# CARDIOVASCULAR PHARMACOLOGY

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# ACE INHIBITORS AND ARBS

**ACE-I & ARBs | Mechanism of Action, Indications, Adverse Reactions, Contraindications**

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## OUTLINE



## I) INTRODUCTION

ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors
ARBs = Angiotensin-II Receptor Blockers

### (A) RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM PHYSIOLOGY

#### Components of RAAS

- Renin
  - Enzyme produced by the kidneys
- Angiotensinogen
  - Protein produced by the liver
  - circulates in the blood
- Angiotensin-I
  - precursor molecule
- Angiotensin Converting Enzyme (ACE)
  - Mostly Produced by Capillary endothelial cells of the lungs
- Angiotensin-II
  - Extremely potent vasoconstrictive agent

#### Production of ANG-II

1) ↓Systemic BP, ↓ Blood Flow to the kidneys → stimulates Juxtaglomerular cells in the Afferent arteriole of glomerulus in the kidney to release **Renin**
2) Renin converts **Angiotensinogen** made by the liver into **Angiotensin-I**
3) Angiotensin-I circulates in the body and goes to lungs
4) Angiotensin-I in lungs reacts with **Angiotensin Converting enzyme (ACE)**
5) ACE converts Angiotensin-I into **Angiotensin-II**

#### Angiotensin-II Effects:

1) Vasoconstriction
   a. Angiotensin-II receptors on the vascular smooth muscle→ Contraction of the smooth muscle → Vasoconstriction → ↓Vessel Diameter→ ↑Total Peripheral Resistance (TPR) → ↑BP

   BP= CO x TPR

2) Antidiuretic Hormone ADH
   a. Angiotensin-II Stimulates Posterior Pituitary→ ↑ADH release→ Acts on Kidneys →↑water reabsorption in Collecting duct of kidneys→ ↑Blood Volume→ ↑BP
3) Aldosterone
   a. Steroid Hormone produced by Zona Glomerulosa of the adrenal medulla
   b. Angiotensin-II Stimulates Aldosterone Production from Adrenal Cortex→ Aldosterone →Acts on Kidneys→ ↑Na+ and H20 reabsorption in Distal Convoluted Tubules of kidney→ ↑ Blood Volume→ ↑BP
   c. Aldosterone initiates $K^+$ Excretion in the Urine→ Hypokalemia

## II) MECHANISM OF ACTION

#### ACE Inhibitors

- Inhibits the production of ACE → Inhibits the conversion of Angiotensin-I to Angiotensin-II → ↓ Angiotensin-II

- ↓ Angiotensin-II
  - Vasodilation → ↑Diameter of the blood vessels →↓TPR →↓BP
  - ↓ADH →↓ H2O Reabsorption →↓Blood Volume→ ↓BP
  - ↓ Aldosterone →↓ H2O, $Na^+$ Reabsorption →↓Blood Volume→ ↓BP
  - ↓ Aldosterone→ ↓ excretion of $K^+$→ Hyperkalemia

#### ARBs

- Inhibits Angiotensin-II from Binding to its Receptors
  - Inhibits Angiotensin-II from Binding to Receptors on the vascular smooth muscle → Vasodilation
  - Inhibits Angiotensin-II from Binding to Receptors in the Posterior Pituitary→↓ADH
  - Inhibits Angiotensin-II from Binding to Receptors in the Adrenal Cortex →↓ Aldosterone

- Both can also decrease the Stress on the heart by decreasing the Afterload and Preload:
  - Stress on the heart
    - Vasoconstriction→ ↓Vessel Diameter→ ↑Total Peripheral Resistance (TPR) → ↑Afterload →↑Stress on the heart
    - ↑BV →↑Preload →↑EDV →↑Stress on the heart
  - ACE-Is and ARBs effects
    - ACE-Is and ARBs effects → Vasodilation →↓ TPR→↓ Afterload
    - ACE-Is and ARBs effects →↓ H2O, $Na^+$ Reabsorption→↓Blood Volume →↓ Preload

## III) DRUGS NAMES

#### (1) ACE Inhibitors

- Benazepril
- Captopril
- Enalapril
- Lisinopril

#### (2) ARBs

- Candesartan
- Losartan
- Valsartan

## IV) INDICATIONS

- Hypertension
  - African American and older patients who have low-renin hypertension may not respond to ACE-I and ARBs.

**"Low Renin" vs "High Renin" Hypertension Treatment** [Williams et al., 2004]

People who are younger than 55 and white tend to have higher renin concentrations than people aged 55 or older or the black population (of African descent). ACE-I, ARBs and Beta blockers are therefore generally more effective as initial blood pressure lowering treatment in younger white patients than Calcium Channel Blockers or Diuretics. However, Calcium Channel Blockers or Diuretics are more effective first line agents for older white people or black people of any age.

- Coronary Artery Disease
  - Post MI
- Heart Failure
  - Reducing afterload especially in those who has systolic HF is very beneficial
- Proteinuric Kidney Disease
  - ↓ Protein in the urine
  - **Diabetic Nephropathy**
    - Nephroprotective
- Cardiac Remodeling
  - Mostly seen in patients who have Heart Failure, Heart Attack or Chronic Hypertension
  - ↑Blood Volume →↑ **Preload** → ↑Stress on heart →if on a weak heart → cardiac remodeling
  - Vasoconstriction →↑ TPR→↑ **Afterload** →↑Stress on heart → if on a weak heart → cardiac remodeling

## V) SIDE EFFECTS

- Hyperkalemia
  - Can cause Cardiac Arrythmia
- Hypotension
- Angioedema
  - Mostly by ACE-I
- Dry Cough
  - Specific to ACE-I

### How do ACE-Is cause Angioedema and Cough?

By inhibiting the degradation of Bradykinin

Bradykinin Production

- Pre-kallikrein → Kallikrein
  - C1E-I: C1 Esterase Inhibitor, Inhibits the conversion
  - XII a: Stimulates the conversion
- Kallikrein → Converts HMWK (High Molecular Weight Kininogen) into→ Bradykinin
- Bradykinin effects:
  - **Bronchoconstriction**
    - **Cough**
    - Respiratory distress
  - ↑ **Capillary permeability and blood flow**
    - **Edema and Swelling →angioedema**
  - Certain nerves
    - Pain
- ACE → ↑ breaking down (Degradation) of Bradykinin

**In C1E-I deficiency, ACE-I administration may exacerbate the side effects because of ↑↑ Bradykinin**

## VI) CONTRAINDICATIONS

- Angioedema
- Pregnancy
  - Teratogenic
- Drug interactions
  - Anti-Hypertension drugs
    - ↑ risk of hypotension
  - Potassium sparing diuretics
    - Spironolactone
  - NSAID
    - Increase sodium and water retention
  - Lithium
    - Decrease the elimination of Lithium
- Bilateral Renal Artery Stenosis
- Severe Chronic Kidney disease
- C1 Esterase Inhibitor Deficiency

## VII) REVIEW QUESTIONS

1) **A significant number of patients started on ACE inhibitor therapy for hypertension are intolerant and must be switched to a different class of drug. What is the most common manifestation of this intolerance?** [Trevor et al, 2018]
   a. Angioedema
   b. Glaucoma
   c. Headache
   d. Incessant cough
   e. Ventricular arrhythmias

2) **A 54-year-old man with diabetes presents to clinic for a routine checkup. At his prior two visits, he had an elevated blood pressure and has tried lifestyle changes to improve it. Today, his blood pressure is 142/88 mm Hg. His last urinalysis showed a urine microalbumin of 150 mcg. What is the most appropriate initial anti-hypertensive for this patient?** [Zaslau, 2013]
   a. Doxazosin
   b. Hydrochlorothiazide
   c. Lisinopril
   d. Metoprolol
   e. Nifedipine

**CHECK YOUR ANSWERS**

## VIII) REFRENCES


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