ΕΛΛΗΝΙΚΗ ΝΕΦΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC SOCIETY OF NEPHROLOGY

25ο Πανελλήνιο Συνέδριο ΝΕΦΡΟΛΟΓΙΑΣ

19-21 ΙΟΥΝΙΟΥ 2024

ΜΕΓΑΡΟ ΔΙΕΘΝΕΣ ΣΥΝΕΔΡΙΑΚΟ ΚΕΝΤΡΟ - ΑΘΗΝΑ

Γενομικές και μη-γενομικές δράσεις της αλδοστερόνης: νεότερα δεδομένα για την νεφρική και την καρδιακή βλάβη

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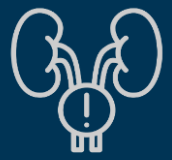
Γ.Ν.Θ. Ιπποκράτειο

The global burden of kidney failure

7600 million – global population



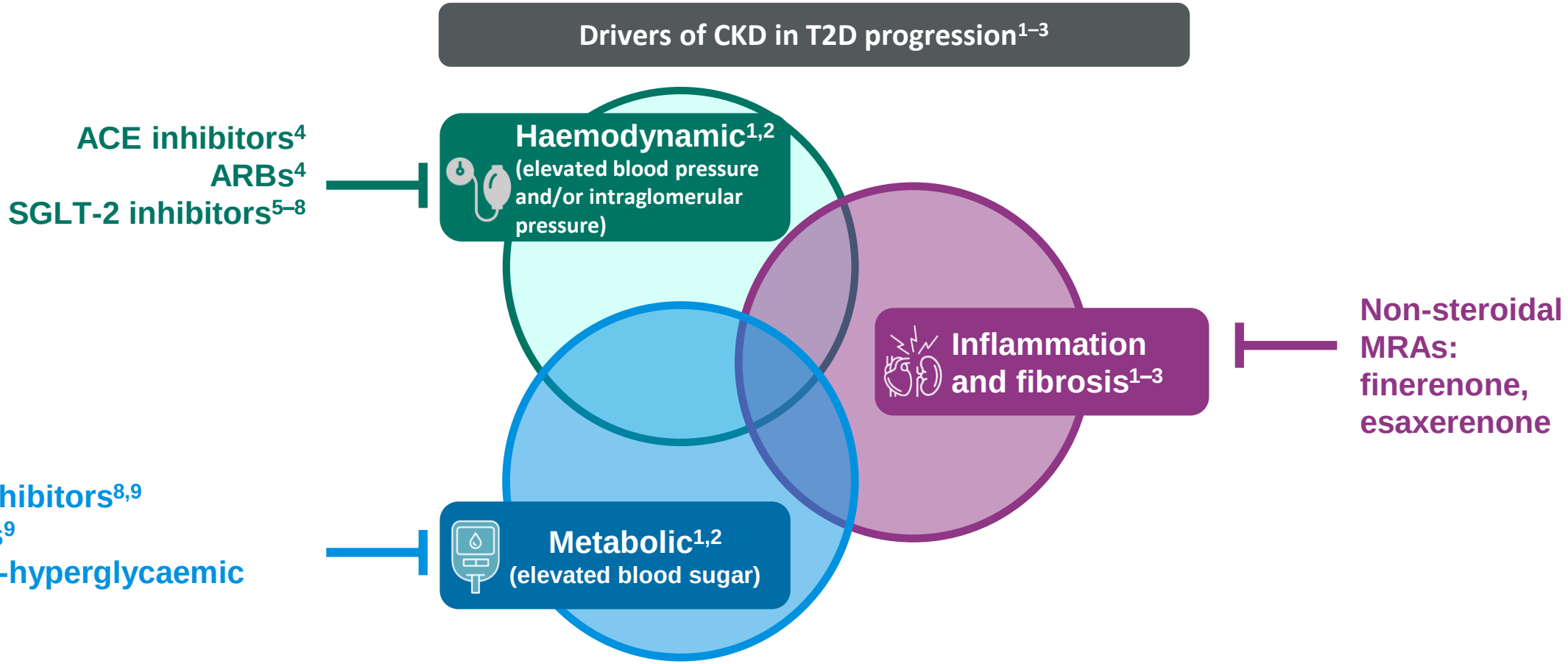
844 million – global prevalence of CKD

3.9 million – patients on KRT

As many might die due to lack of KRT

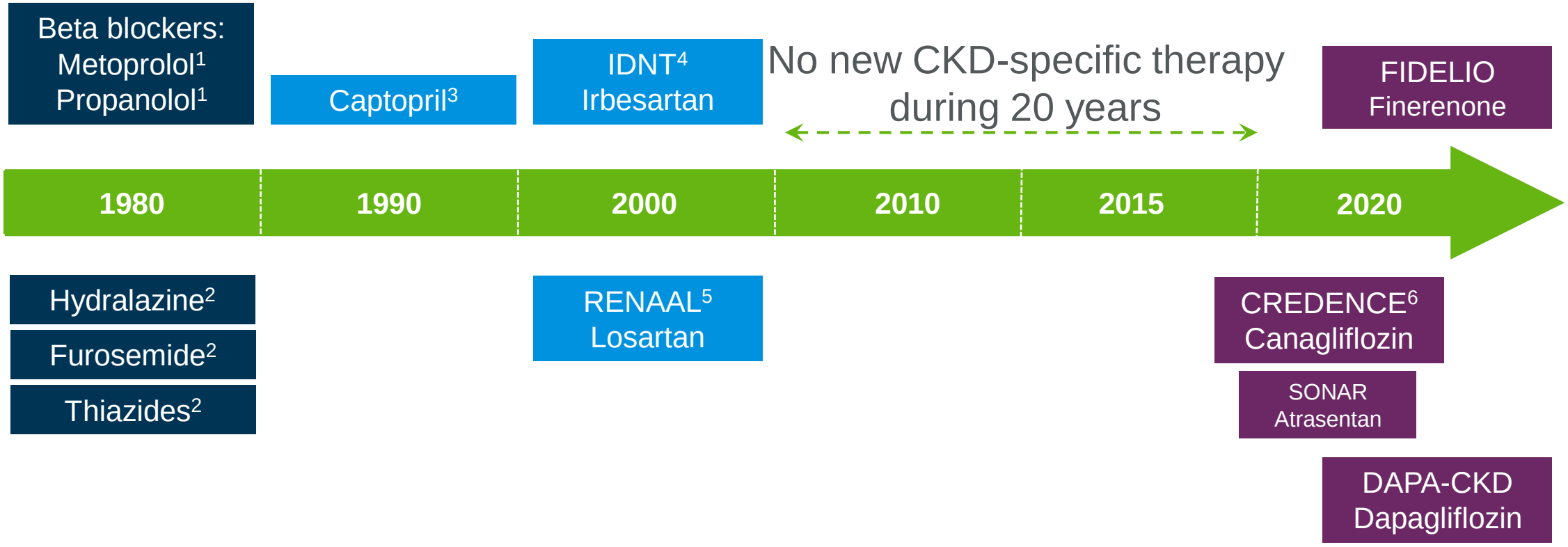
CKD, chronic kidney disease
Estimates for 2017. Jager KJ, *et al. NDT* 2019;34:1803

Inflammation and fibrosis is a potential treatment target to address the residual risk in CKD and T2D



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* 2020;43(Suppl 1):S135-151; 5. Kidokoro K, *et al*. *Circulation* 2019:140;303–315; 6. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 7. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 8. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434; 9. American Diabetes Association. *Diabetes Care* 2020;43(Suppl 1):S98–S110

The history of nephroprotection



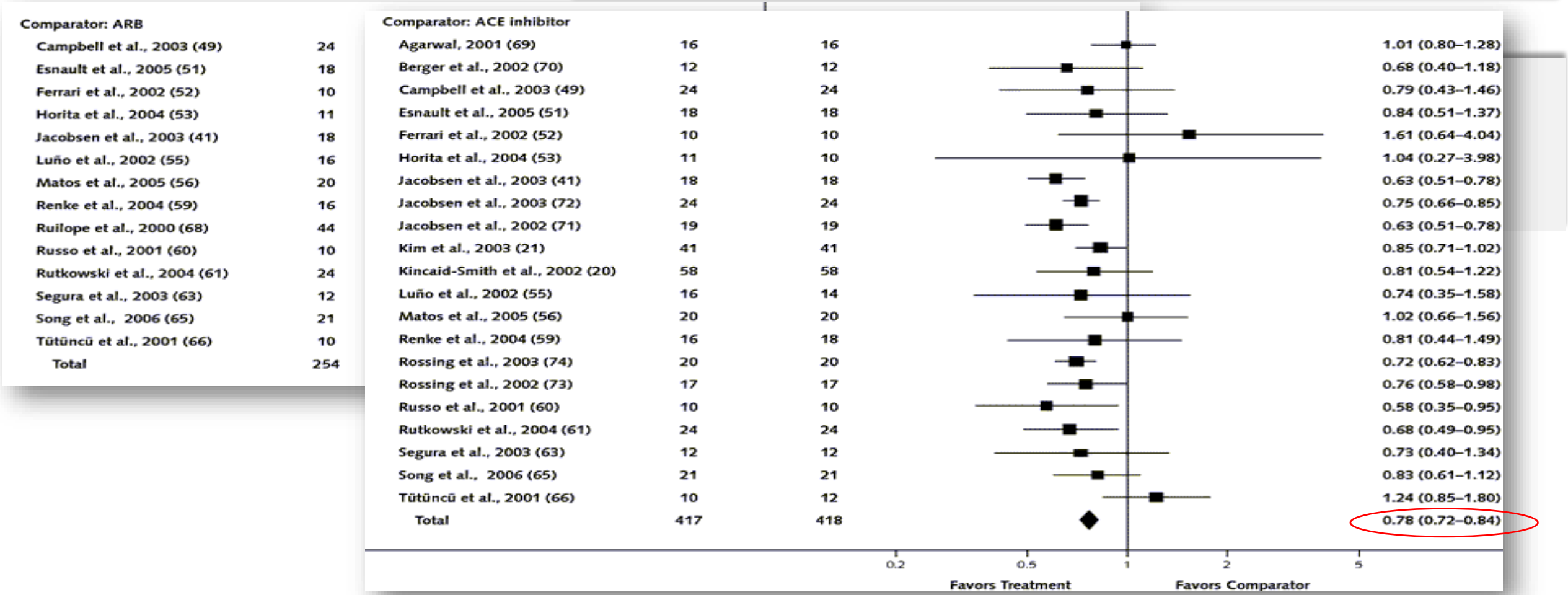
1. Mogensen CE, et al. *Br Med J*.1982;285(6343):685-688., 2. Parving HH, et al. *Lancet*.1983;1(8335):1175-1179, 3. Lewis EJ, et al. *N Engl J Med*. 1993;329(20):1456-1462, 4. Lewis EJ, et al. *N Engl J Med*. 2001;345(12):851-860, 5. Brenner BM, et al. *N Engl J Med*. 2001;345(12):861-869, 6. Perkovic V, et al. *N Engl J Med.* 2019;380(24):2295-2306.
7.Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 2. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356

Διπλός αποκλεισμός του άξονα και πρωτεϊνουρία

REVIEW | Annals of Internal Medicine

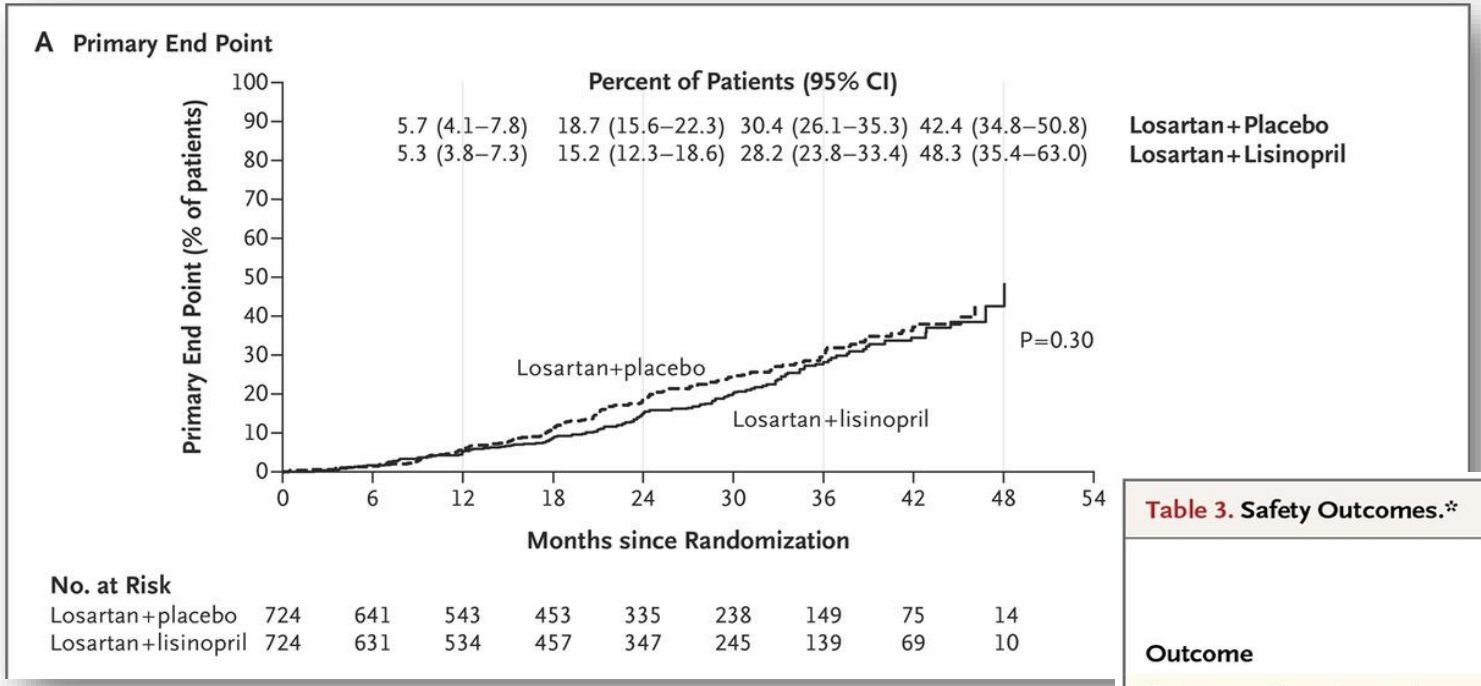
Meta-analysis: Effect of Monotherapy and Combination Therapy with Inhibitors of the Renin–Angiotensin System on Proteinuria in Renal Disease

Regina Kunz, MD, MSc(Epi); Chris Friedrich, MD; Marcel Wolbers, PhD; and Johannes F.E. Mann, MD



Kunz et al, Ann Intern Med. 2008;148:30-48

Διπλός αποκλεισμός ΣΡΑ και δυσμενής έκβαση σε μελέτες νεφροπροστασίας



Primary endpoint:

- eGFR decline≥30ml/min/1.73m^2
- eGFR decline≥50%
- ESKD
- death

Table 3. Safety Outcomes.*

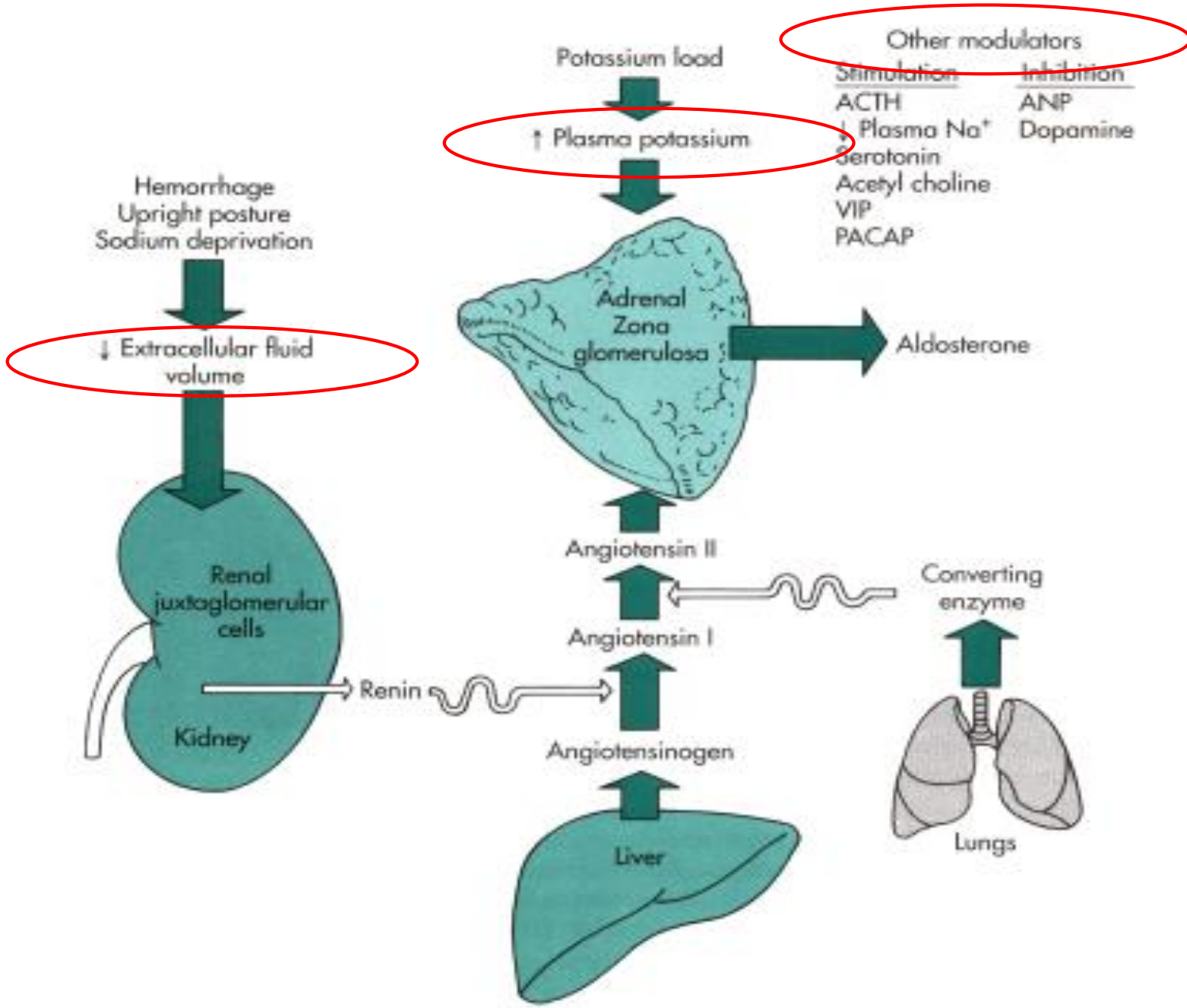
Outcome	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)	Hazard Ratio with Losartan plus Lisinopril (95% CI)	P Value
Patients with serious adverse events — no. (%)	380 (52.5)	416 (57.5)	NA	0.06
No. of serious adverse events	1274	1539†	NA	
Attribution of serious adverse events to study drugs — no. of events (%)†				0.049
Not attributed	1159 (91.0)	1365 (88.7)	NA	
Possibly attributed	104 (8.2)	146 (9.5)	NA	
Attributed	11 (0.9)	27 (1.8)	NA	
Acute kidney injury — no. of patients (%)	80 (11.0)	130 (18.0)	1.7 (1.3–2.2)	<0.001
Hyperkalemia — no. of patients (%)	32 (4.4)	72 (9.9)	2.8 (1.8–4.3)	<0.001

* NA denotes not applicable.
† For one of the serious adverse events in the monotherapy group, information was not available to determine whether the event was attributable to study medications. The percentages are based on the total number of serious adverse events in each group.

Fried et al, N Engl J Med. 2013;369:1892-903

Ο ρόλος της αλδοστερόνης

Ρύθμιση της έκκρισης αλδοστερόνης



kidney and dialysis

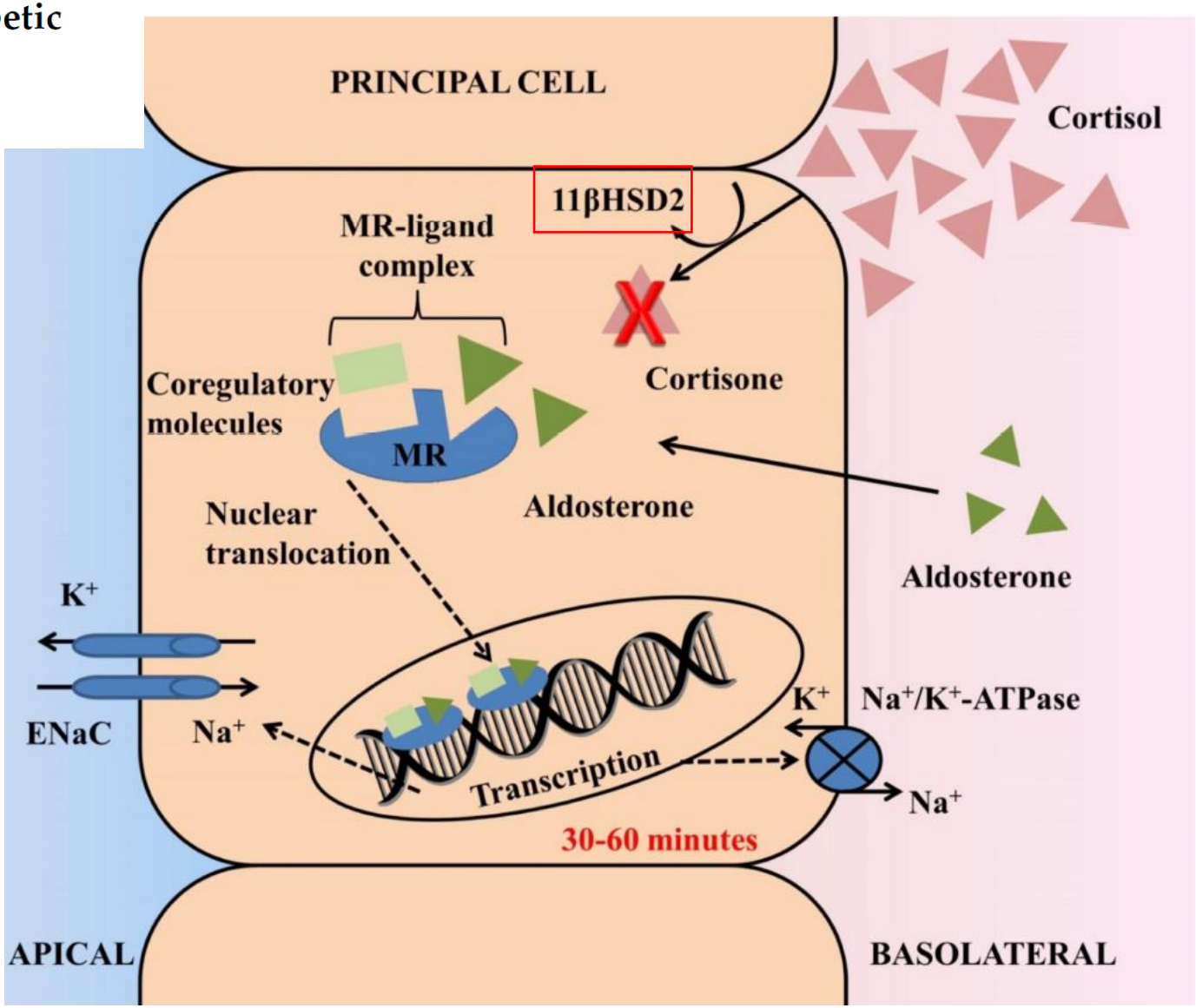
MDPI

Review

Role of Mineralocorticoid Receptor Antagonists in Diabetic Kidney Disease

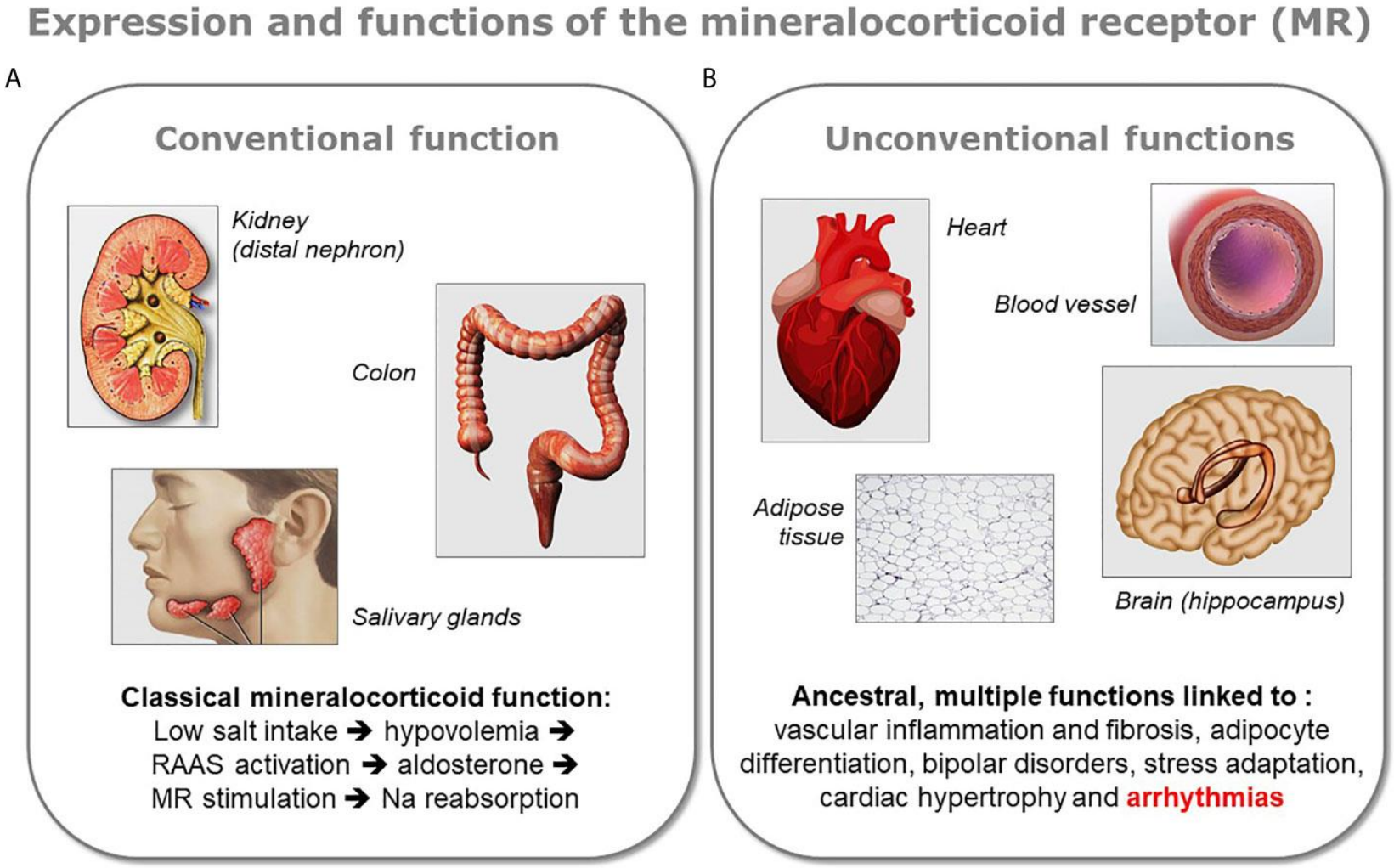
Maria-Eleni Alexandrou, Marieta P. Theodorakopoulou and Pantelis A. Sarafidis *

Λειτουργία υποδοχέων αλδοστερόνης στον άπω νεφρώνα



Alexandrou ME et al, Kidney Dial 2022;2(2):163-182

Έκφραση και λειτουργία των υποδοχέων των αλατοκορτικοειδών



Rossier M, Front Endocrinol (Lausanne) 2021;12:694758.

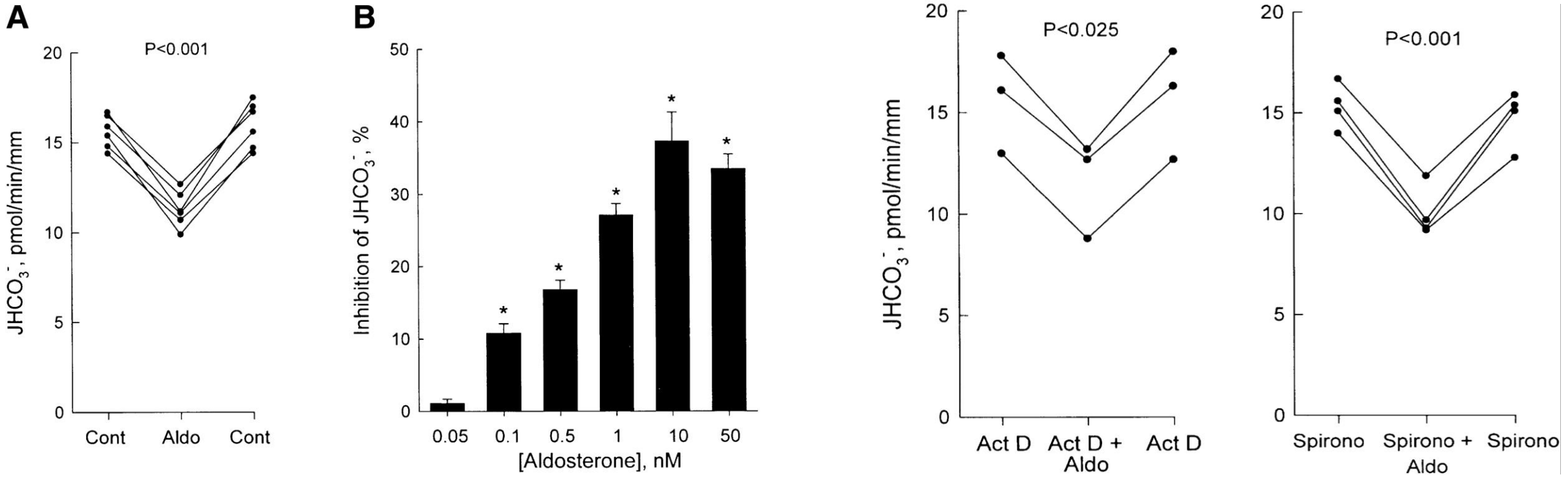
Δράσεις της αλδοστερόνης

- The nongenomic response includes rapid effects of aldosterone that cannot be explained by the traditional pathway, nor be blocked by inhibitors of gene transcription such as actinomycin D or MRAs.
- These rapid effects are considered to be also mediated by MR and associated with enhanced activity of the Na+-K+-2Cl- cotransporter and the Na+-K+-ATPase in the heart, and of the Na+-H+ antiporter, the ENaC and Na+-K+-ATPase in the kidney, and are connected to subcellular trafficking.
- In recent years, an important role of cofactors that modulate the transcription factor activity of MRs to regulate gene transcription has emerged.
- Coactivator or corepressor proteins are recruited according to distinct MR conformations induced by binding of different agonist ligands, resulting in transcription of different sets of genes
- A few years ago, ligand-selective peptides acting as potent antagonists of MR-mediated transcription were identified.

Sarafidis et al., Clin Kidney J 2023

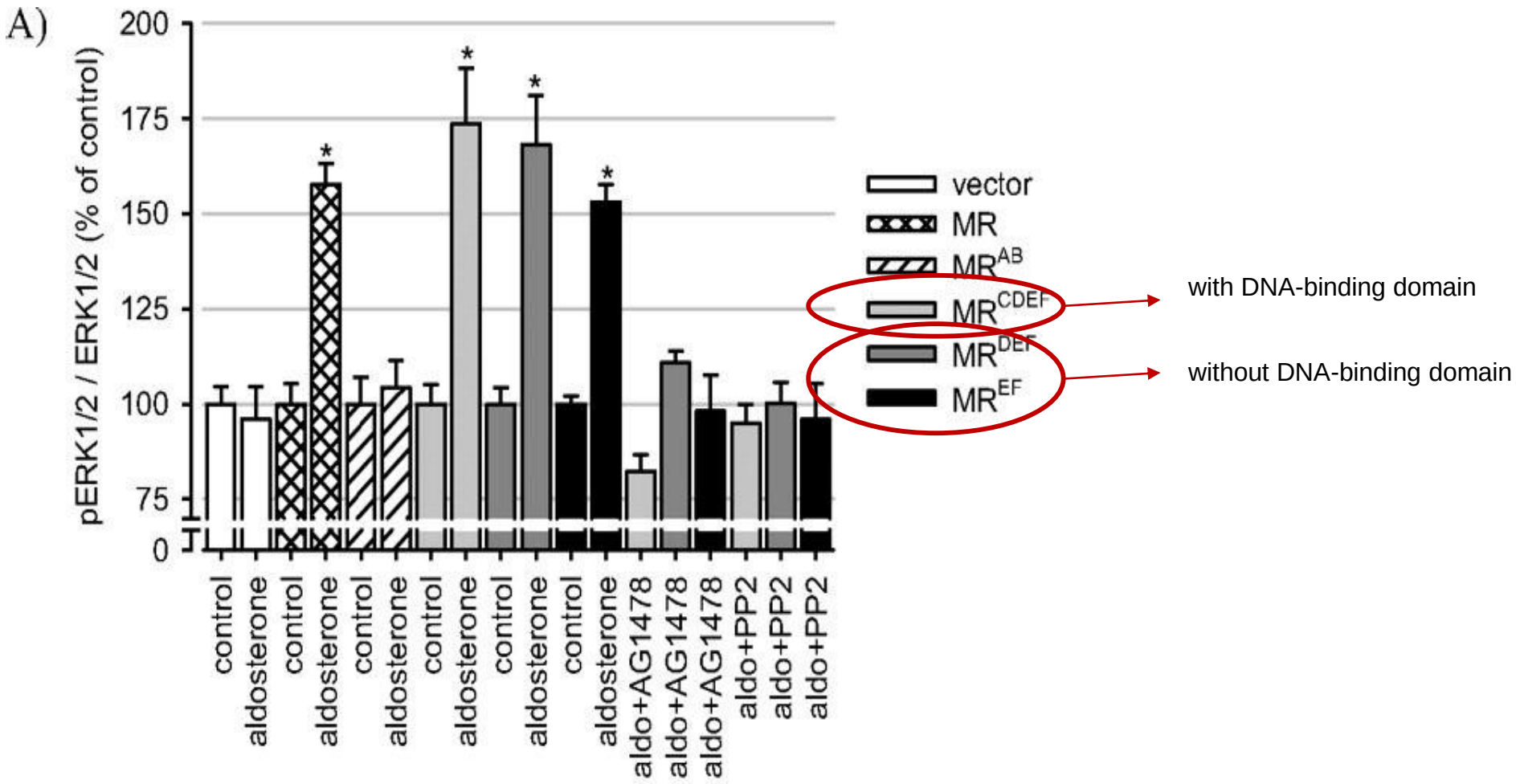
Μη γενομικές δράσεις – αναστολή NHE3

1 nM aldosterone decreased HCO_3^- absorption by 28%,
from 15.8±0.5 to 11.4±0.5 pmol · min^{-1} · mm^{-1}($p < 0.001$)

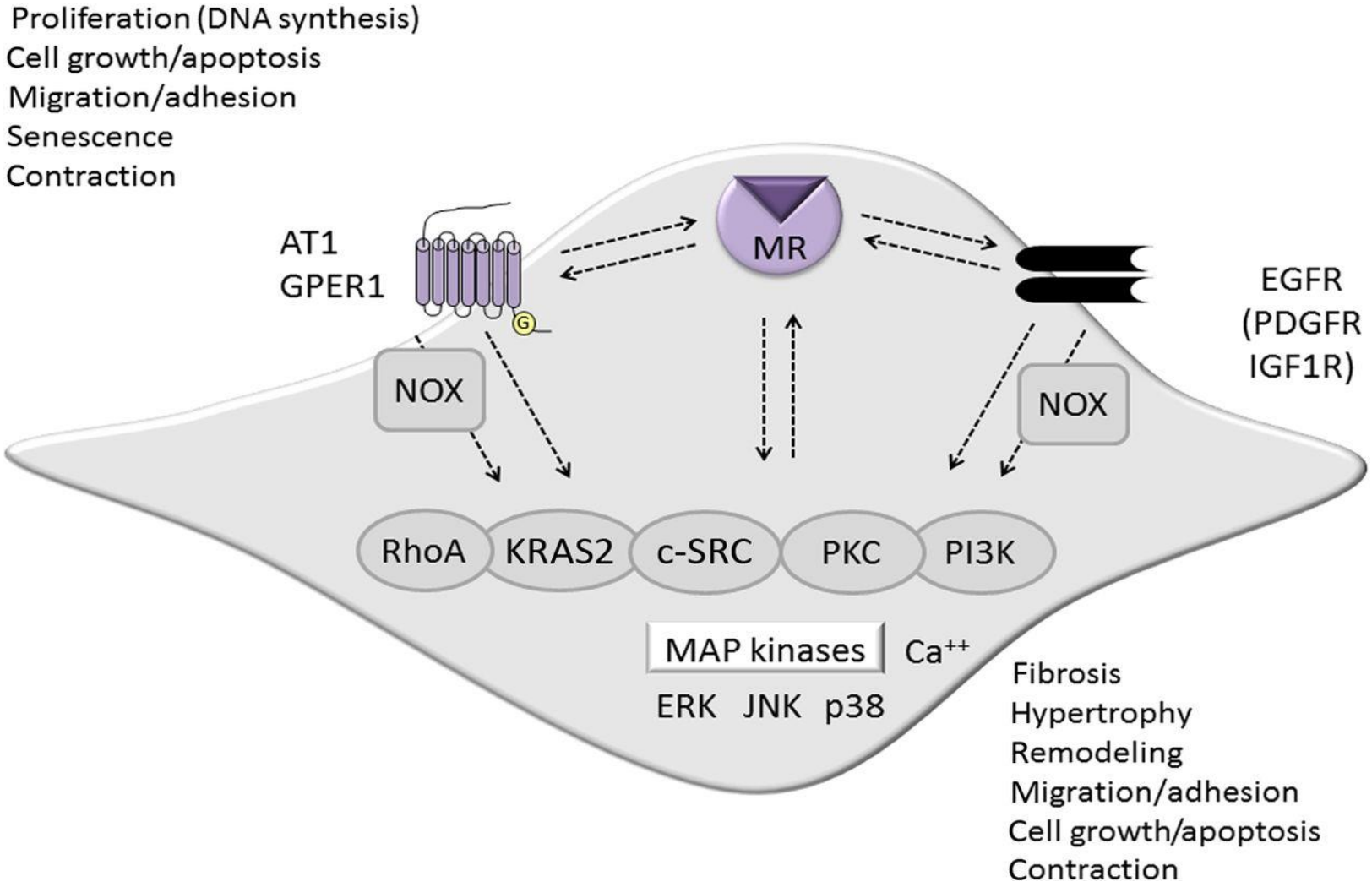


Good et al., Am J Physiol Renal Physiol. 2002;283(4):F699-706

Μη γενομικές δράσεις – ERK1/2 phosphorylation



Rapid aldosterone signaling in VSMCs



Ruhs et al., J Endocrinol 2017;234(1):T107-T124.

Μηχανισμοί πρόκλησης νεφρικής και μυοκαρδιακής βλάβης

Δεδομένα σε πειραματόζωα

Table II. Data from Study 2 at End of 4 wk

	Final body weight	Body weight gain	Left kidney weight	SBP	Heart weight	$U_{PROT}V$	P_K	Adrenal weight	Glomerular sclerosis
	grams	*grams*	*grams*	*mmHg*	*grams*	*mg/24 h*	*mM*	*mg*	*%*
SHAM	347	99	1.19	118	1.03	19	5.0	46	1.9
($n = 6$)	±18	16	0.08	10	0.05	6	0.6	2	1.2
REM	309	96	1.91*	212*	1.33*	203*	5.0	69*	37.2*
($n = 7$)	50	40	0.55	20	0.19	103	0.4	9	26.5
REM AIIA	307	97	1.47*	109‡	0.88*‡	30‡	6.2*‡	57*	4.7‡
($n = 7$)	25	20	0.18	11	0.11	15	0.4	4	5.2
REM AIIA + ALDO	312	106	2.03*	186*§	1.28*§	217*§	4.5§	60*	25.3*§
($n = 6$)	24	26	0.48	26	0.12	71	0.5	8	11.1

Values are means±standard deviations. *$P < 0.05$ vs SHAM, ‡$P < 0.05$ vs REM, §$P < 0.05$ vs REM AIIA. P_K, plasma potassium level; SBP, conscious systolic blood pressure; $U_{PROT}V$, protein excretion rate.

Greene et al., J Clin Invest 1996 Aug 15;98(4):1063-8

Φαινόμενο «διαφύγης» της αλδοστερόνης

- Σε ποσοστό 30-50% των ασθενών τα επίπεδα αλδοστερόνης ορού αυξάνονται εκ νέου 6-12 μήνες μετά την έναρξη ενός RAS blocker
- Με αυξημένα επίπεδα αγγειοτενσίνης II
- Κίνδυνος εξέλιξης νεφρικής νόσου παρά τη χορήγηση standard-of-care αγωγής

Table 1 Overview of studies reviewed during preparation of this article.

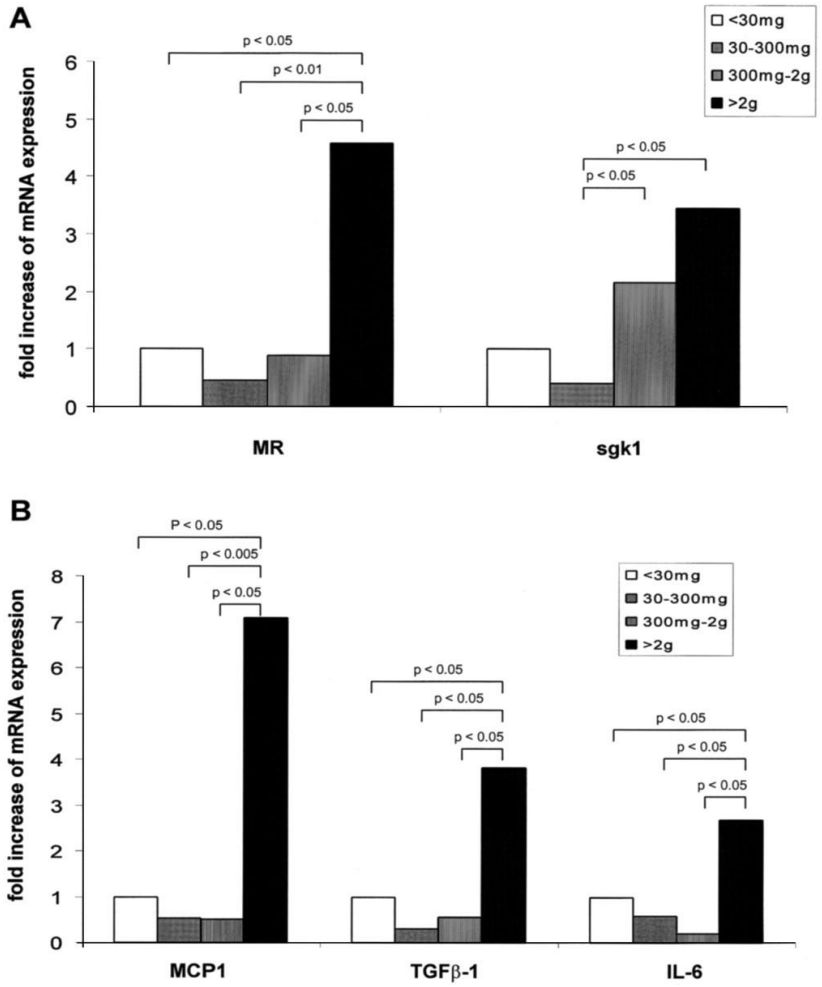
Study	Subjects	Congestive heart failure	Chronic kidney disease	Renin–angiotensin–aldosterone system blockade	Definition of aldosterone breakthrough	Incidence of aldosterone breakthrough
Lee *et al.* (1999)[27]	22	Yes	No	ACE inhibitor titrated to maximum tolerated dose for 18 months	Aldosterone >80 pg/ml[a] after 18 months	23% (5/22)
MacFadyen *et al.* (1999)[6]	91	Yes	No	"Stable ACE inhibitor therapy" for at least 4 weeks	Aldosterone >144 pg/ml[a] after at least 4 weeks	38% (35/91)
Sato and Saruta (2001)[32]	75	No	No	ACE inhibitor for 40 weeks	Aldosterone ≥baseline levels after 40 weeks	51% (38/75)
Cicoira *et al.* (2002)[28]	141	Yes	No	ACE inhibitor for at least 6 months	Aldosterone >0.42 nmol/l[a] after at least 6 months	10% (14/141)
Tang *et al.* (2002)[29]	75	Yes	No	Enalapril 2.5 mg twice per day or 20 mg twice per day for 6 months	Aldosterone ≥160 pg/ml[a] after 6 months	35% (26/75)
Sato *et al.* (2003)[30]	45	No	Yes	Trandolapril titrated to goal blood pressure of 130/85 mmHg for 40 weeks	Aldosterone ≥baseline levels after 40 weeks	40% (18/45)
Schjoedt *et al.* (2004)[4]	63	No	Yes	Losartan 100 mg per day for 24–42 months	Aldosterone ≥baseline levels after 24–42 months	41% (26/63)
Horita *et al.* (2006)[31]	43	No	Yes	Temocapril 1 mg per day, losartan 12.5 mg per day, or both, for 12 months	Aldosterone ≥baseline levels after 12 months	53% (23/43)

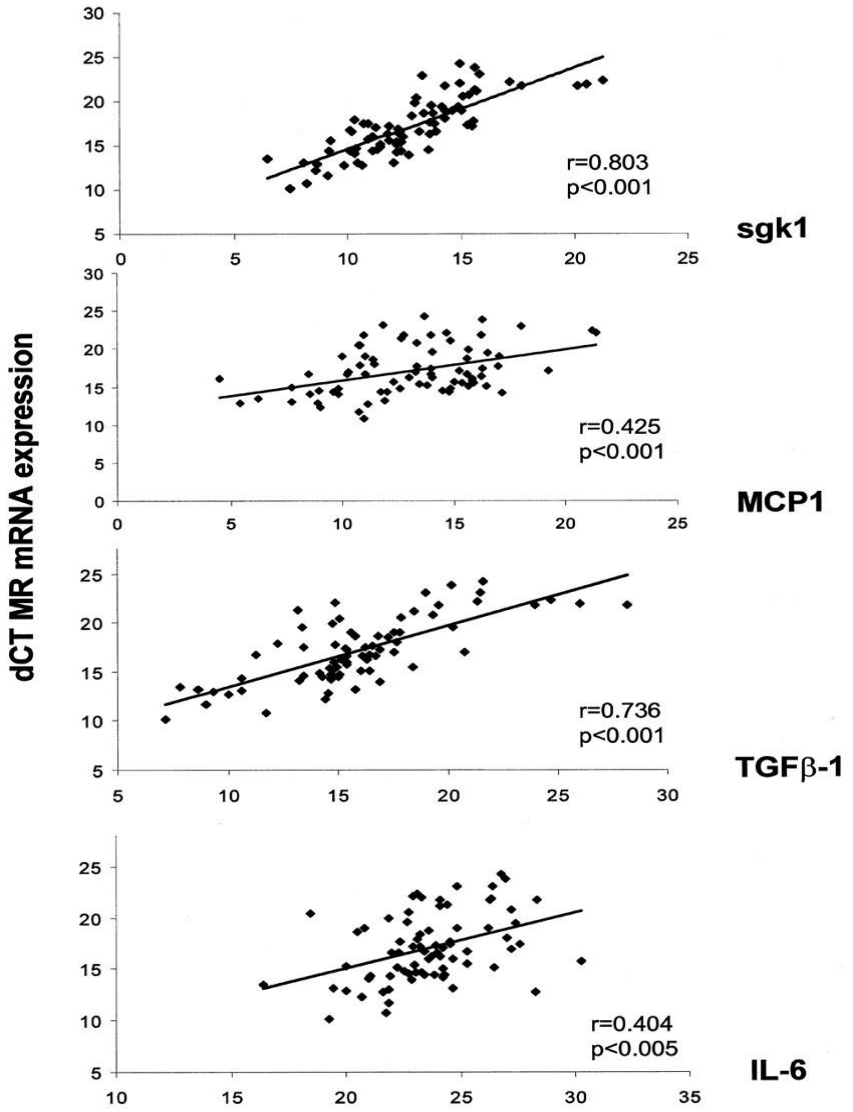
[a]In normal subjects with normal sodium intake, values for plasma aldosterone range from 50 to 150 pg/ml (0.139 to 0.416 nmol/l). Abbreviation: ACE, angiotensin-converting enzyme.

Bomback et al, Nat Clin Pract Nephrol 2007; 3:486–492

Δεδομένα σε βιοψίες νεφρού ασθενών με ΧΝΝ

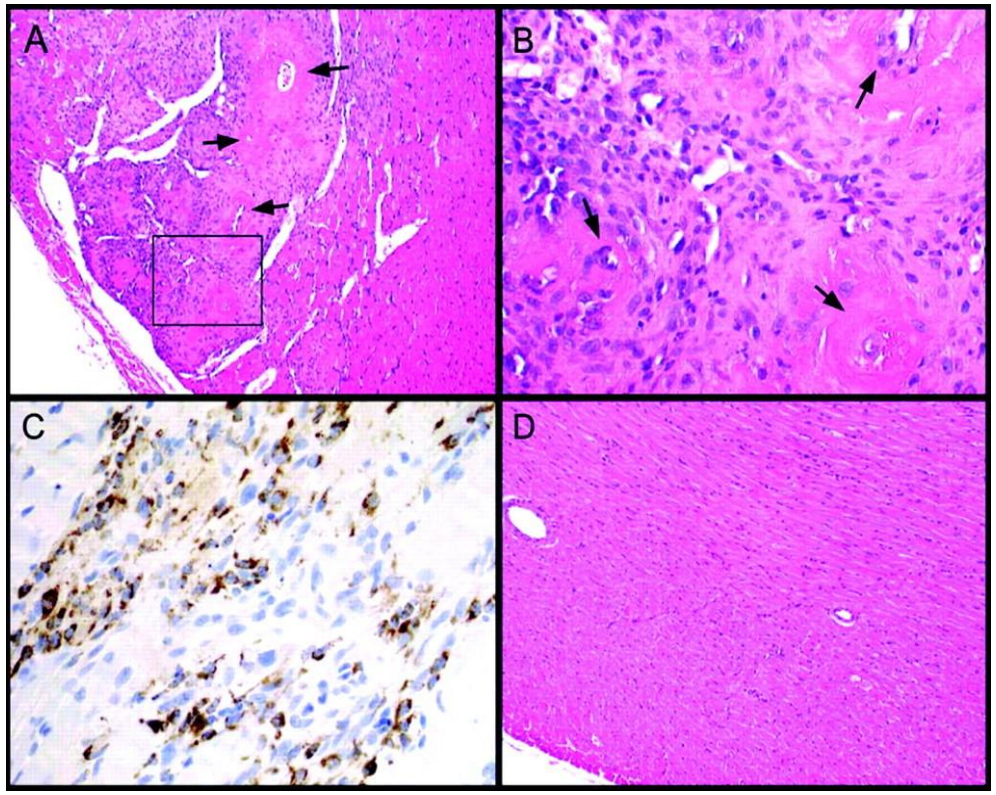
mRNA expression on kidney tissue

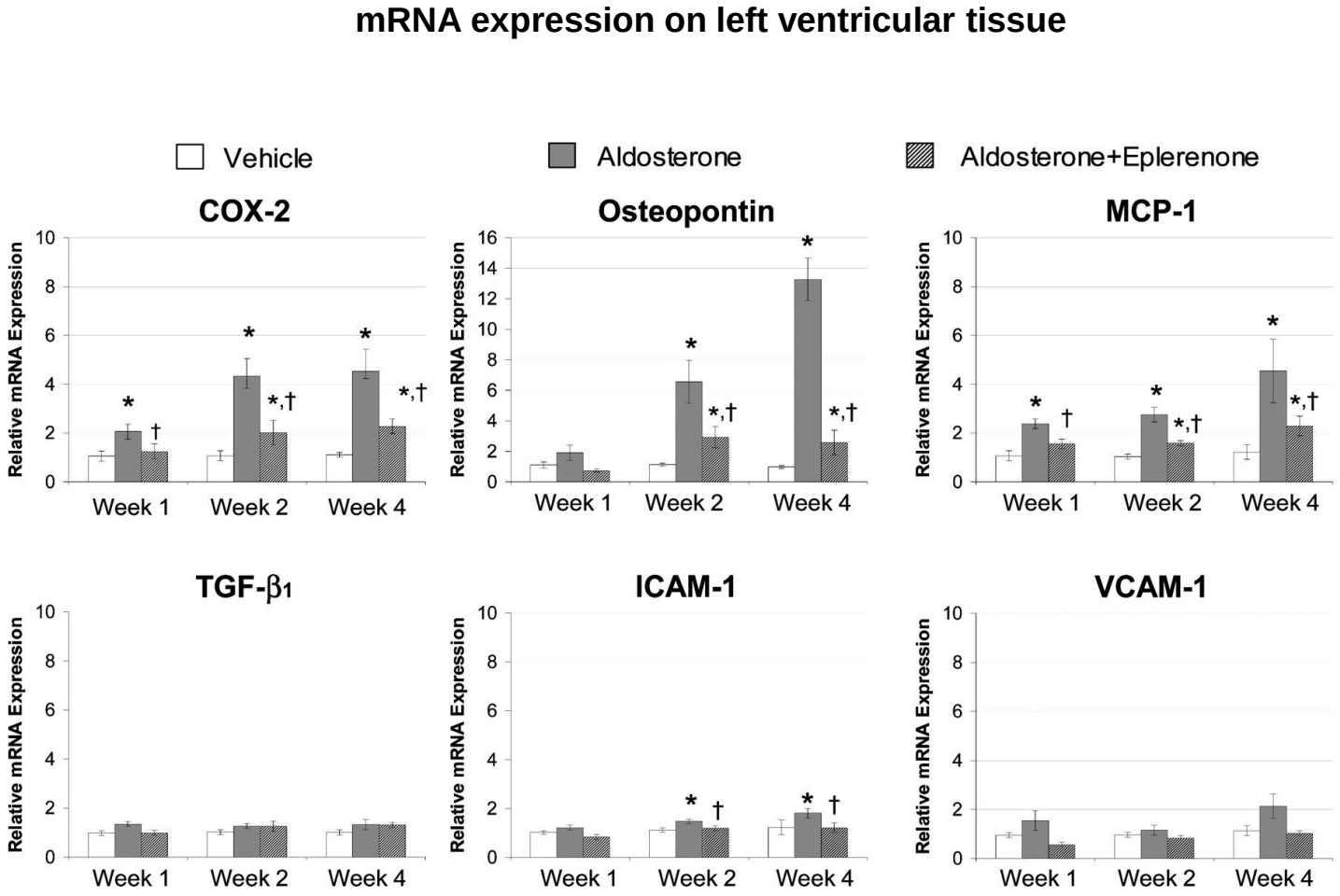




Quinkler et al., Circulation. 2005 Sep 6;112(10):1435-43

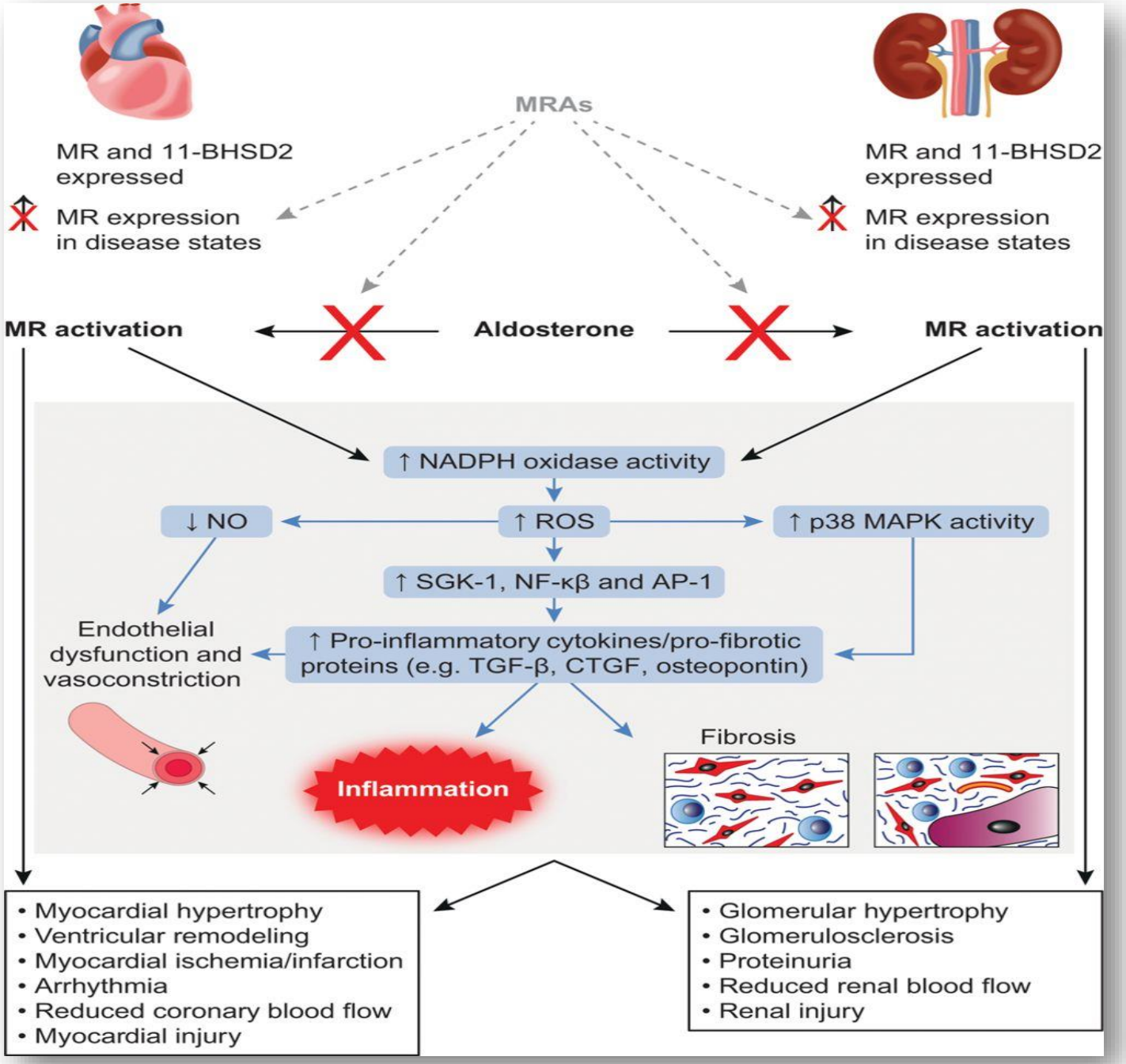
Αγγειακή φλεγμονή και μυοκαρδιακή βλάβη





Rocha et al., Am J Physiol Heart Circ Physiol. 2002;283(5):H1802-10

Μηχανισμοί πρόκλησης ιστικής βλάβης μέσω ενεργοποίησης των MRs



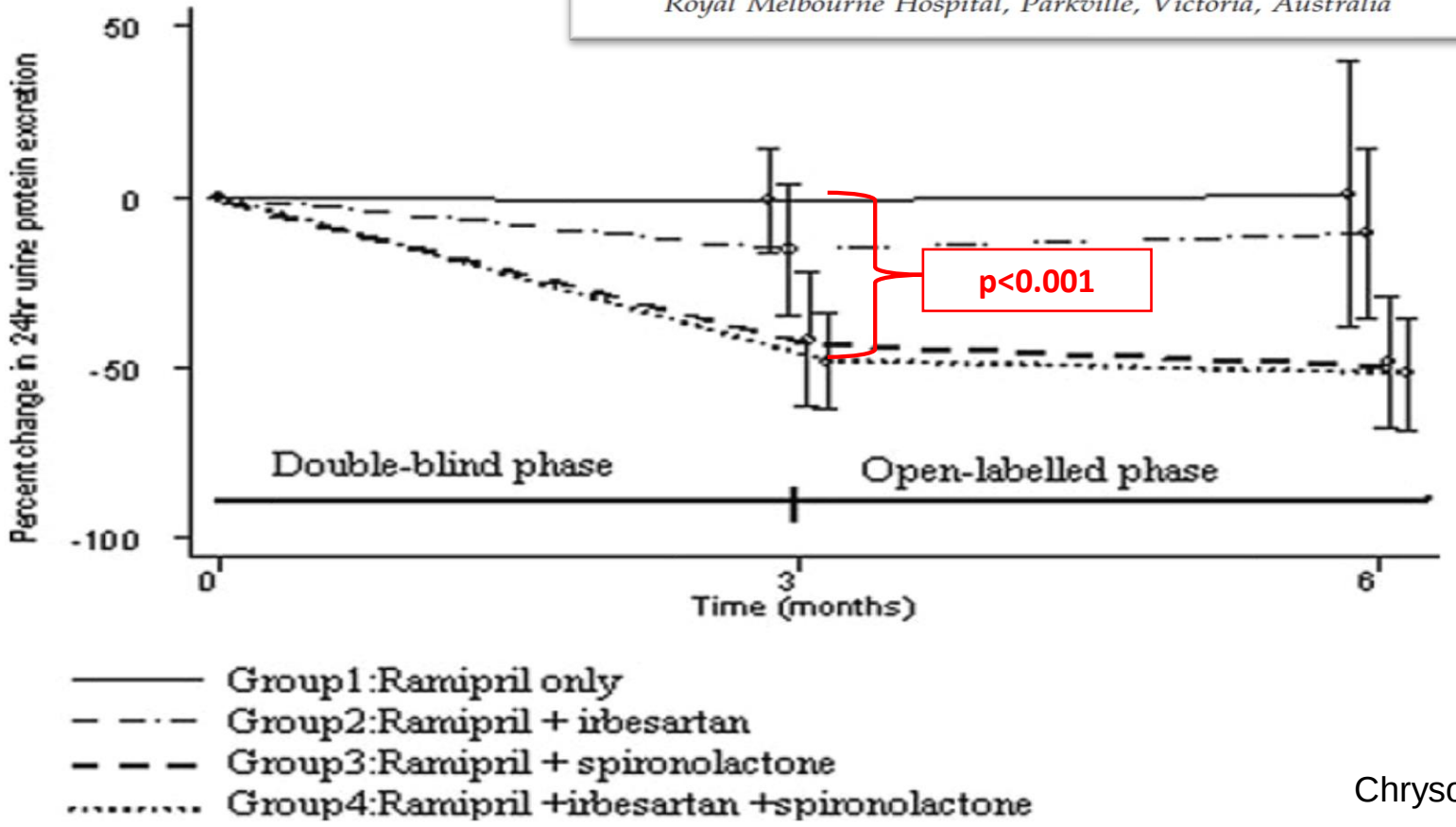
Bauersachs et al, Hypertension 2015;65:257–263

Αποκλεισμός αλδοστερόνης και νεφρο- και καρδιοπροστασία

Original Articles

Double-Blind, Placebo-Controlled Study on the Effect of the Aldosterone Receptor Antagonist Spironolactone in Patients Who Have Persistent Proteinuria and Are on Long-Term Angiotensin-Converting Enzyme Inhibitor Therapy, with or without an Angiotensin II Receptor Blocker

Anastasia Chrysostomou, Eugenia Pedagogos, Lachlan MacGregor, and Gavin J. Becker
Royal Melbourne Hospital, Parkville, Victoria, Australia



- 41 patients
- CKD, UPE>1,5 g/24h

Chrysostomou et al, Clin J Am Soc Nephrol 2006;1:256–262

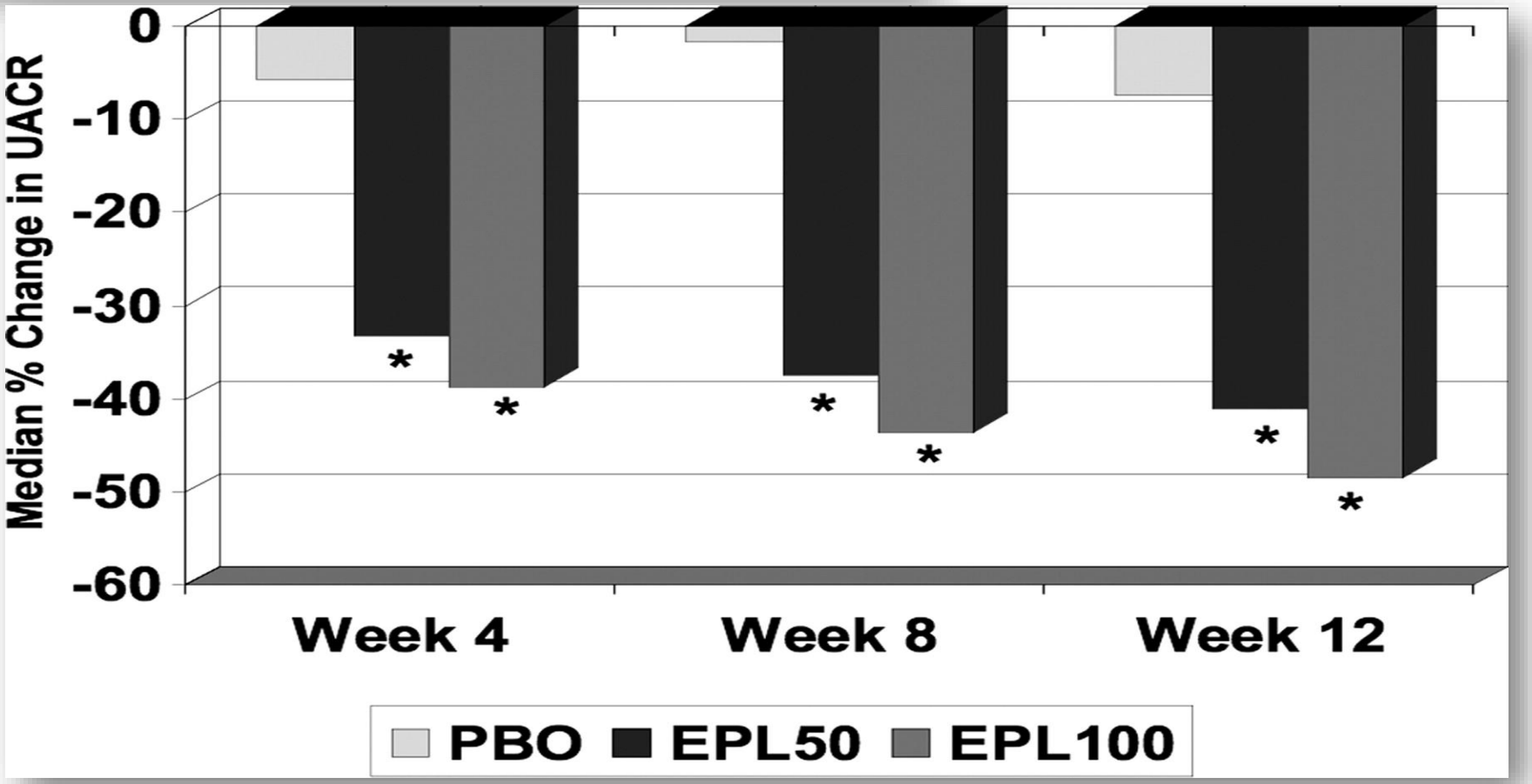
Selective Aldosterone Blockade with Eplerenone Reduces Albuminuria in Patients with Type 2 Diabetes

Murray Epstein,* Gordon H. Williams,† Myron Weinberger,‡ Andrew Lewin,§ Scott Krause,‖ Robin Mukherjee,‖ Rajiv Patni,‖ and Bruce Beckerman‖

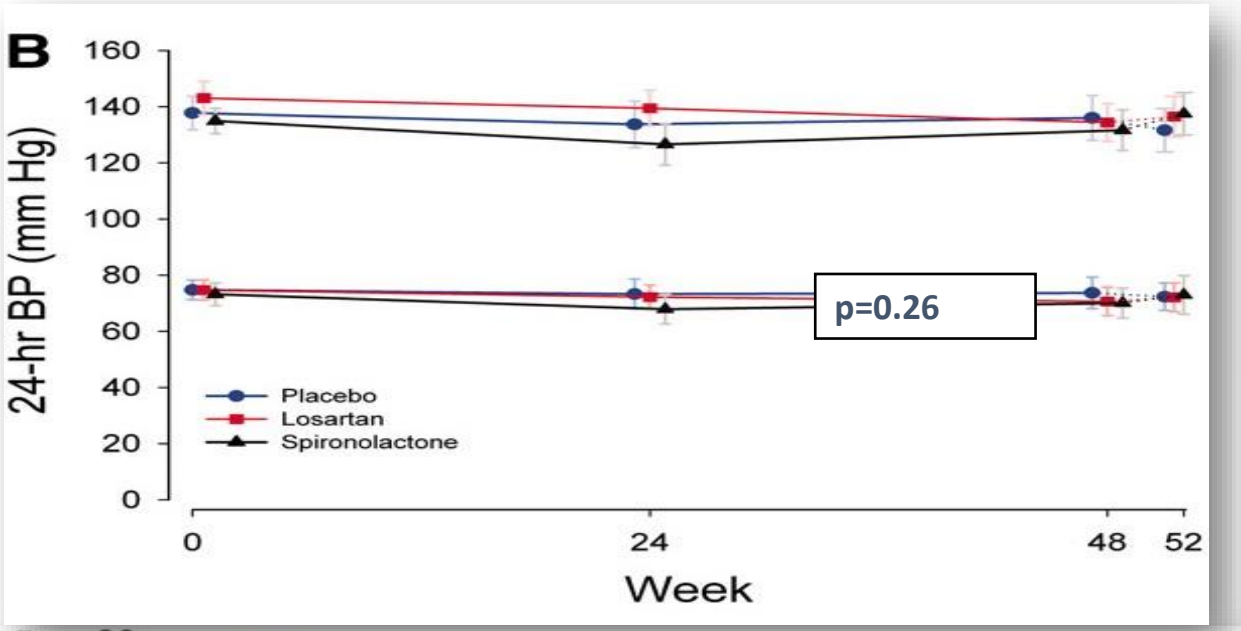
*University of Miami School of Medicine, Miami, Florida; †Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts; ‡Indiana University School of Medicine, Indianapolis, Indiana; §National Research Institute, Los Angeles, California; and ‖Pfizer Inc., New York, New York

CJASN

- 268 patients
- Type 2 DM
- UACR >50 mg/g
- Run in phase: enalapril



Epstein et al, Clin J Am Soc Nephrol 2006;1:940-51.

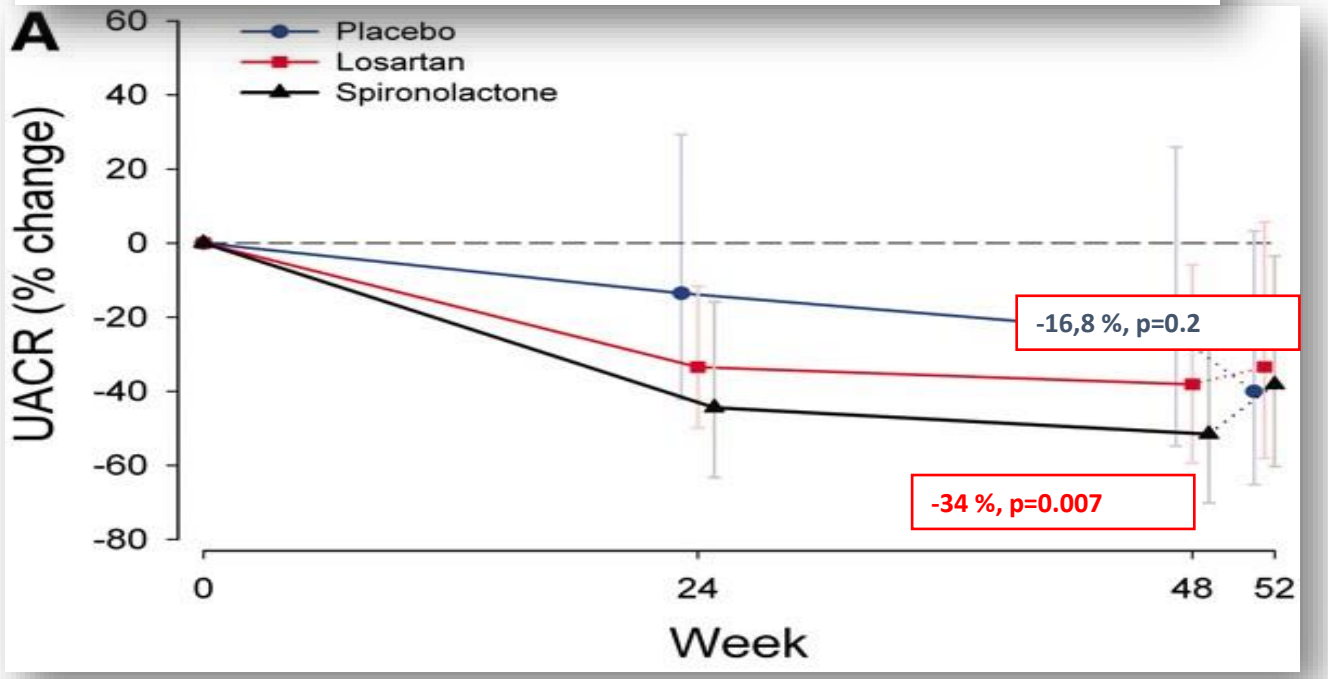


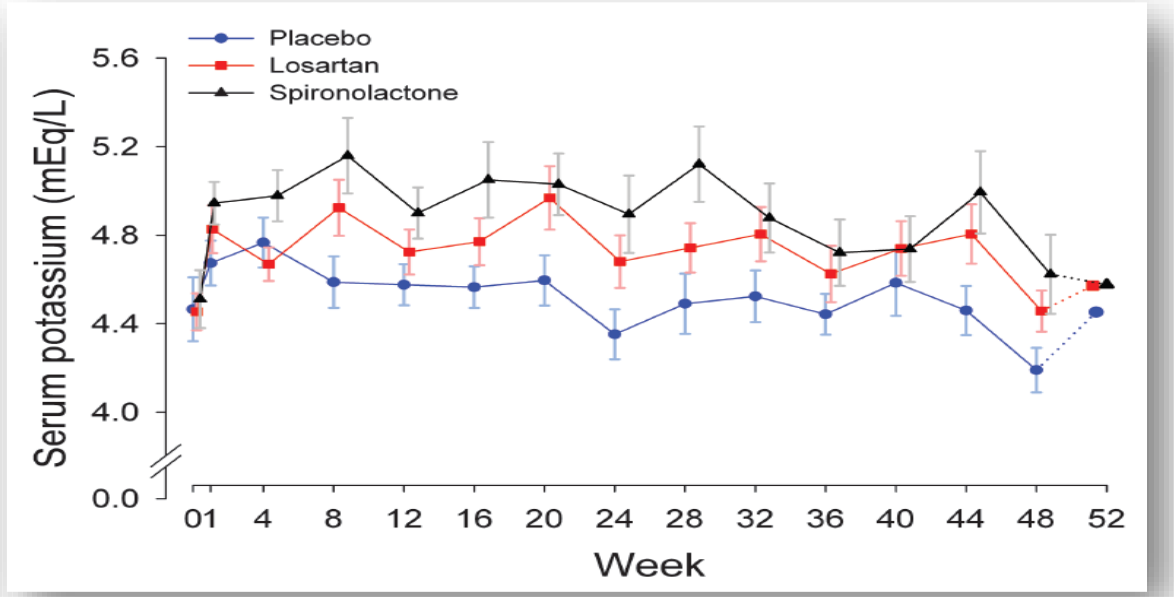
CLINICAL RESEARCH www.jasn.org

Addition of Angiotensin Receptor Blockade or Mineralocorticoid Antagonism to Maximal Angiotensin-Converting Enzyme Inhibition in Diabetic Nephropathy

Uzma F. Mehdi,* Beverley Adams-Huet,*† Philip Raskin,* Gloria L. Vega,‡ and Robert D. Toto*†

- 81 ασθενείς
- ΣΔ + ΑΥ
- UACR >300 mg/g
- Lisinopril 80mg

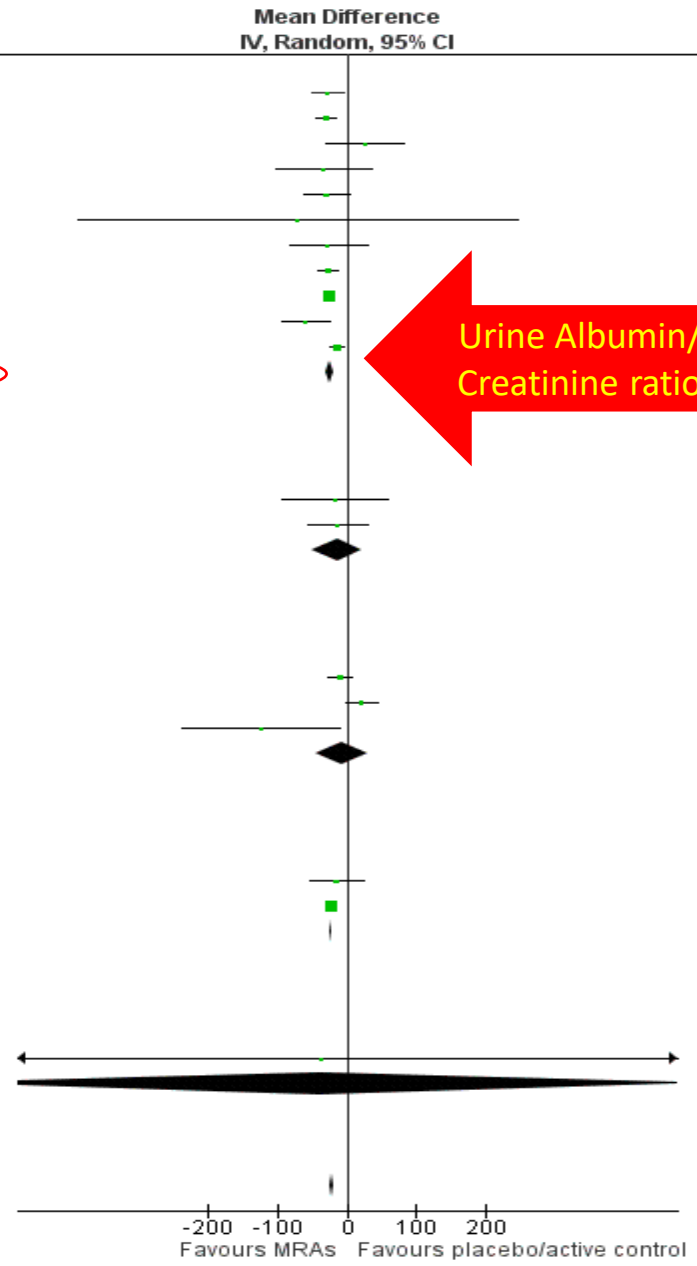




Mehdi et al, J Am Soc Nephrol. 2009;20:2641-50

31 RCTs
2767 patients

Study or Subgroup	MRAs Mean	SD	Total	placebo/active control groups Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 MRAs vs placebo								
Ando 2014	-17.3	104.6673	158	10.3	104.6673	146	2.9%	-27.60 [-51.15, -4.05]
Bakris 2015	-36.3537	44.4285	337	-6.2	71.7784	94	6.1%	-30.15 [-45.42, -14.89]
Eguchi 2016	-2.3	115.9637	33	-29.2	86.8431	19	0.6%	26.90 [-28.69, 82.49]
Kalizki 2017	-33.3	174.3092	25	0	0.0024	26	0.4%	-33.30 [-101.63, 35.03]
Katayama 2017	-23.15	43.2977	24	6.2	48.3183	12	1.6%	-29.35 [-61.71, 3.01]
Lindhardt 2018	-56	767.387	57	14	921.787	54	0.0%	-70.00 [-386.44, 246.44]
Mehdi 2009	-51.6	76.3423	27	-24.6	127.6584	27	0.6%	-27.00 [-83.11, 29.11]
Oxlund 2013	-26.6	60.0406	61	-0.0001	0.038	58	6.3%	-26.60 [-41.67, -11.53]
Pitt 2013	-21.2456	7.3737	114	4	2.66	51	29.4%	-25.25 [-26.78, -23.71]
Van der Meiracker 2006	-44.2	47.8375	24	14.3	76.7654	29	1.5%	-58.50 [-92.37, -24.63]
Ziaee 2013	-52.9	23.5	29	-38.4	16	31	11.0%	-14.50 [-24.74, -4.26]
Subtotal (95% CI)			**889**			**547**	**60.3%**	**-24.55 [-29.57, -19.53]**
Heterogeneity: Tau² = 11.55; Chi² = 11.95, df = 10 (P = 0.29); I² = 16%								
Test for overall effect: Z = 9.58 (P < 0.00001)								
1.1.2 MRAs vs RAS blockers								
Epstein 2002	-62	267.6091	74	-45	194.2324	74	0.3%	-17.00 [-92.34, 58.34]
Mehdi 2009	-51.6	76.3423	27	-38.2	79.9686	26	1.0%	-13.40 [-55.52, 28.72]
Subtotal (95% CI)			**101**			**100**	**1.3%**	**-14.26 [-51.02, 22.51]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 0.76 (P = 0.45)								
1.1.3 MRAs vs other diuretics								
Hase 2013	-57.6	21.3	18	-48.4	27.1	15	5.2%	-9.20 [-26.08, 7.68]
Morales 2014	-31.1	20	29	-52.2	57.5741	29	3.2%	21.10 [-1.08, 43.28]
Verdales 2017	-56.6	73.6387	15	66.6	210.1937	15	0.1%	-123.20 [-235.91, -10.49]
Subtotal (95% CI)			**62**			**59**	**8.6%**	**-6.20 [-43.51, 31.10]**
Heterogeneity: Tau² = 696.51; Chi² = 9.21, df = 2 (P = 0.01); I² = 78%								
Test for overall effect: Z = 0.33 (P = 0.74)								
1.1.4 MRAs vs CCBs								
Takebayashi 2006	-30.7	47.7389	23	-15.7	62.2839	14	1.2%	-15.00 [-53.01, 23.01]
White 2003	-27.5	2.5962	106	-5	10.6326	111	28.6%	-22.50 [-24.54, -20.46]
Subtotal (95% CI)			**129**			**125**	**29.8%**	**-22.48 [-24.51, -20.44]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 21.64 (P < 0.00001)								
1.1.5 MRAs vs renal denervation								
Oliveras 2018	-96.9	80.9159	13	-59.6	966.202	11	0.0%	-37.30 [-609.97, 535.37]
Subtotal (95% CI)			**13**			**11**	**0.0%**	**-37.30 [-609.97, 535.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.13 (P = 0.90)								
Total (95% CI)			**1194**			**842**	**100.0%**	**-21.58 [-25.81, -17.36]**
Heterogeneity: Tau² = 15.19; Chi² = 38.51, df = 18 (P = 0.003); I² = 53%								
Test for overall effect: Z = 10.01 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.52, df = 4 (P = 0.82), I² = 0%								

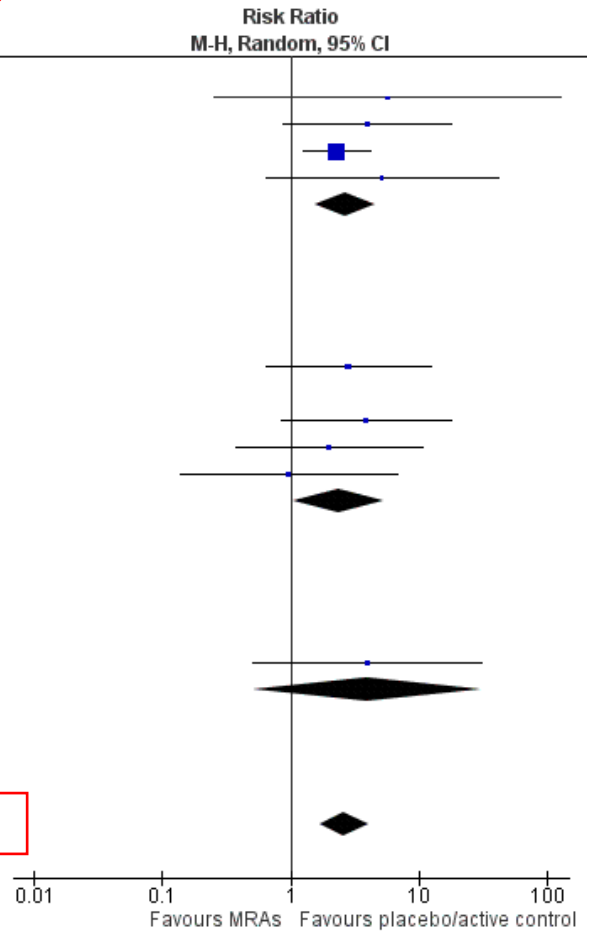


Alexandrou M et al, J Hypertens 2019;37:2307–2324

Επίπτωση υπερK+

↑ 2,6 υψηλότερος κίνδυνος υπερκαλιαιμίας

Study or Subgroup	MRAs Events	Total	placebo/active control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Hyperkalemia >6mEq/L						
Chrysostomou 2006	1	10	0	20	2.0%	5.73 [0.25, 129.23]
Epstein 2002	8	74	2	74	8.5%	4.00 [0.88, 18.21]
Mehdi 2009	14	27	12	53	51.3%	2.29 [1.24, 4.24]
Van der Meiracker 2006	5	29	1	30	4.5%	5.17 [0.64, 41.63]
Subtotal (95% CI)		**140**		**177**	**66.3%**	**2.67 [1.55, 4.60]**
Total events	28		15			
Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
8.1.2 Hyperkalemia >5.5mEq/L						
Epstein 2006	11	171	2	88	8.8%	2.83 [0.64, 12.49]
Katayama 2017	0	36	0	12		Not estimable
Pitt 2003	7	64	2	71	8.3%	3.88 [0.84, 18.02]
White 2003	4	134	2	135	6.9%	2.01 [0.38, 10.82]
Williams 2004	2	253	2	246	5.1%	0.97 [0.14, 6.85]
Subtotal (95% CI)		**658**		**552**	**29.1%**	**2.37 [1.05, 5.37]**
Total events	24		8			
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 2.07 (P = 0.04)						
8.1.3 Hyperkalemia (non defined level of potassium)						
Pitt 2013	8	131	1	65	4.6%	3.97 [0.51, 31.07]
Subtotal (95% CI)		**131**		**65**	**4.6%**	**3.97 [0.51, 31.07]**
Total events	8		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**929**		**794**	**100.0%**	**2.63 [1.69, 4.08]**
Total events	60		24			
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 8 (P = 0.95); I² = 0%						
Test for overall effect: Z = 4.29 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.22, df = 2 (P = 0.90), I² = 0%						



Alexandrou ME et al, J Hypertens 2019;37:2307–2324

Cardiovascular outcome studies with MRAs in patients with HF

Trial	Year	Treatment arms	Study Population	Primary and secondary endpoints (MRAs versus control)	Subgroup analysis according to kidney function(MRAs versus control)
		(50mgifeGFR≥50 mL/min/1.73m^{2}or≤25mgif eGFR30-49mL/min/1.73m^2) or placebo (double blind, 1:1 ratio)	HFNYHAIand LVEF<35%	deathor HHF (HR 0.63, 95%CI 0.54-0.74), all-cause mortality (HR 0.76, 95%CI 0.62-0.93)	HHF was significantly reduced in patients with either eGFR ≥50 mL/min/1.73m^2 (HR 0.58, 95%CI 0.45-0.74) or eGFR 30-49 mL/min/1.73m^2 (HR 0.62, 95%CI 0.49–0.78) (P-for-interaction=0.89)

Journal of Human Hypertension

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REVIEW ARTICLE

Check for updates

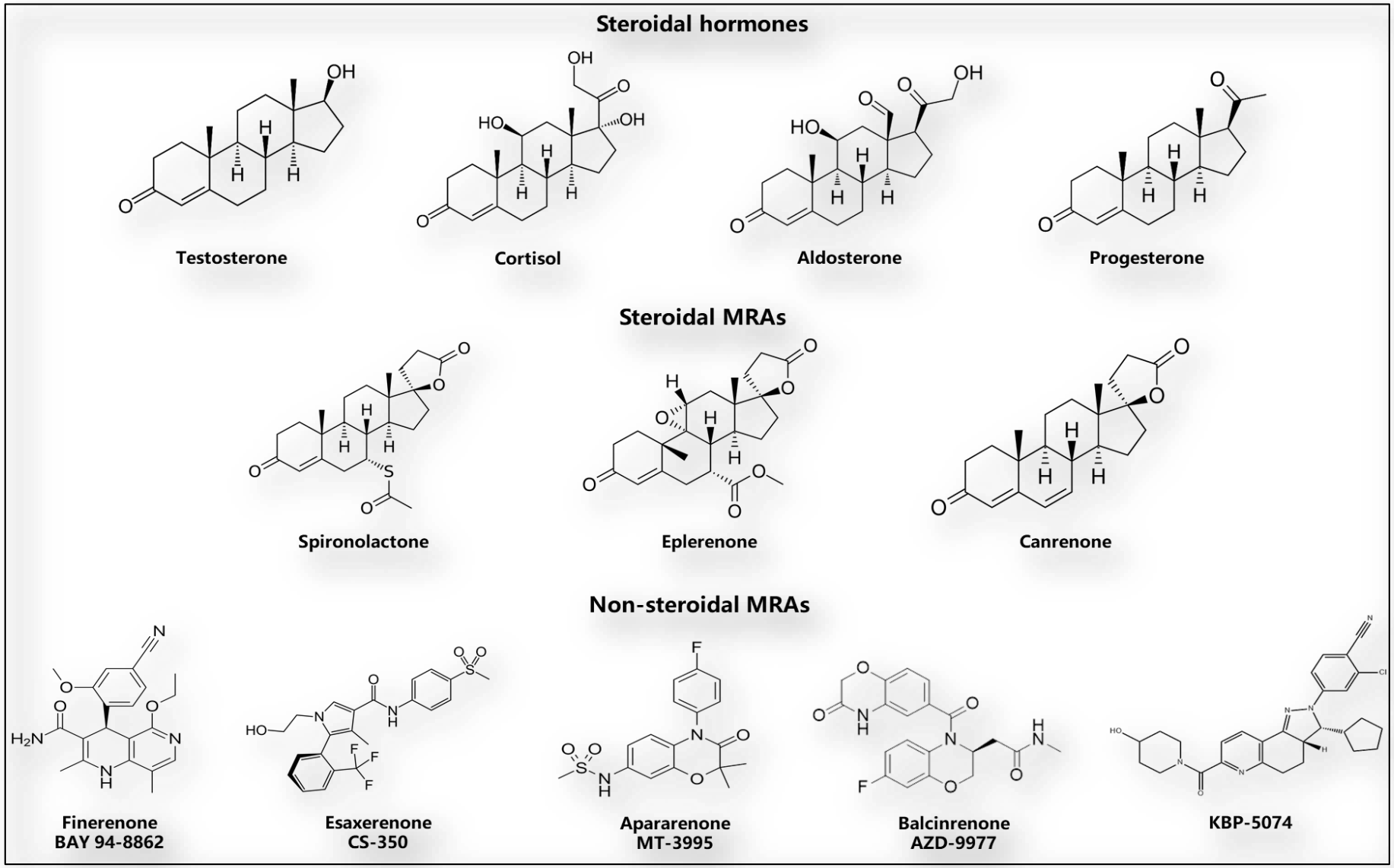
Mineralocorticoid receptor antagonists for cardioprotection in chronic kidney disease: a step into the future

Maria-Eleni Alexandrou[1], Marieta P. Theodorakopoulou[1], Mehmet Kanbay[2] and Pantelis A. Sarafidis[1]✉

Alexandrou et al. J Hum Hypertens 2022

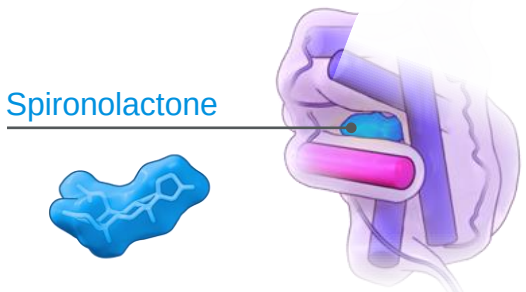
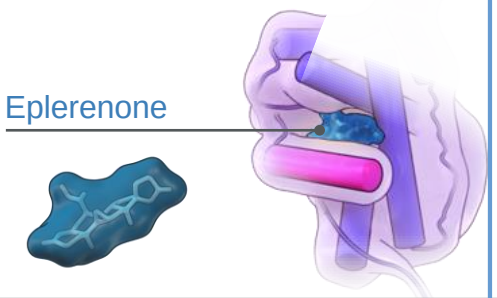
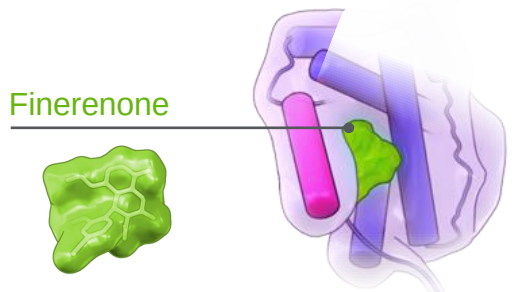
Διαφορές στεροειδικών και μη στεροειδικών MRAs

Older and newer MRAs



Sarafidis P. et al. Clin Kidney J 2023

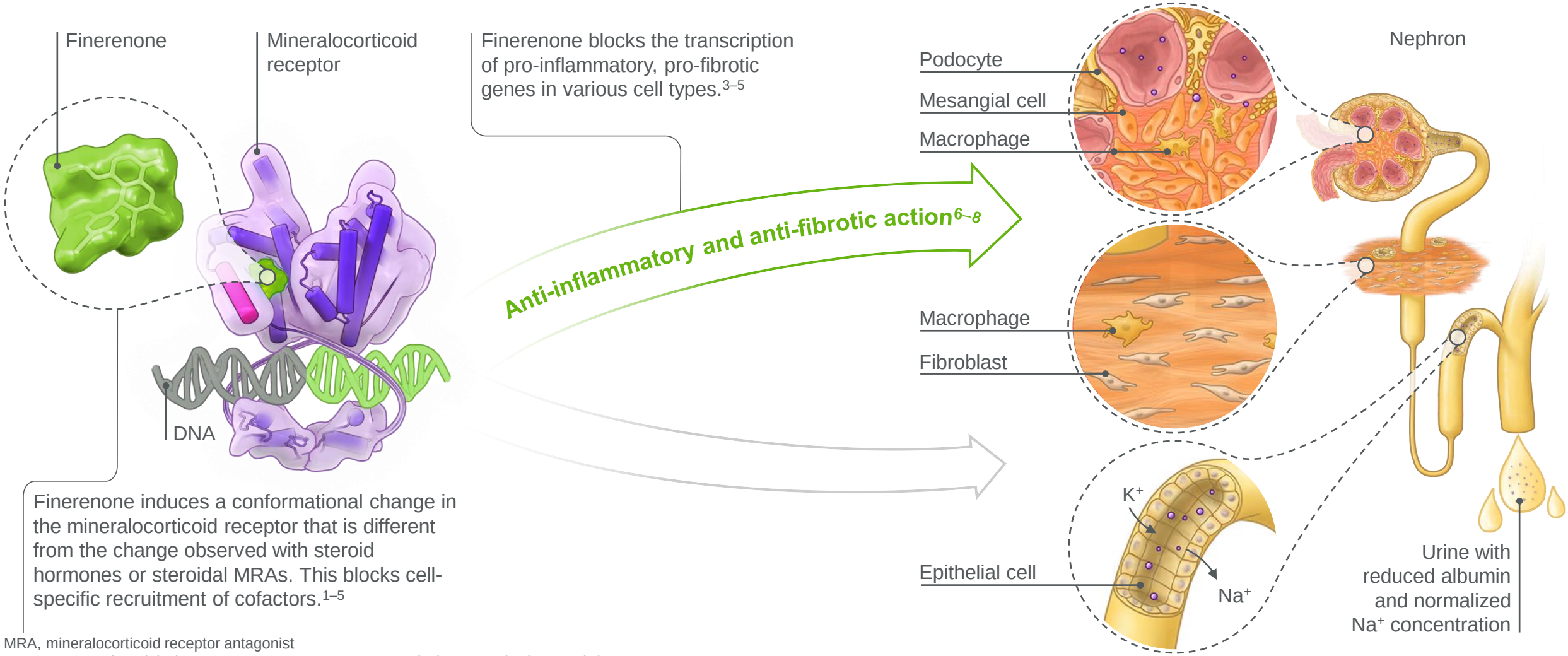
Finerenone is a novel, nonsteroidal and selective MR antagonist that is different from available steroidal drugs[1–3]

	Steroidal MR antagonists		Finerenone
			
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)[1,5]
Potency to MR	High[4,8]	Moderate[1,4,10]	High[1,2,8]
Selectivity to MR	Low[4,8]	Moderate[4,10]	High[1,2,8]
CNS penetration	Yes	Yes	No, based on preclinical data[3]
Sexual side effects	Yes (gynecomastia)[4]	Less than spironolactone[4]	No signal, based on phase III data[7]
Hyperkalaemia	Yes[4]	Yes[4]	Moderately increased*,[7]
Tissue distribution	Kidney > heart (at least 6-fold)[6,8]	Kidney > heart (~3-fold)[6,8]	Balanced kidney : heart (1:1)[6,8]

*Hyperkalaemia was moderately increased in the FIDELIO-DKD trial; CNS, central nervous system

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. Bakris GL, *et al*. *N Engl J Med* 2020; doi: 10.1056/NEJMoa2025845; 8. Kolkhof P, *et* al. *Handb Exp Pharmacol*. 2017;243:271-305

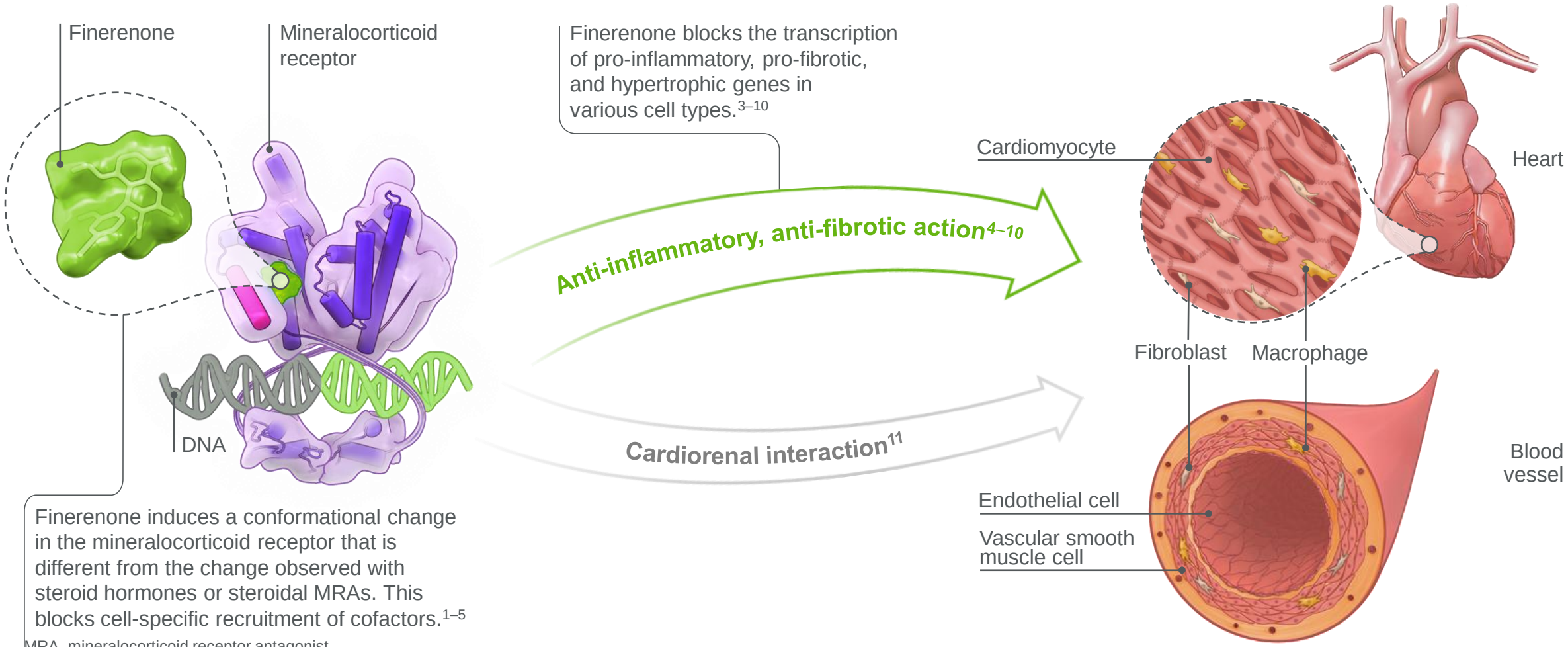
Proposed mode of action of finerenone in the kidney



MRA, mineralocorticoid receptor antagonist

1. Fagart J, *et al. J Biol Chem* 2010;285:29932–29940; 2. Bärfacker L, *et al. ChemMedChem* 2012;7:1385–1403;
3. Amazit L, *et al. J Biol Chem* 2015;290:21876–21889; 4. Grune J, *et al. J Cardiovasc Pharmacol* 2016;67:402–411; 5. Grune J, *et al. Hypertension* 2018;71:599–608;
6. Kolkhof P, *et al. J Cardiovasc Pharmacol* 2014;64:69–78; 7. Lattenist L, *et al. Hypertension* 2017;69:870–878; 8. Barrera-Chimal J, *et al. Kidney Int* 2018;93:1344–1355

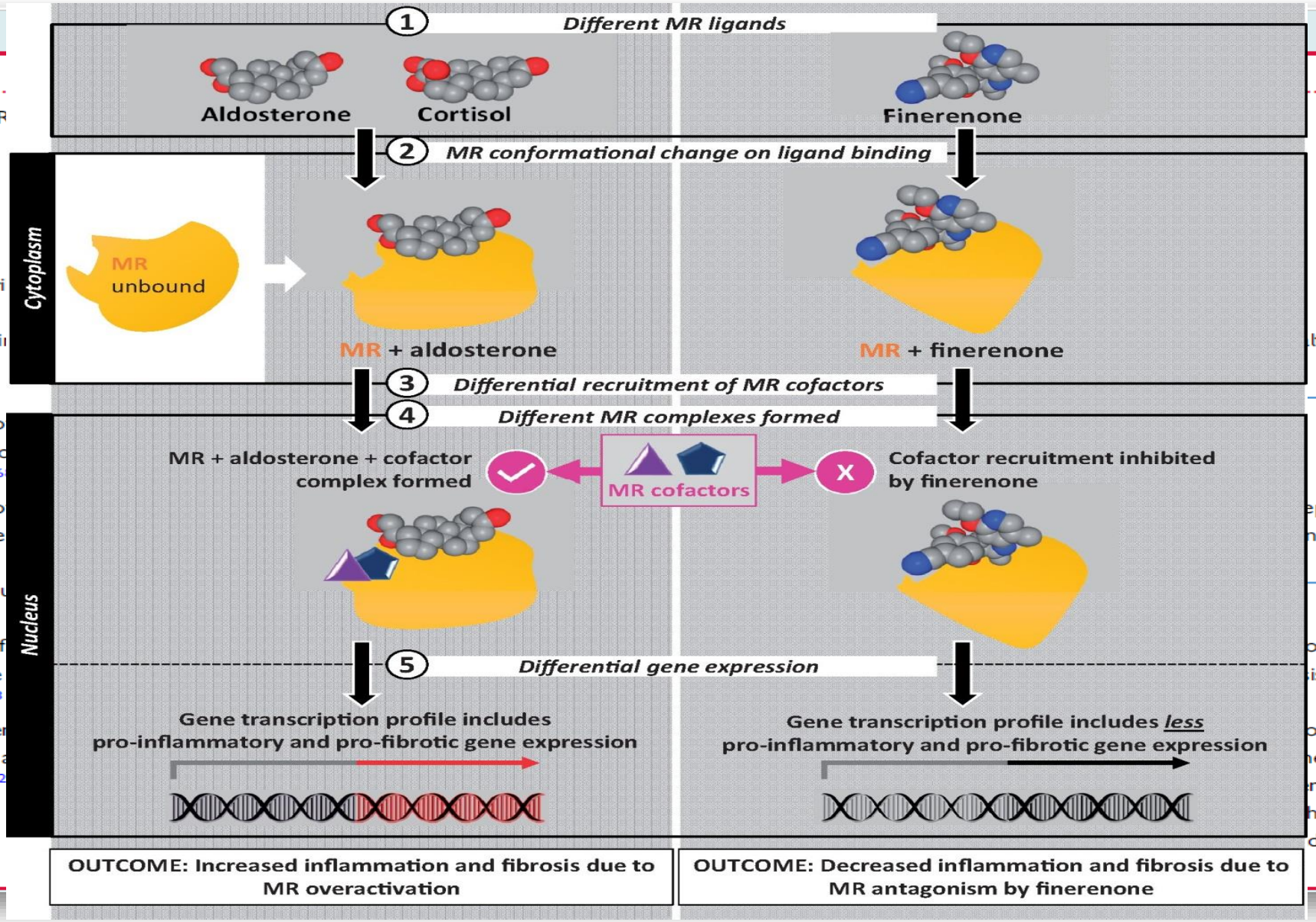
The proposed mode of action of finerenone in the heart and blood vessels



MRA, mineralocorticoid receptor antagonist

1. Fagart J, *et al. J Biol Chem* 2010;285:29932–29940; 2. Bärfacker L, *et al. ChemMedChem* 2012;7:1385–1403; 3. Amazit L, *et al. J Biol Chem* 2015;290:21876–21889; 4. Grune J, *et al. J Cardiovasc Pharmacol* 2016;67:402–411; 5. Grune J, *et al. Hypertension* 2018;71:599–608; 6. Kolkhof P, *et al. J Cardiovasc Pharmacol* 2014;64:69–78; 7. Martínez-Martínez E, *et al. Hypertension* 2017;70:1148–1156; 8. Dutzmann J, *et al. PLoS ONE* 2017;12:e0184888; 9. Lavall D, *et al. Biochem Pharmacol* 2019;168:173–183;
10. Gil-Ortega M, *et al. Am J Nephrol* 2020;51:294–303; 11. Zannad F & Rossignol P. *Circulation* 2018;138:929–944

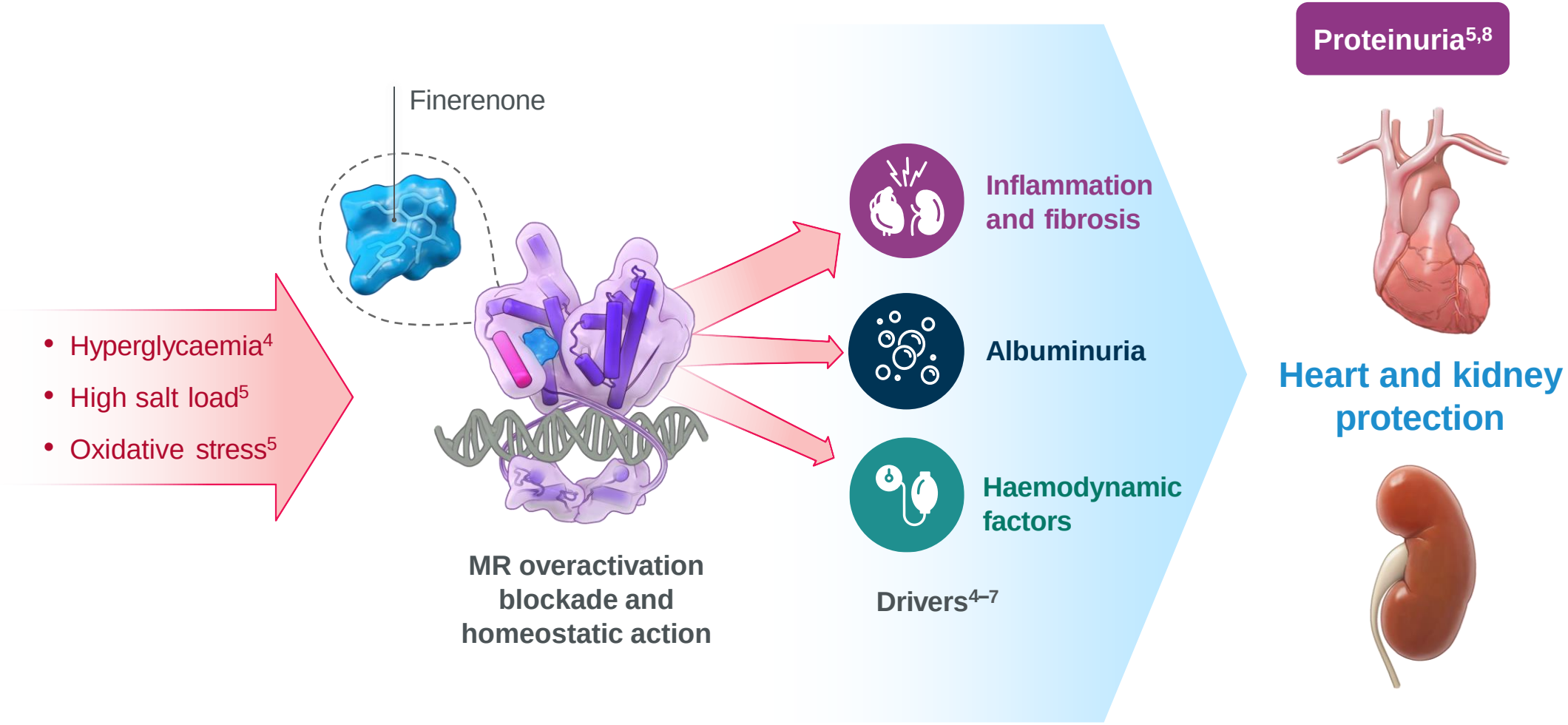
Cofactor recruitment



Agarwal R, et al. Eur Heart J 2021;42:152-161

Δεδομένα από μελέτες με μη στεροειδικούς MRAs

Finerenone, a selective, nonsteroidal MRA, blocks MR overactivation, which slows kidney and CV disease progression[1–3]



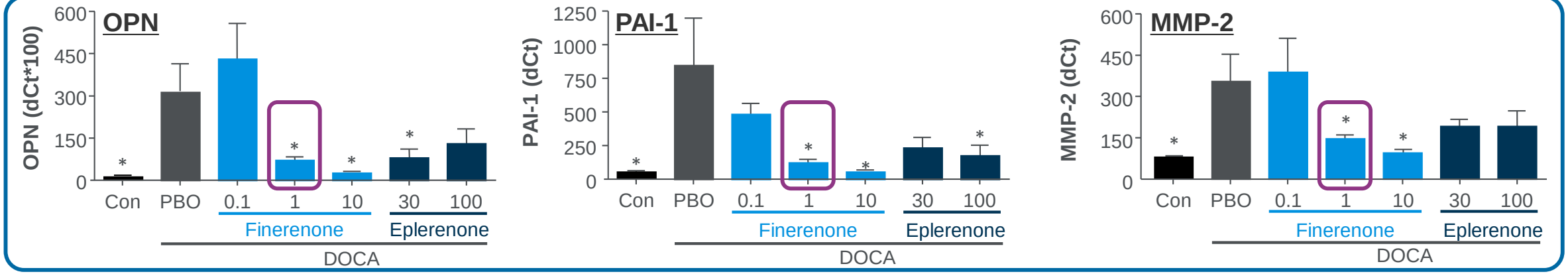
Finerenone is indicated in the EU for the treatment of CKD (with albuminuria) associated with T2D in adults. CV prevention is not an approved indication for finerenone in the EU

MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist

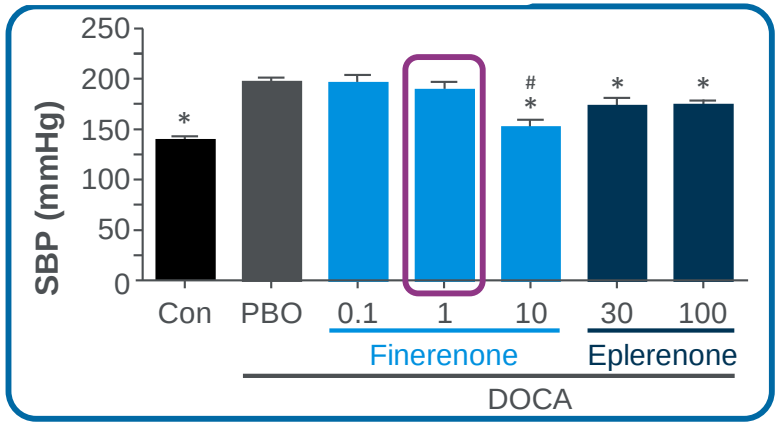
1. Kintscher U, *et al. Br J Pharmacol* 2022;179:3220–3234; 2. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 3. Agarwal R, *et al. Nephrol Dial Transplant* 2022;37:1014–1023; 4. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 5. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 6. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 7. Khan MS, *et al. JACC Rev* 2023;81:270–282; 8. Amazit L, *et al. J Biol Chem* 2015;290:21876–21889

Preclinical models comparing mRNA expression of inflammatory and fibrotic markers and SBP

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



Effect on SBP



Finerenone reduced mRNA expression of pro-inflammatory and pro-fibrotic markers in kidney tissue to a greater extent than equinatriuretic doses of eplerenone in a rat DOCA–salt model of kidney injury

Finerenone 1 mg/kg/day inhibited inflammation and fibrosis without significantly affecting BP; however, eplerenone doses tested inhibited inflammation and fibrosis and significantly reduced BP

Data are mean±SEM; there were 7–12 rats per group; drug doses are in mg/kg/day; *p<0.05 versus placebo; #p<0.05 versus eplerenone
BP, blood pressure; DOCA, deoxycorticosterone acetate; MMP-2, matrix metalloproteinase-2; mRNA, messenger ribonucleic acid; NaCl, sodium chloride; OPN, osteopontin; PAI-1, plasminogen activator inhibitor type 1; SEM, standard error of the mean
Kolkhof P, *et al*. *J Cardiovasc Pharm* 2014;64:69–78

FIGARO-DKD biomarker substudy

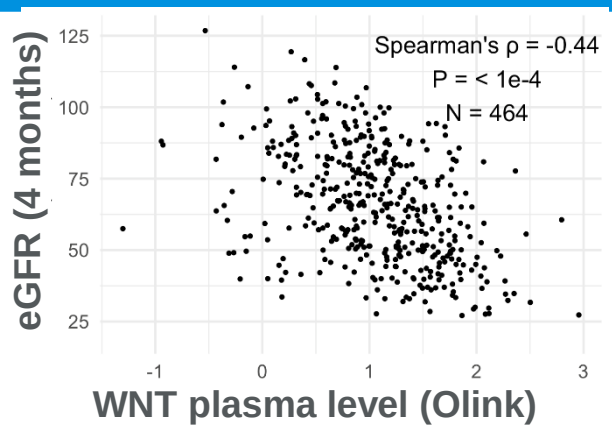
In a longitudinal analysis using **plasma samples** from the **FIGARO-DKD trial**, **finerenone** significantly **modulated 373 biomarkers**

These included **markers of inflammation and fibrosis** such as IL-17 family members, FN1 and **WNT9a**

Finerenone **downregulated WNT9a,**[1] a biomarker that is **implicated** in **kidney fibrosis**[2]

WNT9a negatively correlated with eGFR, which may reflect **anti-fibrotic activity**[1]

WNT9a and eGFR[1]



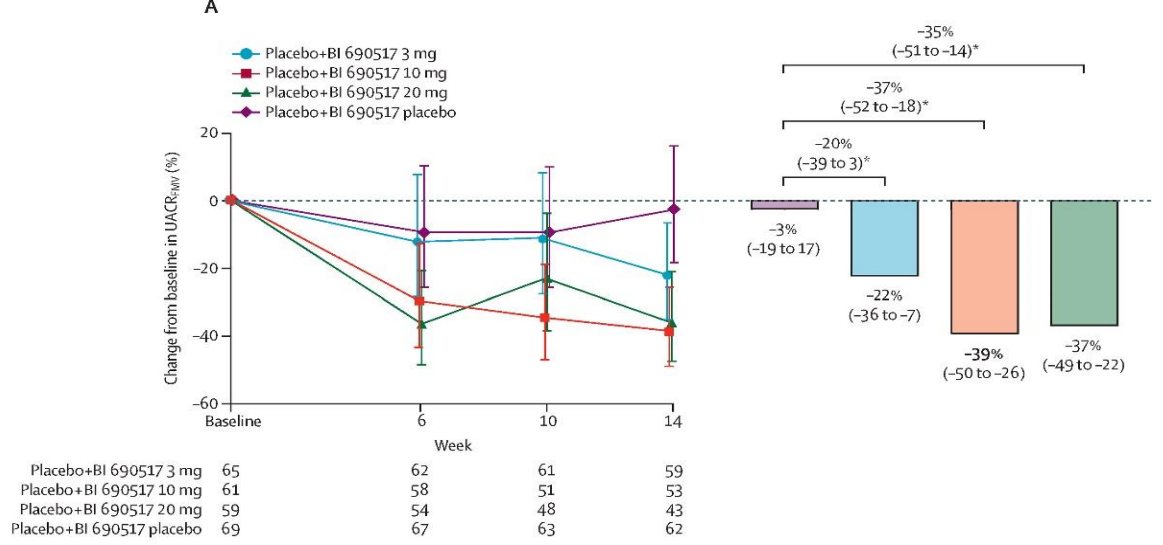
Finerenone also **downregulated NPY,**[1] a marker of **aldosterone secretion** that may play a role in **albuminuric kidney disease**[3,4]

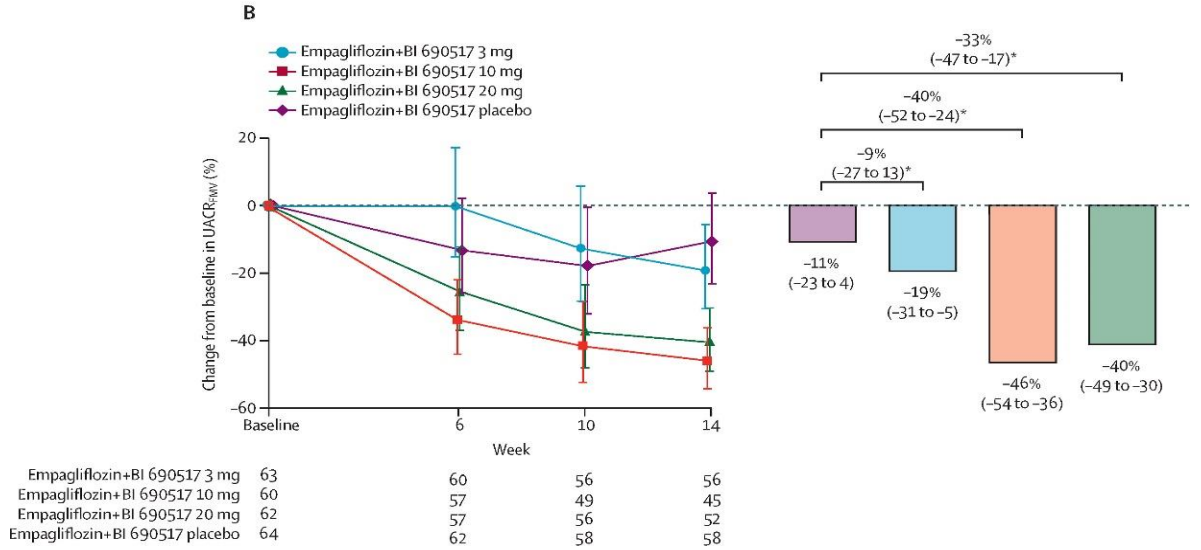
FN1, fibronectin1; IL-17, interleukin 17; NPY, neuropeptide Y; WNT9a, wingless related integration site family member 9a

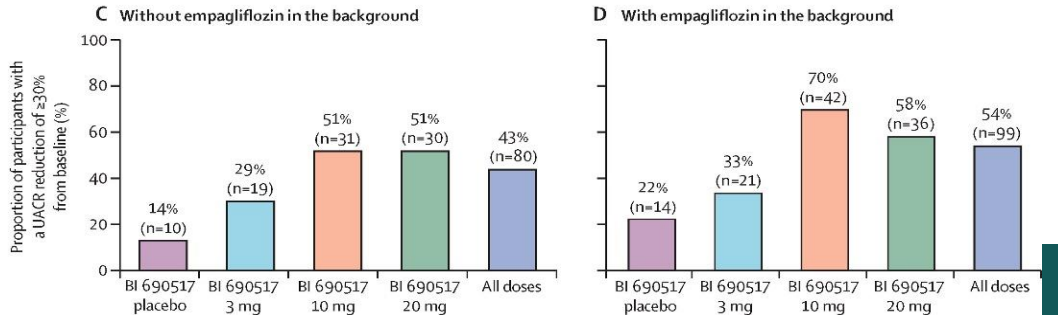
1. Berger M, *et al. ASN Kidney Week* 2023; oral presentation (abstract TH-OR53); 2. Luo C, *et al. J Am Soc Nephrol* 2018;29:1238–1256; 3. Renshaw D, *et al. Endocrinology* 2000;141:169–173;
4. Lay AC, *et al. Proc Natl Acad Sci USA* 2000;117:15862–15873

aldosterone synthase inhibition with and without empagliflozin

- 586 patients
- eGFR 30 to 90 ml/min/1,73m^2
- UACR 200 to <5000 mg/g
- ACEi/ARB
- empagliflozin or placebo run-in
- BI 690517 3 mg, 10 mg, or 20 mg, or placebo







Tuttle K. et al., Lancet. 2024 Jan 27;403(10424):379-390

Phase III trial of aldosterone synthase inhibition with empagliflozin

Συμπεράσματα

- Η ενεργοποίηση των MR ενεργοποιεί μέσω γενομικών ή μη-γενομικών ταχέων δράσεων σηματοδοτικά μονοπάτια που οδηγούν σε φλεγμονή και ίνωση συμβάλλοντας στην πρόκληση νεφρικής και καρδιαγγειακής βλάβης.

- Το φαινόμενο της διαφυγής της αλδοστερόνης αποτελεί σημαντικό αίτιο της παρουσίας υψηλού υπολειπόμενου καρδιαγγειακού κινδύνου και κινδύνου εξέλιξης της ΧΝΝ υπό θεραπεία με μονό αποκλεισμό του ΣΡΑ, ιδίως στους ασθενείς με ΔΝΝ.

- Οι νεότεροι εκλεκτικοί μη στεροειδικοί MRAs επιδεικνύουν μεγαλύτερη εκλεκτικότητα και υψηλότερη συγγένεια, καθώς και διαφορετικούς μηχανισμούς πρόσδεσης συμπαραγόντων και κατανομή στους ιστούς συγκριτικά με παλαιότερους παράγοντες.

- Τα αποτελέσματα προ-κλινικών και κλινικών μελετών φάσης ΙΙΙ έδειξαν ότι η προσθήκη της φινερενόνης οδήγησε σε μείωση δεικτών φλεγμονής και ίνωσης, καθυστέρηση της εξέλιξης της ΧΝΝ και βελτίωση στην καρδιαγγειακή έκβαση σε ασθενείς με ΔΝΝ.

Σας ευχαριστώ!