RENE E DIABETE: INTERAZIONI FISIOPATOLOGICHE E NOVITA' TERAPEUTICHE

Bologna, 20-21 gennaio 2023

Finerenone: meccanismi d'azione

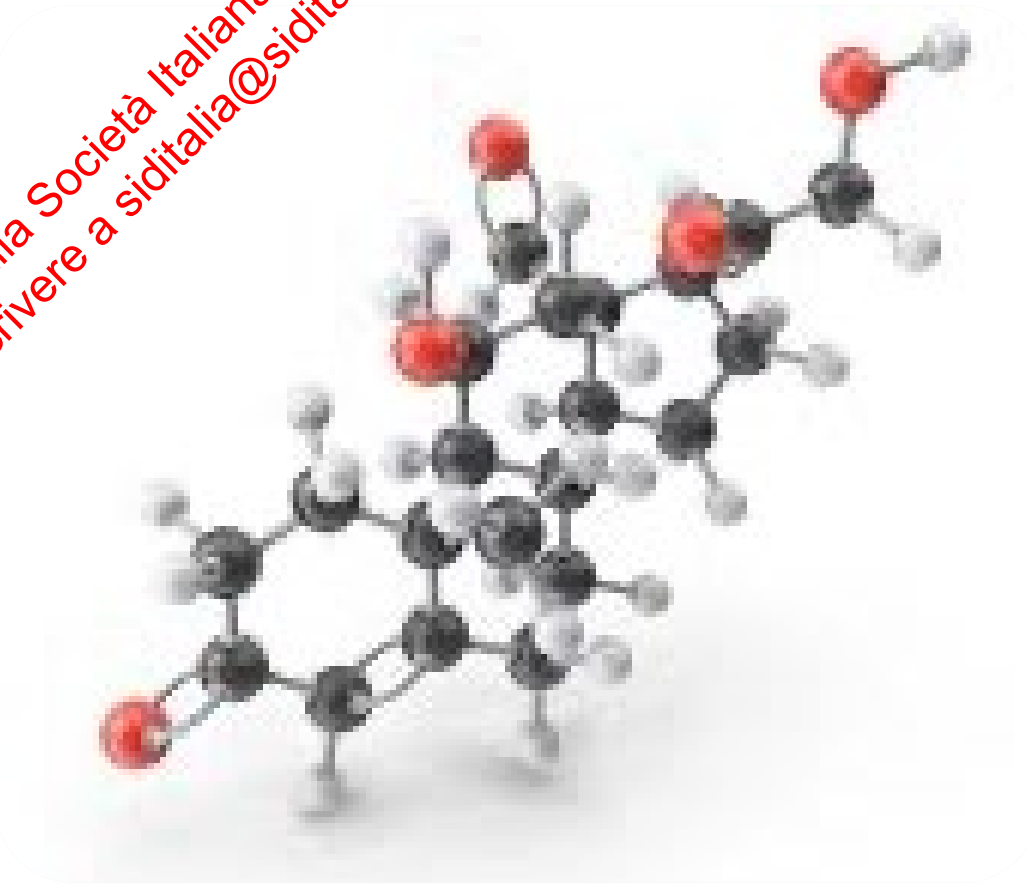
Lucia Del Vecchio

UO Nefrologia e Dialisi

Ospedale Sant'Anna, ASST Lariana, Como

L'ALDOSTERONE

- E' un ormone steroide prodotto dalla corticale del surrene
- E' parte della famiglia degli ormoni steroidei (cortisolo e corticosterone)
- La principale funzione è mantenere costante la pressione arteriosa e il volume ematico, regolando il bilancio idroelettrolitico.
- In condizioni di ridotta perfusione (e quindi di ridotto volume di sangue), l'aldosterone stimola il riassorbimento del sodio e dell'acqua da parte dei tubuli renali eliminando potassio.



Isolato nel 1954 da Simpson et al da estratti surrenalici

Iperaldosteronismo primitivo

Conn (1964)

154 casi con iperaldosteronismo

severo:

→ 85% con proteinuria severa

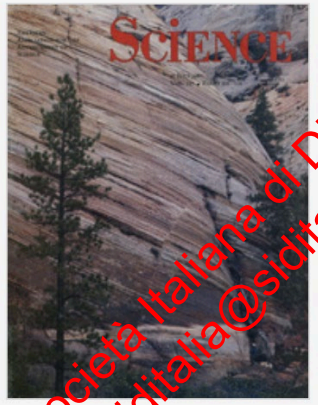
→ Ipertensione arteriosa severa + ipopotassiemia

La " carica " delle 600. Tutti al mare!
Sulla nuova autostrada del Sole

Research Articles

Cloning of Human Mineralocorticoid Receptor Complementary DNA: Structural and Functional Kinship with the Glucocorticoid Receptor

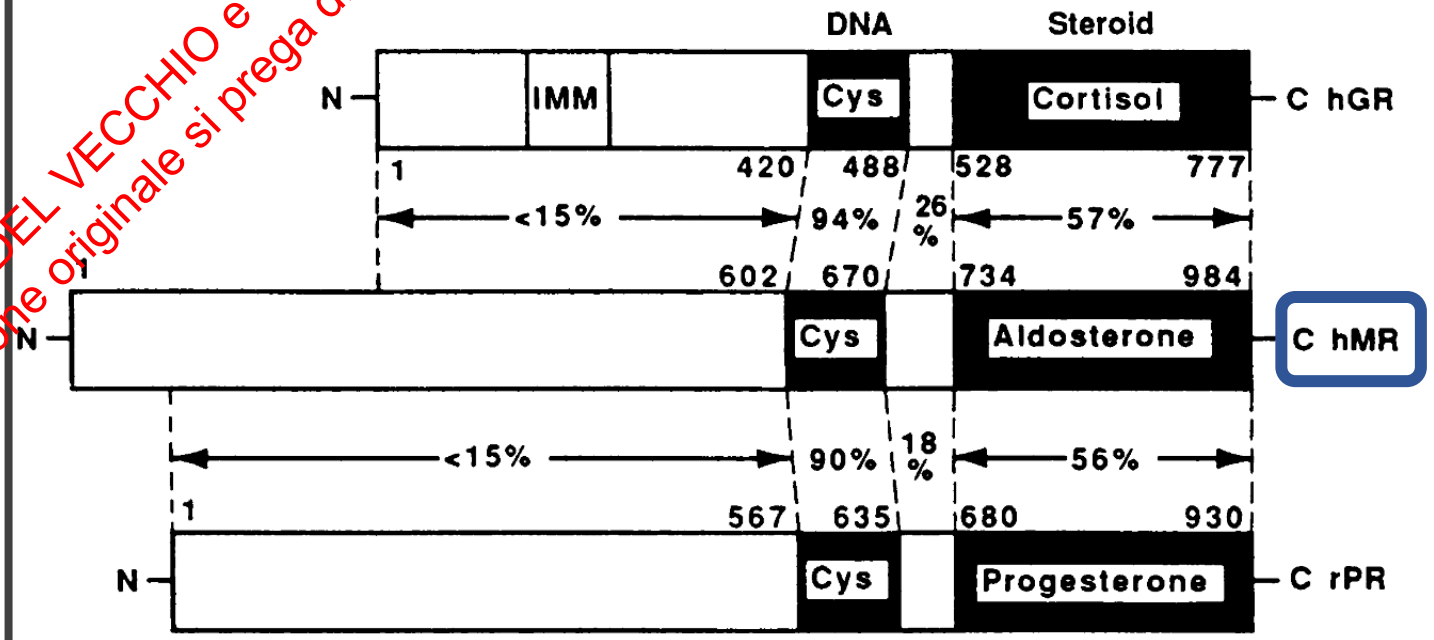
JEFFREY L. ARRIZA, CARY WEINBERGER,* GAIL CERELLI, TOM M. GLASER, BARBARA L. HANDELIN, DAVID E. HOUSMAN, RONALD M. EVANS



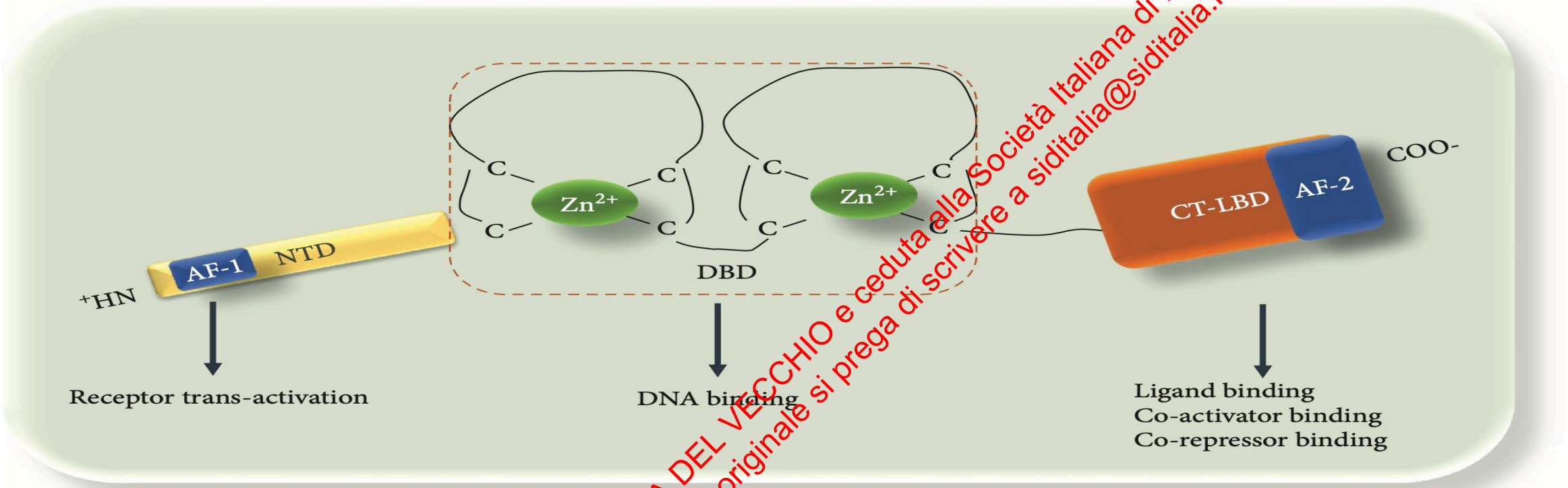
17 JULY
Volume 237 | Issue 4812

1987

- **Extensive amino acid sequence identity in the presumptive steroid-binding domains of hMR, hGR, and rPR:** similar ligand-binding properties
- The MR binds glucocorticoids with an affinity equal to that for aldosterone
- Only in tissues additional mechanisms confer selective response to aldosterone



STRUCTURE OF THE MINERALCORTICOID RECEPTOR



An amino-terminus domain (NTD), which contains a NH2-terminal ligand-independent transcriptional activation (AF-1) and contributes to transactivation of other receptors

A central cysteine-rich DNA-binding domain (DBD), which contains two zinc fingers (ZFs

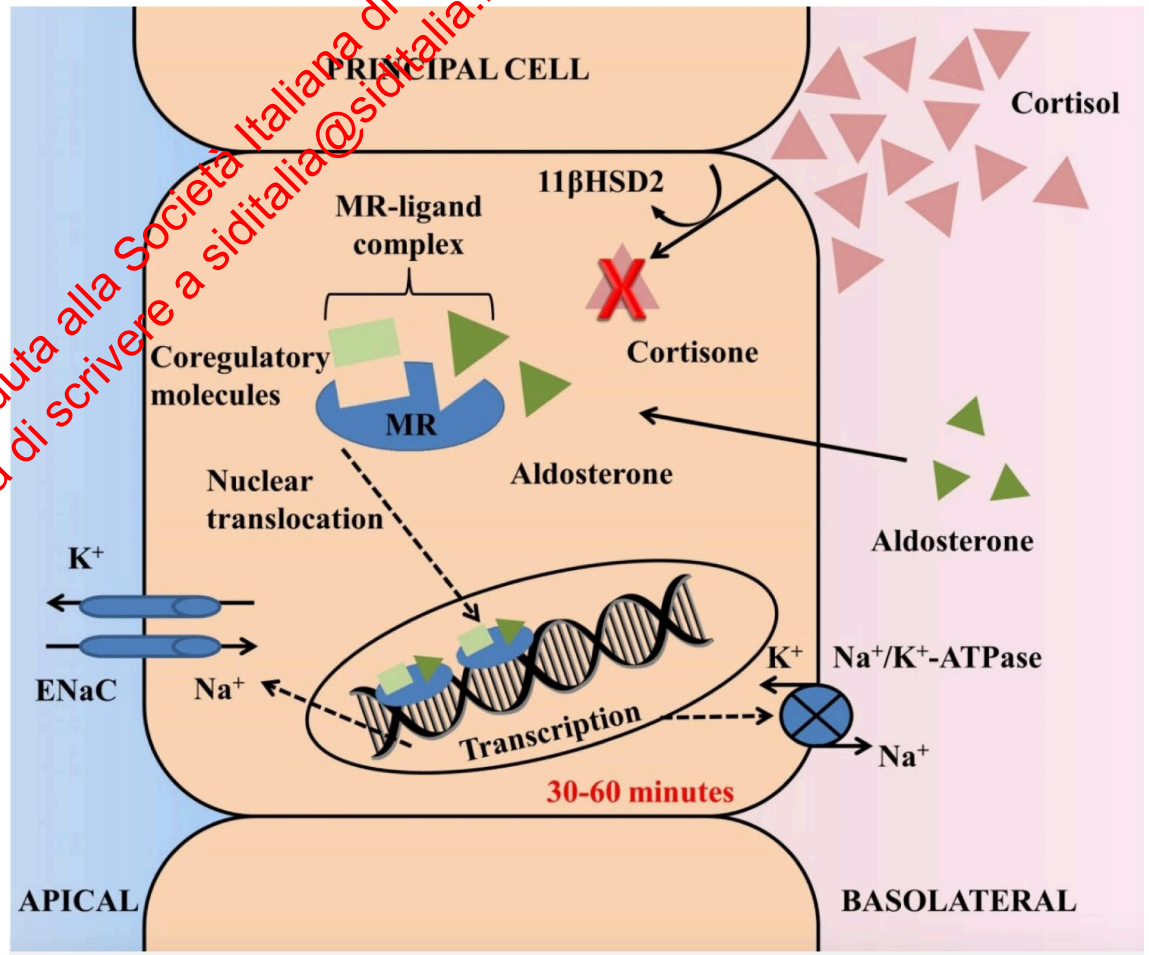
A carboxy-terminal- (CT-) ligand-binding domain (CT-LBD) which contains an activation function 2 domain (AF-2), which is crucial for ligand and coregulator binding

Cannavo et al. Oxidative Medicine and Cellular Longevity, 2018

ALDOSTERONE FUNCTION

- Major role in the maintenance of sodium, potassium, and acid-base balance through its effects on renal electrolyte excretion.
- Aldosterone-induced stimulation of:
  - Na^+ absorption
  - K^+ secretion
  - H^+ secretion by the distal nephron, particularly segments of the collecting duct

Classical actions:
Transcription of the epithelial sodium channel (**ENaC**), Cl^-/HCO_3^- exchangers and ROMK channels



11beta-hydroxysteroid dehydrogenase type 2

ALDOSTERONE: GENOMIC AND NON-GENOMIC EFFECTS

Genomic response

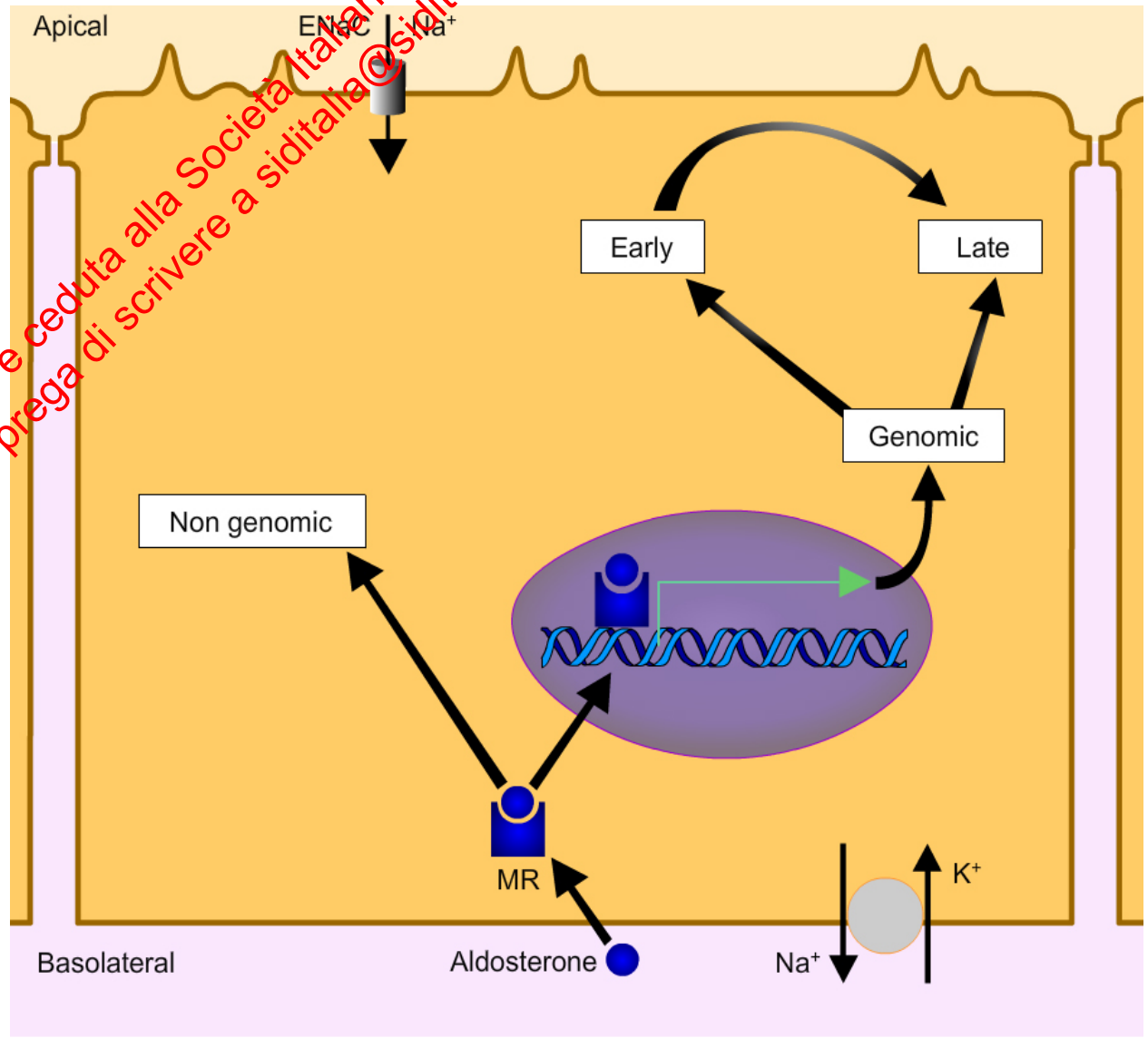
Classical steps of cell membrane diffusion:

- Binding to the MR in the cytoplasm
- Translocation to the nucleus and activation of gene transcription
- Increase of ENaC concentration in epithelial cells (i.e., distal tubule, colon)

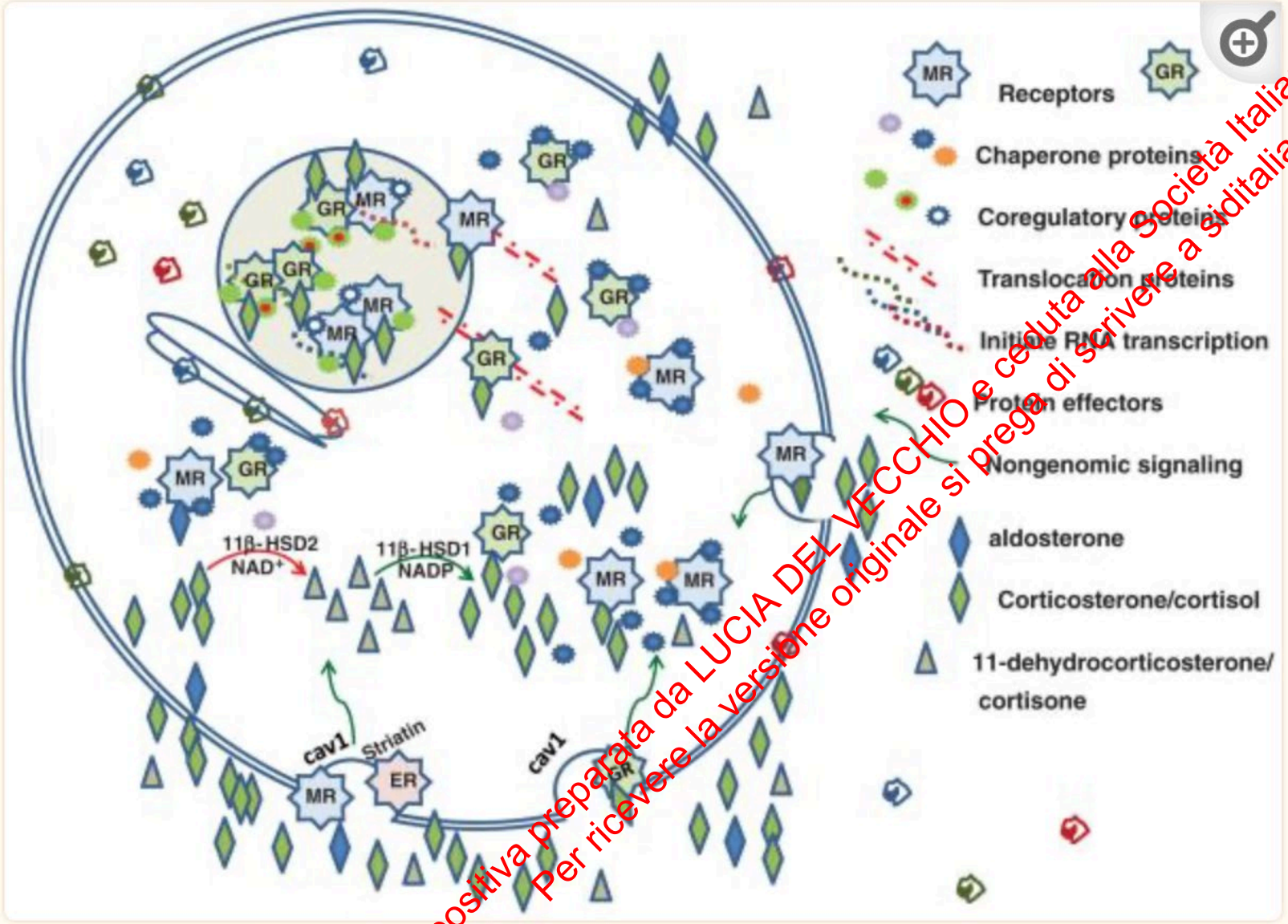
Non-genomic response

Rapid effects not explained by the traditional pathway and not blocked by inhibition of the transcriptional process molecules (actinomycin D and aldosterone blockers)

- Enhanced activity of the Na^+-K^+-$2Cl^-$ cotransporter and Na^+-K^+-ATPase in the heart
- Enhanced activity of Na^+-H^+ antiporter, ENaC and Na^+-K^+-ATPase in the kidney
- Connected to subcellular trafficking



CHAPERONE AND SCAFFOLDING PROTEINS



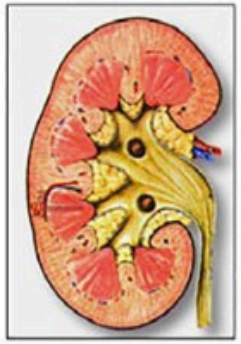
- MR and GR reside primarily in the cytoplasm bound to chaperone and scaffolding proteins when not bound to an agonist
- These proteins facilitate posttranslational modification of the receptors (phosphorylation), ligand binding, and attachment to the mechanism that shuttles the receptors between the cytoplasm and nucleus
- Scaffolding proteins are also associated with rapid nonnuclear effects.

Heat shock proteins 90 and 70 and immunophylins

Gomez-Sanchez E and Celso E. Compr Physiol 2014; 4(3): 965–994

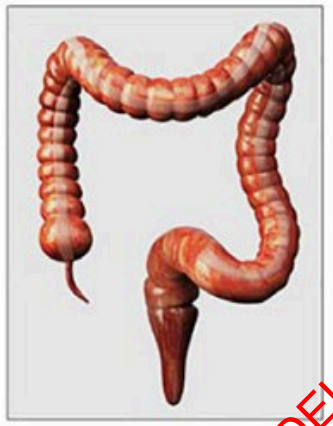
EXPRESSION AND FUNCTIONS OF THE MINERALOCORTICOID RECEPTOR

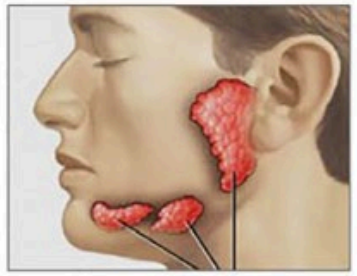
Conventional function



Kidney (distal nephron)

Colon





Salivary glands

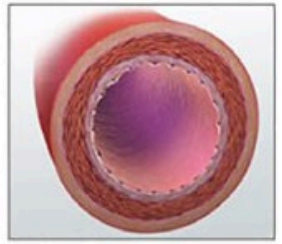
Classical mineralocorticoid function:

Low salt intake ➔ hypovolemia ➔
RAAS activation ➔ aldosterone ➔
MR stimulation ➔ Na reabsorption

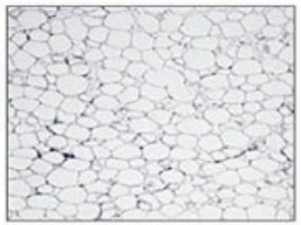
Unconventional functions

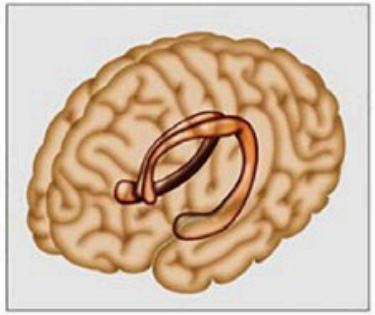
Heart

Blood vessel



Adipose tissue



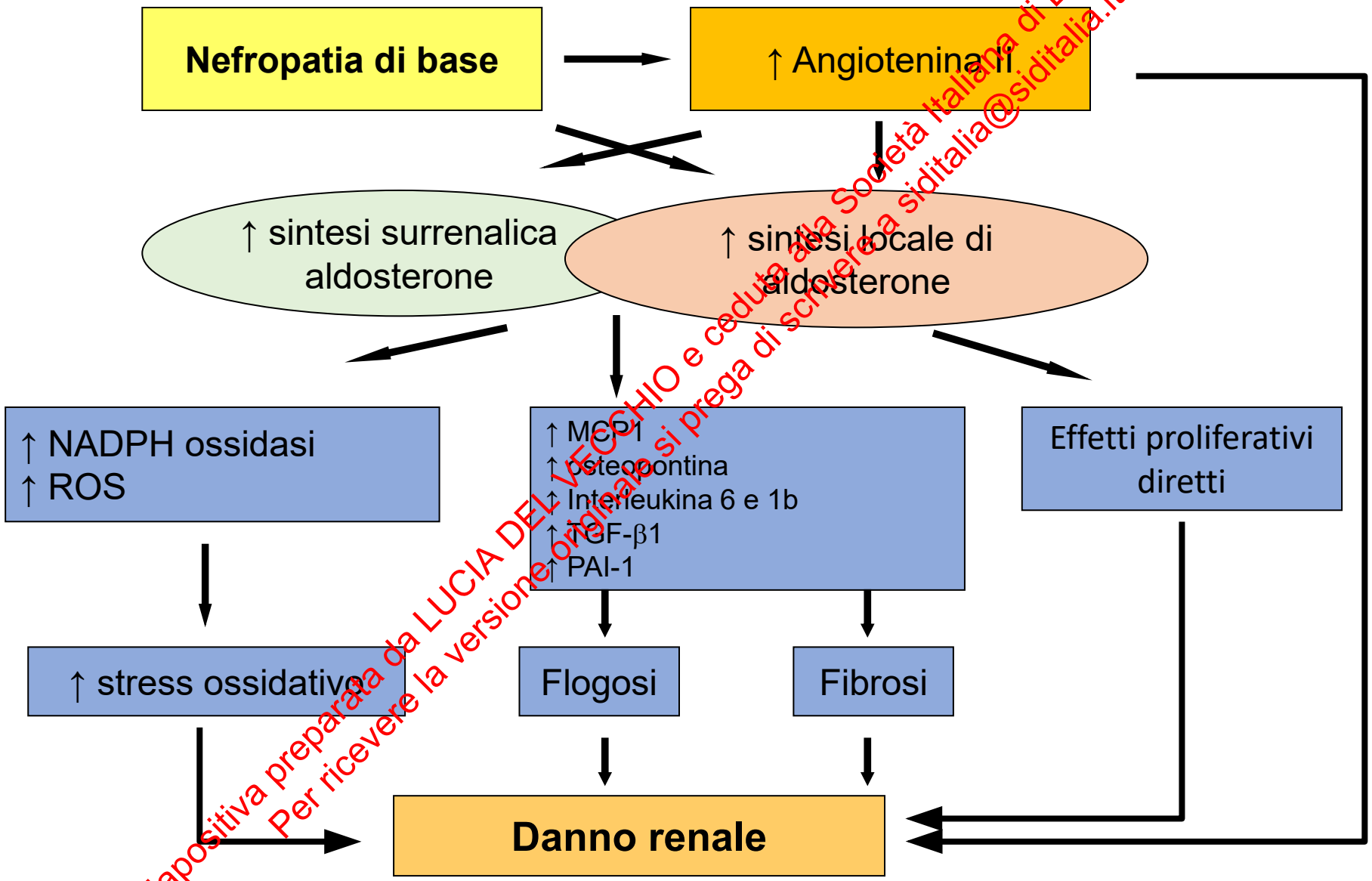


Brain (hippocampus)

Ancestral, multiple functions linked to :
vascular inflammation and fibrosis, adipocyte differentiation, bipolar disorders, stress adaptation, cardiac hypertrophy and **arrhythmias**

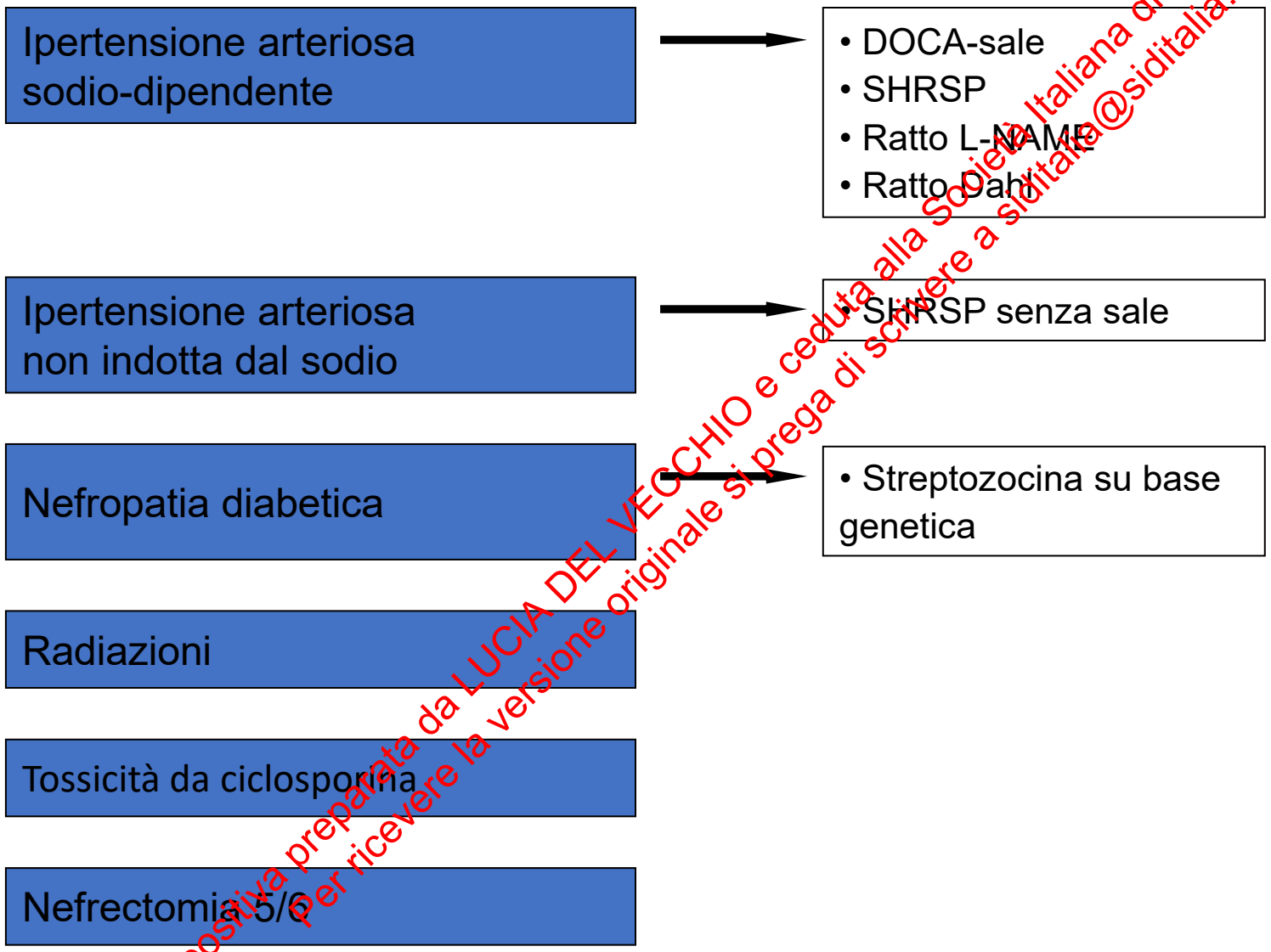
Rossier MF. Front. Endocrinol., 28 June 2021

MECCANISMI PATOGENETICI DEL DANNO RENALE INDOTTO DALL'ALDOSTERONE



Del Vecchio L, Sitia S. G Ital Nefrol 2009;26(3):347-54

Modelli sperimentali di danno renale e aldosterone



Del Vecchio L, Sitia S. G Ital Nefrol 2009;26(3):347-54

JCI The Journal of Clinical Investigation
Scholarly science. Biomedical impact. Free access.
Home Current issue Archive Subscription About the journal

Role of aldosterone in the remnant kidney model in the rat

E L Greene, S Kren, and T H Hostetter

1996 August 15; 98(4): 1063–1068.

SHAM-operated

Untreated remnant rats (REM)

REM rats + losartan and enalapril

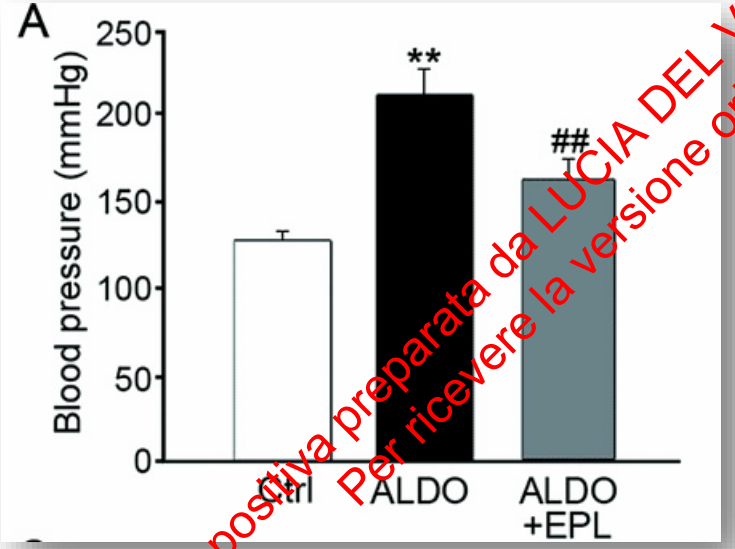
REM AIIA rats infused with exogenous aldosterone

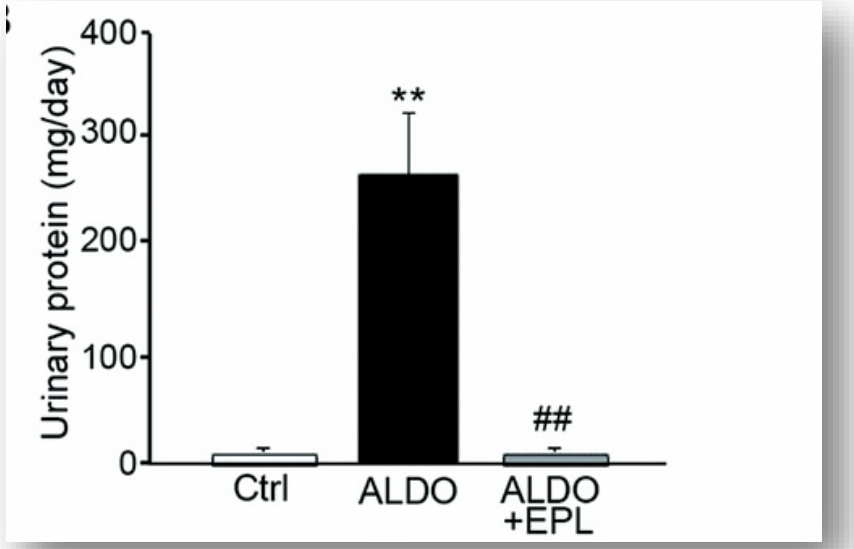
REM AIIA + ALDO rats manifested greater proteinuria, hypertension, and glomerulosclerosis than REM AIIA rats.

Hypertension

Aldosterone and podocyte damage: oxydative stress and Sgk-1

Mononephrectomy
Aldosterone infusion
Hypersodic diet

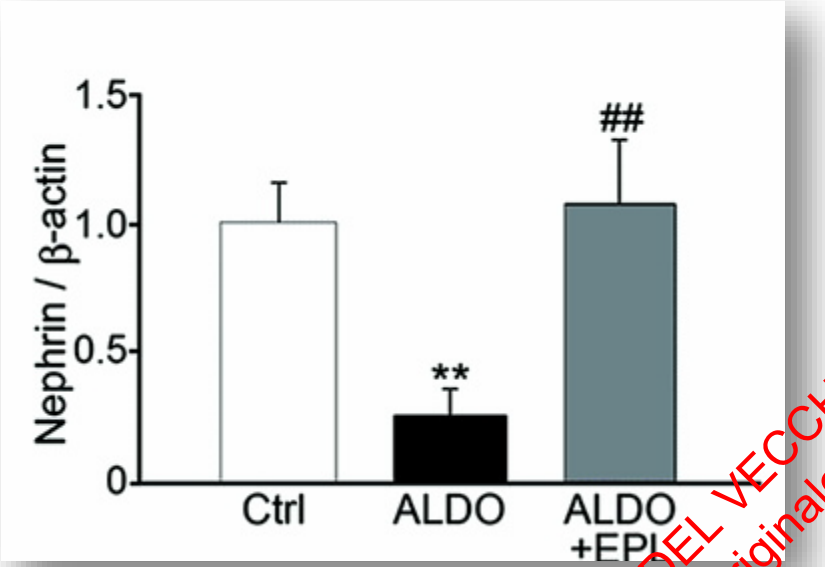


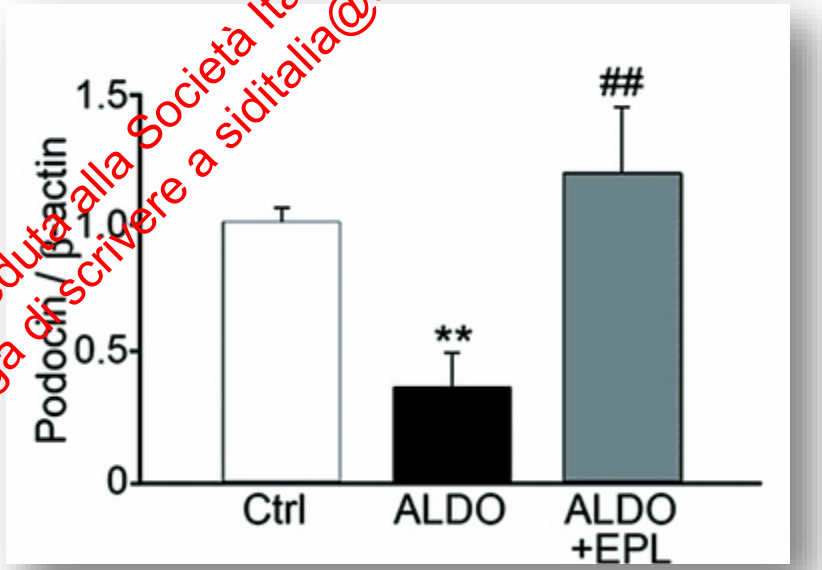


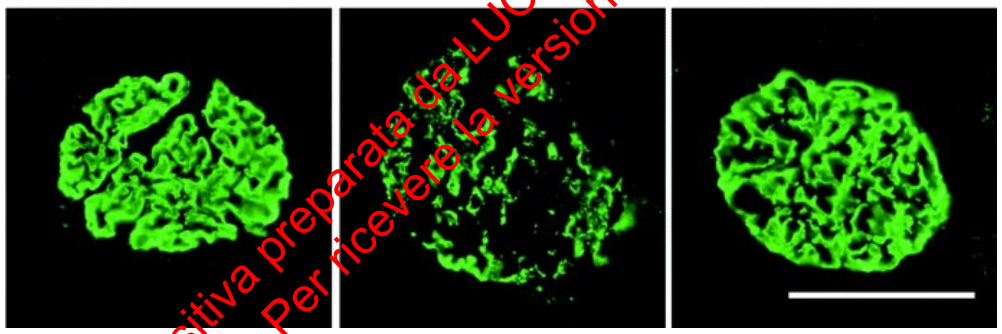
Shibata S et al. Hypertension 2007 Feb;49(2):355-64

Aldosterone and podocyte damage

Nephrin and podocine expression





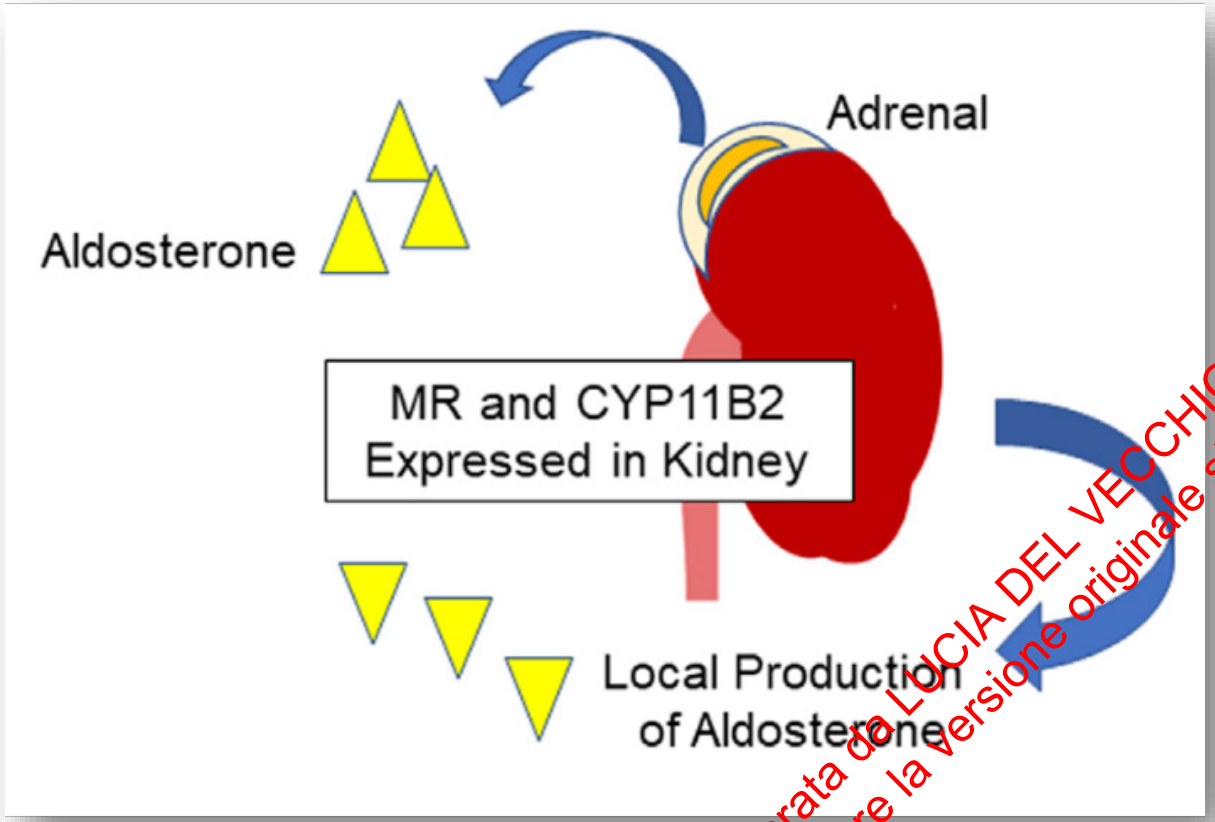


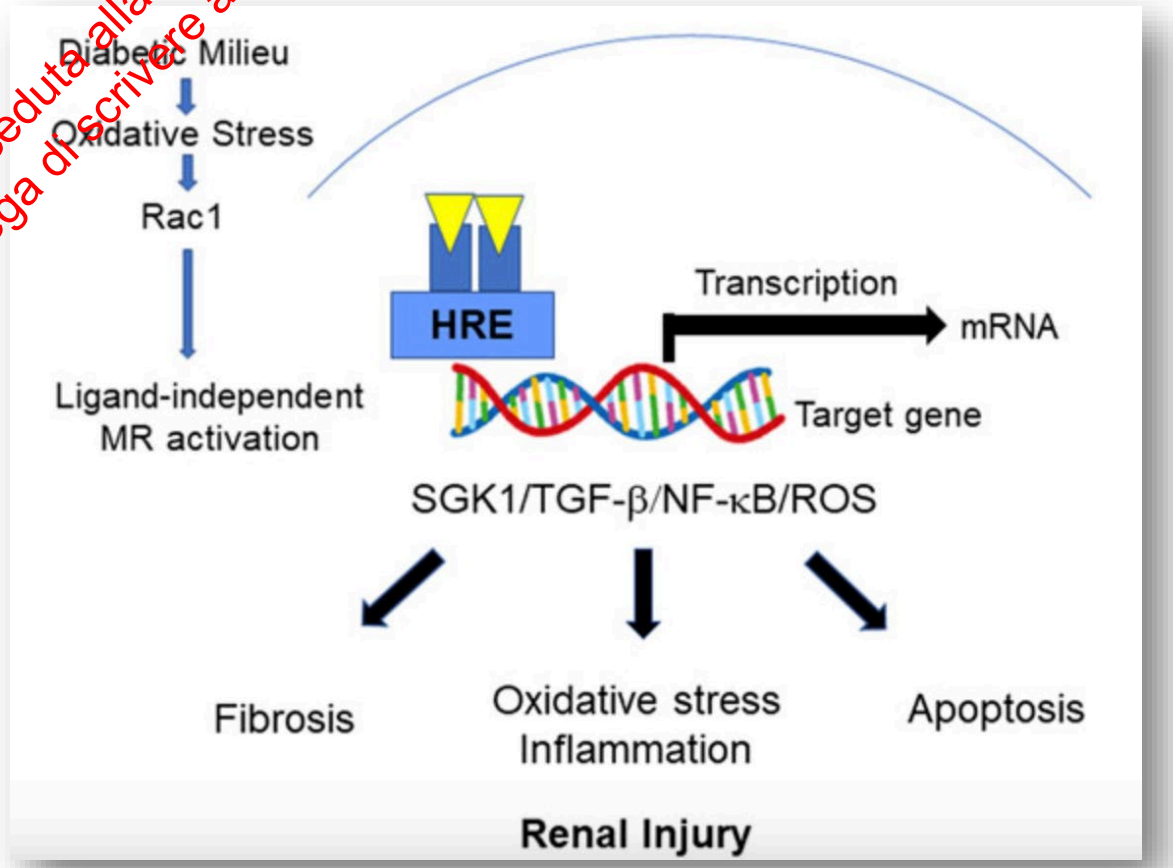
Controls *Aldosterone* *Aldo + Eplerenone*

Nephrin staining

Shibata S et al. Hypertension 2007 Feb;49(2):355-64

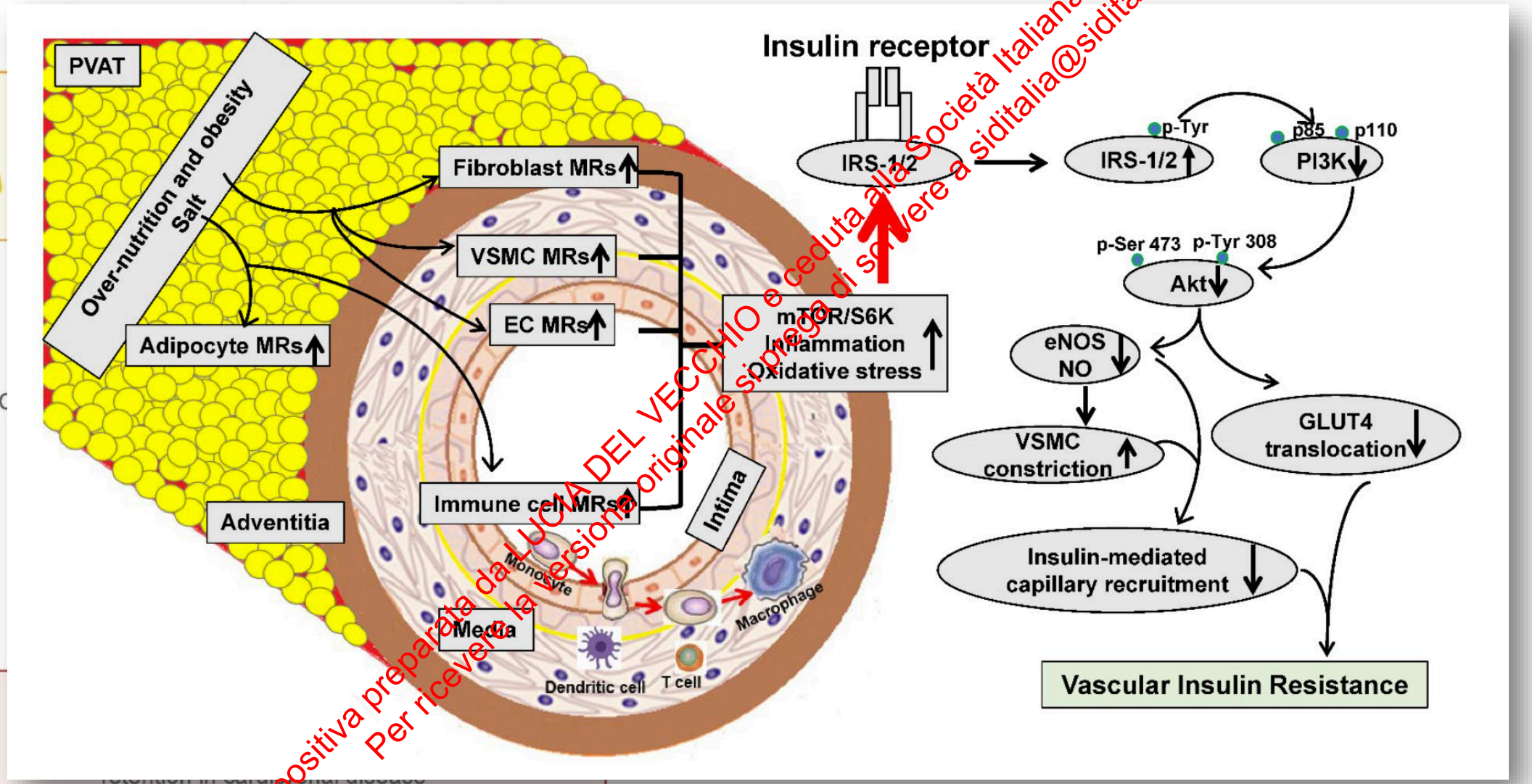
MECCANISMI DI DANNO RENALE INDOTTO DALL'ALDOSTERONE NELLA NEFROPATIA DIABETICA





Kawanami D et al. Front Pharmacol. 2021;12:754239

INAPPROPRIATE MINERALORTICOID RECEPTOR ACTIVATION IN THE PATHOGENESIS OF VASCULAR INSULIN RESISTANCE



Edgar V. Lerma & Daniel J. Wilson, 2022

Int. J. Mol. Sci. **2022**, *23*, 8954

Hypertension
Volume 41, Issue 1, 1 January 2003; Pages 64-68
https://doi.org/10.1161/01.HYP.0000044937.95080.E9

SCIENTIFIC CONTRIBUTIONS

Effectiveness of Aldosterone Blockade in Patier Diabetic Nephropathy

Atsuhisa Sato, Koichi Hayashi, Mitsuhide Naruse, and Takao Saruta

- 45 patients with type 2 diabetes and early nephropathy treated with an ACE inhibitor for 40 weeks
- Overall, aldosterone concentrations did not change after treatment with an ACE inhibitor for 40 weeks
- They eventually increased in 40% (aldosterone escape), and fell in the remaining 60%

TABLE 2. Clinical Data of Patients With or Without Aldosterone Escape

Characteristic	Escape (−)	Escape (+)
No. (men/women)	27 (15/12)	18 (10/8)
Age, y	64±12	61±10
Systolic BP, mm Hg	136±13	135±12
Diastolic BP, mm Hg	84±11	83±10
Heart rate, beats/min	73±3	72±3
Na, mEq/L	142.5±1.8	142.3±1.6
K, mEq/L	4.1±0.3	4.3±0.2
BUN, mg/dL	13.5±1.8	12.8±1.3
Cr, mg/dL	0.88±0.25	0.90±0.20
UAE, mg/g Cr	119±95	368±142*
PRA, ng/mL per hour	3.98±1.66	3.15±1.58
PAC, pg/mL	53.2±15.1	112.0±18.7*
HbA1c	7.2±0.4	7.1±0.3
Urinary sodium excretion, mEq/d	158±33	149±34
Urinary potassium excretion, mEq/d	44±8	42±10

All values are mean±SD. (−) indicates group without aldosterone escape; (+), group with aldosterone escape.
*P< 0.05 vs the value in the group without aldosterone escape.

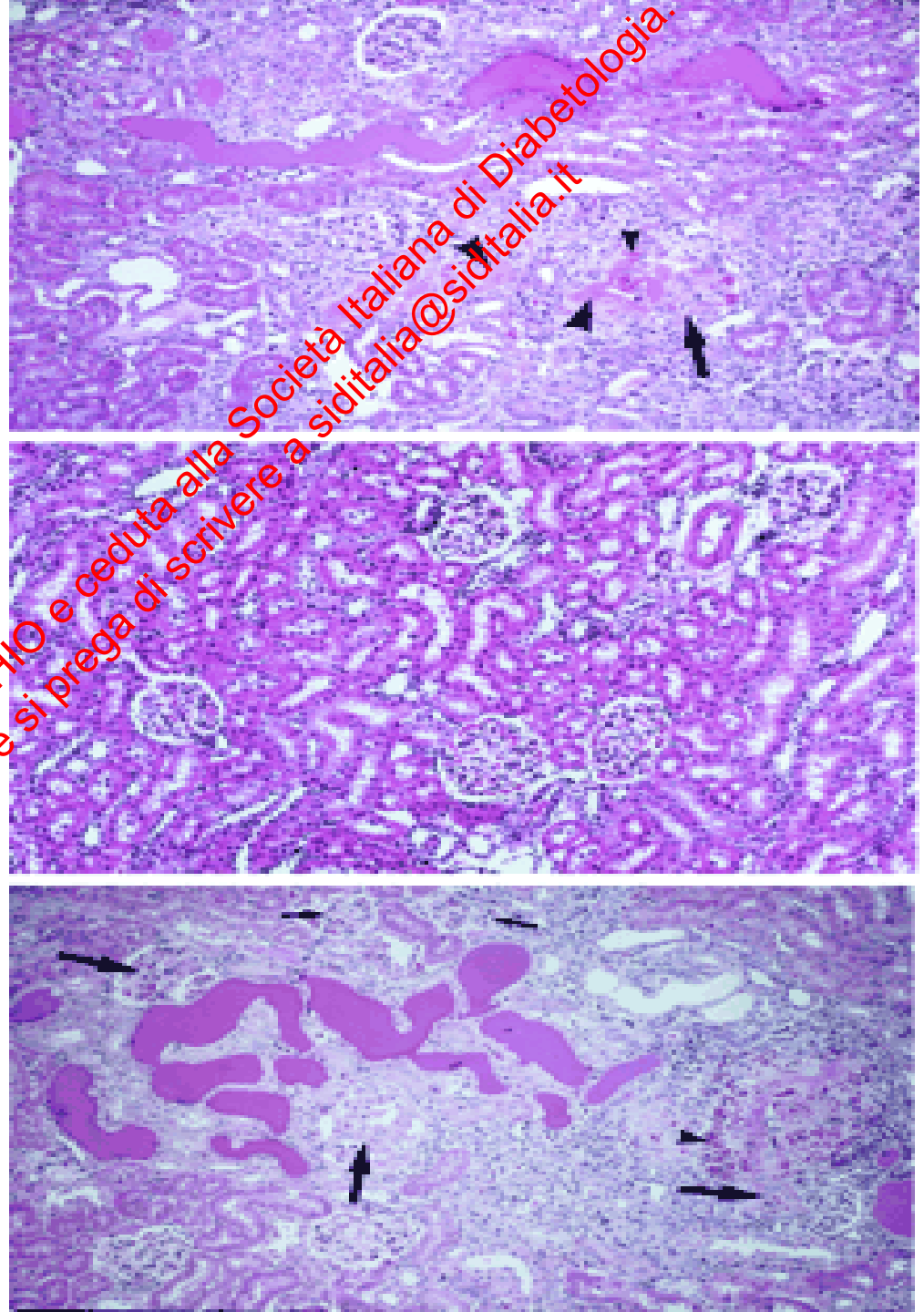
ALDO- induced renal injury (Rocha et al, *Hypertension* 1999)

Stroke-prone spontaneously hypertensive rat model

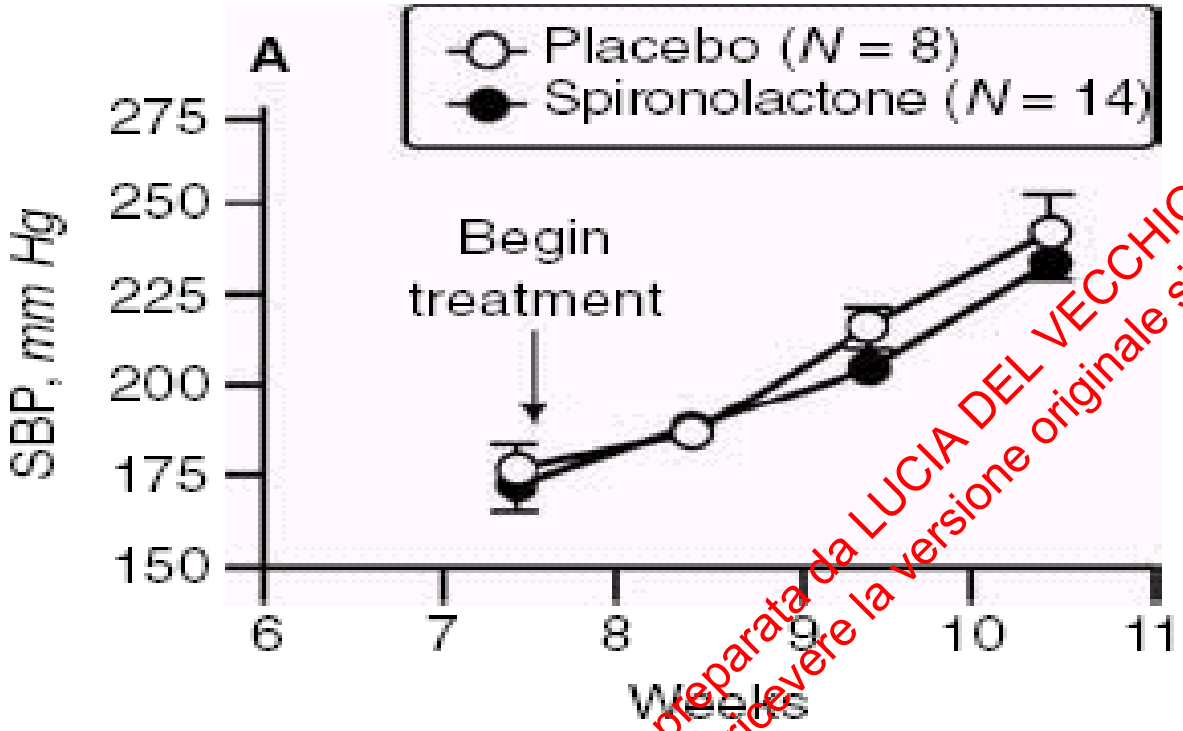
A. vehicle

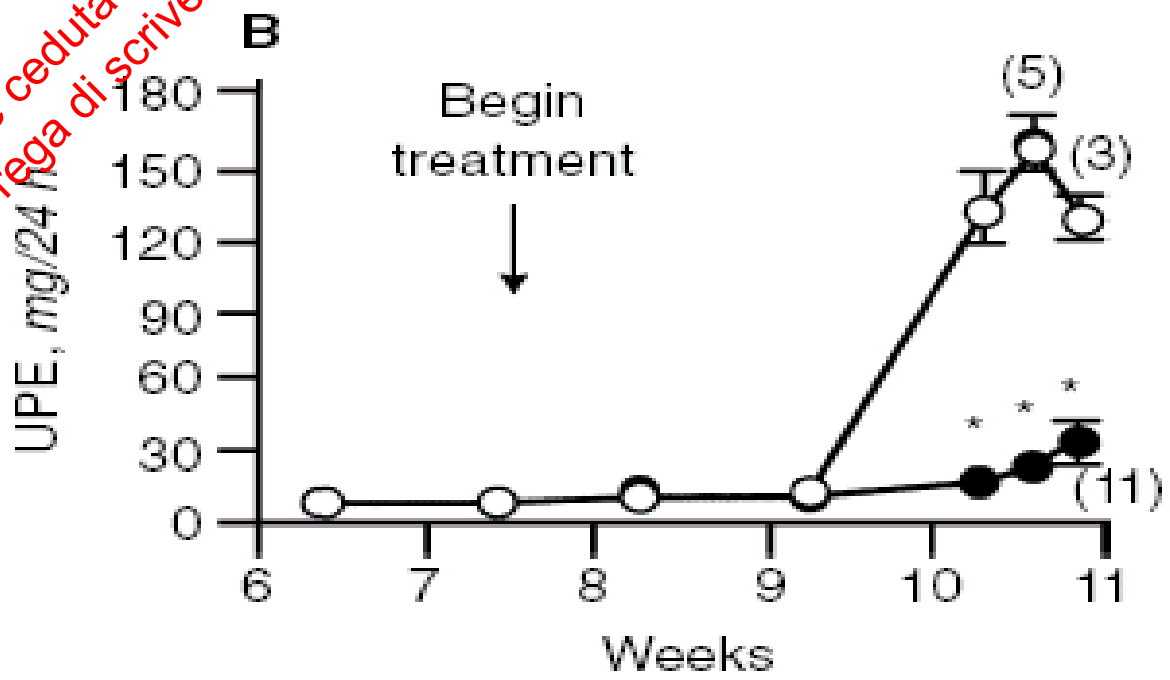
B. vehicle + CAPTO

C. vehicle + CAPTO +ALDO



Spironolactone and proteinuria
Rocha et al, *Hypertension* 1999





CORRESPONDENCE

Spironolactone in Addition to ACE Inhibition to Reduce Proteinuria in Patients with Chronic Renal Disease

The NEW ENGLAND JOURNAL of MEDICINE

September 20, 2001
N Engl J Med 2001; 345:925-926
DOI: 10.1056/NEJM200109203451215

Anastasia Chrysostomou, B.M., B.S.
Gavin Becker, M.D., M.B., B.S.
Royal Melbourne Hospital, Parkville 3052, Australia

TO THE EDITOR:

- ✓ Over the past 12 months, we studied eight patients with various renal diseases and persistent proteinuria (>1 g/day), despite treatment with enalapril for more than 12 months
- ✓ Spironolactone (25 mg/day) was added to the medication, and protein excretion was measured 4 weeks later
- ✓ After treatment, there was a 54% reduction in protein excretion (from 3.81±2.50 to 1.73±1.02 g/day)

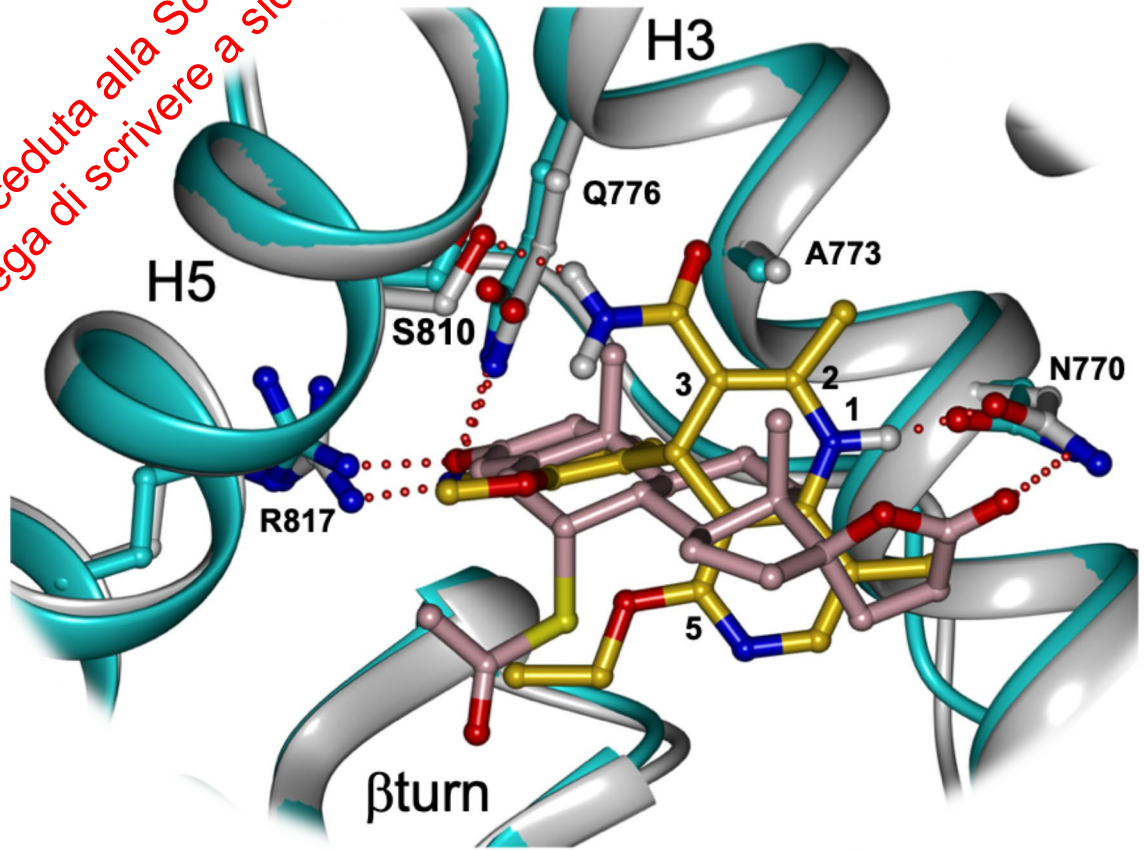
FINERENONE

- Finerenone is a selective, nonsteroidal MR antagonist
- Developed to reduce the risk of sustained eGFR decline, ESKD, infarction, and HHF in patients with CKD associated with T2D

CHEMICAL NAME:

(4S)-4-(4-cyano- 2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro- 1,6-naphthyridine-3-carboxamide)

Accommodation mode of finerenone within the MR ligand-binding pocket



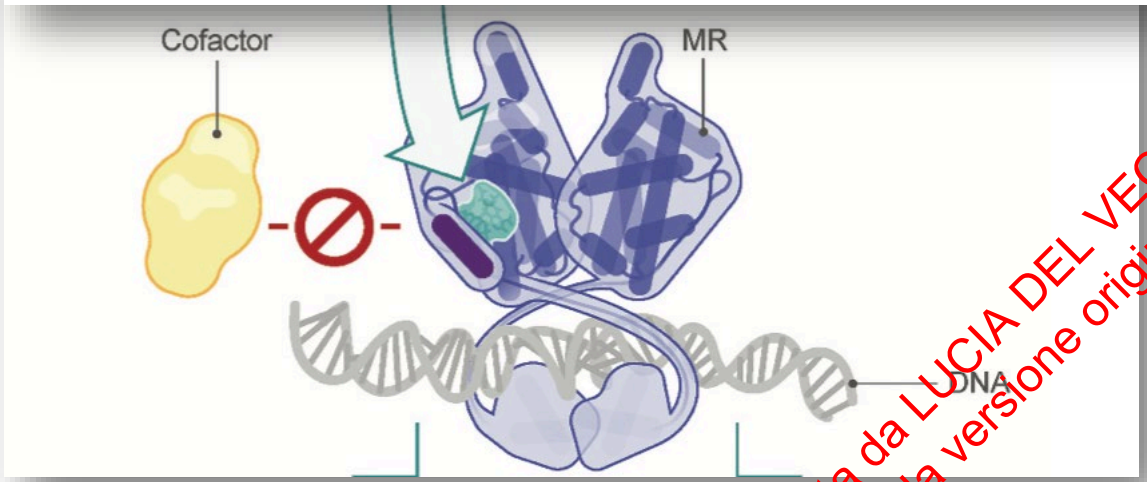
Amazit

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 290, NO. 36, pp. 21876–21889, September 4, 2015

Finerenone Impedes Aldosterone-dependent Nuclear Import of the Mineralocorticoid Receptor and Prevents Genomic Recruitment of Steroid Receptor Coactivator-1*

Received for publication, April 10, 2015, and in revised form, July 16, 2015 Published, JBC Papers in Press, July 22, 2015, DOI 10.1074/jbc.M115.657957

Larbi Amazit[‡§¶1], **Florian Le Billan**[‡§1,2], **Peter Kolkhof**[‖], **Khadija Lamribet**[‡§], **Say Viengchareun**[‡§], **Michel R. Fay**[**‡‡], **Junaid A. Khan**[‡§3], **Alexander Hillisch**[§§], **Marc Lombès**[‡§], **Marie-Edith Rafestin-Oblin**[**‡‡], **and Jérôme Fagart**[‡§**‡‡4]

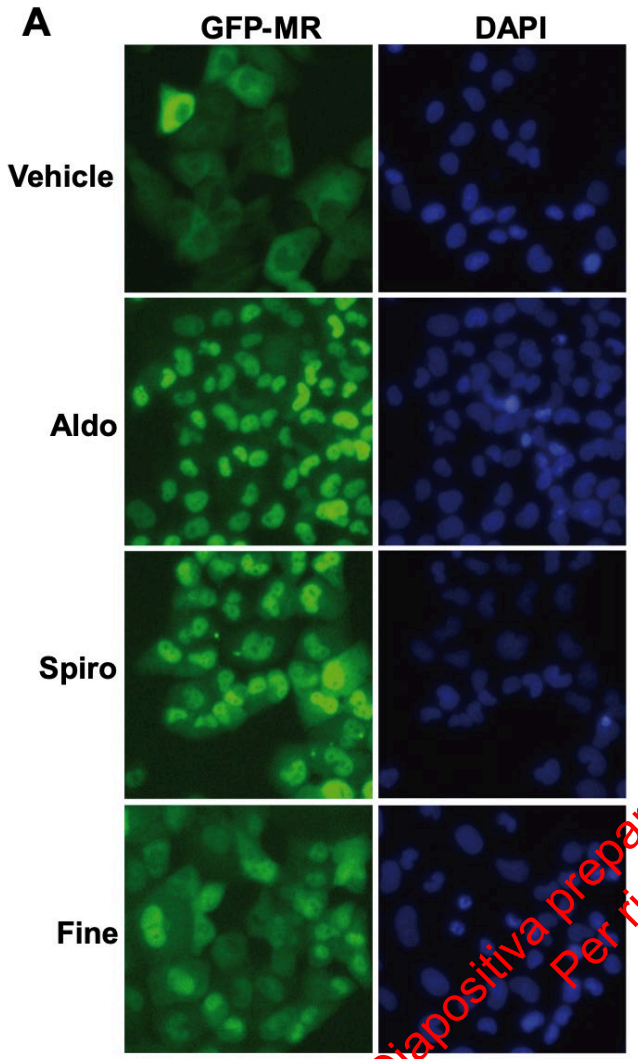


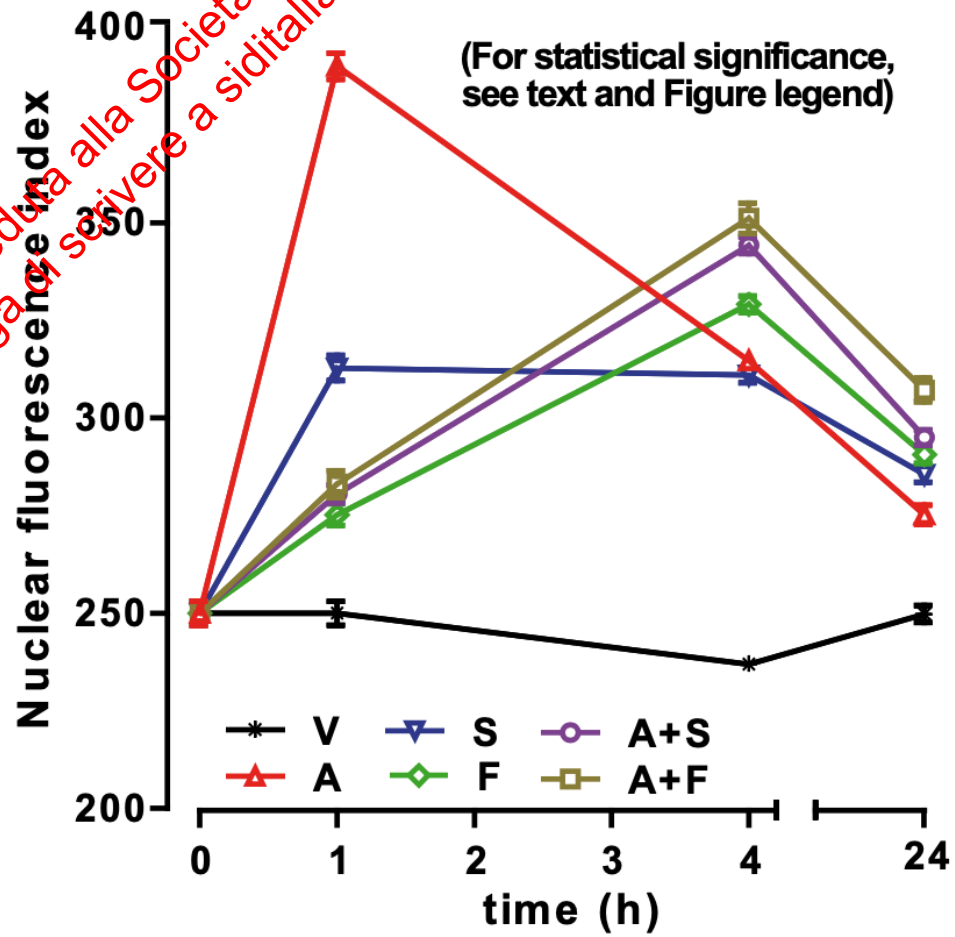
Edgar V. Lerma & Daniel J. Wilson, 2022

- Finerenone blocks the MR as a bulky, passive antagonist
- This mechanism is distinct from steroid-MRAs, which might impact its differential clinical response

*Molecular modeling and mutagenesis approaches allowed identification of **Ser-810 and Asn-773** as **key residues for the high MR selectivity of finerenone***

FINERENONE AND SPIRONOLACTONE DELAY THE LIGAND-INDUCED NUCLEAR TRANSLOCATION OF THE MINERALOCORTICOID RECEPTOR

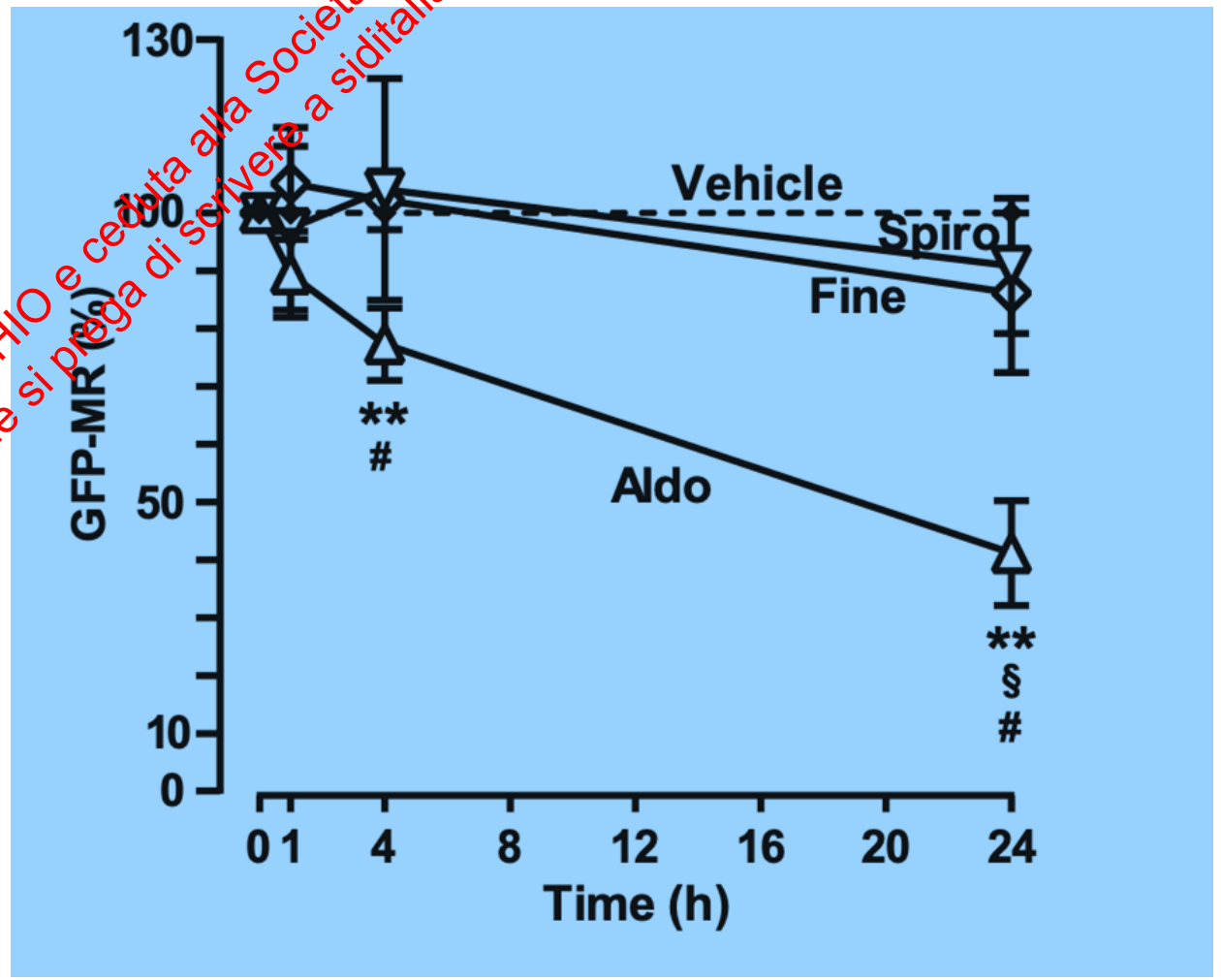




J Biol Chem. 2015 Sep 4;290(36):21876-89

ALDOSTERONE-DEPENDENT DOWN-REGULATION OF THE MINERALOCORTICOID RECEPTOR

- Steroid receptor transcriptional activation is directly coupled to the receptor degradation by the ubiquitin-proteasome pathway.
- Gene transactivation could not occur when the receptor is not down-regulated

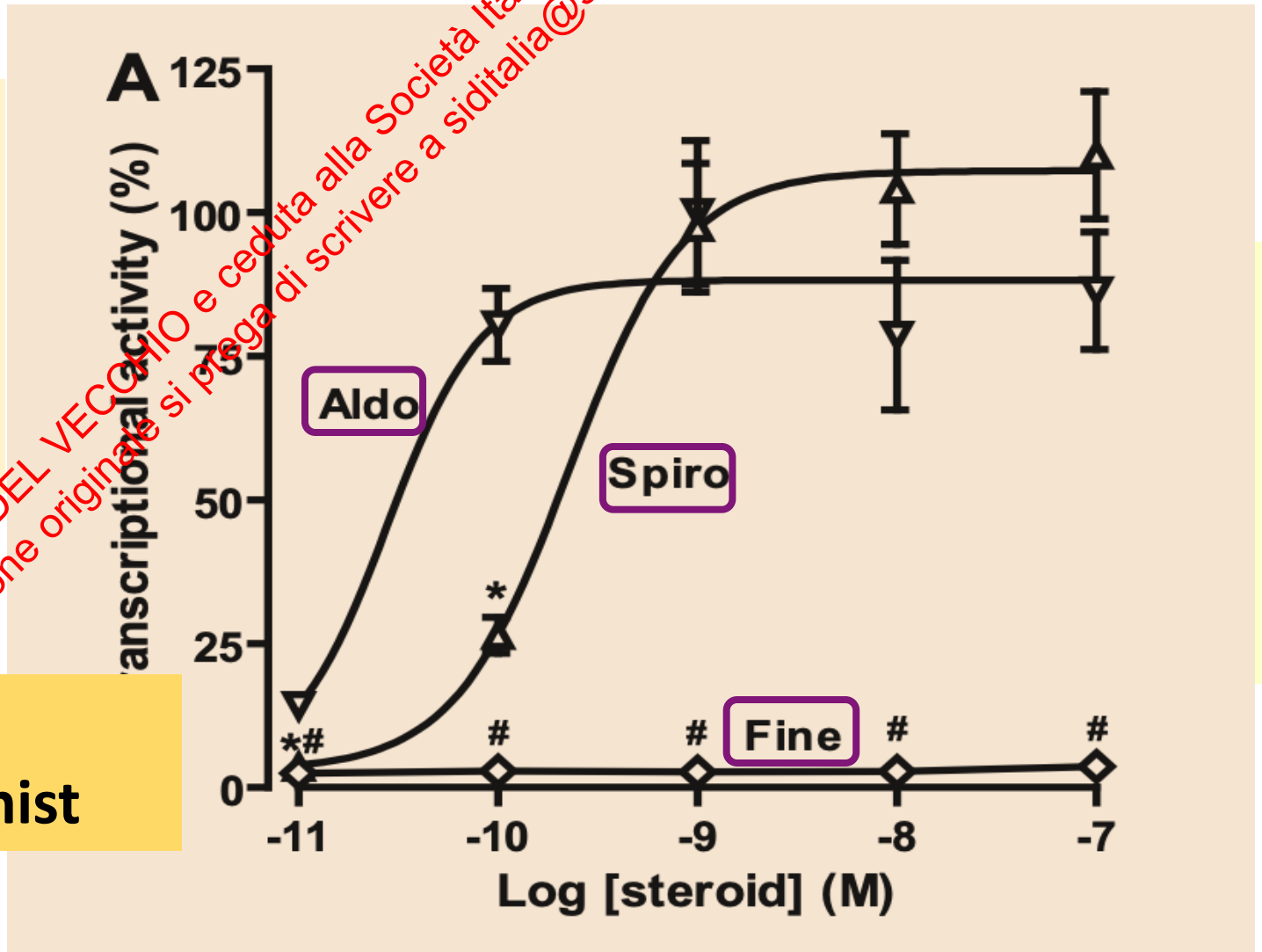


J Biol Chem. 2015 Sep 4;290(36):21876-89

FINERENONE AND SPIRONOLACTONE DIFFERENTIALLY AFFECT RECRUITMENT OF TRANSCRIPTIONAL COFACTORS ON A MINERALOCORTICOID RECEPTOR TARGET PROMOTER

High throughput microscope experiments indicated that finerenone and spironolactone have different effects on MR nuclear translocation kinetics

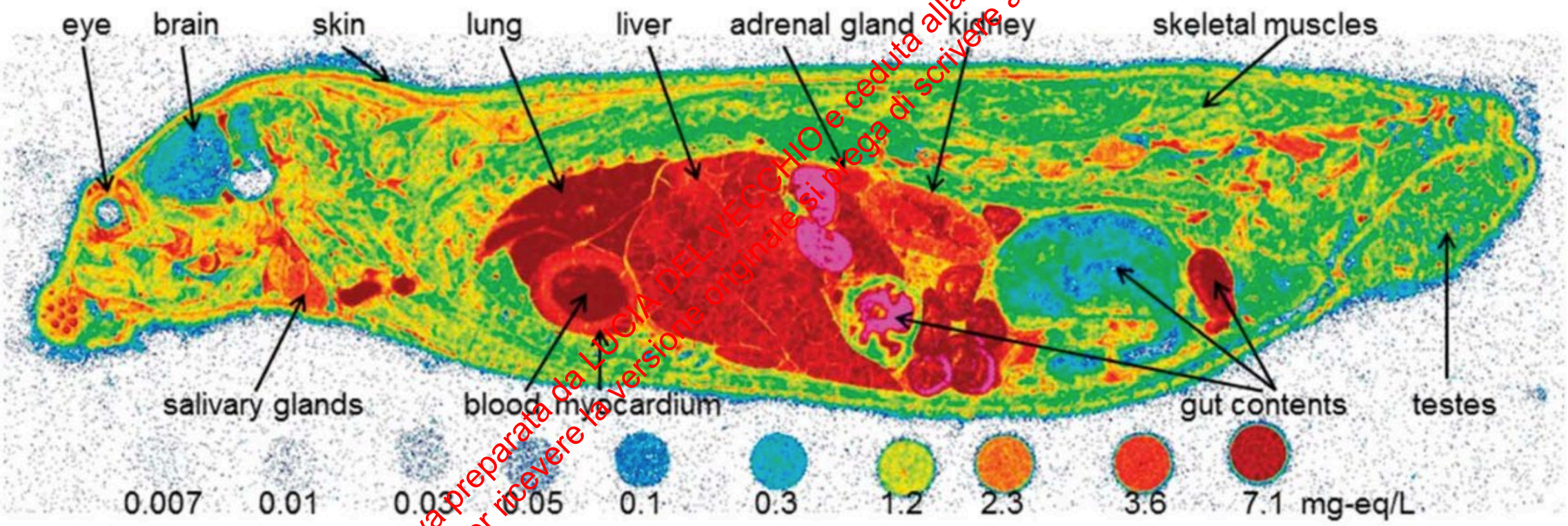
Finerenone acts as an inverse mineralocorticoid receptor agonist



Amazit L et al. J Biol Chem. 2015;290(36):21876-89

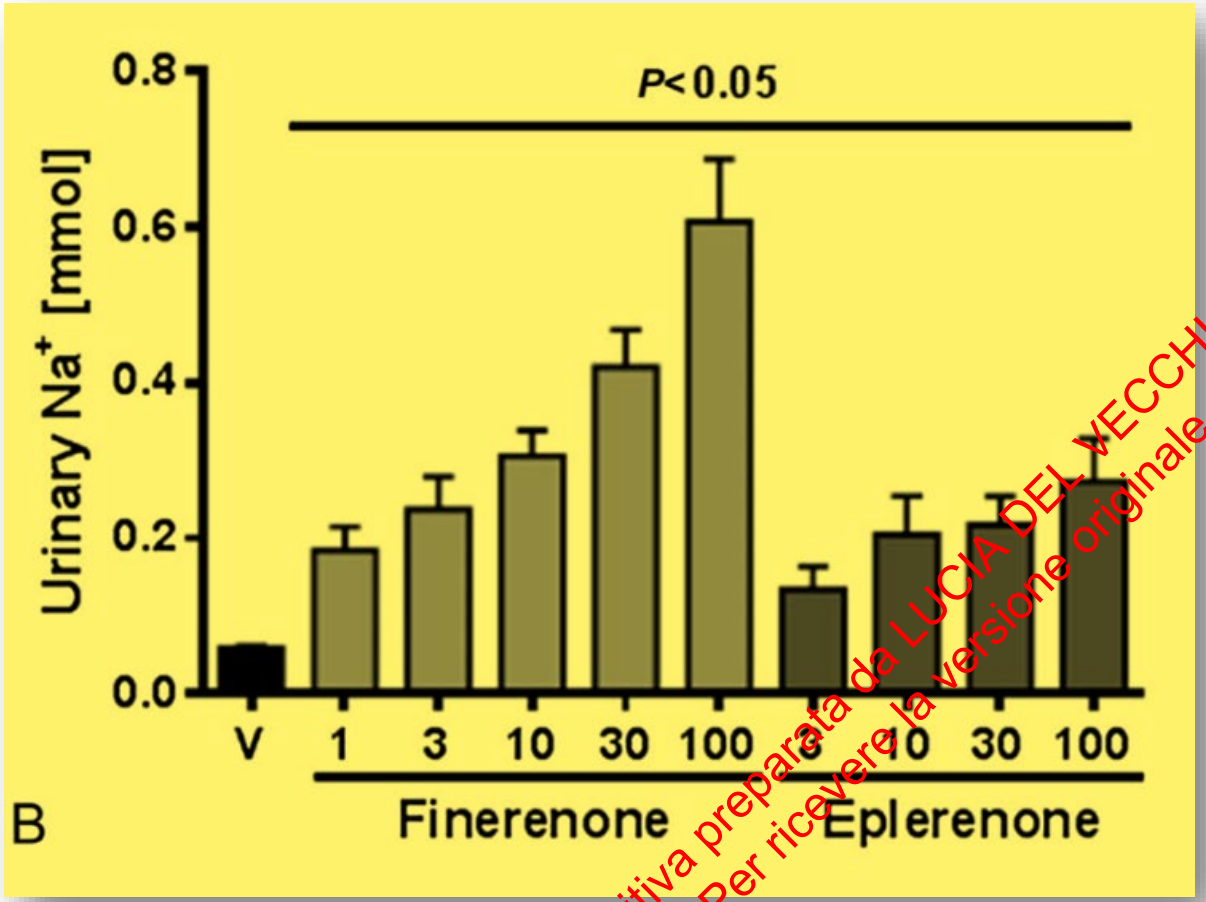
FINERENONE DISTRIBUTES EQUALLY INTO CARDIAC AND RENAL TISSUES

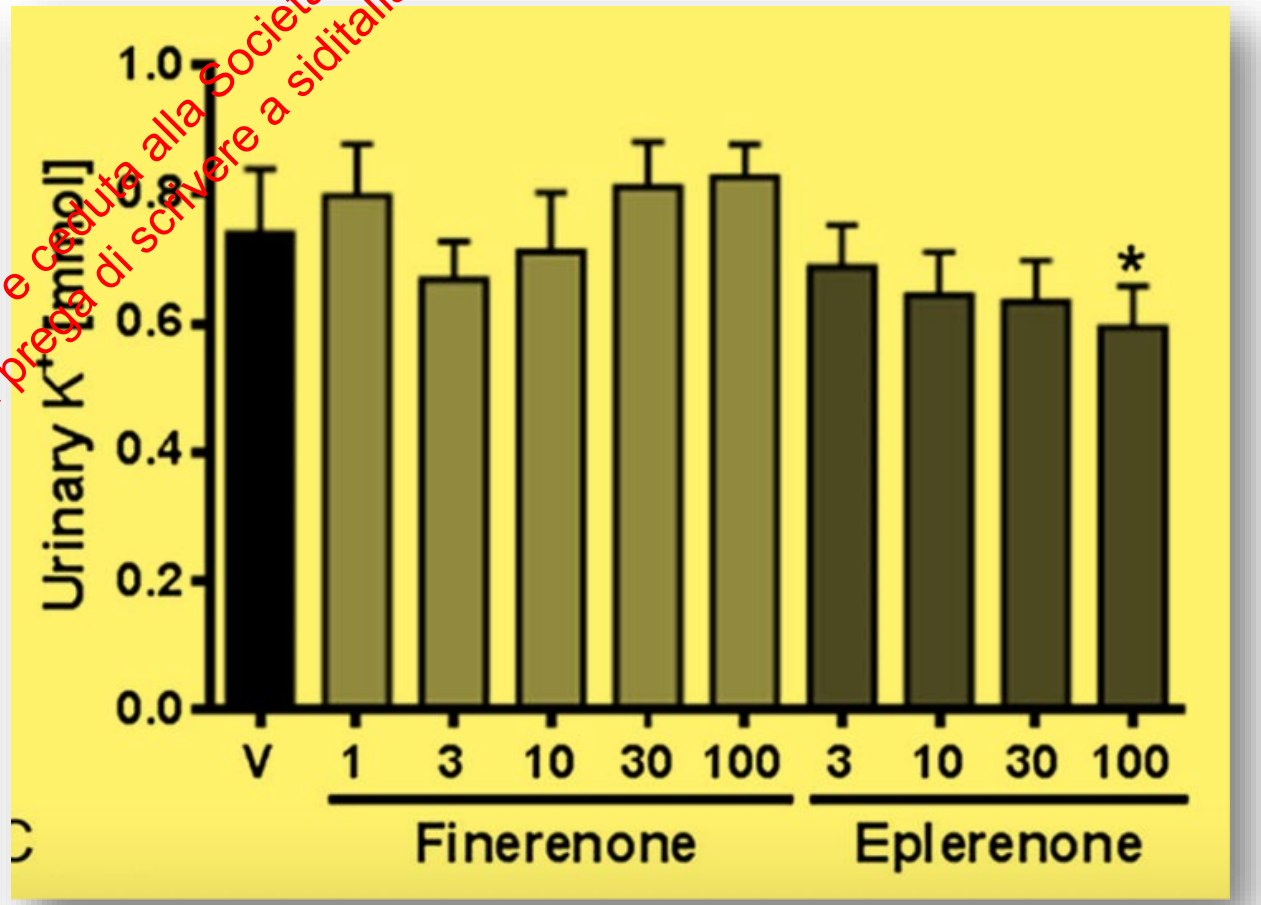
Distribution of radioactivity in a male Wistar rat 1 hour after oral administration of 3 mg/kg [$_{14}$C]- labeled finerenone



Kolkhof et al. J Cardiovasc Pharmacol 2014;64:69–78

DIURETIC EFFECTS OF FINERENONE AND EPLERENONE





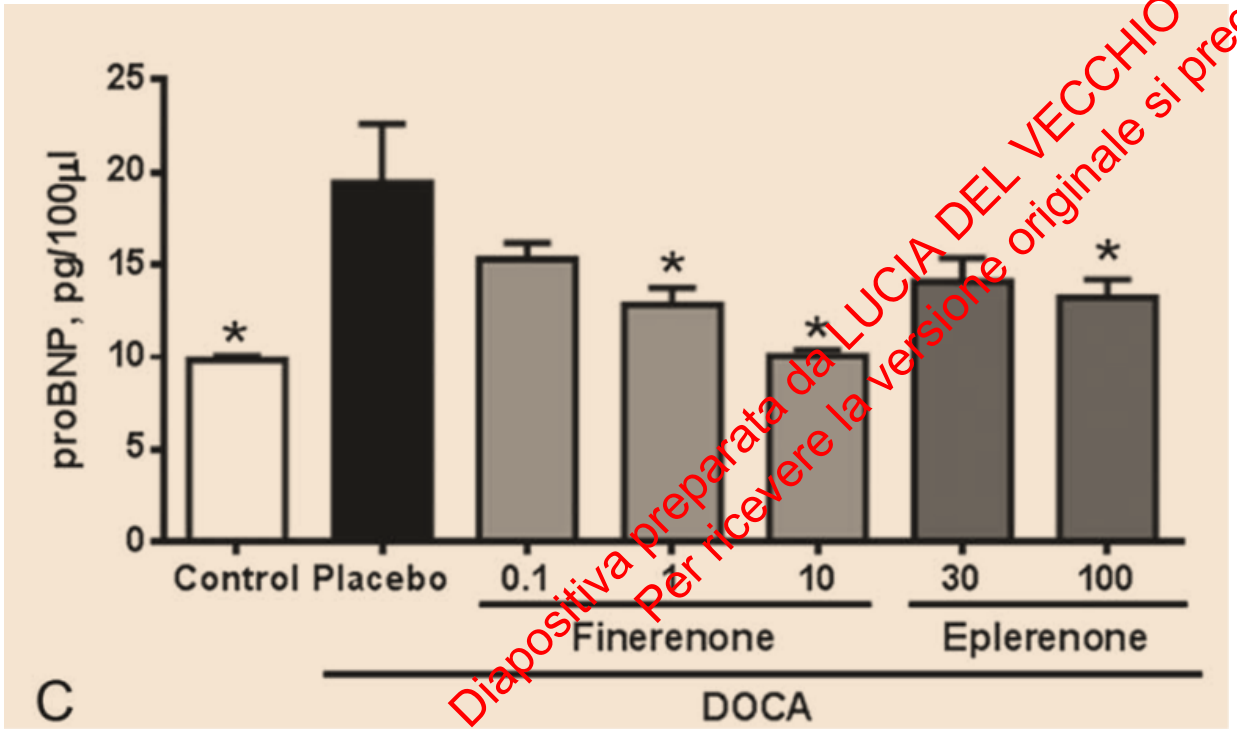
J Cardiovasc Pharmacol 2014;64:69–78

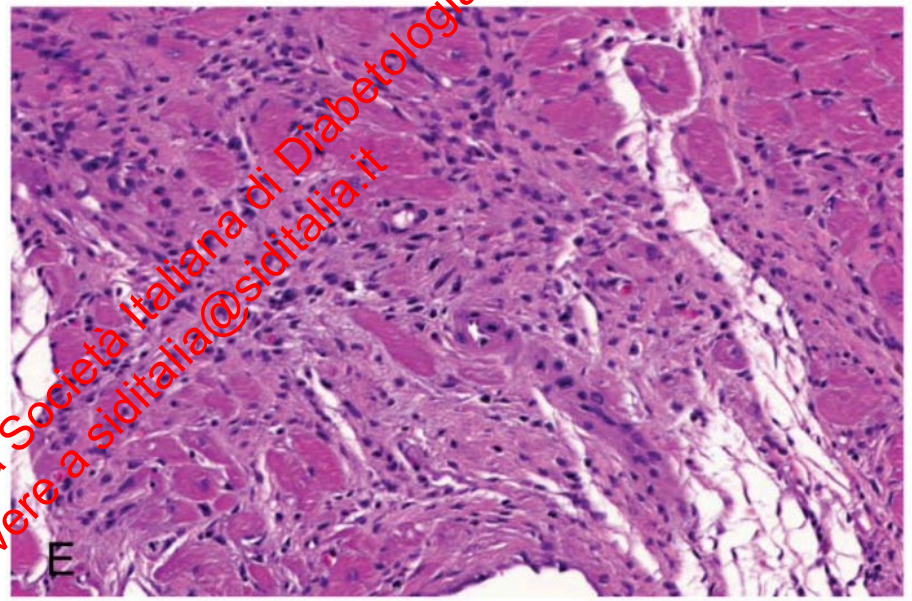
DOCA/salt treatment

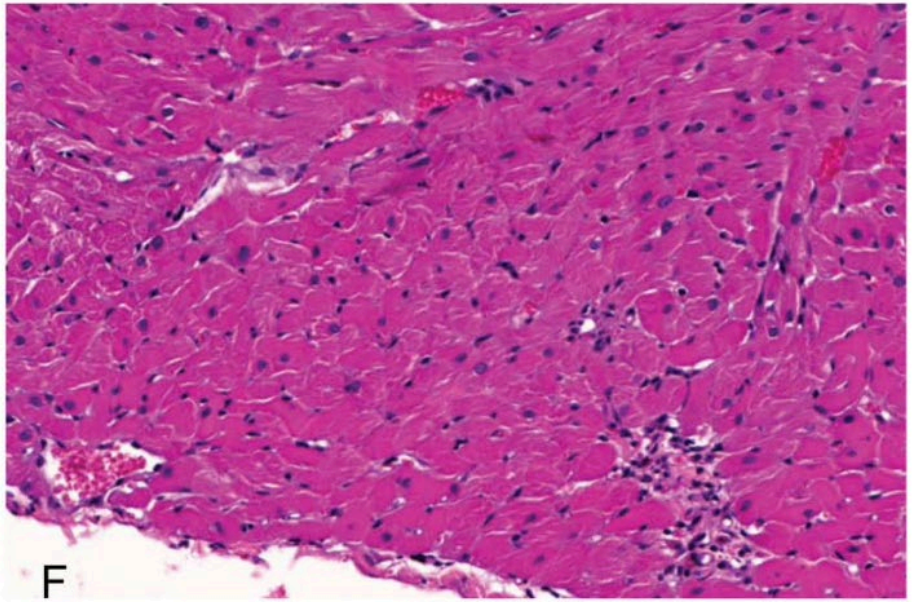
Treatment with 10 mg/kg finerenone

HEART

- Moderate myocardial degeneration
- Fibrosis
- Focal vasculopathy







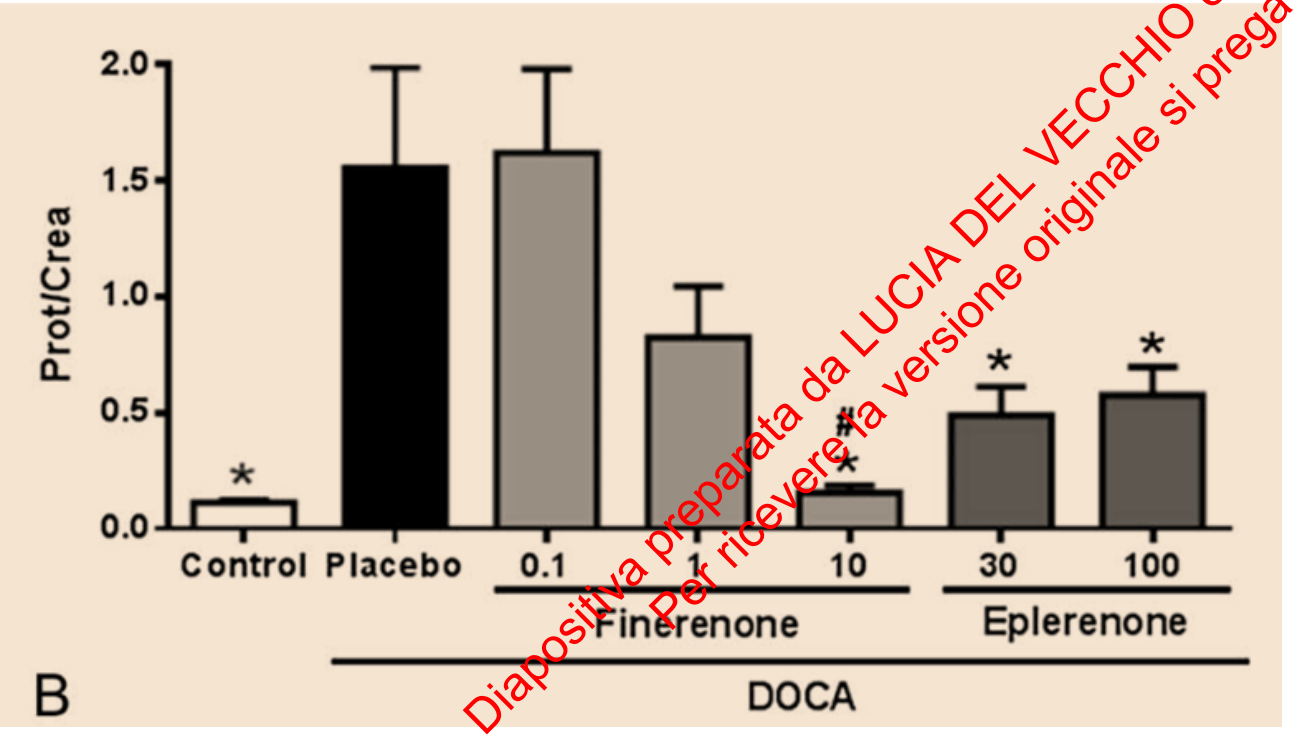
J Cardiovasc Pharmacol 2014;64:69–78

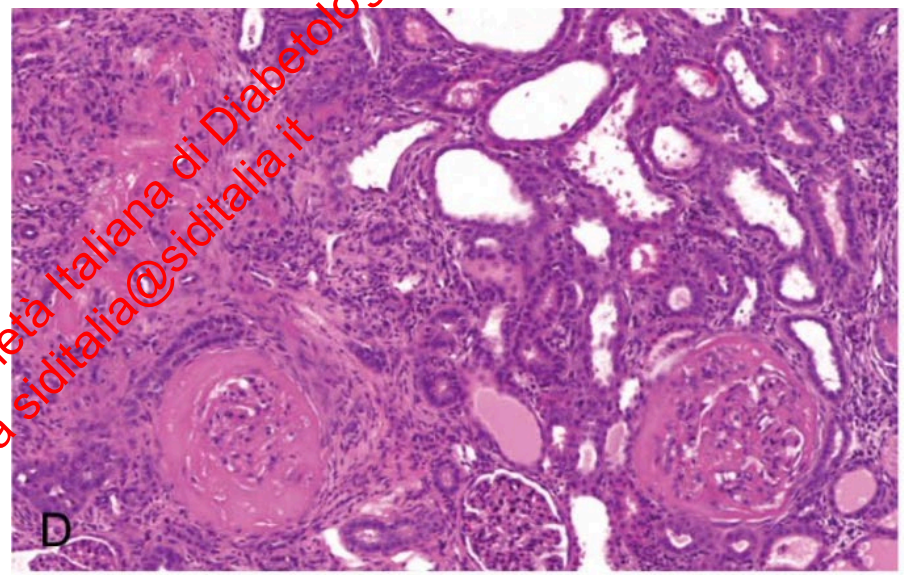
DOCA/salt treatment

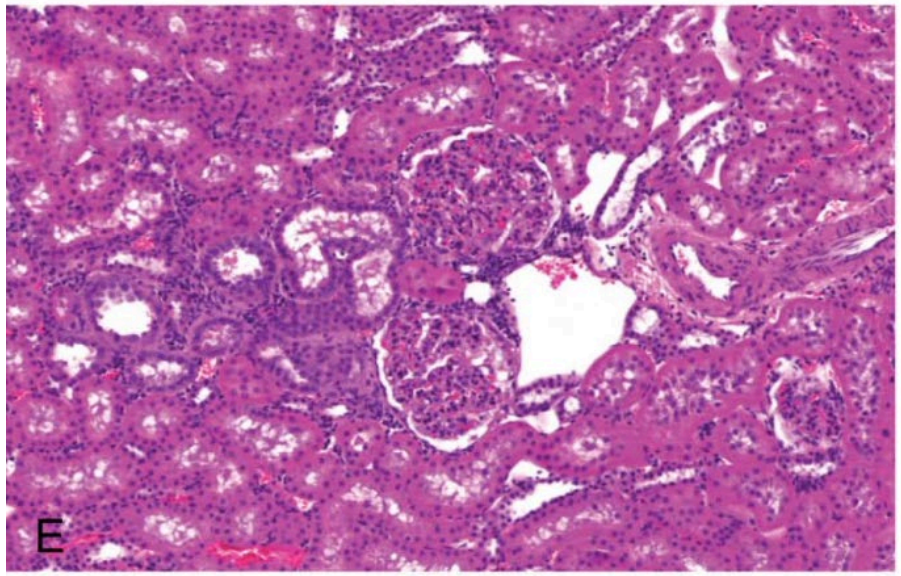
Treatment with 10 mg/kg finerenone

KIDNEY

- ❑ Glomerulopathy
- ❑ Tubular degeneration
- ❑ Vasculopathy







J Cardiovasc Pharmacol 2014;64:69–78

ORIGINAL ARTICLE

Hypertension

Volume 69, Issue 5, May 2017; Pages 870-878

Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone Protects Against Acute Kidney Injury–Mediated Chronic Kidney Disease

Role of Oxidative Stress

Lionel Lattenist, Sebastian M. Lechner, Smail Messaoudi, Alan Le Mercier, Soumaya El Moghrabi, Sonia Prince, Norma A. Bobadilla, Peter Kolkhof, Frédéric Jaisser*, and Jonatan Barrera-Chimal*

Acute stu

18 rats di

renal isch

rats that received 3 doses of

ts that

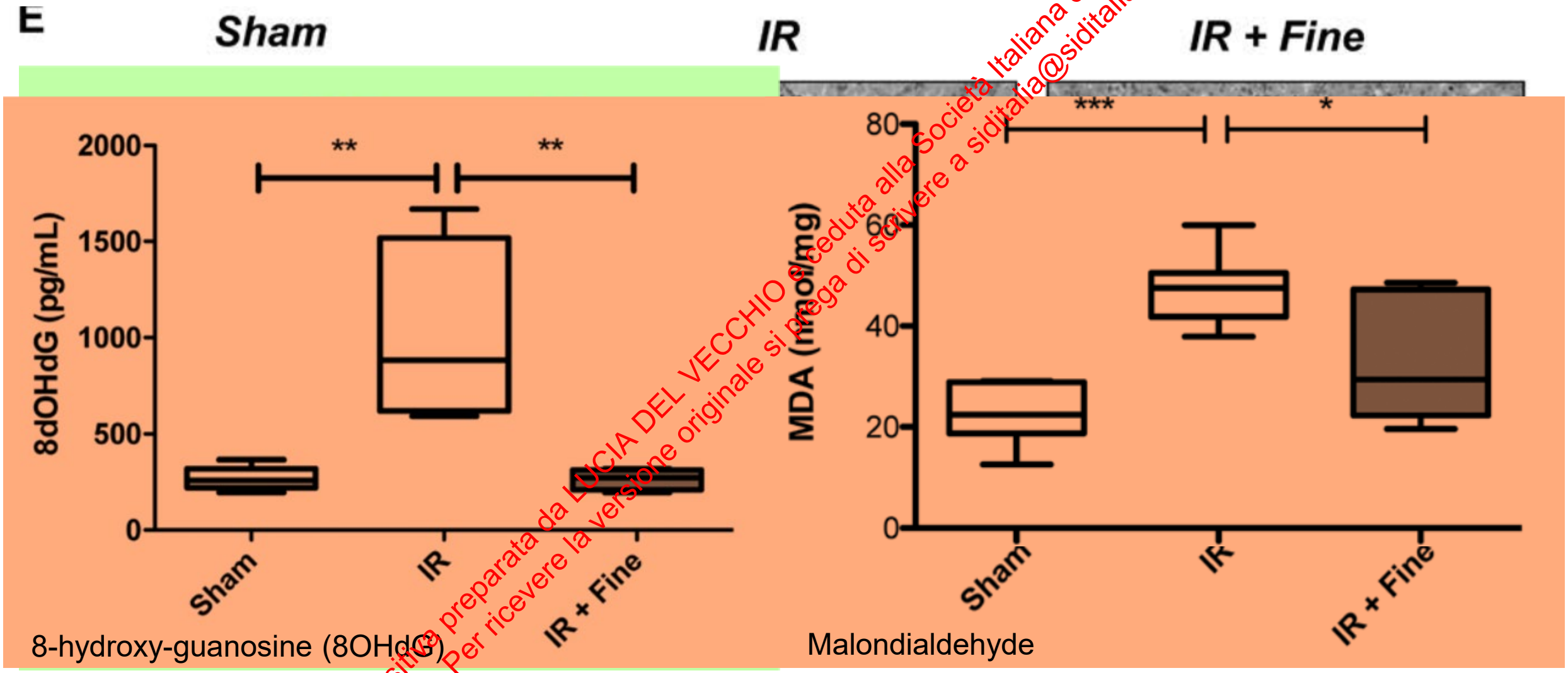
lateral

ischemia, and rats treated with

After 24 hours of reperfusion, the untreated IR rats presented kidney dysfunction and tubular injury

After 4 months, the IR rats developed chronic kidney disease, with kidney dysfunction, increased proteinuria and renal vascular resistance, tubular dilation, extensive tubule-interstitial fibrosis

ACUTE CONSEQUENCES OF RENAL ISCHAEMIA REPERFUSION

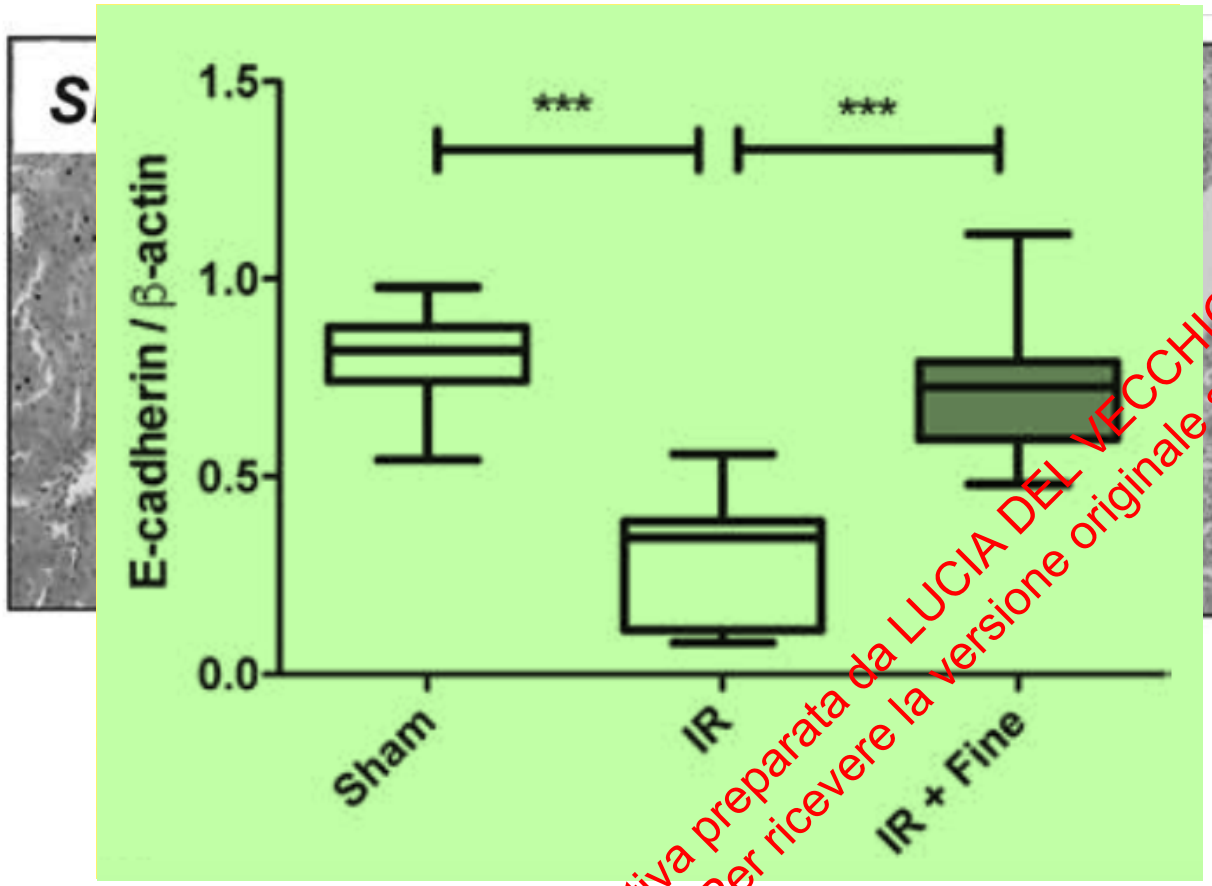


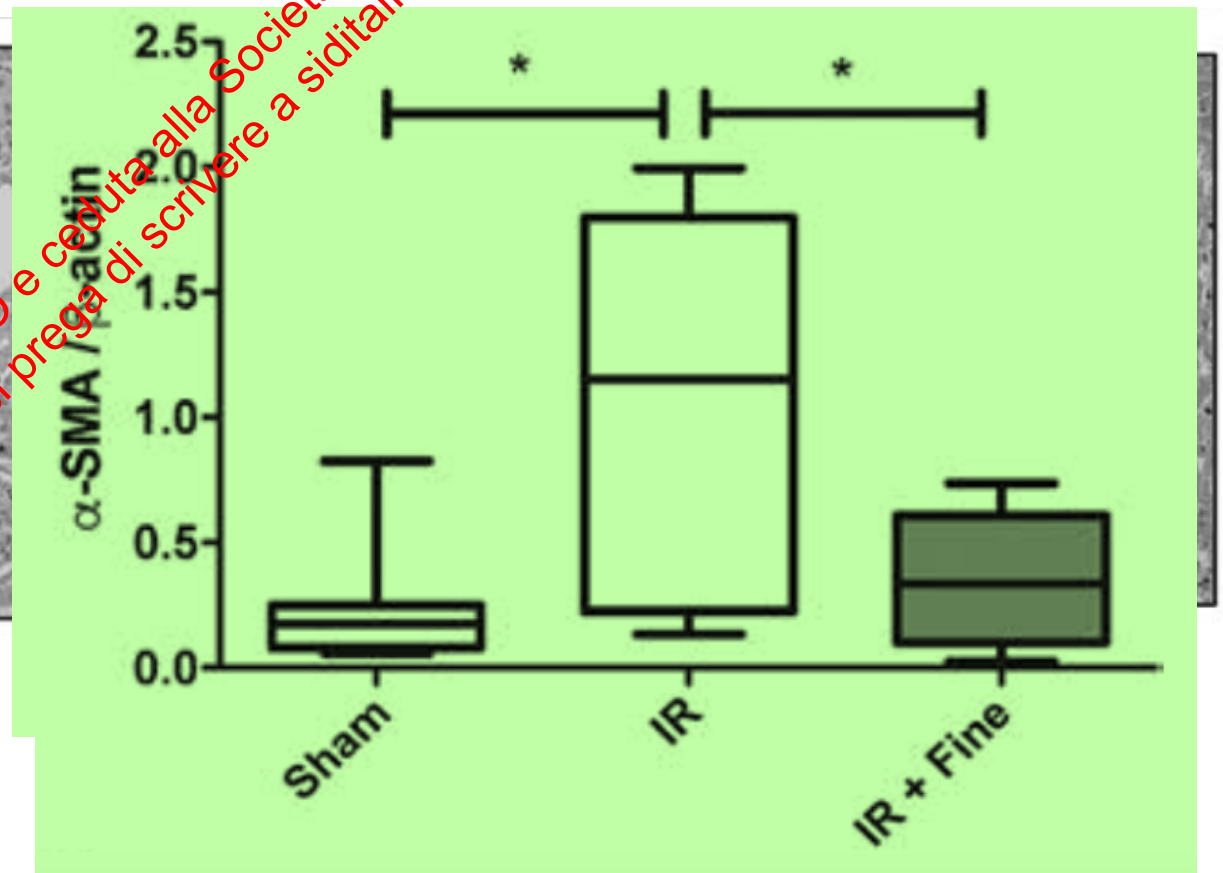
8-hydroxy-guanosine (8OHdG)

Malondialdehyde

Hypertension. 2017;69:870-878

FINERENONE ADMINISTRATION PREVENTS THE AKI TO CKD TRANSITION





Hypertension. 2017;69:870-878

basic research www.kidney-international.org

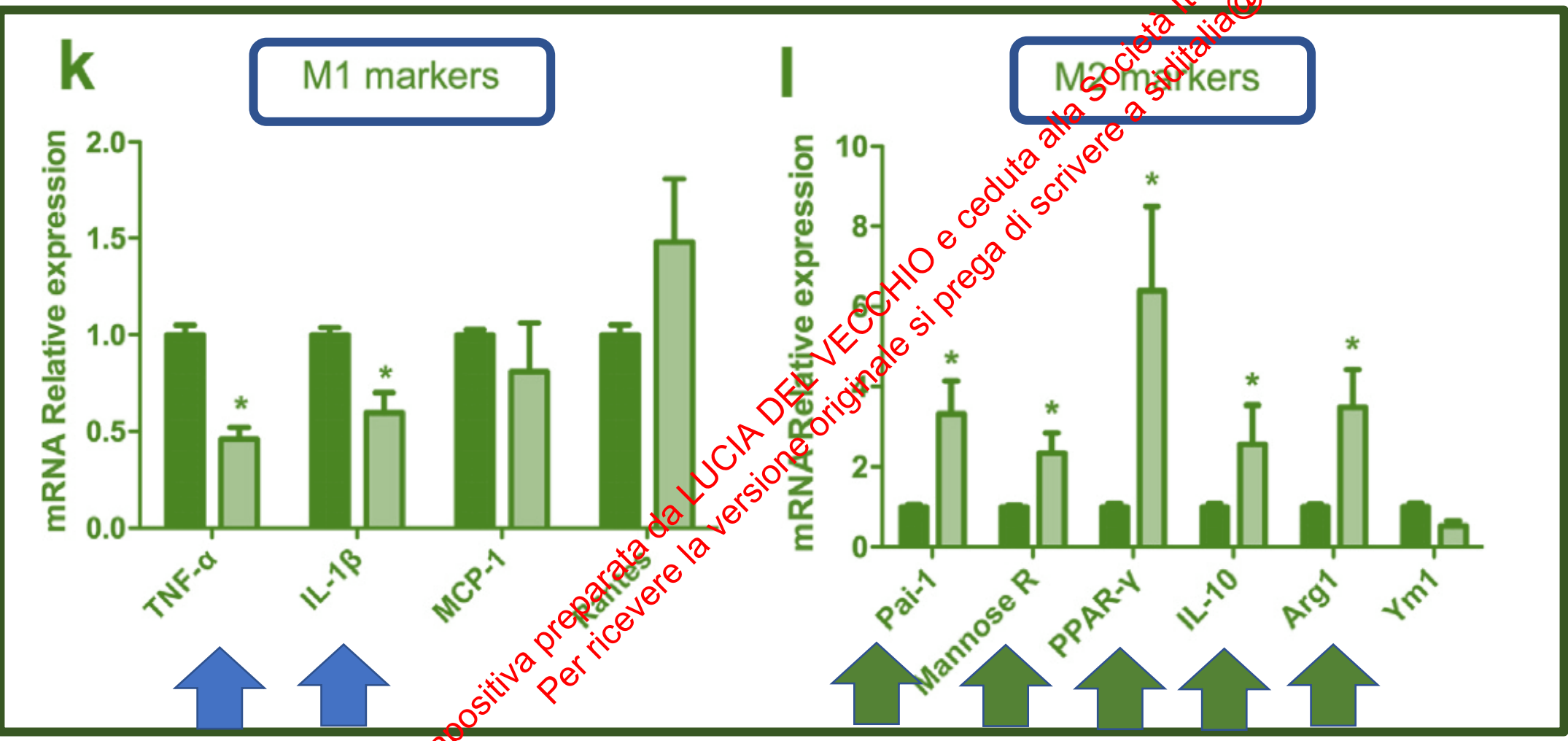
The myeloid mineralocorticoid receptor controls inflammatory and fibrotic responses after renal injury via macrophage interleukin-4 receptor signaling

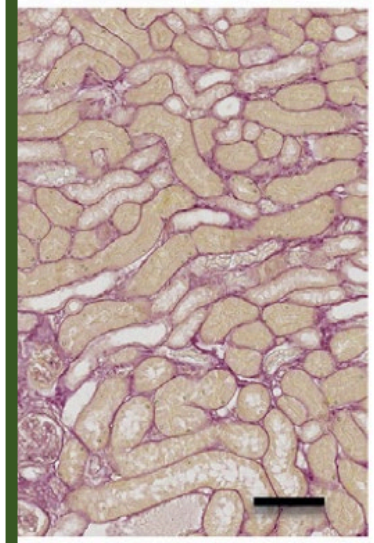
Jonatan Barrera-Chimal[1,2], Gabriel R. Estrela[1,9], Sebastian M. Lechner[1,9], Sébastien Giraud[3,4,5], Soumaya El Moghrabi[1], Shiem Kaaki[3,6], Peter Kolkhof[7], Thierry Hauet[3,4,5] and Frédéric Jaisser[1,8]

- ❑ MR is expressed in myeloid cells
- ❑ The infiltration of inflammatory cells early after an AKI episode plays an important role in defining effective versus maladaptive repair
- ❑ Myeloid MR may potentially be involved in the development of kidney fibrosis after an ischemic AKI episode
- ❑ A model of bilateral IR-induced CKD in mice

Kidney International (2018) 93, 1344–1355

FINERENONE PROTECTS AGAINST THE TRANSITION FROM ACUTE KIDNEY INJURY TO CHRONIC KIDNEY DISEASE

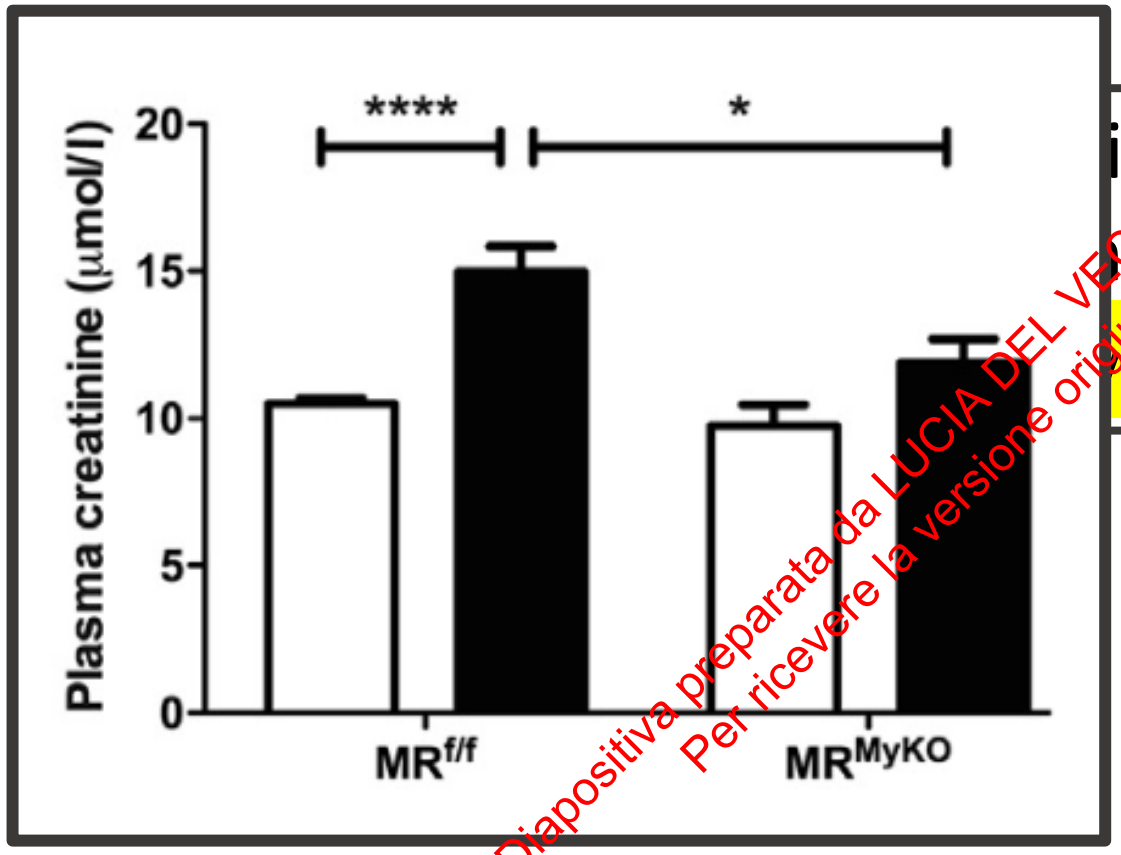


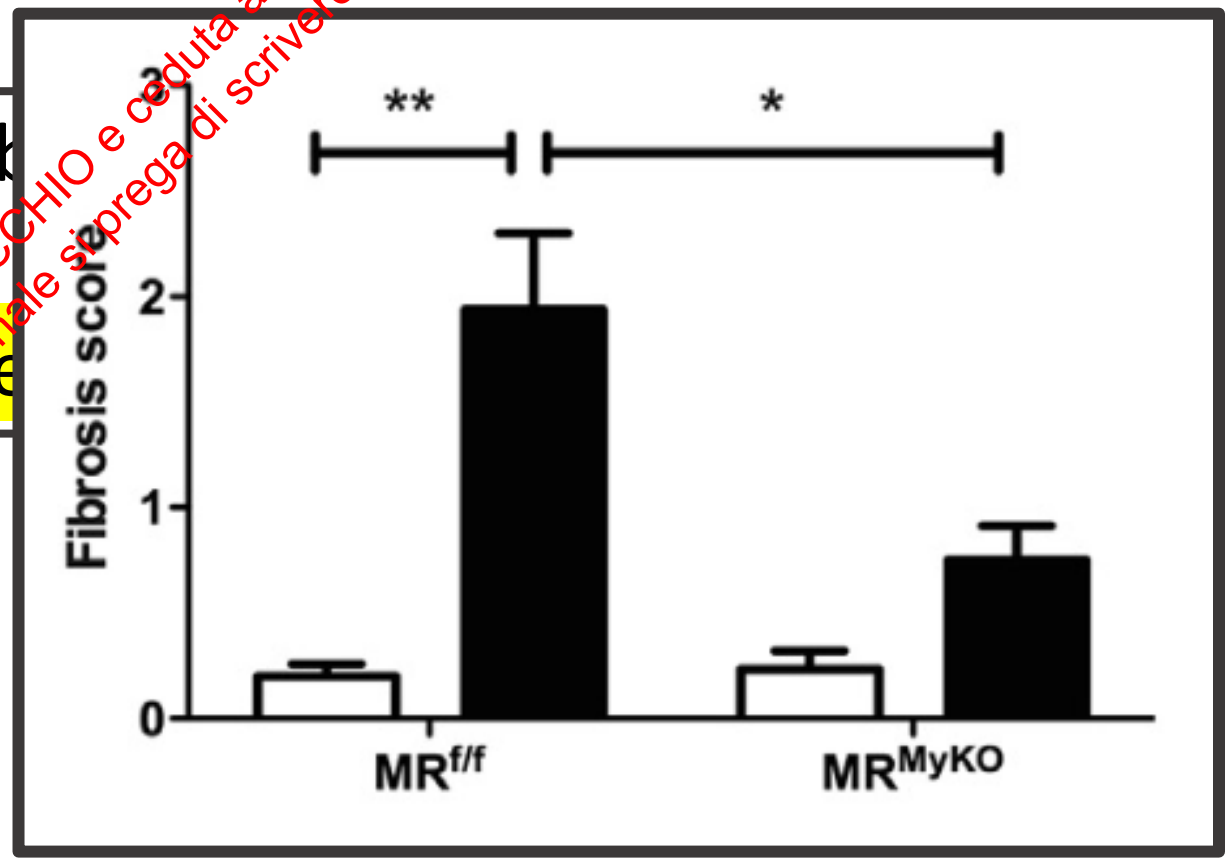


Kidney International (2018) 93, 1344–1355

MINERALOCORTICOID RECEPTOR DEFICIENCY IN MYELOID CELLS PROTECTS AGAINST CHRONIC DYSFUNCTION AND FIBROSIS INDUCED BY ISCHEMIA-REPERFUSION

Kidney International (2018) 93, 1344–1355





Direct Blood Pressure-Independent Anti-Fibrotic Effects by the Selective Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone in Progressive Models of Kidney Fibrosis

Karoline Droebner[a] Mira Pavkovic[b] Manuel Grundmann[a] Elke Hartmann[c]
Laura Goea[a] Johannes Nordlohne[a] Jürgen Klar[a] Frank Eitner[a] Peter Kolkhof[a]

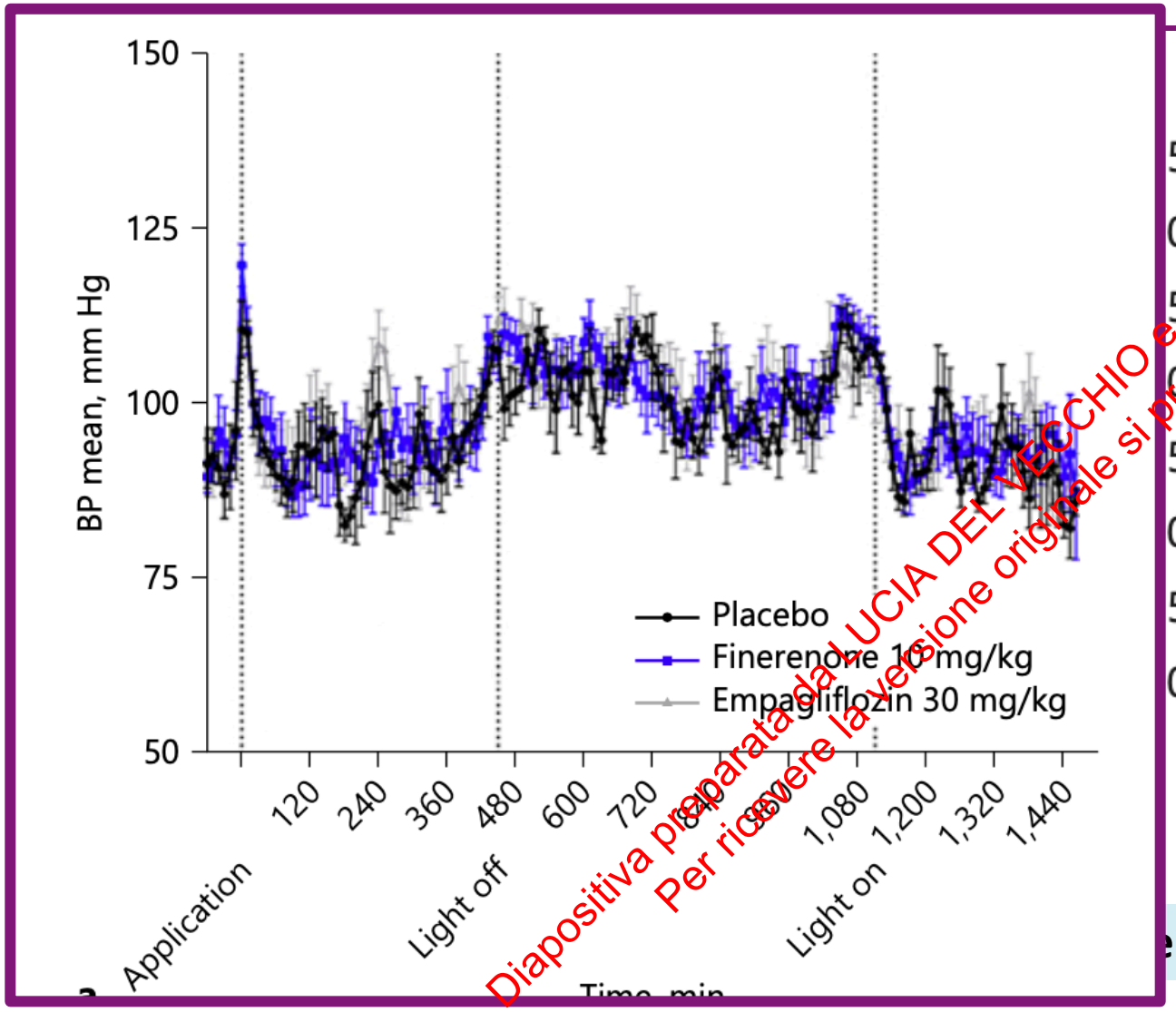
Kidney fibrosis induced in mice via unilateral ureteral obstruction or ischemia

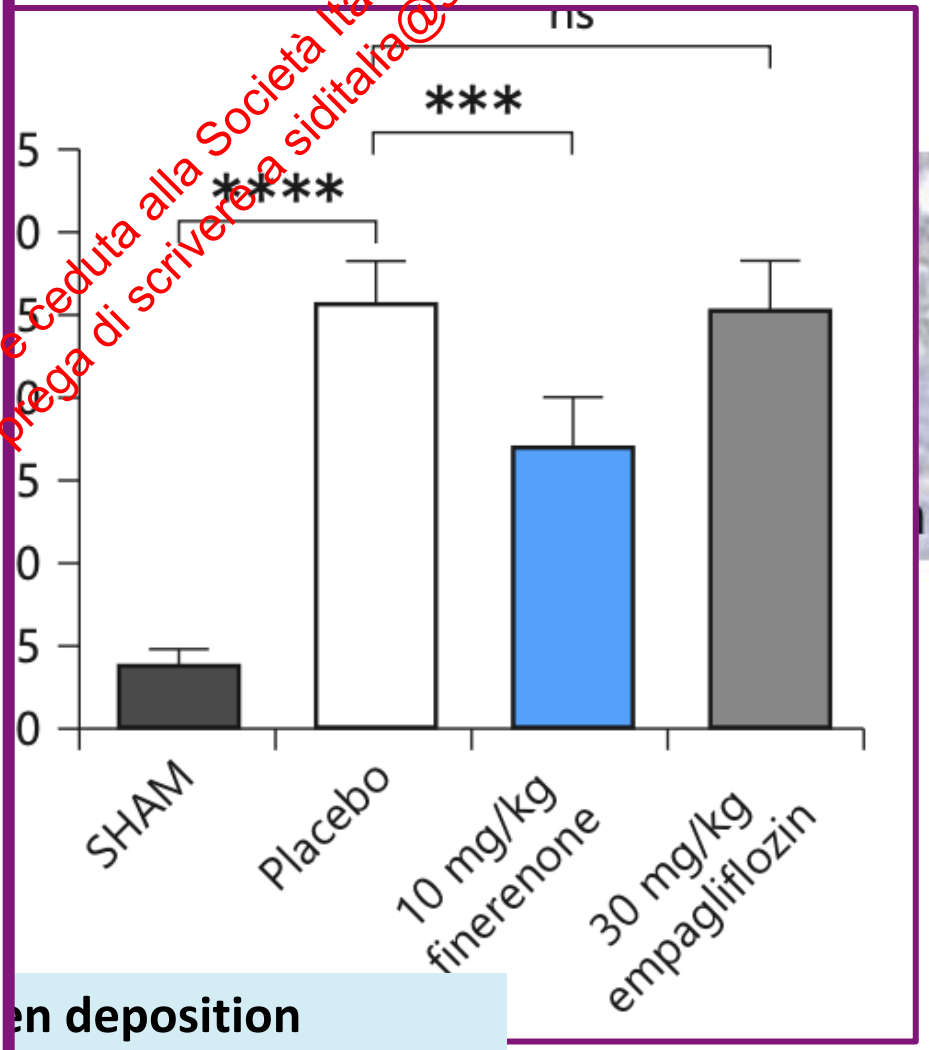
Treated orally with:
- ❑ Finerenone (3 or 10 mg/kg)
- ❑ Empagliflozin (10 or 30 mg/kg)
- ❑ Both drugs

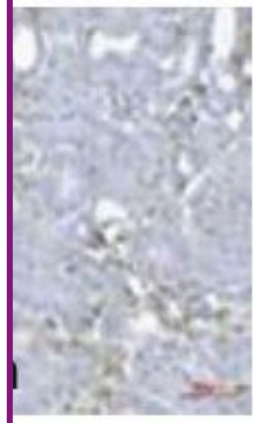
Interstitial myofibroblast accumulation quantified via alpha-smooth muscle actin and interstitial collagen deposition via Sirius Red/Fast Green staining in both models

Am J Nephrol 2021;52:588–601

RENAL FIBROSIS IN UNILATERAL URETERAL OBSTRUCTION MODEL



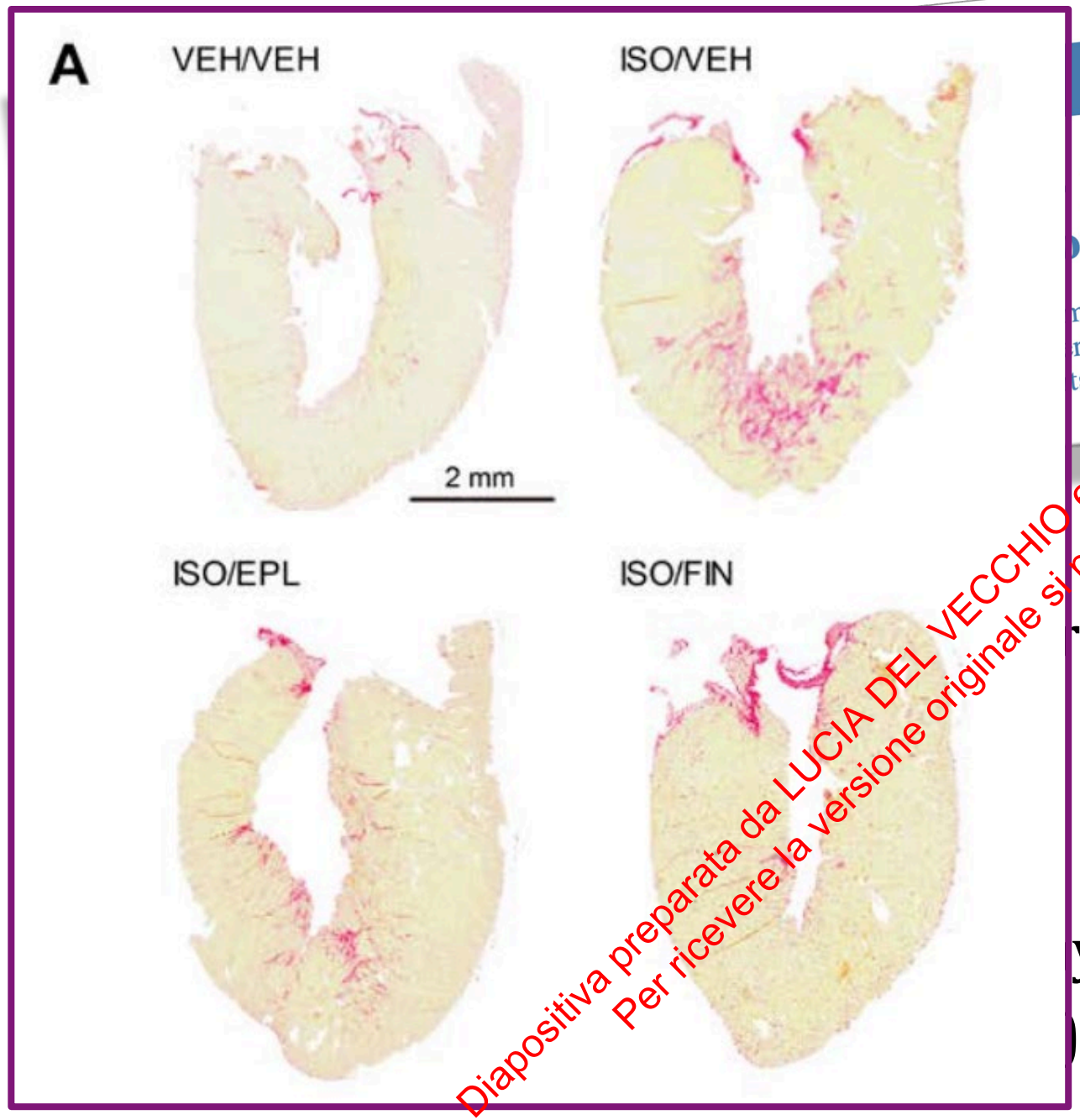


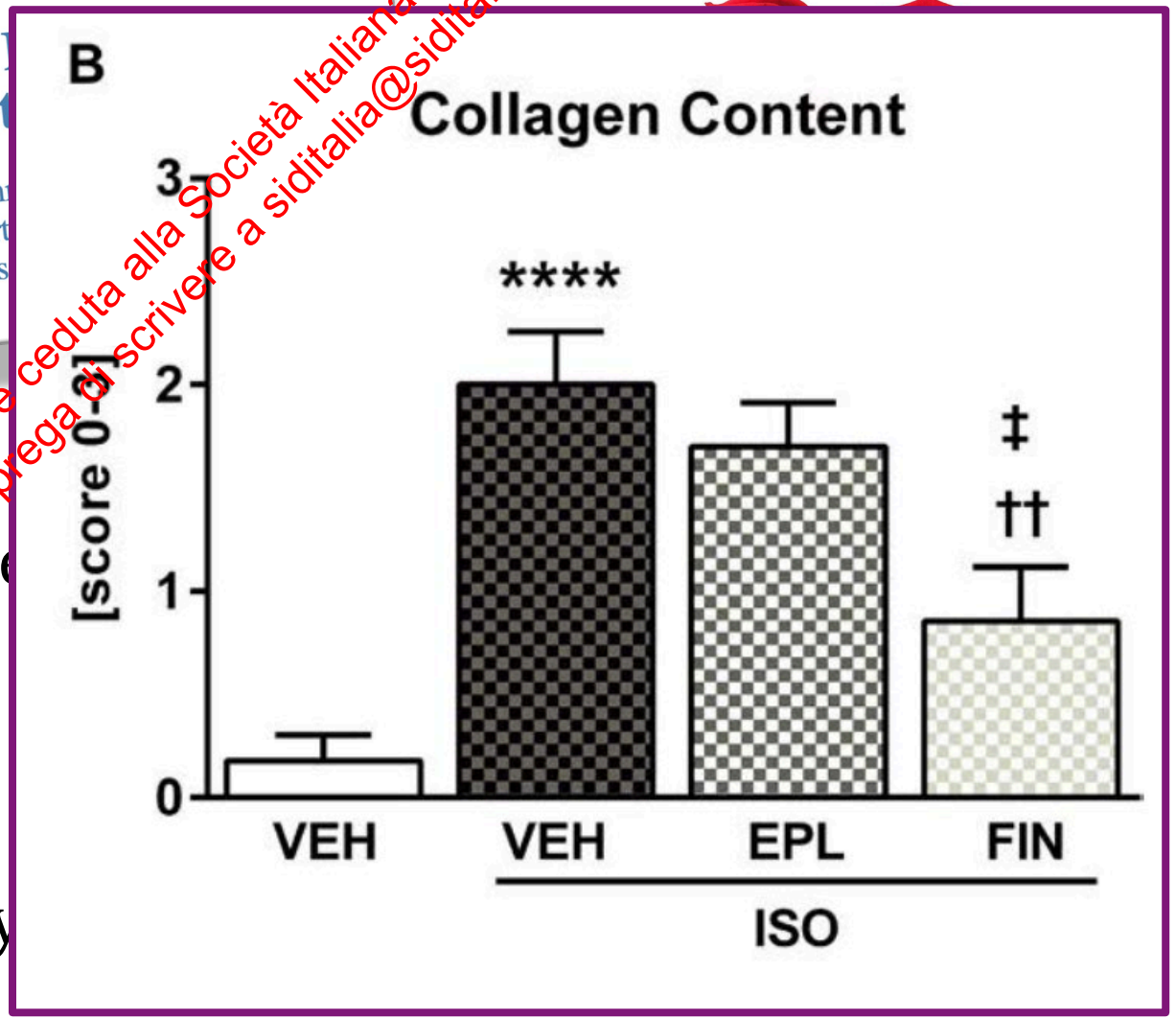


en deposition

Am J Nephrol 2021;52:588–601

Hypertension 2018;71(4):599-608

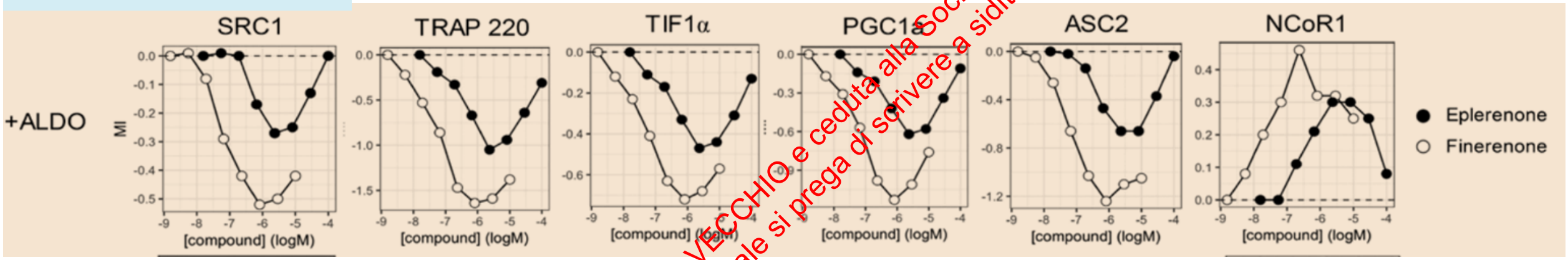




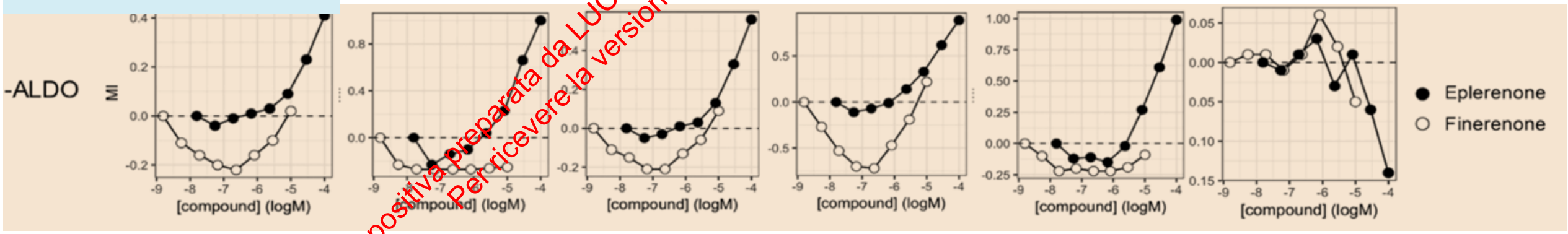
EPLERENONE AND FINERENONE INDUCE LIGAND-SPECIFIC MR COFACTOR BINDING

The gene expression of published MR-coregulators in H9C2/MR+ cells

ALDOSTERONE +



ALDOSTERONE -



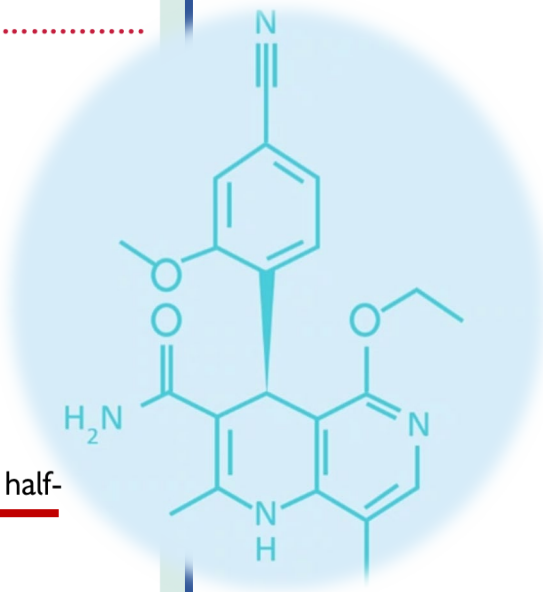
Grune et al Hypertension 2018 ;71(4):599-608

Finerenone

A nonsteroidal, selective mineralcorticoid receptor antagonist

Table I **Key differences between steroidal MRAs and nonsteroidal finerenone**

	Steroidal MRAs		Nonsteroidal finerenone
	Spironolactone	**Eplerenone**	**Finerenone**
Mode of MR antagonism	Potent and unselective (first generation)	Less potent and more selective than spironolactone (second generation)	Potent and selective[59] Bulky and passive[61]
Tissue distribution (in rodents)	Passive *Spironolactone* Kidney > heart[63]	*Eplerenone* Kidney > heart[64]	*Finerenone*: balanced kidney–heart[62]
Pharmacokinetics	*Spironolactone*: prodrug with multiple active metabolites with long half-lives[65] *Eplerenone*: no active metabolites; half-life 4–6 h[64]		*Finerenone*: no active metabolites and short half-life[66,67]
Effect on cofactor recruitment in absence of aldosterone *in vitro*[61,68]	*Spironolactone and eplerenone*: partial agonistic cofactor recruitment		*Finerenone*: inverse agonist (inhibits cofactor binding in the absence of aldosterone)
Effect on cofactor recruitment in the presence of aldosterone *in vitro*	*Spironolactone and eplerenone*: inhibition of cofactor recruitment[68]		*Finerenone*: more potent and efficacious than eplerenone in blocking MR cofactor binding and inducing corepressor binding[68]



European Heart Journal (2021) 42, 152–161

GRAZIE PER L'ATTENZIONE