RAAS Blockers in Cardiorenal Syndrome

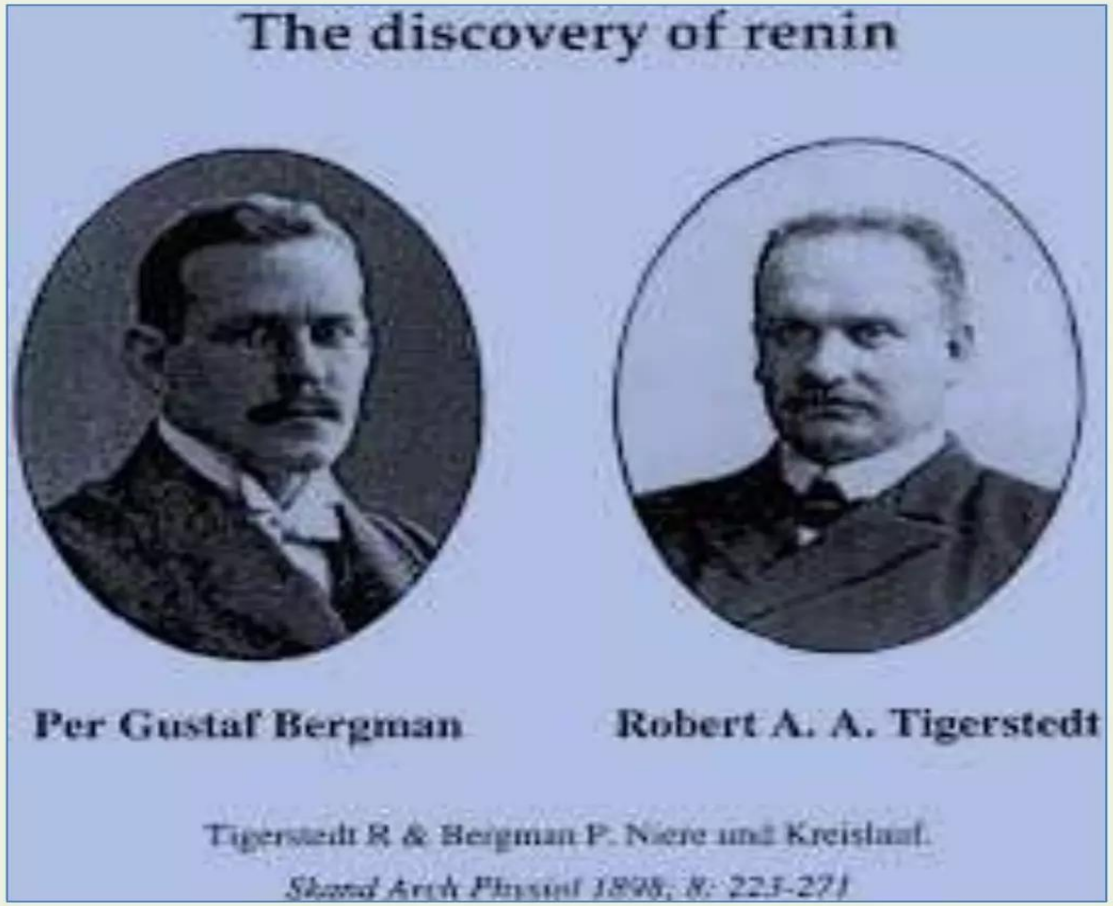
Zahra Shafii, MD.

Assistant Professor of Nephrology

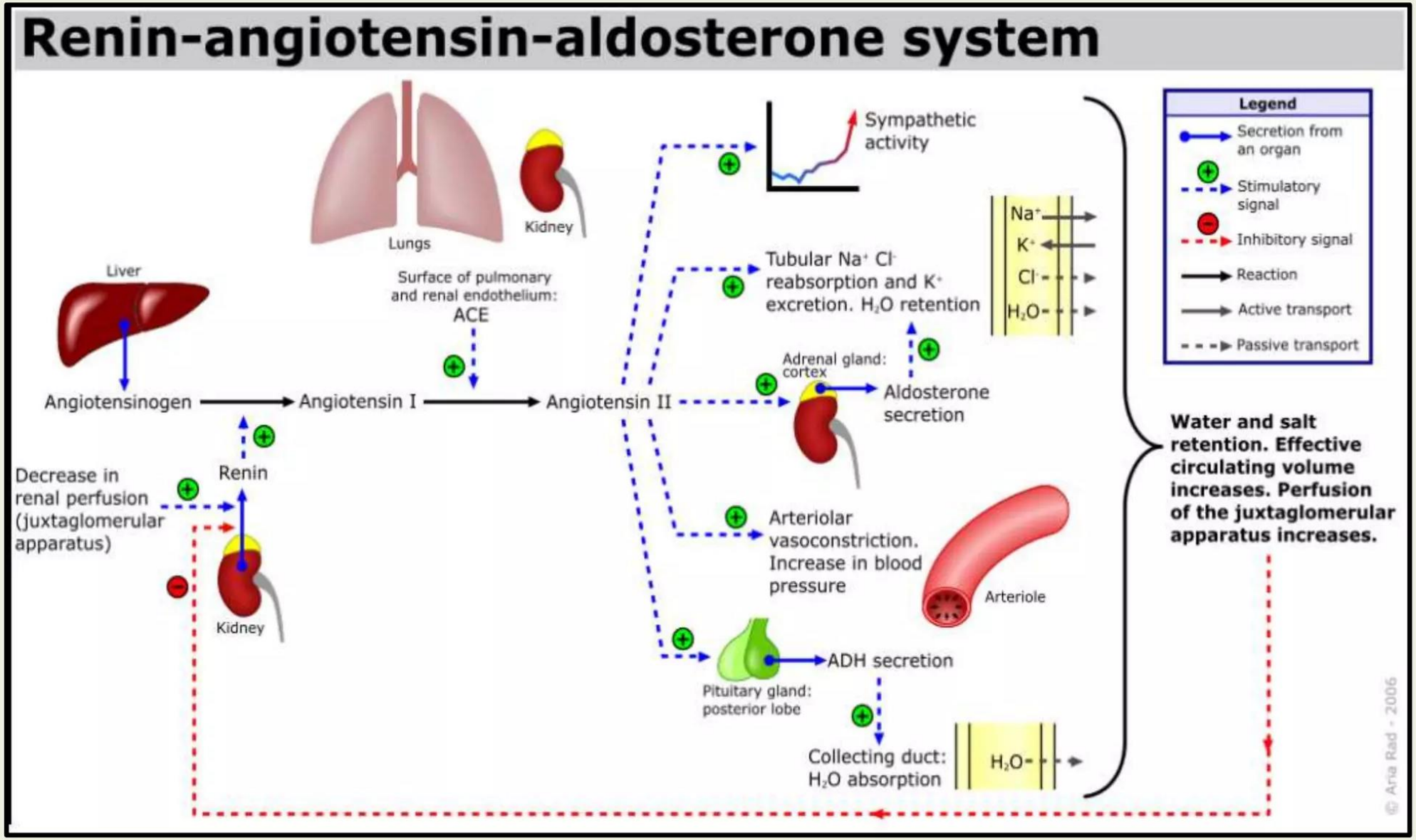
Rajaie Cardiovascular Medical and Research Center

Historical Perspective

The RAAS has been discovered for more than a century



The history of the discovery of the renin-angiotensin system began in **1898** with the studies made by Tigerstedt and Bergman, **who reported the pressor effect of renal extracts**; they named the renal substance ***renin*** based on its origin.


Renin-angiotensin-aldosterone system
Lungs
Kidney
Liver
Surface of pulmonary and renal endothelium:
ACE
Angiotensinogen
Angiotensin I
Angiotensin II
Renin
Decrease in renal perfusion (juxtaglomerular apparatus)
Kidney
Sympathetic activity
Tubular Na+ Cl- reabsorption and K+ excretion. H2O retention
Na+
K+
Cl-
H2O
Adrenal gland: cortex
Aldosterone secretion
Arteriolar vasoconstriction. Increase in blood pressure
Arteriole
ADH secretion
Pituitary gland: posterior lobe
Collecting duct: H2O absorption
H2O
Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Legend
Secretion from an organ
Stimulatory signal
Inhibitory signal
Reaction
Active transport
Passive transport
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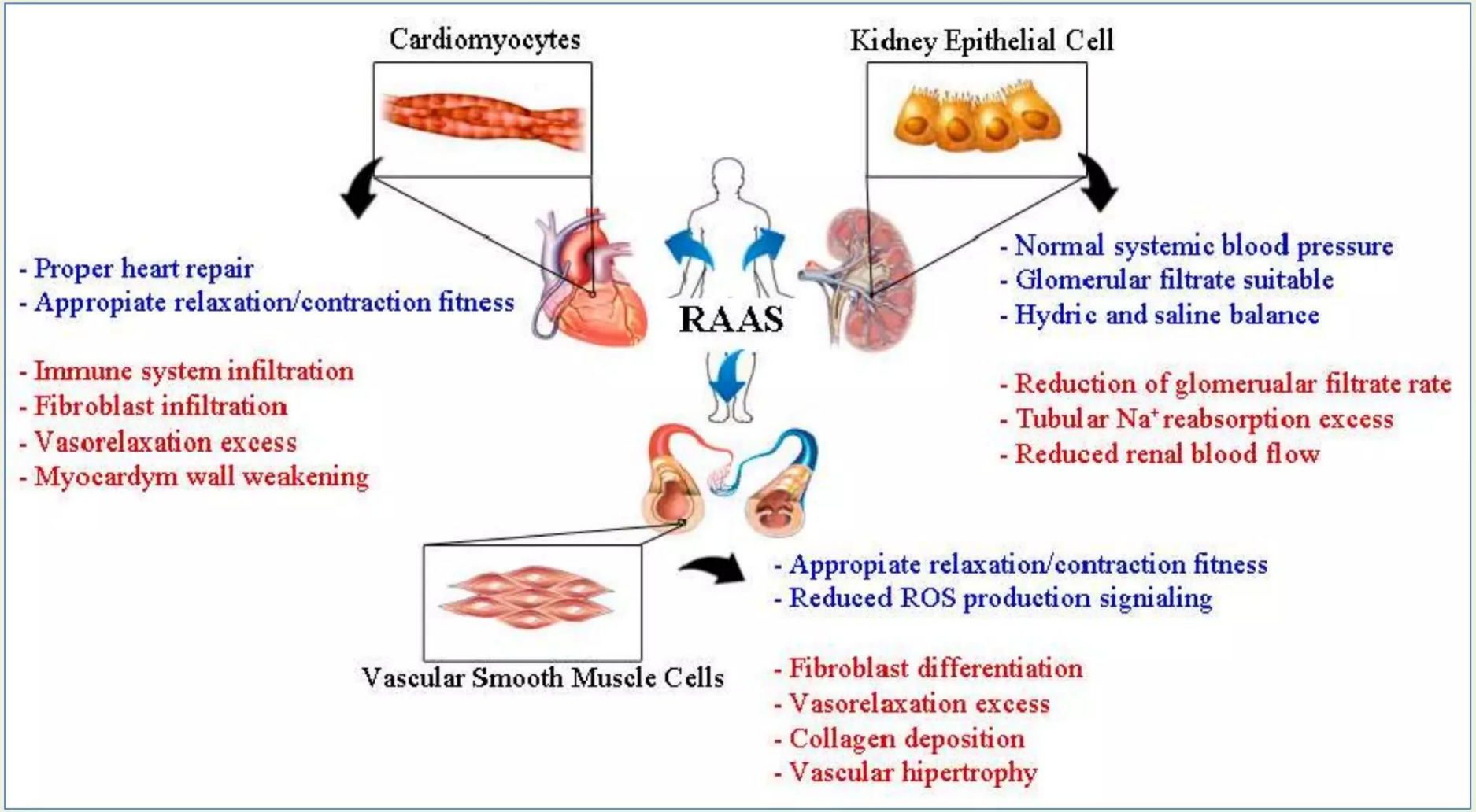
Physiological and detrimental roles of RAAS molecules in cardiac, vascular tissues and kidneys.



Aldosterone and Ang II are the principal RAAS molecules involved in cardiovascular and renal system changes during hypertension. Both molecules are also involved in the physiological control of blood pressure (blue text), directly impacting cardiomyocytes, kidney epithelial cells, and vascular smooth muscle cells. ***During hypertension, excesses of these molecules have also been linked with cardiovascular and kidney tissue hypertrophy and fibrosis (red text)***

RAAS Activation In Cardiorenal syndrome

Maladaptive response

- Altered hemodynamics, sympathetic signaling, and progressive renal dysfunction

Raas Activation

- Extreme sodium avidity and ventricular remodeling

Types of RAAS inhibitors

- Angiotensin-converting enzyme inhibitors (ACE inhibitors)
- Angiotensin-receptor blocker (ARBs, sartans)
- Angiotensin receptor-neprilysin inhibitors (ARNIs)
- Mineralocorticoid receptor antagonist (MRA)

RAAS Inhibition In Cardiorenal syndrome

- ACE inhibition and aldosterone antagonist: blockade of the intracardiac RAAS, reduction in adrenergic tone, improvement in endothelial function, and prevention of myocardial fibrosis
- RAAS inhibition in HF: improved outcomes
- little is known about the long-term benefits or adverse effects of RAAS inhibition on kidney function in HF.

- Renoprotective role of ACE inhibitors and angiotensin receptor blockers in systolic HF independence of direct preservation of ventricular function has not been established.
- ACE inhibitors and ARB cause dose-dependent increases in angiotensin II (AT-II) that contribute to the phenomenon described as escape from ACE inhibition.
- AT-II directly contributes to kidney damage by upregulates the cytokines TGF-β, TNF-α, NF-κB, and IL-6 and stimulates fibroblasts, resulting in cell growth, inflammation, and fibrotic damage in the renal parenchyma

EFFECT ON GFR

- increase GFR in only 10 to 25 percent of patients, while an increase in the plasma creatinine concentration is a more common finding usually occurs within the first week

RAAS Blockers contraindication

Do not start or continue ARNI, ACE inhibitor, or ARB in:

- **Hypotension or decompensated heart failure** :SBP ≥90 mmHg & no signs of worsening or severely DHF.
- **Chronic or acute kidney disease and hyperkalemia –** cautiously started at the lowest doses in eGFR <30 mL/min per 1.73 m^2 and should not be initiated or dose-increased if the potassium level is greater than 5.0 mEq/L
- **Angioedema** :Prior angioedema is an absolute contraindication for ARNI and ACEI not ARB therapy
- **Use in pregnancy and during breastfeeding**
- **Simultaneous use of multiple renin-angiotensin-aldosterone system (RAAS)-neprilysin inhibitors**
- **Bilateral renal artery stenosis**

ARNIs

- ARNI therapy has the greatest efficacy relative to ACE inhibitors, ARBs, and hydralazine-isosorbide dinitrate.
- In patients with NYHA class II to III symptoms and LVEF ≤40 percent who are treated for volume overload and who are otherwise clinically well-compensated ARNI (sacubitril-valsartan) is better than ACE inhibitor and ARB
- In patients who have a systolic blood pressure ≥100 mmHg and can reliably afford the drug.
- Other vasodilator therapies, except for vasodilating beta blockers and MRAs
- If not tolerate sacubitril-valsartan (eg, hypotension) or cannot obtain it reliably: treatment with an ACE inhibitor or ARB rather than other vasodilating agents.

Transition from an ACEI or ARB to ARNI

- -**Transition between an ACE inhibitor and sacubitril-valsartan** : not administer ARNI to who have taken an ACE inhibitor within the previous 36 hours due to the risk of angioedema (see above). This is true for starting sacubitril-valsartan in patie
- -**Transition from an ARB to sacubitril-valsartan** : the valsartan in sacubitril-valsartan is more bioavailable . 26, 51, and 103 mg of in the sacubitril-valsartan are equivalent to 40, 80, and 160 mg of valsartan in other marketed tablet formulations
- No washout period is required in changing from ARB to sacubitril-valsartan

Monitoring for ARNI, ACEI or ARB

- Baseline and follow-up blood tests (serum potassium, blood urea nitrogen, serum creatinine) at one to two weeks following drug initiation or after any dose increase.
- Any increase in dose only as tolerated without symptomatic hypotension, hyperkalemia, or a significant decline in kidney function.
- After the target dose or the maximally tolerated dose checked periodically every three to six months

Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure - PARADIGM-HF

Oct 20, 2020

Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode - PIONEER-HF

Oct 21, 2020

Serum NT-proBNP) level may be helpful but not BNP as ARNI causes elevation of BNP (not NT-proBNP)

Monitoring

- Check baseline BUN, serum creatinine, and electrolytes
- Recheck labs approximately 1 to 2 weeks after initiation or uptitration
- During stable maintenance therapy, recheck labs every 3 to 6 months (sooner if patient has clinical or laboratory evidence of instability)
- For worsening renal function and/or hyperkalemia, check labs frequently and serially until creatinine and potassium have decreased and stabilized

Complication

- Deterioration of eGFR with persistence of congestion indicates a worse prognosis and increased mortality, hence decongestion is a major target in AHF
- RAAS inhibitors have convincing evidence of benefit on prolonging survival and reducing mortality in patients with HFrEF and both US and europian guidelinesgive evidence A recommendation for their use
  The risk of adverse events is higher in CKD patients
  Minority of patients have an increase in GFR but most have moderate reduction in GFR that can be ameliorated by reducing the intensity of diuretic therapy

Reduction in GFR

Most likely when maintenance of the GFR is dependent upon high ambient angiotensin II levels:

- high-dose diuretic with relative hypovolemia
- Relative hypotension (MAP below 75 mmHg)
- Pretreatment plasma sodium below 137 mEq/L (marker for marked neurohumoral activation)
- Significant renovascular disease, (common finding)

Approach to changes in glomerular filtration rate

- Avoid concomitant nephrotoxic drugs (eg, NSAIDs)
- Evaluate and treat other potential causes of worsening renal function
- If no congestion is present, reduce or suspend diuretic therapy
- Hold or stop mineralocorticoid receptor antagonist if needed

- Decrease dose by one-half and recheck after a week if serum cr increase by >50% above baseline or serum cr 3.1 to 3.5 mg/dL or eGFR is 20 to 25 mL/min per 1.73 m2.
- Stop if serum creatinine >3.5 mg/dL or eGFR <20 mL/min per 1.73 m2.

- If the response to decreasing the dose is not satisfactory, specialist advice should be sought.
- By contrast, the following changes in kidney function are generally considered acceptable:
- An increase in serum creatinine of up to 50 percent above baseline
- An increase in serum creatinine up to 3 mg/dL (266 micromol/L)
- An estimated GFR that falls as low as 25 mL/min/1.73 m^2

HYPERKALEMIA

decreased sodium and water delivery to the potassium secretory site in the collecting tubules

. Maintenance of adequate potassium secretion is dependent upon increased secretion of aldosterone,

a response is partially impaired if there is diminished production of angiotensin II (since angiotensin II is the primary mediator of the hypoperfusion-induced increase in aldosterone release).

Approach to patients at risk for hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system

Estimate glomerular filtration rate to assess specific risk of hyperkalemia
Discontinue nonsteroidal antiinflammatory drugs and other drugs that interfere with renal potassium excretion
Inquire about use of herbal preparations
Prescribe a low-potassium diet
Inquire about use of potassium-containing salt substitutes
Prescribe thiazide or loop diuretics to increase potassium excretion
Prescribe sodium bicarbonate to correct metabolic acidosis if present
When initiating ACE inhibitor, angiotensin receptor blocker, or mineralocorticoid receptor antagonist, use low doses
Measure serum potassium concentration one week after initiating therapy or after increasing dose of these agents
If hyperkalemia develops (refer to content on specific drugs for thresholds), reduce or discontinue the drug(s) causing hyperkalemia.

Cough

- A dry, hacking cough in 5 to 20 percent of patients treated with an ACE inhibitor with following clinical features:
- begins within one to two weeks of instituting therapy
- Females more than males.
- resolves within one to four days of discontinuing therapy
- recurs with rechallenge(the same or a different ACE inhibitor)
- Not more frequently in patients with asthma
- The mechanism is not known
- NSAIDs and Aspirin can improve it

Other complication

- Anemia
- Angioedema and anaphylactoid reactions
- Drug-induced pancreatitis

Cancer and myocardial infarction risk not increased

NATRIURETIC RESPONSE TO DIURETICS

- ACE inhibitors can increase the natriuretic response to diuretics under certain circumstances : like acutely given in very low doses the response to a loop diuretic is enhanced.
- This is mediated by a decline in proximal sodium reabsorption induced by the reduction in intrarenal angiotensin II . the GFR is stable in this setting, presumably because sufficient angiotensin II is available to sustain efferent arteriolar tone.
- This interplay between ACE inhibitors and diuretics may be clinically important. One study that evaluated patients chronically treated with captopril (given at 12.5 mg three times daily) found that ACE inhibition moderately increased the diuretic response to furosemide by approximately 20 percent, despite reductions in blood pressure and GFR

ACE INHIBITORS VERSUS ARBS


ORIGINAL ARTICLE

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

- 25,000 patients
- Compared telmisartan to ramipril or both drugs
- Similar rates of hyperkalemia, acute kidney injury and syncope
- The rate of drug discontinuation: lower with Telmisartan
- Significantly higher rates of cough with Ramipril
- Telmisartan : higher rate of symptomatic hypotension

COMBINATION OF ACE INHIBITORS AND ARBs

- Increased adverse effects

ONTARGET

Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

Trial designed to assess whether ramipril plus telmisartan was more effective than either drug alone in the treatment of vascular disease and high-risk diabetes.

- **Design:** randomized, double blind
- **Patients:**25,620
- **Centers:** 733
- **Countries:** 40

Results: Patients in the telmisartan (n=8,542) and telmisartan/ramipril (n=8,502) groups had lower mean BP than those in ramipril alone (n=8,576). Primary outcome (death from CV causes, MI, stroke or hospitalization for HF) occurred in 1,412 patients in the ramipril group (16.5%) and 1,423 in the telmisartan group. The two drugs separately were equivalent and were linked to less angiodema. The combination was associated with more adverse events and no increased benefit. *Presented at ACC 2008.*

CARDIOLOGYtoday

- increased medication discontinuation
- Possible increased risk of cancer

Mineralocorticoid receptor antagonist

- Eplerenone suggested rather than spironolactone (risk gynecomastia, impotence in males)
- Initiation of MRA therapy is limited to patients who can be carefully monitored a with baseline serum potassium <5.0 mEq/L and an eGFR ≥30 mL/min per 1.73 m2.
- Periodic monitoring for hyperkalemia is required for all patients
- If K is 5.5 to 6.0 mEq/L, the dose should be decreased and If >6.0 mEq/L or renal function is worsening, should be discontinued
- The endocrine side effects : gynecomastia, breast pain, menstrual irregularities, impotence, and decreased libido

Thanks for your attention.