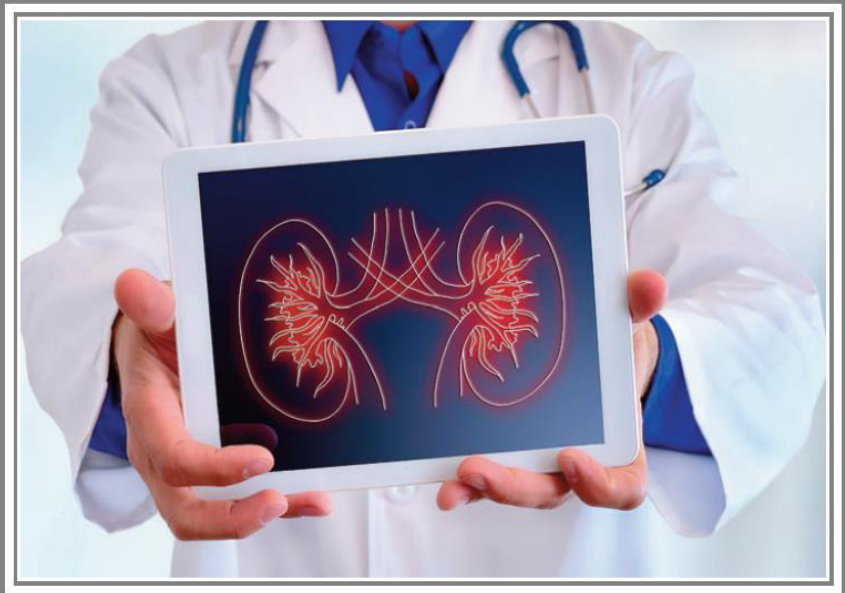
ORIGINATE-DKD:
Nuove **O**ppo**R**tun**I**tà farmacolo**GI**che per il tratta**N**to del p**A**zien**TE** con nefropatia diabetica

Bologna, 29 Marzo 2023

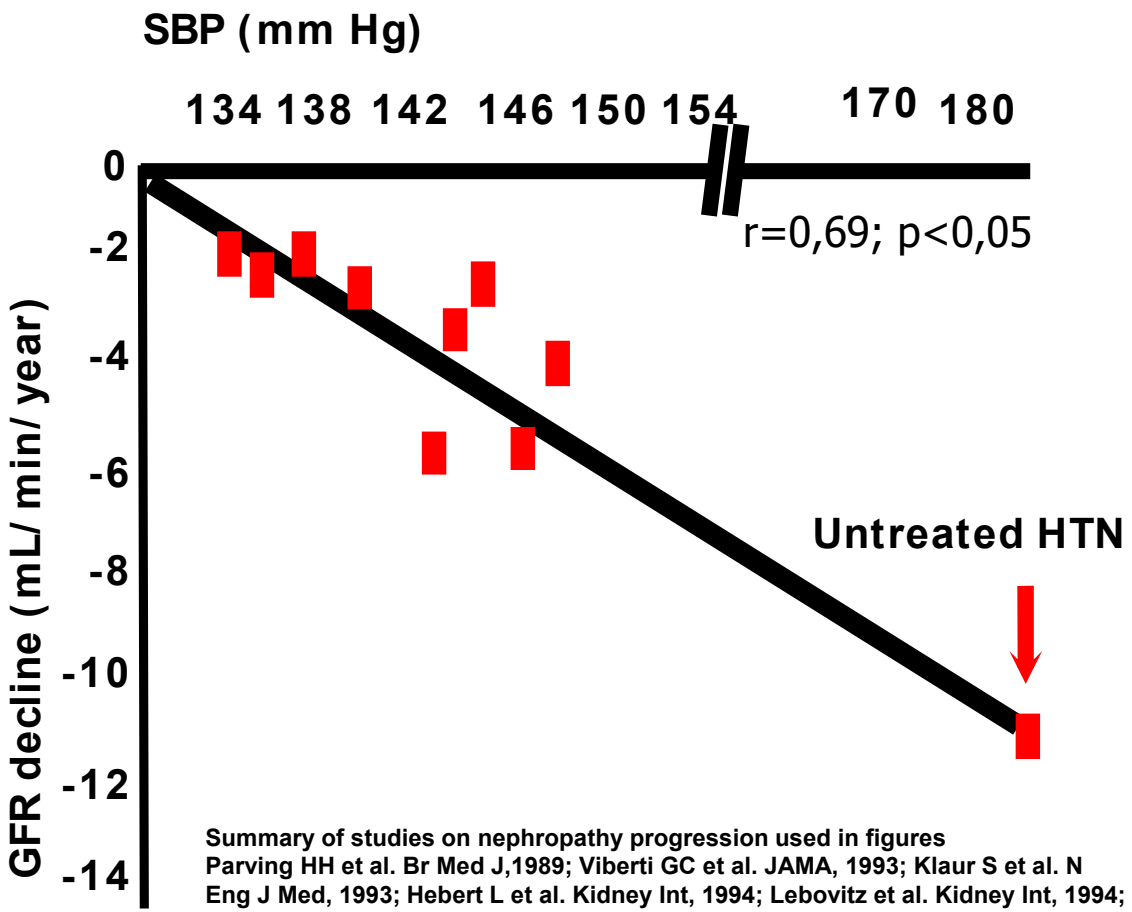


Sede del Congresso:
Hotel NH De La Gare - Bologna

12:30-12:45 Finerenone: il meccanismo d'azione
G. La Manna

ORIGINATE-DKD:
Nuove **O**ppo**R**tun**I**tà farmacolo**GI**che per il tratta**N**to del p**A**zien**TE** con nefropatia diabetica

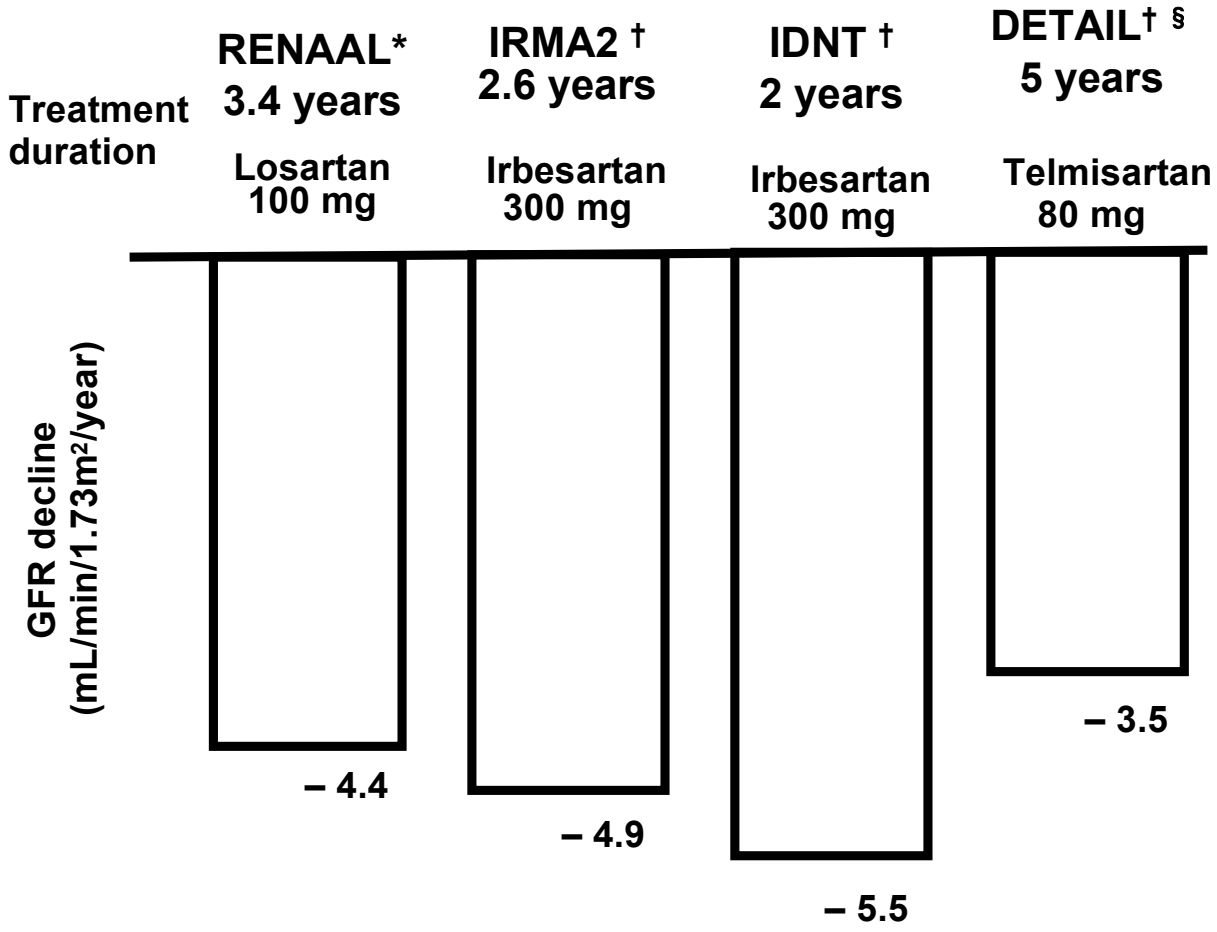
Renoprotection with ACEi



Summary of studies on nephropathy progression used in figures
Parving HH et al. Br Med J,1989; Viberti GC et al. JAMA, 1993; Klaur S et al. N Eng J Med, 1993; Hebert L et al. Kidney Int, 1994; Lebovitz et al. Kidney Int, 1994; Bakris GL et al. Kidney Int, 1996; Maschio G et al. N Eng J Med, 1996; Bakris GL Hypertension, 1997; GISEN Group, Lancet, 1997

Adapted from Bakris et al. Am J Kidney Dis. 2000;36:646-661.

Renoprotection with ARBs



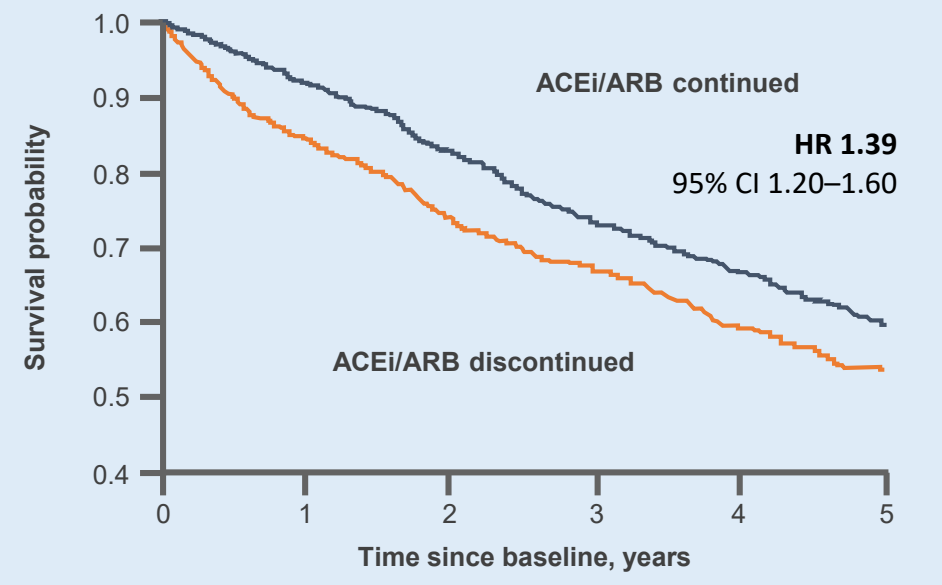
* Median; † Mean; § Completers

Barnett A.H., et al. N Engl J Med 2004;351:1952–1961 correction N Engl J Med 2005;352:1731; Barnett A.H., et al. Acta Diabetol 2005;42(Suppl 1):S42–S49

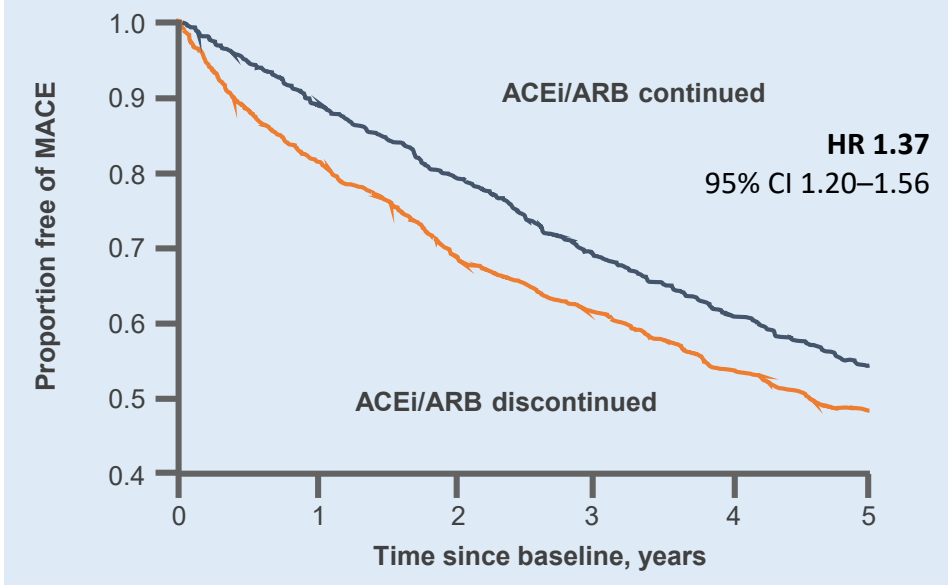
ACEI/ARB discontinuation following eGFR decrease is associated with poor CV outcomes In patients with Declining Kidney Function

Objective: a retrospective, propensity score-matched cohort study investigated the association of ACEi/ARB discontinuation after eGFR decrease (<30 mL/min/1.73 m^2) and risk of mortality, MACE, and ESKD

ACEi/ARB discontinuation was associated with a higher risk of mortality



ACEi/ARB discontinuation was associated with a higher risk of MACE



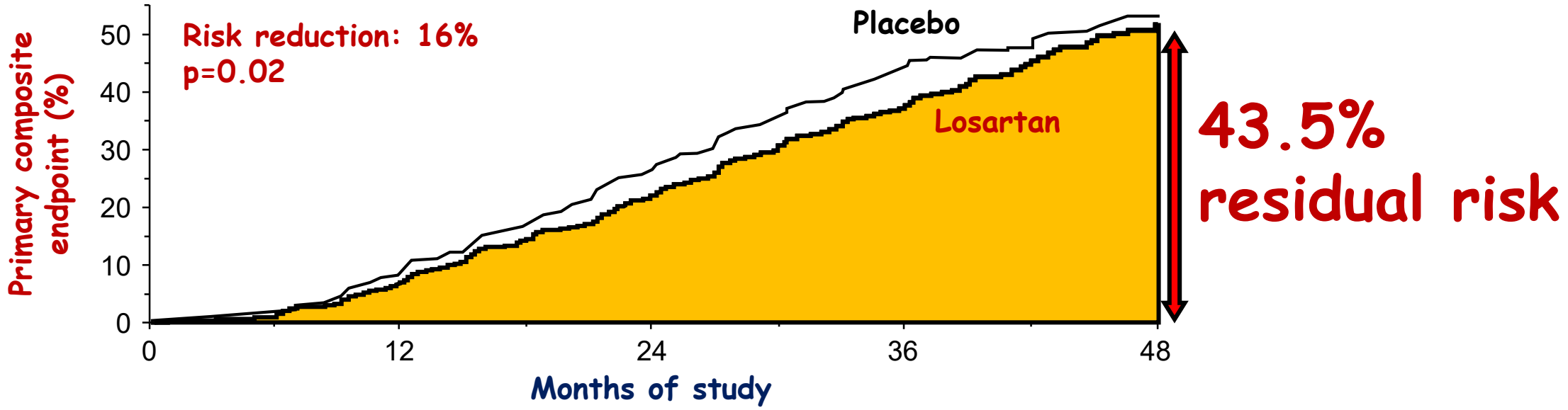
- ACEi/ARB discontinuation was not significantly associated with ESKD risk (HR 1.19; 95% CI 0.86–1.65)

- ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular events.
Qiao Y, *et al. JAMA Intern Med.* 2020;180:718–26.

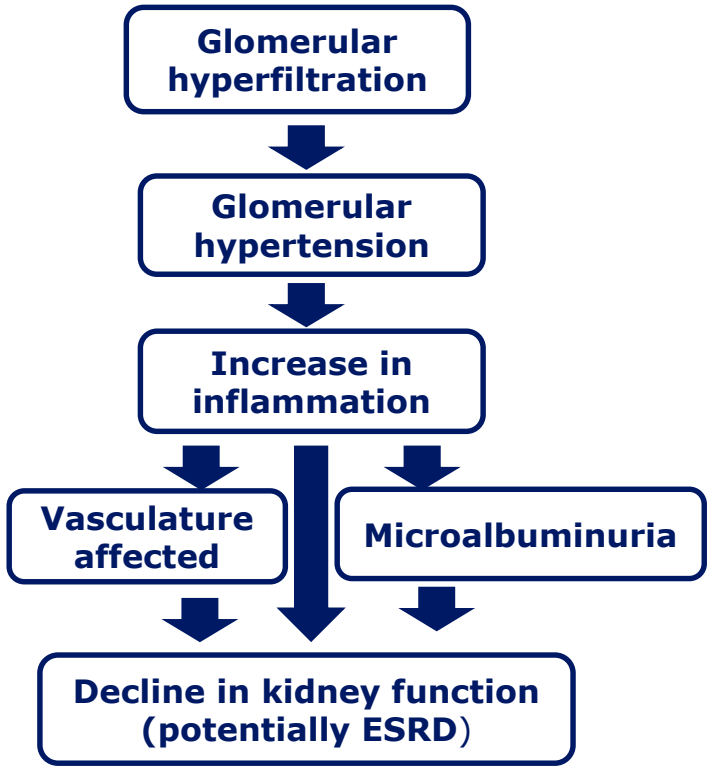
RISCHIO SIGNIFICATIVO

DI PROGRESSIONE DELLA MALATTIA

RENAAL: Risk of dSCr, ESKD, or death with placebo versus losartan in patients with T2D and nephropathy



Mechanisms behind kidney disease progression

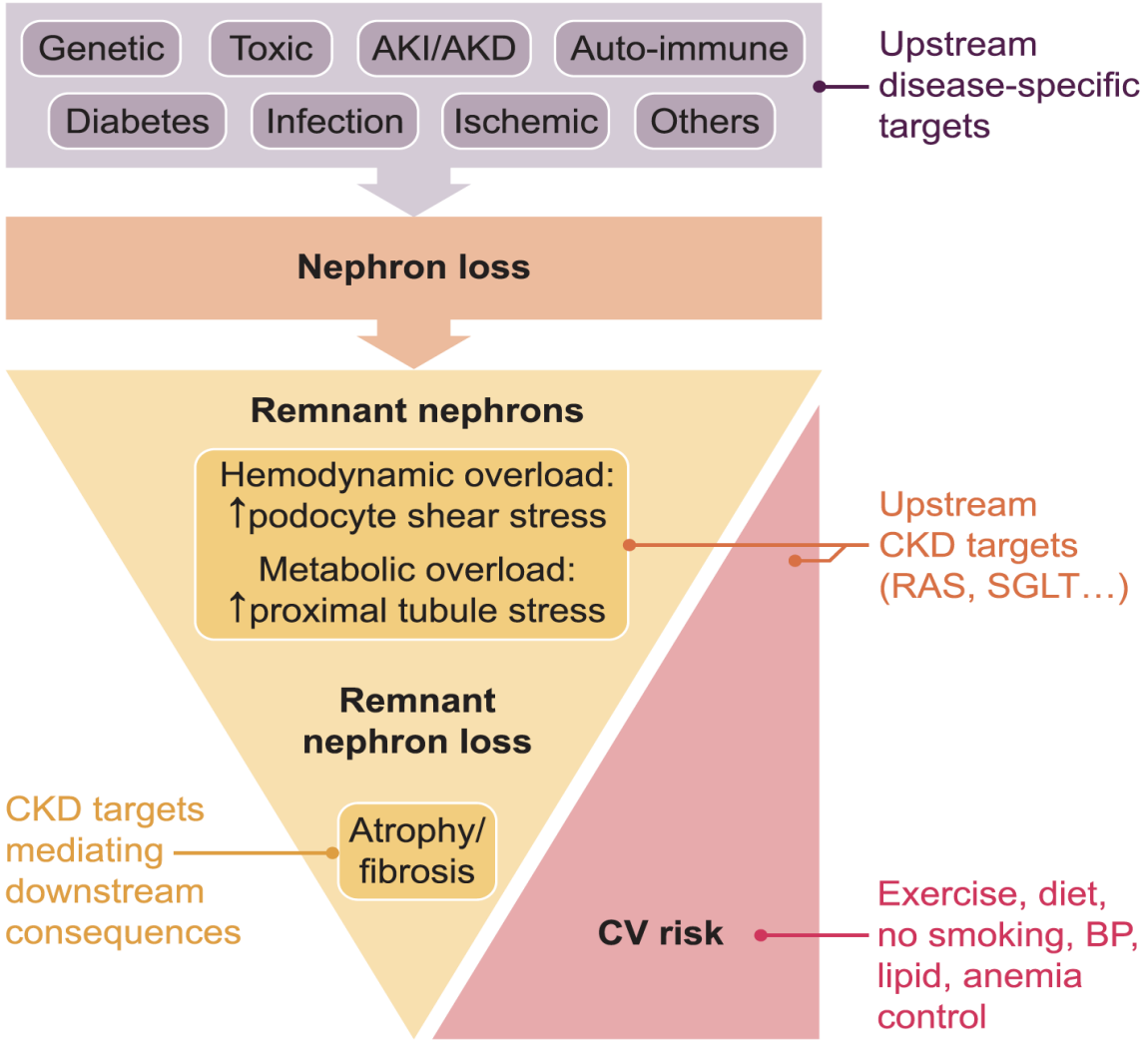


Nephrol Dial Transplant (2022) 37: 1609–1615
doi: 10.1093/ndt/gfaa329
Advance Access publication 13 December 2020

ndt

SGLT2 inhibition requires reconsideration of fundamental paradigms in chronic kidney disease, 'diabetic nephropathy', IgA nephropathy and podocytopathies with FSGS lesions

Hans-Joachim Anders[1], Anna Julie Peired[2,3] and Paola Romagnani[3,4]



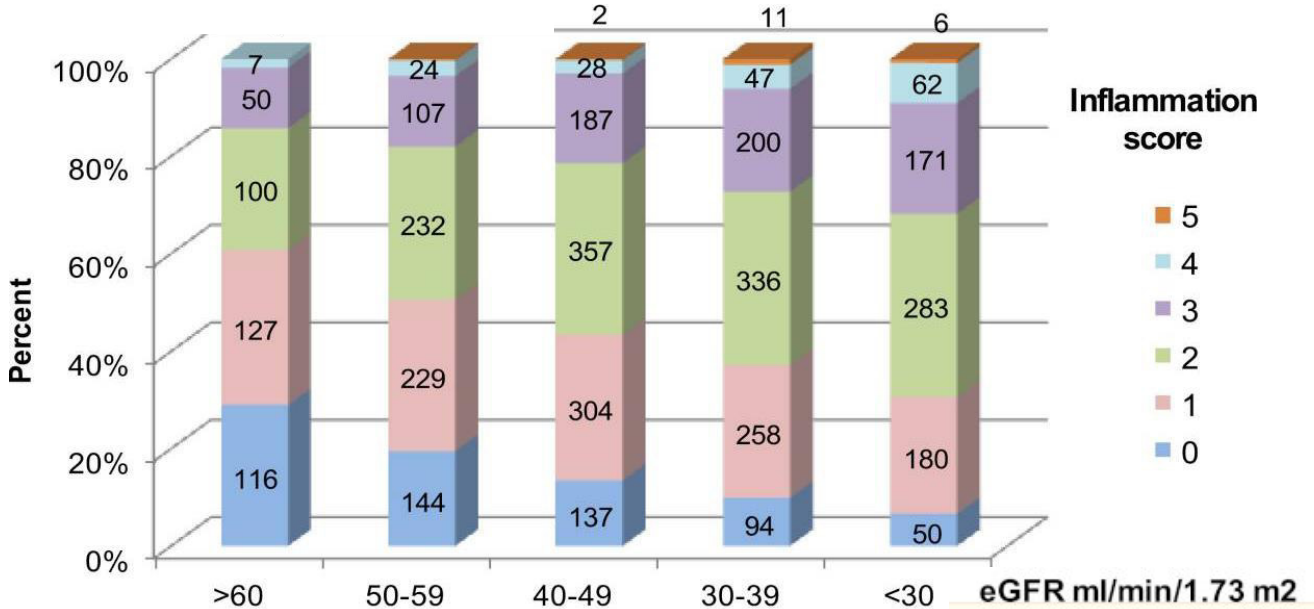
Association between Albuminuria, Kidney Function, and Inflammatory Biomarker Profile in CKD in CRIC

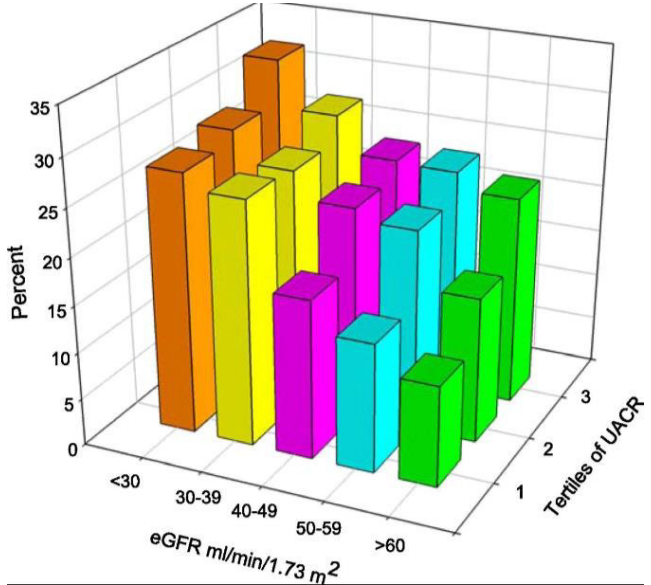
Gupta, Jayanta[*]; Mitra, Nandita[*]; Kanetsky, Peter A.[*]; Devaney, Joe[†]; Wing, Maria R.[†]; Reilly, Muredach[*]; Shah, Vallabh O.[‡]; Balakrishnan, Vaidyanathapura S.[§]; Guzman, Nicolas J.[†]; Girndt, Matthias[‖]; Periera, Brian G.[§]; Feldman, Harold I.[*]; Kusek, John W.[¶]; Joffe, Marshall M.[*]; Raj, Dominic S.[†] for the CRIC Study Investigators

The CRIC study is a prospective observational cohort study of 3939 participants with established CKD

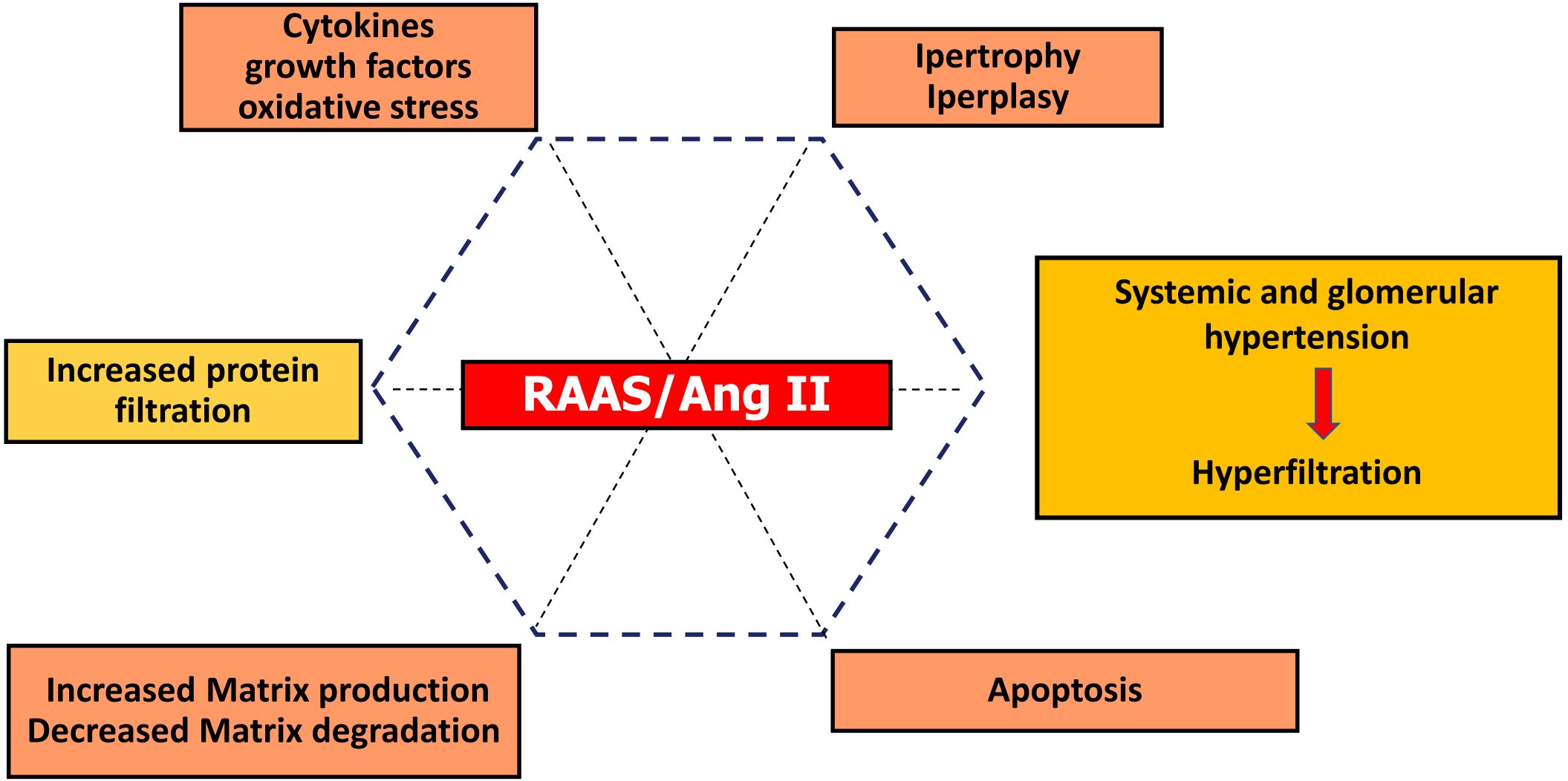
Table 1. Baseline demographic and clinical characteristics of the Chronic Renal Insufficiency Cohort study population overall and by UACR

	Entire Cohort (*n*=3939)	UACR (µg/mg) (*n*=3791)[a]			
		Tertile 1 (*n*=1263)	Tertile 2 (*n*=1264)	Tertile 3 (*n*=1264)	*P* Value
Male	2161 (54.9)	589 (46.6)	712 (56.3)	775 (61.3)	<0.001
Ever smoked	2158 (54.8)	659 (52.2)	726 (57.4)	703 (55.6)	0.03
Current smoker	517 (13.1)	121 (9.6)	173 (13.7)	201 (15.9)	<0.001
Hypertension[b]	3391 (86.1)	982 (77.8)	1114 (88.1)	1166 (92.3)	<0.001
Diabetes[c]	1907 (48.4)	400 (31.7)	605 (47.9)	824 (65.2)	<0.001
Age (yr)	60 (52, 66)	61 (55, 67)	61.0 (54.0, 67.5)	57 (48, 64)	<0.001
Body mass index (kg/m^2)	30.9 (26.8, 36.1)	30.5 (26.7, 35.6)	30.7 (26.6, 35.6)	31.6 (27.1, 37.3)	0.001
Hemoglobin (gm/dl)	12.5 (11.4, 13.6)	13.0 (11.9, 14.1)	12.6 (11.5, 13.6)	12.1 (11.0, 13.3)	<0.001
WBC (×10^3/µl)	6.3 (5.2, 7.7)	5.9 (4.9, 7.1)	6.4 (5.2, 7.8)	6.6 (5.4, 8.0)	<0.001
Platelet count (10^3/µl)	237 (195, 284)	237 (195, 279)	232 (191, 278)	241 (200, 292)	<0.001
eGFR (ml/min per 1.73 m^2)	42.2 (32.6, 51.9)	48.5 (39.9, 57.0)	42.0 (32.7, 50.7)	35.8 (28.1, 45.1)	<0.001
Serum creatinine (mg/dl)	1.7 (1.4, 2.1)	1.4 (1.2, 1.7)	1.7 (1.4, 2.1)	2.0 (1.6, 2.6)	<0.001
Serum cystatin C (mg/L)	1.4 (1.1, 1.8)	1.2 (0.9, 1.4)	1.4 (1.2, 1.8)	1.7 (1.4, 2.1)	<0.001
BUN (mg/dl)	26 (20, 36)	22 (17, 28)	27 (21, 37)	32 (24, 42)	<0.001
Acute phase protein					
Serum albumin (g/dl)	4.0 (3.7, 4.2)	4.1 (3.9, 4.3)	4.1 (3.8, 4.3)	3.7 (3.4, 4.0)	<0.001
hs-CRP (mg/L)	2.6 (1.1, 6.5)	2.2 (1.0, 5.9)	2.8 (1.1, 7.0)	2.7 (1.1, 6.5)	0.002
Fibrinogen (g/L)	4.0 (3.4, 4.8)	3.7 (3.2, 4.4)	4.0 (3.3, 4.6)	4.5 (3.8, 5.3)	<0.001
Cytokines					
IL-1β (pg/ml)	0.2 (0, 1.3)	0 (0, 0.9)	0.2 (0, 1.2)	0.4 (0, 1.8)	<0.001
IL-1RA (pg/ml)	715.7 (390.0, 1551.0)	672.7 (360.2, 1404.1)	676.2 (383.4, 1492.7)	834.6 (419.4, 1732.6)	<0.001
IL-6 (pg/ml)	1.9 (1.2, 3.2)	1.5 (0.9, 2.5)	2.0 (1.2, 3.3)	2.2 (1.4, 3.5)	<0.001
TNF-α (pg/ml)	2.2 (1.5, 3.2)	1.7 (1.2, 2.6)	2.2 (1.5, 3.2)	2.8 (1.9, 3.8)	<0.001
TGF-β (pg/ml)	11.0 (6.5, 17.9)	10.4 (5.7, 17.5)	10.6 (6.3, 17.2)	11.6 (7.3, 18.7)	<0.001

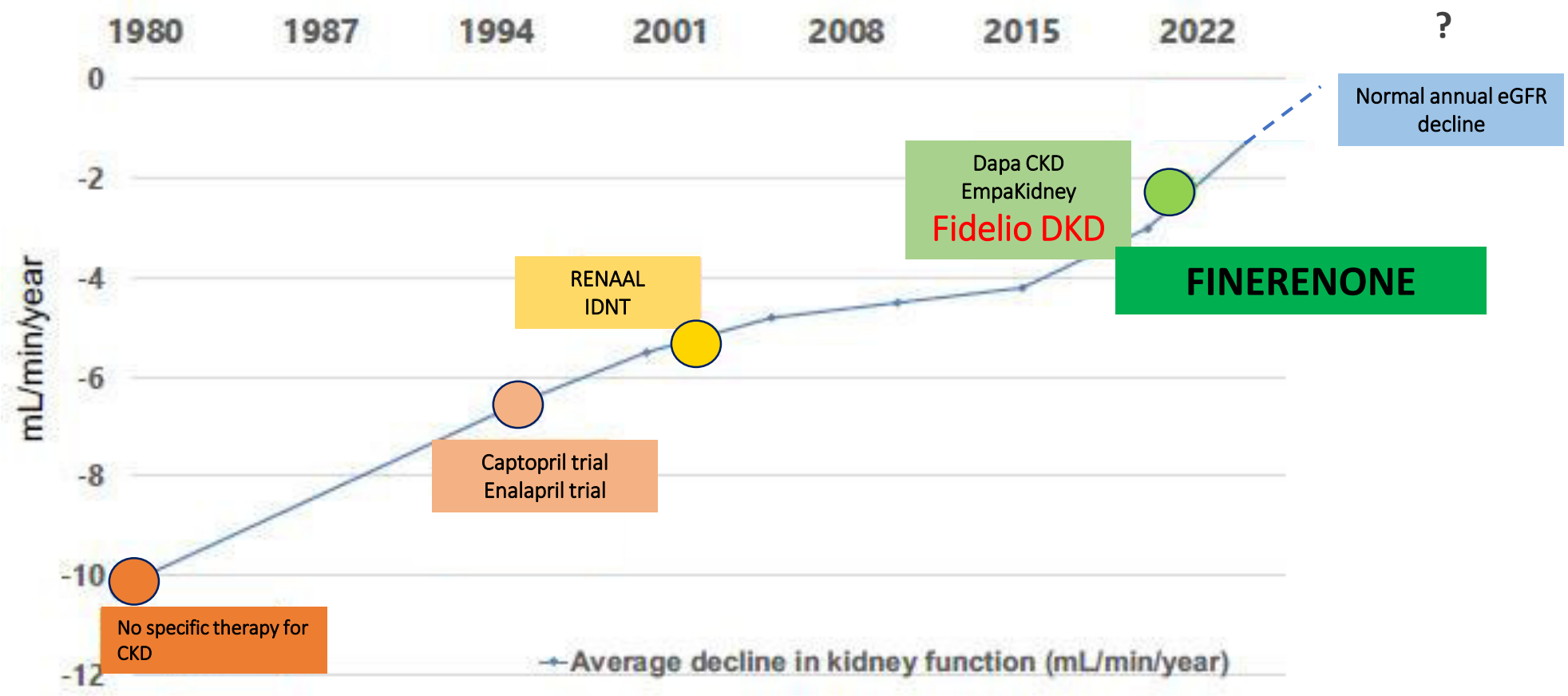




Pathogenesis of Renal Disease Progression



A Menu of Therapies Drives Personalized Kidney Protection



modified, from Bakris EDTA 2022

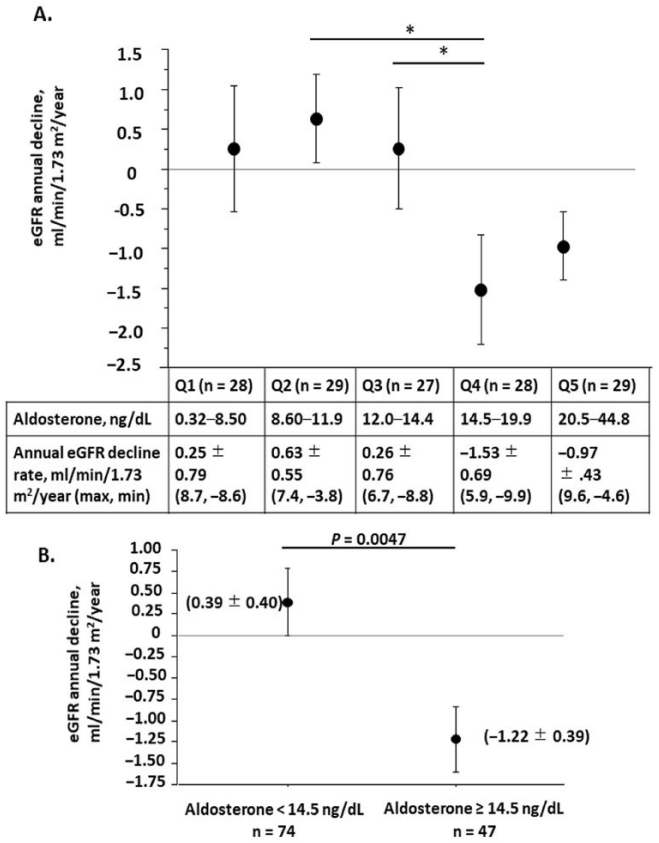
SCIENTIFIC REPORTS | (2020) 10:16626 | https://doi.org/10.1038/s41598-020-73638-4

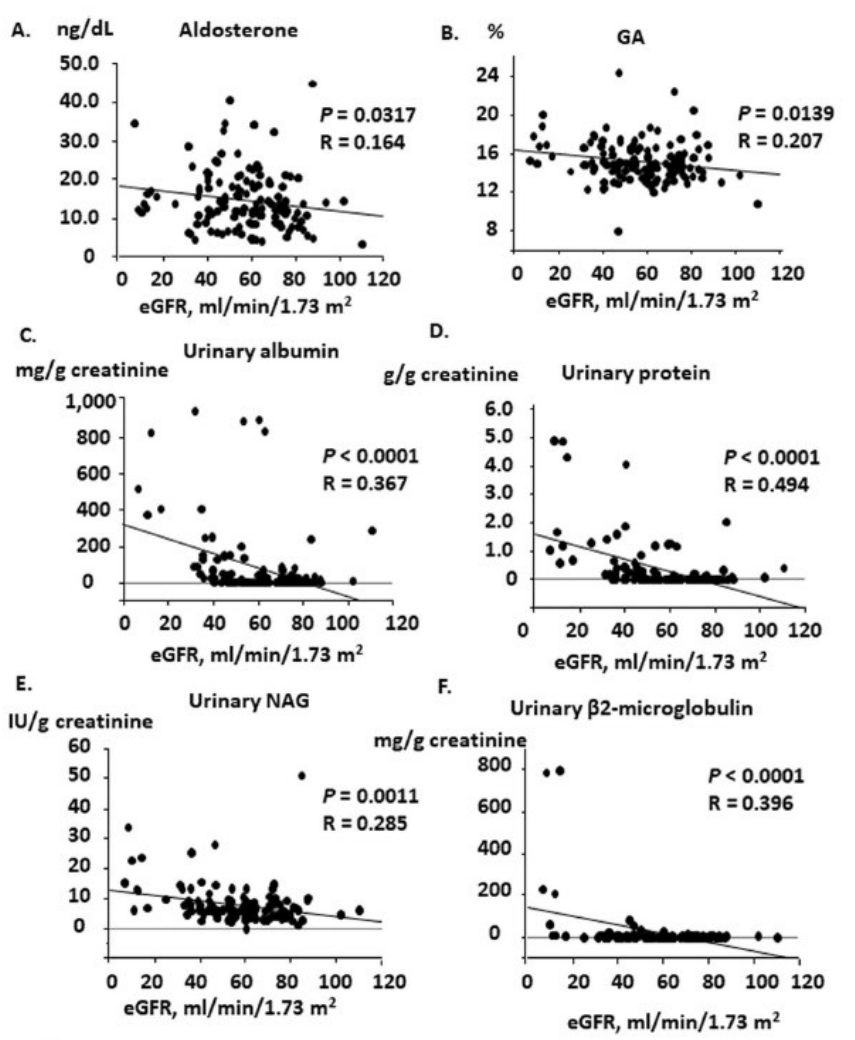
The effect of aldosterone and aldosterone blockade on the progression of chronic kidney disease: a randomized placebo-controlled clinical trial

Hitoshi Minakuchi, Shu Wakino, Hidenori Urai, Arata Kurokochi, Kazuhiro Hasegawa, Takeshi Kanda, Hirobumi Tokuyama & Hiroshi Itoh

Patients. From April 2007 through July 2007, we recruited consecutive patients with CKD from the patients referred to the renal division of our department. Enrollees were diagnosed with CKD according to either one of the following criteria: (1) eGFR below 60 ml/min/1.73 m^2, or (2) kidney damage evident from dipstick-detected urinary protein excretion for more than 3 months. Patients undergoing hemo- or peritoneal dialysis were excluded from this study. We prospectively observed the enrolled patients for 3 years during the 2007 to 2011 period. The main objective of this observation was to evaluate the long-term effects of various biochemical or

Number	141
Age, years (oldest, youngest)	66.8 ± 1.6 (88, 16)
Gender, male/female	73/68
Cause of CKD (%)	
Nephrosclerosis	79 (56.0%)
Chronic glomerulonephritis	41 (29.1%)
Diabetic nephropathy	20 (14.2%)
Other	1 (0.7%)
CKD stage (%)	
G1	3 (2.1%)
G2	68 (48.2%)
G3a	34 (24.1%)
G3b	27 (19.1%)
G4	2 (1.4%)
G5	7 (5.0%)





Significant associations were observed **between eGFR and the levels of plasma aldosterone** concentration.

Aldosterone in chronic kidney disease and renal outcomes

The **CRIC study** is a multicentre, prospective, observational cohort study designed to investigate the **risk factors for death, cardiovascular disease, and CKD progression in participants with known CKD**.
From 8 April 2003, through 3 September 2008 (Phase 1), **3939 participants**, 21–74 years old, were enrolled across seven clinical centres in the USA, with an **eGFR ranging from 20 to 70 mL/min/1.73 m2**.

Chronic renal insufficiency cohort

3680

- Baseline serum aldosterone
- Age: 21 to 74 years
- eGFR 20 to 70 ml/min per 1.73 m^2
- Common forms of CKD
- Not using aldosterone antagonists

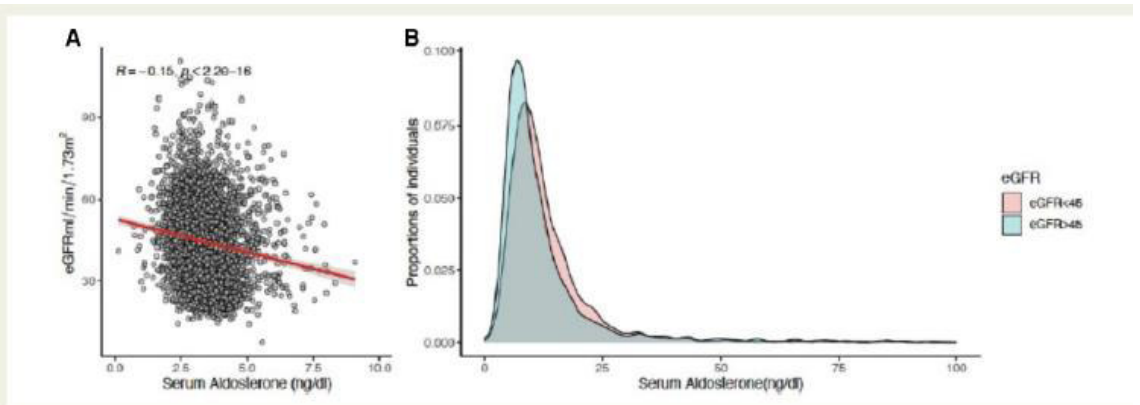
Median follow up: **9.6 years**

Baseline serum aldosterone (ng/dl)

Kidney outcomes

In adjusted models, each doubling of serum aldosterone

Cox-proportional hazard models used to examine the association of baseline serum aldosterone and kidney outcomes



European Heart Journal (2022) 43, 3781–3791

Podocyte as the Target for Aldosterone
Roles of Oxidative Stress and Sgk1

Shigeru Shibata, Miki Nagase, Shigetaka Yoshida, Hiroshi Kawachi, Toshiro Fujita

(Hypertension. 2007;49:355-364.)

Protocol 1: Renal Injury in Aldosterone-Infused Rats at 2, 4, and 6 Weeks

Protocol 2: Effects of Eplerenone, Tempol, and Hydralazine on Aldosterone-Induced Renal Damage

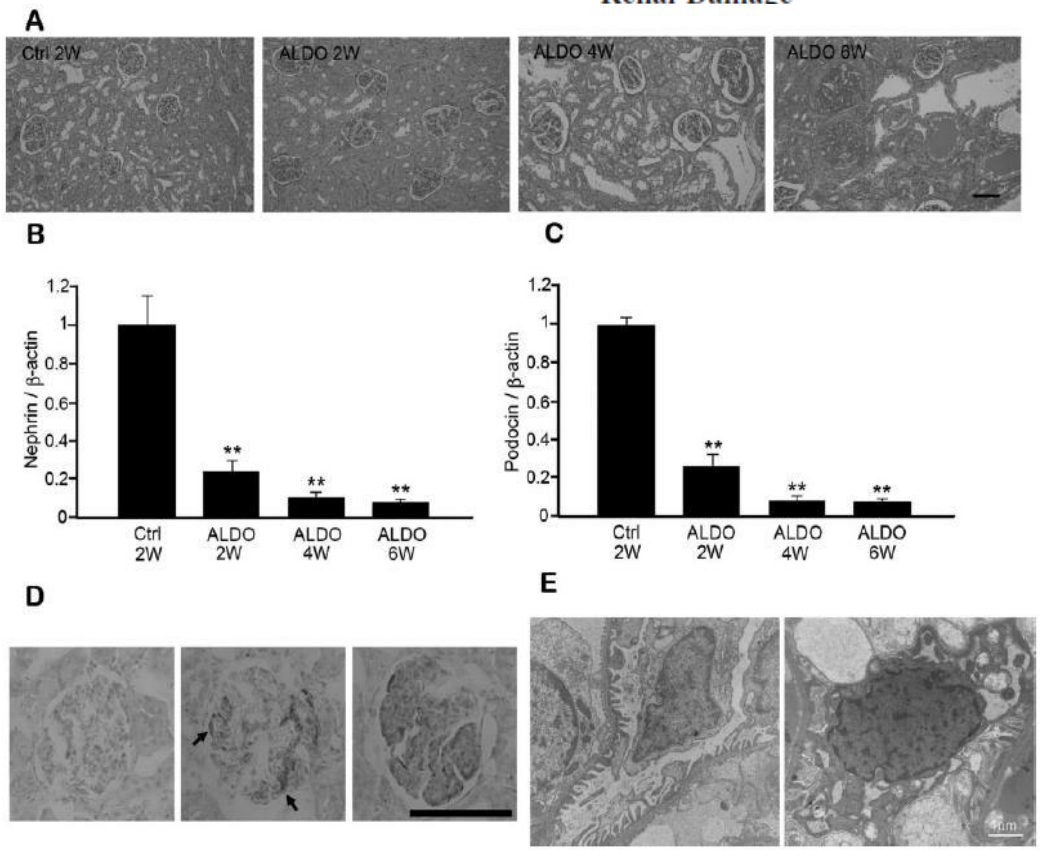
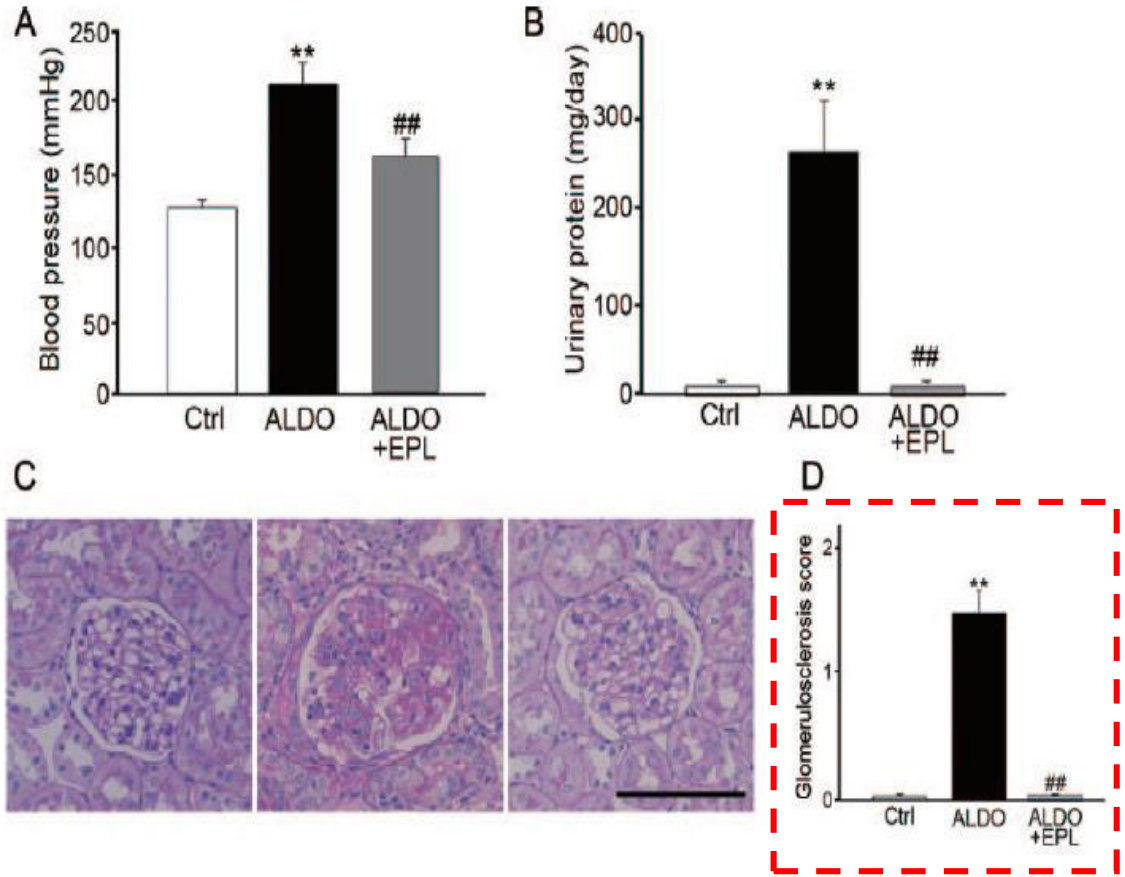


Figure 1. A, Periodic acid-Schiff (PAS)–stained kidney sections from control and aldosterone-infused rats. Ctrl indicates control; ALDO, aldosterone-infused rats; W, weeks. B and C, Quantitative analysis of nephrin (B) and podocin (C) gene expressions in the glomeruli. $^{**}P<0.01$ vs Ctrl. D, Immunostaining for desmin. Left, Control rat glomeruli. Middle, Aldosterone-infused rats at 2 weeks. Desmin expression was increased in podocytes (arrows). Right, Staining was enhanced along the capillary loop at 4 weeks. E, Transmission electron micrographs of control (left) and aldosterone-infused rats at 2 weeks (right). Control rats showed normal structure of podocytes. In aldosterone-infused rats, podocytes exhibited degeneration of the cell body and retraction of the foot processes. Scale bars: A and D, 100 μm; E, 1 μm.

Eplerenone: Proteinuric effect in rat model. Eplerenone protection



In conclusion, **podocytes are injured at the early stage in aldosterone-infused rats**, resulting in the occurrence of proteinuria. Aldosterone can directly modulate podocyte function, possibly through the induction of oxidative stress and Sgk1.

Local renal aldosterone production induces inflammation and matrix formation in kidneys of diabetic rats

Helmy M. Siragy and Chun Xue

Exp Physiol. 2008 July ; 93(7): 817–824.
doi:10.1113/expphysiol.2008.042085

Aldosterone Synthase inhibitor (FAD 286): Hyperfiltration reduction in diabetic rat model

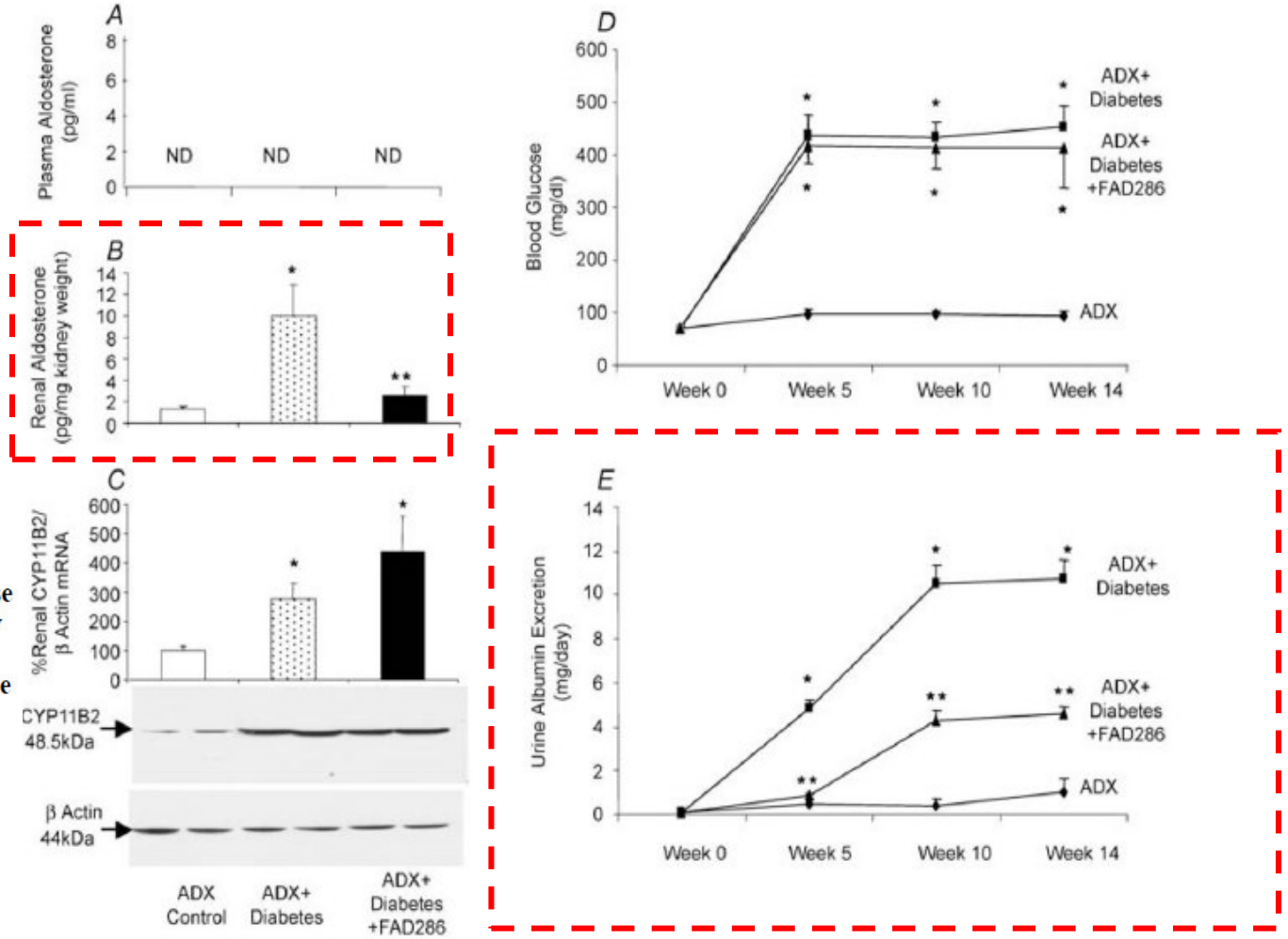


Figure 1. Plasma aldosterone (*A*), renal aldosterone (*B*), representative renal aldosterone synthase (CYP11B2) mRNA (*C*, upper panel) and protein (*C*, lower panel), blood glucose (*D*) and urinary albumin excretion (*E*) in adrenalectomized (ADX) normoglycaemic (ADX control), adrenalectomized diabetic (ADX + Diabetes) and adrenalectomized diabetic rats treated with the aldosterone synthase inhibitor FAD286 (ADX + Diabetes + FAD286)
$^{*}P < 0.01$ from control; $^{**}P < 0.01$ from control or ADX + Diabetes. $n = 8$ each group.

Aldosterone: Mesangial proliferation in diabetic rat model

J Am Soc Nephrol. 2005 Aug;16(8):2296-305. doi: 10.1681/ASN.2005020129. Epub 2005 Jun 23.

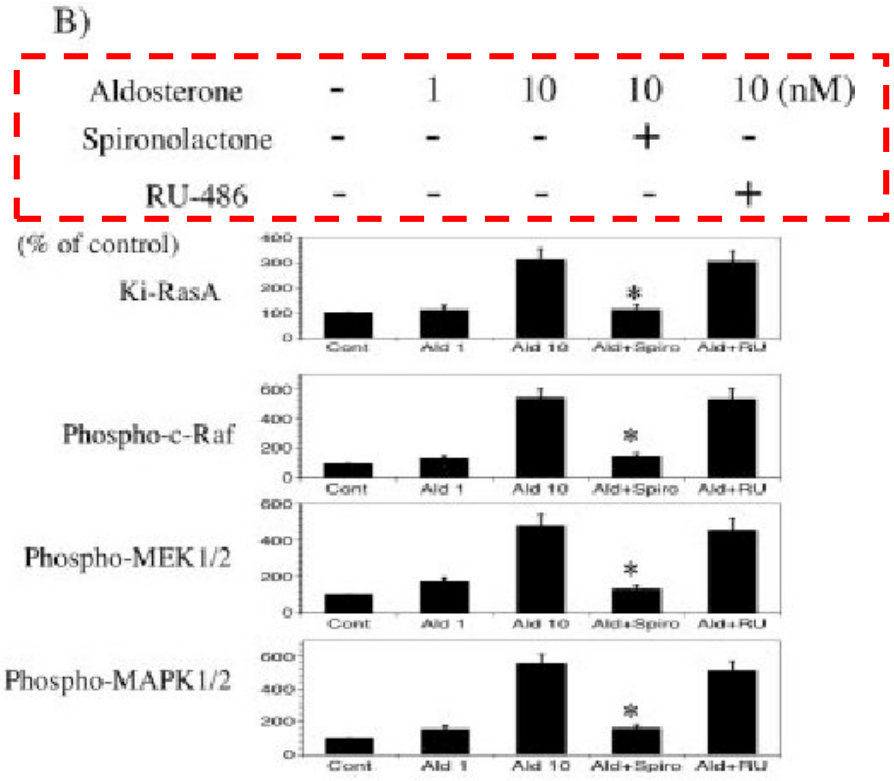
Aldosterone stimulates proliferation of mesangial cells by activating mitogen-activated protein kinase 1/2, cyclin D1, and cyclin A

Yoshio Terada [1], Takahiko Kobayashi, Hitoshi Kuwana, Hiroyuki Tanaka, Seiji Inoshita, Michio Kuwahara, Sei Sasaki

Affiliations + expand

PMID: 15975997 DOI: 10.1681/ASN.2005020129

In conclusion, **aldosterone seems to exert mainly MR-induced effects that stimulate c-Raf, MEK1/2, MAPK1/2, the activities of CDK2 and CDK4, and the cell-cycle progression in mesangial cells**. MR antagonists may serve as a potential therapeutic approach to mesangial proliferative disease.

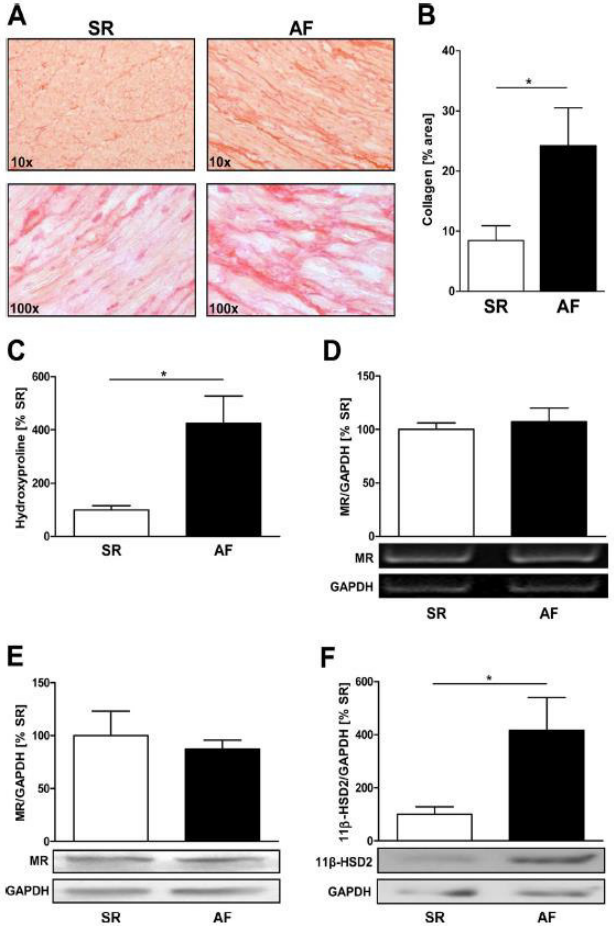


The Mineralocorticoid Receptor Promotes Fibrotic Remodeling in Atrial Fibrillation*

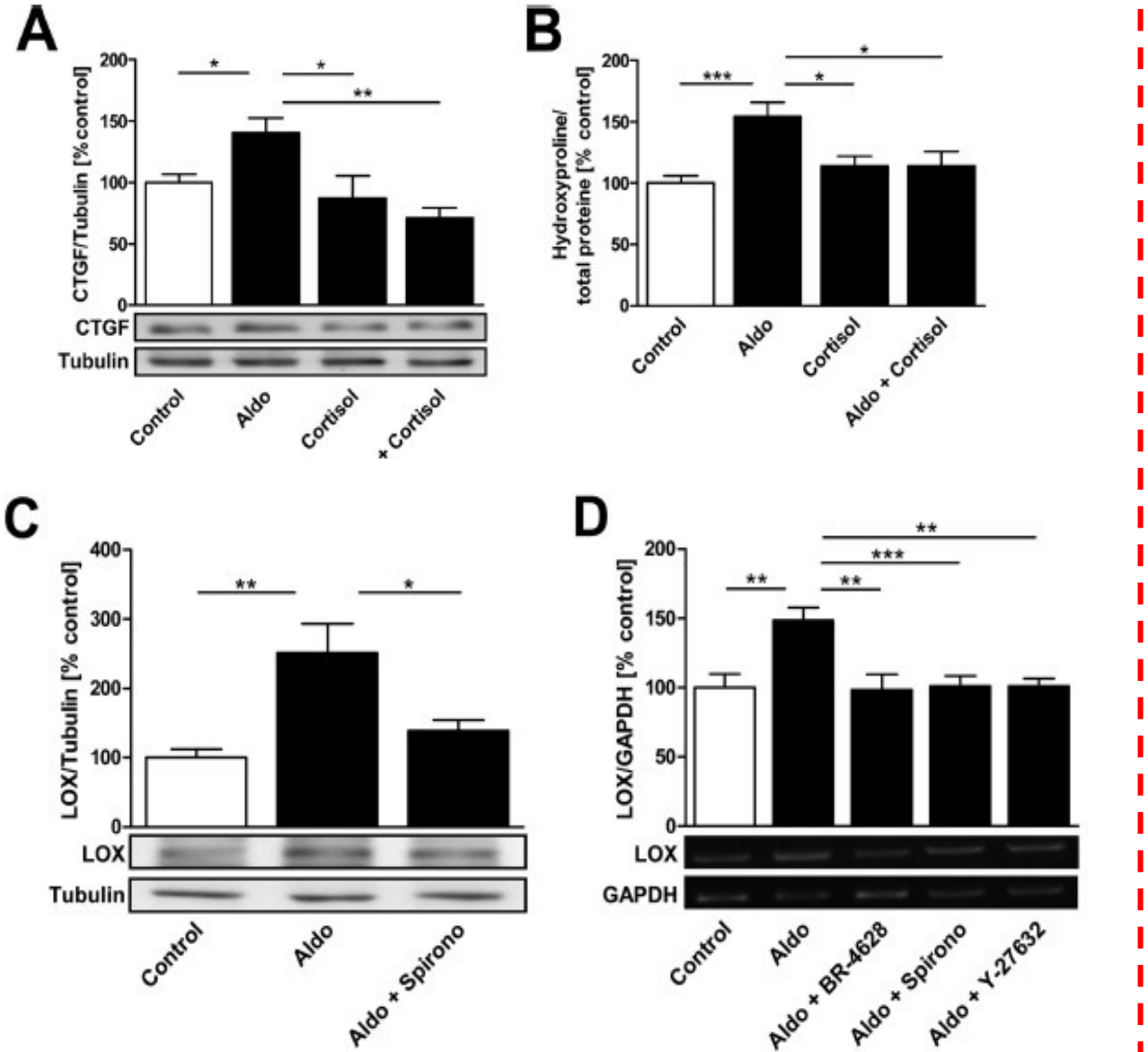
Received for publication, September 16, 2013, and in revised form, January 17, 2014 Published, JBC Papers in Press, January 27, 2014, DOI 10.1074/jbc.M113.519256

Daniel Lavall[‡1], Christian Selzer[‡], Pia Schuster[‡], Matthias Lenski[‡], Oliver Adam[‡], Hans-Joachim Schäfers[§], Michael Böhm[‡], and Ulrich Laufs[‡]

Human Left Atrial Tissue—Tissue samples of the left atrial appendage of patients undergoing mitral valve surgery were analyzed in patients with sinus rhythm (SR) and with permanent AF (documented by ECG for >3 months). The samples



Spironolactone: Profibrotic effect in human cardiomiocytes

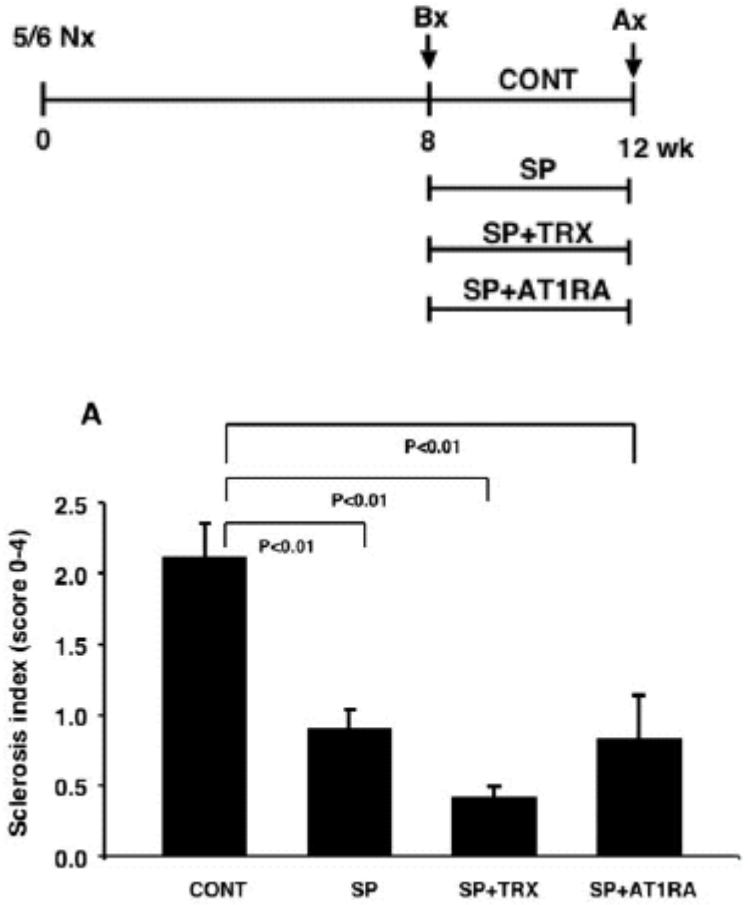


Regression of Existing Glomerulosclerosis by Inhibition of Aldosterone

Jean Claude Aldigier, Talerngsak Kanjanbuch, Li-Jun Ma, Nancy J. Brown, and Agnes B. Fogo

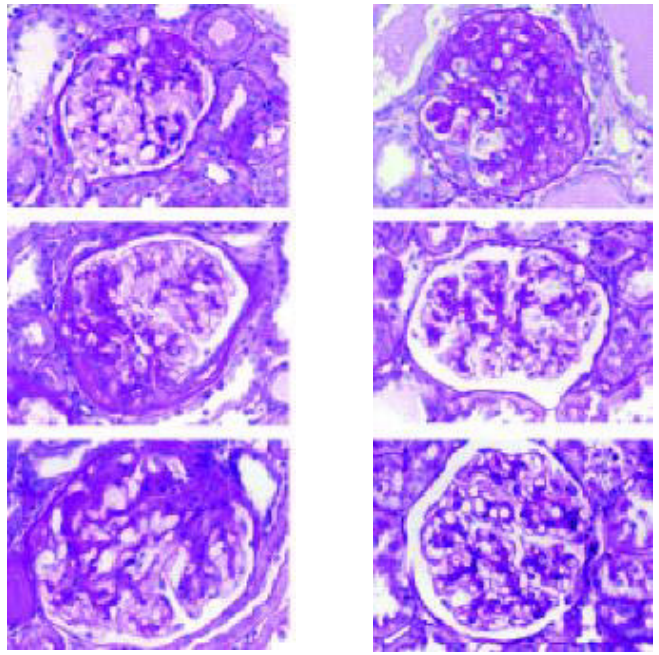
Departments of Pathology and Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Spironolactone: Glomerulosclerosis regression in diabetic rat model



8 weeks after 5/6 nephrectomy (biopsy)

After 4 weeks of treatment (autopsy)



CONTROLS progression

SPIRO regression

SPIRO+AT1RA regression

Aldigier et al. J Am Soc Nephrol, 2005

Aldosterone

MR

Epithelial Cells
(Kidney, Colon, Salivary glands etc)

"Fast"
(minutes)

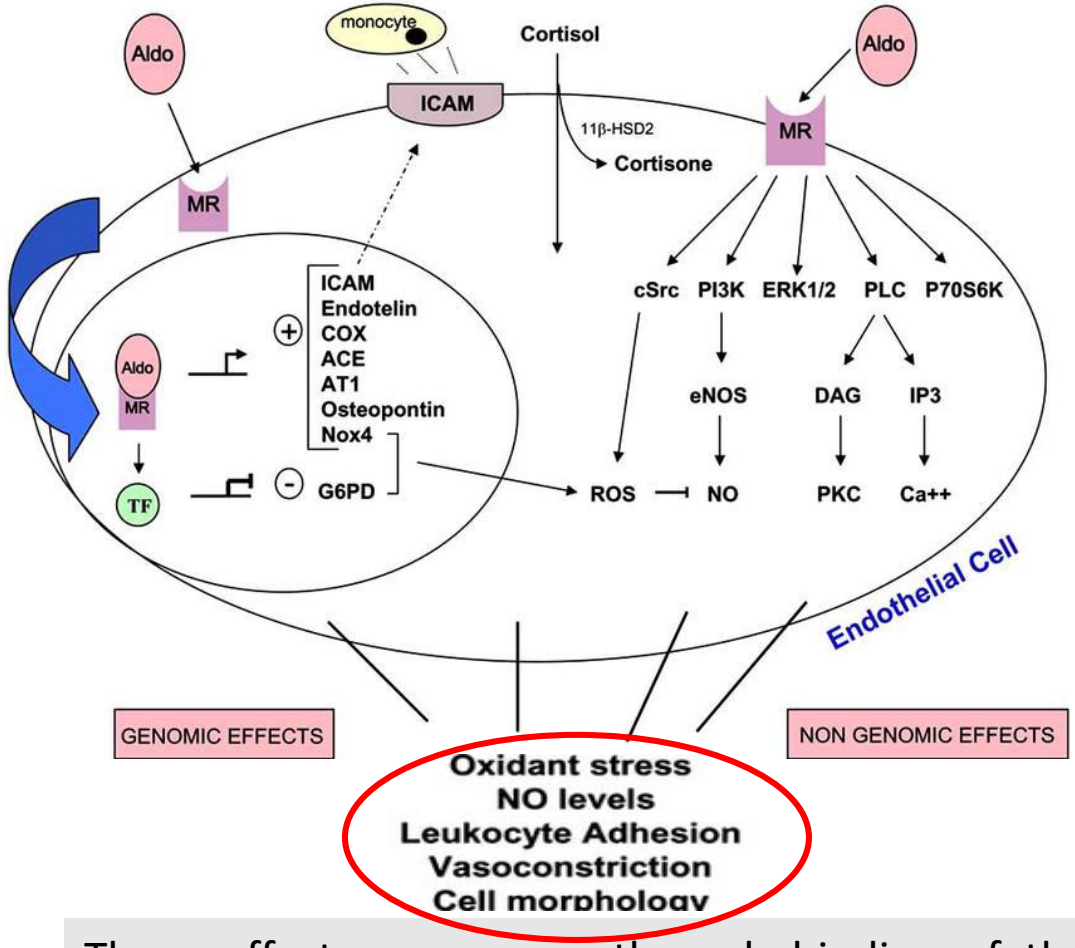
- ↑Sodium and water reabsorption
- ↑Potassium excretion
- ↑Intravascular volume
- ↑Blood pressure

MR

Fibroblasts,
Podocytes
Endothelial Cells
Cardiomyocites

"Slow"
(hours)

- ↑Endothelial dysfunction
- ↑PAI – 1
- ↑Vascular inflammation
- ↑Oxidative stress
- ↑Endothelin and Angio II receptors
- ↑Proliferation of myocytes and fibroblasts
- ↑Perivascular and interstitial fibrosis

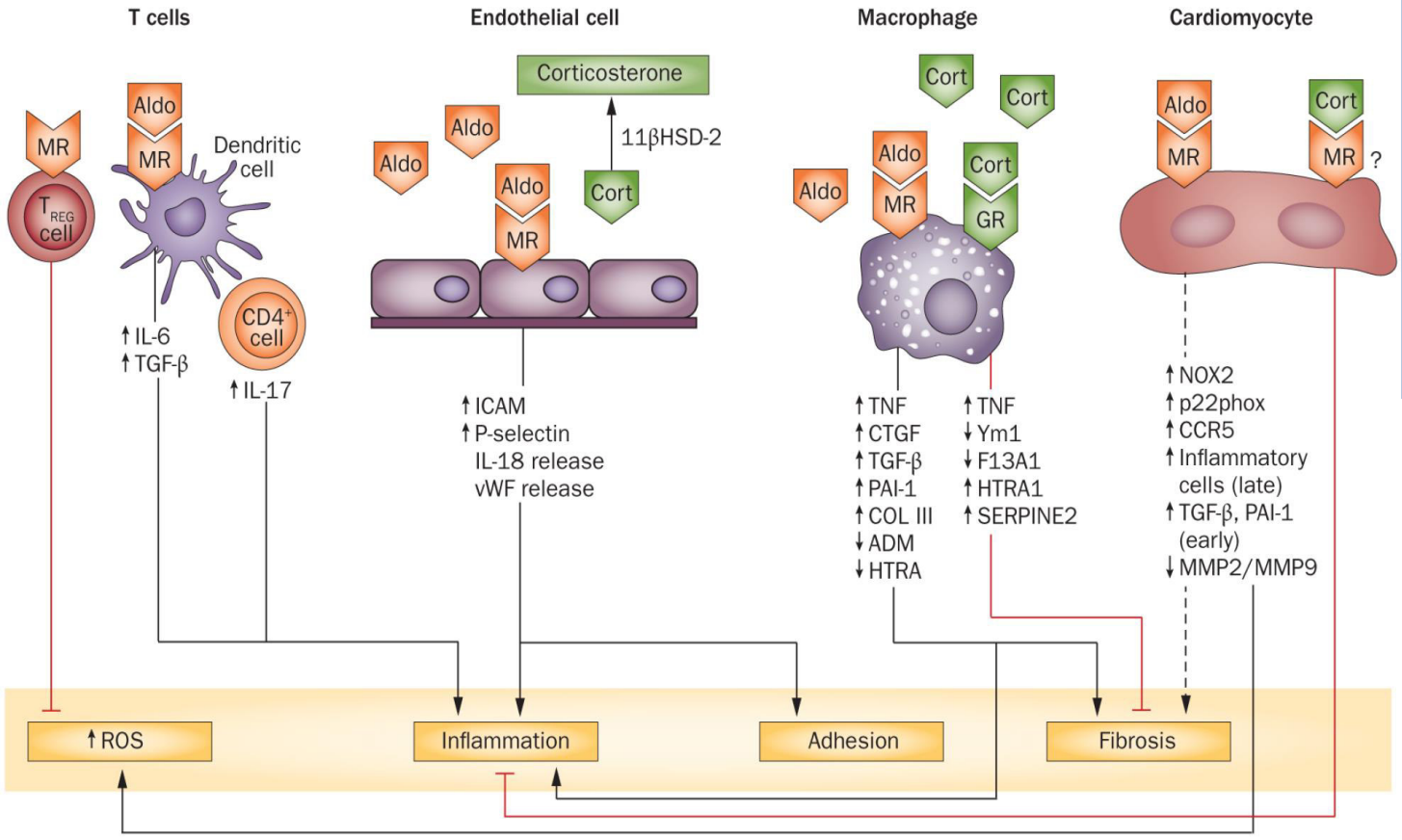


These effects may occur through binding of the liganded MR to an MR responsive element to initiate **de novo gene transcription** (genomic), through MR-dependent activation of other transcription factors that regulate gene transcription, or through **activation of receptor-mediated signaling pathways in the absence of transcription** (non genomic).

Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis

Nat Rev Nephrol. 2013 August ; 9(8): 459–469. doi:10.1038/nrneph.2013.110

Nancy J. Brown



Key points

- Aldosterone or mineralocorticoid-receptor activation trigger the formation of reactive oxygen species by NADPH oxidase and mitochondria that, in turn, induce a proinflammatory and profibrotic phenotype
- Under conditions of high salt intake, Rac1 activates the mineralocorticoid receptor and increases the formation of reactive oxygen species
- Aldosterone exerts rapid, transcription-independent effects (nongenomic effects) that may be mediated by G-protein-coupled receptor 30 and transactivation of the epithelial growth factor receptor
- Studies in mice in which the mineralocorticoid receptor has been selectively deleted on specific cells indicate that systemic mineralocorticoid-receptor activation is not necessary to induce local inflammation and fibrosis
- Aldosterone-synthase inhibition or deficiency prevents inflammation and fibrosis in many rodent models of cardiovascular or renal injury

1. In conclusion, aldosterone **stimulates the production of ROS, inflammation and fibrosis** of the heart, vasculature, and kidney through both MR-dependent and MR-independent mechanisms.

2. Studies in mice treated with **aldosterone synthase inhibitors suggest that aldosterone is the primary ligand involved in cardiac and vascular fibrosis**, but that MR antagonism may be necessary to prevent renal injury.

Spironolactone, in addition to ACEi/ARB, may reduce proteinuria and retard renal progression in CKD patients

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

http://www.kidney-international.org
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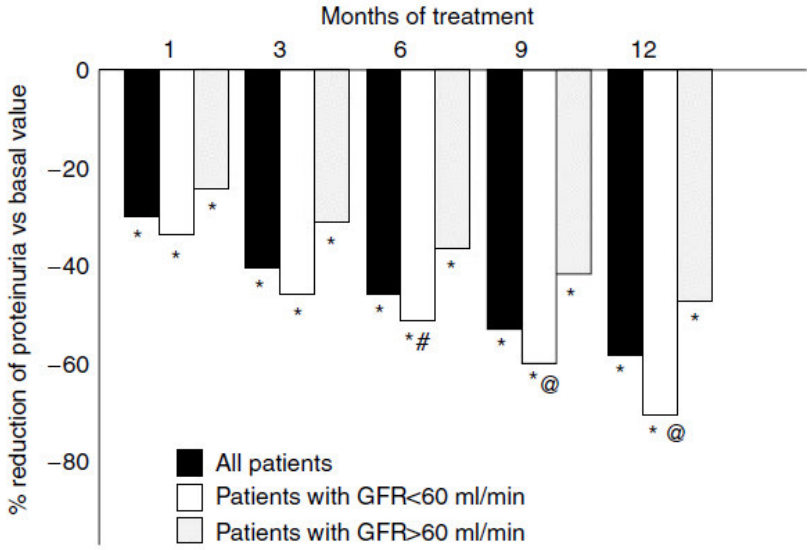
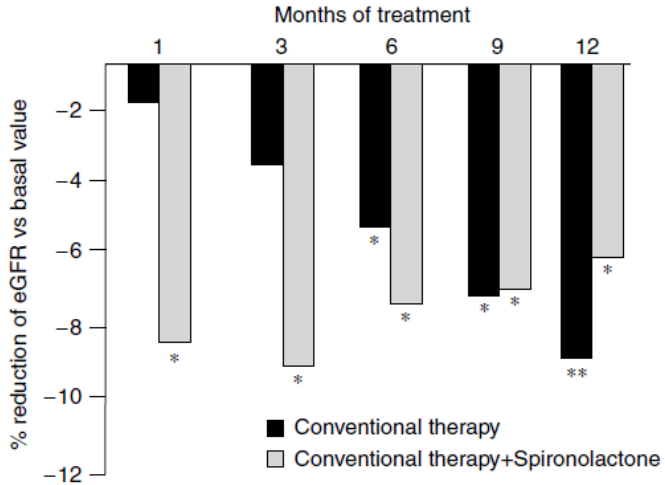
Bianchi S. et al Kidney International 2006; 70: 2116-2123

- 165 proteinuric CKD patients
- 1 year follow up
- Conventional therapy = ACEi or ARB or both
- Spironolactone 25 mg/day

	All	Conventional therapy	Conventional therapy plus spironolactone
No. of patients	165	82	83
Age (years)	54.7±0.8	54.4±1.2	55.0±1.2
Sex (M/F)	106/59	50/32	56/27
BMI	24.9±0.2	24.8±0.2	24.9±0.2
Smokers (Y/N)	41/124	21/61	19/64
Basal SBP (mmHg)	132.3±0.5	131.6±0.6	132.9±0.8
Basal DBP (mmHg)	78.3±0.3	78.1±0.4	78.5±0.5
eGFR (ml/min/1.73 m^2)	62.3±1.6	62.2±2.1	62.4±2.4
Uprotein (g/g creatinine)	2.1±0.05	2.0±0.07	2.1±0.08
Serum K^+ (mEq/l)	4.3±0.03	4.2±0.03	4.2±0.04
Basal aldosterone (pg/ml)	132.1±4.7	130.4±6.5	134.7±6.9
Antihypertensive drugs			
ACEIs	50	21	29
ARBs	35	18	17
Both ACEIs and ARBs	80	43	37
Other antihypertensive drugs			
Number (O/1/2/3)	20/69/60/16	8/36/34/4	12/33/26/12
Diuretics (Y/N)	116/49	56/26	60/23
Statins (Y/N)	146/19	72/10	74/9





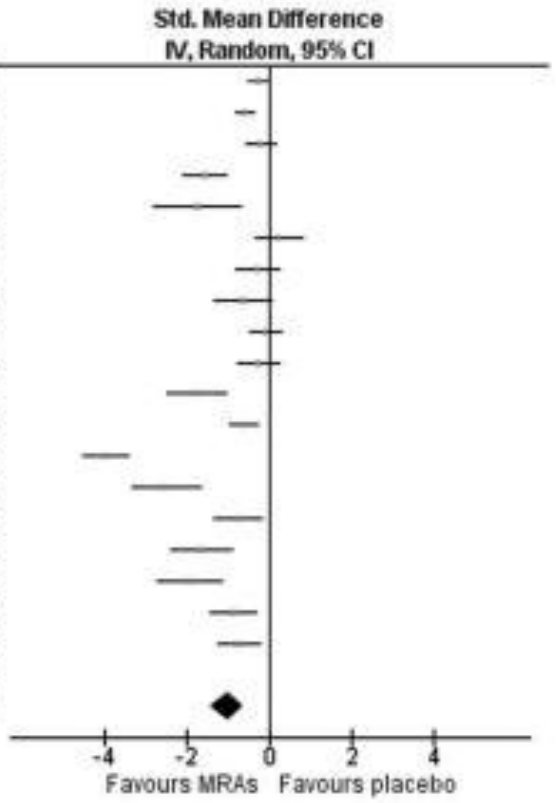
Effects of mineralocorticoid receptor antagonists in proteinuric kidney disease: a systematic review and meta-analysis of randomized controlled trials

Use of MRAs alone or on top of RAS blockade confers important **antiproteinuric** effects in patients with CKD, with a slight **increase in mean potassium** levels

(a)

Study or Subgroup	MRAs Mean	MRAs SD	MRAs Total	placebo Mean	placebo SD	placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ando 2014	-17.3	104.6673	158	10.3	104.6673	146	5.8%	-0.26 [-0.49, -0.04]
Bakris 2015	-36.3537	44.4285	337	-6.2	71.7784	94	5.8%	-0.58 [-0.82, -0.35]
Bianchi 2010	-83	192.3651	64	-52.7	122.1403	64	5.7%	-0.19 [-0.53, 0.16]
Boesby 2011	-28.4	13.6905	40	-6.4	13.6905	40	5.4%	-1.59 [-2.10, -1.09]
Chrysostomou 2006	-42	23.0654	10	-1.4	21.3879	10	4.2%	-1.75 [-2.81, -0.68]
Eguchi 2016	-2.3	115.9637	33	-29.2	86.8431	19	5.3%	0.25 [-0.32, 0.82]
Kalizki 2017	-33.3	174.3092	25	0	0.0024	26	5.3%	-0.27 [-0.82, 0.28]
Katayama 2017	-23.15	43.2977	24	6.2	48.3183	12	5.0%	-0.64 [-1.35, 0.07]
Lindhardt 2018	-56	767.387	57	14	921.787	54	5.7%	-0.08 [-0.45, 0.29]
Mehdi 2009	-51.6	76.3423	27	-24.6	127.6584	27	5.4%	-0.25 [-0.79, 0.28]
Nielsen 2012	-60	33.0656	21	0	33.0656	21	5.0%	-1.78 [-2.51, -1.06]
Oxlund 2013	-26.6	60.0406	61	-0.0001	0.038	58	5.7%	-0.61 [-0.98, -0.25]
Pitt 2013	-21.2456	7.3737	114	4	2.66	51	5.3%	-3.98 [-4.53, -3.43]
Rossing 2005	-31.8	12.9075	20	1.2	12.9075	20	4.7%	-2.51 [-3.35, -1.66]
Saklayen 2008	-57	87.3241	24	24	123.2439	24	5.3%	-0.75 [-1.33, -0.16]
Schjoedt 2005	-29.7	17.7478	20	0.3	17.7478	20	5.0%	-1.66 [-2.39, -0.93]
Schjoedt 2006	-32	16.1344	20	0	16.1344	20	4.9%	-1.94 [-2.71, -1.18]
Van der Meiracker 2006	-40.6	40.7329	24	13.5	74.6622	29	5.3%	-0.86 [-1.43, -0.30]
Ziaee 2013	-52.9	23.5	29	-38.4	16	31	5.4%	-0.72 [-1.24, -0.19]
Total (95% CI)			**1108**			**766**	**100.0%**	**-1.02 [-1.42, -0.63]**

Heterogeneity: Tau² = 0.69; Chi² = 247.70, df = 18 (P < 0.00001); I² = 93%
Test for overall effect: Z = 5.07 (P < 0.00001)



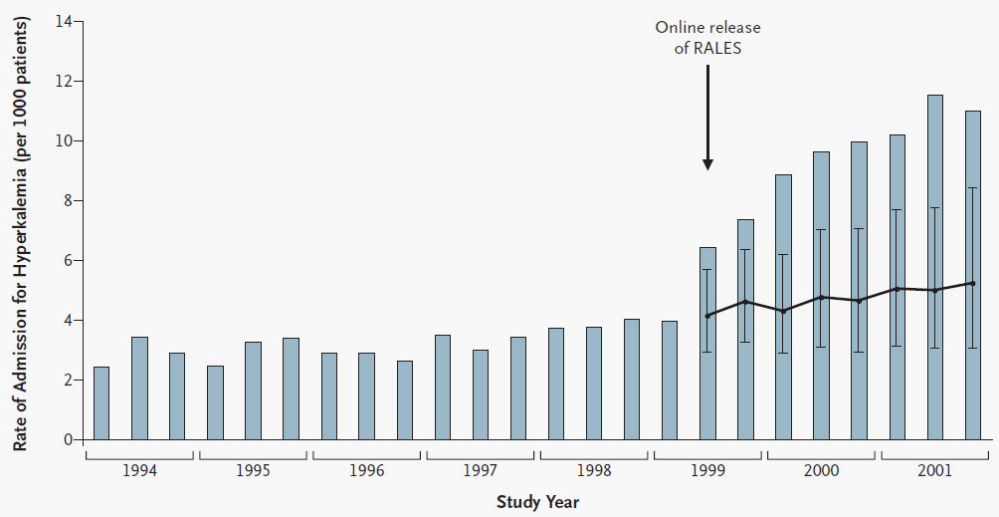
Alexandrou ME, Papagianni A, Tsapas A, Loutradis C, Boutou A, Piperidou A, Papadopoulou D, Ruilope L, Bakris G, Sarafidis P. Effects of mineralocorticoid receptorantagonists in proteinuric kidney disease: a systematic review and metaanalysisof randomized controlled trials. J Hypertens 2019;37:2307–2324.

ORIGINAL ARTICLE

N Engl J Med 2004;351:543-51.

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

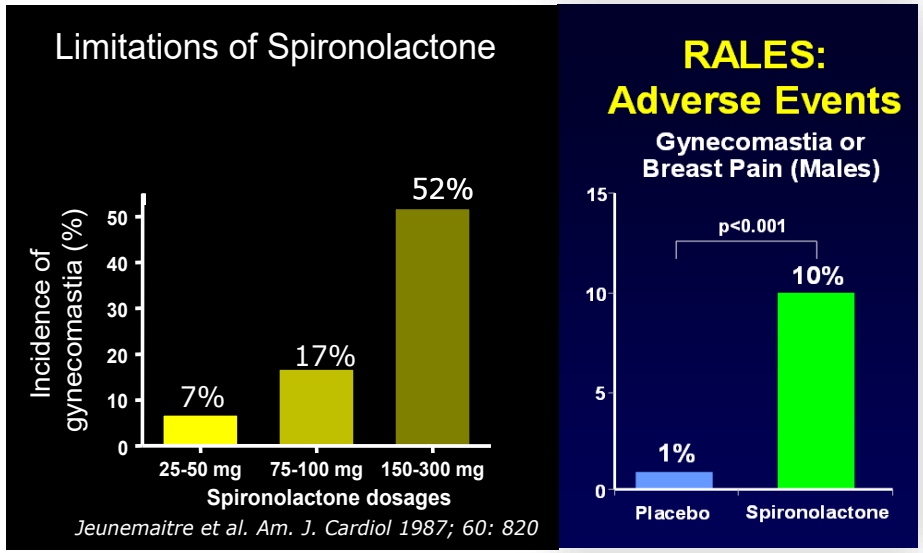
David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter C. Austin, Ph.D., Andreas Laupacis, M.D., and Donald A. Redelmeier, M.D.

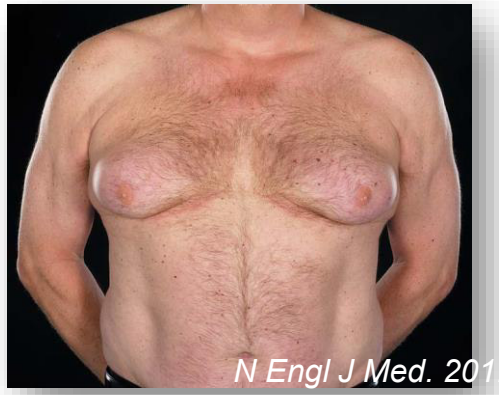


CONCLUSIONS

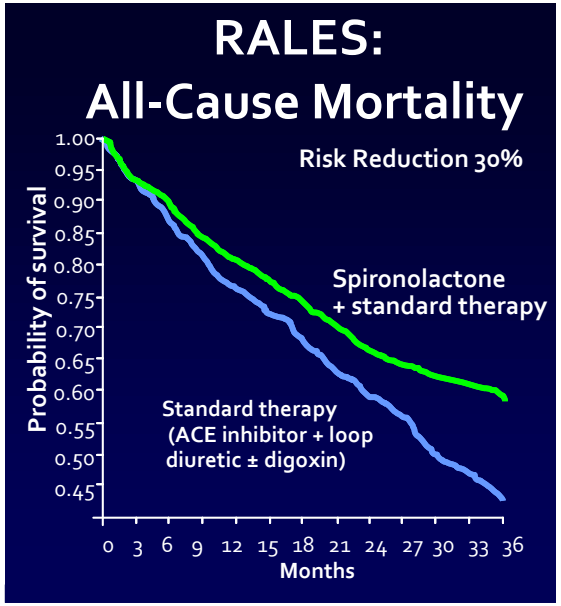
The publication of RALES was associated with abrupt increases in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality. Clos-

Spironolactone is a non-selective steroidal MRA



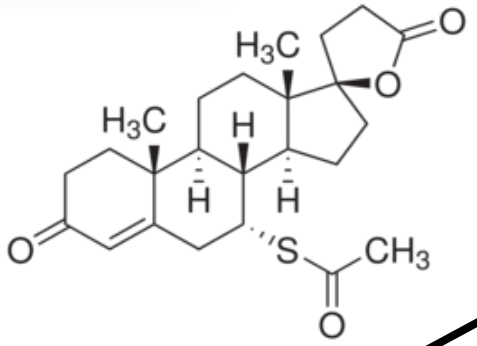


gynecomastia



menstrual irregularities

impotence



spironolactone

Significant increase in the risk of hyperkalemia with the addition of spironolactone to ACEi and/or ARB (relative risk 3.06, 95% CI 1.26, 7.41).

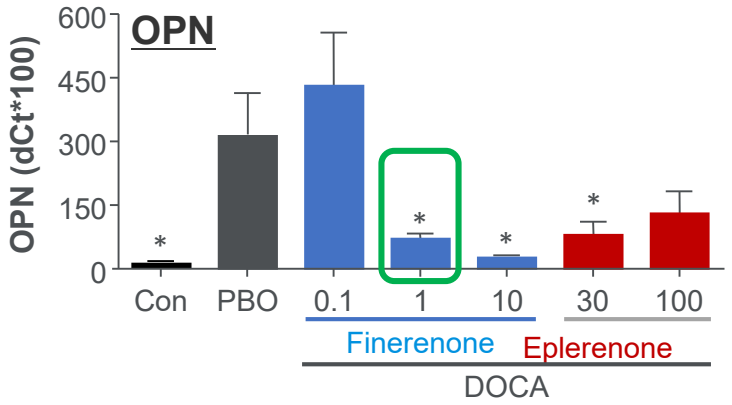
Finerenone

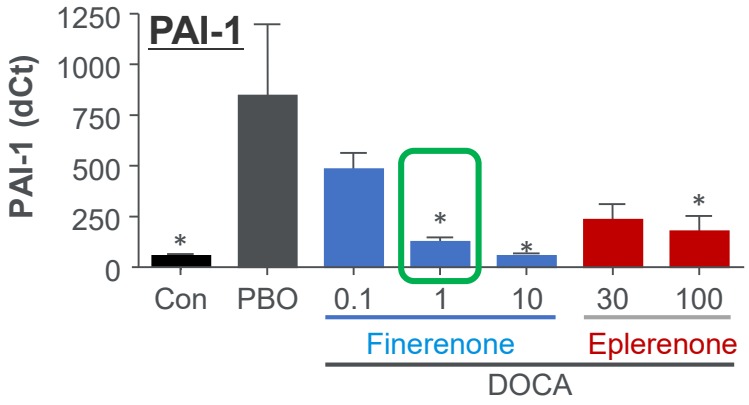
Finerenone is a third-generation dihydropyridine-derived nonsteroidal MR antagonist. The compound has higher affinity to MR than spironolactone (EC 50 = 18 nM) and lacks affinity for the other steroid receptors. Binding of finerenone to the MR generates a highly unstable complex, unable to bind to coregulators.

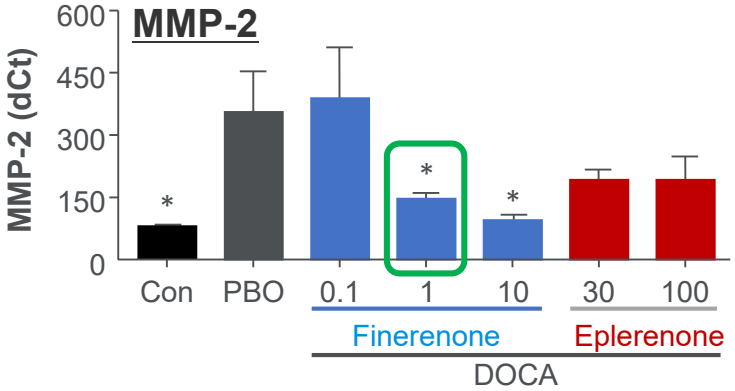
	Spironolactone	**Eplerenone**	**Finerenone**
Chemistry	Steroidal		Non – steroidal, Dihydropyridine
Distribution	Higher concentrations in renal tissue in comparison to cardiac tissue.		Distributed relatively equally between the heart and the kidney.
Mineralocorticoid receptor	24	990	18
Glucocorticoid receptor	2400	22,000	>10,000
Androgen receptor	77	21,200	>10,000
Progesterone receptor	740	31,200	>10,000

Finerenone 1 mg/kg/die reduces mRNA expression of inflammation and fibrosis markers without significant effect on SBP

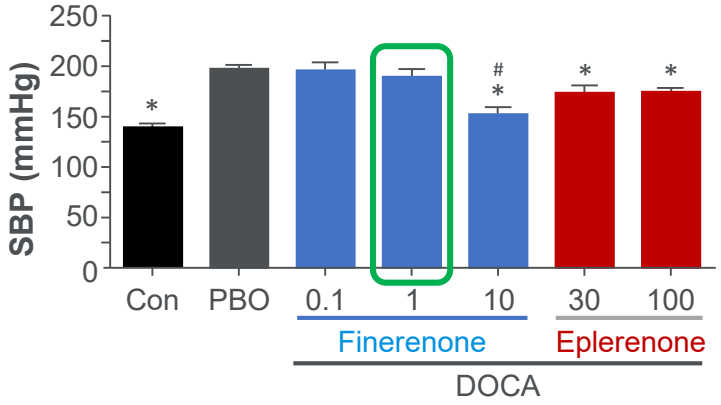
Effect on mRNA expression of inflammatory and fibrotic markers in kidney tissue







Effect on systolic BP



Fibrosis Biomarkers:

- Osteopontine
- Kidney plasminogen activator inhibitor-1
- Matrix metalloproteinase-2

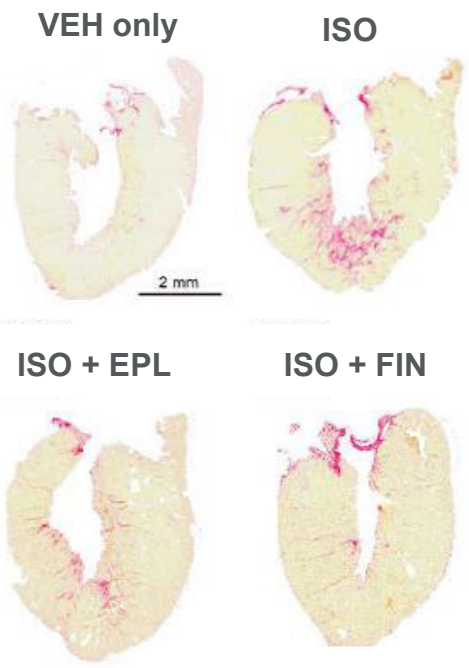
Finerenone dosed at equinatriuretic doses of eplerenone in a rat DOCA–salt model of kidney injury

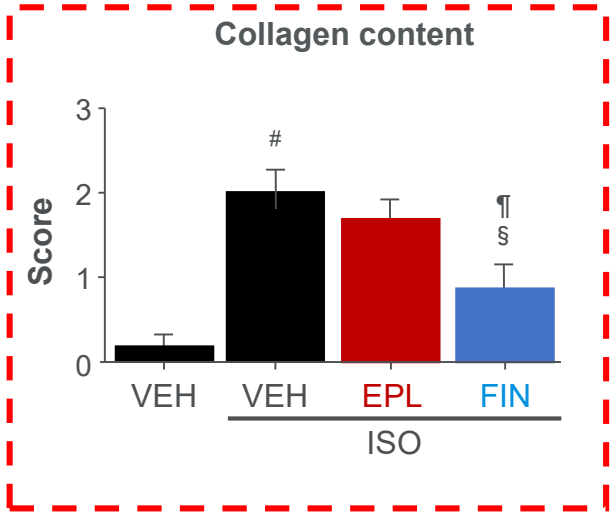
*p<0.05 versus placebo; #p<0.05 versus eplerenone

Kolkhof P, et al. *J Cardiovasc Pharm* 2014;64:69–78

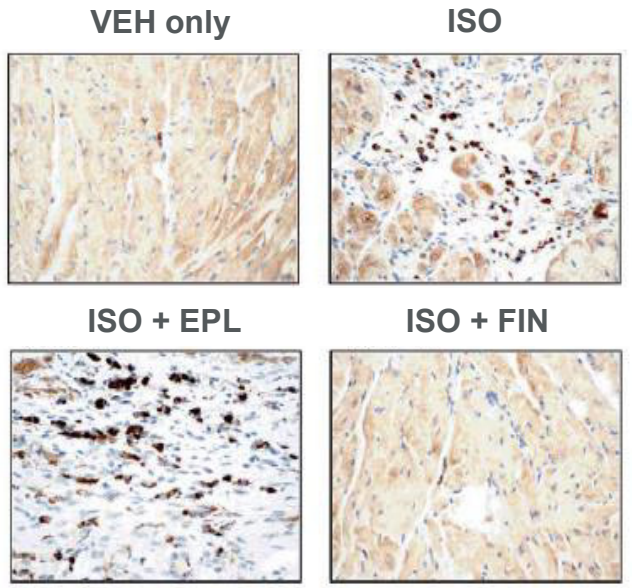
Finerenone reduces accumulation of collagen and macrophage infiltration in in preclinical models of cardiac injury

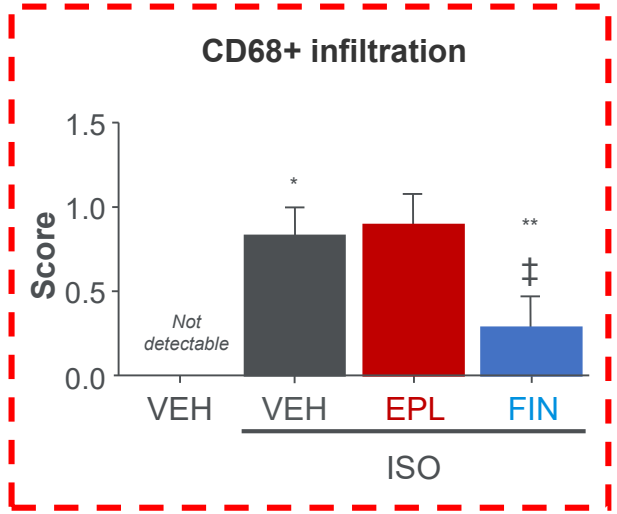
- Cardiac fibrosis





- Cardiac inflammation



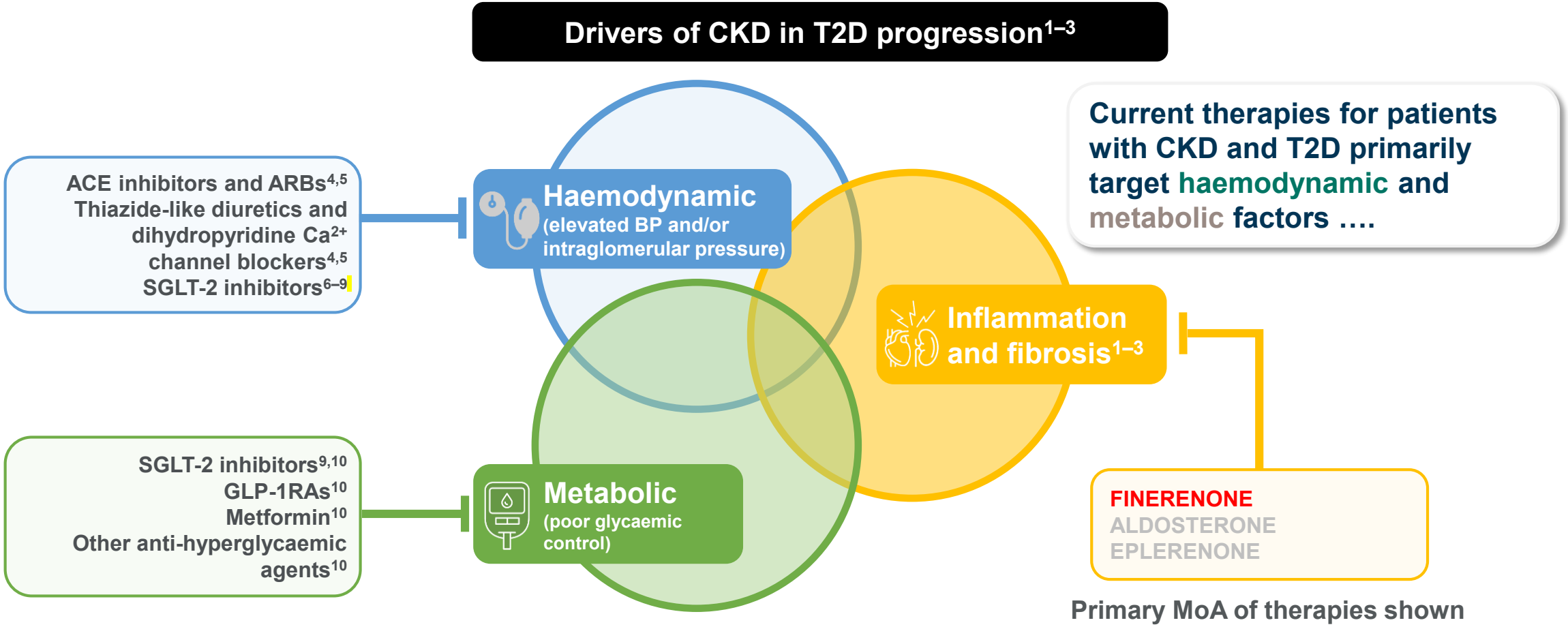


Finerenone compared with eplerenone in a mouse model of isoproterenol-induced cardiac fibrosis and inflammation.

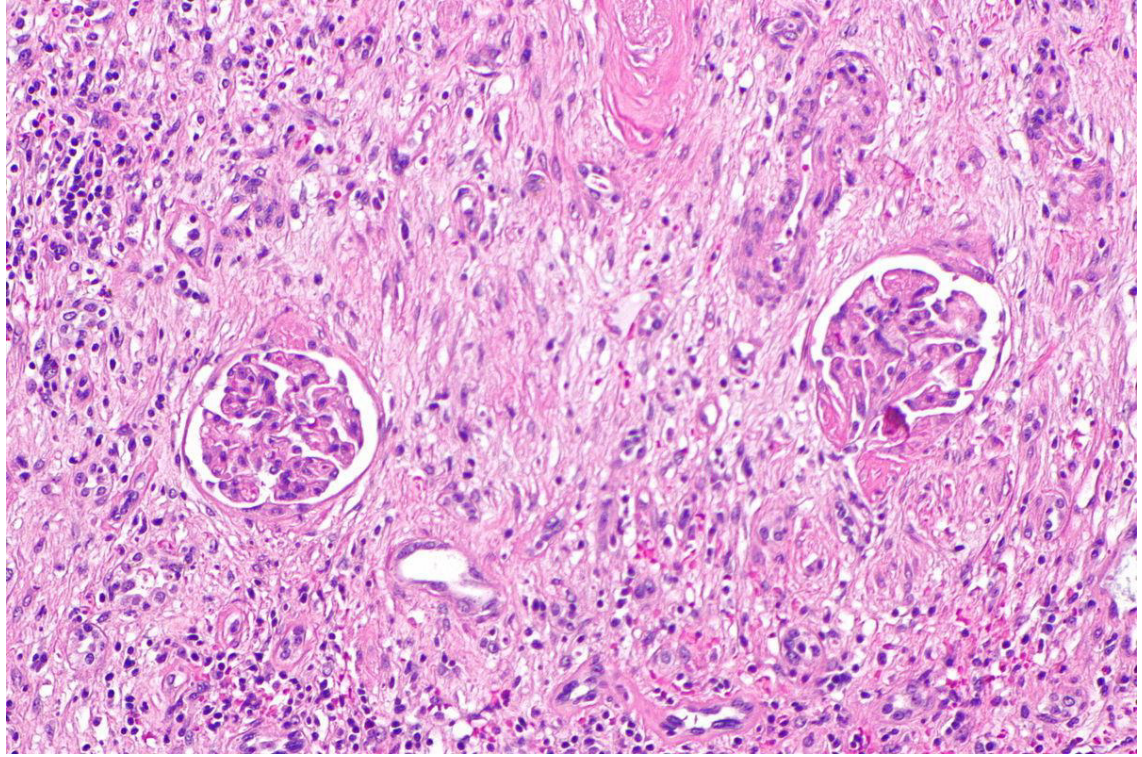
*p<0.001; #p<0.0001 vs VEH/VEH group; ‡ p<0.05; § p<0.01 vs ISO/VEH group; ¶ p<0.05; **p<0.01 vs ISO/EPL group

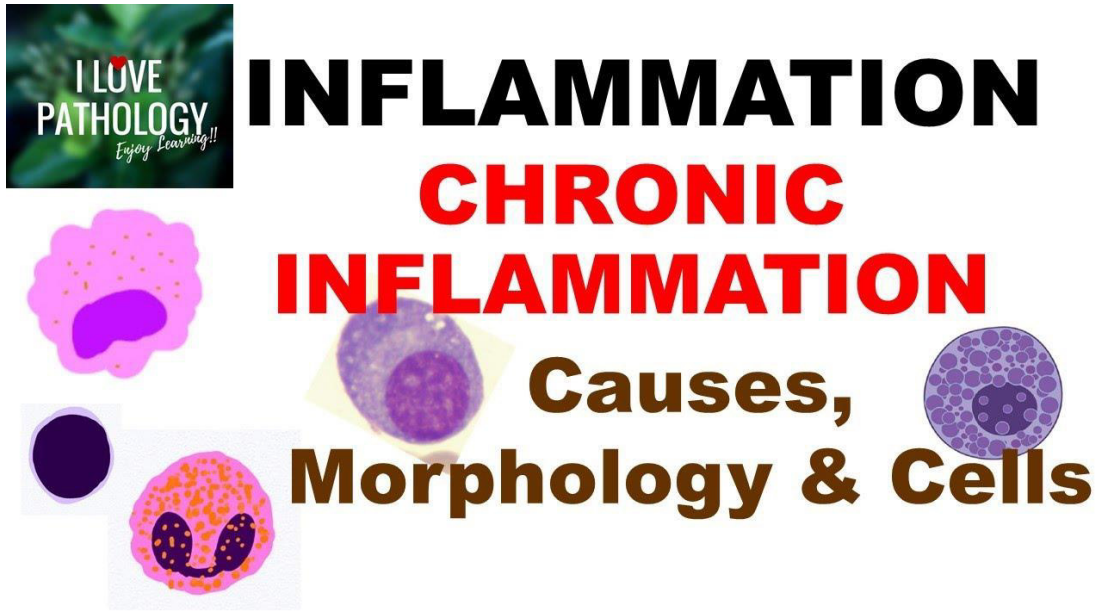
Grune J, et al. *Hypertension* 2018;71:599–608

CKD in T2D progression, associated with increased CV risk, is driven by the combined effects of metabolic, haemodynamic, inflammatory and fibrotic factors



1. Alicic RZ, *et al*. *Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al*. *J Physiol* 2014;18:3997; 3. Bauersachs J, *et al*. *Hypertension* 2015;65:257–263;
4. American Diabetes Association. *Diabetes Care* 2022;45:S175–184; 5. American Diabetes Association. *Diabetes Care* 2022;45:S144–174; 6. Kidokoro K, *et al*. *Circulation* 2019:140;303–315; 7. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 8. Heerspink HJ, *et al*. *Circulation* 2016;134:752–772; 9. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434; 10. American Diabetes Association. *Diabetes Care* 2022;45:S125–S143; 11. Alicic RZ, *et al*. *Adv Chronic Kidney Dis* 2018;25:181–191

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