The contemporary Approach to MRA and Aldosterone in the Kidney and Heart

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FACULTY DISCLOSURE

Company	Nature of Affiliation	Unlabeled Product Usage
		NONE
• Boehringer Ingelheim • Lilly • Janssen (J&J) • Forest • AstraZeneca	Speakers Bureau	

Primary Aldosteronism and Hypertension

Presence of elevated urine aldosterone (> 12 mug/24hr) in > 1,000 patients with essential hypertension after an oral salt loading suppression test in

Hypertension

stage I (115)	15.7 %
stage II (203)	21.0%
refractory HTN	22.0%

Conclusion

Prevalence of primary hyperaldosteronism is high (10 -20 %) and unrecognized

Brown, JF et. .al. Annals Int. Medicine 2020;170 *(1)*

Spironolactone in Refractory Hypertension

1411 patients with refractory hypertension

mean age 63

40% type 2 diabetes.

Spironolactone ~ 25 mg added to ~ 2.9 drugs .

baseline BP 156 / 85 mmHg

Results

BP reduction = 21.9 / 9.5 mmHg (+/- 18/ 11.5)

Chapman N et. al. Hypertension 2007; 49: 839

Mineralocorticoid Receptor Antagonists Therapy in Heart Failure

Reduction of Risk (Cardiovascular death / hHF)

Rales	(HEF ref)	30%	(spironolactone)
Ephesus	(post MI)	15%	(eplenrenone)
Emphasis	(mild HEF ref)	23%	(spironolactone)
Topcat	(HEF pef)	18%	(spironolactone) Americas

Spironolactone in CKD

Systemic review of 15 studies (535 CKD patients) on RAS and sprironolactone

15- 54 % reduction albuminuria

No renal function change (5.5% K > 5.5mm/L)

Bomback, AS et.al. Am. J Kidney Dis 2007; 51(2) :199

Cochran Review of spironolactone and eplenrenone in CKD (+/- RAS blockade) in 27 studies(1,449 patients) showed :

39% reduction albuminuria

No consistent effect on eGFR (double the risk of hyperkalemia)

Bolognano, D et..al. Cochrane Data Base Syst Rev. 2014 (4) F 714

Aldosterone – MR -- Rac1 Triangle

Aldosterone – MR – Rac1 function in a multiple directional triangle promoting

inflammation and fibrosis

All 3 are upregulated in multiple disease states

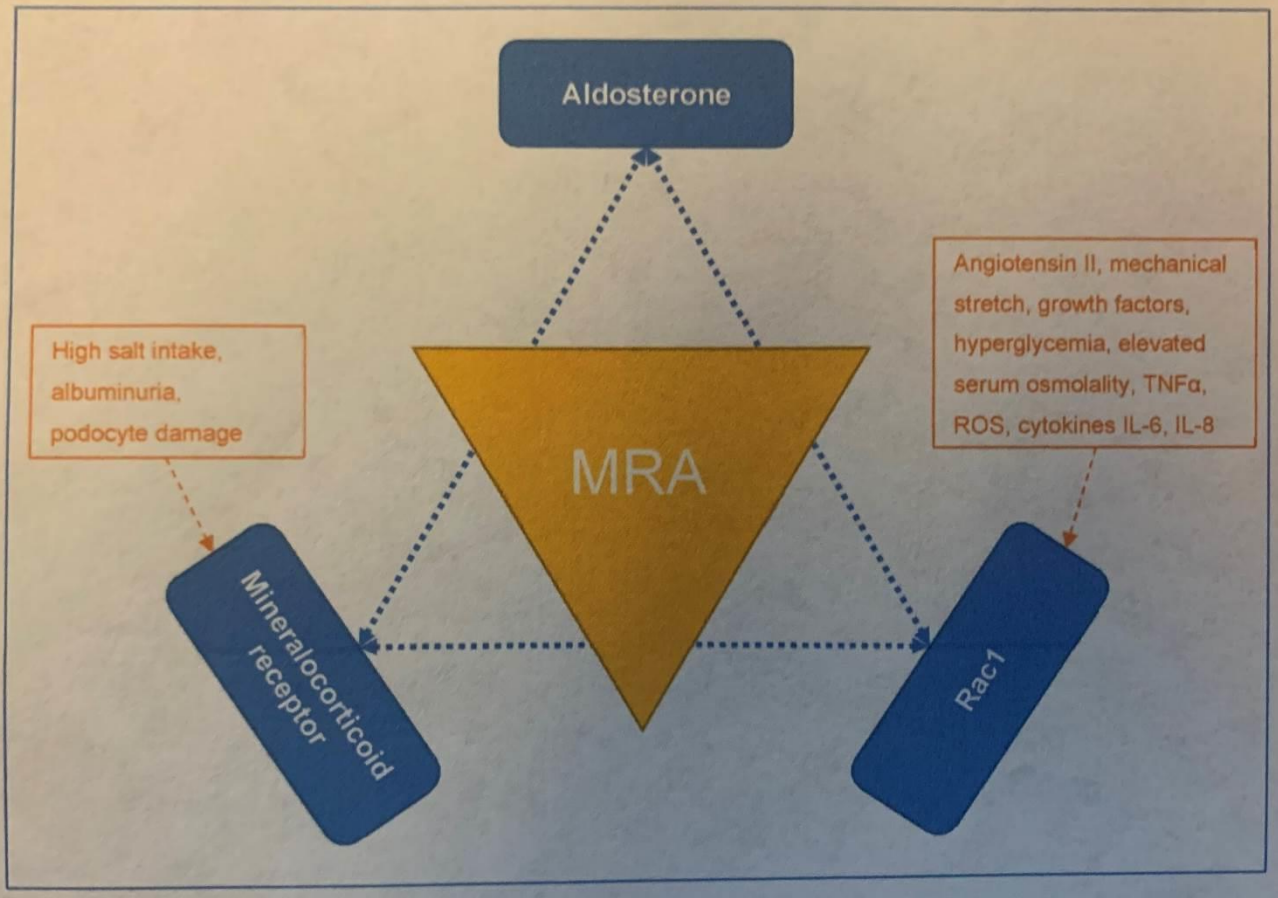
Diabetes

CKD

Albuminuria

CVD

Heart Failure


Aldosterone
High salt intake, albuminuria, podocyte damage
Angiotensin II, mechanical stretch, growth factors, hyperglycemia, elevated serum osmolality, TNFα, ROS, cytokines IL-6, IL-8
MRA
Mineralocorticoid receptor
Rac1

Aldosterone (1)

Aldosterone (discovered in 1950) belongs to the group of lipophilic mineralocorticoids (MR)

including :

testosterone, progesterone, estrogen and glucocorticoids

Synthesized predominantly : zona glomerulosa (adrenals)

alternative production :

Intrarenal : in CKD (irrespective of K) and Diabetes

Adipocytes : increase aldosterone synthase

aldosterone releasing factor (not well delineated)

Synthesis and release of Aldosterone mainly regulated by

hyperkalemia

volume deletion

hypotension (as part of RAAS)

other modulators : Nitric oxide,

Endothelin

Aldosterone (2)

Action sites :

distal tubule (DT) and collecting ducts (CD)

initially thought to be only site for via **Enac** (epithelial Na channel)

Na / K homeostasis

volume

hypotension

now multiple sites :

heart : **myocardium, endothelium**

kidney : **podocytes , mesangium**

tissues : **ATR 1**

macrophages,

fibroblasts

Most locations (except DT and CD) promote

Pro-inflammatory and Pro- fibrotic pathways

Aldosterone (3)

Mode of action

genomic (classic) : slow reaction over hours binding to
mineralocorticoid receptor (MR) i.e. DT / CD

non- genomic : rapid in minutes
via cell membrane and non- MR intracellular receptors with :
mitochondrial release of Reactive Oxygen Species (ROS)
increased cytosolic Calcium
mitogen activated protein kinase
kinase 1/2
ATR1 receptor (without need of Angiotensin II)

Non – genomic pathway is predominant pro-inflammatory / pro-fibrotic

Aldosterone Action independent of MR

Aldosterone mechanism of action **without MR** via

1) Na /H exchange via EGFR, ROS formation
2) cAMP metabolism
3) SGK-1 activation
4) **Direct ATR 1 receptor action**
5) MAPK activity increase

EGFR= epidermal growth factor

SGK-1= serum-glucocorticoid-induced protein kinase -1

MAPK= mitogen activated protein kinase

Mineralocorticoid Receptor (MR)

Discovered 1987 (27 years after Aldo) location is intracellular in multiple cells

Heart : **Cardiomyocytes**

Kidney : **DT/ CD, Podocytes , mesangial cells**

Endothelium

additionally :

smooth muscle cells

muscle

adipocytes

fibroblast

macrophages (TGF beta)

Rac 1

Rac1 (part of the Rho family of small GTPases)

located intracellulary , acting as a switch and second messenger

regulates :

cell signaling , cytoskeletal integrety and cell growth

activates multiple kinases

inflammation and fibrosis

renal location : **podocytes, endothelium , collecting ducts**

potentiates Aldosterone action on MR

MR activation without Aldosterone

EnaC

Aldosterone , MR and Rac 1 are part of a triangle of multidirectional potentiating factors in inflammation and fibrosis

Epithelial Na Channel (Enac)

Location	Distal tubule / Collecting duct (DT/ CD)
	Glycocalix along entire endothelium
Action	Aldosterone increases number / location of Enac
	Retains Na and secretes K
Clinical	
	Hypertension
	Increased vascular stiffness

Aldosterone Breakthrough vs. Escape

With chronic RAAS therapy after 6 - 12 month 30 -50% of patients experience

Aldosterone breakthrough

Aldo levels increase up to, or above , baseline levels with

1) no change in blood pressure
2) worsening UACR and eGFR decline

Schjoedt KJ et.al. Diabetologia 2004; 47 : 1936

Sato A et.al. Hypertension 2003 ;41 : 64

Aldosterone Escape

Absence (usual) of edema in primary aldosteronism

Schrier RW. Nat Rev Nephrol. 2010; 6 :61

MR Overactivation

Hyperglycemia **Insulin resistance** **Hyperinsulinemia** **Obesity**	**augmented transcription**
Elevated Aldosterone levels	
Hypertension , high salt diet	**Rac 1 , RAAS**
CAD and Heart	**Increased Aldosterone** **myocardial stretch**
CKD /Albuminuria	**increased expression of MR , SGK-1** **Rac 1**
Age	**increased RAAS**

Inflammatory and Profibrotic Pathways

1) **Aldosterone / MR** generate Reactive Oxygen Species (**ROS**) in Mitochondria

(Aldosterone can directly initiate ROS production via ATR1)

2) ROS is recognized by intracellular **NLR** (Nod like receptor family)

(NLR senses intracellular pathogens, toxins including ROS)

4) NLR activate **inflammasomes** (multiprotein complexes)

5) Inflammasome (**NLRP3**) activates Caspase 1 with

release **cytokines (IL 1 beta , IL 18)**

Activation of inflammasomes in macrophages and cytokines causes release of

TGF beta (Transforming Growth Factor) = **central role in inflammation and fibrosis**

Mechanism in the Development and Progression of CKD

1) **Metabolic**

Hyperglycemia , Advanced Glycation Products (AGE's)

Insulin Resistance

Obesity

2) **Hemodynamic**

Hyperfiltration, systemic and glomerular hypertension ,

Activation of

RAAS (Angiotensin II , Aldosterone)

Sympathetic nervous system

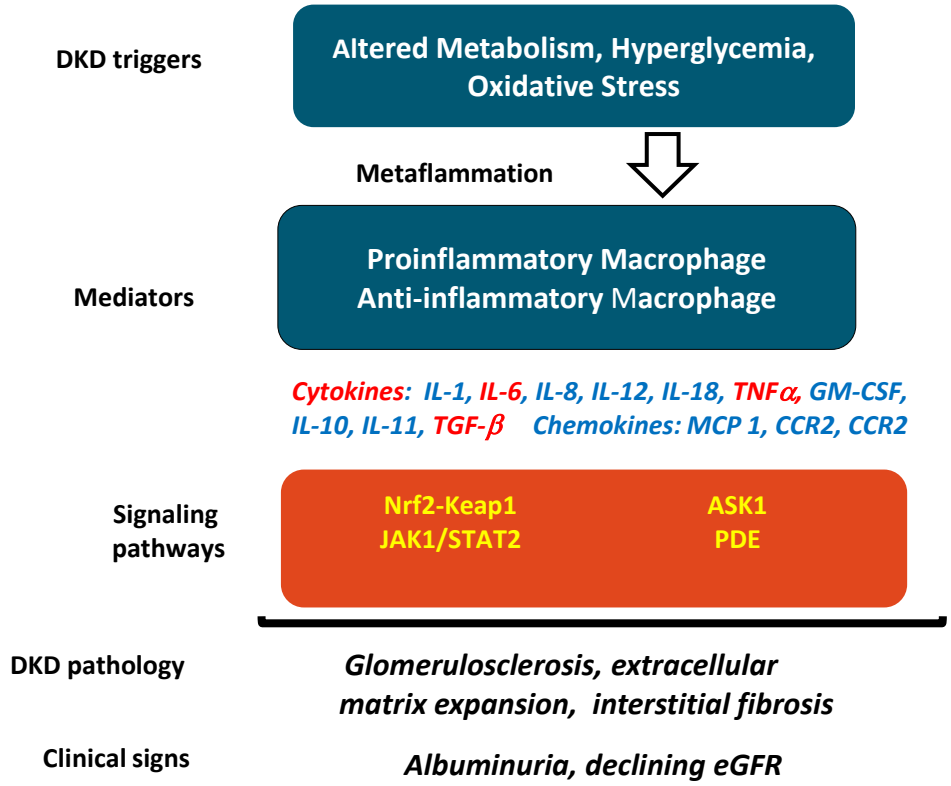
3) **Inflammatory and Fibrotic Factors**

Cytokines : IL 6 , TGF beta , TNF alpha

Angiotensin II , Aldosterone

Reactive Oxygen Species (ROS) , Metalloproteinases

Inflammatory Pathways in DKD



Inflammation and Oxidative Stress in DKD

DKD is marked by chronic, low-grade inflammation and oxidative stress

Dysregulation of homeostatic processes of apoptosis and autophagy may lead to **podocyte loss, albuminuria, and tubular damage** in DKD

Gomerular and tubular damage contribute to albuminuria eGFR loss and can be targeted in DKD management

Nicholas. NephSAP. 2020;19:110.

Spironolactone vs. Finerenone

	Spironolactone	Finerenone
Half life (T/2)	> 72 hrs	2- 3 hrs
selectivity	low	high
potency	high	high
Heart > Kidney	6 fold	1: 1

Finerenone

different binding sites (nucleus)

No gynecomastia , dysmenorrhea (no hormonal action)

less hyperkalemia (vs. spironolactone)

Finerenone Studies

Fidelio - DKD

5,734 T2D with albuminuric CKD on max. tolerated RAAS

K ≤ 4.8 mm/L , 4.5 % on SGLT2 inhibitors

a) eGFR 25-60 ml/min,UACR 30- 300mg/g + retinopathy

b) eGFR 25- 75 ml/min and UACR 300- 5000 mg/g

Primary endpoint = **18% Reduction**

Kidney failure (eGFR< 15), sustained 40% eGFR decline, renal death

Secondary endpoint = **14% Reduction**

Cardiovascular death, non-fatal MI , non-fatal CVA, HF admission

Figaro DKD

7,352 Type 2 diabetes patients with CKD ,mean eGFR 67.8 ml/min ,
8% on SGLT2 inhibitors

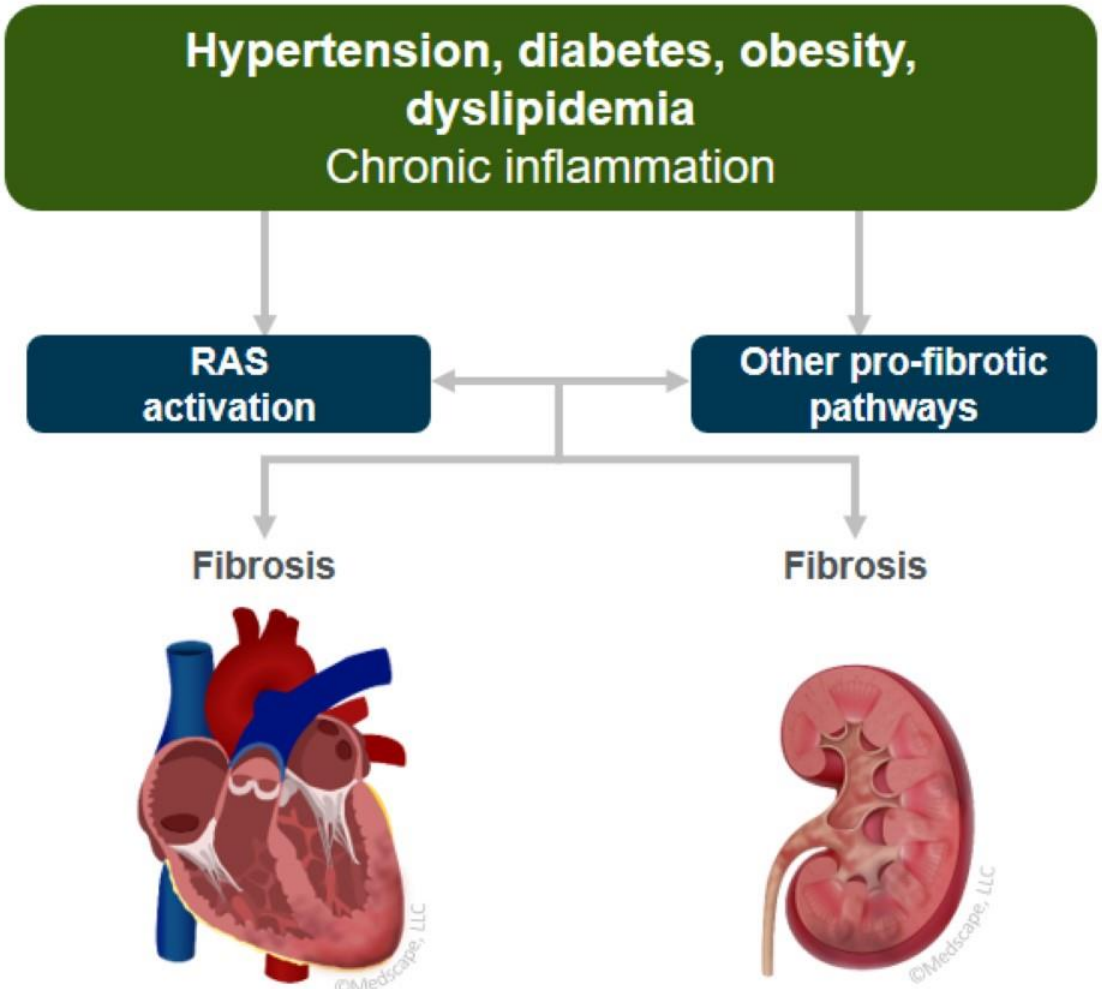
a) eGFR 25 -90 ml/min and UACR 30 - < 300 mg/g or
b) eGFR ≥ 60 ml/min and UACR 300 – 5,000 mg/g
c) K ≤ 4.8 mmol/ L , mean eGFR 67.8 ml/ min

Primary endpoint = 13 % Reduction (mainly hHF)
composit of death from CV causes , non-fatal MI, non- fatal CV

Secondary endpoint = 13 % Reduction (NS)
composit of kidney failure , 40% decline of eGFR , renal death

Main side effect in Finerenone studies: **Hyperkalemia**
18 % (vs. 9 %) Fidelio
10.8% (vs 5.3 %) Figaro

Signaling and Crosstalk Leads to Kidney Fibrosis



Zannad F, et al. *Circulation*. 2018;138:929-944.

MRA Therapy

MRA play central role in Heart and Kidney Disease treatment

Quadruple Therapy in Heart Failure :

ACEinhib. / ARB's or ARNI

BB

SGLT2 Inhib

MRA

Triple Therapy in CKD

ACE inhib./ ARB'S

SGLT2 inhib

MRA

Conclusion

1) **Aldactone = MRA = Rac 1 :**

all 3 function in a multiple directional triangle

2) **Overactivation** in

Diabetes , CKD and Heart Failure

lead to increased ROS with chronic inflammation and fibrosis

3) **MRA are important therapeutic options** in

CKD

Heart Failure