

# CE for Pharmacists

## Hypertension Management Updates



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# Objectives

- Discuss the epidemiology of hypertension and the financial burden it places on the United States' healthcare system.
- Identify patients at high risk for developing hypertension, and patients at high risk of complications for hypertension.
- Review the management of hypertension based on the most recent treatment guidelines and therapies.
- Using case-based studies, assess hard to treat hypertension cases.

# Global Epidemiology of Hypertension

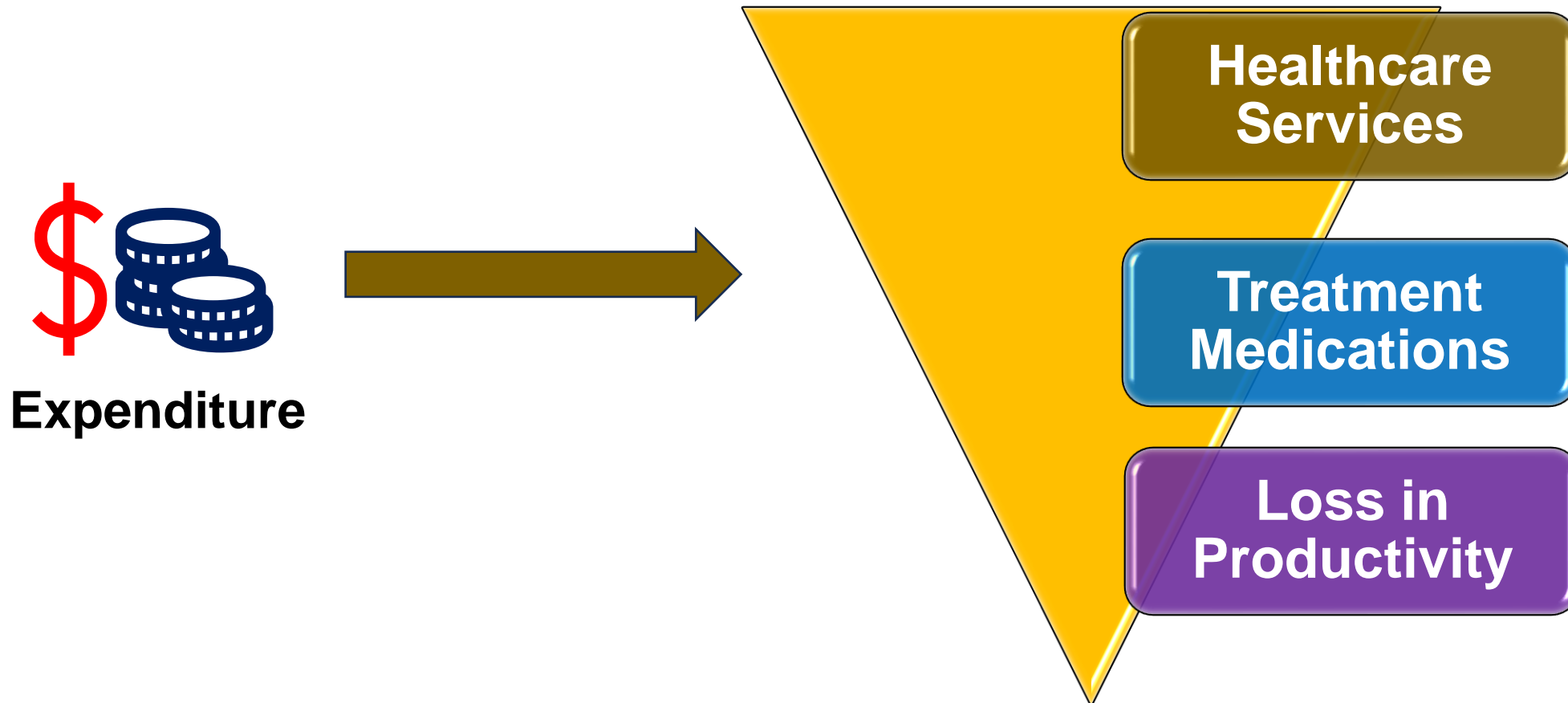
- The global hypertension cases among adults aged 30 – 79 years increased from 324 million in 1990 to 639 million in 2019.<sup>1</sup>
- Lowest prevalence reported in Peru and Canada (both men and women), UK and Spain (for women), and Bangladesh and Ethiopia (for men).
- Control rates for hypertension remain as low as 18% in men and 23% in women.
- Improvement in treatment rates are higher in high income countries than low income countries in Sub-Saharan Africa and Oceania.
- Treatment and control rates are highest in Canada, South Korea, Iceland, USA, and Costa Rica.

# Epidemiology of Hypertension in the USA

- Hypertension affects 108 million adult Americans.<sup>2</sup>
- 3 out of every 4 high blood pressure cases (76%) are uncontrolled.
- More than 1 in 7 or 37 million US adults have chronic kidney disease (CKD).
- Uncontrolled hypertension is the second leading cause of CKD.
- 20% of US adults with hypertension may have CKD

# Economic/Financial Burden in the USA

➤ The US spends \$131 to \$198 billion on hypertension annually.<sup>3</sup>



# Secondary Financial Burden: CKD Costs

- Untreated hypertension leads to serious complications, hence elevated costs incurred by governments.
- Hypertension can directly cause CKD.
- Hypertension and diabetes contribute to 75% of CKD new cases.
- Medicare payments alone to CKD treatment alone were \$87 billion in 2019.<sup>4</sup>
- Another \$37.3 billion is spend on dialysis and kidney transplant.

# Causes of Hypertension: Primary Hypertension

➤ High blood pressure that does not result from any other medical condition.



**Unhealthy Diets**



**Obesity and overweight**



**Family history**



**Alcohol**



**Physical inactivity**



**Tobacco smoking**

# Causes of Hypertension: Secondary Hypertension

- Secondary hypertension is high blood pressure caused by another medical condition
- It is caused by diseases that affect:
  - Endocrine system
  - Arteries
  - Kidneys



# Causes of Hypertension: Secondary Hypertension

## Kidney Conditions

- Diabetic nephropathy
- Polycystic kidney disease
- Glomerular disease

## Artery Conditions

- Sleep apnea
- Coarctation of the aorta

## Endocrine System Conditions

- Aldosteronism
- Hyperparathyroidism

# Risk Factors for Hypertension

## Physical and Hereditary

- Family history of hypertension
- Age over 65 years
- Underlying conditions like CKD

## Modifiable

- Physical inactivity
- Unhealthy diets
- Obese & overweight
- Alcohol and Tobacco use

# Question

- ❖ List common unhealthy diets that increase the risk of hypertension

# Answer

## ❖ Diets that increase the risk of hypertension<sup>5</sup>

- ✓ High in sodium, from salt
- ✓ High in calories
- ✓ High amounts of saturated/trans fats
- ✓ High amounts of sugar
- ✓ Low intake of fruits and vegetables

# Complications of Hypertension

- Fluid build up in the lungs
- Vision loss
- Kidney damage
- Memory loss
- Erectile dysfunction

# Management of Hypertension – An Overview

- Hypertension can be managed through lifestyle modifications or use of medicines
- European and US guidelines recommend systolic BP of 120 – 130 mmHg and diastolic BP of 70 – 80 mmHg.<sup>6</sup>
- First-line medications for the treatment of hypertension:<sup>6</sup>
  - ❑ Calcium Channel Blockers (CCB)
  - ❑ Angiotensin Converting Enzyme (ACE) inhibitors (ACE-I)
  - ❑ Angiotensin Receptor Blockers (ARBs)
  - ❑ Thiazide Diuretics

# ACE-Inhibitors: Background

- Angiotensin II enzyme causes muscular walls of arterioles and venules to narrow, among other effects.
- The narrowing can lead to high blood pressure, forcing the heart to work harder.
- ACE inhibitors is administered to relax the blood vessels.
- The relaxation of the blood vessels lowers blood pressure.

# ACE-Inhibitors: HTN Patients

- Administered alone or in combination with other antihypertensives in adults or children above 6 years.
- Initiate ACE inhibitors to manage HTN to lower blood pressure.
- Given to patients with out of office daytime BP greater than 135/85 mmHg or office BP of greater than 140/90 mmHg.<sup>7</sup>
- Patients with in/out office pressure above 130/80 mmHg in a combination of factors like:
  - Age of 65+
  - CKD
  - Type 2 diabetes mellitus
  - History of cardiovascular disease



# ACE-Inhibitors: HTN and CKD

- Regardless of race or diabetes mellitus status, ACE inhibitors are recommended as initial therapy to improve kidney outcomes.<sup>7</sup>
- Recommended as initial antihypertensive therapy for non-Black population with diabetes and without CKD.
- ACE inhibitors not recommended as an initial antihypertensive therapy in Black population with diabetes mellitus but no CKD.

# ACE-Inhibitors: Groups

## Sulfhydryl-containing ACE-I

- Captopril**
  - HTN therapy of 25mg
  - Max. therapy of 450mg

## Phosphorus-Containing ACE-I

- Fosinopri**
  - HTN therapy dosing – 10mg
  - Max. does – 80mg

## Dicarboxylic-containing ACE-I

- Benazepril** – 10mg to 80mg
- Lisinopril** – 10mg to max of 80mg
- Enalapril** – 5mg to 40mg

# ACE Inhibitors: Adverse Effects

- Dry Cough – 10% to 20%.<sup>7</sup>
- Dizziness – 12% to 19%
- Hypotension – 7% to 11%
- Increased BUN and Creatinine – 2% to 11%
- Syncope – 5% to 7%
- Hyperkalemia – 2% to 6%

# ACE Inhibitors: Contraindications

## ➤ Absolute contraindications<sup>7</sup>

- History of hypersensitivity reactions to any ACE inhibitor or its component.
- Women with or may become pregnant

## ➤ Relative contraindications

- Patients with abnormal renal function
- Patients with aortic valve stenosis
- In hypovolemia cases

# ACE Inhibitors: Enhancing Patient Outcomes

- Familiarize with potential side effects and contraindications
- Try another antihypertensive drug in case of chronic dry cough
- Regularly monitor patient's renal function and electrolyte concentrations
- Verify propriety of the dose and check for possible drug interactions
- Keep accurate and clear records of your observations and interventions in the patient's medical record
- Ensure an interprofessional team approach.

## Question #2

**What is the most common adverse effect experienced by patients taking ACE inhibitors?**

- A. Peripheral edema
- B. Cough
- C. Palpitations
- D. Hypokalemia

# Question #2: Answer and Explanation

## B. Cough

- ACE-Is reduce aldosterone secretion
- Their common side effects include cough, dizziness, and hypotension
- They block bradykinin degradation, which leads to its accumulation and dry cough
- Patients experiencing this problem are usually switched to an ARB

# ARBs: Introduction

- Indications for the use of ARBs are similar for ACEIs
- ARBs offer alternative options for patients intolerant to ACEIs when they lead to ACEI-induced cough or angioneurotic edema.
- Have better pharmacological tolerability.<sup>6</sup>
- Protects the patient from developing CV and renal damage
- Unlike beta-blockers and diuretics, ARBs have a neutral metabolic effect



# ARBs: Mechanism of Action

- ARBs also target the blocking of the renin-angiotensin-aldosterone system (RAAS) in treating hypertension.
- This class of drugs selectively inhibit angiotensin II by competitively antagonizing angiotensin II receptors.
- They displace angiotensin II from the angiotensin I receptor, lowering blood pressure by antagonizing angiotensin II-induced vasoconstriction, release of catecholamine, arginine vasopressin, and aldosterone, water intake, and hypertrophic response.<sup>8</sup>

# Some FDA Approved ARBs and Dosing

## Azilsartan

- 40 mg and 80 mg tablets
- Initial: 20 mg once daily, max daily dose: 80 mg

## Candesartan

- 4 mg, 8 mg, 16 mg, and 32 mg tablets
- Initial: 16 mg once daily, max dose 32 daily

## Eprosartan

- 400 mg and 600 mg tablets
- Initial: 600 mg once daily, max daily dose: 900 mg

## Irbesartan

- 10 mg, 25 mg, and 50 mg tablets
- Initial: 150 mg once daily, max daily dose: 300 mg

## Valsartan

- 40 mg, 80 mg, 160 mg, and 320 mg
- Initial: 80 – 160 mg once daily, max daily dose: 320 mg

## Losartan

- 10 mg, 25 mg, and 50 mg
- Initial: 50 mg once daily, max daily dose: 100 mg

# ARBs Combined with other Medications

- Valsartan and nebivolol
- Valsartan and hydrochlorothiazide
- Valsartan and amlodipine
- Valsartan and sacubitril
- Irbesartan and hydrochlorothiazide
- Losartan potassium and hydrochlorothiazide

# Combined ARB Therapies

- Effectively combined with thiazide-diuretics and dihydropyridine CCBs to enhance their ability to lower BP.
- Combinations result in high tolerability and prescription adherence.<sup>6</sup>
- Combinations lead to Optimal pharmacodynamic properties of each class, delivering excellent antihypertensive efficacy and safety standards, e.g. ARB/CCB
- Combinations report lower incidence of oedema than monotherapies of CCB
- Sub-optimal dual combinations can be substituted with triple combinations to realize recommended BP treatment targets.

# Side Effects of ARBs

- a. Generally, ARBs are well tolerated, however;
- b. They report less incidence of angioedema than ACEIs.
- c. They can lead to hypotension in patients whose arterial BP is highly dependent on renal-angiotensin-aldosterone system.<sup>9</sup>
- d. Dizziness, lightheadedness, or faintness upon rising
- e. Diarrhea and severe vomiting
- f. Insomnia, irregular heartbeat, and back and leg pain

# Contraindications of ARBs

## ➤ Not recommended in:

- Expectant women or who become pregnant during ARB therapy
- Breastfeeding mothers or use with caution
- Patients taking agents likely to cause hyperkalemia

## ➤ ARBs lower the efficacy of other antihypertensive drugs

## ➤ Combined use of ARBs with ACEIs or direct renin inhibitors (DRIs) is not recommended because they can lead to hypotension, acute renal failure or hyperkalemia

# ARBs: Enhancing Patient Outcomes

- Ensure interprofessional team approach to address various etiologies of hypertension
- Early diagnosis and treatment have greater success
- Verify dosing, check for ARB interactions and contraindications
- Closely monitor patient progress relating to ARB adverse effects
- Terminate ARBs immediately the patient becomes pregnant
- Try with dual to triple combinational therapies to increase efficacy

# Question #3

**Are ARBs equivalent to ACE-Is as first-line treatment options for hypertension?**



## Question #3: Answer and Explanation

- Most European and American guidelines consider ARB and ACE inhibitor therapy as equally effective in the management of hypertension related cardiovascular (CV) outcomes.<sup>10</sup>
- However, there is limited head-to-head trials comparing the two classes of drugs, implying conflicting evidence of their equivalence
- The choice between which class to use largely depends on tolerability, affordability, availability, and treatment protocols
- The only broad consensus is that one should not use the two classes of drugs in a dual combination therapy
- Also, there is significant differentiation between ACE-I and ARB in the relative frequency of cough as a side effect, which is more frequent in ACE-I than ARB.
- ARB are often considered an alternative when ACE-I is discontinued due to the persistent cough.

# Management: Thiazide Diuretics

They inhibit reabsorption of 3-5% of luminal sodium in the distal convoluted tubule of nephron.<sup>11</sup>

This promotes natriuresis and diuresis

Natriuresis – Excretion of sodium in urine

Diuresis – Increased excessive production of urine

**Examples:** Hydrochlorothiazide, indapamide, and chlorthalidone for managing primary hypertension

# Thiazide Diuretics: Administration

- Administered orally as tablets
- Patients take these drugs in the morning with food
- Low dosage for hydrochlorothiazide (HCTZ), from 25mg daily to max of 50mg
- Lower dosage for chlorthalidone, from 25mg daily to max of 100mg
- Increase the dose based on individual therapeutic needs of the patient

# Thiazide Diuretics: Adverse Effects

- **Hypokalemia** (Most common) – monitor during first 2 -3 weeks of HCTZ therapy.
- **Hyponatremia** – only during the first 2 – 3 weeks of therapy
- **Hyperuricemia** – and increase the risk of developing gout
- **Hyperlipidemia** – as an acute response to high-dose thiazide
- **Arrhythmias** – only few reports exist to date

# Thiazide Diuretics: Contraindications

- Patients with anuria and sulfonamide allergies
- Relative contraindications include gout, hyperlipidemia, hyperglycemia, and hypercalcemia
- Avoid thiazide diuretic use in severe hypokalemia

# Thiazide Diuretics: Enhance Patient Outcome

Monitor patient electrolyte levels, fluid overload, and lipid levels<sup>12</sup>

Avoid thiazide diuretic use in patients with history of gout

Avoid polypharmacy in the elderly

Prescribe lower dose regimens with food in the morning

Guide patients to restrict their sun exposure

Ensure patient education on their adverse effects

Recommend potassium-rich diets for patients prone to hypokalemia

# Question #4

**Which condition is a relative contraindication to thiazide diuretics**

- A. Gout
- B. Heart block
- C. Peripheral vascular disease
- D. Hyperkalemia

# Question #4: Answer and Explanation

## A. Gout

- Gout is a form of arthritis caused by the buildup of uric acid crystals in a joint
- Generally, thiazide diuretics should be avoided in patients with gout because of its association with elevated serum uric acid levels (SUA)
- These drugs increase direct urate reabsorption in the proximal renal tubules
- Elevated SUA independently increase the risk for gout



# Management: CCBs

- Calcium squeezes the heart and arteries more strongly.
- CCBs prevent calcium from entering the heart and arterial cells.
- The calcium channel blockade lowers BP by allowing
  - ❑ Blood vessels to relax and open
  - ❑ Reduction in heart rate
- Can be administered intravenously or orally
- They are classified into dihydropyridines (e.g. Nifedipine and Amlodipine) and non-dihydropyridines (e.g. Diltiazem and Verapamil)
- Nifedipine and Amlodipine are the most commonly used CCBs

# CCBs: Side Effects

- Dihydropyridines can result in lightheadedness, flushing, and headaches.
- Nifedipine has the highest incidence of peripheral edema among dihydropyridines.<sup>13</sup>
- Non-dihydropyridines may cause constipation (25% chance), which worsens cardiac output and bradycardia
- They can also lead to gingival hyperplasia and hypotension

# CCBs: Contraindications

## Dihydropyridine<sup>14</sup>

- Unstable angina
- Severe aortic stenosis
- Cardiogenic shock
- Hepatic and renal impairment (relatively)

## Non-dihydropyridines<sup>14</sup>

### **Relatively contraindicated in:**

- Congestive heart failure
- Second/third degree atrioventricular blockade
- Sick sinus syndrome
- Reduced ejection fraction

# CCBs: Enhancing Patient Outcomes

- Familiarized with CCBs' side effects when prescribing these drugs
- Monitor the patients for adverse effects such as hypotension and bradycardia
- Symptomatic hypotension or bradycardia patients require emergency care
- Withhold the drug in asymptomatic side effect cases and change dosage or consider alternative drug class.
- Consider interprofessional team monitoring with clinicians and nurses

## Question #5

**A 56-year old patient presents BP reading of 171/102 mmHg. The patient has been started on amlodipine 5 mg/day. During monthly follow-up, BP reading shows 152/93.**

**How would you manage this patient?**

## Question #5: Answer

- Because the BP is still higher than the BP goal, ask the patient if he complies and adheres to the prescription.
- If the patient adheres to the treatment regimen, double the current daily amlodipine dosage
- Schedule another follow up after one month and make judgement from there

# Management: Beta-Blockers

- Not indicated as primary treatment unless there is a particular indication of myocardial infarction and heart failure
- Associated with reduced CV morbidity and mortality in young patients
- But less protective in older patients above 65 years
- Generally, they increase the risk of stroke

# Management: Combination Therapy

- This involves combining drugs from two different classes
- 70 – 80% of treated hypertension patients require combination therapy
- Consider combination therapy once a monotherapy fails
- Combination therapy is recommended for stage 2 hypertension.<sup>14</sup>
- Combination therapy reduces BP 5X greater than doubling dosage of one drug.
- ARB/diuretic or ACEI/CBB is better than beta-blocker/diuretic combination.
- Beta-blocker/diuretic has a higher incidence of diabetes



# Management: Combination Therapy

- Combinations with beta-blockers are useful when beta-blockers are indicated in cases of post-myocardial infarction, tachycardia, and heart failure.<sup>14</sup>
- ARB or ACEI-based combinations are the most preferred.
- ARB or ACEI-based combinations should be used in CKD cases
- Avoid ACEI-ARB combinations due to high incidence of side effects with no additional benefits

# Management: Combination Therapy

- Add a third agent from first-line antihypertensives when dual combination therapy fails
- Single pill of combination therapies have been effective in reducing and sustaining BP due to improved adherence to medication.<sup>15</sup>
- If triple combination therapy fails, consider it resistant hypertension and add another monotherapy agent

# Choice of Initial Therapy in Secondary/Primary HTN

- The first-line antihypertensive recommended by the US guidelines are ACEIs, ARBs, CCBs, and Thiazide Diuretics
- Depending on the patient condition, initiate a low dose of monotherapy or combination therapy
- Initiate monotherapy in stage I hypertension
- Initial monotherapy is also recommended in patients at high risk of adverse effects, including those on low salt intake, underweight, frail, multiple drug allergies and intolerances, and orthostatic reduction in BP

## Choice of Initial Therapy in Secondary/Primary HTN

- Usually, initiate combination therapy in patients with systolic pressure 10 – 20 mmHg above the goal and/or diastolic pressure 10 mmHg above goal
- The initial combination therapy should be of low to moderate dose
- Single pill combination is good in initial combination therapy

# Case Studies

# Case #1: Description of the case

**A 35-year old woman previously diagnosed with diabetes comes at your community healthcare facility and is found to have a BP of 151/97 mmHg. Her old record from three months earlier shows a BP of 145/93 mmHg. She is currently not taking any antihypertensives.**

# Case #1: Questions about the case

- 1. Should any investigations be done for her before starting treatment?**
- 2. What medications should she be started on?**
- 3. What other history should you elicit?**

# Case #1: Answer and Explanation

- You can establish a diagnosis of hypertension because the patient has two elevated BP measurements recorded over one month apart.
- Therefore, start the treatment with medication.
- Because this woman has the potential to become pregnant, it is recommended to start with an initial daily dose of 5 mg amlodipine
- Start a treatment card and encourage healthy lifestyle choices
- When available, ensure frequent lab monitoring of the patient's fasting blood glucose, serum creatinine, lipid profile, thyroid-stimulating hormone, urinalysis, K, Ca, and complete blood count



# Case #2: Description of the case

**A previously diagnosed 60-year old man visits a primary health clinic to see a physician. The patient has a BP of 153/87 mmHg and is currently on atenolol 50 mg. He does not smoke and has no history of heart attack over the last three years.**

# **Case #2: Question about the case**

**What advice should the doctor give?**

# Case #2: Answer and Explanation

- Determine if the patient adheres to the medication, where is he gets his medication from, and whether he has any side effects.
- Consider revising the medication because the BP is not under control
- Due to lack of history of heart attack in the last three years, discontinue atenolol and replace it with another agent per the protocol
- Beta-blockers are not recommended for treatment of primary hypertension in most cases since first-line antihypertensives have better CV outcomes in clinical trials.

# Case #3: Description of the Case

**A primary care physician is attending to a 64-year old man with hard to control hypertension. The patient has been diagnosed with CKD 3 and is on a triple combination therapy comprising of hydrochlorothiazide 12.5 mg, valsartan 320 mg, and amlodipine 10 mg, all per day.**

# Case #3: Question about the Case

Comparing office BP readings and home values shows that he is consistently above his target BP. What should the doctor do?

- A. Consider the case resistant and initiate spironolactone at 25 mg/day
- B. Add furosemide once daily
- C. Consider an alternative thiazide diuretic prescription before classifying his case as resistant
- D. Double the daily amlodipine dosage in the combination therapy

# Case #3: Answer and Explanation

## **C. Consider an alternative thiazide diuretic prescription before classifying his case as resistant**

- Hydrochlorothiazide is not a potent antihypertensive.
- In fact, at low doses like the 12.5/day makes it weaker and unable to add anything significant to the regimen.<sup>16</sup>
- Considering alternative diuretics with better dosage like chlorthalidone 12.5 to 25mg/day could potentially improve the situation
- Also, the potency of diuretics worsens at worse states such as CKD 3 and beyond. Hence revising the diuretic agent type and better dose is recommended

# Recommendations/Conclusion

- Hypertension is one of the leading preventable causes of death and diseases in the US.
- Failure to detect hypertension early and treat it properly can lead to serious CV and renal failure
- Initiate antihypertensive treatment when BP is 150/90 mmHg or higher in adults 60+ years or 140/90 mmHg in adults below 60 years
- In hypertension cases with diabetes or CKD, initiate therapy when BP is 140/90 mmHg or higher, regardless of the age
- JNC 8 recommends initial antihypertensives of ARB, CCB, ACEI, or thiazide diuretic in non-blacks whereas it recommends thiazide diuretic or CCB in general black population

# Recommendations/Conclusion

- Increase the initial dosage or consider combination therapy if the BP goal is not reached within a month
- Do not combine an ACEI with an ARB or drug from the same class
- Monitor the BP progress and adjust treatment regimen until the goal is reached
- A third drug should be added if necessary or try other drug classes beside first-line
- Consider an initial dose of ACEI or ARB or add-on therapy in cases with CKD
- The ultimate choice of antihypertensive should be made on available evidence on drug indications with respect to contraindications



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**QUESTIONS?**