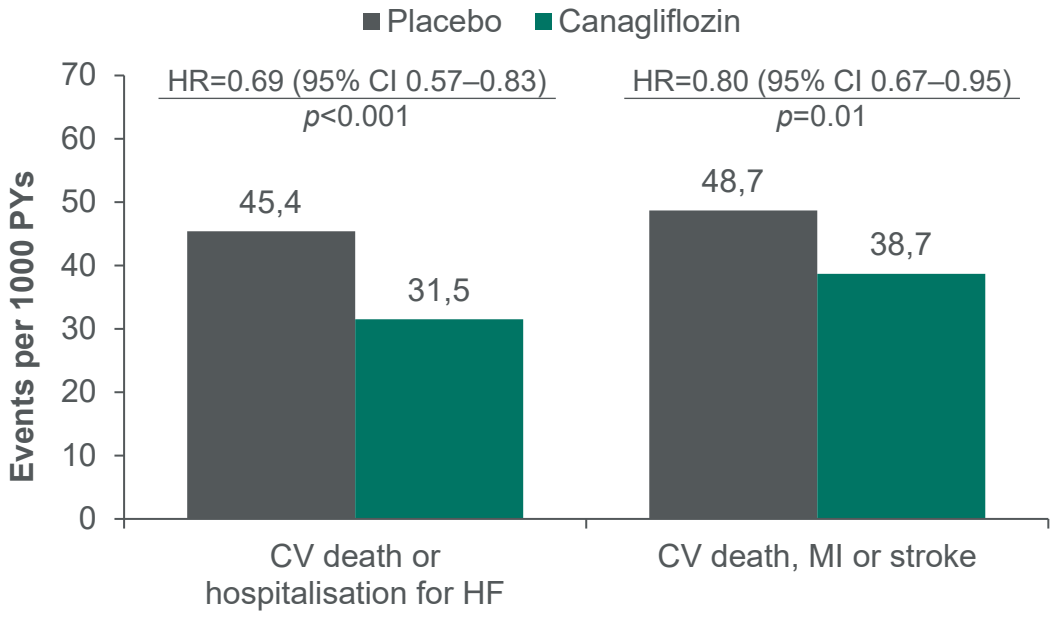
Journal of Hypertension 2018, 36:1719–1728

Despite RAS blockade and SGLT-2 inhibition, patients with CKD and T2D are at high risk of CKD progression and CV events

CREDENCE: Canagliflozin (+ ACEi or ARB)[1]



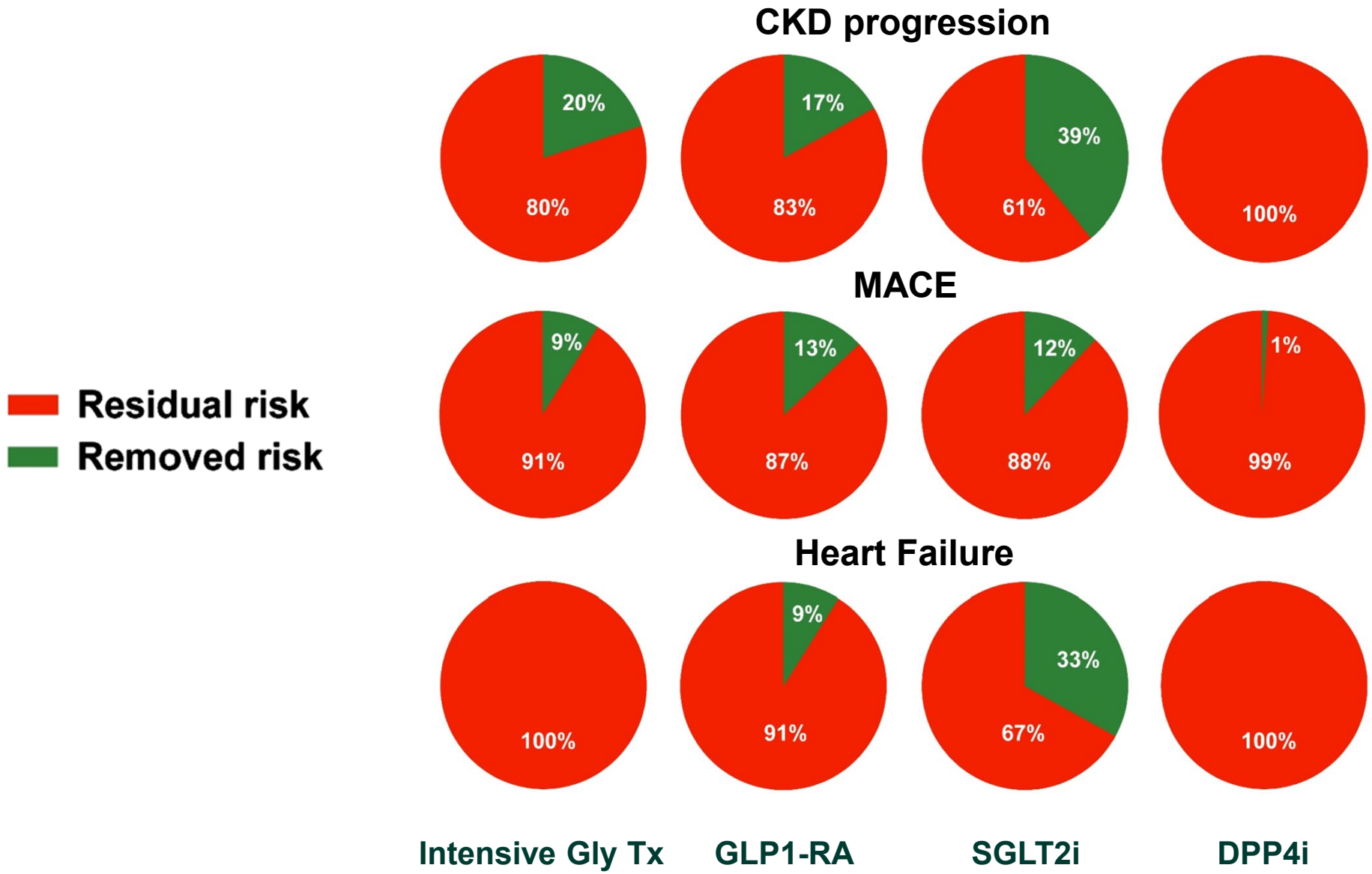
Primary composite endpoint:
Doubling of SCr, ESKD, or renal/CV death



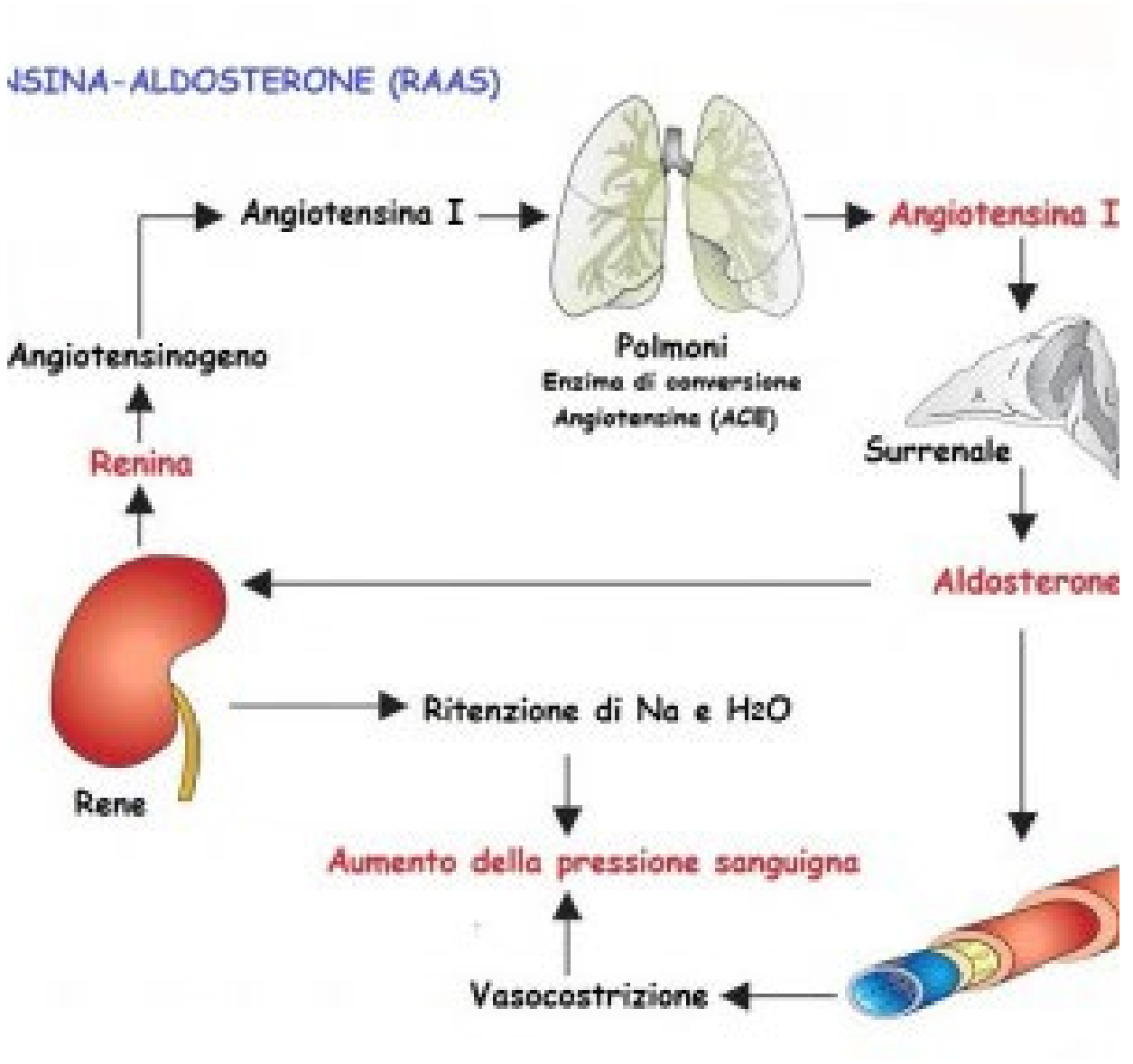
Secondary composite CV endpoints

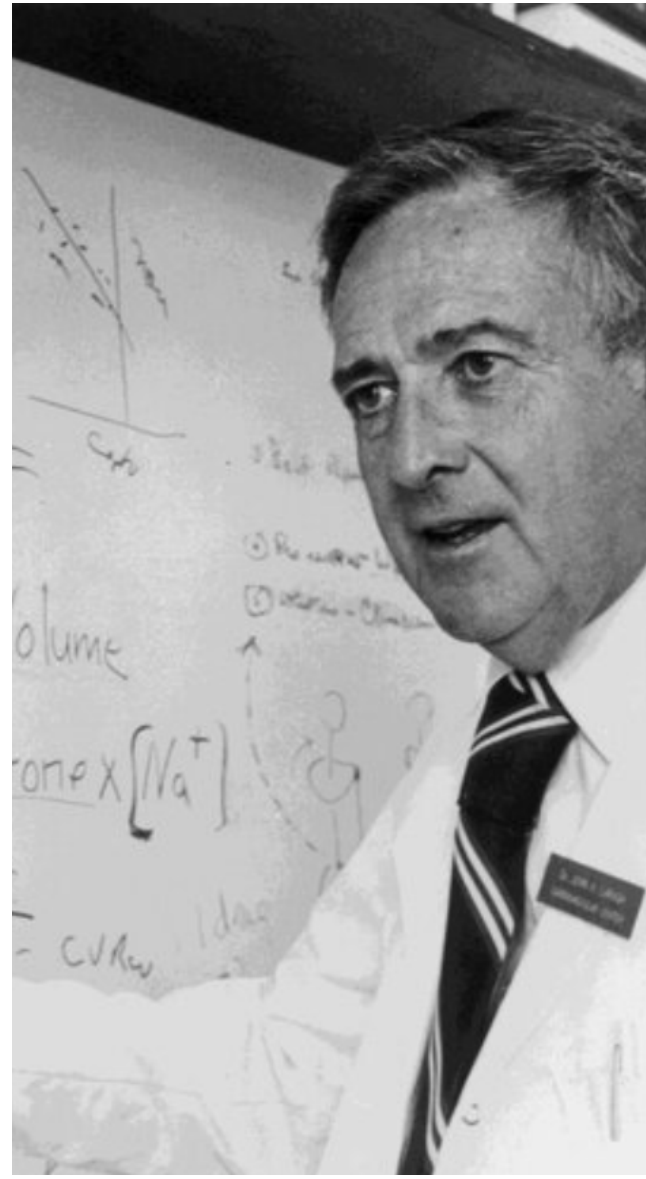
Perkovic V, *et al*. *N Engl J Med* 2019;380:2295–2306

Residual Cardiorenal Risk in Type 2 Diabetes… even for new agents

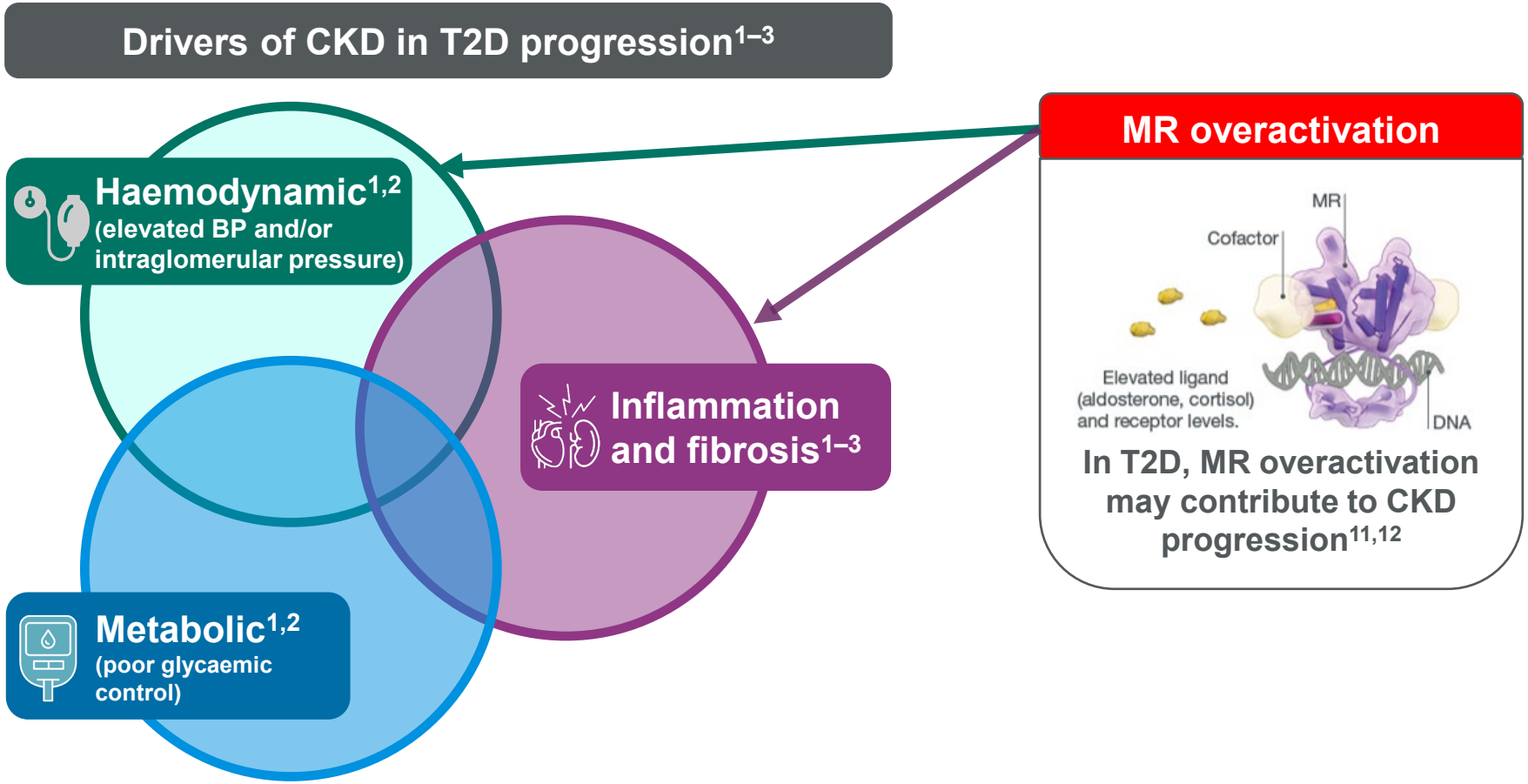


Giugliano D et al. *Cardiovasc Diabetol* 2021; 20(1):36


ISINA-ALDOSTERONE (RAAS)
Angiotensina I
Polmoni
Enzima di conversione
Angiotensina (ACE)
Angiotensina I
Angiotensinogeno
Surrenale
Renina
Aldosterone
Ritenzione di Na e H2O
Rene
Aumento della pressione sanguigna
Vasocostrizione



Finerenone targets MR overactivation, which may contribute to CKD and CVD progression in patients with CKD and T2D



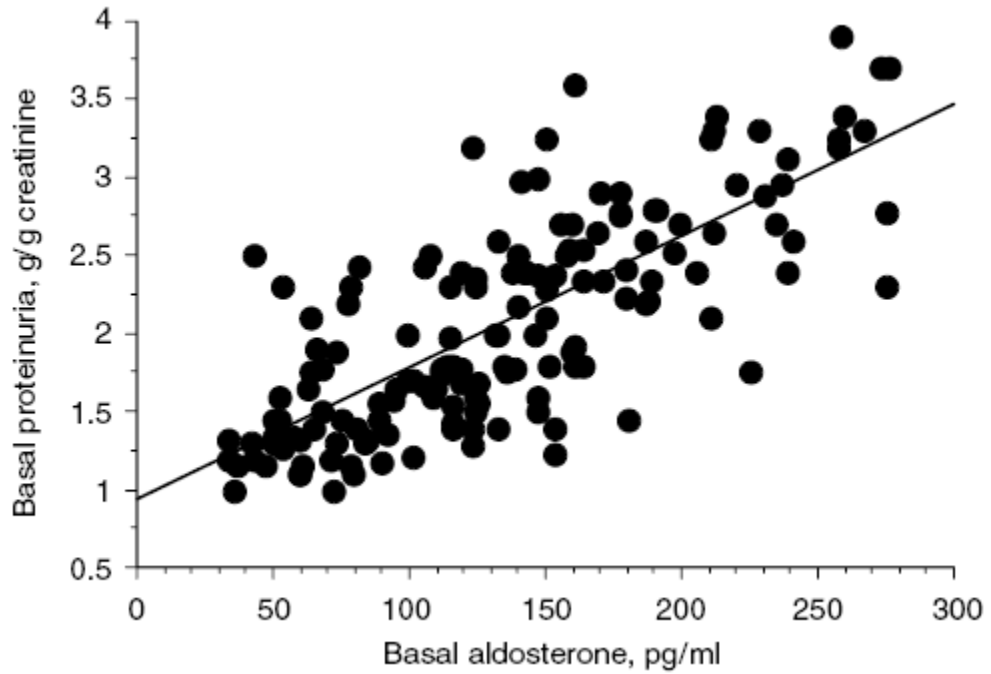
MR, mineralocorticoid receptor

1. Agarwal R, *et al. Eur Heart J* 2021;42:152–162; 2. Agarwal R, *et al. Nephrol Dial Transplant* 2020; doi: 10.1093/ndt/gfaa294; 3. Bakris GL, *et al. JAMA* 2015;314:884–894; 4. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 5. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 6. Mora-Fernández C, *et al. J Physiol* 2014;18:3997–4102; 7. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 8. American Diabetes Association. *Diabetes Care* 2020;43:S135–S151; 9. American Diabetes Association. *Diabetes Care* 2020;43:S111–S134; 10. Kidokoro K, *et al. Circulation* 2019;140;303–315; 11. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 12. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 13. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434; 14. American Diabetes Association. *Diabetes Care* 2020;43:S98–S110

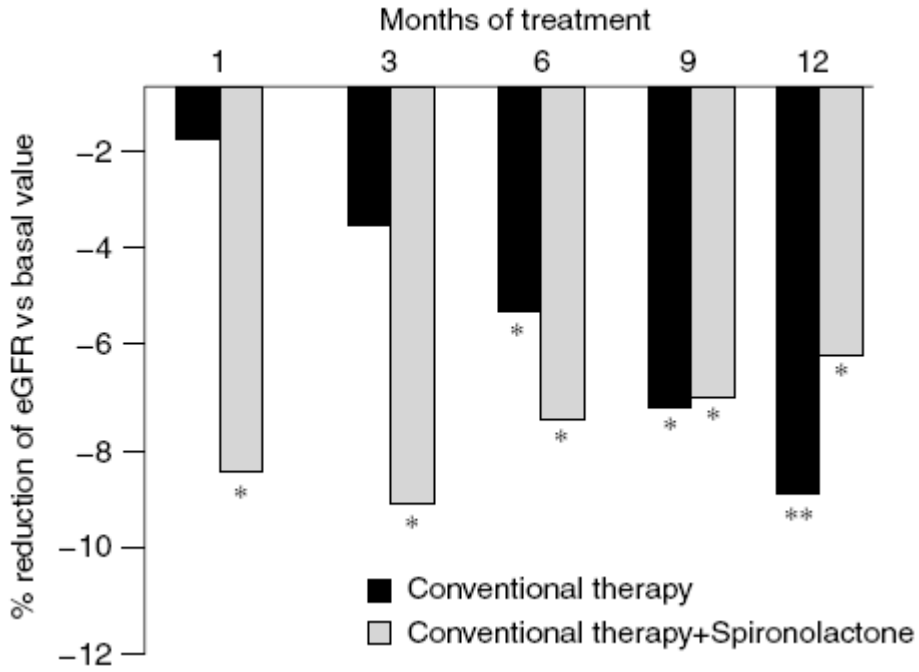
http://www.kidney-international.org

Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease

S Bianchi[1], R Bigazzi[1] and VM Campese[2]



Regression between basal aldosterone and proteinuria in the 165 patients (r=0.766, P=0.0001)



eGFR decline in patients treated with spironolactone and those treated with conventional therapy

Differential MR binding of steroidal MRAs vs finerenone results in distinct effects on gene expression

	Aldosterone antagonists		Finerenone
			
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)[1,5]
Potency to MR	High[4,10]	Moderate[1,4,10]	High[1,2,10]
Selectivity to MR	Low[4,10]	Moderate[4,10]	High[1,2,10]
Half-life	>20 hours*	4–6 hours*	2–3 hours#
Active metabolites	++	–	–
CNS penetration	Yes	Yes	No based on preclinical data[3]
Gynecomastia	Yes[4]	Less than spironolactone[4]	No signal in phase II studies[7-9]
Hyperkalaemia	Yes[4]	Yes[4]	Moderately increased*[,7-9]
Indication (SmPC)	Congestive HF[2]	HF and LVEF ≤40% or ≤30%[3]	CKD with albuminuria, associated with T2D[4]

Based on preclinical data and ARTS phase II programme

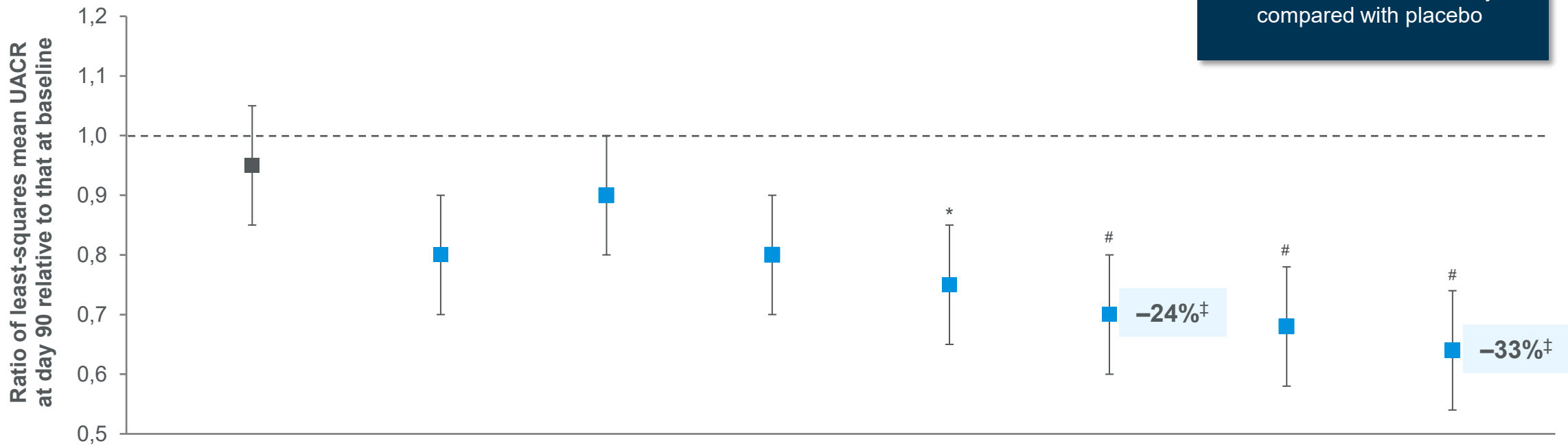
MR, mineralocorticoid receptor

1. Bärfacker L, *et al. ChemMedChem* 2012;7:1385–1403; 2. Pitt B, *et al. Eur J Heart Fail* 2012;14:668–675; 3. Kolkhof P, *et al. J Cardiovasc Pharmacol* 2014;64:69–78; 4. Sica DA. *Heart Fail Rev* 2005;10:23–29; 5. Amazit L, *et al. J Biol Chem* 2015;290:21876–21889; 6. Kolkhof P, *et al. Curr Opin Nephrol Hypertens* 2015;24:417–424; 7. Pitt B, *et al. Eur Heart J* 2013;34:2453–2463; 8. Bakris GL, *et al. JAMA* 2015;314:884–894; 9. Filippatos G, *et al. Eur Heart J* 2016;37:2105–2114; 10. kolkhof P, *et* al. *Handb Exp Pharmacol*. 2017;243:271-305

Finerenone reduces UACR in a dose-dependent manner in patients with CKD and T2D receiving a RAS blocker

ARTS-DN (phase IIb) study: Results[1]

Dose-dependent improvement in UACR with finerenone at day 90 compared with placebo

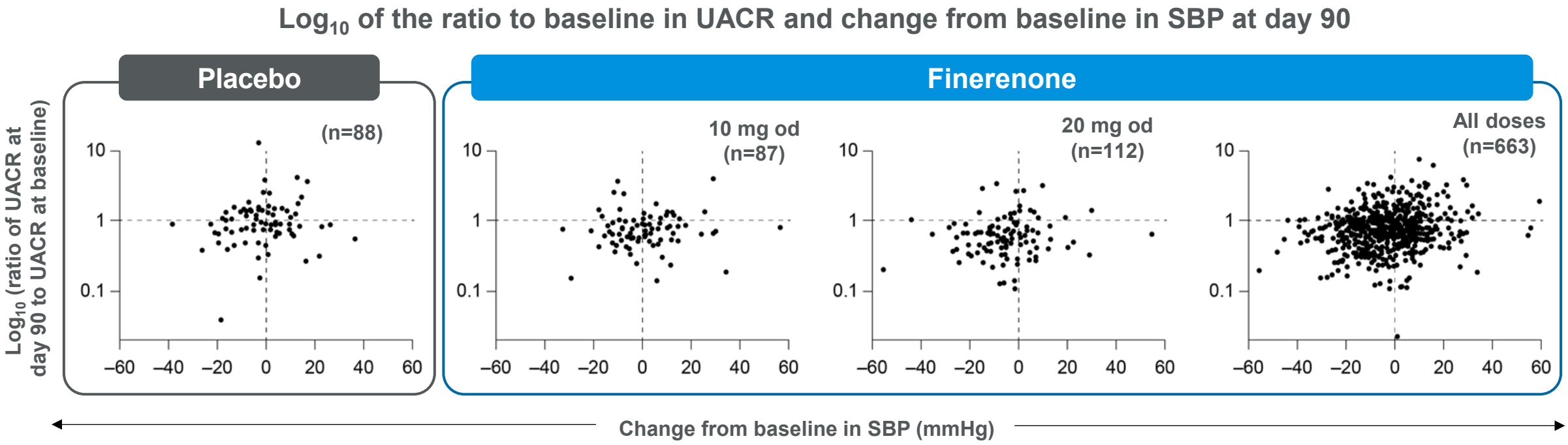


	Placebo	Finerenone od (mg/day)						
		1.25	2.5	5	7.5	10†	15	20‡
No. of patients	94	96	92	98	96	96	123	117

Change in least-squares mean UACR at day 90 relative to baseline – full-analysis set. Error bars represent 90% confidence intervals. *p<0.01; #p<0.001; ‡percentage reduction calculated from mean placebo-corrected ratios of UACR; §finerenone doses in phase III trials[2,3]
CKD, chronic kidney disease; od, once daily; RAS, renin–angiotensin system; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio
1. Bakris GL, *et al*. *JAMA* 2015;314:884–894; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 3. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356

In patients with CKD and T2D treated with finerenone, there was no correlation between reduction in UACR and change in SBP

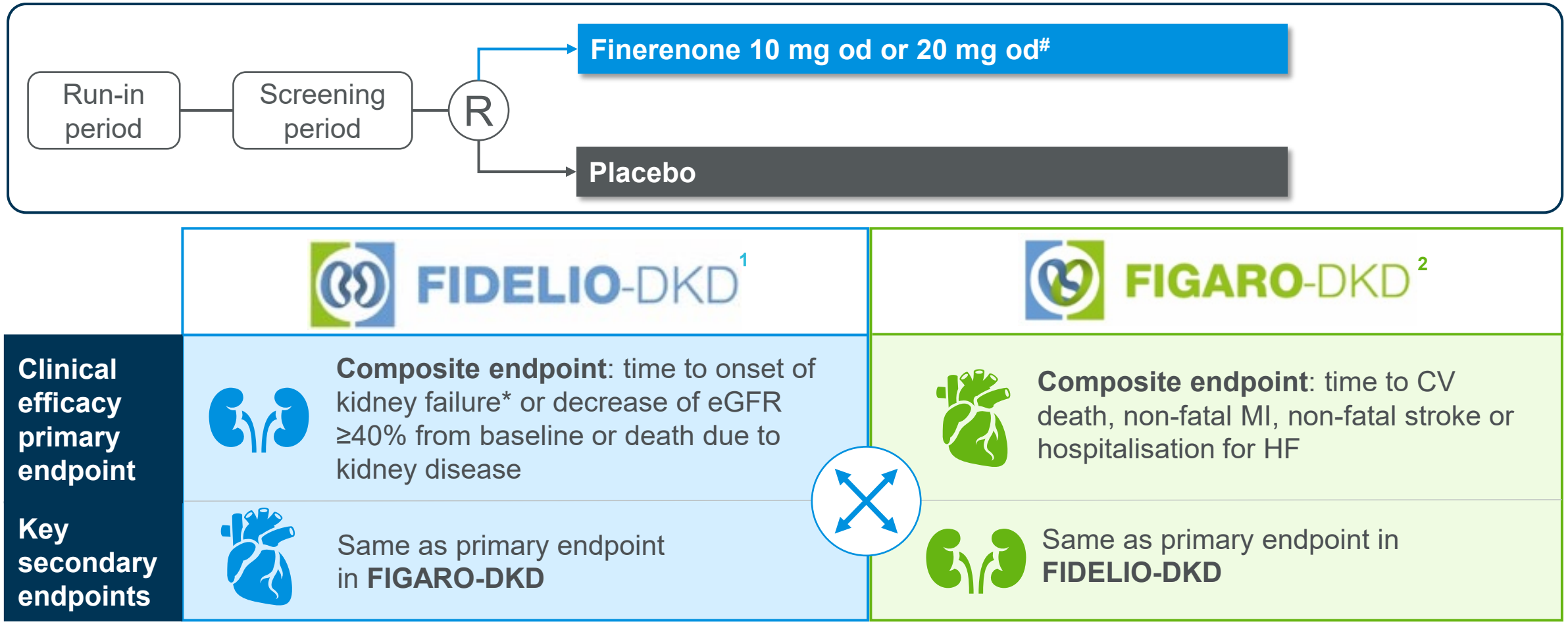
ARTS-DN (phase IIb) study: Results[1]



Results from the phase II ARTS-DN study suggest that the reduction in albuminuria with finerenone was independent of measured haemodynamic changes

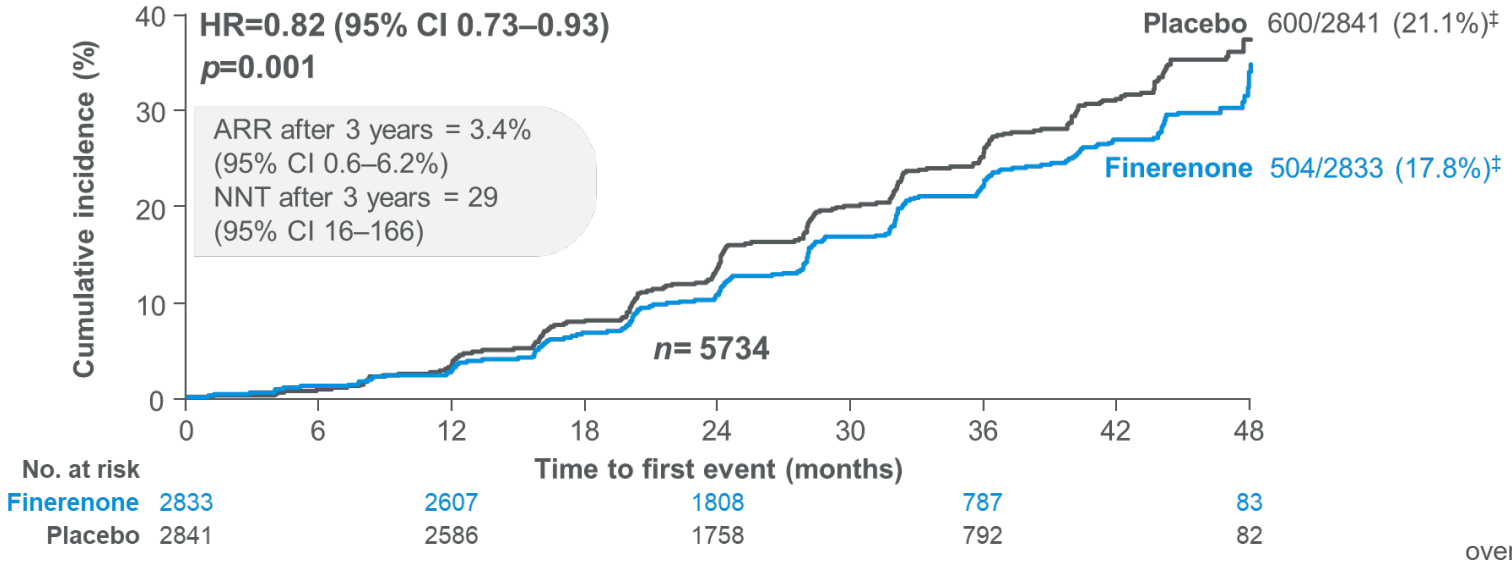
Horizontal dashed lines indicate unity
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; od, once daily; RAS, renin–angiotensin system; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio
Bakris GL, *et al*. *JAMA* 2015;314:884–894

FIDELIO-DKD and FIGARO-DKD are investigating effects of finerenone on kidney and CV outcomes in patients with CKD and T2D



1. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 2. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356

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



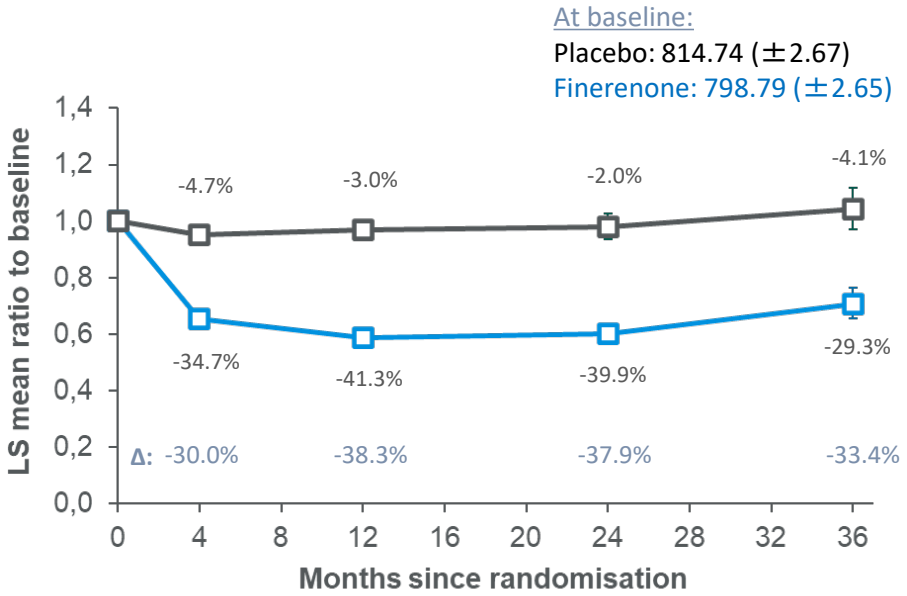
over a median follow-up of 2.6 years

Outcome	Finerenone (n=2833) n (%)	Finerenone (n=2833) n per 100 PY	Placebo (n=2841) n (%)	Placebo (n=2841) n per 100 PY	HR (95% CI)	p-value
Primary composite kidney outcome	**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 et al., N Engl J Med 2020; doi: 10.1056/NEJMoa2025845

Finerenone reduces UACR starting from 4th months and worsening of eGFR overtime

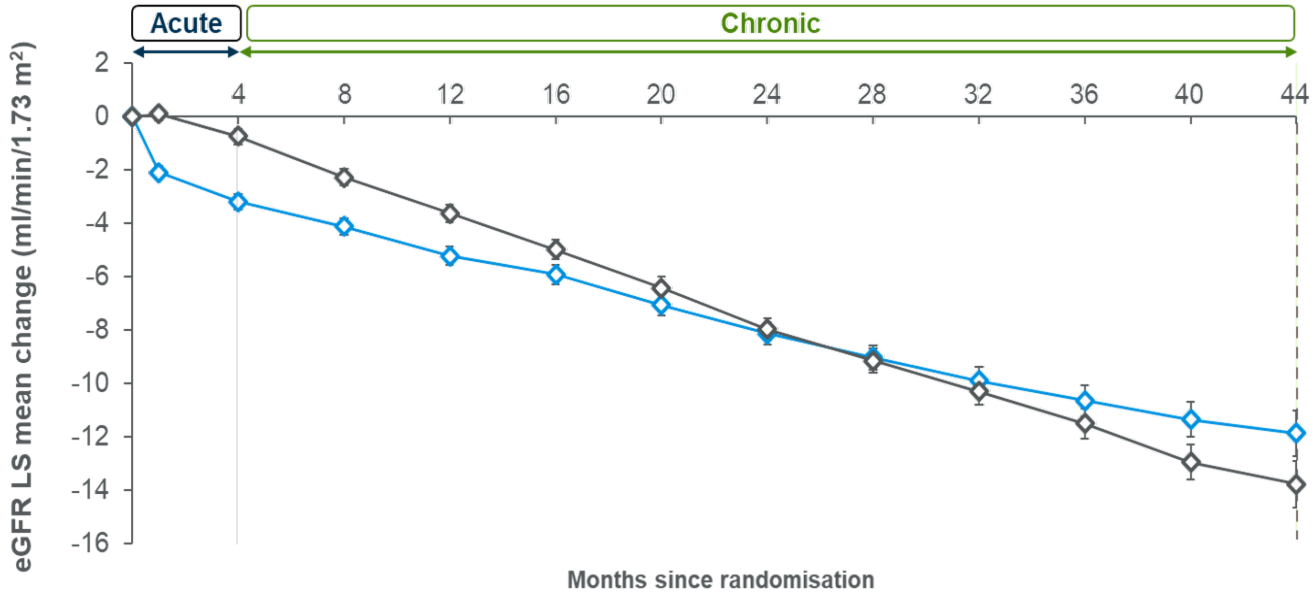
UACR



No. of patients				
Finerenone	2831	2582	1841	856
Placebo	2840	2598	1825	834

Ratio of least-squares mean change from baseline [Finerenone vs placebo]= **0.69; 95% CI 0.66–0.71**

eGFR



Finerenone	2799	2722	2613	1870	867	336
Placebo	2800	2720	2611	1846	844	339

At baseline:
Placebo: 44.3 (±12.6)
Finerenone: 44.4 (± 12.6)

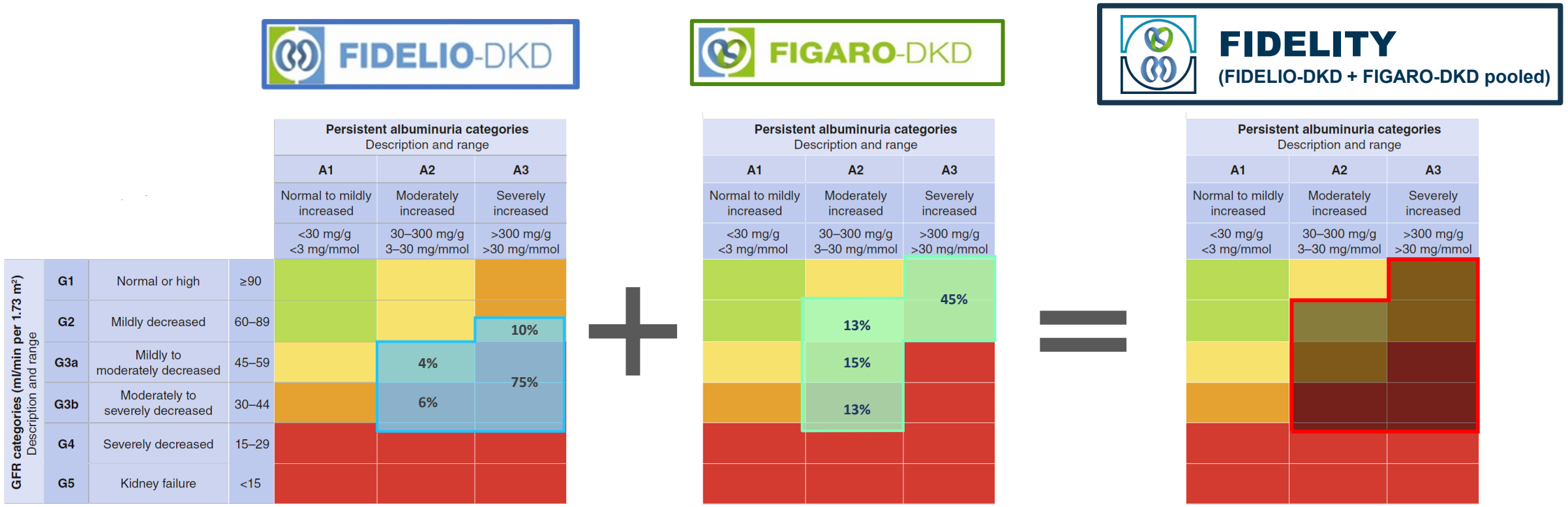
→

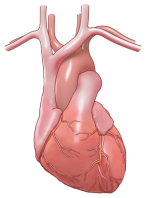
Acute eGFR change:
Placebo: -0.73 (-1.03 to -0.44)
Finerenone: -3.18 (-3.44 to -2.91)

Chronic annulised eGFR change:
Placebo: -3.97 (-4.27 to -3.66)
Finerenone: -2.66 (-2.96 to -2.36)

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

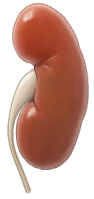
FIDELITY Pooled Analysis





PRIMARY CV ENDPOINT

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



KEY SECONDARY KIDNEY ENDPOINT

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**

30≤UACR<300 mg/g and
25≤eGFR<90 mL/min/1.73m^2

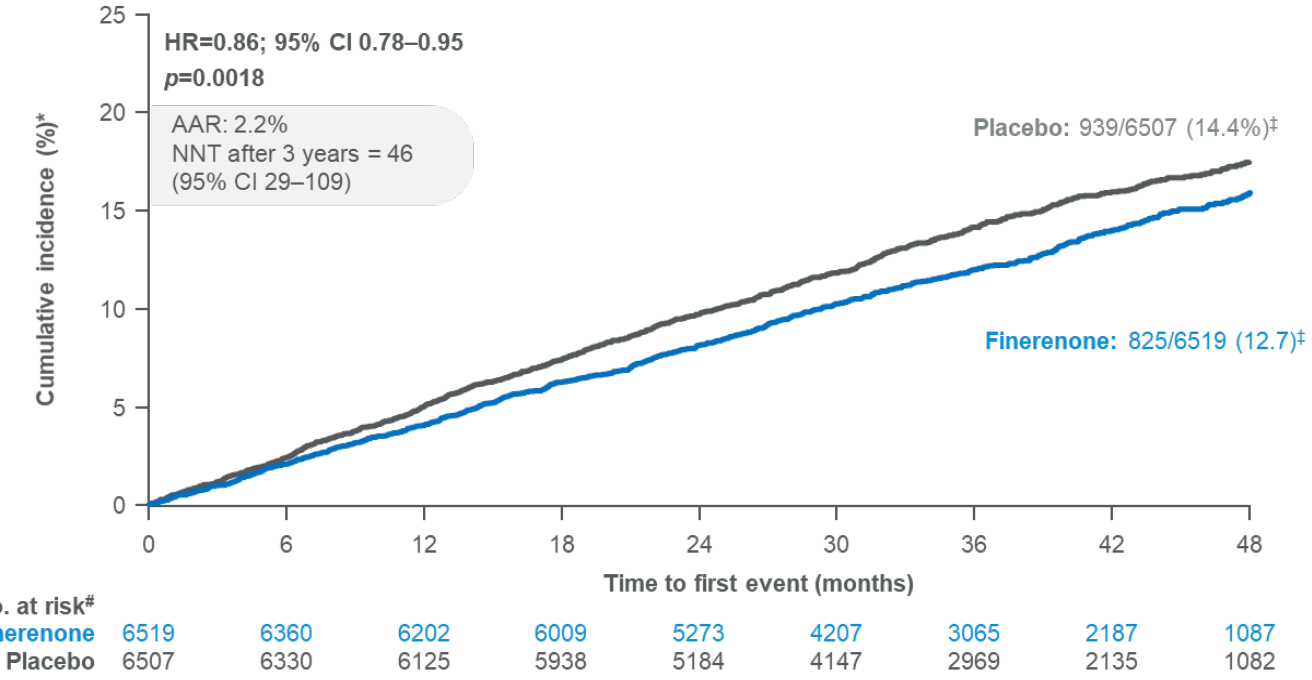
or

300≤UACR≤5000 mg/g and
eGFR≥25 mL/min/1.73m^2

*Please see slide notes for recruitment caps and eGFR/UACR cut-off details

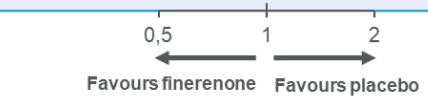
1. KDIGO. *Kidney Int* 2020;98:S1–S115; 2. Ruilope LM, *et al*. *Am J Nephrol* 2019;50:345–356; 3. Bakris GL, *et al*. *Am J Nephrol* 2019;50:333–344 4. Agarwal R et al. *Eur Heart J* 2021. DOI: 10.1093/eurheartj/ehab777/6433104

Finerenone significantly reduced the risk of the CV composite outcome by 14% and had consistent effects on CV death, MI and hospitalisation for HF



median of 3.0 years of follow-up

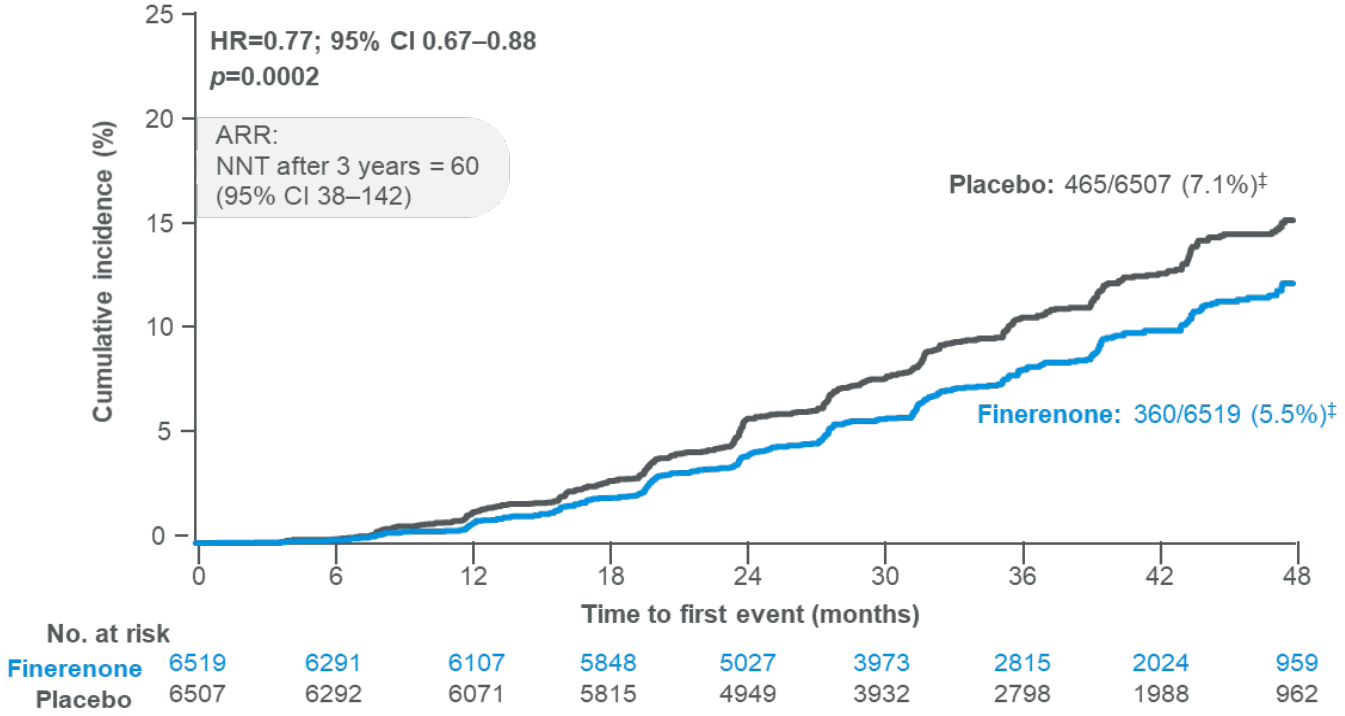
Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	Hazard ratio (95% CI)	p-value
Composite CV outcome§	**825 (12.7)**	**939 (14.4)**	**0.86 (0.78–0.95)**	**0.0018**
CV death	322 (4.9)	364 (5.6)	0.88 (0.76–1.02)	0.0922
Non-fatal MI	173 (2.7)	189 (2.8)	0.91 (0.74–1.12)	0.3601
Non-fatal stroke	198 (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



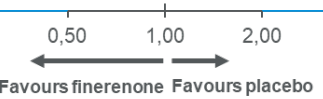
*Cumulative incidence calculated by Aalen-Johansen estimator using deaths due to other causes as competing risk; #at-risk subjects were calculated at start of time point; ‡number of patients with an event over a median of 3.0 years of follow-up; § composite of time to first onset of CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF

Agarwal R et al. Eur Heart J 2021. DOI: 10.1093/eurheartj/ehab777/6433104

Finerenone reduced the risk of the renal composite outcome by 23% and had consistent effects on kidney failure and ≥57% decrease in GFR respect baseline



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



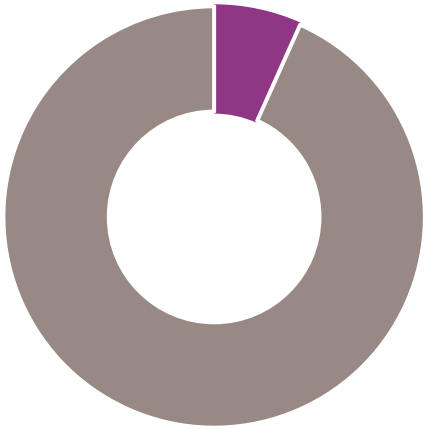
*ESKD or sustained decrease in eGFR <15 ml/min/1.73 m^2; #confirmed by two eGFR measurements ≥4 weeks apart; ‡events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; § number of patients with an event over a median of 3.0 years of follow-up; ¶analyses for *p*-values not prespecified

Agarwal R et al. Eur Heart J 2021. DOI: 10.1093/eurheartj/ehab777/6433104

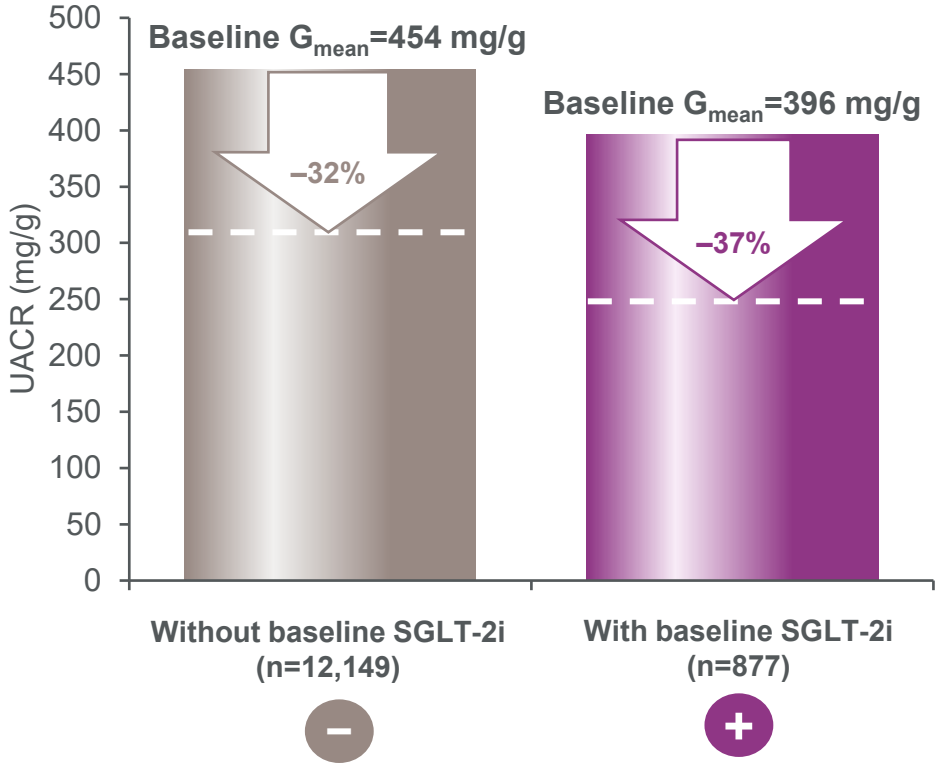
Finerenone improved UACR in patients with CKD and T2D irrespective of SGLT-2i use at baseline

SGLT-2i use at baseline

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



Reduction in UACR (%) with finerenone vs placebo



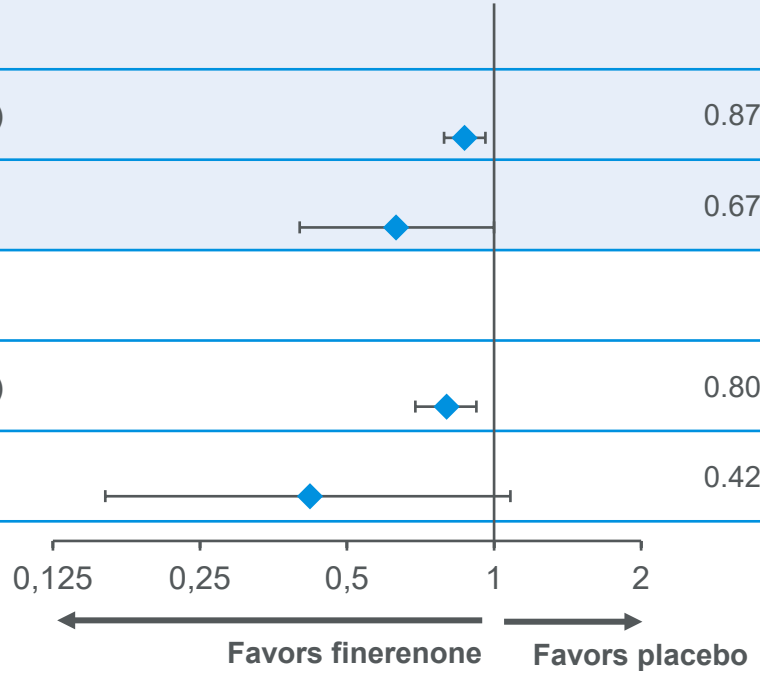
Full analysis set. Mixed model with factors for treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history; time, treatment*time, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariates

G_{mean}, geometric mean

Rossing P et al. *Diabetes Care* 2022; DOI: 10.2337/dc22-0294

The CV benefit of finerenone was consistent irrespective of SGLT-2i use at baseline

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
CV composite#					
No SGLT-2i	786/6081 (4.4)	887/6068 (5.1)		0.87 (0.79–0.96)	0.46
SGLT-2i	39/438 (3.0)	52/439 (4.1)		0.67 (0.42–1.07)	
eGFR 57% kidney composite#					
No SGLT-2i	351/6081 (2.1)	448/6068 (2.6)		0.80 (0.69–0.92)	0.29
SGLT-2i	9/438 (0.7)	17/439 (1.4)		0.42 (0.16–1.08)	



*Adjusted HR for HbA1c, SBP, UACR at baseline (log-transformed), eGFR at baseline; #eGFR 57% kidney composite outcome defined as kidney failure (end-stage kidney disease or eGFR <15 ml/min/1.73 m^2), a sustained ≥57% decrease in eGFR from baseline (equivalent to a doubling of serum creatinine) for ≥4 weeks, or renal death PY, patient-years

Rossing P et al. *Diabetes Care* 2022; DOI: 10.2337/dc22-0294

Comparison of RCTs

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

Background

Both finerenone and canagliflozin reduce cardiovascular and renal risk in patients with type 2 diabetes and CKD with albuminuria

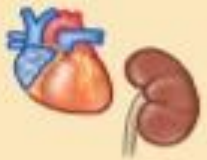
≠

There are key differences in trial inclusion/exclusion criteria and end point definitions in CREDENCE and FIDELIO-DKD

Methods

Participants in two RCTs:
- CREDENCE (canagliflozin)
- FIDELIO-DKD (finerenone)

Restricted to participants who met inclusion criteria for CREDENCE:
- UACR > 300–5000 mg/g
- eGFR 30– < 90 ml/min/1.73 m²



Endpoints:
- Composite cardiorenal
- Kidney-specific

Results

N=4619 met 'CREDENCE-LIKE' criteria

Finerenone:
2291/4619 (49.6%)
Placebo:
2328/4619 (50.4%)

Treatment effects of canagliflozin and finerenone assessed and compared in CREDENCE and 'CREDENCE-LIKE' FIDELIO-DKD subgroup

	FIDELIO-DKD 'CREDENCE-LIKE'	CREDENCE
Composite cardiorenal	**HR 0.74** (95% CI 0.63–0.87)	**HR 0.70** (95% CI 0.59–0.82)
Kidney-specific	**HR 0.69** (95% CI 0.57–0.84)	**HR 0.66** (95% CI 0.53–0.81)

Cox regression: hazard ratio (HR) and (95% CI)

Conclusion

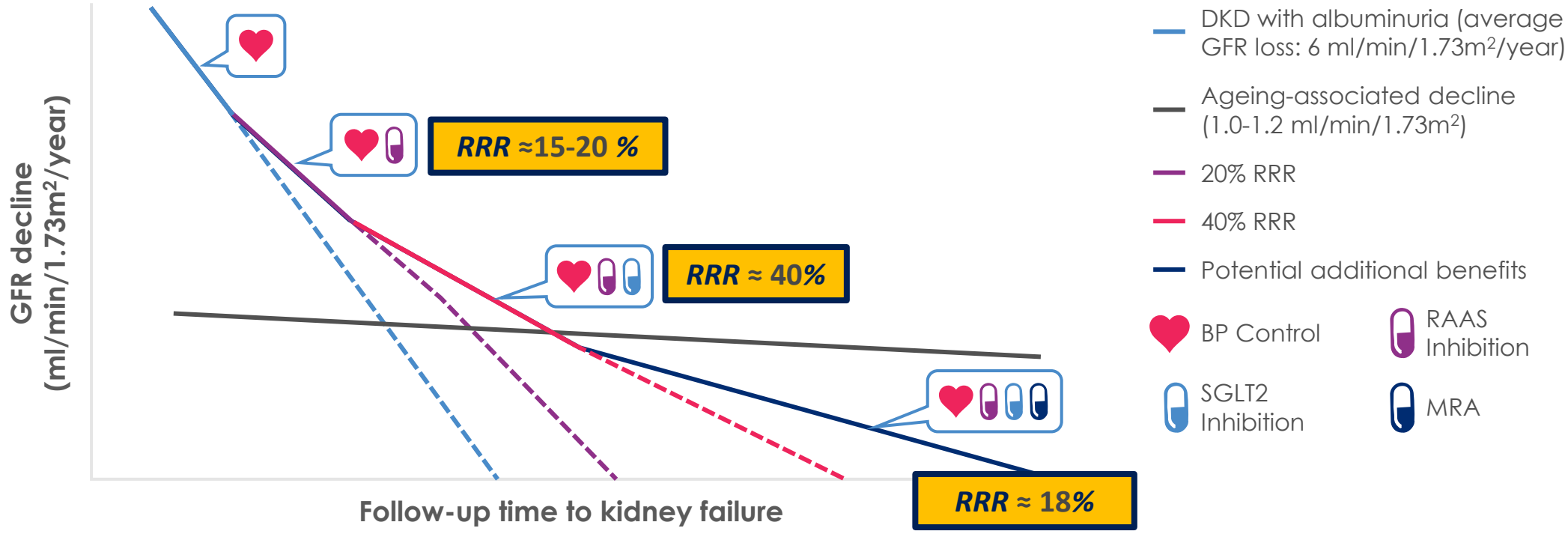
After accounting for trial differences, both the SGLT2i canagliflozin and the non-steroidal MRA finerenone are similarly effective in patients with type 2 diabetes and CKD with very high albuminuria in reducing the risk of cardiorenal outcomes.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

Agarwal, R. et al. NDT (2021)
@NDTSocial

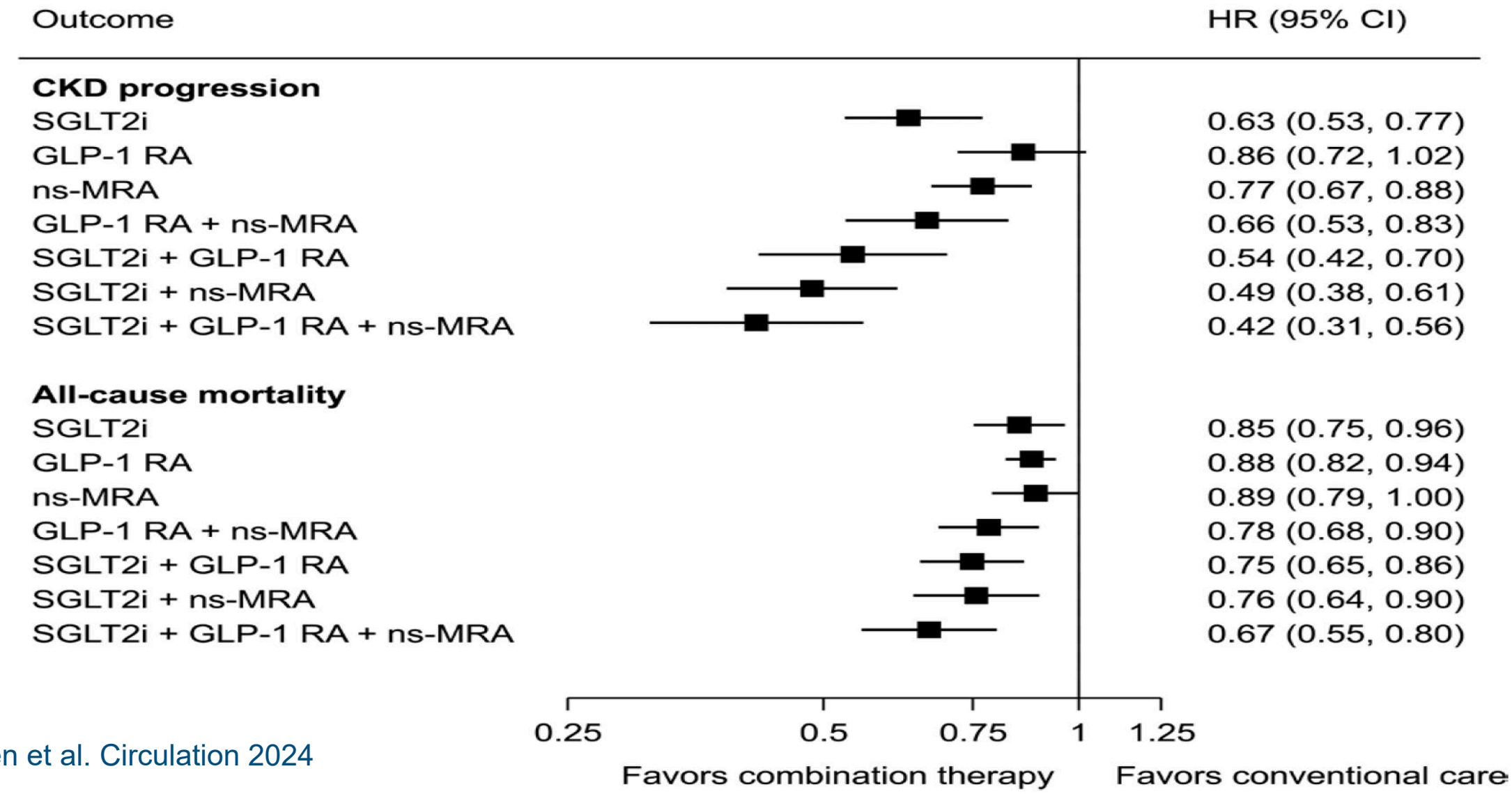
With multifactorial intervention, the course of CKD has changed considerably

Incremental Benefit of Multifactorial Intervention on GFR Decline in Patients with CKD and T2D



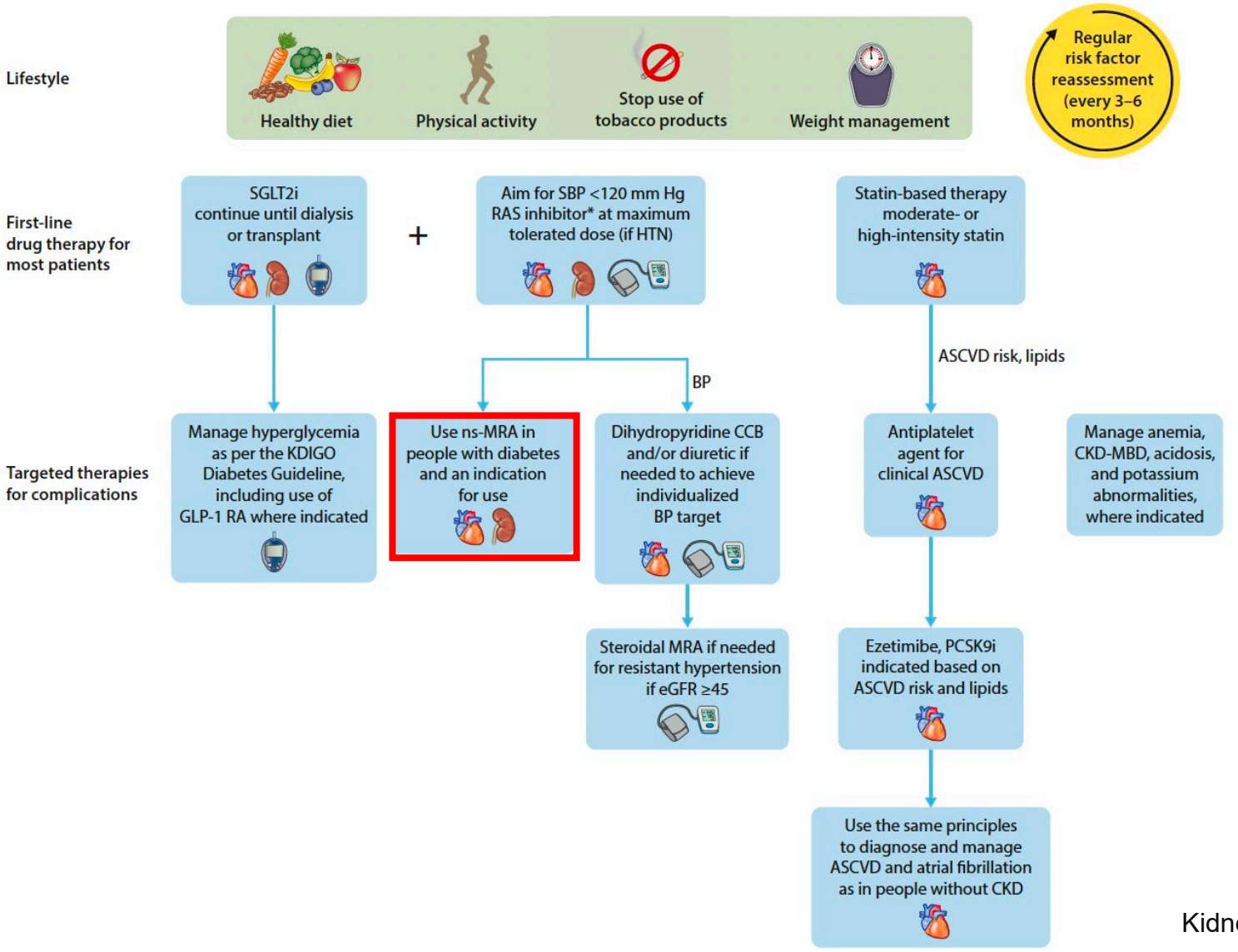
BP, blood pressure; CKD, chronic kidney disease; DKD, diabetic kidney disease; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; RRR, relative risk reduction; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes. Fioretto P & Pontremoli R. Nat Rev Nephrol 2022;18:78

Estimated treatment effects on CKD progression and all cause mortality with SGLT2i, GLP-1 RA, and ns-MRA, *alone and in combination*, when added to RAS blockade in patients with T2D



Neuen et al. Circulation 2024

KDIGO 2024: Finerenone for patients with CKD and diabetes



Kidney International, march 14 2024