ALDOSTERONE ANTAGONISTS

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LEARNING OBJECTIVES

- Describe the mechanism of action, clinical uses and adverse effects of Spironolactone

- (Apart from being used as diuretic)

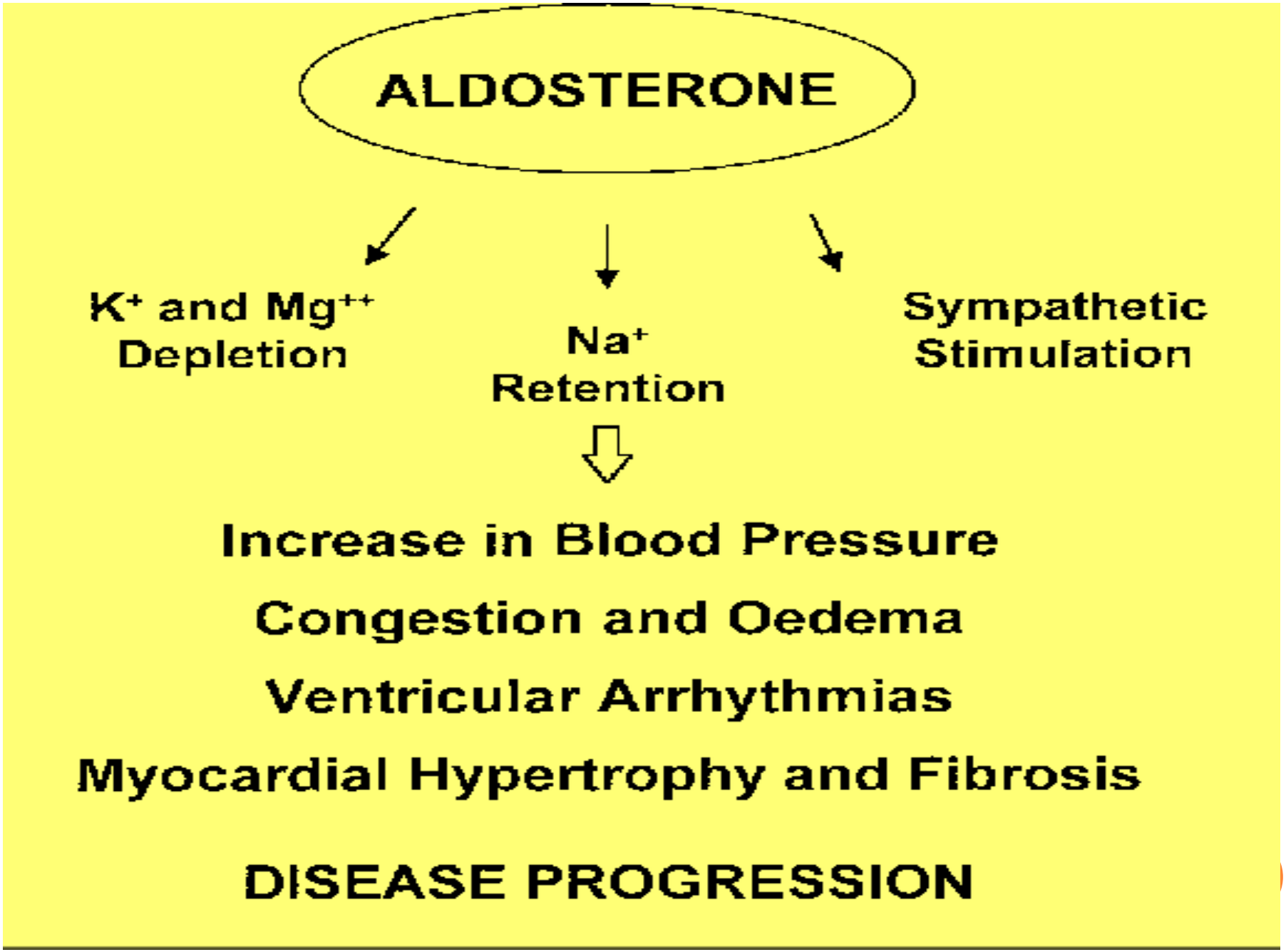
Physiological role of aldosterone

- Increased Na+ absorption in:
  - DCT
  - Salivary Glands
  - Colon
- Increased renal secretion of K+

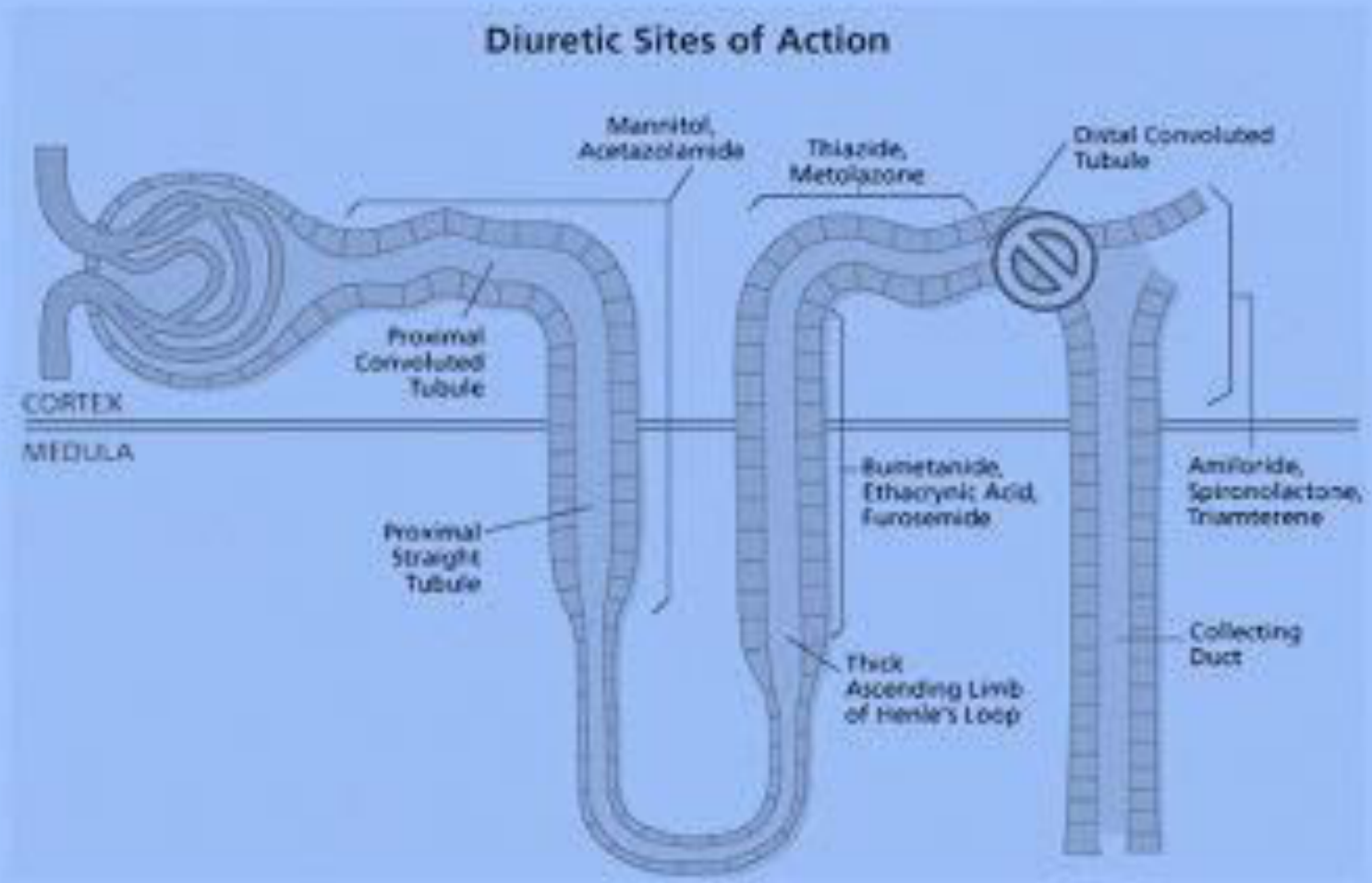
REGULATOR OF ALDOSTERONE

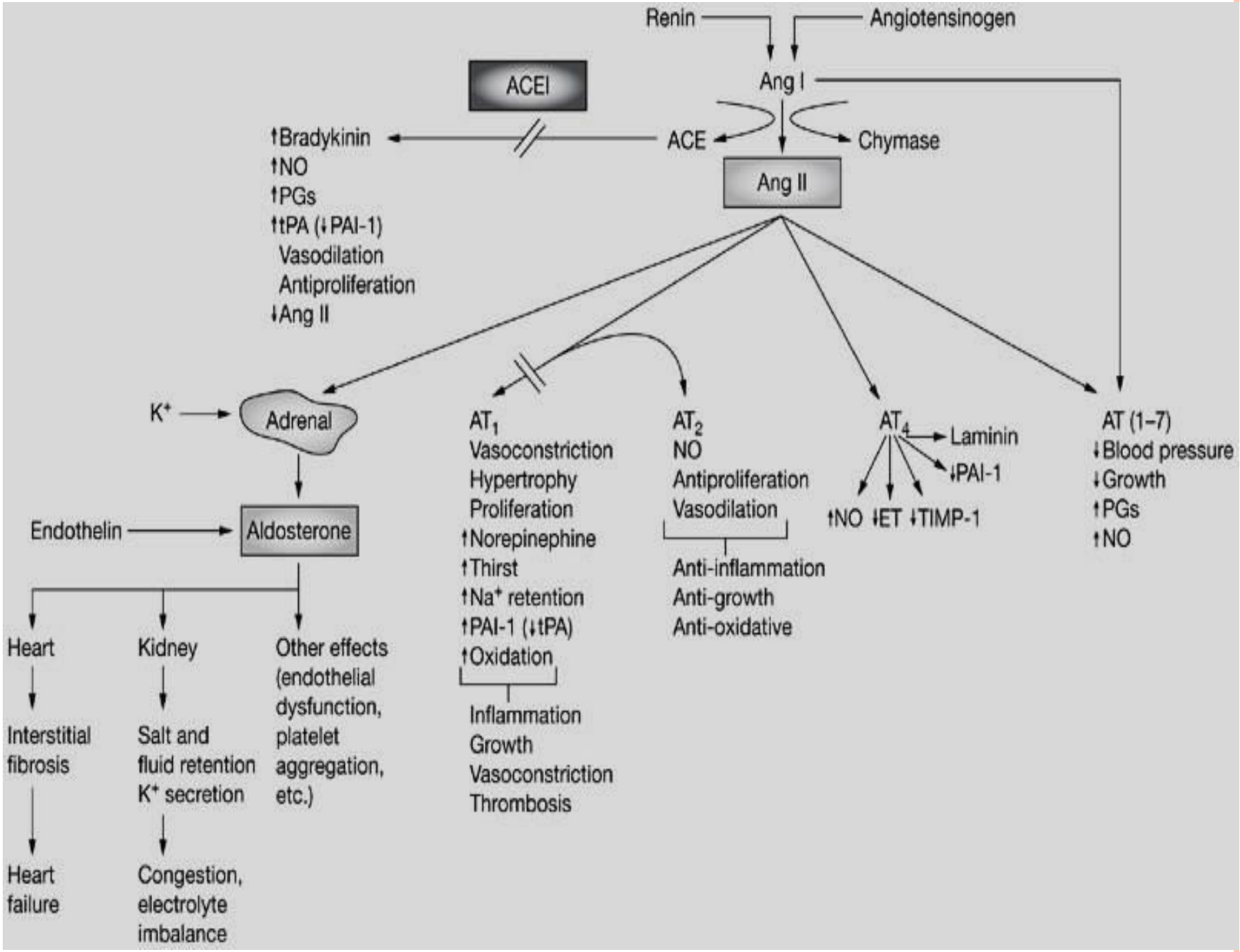
Via Negative Feedback

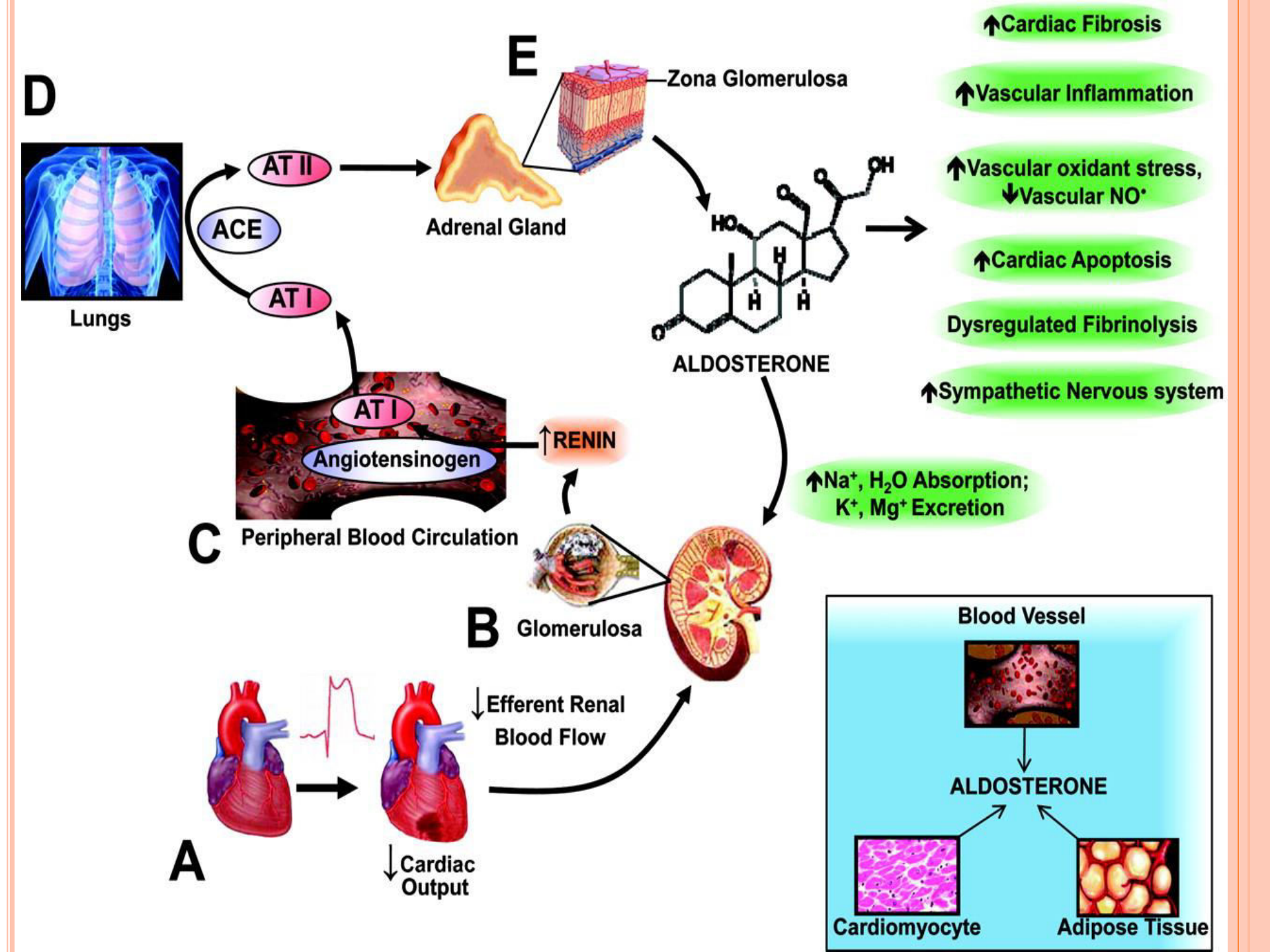
- Angiotensin II : Main Regulator
- Hyperkalemia


ALDOSTERONE
K+ and Mg++ Depletion
Na+ Retention
Sympathetic Stimulation
Increase in Blood Pressure
Congestion and Oedema
Ventricular Arrhythmias
Myocardial Hypertrophy and Fibrosis
DISEASE PROGRESSION

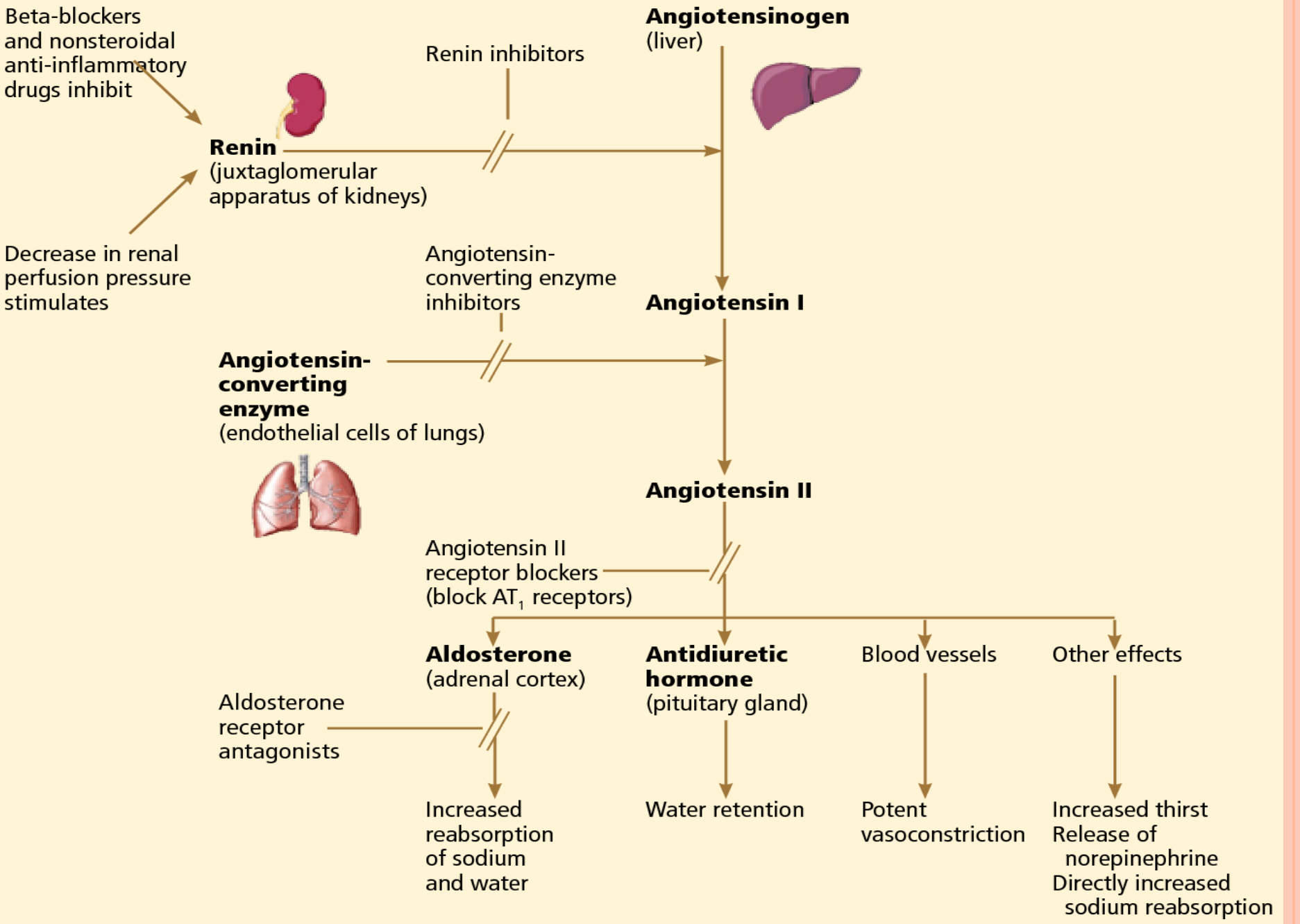
Aldosterone Antagonists

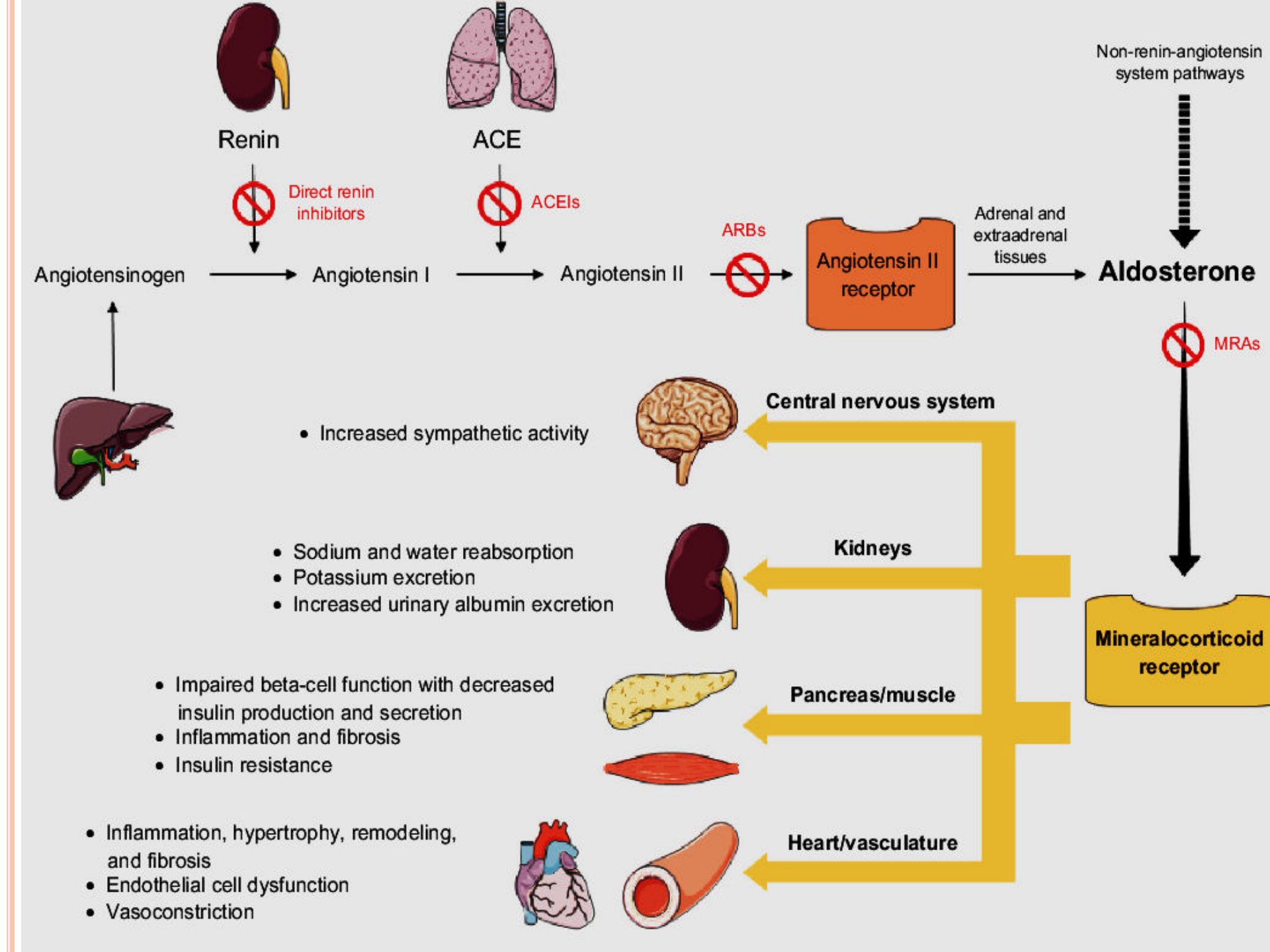



Renin
Angiotensinogen
ACEI
Ang I
↑Bradykinin
↑NO
↑PGs
↑tPA (↓PAI-1)
Vasodilation
Antiproliferation
↓Ang II
ACE
Chymase
Ang II
K+
Adrenal
Endothelin
Aldosterone
Heart
Kidney
Other effects (endothelial dysfunction, platelet aggregation, etc.)
Interstitial fibrosis
Salt and fluid retention
K+ secretion
Heart failure
Congestion, electrolyte imbalance
AT1
Vasoconstriction
Hypertrophy
Proliferation
↑Norepinephine
↑Thirst
↑Na+ retention
↑PAI-1 (↓tPA)
↑Oxidation
Inflammation
Growth
Vasoconstriction
Thrombosis
AT2
NO
Antiproliferation
Vasodilation
Anti-inflammation
Anti-growth
Anti-oxidative
AT4
Laminin
↓PAI-1
↑NO ↓ET ↓TIMP-1
AT (1–7)
↓Blood pressure
↓Growth
↑PGs
↑NO


↑Cardiac Fibrosis
↑Vascular Inflammation
↑Vascular oxidant stress,
↓Vascular NO•
↑Cardiac Apoptosis
Dysregulated Fibrinolysis
↑Sympathetic Nervous system
D
E
Zona Glomerulosa
AT II
ACE
AT I
Lungs
Adrenal Gland
ALDOSTERONE
AT I
Angiotensinogen
↑RENIN
C
Peripheral Blood Circulation
↑Na+, H2O Absorption;
K+, Mg+ Excretion
B
Glomerulosa
↓Efferent Renal
Blood Flow
A
↓Cardiac
Output
Blood Vessel
ALDOSTERONE
Cardiomyocyte
Adipose Tissue

The renin-angiotensin-aldosterone system and drugs that block it




Renin
ACE
Non-renin-angiotensin system pathways
Direct renin inhibitors
ACEIs
ARBs
Angiotensinogen
Angiotensin I
Angiotensin II
Angiotensin II receptor
Adrenal and extraadrenal tissues
Aldosterone
MRAs
Central nervous system
• Increased sympathetic activity
Kidneys
• Sodium and water reabsorption
• Potassium excretion
• Increased urinary albumin excretion
Mineralocorticoid receptor
Pancreas/muscle
• Impaired beta-cell function with decreased insulin production and secretion
• Inflammation and fibrosis
• Insulin resistance
Heart/vasculature
• Inflammation, hypertrophy, remodeling, and fibrosis
• Endothelial cell dysfunction
• Vasoconstriction

K- SPARING DIURETICS

- Potassium-sparing diuretics prevent potassium secretion by antagonizing the effects of aldosterone in collecting tubules.

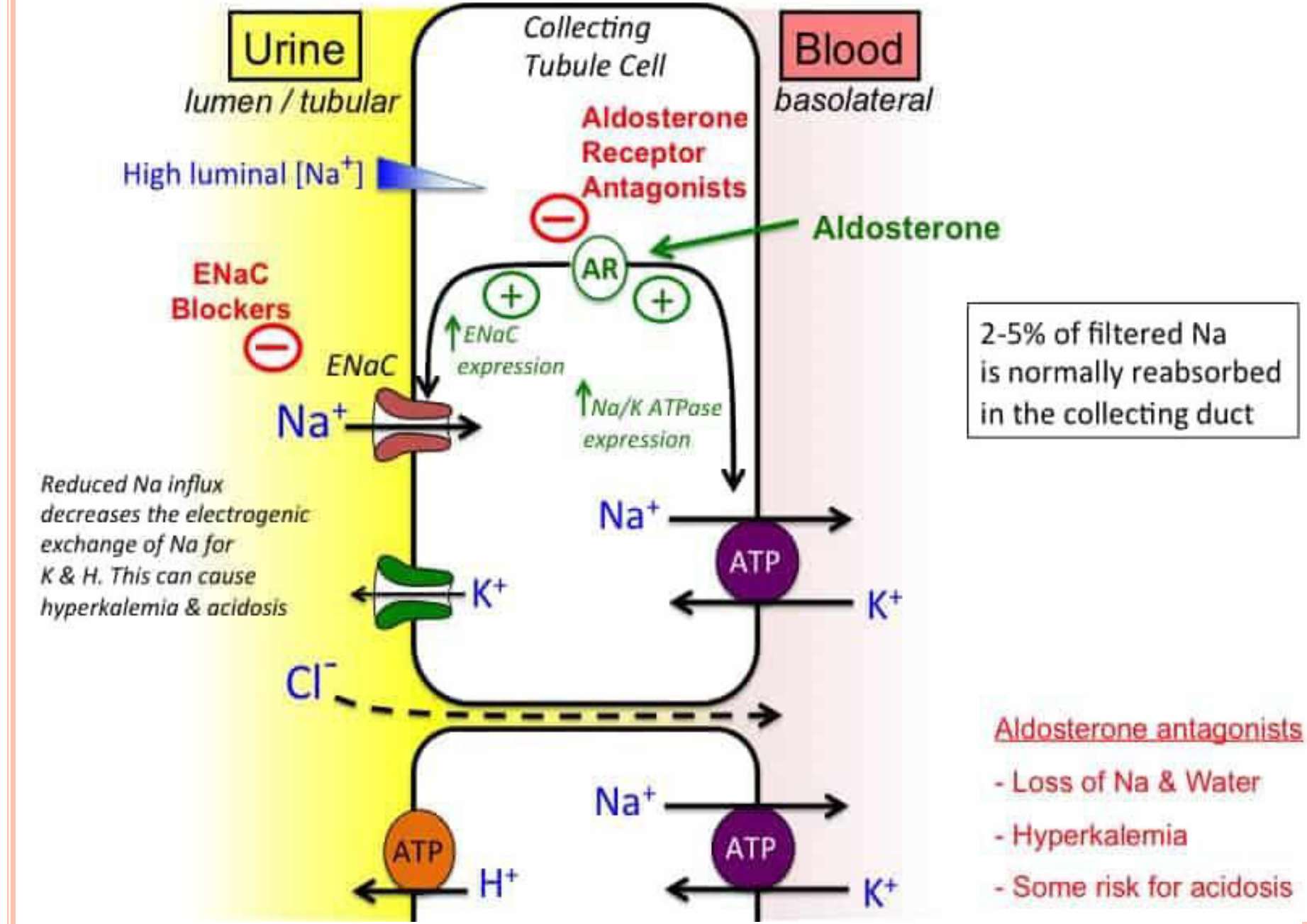
Inhibition may occur by:

- direct pharmacologic antagonism of mineralocorticoid receptors (spironolactone, eplerenone)
- inhibition of sodium influx through ion channels in the luminal membrane (amiloride, triamterene)

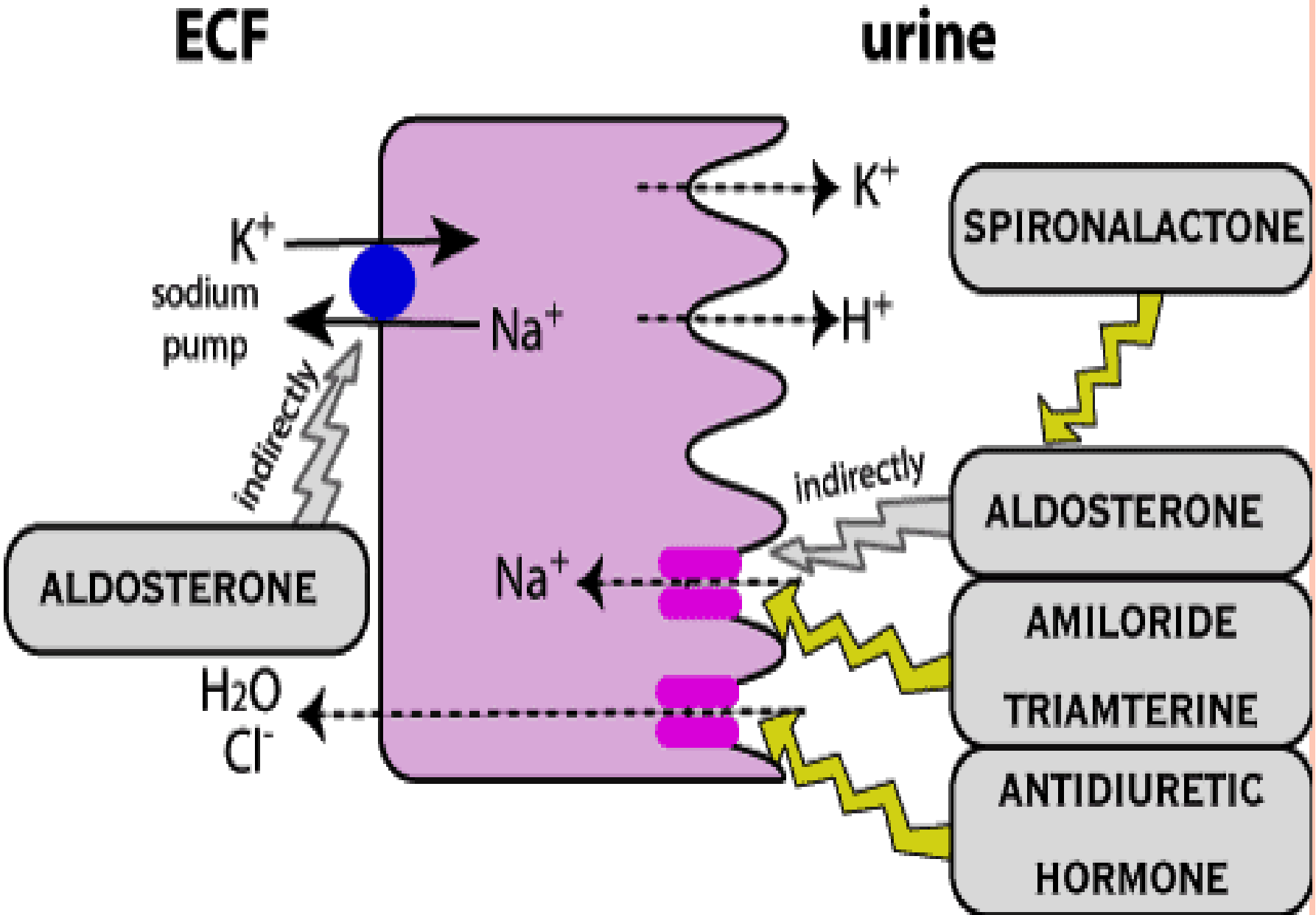
Potassium-sparing diuretics

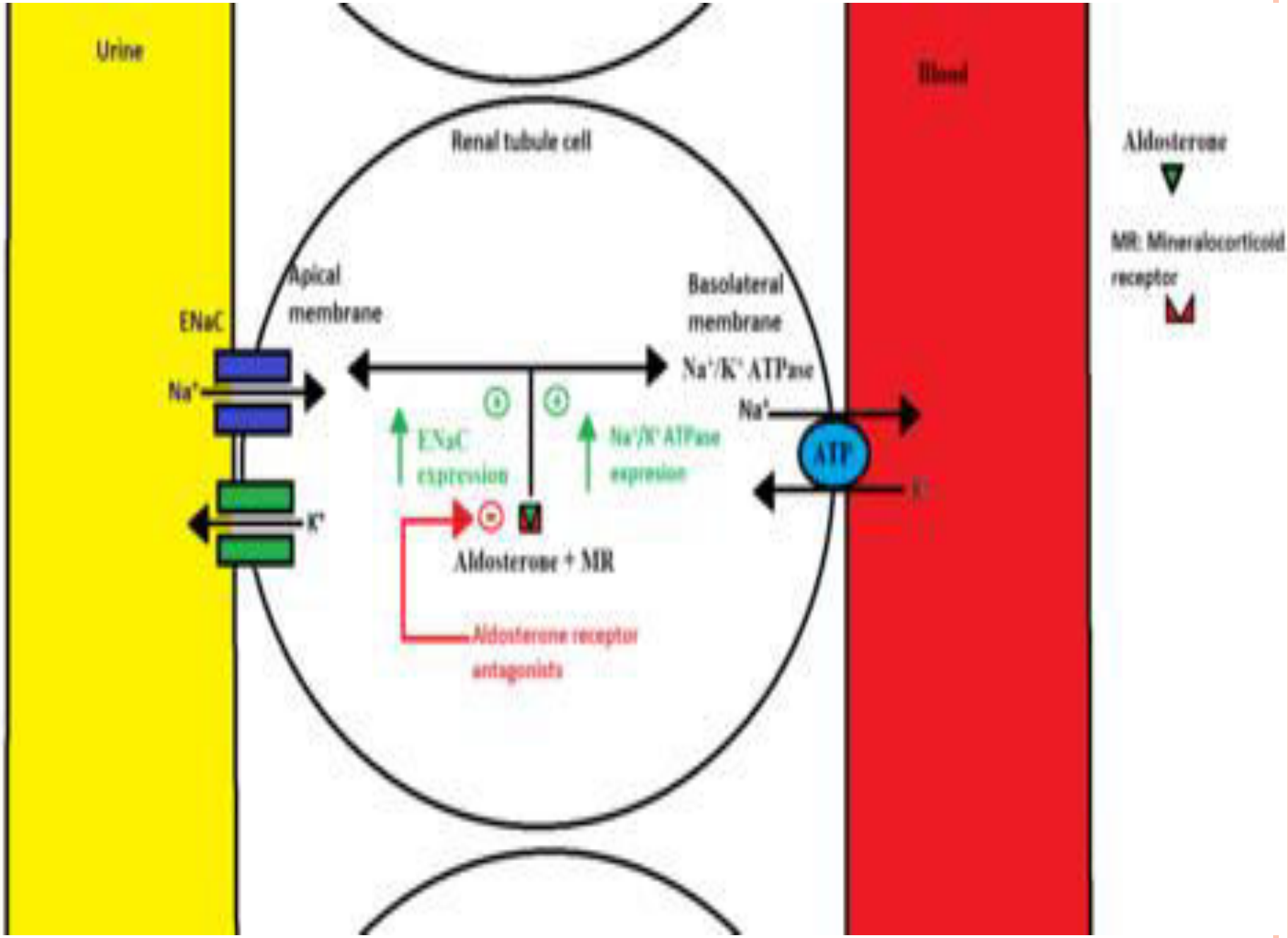
Competitive aldosterone antagonists:
- Spironolactone
- eplerenone

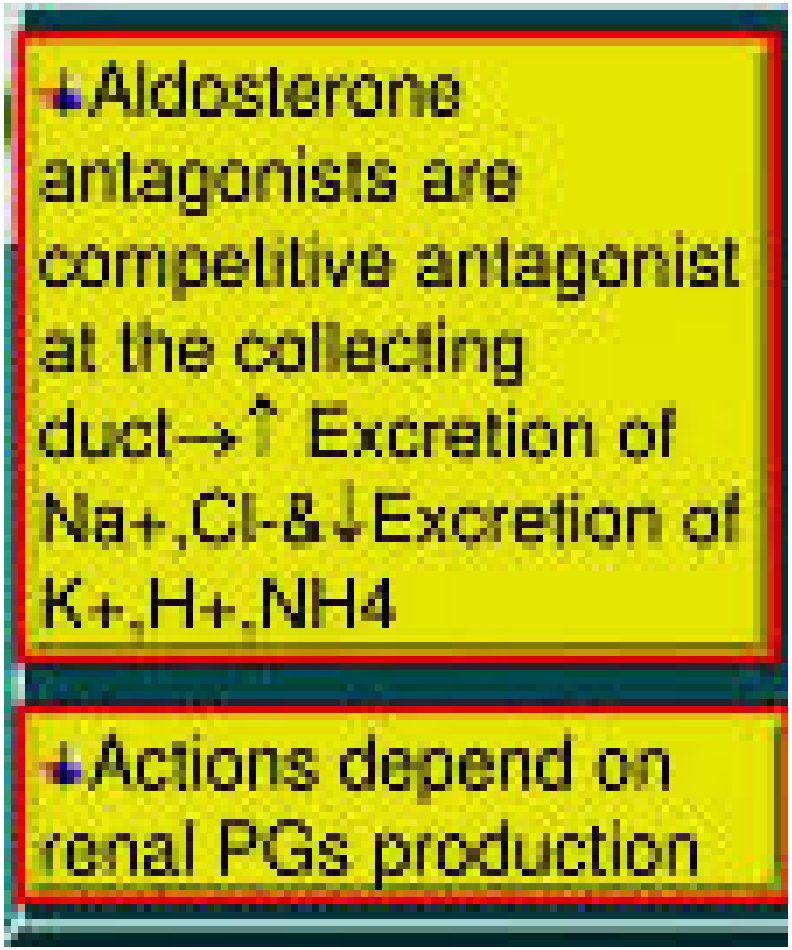
Inhibitors of Na^+ channels:
- Amiloride
- Triamterene


Urine
lumen / tubular
Collecting
Tubule Cell
Blood
basolateral
Aldosterone
Receptor
Antagonists
High luminal [Na+]
Aldosterone
AR
ENaC
Blockers
ENaC
ENaC
expression
Na/K ATPase
expression
Na+
Reduced Na influx
decreases the electrogenic
exchange of Na for
K & H. This can cause
hyperkalemia & acidosis
Na+
ATP
K+
K+
Cl-
Na+
ATP
ATP
H+
K+
2-5% of filtered Na
is normally reabsorbed
in the collecting duct
Aldosterone antagonists
- Loss of Na & Water
- Hyperkalemia
- Some risk for acidosis

POTASSIUM SPARING DIURETICS

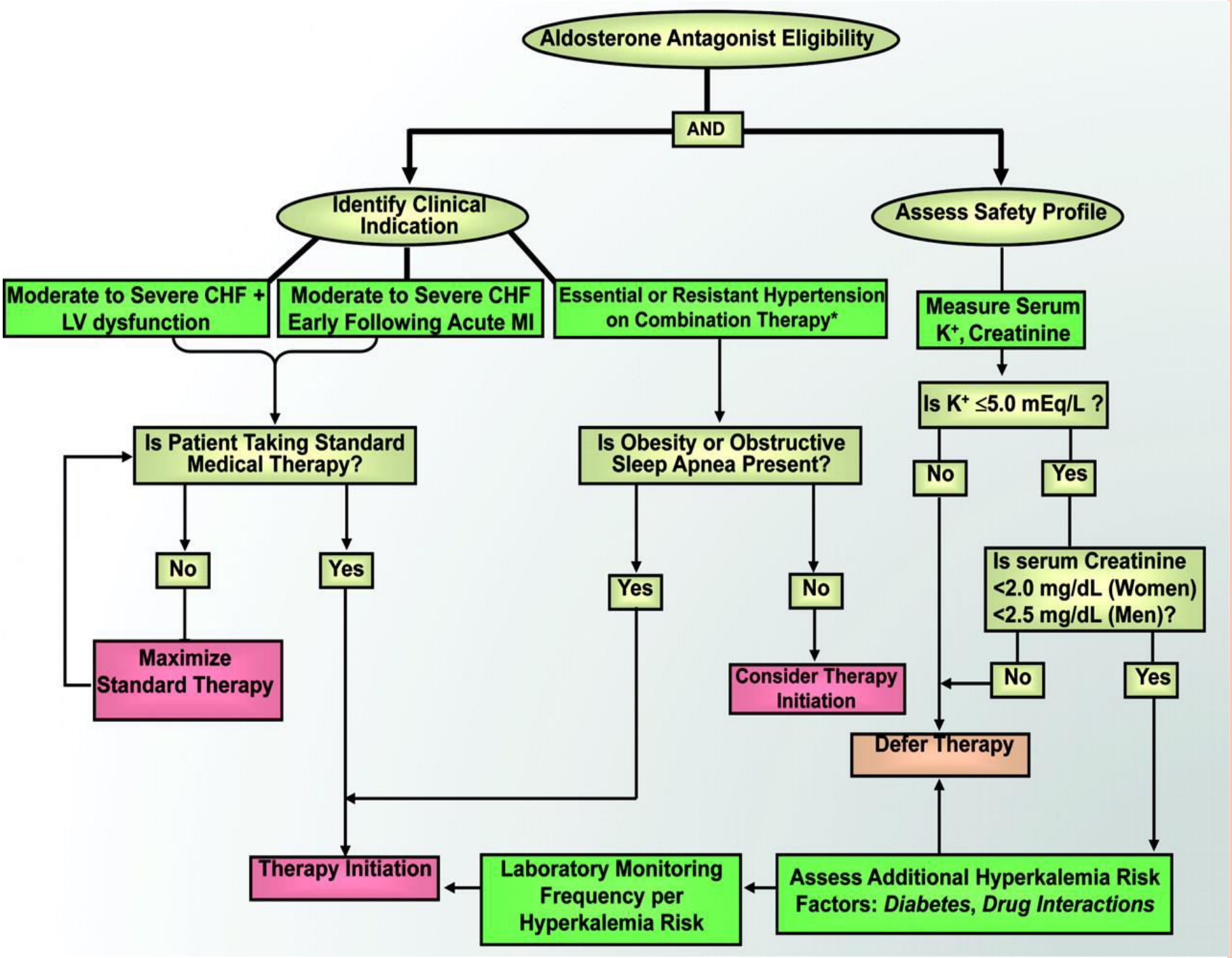



Urine
Blood
Renal tubule cell
Aldosterone
MR: Mineralocorticoid receptor
Apical membrane
Basolateral membrane
ENaC
Na+
K+
Na+/K+ ATPase
Na+
ATP
K+
ENaC expression
Na+/K+ ATPase expression
Aldosterone + MR
Aldosterone receptor antagonists


Aldosterone antagonists are competitive antagonist at the collecting duct→↑ Excretion of Na+,Cl-&↓Excretion of K+,H+,NH4
Actions depend on renal PGs production

ALDOSTERONE ANTAGONISTS

- Spironolactone: Non selective
  - Aldactone®: 25 mg, 100 mg
  - Component of Spiromide 20®, Spiromide 40®
  - CaroSpir®
- Eplerenone: Selective
  - Inspra®
- Finerenone:
  - Kerendia®


Aldosterone Antagonist Eligibility
AND
Identify Clinical Indication
Assess Safety Profile
Moderate to Severe CHF + LV dysfunction
Moderate to Severe CHF Early Following Acute MI
Essential or Resistant Hypertension on Combination Therapy*
Measure Serum K+, Creatinine
Is K+ ≤5.0 mEq/L ?
No
Yes
Is Patient Taking Standard Medical Therapy?
Is Obesity or Obstructive Sleep Apnea Present?
Is serum Creatinine <2.0 mg/dL (Women) <2.5 mg/dL (Men)?
No
Yes
Yes
No
No
Yes
Maximize Standard Therapy
Consider Therapy Initiation
Defer Therapy
Therapy Initiation
Laboratory Monitoring Frequency per Hyperkalemia Risk
Assess Additional Hyperkalemia Risk Factors: Diabetes, Drug Interactions

POTASSIUM-SPARING DIURETICS

1. *Aldosterone antagonists*:

Spironolactone and eplerenone:

- The spironolactone-receptor complex is inactive complex results in a failure to produce proteins (which is normally stimulate the Na^+ /K^+ exchange sites of the collecting tubule.
- Eplerenone may have less endocrine effects than spironolactone.
- Spironolactone is completely absorbed orally and is strongly bound to proteins. It induces hepatic cytochrome P450.

SPIRONOLACTONE

Indication Other than diuresis

- Spironolactone is an aldosterone receptor antagonist
- It is a potassium-sparing diuretic.
- Also used to treat:-
  - Edema
  - Hypertension
  - Heart failure
  - Aldosteronism
    - Primary
    - Secondary

SPIRONLACTONE: PHARMACOKINETICS

Spironolactone is a synthetic steroid that acts as competitive antagonist to aldosterone.

Substantial inactivation of spironolactone occurs in the liver.

It has slow onset of action, requiring several days before full therapeutic effect is achieved.

SPIRONLACTONE: MECHANISM OF ACTION

- Potassium-sparing diuretics reduce sodium absorption in the collecting tubules and ducts.
- Potassium absorption and secretion at this site is regulated by aldosterone.
- Aldosterone antagonists interfere with this process.

RATIONALE OF USE

Hypokalemia	→	*Associated with loop and thiazide diuretics*
Moderate to Severe HF	→	*Reduce cardiac work*
Hypertension	→	*Reduce sodium levels*
Hyperaldosteronism	→	*Antagonize aldosterone*

Potassium-sparing diuretics

Clinical Indications:

- **In states of mineralocorticoid excess:**

  Primary hypersecretion (Conn's syndrome, ectopic ACTH production)

  Secondary aldosteronism (from heart failure, hepatic cirrhosis, nephrotic syndrome, and other conditions associated with diminished effective intravascular volume)

- **Combined with other diuretic drugs**

INDICATIONS

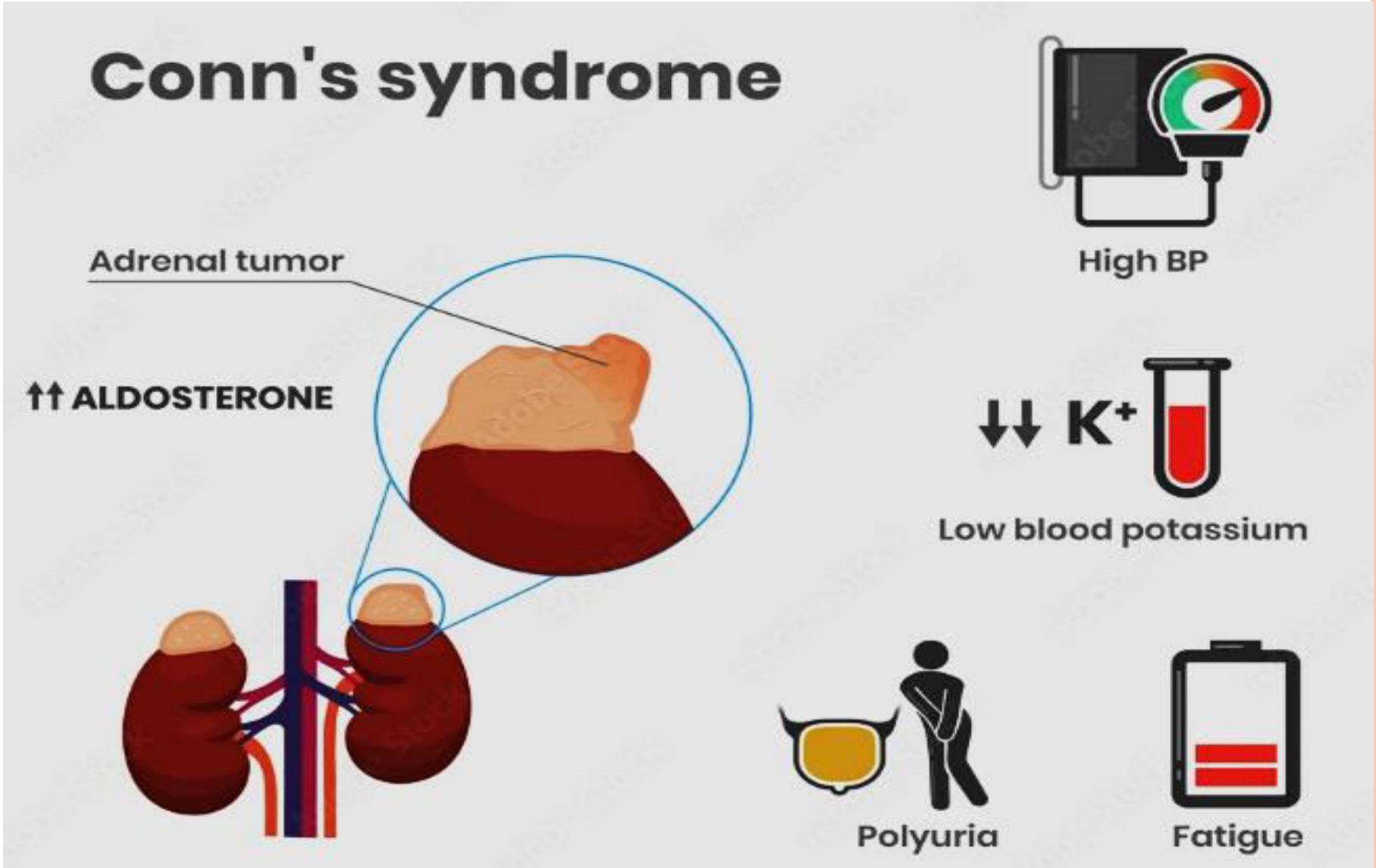
Clinical uses of potassium-sparing diuretics (e.g. amiloride, spironolactone)

- in *heart failure*, where either of these improves survival
- in primary *hyperaldosteronism* (Conn's syndrome)
- in *resistant essential hypertension* (especially low-renin hypertension)
- in *secondary hyperaldosteronism* caused by hepatic cirrhosis complicated by ascites.

INDICATIONS

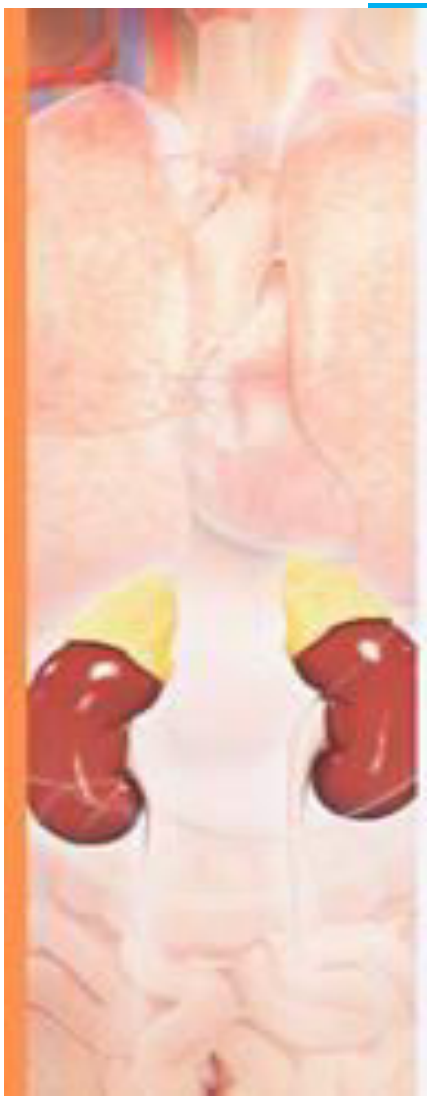
- Use of thiazides or loop agents can exacerbate volume depletion and causes secondary hyperaldosteronism.
- eplerenone has been found to reduce myocardial perfusion defects after MI.
- eplerenone reduced mortality rate by 15% (compared with placebo) in heart failure after MI.

CONN'S SYNDROME



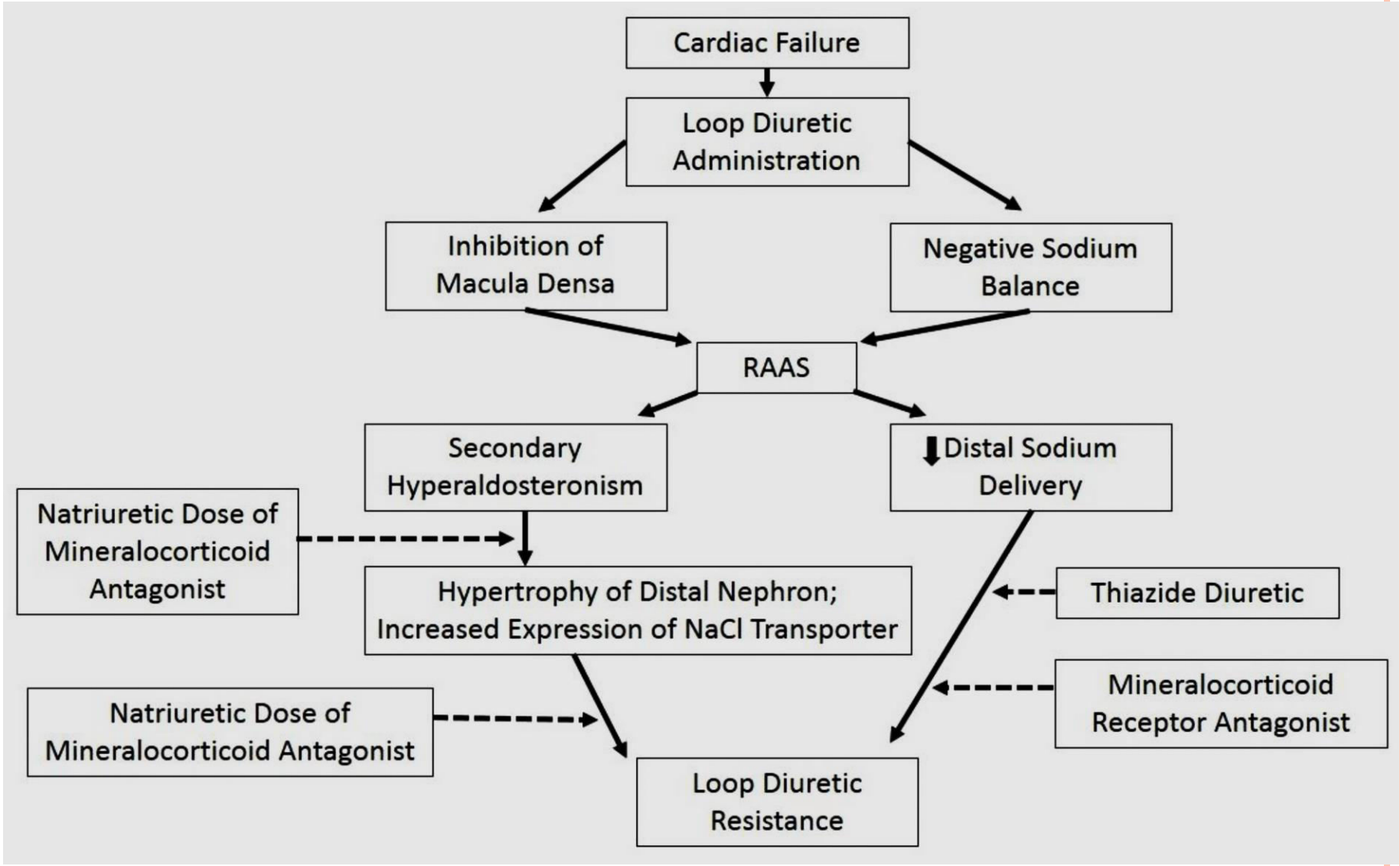
PRIMARY HYPERALDOSTERONISM

CONN'S SYNDROME ?????



- Drug-resistant hypertension
- Hypertension requiring many medications
- Hypertension at a young age
- (< 50 years of age)
- Hypertension with low blood potassium
- Hypertension with an adrenal incidentaloma
- Hypertension and sleep apnea
- Hypertension and a family history of early-onset hypertension or stroke
- Hypertension and a family history of any type of adrenal tumor
- Hypertension that is episodic

FRUSEMIDE *OR* THIAZIDE + SPIRONOLACTONE



ALDOSTERONE ANTAGONIST DOSES

Aldosterone antagonist	Dosing
Spironolactone	■ Initial dose: 25 mg daily in those with a serum potassium <5 mmol/L and serum creatinine <2.5 mg/dL ■ Target dose: 50 mg once daily as clinically indicated ■ If 25 mg once daily is not tolerated, reduce the dose to 25 mg on alternate days
Eplerenone	■ Initial dose: 25 mg once daily ■ Target dose: 50 mg once daily

Adverse effects

- Potassium-Sparing diuretics
  - Hyperkalemia
  - Hyperchloremic metabolic acidosis
  - Kidney stones

CONTRAINDICATIONS

- Potassium-sparing agents can cause severe, even fatal, hyperkalemia in susceptible patients.
- Patients with chronic renal insufficiency are especially vulnerable.

EPLERENONE

EPLERENONE

- Derived from a hydride of Pregnane, it is a steroidal Mineralocorticoid antagonist
- It lacks the anti-androgenic side effects of spironolactone.
- At equipotent doses, eplerenone might cause less hyperkalemia than spironolactone in patients with hypertension

EPLERENONE

- Both Spironolactone and Eplerenone are Steroidal MR antagonists (MRAs)
  - Spironolactone (first generation MRA)
  - Eplerenone (second generation MRA)
- Both of them are Shown to be effective in reducing:-
  - Cardiovascular mortality and morbidity in patients with Chronic HF and a reduced left ventricular ejection fraction (HFrEF).

EPLERENONE

::::VERSUS SPIRONOLACTONE::::

- **Spironolactone** is structurally similar to progesterone and binds to BOTH progesterone, androgen and mineralocorticoid receptors
- **Eplerenone** is a selective mineralocorticoid receptor antagonist
- It DOES NOT binds to progesterone and androgen receptors
- It lacks the anti-androgenic side effects of Spironolactone

EPLERENONE

USES

- FDA approved for uncomplicated Essential Hypertension since 2003

- The so called salt substitutes called LO-SALTS should preferably be avoided with Eplerenone as they are rich in Potassium

FINERENONE

FINERENONE

MOA

- Inhibits the effects of mineralocorticoids like aldosterone and cortisol when the MR is over activated

- Possibly reduces inflammation and fibrosis in the heart and kidney.

FINERENONE

PHARMACOLOGICAL ACTIONS

- Lower risk of CKD progression especially when used in combination with SGLT 2 inhibitors
  - Empagliflozin
  - Canagliflozin
  - Dapagliflozin
  - Bexaglifloxin
  - Ertugliflozin
- Lower risk of cardiovascular events than placebo.

FINERENONE

Versus spironolactone and Eplerenone

- 10 – 20 mg OD
- A high affinity for the mineralocorticoid receptor. (significantly higher than both spironolactone and eplerenone)
- Non-steroidal type MRA
- Absence of gynecomastia

DIURETIC-DRUG INTERACTIONS

Selected Drug-Diuretic Interactions

Drug	Diuretics	Problems
digitalis	loop & thiazide	hypokalemia → dig toxicity
ACE-inhibitors	K^+ sparing	hyperkalemia → arrhythmias
aminoglycoside	loop	ototoxicity & nephrotoxicity
adrenal steroids	loop & thiazide	severe hypokalemia
Chlorpropamide	thiazide	hyponatremia
NSAIDs	loop & thiazide	decreased diuretic effect
Probenecid	loop & thiazide	decreased diuretic effect
Lithium	loop & thiazide	increased plasma [Lithium]

Aldosterone receptor antagonists: side effects and the risk of hyperkalemia

MAJOR ADVERSE EFFECTS

Electrolyte abnormalities
- Hyperkalemia
- Hyponatremia
- Hyperchloremic metabolic acidosis

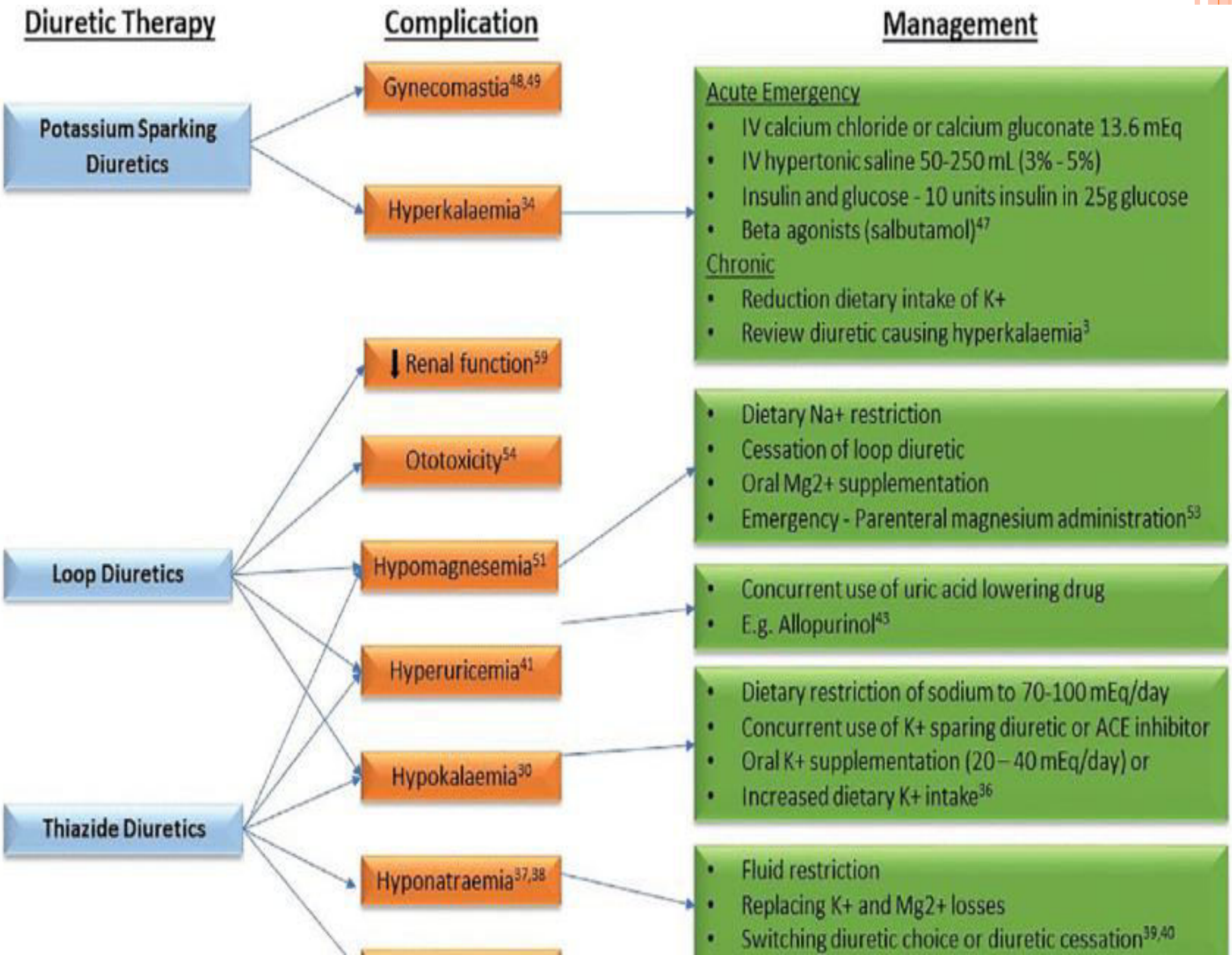
Decline in glomerular filtration rate (GFR)

Antiandrogenic effects (dose-related, negligible with eplerenone)
- Gynecomastia
- Breast tenderness
- Impotence

Upper gastrointestinal side effects

RISK FACTORS FOR HYPERKALEMIA

Chronic kidney disease (risk inversely proportional to the GFR)
Concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker
Concomitant use of other drugs that could cause hyperkalemia, eg, nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics
Older age
Diabetes
Prerenal failure (due to volume depletion)
Diarrhea
Renovascular disease


Diuretic Therapy
Complication
Management
Potassium Sparking Diuretics
Gynecomastia[48,49]
Hyperkalaemia[34]
Acute Emergency
• IV calcium chloride or calcium gluconate 13.6 mEq
• IV hypertonic saline 50-250 mL (3% - 5%)
• Insulin and glucose - 10 units insulin in 25g glucose
• Beta agonists (salbutamol)[47]
Chronic
• Reduction dietary intake of K+
• Review diuretic causing hyperkalaemia[3]
Loop Diuretics
↓ Renal function[59]
Ototoxicity[54]
Hypomagnesemia[51]
Hyperuricemia[41]
Hypokalaemia[30]
• Dietary Na+ restriction
• Cessation of loop diuretic
• Oral Mg2+ supplementation
• Emergency - Parenteral magnesium administration[53]
• Concurrent use of uric acid lowering drug
• E.g. Allopurinol[43]
Thiazide Diuretics
Hyponatraemia[37,38]
• Dietary restriction of sodium to 70-100 mEq/day
• Concurrent use of K+ sparing diuretic or ACE inhibitor
• Oral K+ supplementation (20 – 40 mEq/day) or
• Increased dietary K+ intake[36]
• Fluid restriction
• Replacing K+ and Mg2+ losses
• Switching diuretic choice or diuretic cessation[39,40]

MCQ

A 67 year old male is treated for congestive heart failure. A multidrug treatment regimen results is marked improvement of the patient's symptoms. An agent is added to this patient's regimen that is believed to benefit the overall survival. Which of the following is the drug used in this patient?

- Hydrochlorothiazide
- Furosemide
- Spironolactone
- Mannitol
- Acetazolamide

REFERENCES

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