

# **A Pharmacist's Perspective: Use of Angiotensin-Converting Enzyme Inhibitors & Angiotensin Receptor Blockers in Chronic Kidney Disease**

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# Objectives

- Provide a brief overview of the pharmacology of ACE inhibitors and ARBs
- Discuss the recommended dosing and titration of ACE inhibitors and ARBs
- Discuss common adverse effects of ACE inhibitors and ARBs
- Discuss ACE inhibitor / ARB combination therapy and the results of the ONTARGET trial
- Discuss the top 10 things pharmacists would like to emphasize about ACE inhibitor and ARB use

# What are ACE inhibitors & ARBs?

## Both work on the Renin-Angiotensin-Aldosterone System (RAAS)

Angiotensin II causes vasoconstriction and aldosterone release.

The end result for both ACE inhibitors and ARBs is decreased activity of Angiotensin II, thereby causing vasodilation and decreased aldosterone release. ACE inhibitors and ARBs can cause potassium levels to increase because of this decrease in aldosterone release.

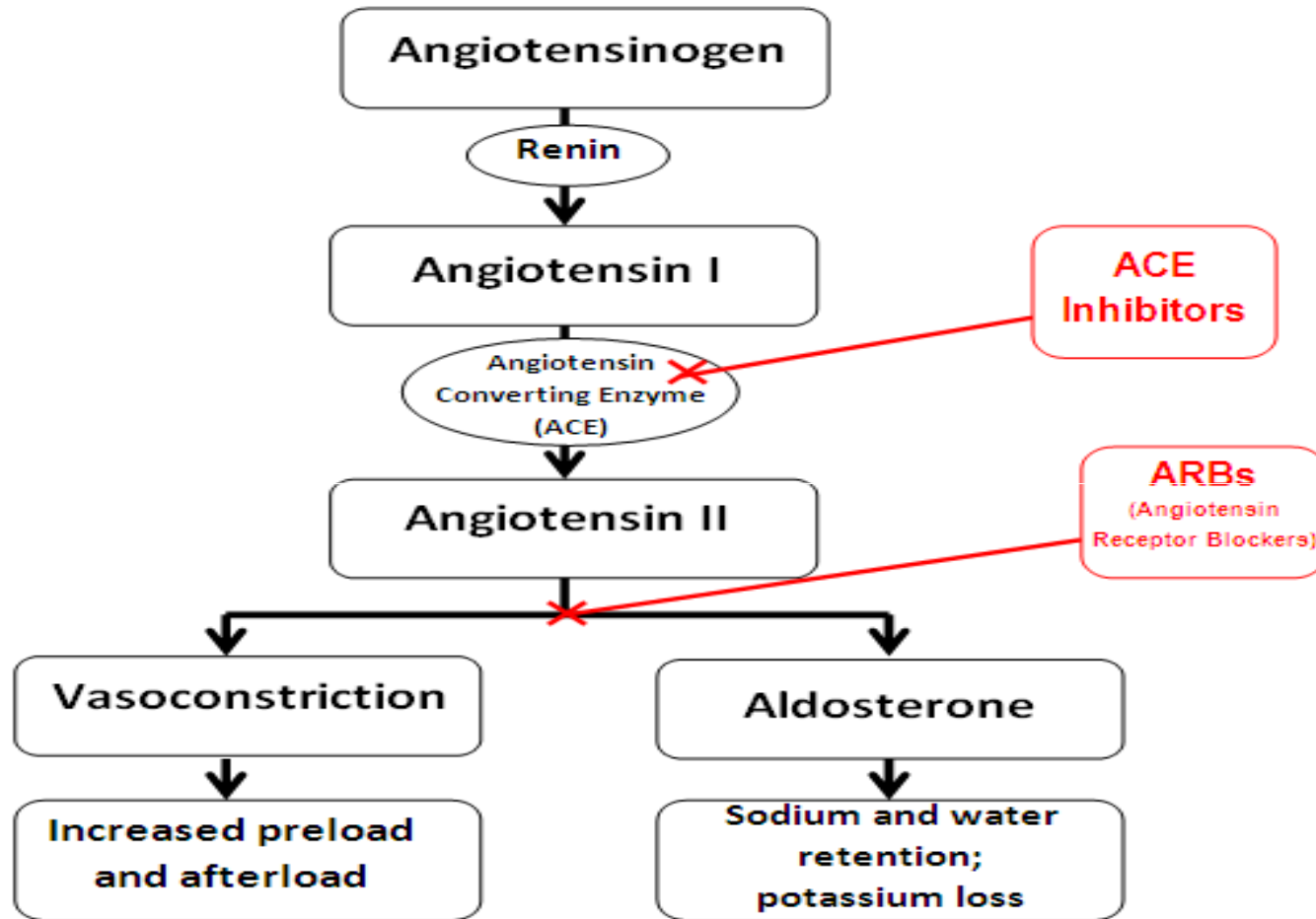
### Angiotensin-Converting Enzyme Inhibitors (ACE inhibitors)

ACE inhibitors work “higher up” in the RAAS by blocking the enzyme (ACE) that converts Angiotensin I to Angiotensin II

### Angiotensin II Receptor Blockers (ARBs)

ARBs work “further down” in the RAAS by blocking the receptor that Angiotensin II attaches itself to

# Action of ACE Inhibitors & ARBs



# Dosing of ACE inhibitors & ARBs in CKD

- Lower starting doses are recommended (15 to 25% of the maximum dose)
- Titrate slowly (every 4 to 8 weeks) to the target dose
- Titrate, as tolerated, to moderate to high doses because some of the benefits of these drugs are independent of blood pressure lowering effect
- “Starting low” and “going slow” can prevent the development of serious side effects (e.g. renal failure, hyperkalemia, hypotension)

## Dosage Range of ACE inhibitors and ARBs in CKD

ACE inhibitors	Usual Dosage Range mg/day (# of Daily Doses)	ARBs	Usual Dosage Range mg/day (# of Daily Doses)
Benazepril (Lotensin®)	20 to 40 (1 - 2)	Candesartan (Atacand®)	16 to 32 (1)
Captopril (Capoten®)	25 to 150 (2 - 3)	Eprosartan (Teveten®)	400 to 800 (1 - 2)
Enalapril (Vasotec®)	10 to 40 (1 - 2)	Ibesartan (Avapro®)	150 to 300 (1)
Fosinopril (Monopril®)	20 to 40 (1 - 2)	Losartan (Cozaar®)	50 to 100 (1 - 2)
Lisinopril (Zestril® / Prinivil®)	20 to 40 (1 - 2)	Olmesartan (Benicar®)	20 to 40 (1)
Moexipril (Univasc®)	5 to 30 (1 - 2)	Telmisartan (Micardis®)	40 to 80 (1)
Perindopril (Aceon®)	4 to 8 (1 - 2)	Valsartan (Diovan®)	80 to 320 (1)
Quinapril (Accupril®)	20 to 80 (1 - 2)		
Ramipril (Altace®)	2.5 to 20 (1 - 2)		
Trandalopril (Mavik®)	2 to 4 (1)		

# Common Side Effects of ACE inhibitors & ARBs

- Dizziness
- Headache
- Fatigue
- Diarrhea
- Hypotension
- Rash
- Nausea
- Hyperkalemia
- Cough (more common with ACE inhibitors than ARBs)
- Angioedema (rare but serious)
- Weight loss associated with taste loss (reported with captopril). Taste impairment is reversible and usually self-limited (2 to 3 months) even with continuous administration

# Common Side effects of ACE inhibitors & ARBs (cont'd)

## Dizziness, Headache, Fatigue, Hypotension

- Typically a result of body's initial adjustment to vasodilation and change in blood pressure
- Generally self limited
- “Starting low” and “going slow” will minimize these
- If severe, patient should seek medical attention immediately

# Common Side effects of ACE inhibitors & ARBs (cont'd)

## Diarrhea, Nausea, Rash

- Generally self-limiting, but can be a sign of a more serious problem
- If severe or persistent, patient should seek medical attention immediately

# Common Side effects of ACE inhibitors & ARBs (cont'd)

## ACE inhibitor induced cough

- Estimated incidence is 5% to 35%
- More common in the following groups:
  - Females
  - Patients of Chinese origin
  - Nonsmokers
  - Patients with CHF
- Only effective treatment is to d/c the ACE inhibitor
- Resolution of cough generally occurs in 1 to 4 weeks after ACE inhibitor is discontinued
  - May take as long as 3 months
- **Switch to an ARB is the most appropriate action**
- ACE inhibitor re-challenge has been studied and shown some success

# Common Side effects of ACE inhibitors & ARBs (cont'd)

## Hyperkalemia

**Not generally seen unless one of the following risk factors is present:**

- NSAID use
- Potassium-sparing diuretic use
- Immunosuppressive therapy use
- Diabetes
- Acidosis

# Common Side effects of ACE inhibitors & ARBs (cont'd)

## Hyperkalemia (cont'd)

### Actions:

- Potassium restricted diet (< 2 – 3 g/day). Dried figs, molasses, and seaweed are especially high in potassium (~1 g of potassium per 100 g of the food)
- Thiazide diuretic therapy (if GFR  $\geq$  30 mL/min)
- Loop diuretic therapy (if GFR < 30 mL/min)
- Discontinuation of ACE inhibitor or ARB therapy should be considered if serum potassium levels remain > 5.5 mEq/L despite diet modifications and treatment efforts

## Some Fruits and Vegetables with High Potassium Content ( > 250mg/100g)

Fruits	Vegetables
Bananas	Avocado
Cantaloupe	Broccoli
Citrus	Carrots
Strawberries	Asparagus
Kiwi	Corn
Mango	Cauliflower
Dried fruit	Peas
Prune juice	Beets
Pineapple juice	Spinach
Honeydew melon	Tomatoes
Passion fruit	Potatoes
Pomegranate	

<b>Thiazide and Loop Diuretics</b>		
<b>Classification</b>	<b>Generic Name (Brand Name)</b>	<b>Usual Dosage Range in mg/day (# of daily doses)</b>
<b>Thiazide</b>	Chlorthalidone (Thalitone®)	12.5 to 50 (1)
	Hydrochlorothiazide / HCTZ (Microzide®; HydroDiuril®)	12.5 to 50 (1)
	Indapamide (Lozol®)	1.25 to 5 (1)
	Metolazone (Zaroxolyn®)	2.5 to 20 (1)
<b>Loop</b>	Bumetanide (Bumex®)	0.5 to 4 (2 - 3)
	Furosemide (Lasix®)	40 to 240 (2 -3)
	Torsemide (Demadex®)	5 to 100 (1 - 2)

# Common Side effects of ACE inhibitors & ARBs (cont'd)

## Angioedema

- Facial and intestinal angioedema reported in the literature
- Rare but can be life threatening
- Reported incidence of about 2 – 5 out of every 1000 patients on an ACE inhibitor
  - Reported incidence of cross-reactivity for ARBs of about 8%, therefore angioedema is a concern for ARBs as well
  - A trial of an ARB may be used **very cautiously** and with **close monitoring** in patients who have developed angioedema from an ACE inhibitor
- More common in African-American patients
- Patients with swelling of the face, lips, mucous membranes, tongue, throat (potential signs of facial angioedema) or abdominal pain (potential signs of intestinal angioedema) should seek medical attention immediately

# Common Side effects of ACE inhibitors & ARBs (cont'd)

## Changes in Serum Creatinine

- Rise in serum creatinine of 10% to 20% is expected due to physiological changes resulting from ACE inhibitor or ARB therapy
- If GFR reduction is 15% to 30% from baseline:
  - Dose reduction or discontinuation of ACE inhibitor or ARB therapy not necessary
  - Re-evaluate in 1 to 2 weeks to determine if reduction in GFR was transient
- If GFR reduction is 30% to 50% from baseline:
  - Rule out additional causes (e.g. dehydration, heart failure, hypotension, urinary obstruction, renal artery disease, NSAIDs)
  - Reduce ACE inhibitor or ARB dose and recheck GFR every 5 to 7 days until GFR is within 30% of baseline
- If GFR reduction is > 50% from baseline:
  - Discontinue ACE inhibitor or ARB therapy and recheck GFR every 5 to 7 days until within 15% of baseline

# Combination Therapy with an ACE inhibitor & an ARB

- ONTARGET trial:
  - Demonstrated that combination therapy with an ACE inhibitor and ARB in patients with high vascular risk significantly increased the frequency of the primary endpoint of dialysis, doubling of serum creatinine, and death when compared to an ACE inhibitor alone and offered no renal benefit despite a reduction in proteinuria compared to an ACE inhibitor alone.
- ACE inhibitor / ARB combo not routinely recommended since ONTARGET data has been published

# **The Top 10 Things Pharmacists Would Like to Emphasize About ACE Inhibitor & ARB Use**

# #10

## **Combination therapy with an ACE inhibitor & ARB not routinely recommended**

- ONTARGET trial demonstrated that combination therapy with an ACE inhibitor and ARB in patients with high vascular risk significantly increased the frequency of the primary endpoint of dialysis, doubling of serum creatinine, and death when compared to an ACE inhibitor alone.

# #9

**An ACE inhibitor or ARB is recommended in *normotensive* patients with type 1 or type 2 diabetes mellitus and microalbuminuria or macroalbuminuria**

# #8

**ARBs have generally not been proven superior to ACE inhibitors and are most appropriate when a patient is intolerant to an ACE inhibitor due to development of a cough (or in some patients that develop angioedema)**

- Renal dysfunction, hypotension, and hyperkalemia similar between ACE inhibitors and ARBs, so switching to an ARB is generally not a suitable alternative for these complications

# #7

## Angioedema is rare (but can be life threatening)

- More common in African-Americans
- ~8% of patients who experience angioedema on an ACE inhibitor will also develop angioedema on an ARB
- An ARB may be used **very cautiously** and with **close monitoring** in patients who develop angioedema from an ACE inhibitor

# #6

## **An ACE inhibitor-induced cough may occur within a few hours of the first dose but up to several months after initiation**

- The only effective treatment is to discontinue the ACE inhibitor
- After discontinuing the ACE inhibitor, resolution of the cough usually occurs within 1 to 4 weeks, but may take as long as 3 months
- A switch to an ARB is the most appropriate change in therapy when a patient experiences an ACE inhibitor-induced cough

# #5

## **ACE inhibitor or ARB therapy will cause serum potassium levels to increase due to a decrease in aldosterone production**

- Can be remedied with the addition of an appropriate diuretic and educating the patient on the importance of adhering to a potassium-restricted diet
- ACE inhibitors or ARBs can be continued unless serum potassium levels remain above 5.5 mEq/L despite diet modifications and treatment efforts

# #4

**A rise in serum creatinine of 10% to 20% is expected due to the physiological changes that result from the initiation of an ACE inhibitor or ARB**

- Do not discontinue or reduce the dose of the ACE inhibitor or ARB with < 30% increase in serum creatinine
- Instead, re-evaluate the serum creatinine in 1 to 2 weeks to determine if the rise was transient

# #3

## **Titrate slowly, every 4 to 8 weeks, to the target dose**

- This can prevent the development of serious side effects including renal failure, hyperkalemia, and hypotension
- Titrate as tolerated to moderate to high doses, since some of the beneficial effects of an ACE inhibitor or ARB on slowing the progression of kidney disease are independent of their blood pressure lowering effect

# #2

**Lower starting doses (15% to 25% of the maximum dose) are recommended for patients with CKD to reduce adverse effects**

# #1

## **When used in hypertension, ACE inhibitors and ARBs have many compelling indications**

- Chronic Kidney Disease (CKD)
- Diabetes
- Heart failure
- Recurrent stroke prevention
- Post-myocardial infarction
- High coronary disease risk

# Questions? Comments?



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This material was prepared by FMQAI, the Medicare Quality Improvement Organization for Florida, under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the U.S. Department of Health and Human Services. The contents presented do not necessarily reflect CMS policy. FL2010F73T1B1911654