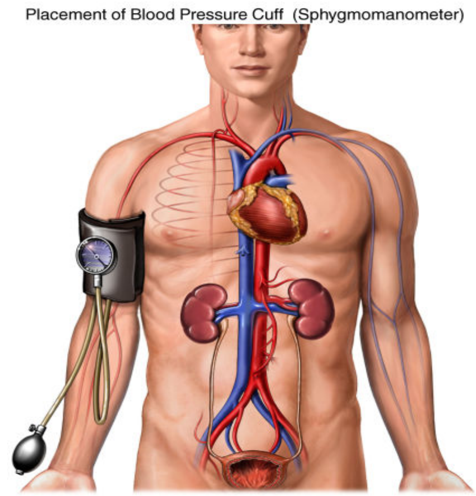
Module 13 – Drugs for Hypertension

13.1 – Hypertension

- Hypertension is simply defined as elevated systemic arterial blood pressure.
- Blood pressure is a measurement of the force against the walls of your arteries as the heart pumps blood through the body.
- Blood pressure is measured with a sphygmomanometer.
- In order to accurately measure blood pressure:



1. The patient should be seated for at least 5 minutes.
2. No caffeine or nicotine within 30 minutes of measurement.
3. Feet should be touching the floor (not dangling).
4. Arm should be elevated to heart level.
5. Two measurements in each arm should be taken 5 minutes apart.
6. Before a diagnosis of hypertension, the patient should have this repeated 3 times at least 2 weeks apart.

<u>Blood Pressure</u>

- Blood pressure is classified by looking at the **systolic and diastolic** blood pressure.
- **Systole** – When the heart contracts.
- **Diastole** – Period of time when the heart fills after a contraction.
- In clinical practice, blood pressure is read as the systolic pressure over the diastolic pressure.
- For example, John's BP is 120/80 would mean John has a systolic blood pressure of 120 mmHg and a diastolic blood pressure of 80 mmHg.

Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	< 120	AND	< 80
Prehypertension	120 – 139	OR	80 - 89
Stage 1 Hypertension	140 – 159	OR	90 – 99
Stage 2 Hypertension	> 160	OR	> 100

Types of Hypertension

Primary Hypertension

- Hypertension of no known cause.
- Approximately 92% of all cases of hypertension.
- 90% of people over the age of 55 have high blood pressure.

Secondary Hypertension

- Hypertension with an identifiable cause.
- Causes include:

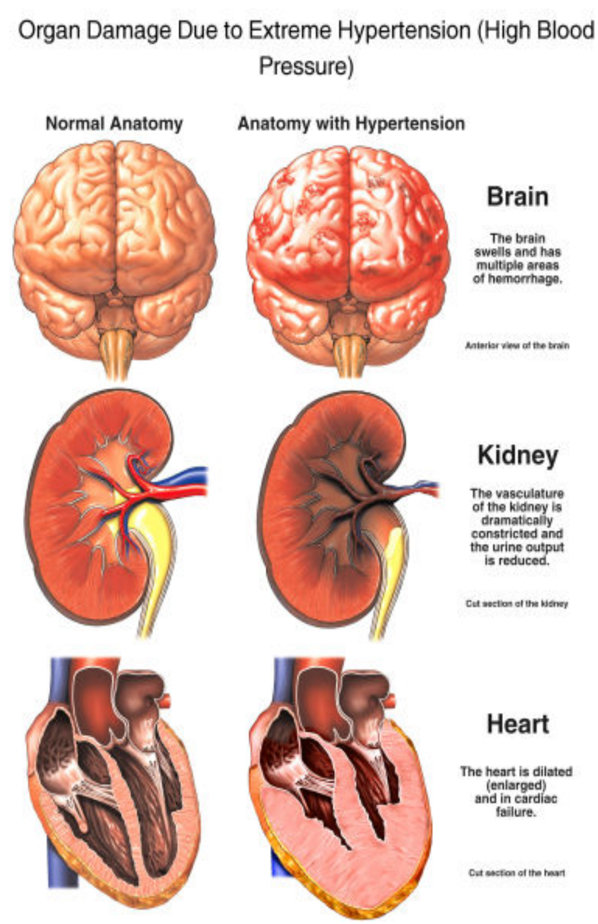
    1. Kidney disease
    2. Hyperthyroidism
    3. Pregnancy
    4. Erythropoietin
    5. Pheochromocytoma – tumour on the adrenal gland that causes excess epinephrine release.
    6. Sleep apnea
    7. Contraceptive use

Consequences of Hypertension

- Chronic hypertension is associated with increased morbidity and mortality.

- If untreated, hypertension can cause myocardial infarction, kidney failure, stroke or retinal damage.

- Unfortunately, hypertension is a "silent killer" as many patients may have elevated blood pressure for years before they show any symptoms.



Why Lower Blood Pressure?

- This one is easy! Lowering blood pressure saves lives.
- Clinical trials have conclusively demonstrated that decreasing blood pressure decreases patient morbidity and mortality.
- Lowering blood pressure decreases the incidence of stroke, myocardial infarction and heart failure.
- It is estimated that decreasing blood pressure by just 5 mmHg can reduce the risk of stroke and heart attack by 20 – 35%.

Determinants of Blood Pressure

Cardiac Output

- Is determined by heart rate, heart contractility, blood volume and venous return.
- An increase in any of these results in an increase in blood pressure.

Peripheral Resistance

- Is determined by arteriolar constriction.
- Constriction of the arteries and arterioles will cause blood pressure to rise.

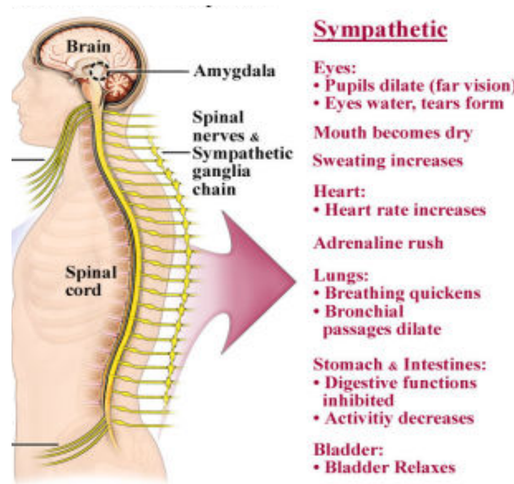
$$\text{Blood Pressure} = \text{Cardiac Output} \times \text{Peripheral Resistance}$$

13.2 Blood Pressure Regulation

- We now know that blood pressure is determined by cardiac output and peripheral resistance.
- There are three systems that our body has to regulate blood pressure:

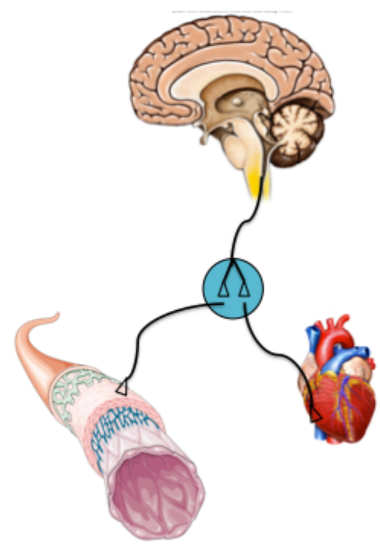
1. The sympathetic nervous system.
2. The renin-angiotensin-aldosterone system (RAAS)
3. Renal Regulation of Blood Pressure

1. The sympathetic nervous system.



- Helps us respond to stress, i.e. the fight-or flight response.
- Is also constantly active to help keep body functions (including blood pressure) in homeostasis.
- The sympathetic nervous system has a reflex circuit called *the baroreceptor reflex* that helps keep blood pressure at a set level.

The Baroreceptor Reflex

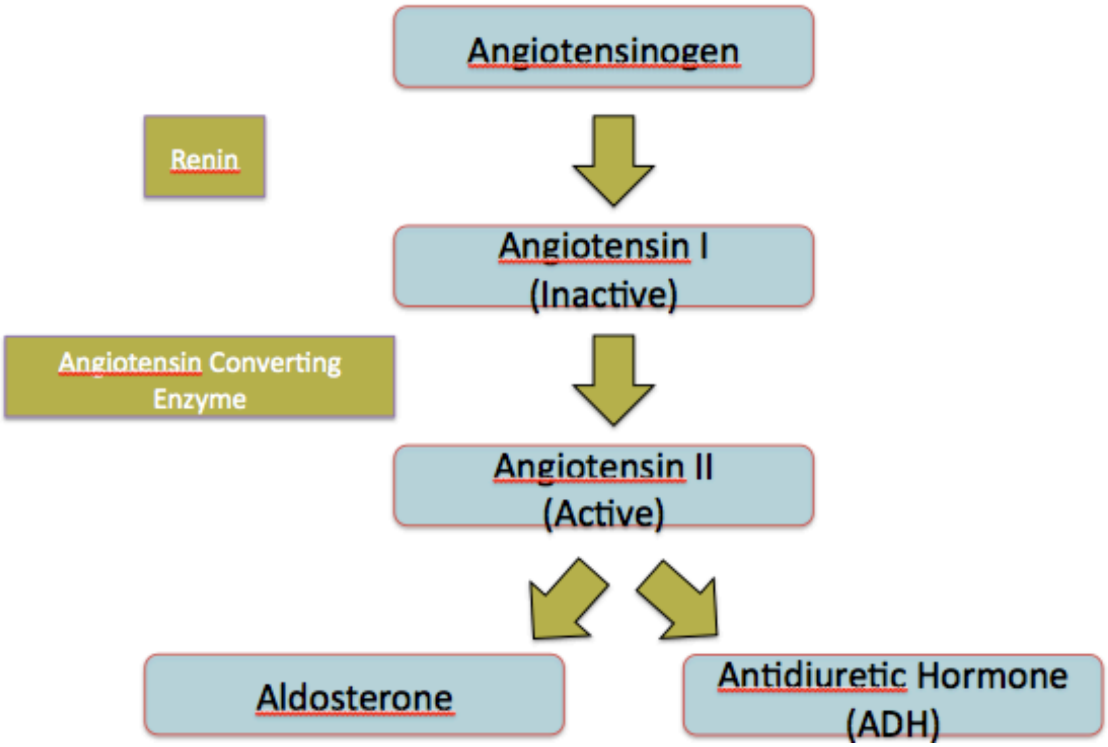


- Baroreceptors on the aortic arch and carotid sinus (in the carotid arteries of the neck) sense blood pressure and relay the information back to the brainstem.
- If BP is perceived to be too low, the brainstem sends impulses along sympathetic neurons that stimulate the heart to cause increased cardiac output and smooth muscle on arteries causing vasoconstriction. This increases BP.
- If BP is perceived to be too high, sympathetic activity is decreased. This causes decreased cardiac output and vasodilation.
- The activity of baroreceptors can oppose our attempts to lower BP with drugs since the “set point” in patients with hypertension is high.
- The baroreceptor reflex responds rapidly (seconds or minutes) to changes in blood pressure.

2. The renin-angiotensin-aldosterone system (RAAS)

- The renin-angiotensin-aldosterone system (RAAS) is comprised of a series of protein hormones.
- The renin-angiotensin-aldosterone system plays a critical role in regulating blood pressure, blood volume and electrolyte balance.
- Activation of the RAAS affects the kidney and vascular smooth muscle to control blood pressure.
- The RAAS is a target for many blood pressure lowering drugs.
- Unlike the baroreceptor reflex, activation of the RAAS may take hours or days to influence blood pressure.

THE RAAS

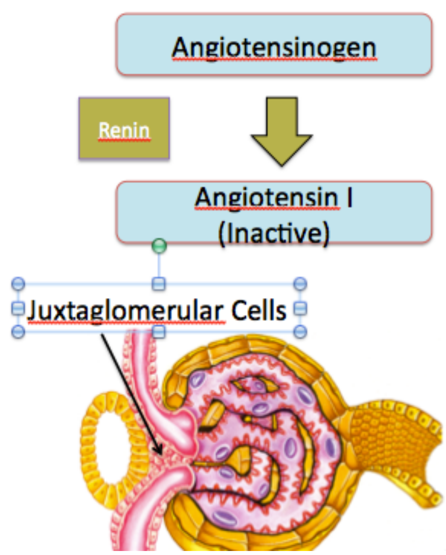


Renin

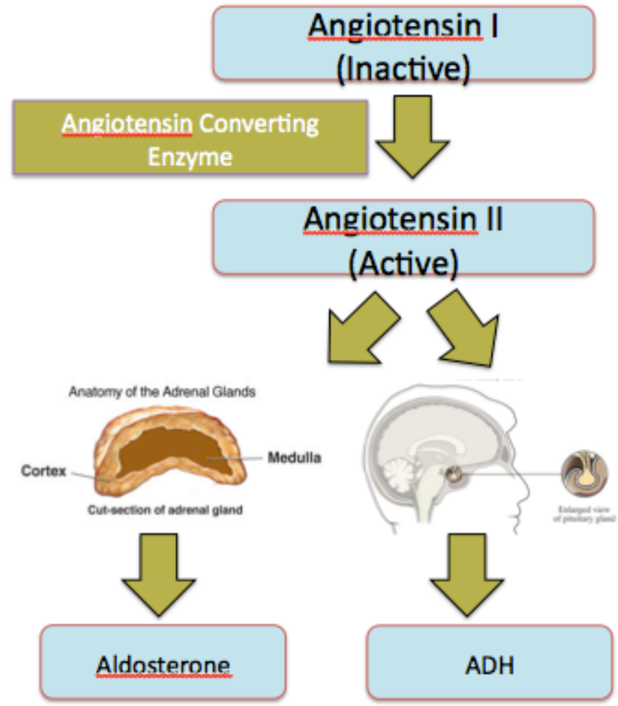
- Catalyzes the formation of angiotensin I from angiotensinogen.
- This represents the rate-limiting step in angiotensin II formation.
- Renin is synthesized and secreted by the juxtaglomerular cells of the kidney into the blood.
- The following increase renin release:

1. Decreased blood volume.
2. Low blood pressure.
3. Stimulation of beta 1 receptors on juxtaglomerular cells of the kidney.

Note: juxtaglomerular = *beside the glomerulus*



Angiotensin Converting Enzyme (ACE)



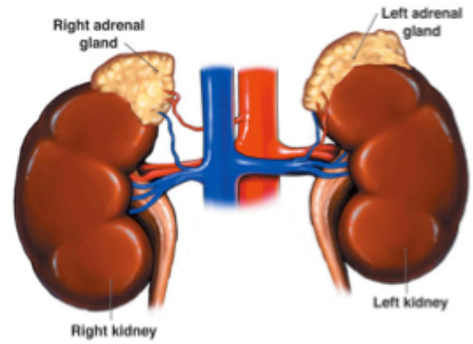
- Angiotensin converting enzyme (ACE) converts the inactive angiotensin I into the active angiotensin II.
- Activated Angiotensin II is:
  - potent vasoconstrictor by binding to its receptor (the AT1 receptor) to produce vasoconstriction.
  - stimulates release of aldosterone from the adrenal cortex. Aldosterone acts on the kidneys to increase sodium retention, which can increase water retention.
- Angiotensin II also acts on the posterior pituitary gland to release antidiuretic hormone (ADH also called vasopressin). ADH causes water retention by the kidney.

Renin Angiotensin Aldosterone System – Summary

- The RAAS system is present to help our bodies regulate blood pressure.
- When the RAAS system is activated it causes vasoconstriction and renal retention of sodium and water.
- Vasoconstriction increases blood pressure by increasing peripheral resistance.
- Increased retention of water and sodium cause an increase in blood volume, which in turn increases cardiac output.

Blood Pressure = Cardiac Output × Peripheral Resistance

3. Renal Regulation of Blood Pressure



- The kidney is a critical organ in terms of blood pressure regulation.
- If blood pressure decreases for a prolonged time period, the kidney retains water.
- This increased water retention leads to increased blood volume.
- Increased blood volume causes increased cardiac output and therefore increased blood pressure.

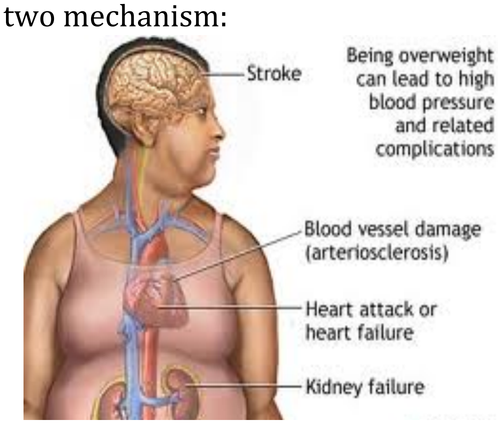
13.3 Non-Drug Treatments For Hypertension

- Non-pharmacological interventions are the initial recommendation for patients with a diastolic blood pressure of approximately 90 – 95 mmHg.
- Further, non-pharmacological treatments augment the effectiveness of drug therapy in patients with higher blood pressure.
- Non-pharmacologic interventions include:

1. Decreasing body weight.
2. Restricting sodium intake.
3. Physical exercise.
4. Potassium supplementation.
5. The DASH diet.
6. Smoking cessation.
7. Alcohol restriction.

1. Decreasing body weight.

- There is a direct relationship between obesity and hypertension.
- Obesity is thought to cause hypertension by two mechanism:



1. Obese patients have increased insulin secretion, which causes tubular reabsorption of Na+ and therefore water reabsorption and a higher blood volume.
2. Obese patients also have increased activity of the sympathetic nervous system.

- Weight loss lowers blood pressure in up to 80% of obese patients.

2. Restricting sodium intake.

- Salt is necessary to our bodies, however when sodium chloride (salt) intake is too high, it has a negative effect on blood pressure.
- The kidney regulates the amount of salt in our body, eliminating excess salt in the urine.
- When salt levels are too high, it causes water to be reabsorbed from the kidney into the blood.
- This causes increased extracellular (blood) volume and therefore increased blood pressure.
- Limiting salt intake to 5 g per day decreases systolic BP by approximately 12 mmHg and diastolic BP by 6 mmHg.

3. Physical exercise.

- Regular exercise decreases blood pressure by an average of 10 mmHg.
- Regular exercise decreases extracellular fluid volume and circulating levels of plasma catecholamines (like epinephrine).
- Importantly, the benefits of exercise are seen even if patients don't restrict sodium or lose weight during the training period.

"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

4. Potassium supplementation.

- Just as total body sodium levels are positively correlated with blood pressure, total body potassium levels are inversely correlated with blood pressure.
- This means high total body potassium results in lower blood pressure.
- High potassium diets decrease blood pressure by increasing sodium excretion, decreasing renin release and causing vasodilation.
- Preferred sources of potassium are fresh fruits and vegetables.
- **IMPORTANT** Patients taking ACE inhibitors should **<u>not</u>** be on a high potassium diet.

5. The DASH diet.

- The "DASH diet" was derived from the dietary approaches to stop hypertension studies.
- These studies gave subjects one of three diets and evaluated blood pressure. The three diets included:

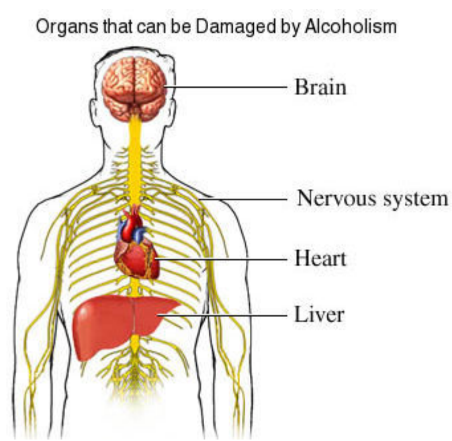
    1. Standard North American diet
    2. Standard North American diet plus extra fruit and vegetables.
    3. A diet rich in fruits, vegetables, low fat dairy, lean meats (poultry and fish), whole grains, nuts and legumes. The diet also excluded foods high in saturated fat, total fat and cholesterol.

- The results were remarkable with most patients achieving lower blood pressure within 14 days without lowering salt intake.
- The best results were seen in patients with prehypertension.
- Patients with severe hypertension are encouraged to stick to this diet in combination with blood pressure lowering medications.

6. Smoking cessation.

- Smoking acutely elevates blood pressure but has not been linked to be causal in the development of hypertension.
- Despite this, patients with hypertension should be encouraged to quit.
- Both smoking and hypertension are risk factors for the development of cardiovascular disease.

7. Alcohol restriction.



- Excessive alcohol consumption increases blood pressure.
- It also can decrease response to some antihypertensive medications.
- Patients with hypertension or prehypertension should consume less than 2 drinks per day and less than 14 drinks per week for men and 9 drinks per week for women.

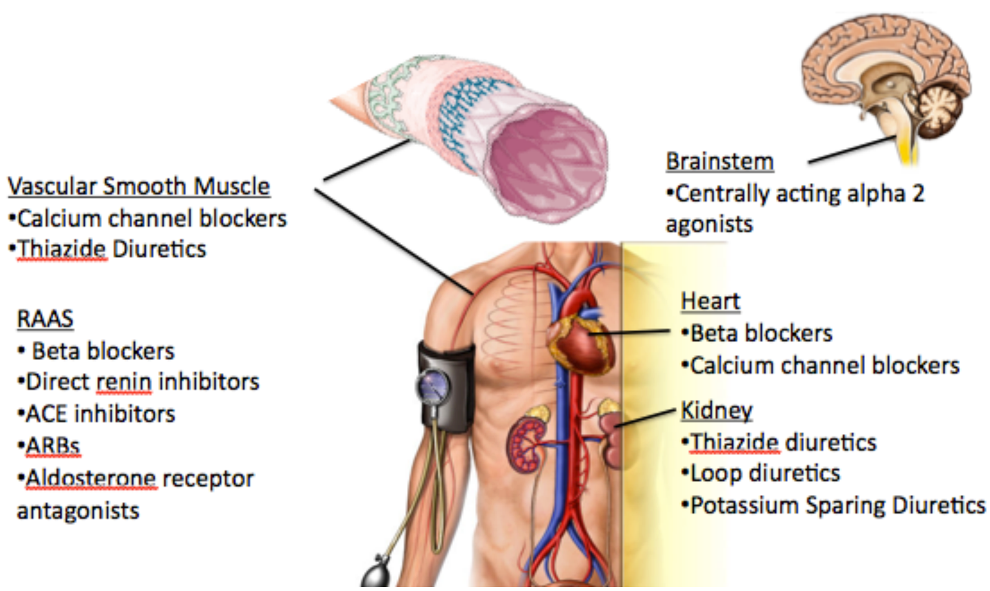
13.4 Antihypertensive Medications

- Remember that blood pressure is a product of cardiac output and peripheral resistance.

Blood Pressure = Cardiac Output × Peripheral Resistance

- Drugs that decrease blood pressure do so by <u>decreasing</u> cardiac output or peripheral resistance.
- Cardiac output is determined by heart rate, heart contractility, blood volume and venous return. Therefore decreasing any of these will decrease cardiac output and therefore decrease blood pressure.
- Peripheral resistance is determined by artery/arteriolar constriction. Therefore decreasing constriction (or increasing dilation) will decrease blood pressure.

<u>Sites of Action for Antihypertensive Medications</u>



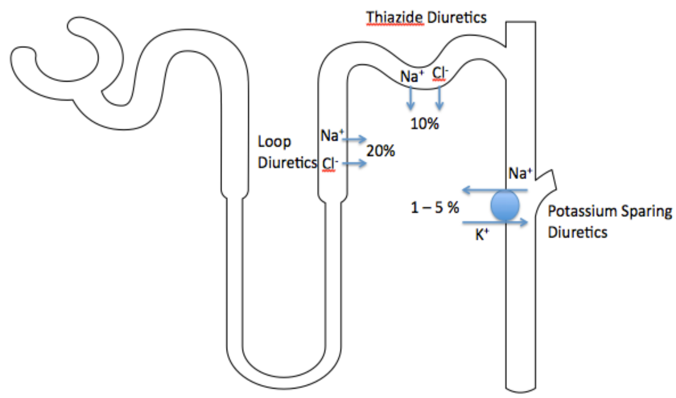
Diuretics

- Diuretics are the mainstay therapy for hypertension.
- There are 3 main classes of diuretics:
  1. loop diuretics
  2. thiazide diuretics
  3. potassium sparing diuretics/aldosterone antagonists

- Diuretics work by blocking sodium and chloride ion reabsorption from the nephron of the kidney.
- By preventing reabsorption of Na+ and Cl- diuretics make an osmotic pressure within the tubule ("attracts the water") that prevents the reabsorption of water.
- The retention of water within the nephron promotes excretion of water and sodium/chloride ions.

Diuretics - Sites of Action

- The diagram shows the site of action for the various types of diuretics.
- It also shows the percentage of sodium reabsorbed at each site.
- Diuretics produce more effective decreases in blood pressure at sites of high sodium reabsorption.
- For example, loop diuretics produce the largest decrease in blood pressure since 20% of sodium is reabsorbed at its site of action.



1. Loop diuretics

- The most effective diuretics available.
- They act by blocking sodium and chloride ion reabsorption in the thick ascending limb of the loop of henle.
- Loop diuretics are usually reserved for situations that require rapid loss of fluid such as:
    1. Edema
    2. Severe hypertension that does not respond to milder diuretics.
    3. In severe renal failure.
- Remember, this fluid is then excreted out in the urine

Adverse effects include:

1. *Hypokalemia – may cause fatal cardiac dysrhythmias
2. Hyponatremia
3. Dehydration
4. Hypotension

*The transporter responsible for reabsorbing Na+ and Cl-, also transports K+ into the blood which is why hypokalemia occurs

2. Thiazide Diuretics

   - Are the most commonly used class of drug to treat hypertension.
   - They act by two main mechanisms:

     1. Blocking sodium and chloride ion reabsorption in the distal tubule.
     2. Decreasing vascular resistance (the mechanism of which is unknown).

   - The maximum amount of diuresis (i.e. urine production) is much less than loop diuretics.
   - For many hypertensive patients thiazide diuretics alone are enough to control blood pressure.

   Adverse Effects include:

   1. Hypokalemia – may cause fatal cardiac dysrhythmias
   2. Dehydration
   3. Hyponatremia

3. Potassium Sparing Diuretics/Aldosterone Antagonists

- Produce minimal lowering of blood pressure.
- Act by inhibiting aldosterone receptors in the collecting duct.
- Aldosterone normally causes sodium reuptake and potassium secretion.
- Blocking aldosterone receptors causes increased sodium excretion and potassium retention (hence "potassium sparing") in the body.
- The main use is in combination with thiazide and loop diuretics to counteract the hypokalemia side effect.
- Potassium sparing diuretics should not be used with ACE inhibitors or renin inhibitors as these drugs also conserve potassium.
- The primary adverse event associated with potassium sparing diuretics is hyperkalemia, which may result in fatal dysrhythmias.

Beta Blockers

- Beta blockers are effective at treating hypertension by two distinct mechanisms:
  1. Blocking cardiac beta 1 receptors
     - Binding of catecholamines (i.e. epinephrine, norepinephrine) to cardiac beta receptors causes increased cardiac output.
     - Blocking beta receptors decreases cardiac output and therefore decreases blood pressure.

2. Blocking beta 1 receptors on juxtaglomerular cells
    - Juxtaglomerular cells release renin which activates the RAAS pathway causing vasoconstriction.
    - Beta blockers decrease renin release therefore decreasing RAAS mediated vasoconstriction (peripheral resistance).

- Beta blocker drugs all have the suffix "olol". For example propanolol, metoprolol etc. Remember, these are antagonists since they block receptors!

Classes of Beta Blockers

- Beta blockers can be classified as either first generation or second generation.

  1st generation beta blockers
- These drugs produce non-selective blockade of beta receptors.
- Inhibit both beta 1 (in the heart and juxtaglomerular cells) and beta 2 (in the lung) receptors.

  2nd generation beta blockers

- These drugs produce selective blockade of beta 1 receptors.

Adverse Effects

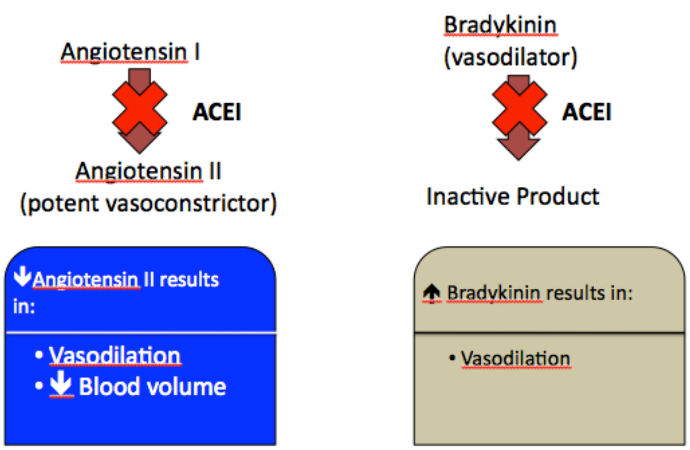
- Selective beta 1 receptor blockers have the following adverse events:
    - Bradycardia (slow heart rate)
    - Decreased cardiac output
    - Heart failure (rare)
    - Rebound hypertension/cardiac excitation if withdrawn abruptly. The dose of beta blockers should be tapered slowly over 10 – 14 days to prevent this.
- Non-selective beta blockers have the same adverse events as selective beta blockers but also cause:
    - Bronchoconstriction due to blockade of beta 2 receptors in the lung. Non-selective beta blockers should be avoided in patients with asthma or other pulmonary diseases.
    - Inhibition of hepatic and muscle glycogenolysis. This can be dangerous in patients with diabetes if they accidentally take too much insulin.

Angiotensin Converting Enzyme Inhibitors (ACEI)

- ACEI decrease blood pressure by two mechanisms:

  1. Decreasing the production of angiotensin II
     - Angiotensin II is a potent vasoconstrictor so decreasing it causes vasodilation.
     - Decreased angiotensin II also decreases total blood volume, therefore ACEI reduce cardiac output and peripheral resistance.
  2. Inhibiting the breakdown of bradykinin.
     - Elevated levels of bradykinin cause vasodilation.

- ACEI all have the suffix “pril”. For example captopril, ramipril.



Adverse Effects

- ACEI are generally well tolerated however there are some adverse effects.
- Adverse effects can be linked to the reduction of angiotensin II or elevated bradykinin.

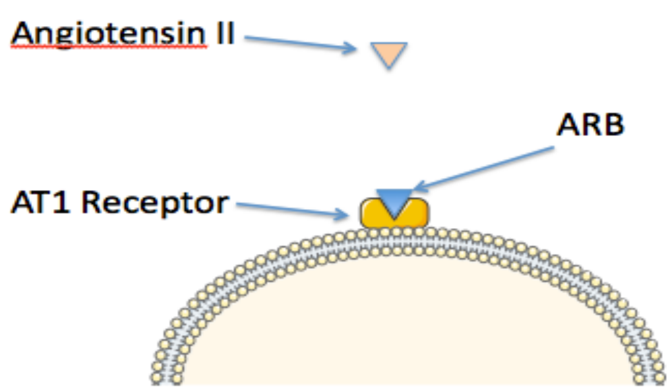
1. Side effects from decreased angiotensin II
   - 1st dose hypotension – first few doses should be low.
   - Hyperkalemia – decreased angiotensin II causes decreased aldosterone release. Decreased aldosterone leads to potassium retention. Potassium supplements and use of potassium sparing diuretics should be avoided.

2. Side effects from increased bradykinin
   - Persistent cough (in 5-10% of patients).
   - Angioedema (rare but potentially fatal).

- Use with certain NSAIDs may decrease the effect of ACE inhibitors.

Angiotensin Receptor Blockers (ARBs)

- ARBs have a similar action to ACEI in that they decrease the actions of angiotensin II, although the mechanism differs.
- ARBs act by blocking the binding of angiotensin II to its receptor (the AT1 receptor).
- Therefore ARB's block the actions of angiotensin II but do not affect its synthesis.
- ARBs cause vasodilation by blocking the action of angiotensin II on arterioles.



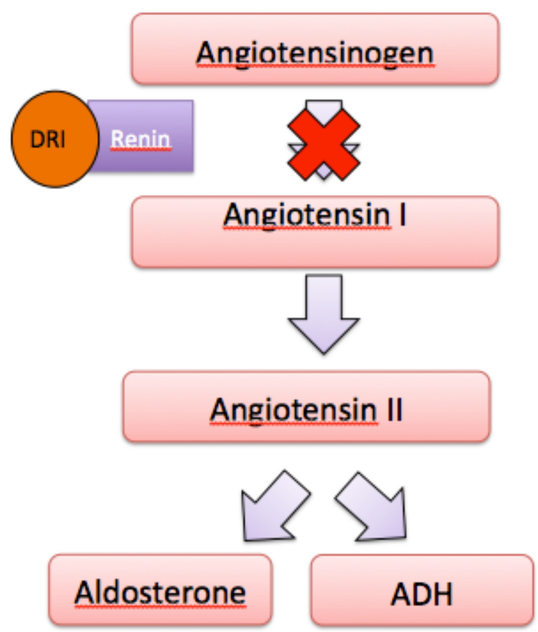
- ARBs also decrease aldosterone release from the adrenal cortex causing increased sodium and water excretion.
- ARBs all have the suffix "sartan". For example lo<u>sartan</u>, val<u>sartan</u> etc.

<u>Adverse Effects</u>

- ARBs don't inhibit bradykinin breakdown as well as ACEI do, so they don't produce persistent cough.
- ARBs also do not cause hyperkalemia and the incidence of angioedema is much lower than with ACEI.

Direct Renin Inhibitors (DRIs)

- DRI's bind to renin and block the conversion of angiotensinogen to angiotensin I.
- Since conversion of angiotensinogen to angiotensin I is the rate-limiting step in the RAAS pathway, DRIs can influence the entire pathway.
- Despite DRI's decreasing plasma renin activity by 50-80%, its blood pressure lowering effect is the same as other classes of drugs (i.e. ACEI and ARBs).



Adverse Effects

- Hyperkalemia – should not be used in combination with other drugs that may cause hyperkalemia (i.e. potassium sparing diuretics, ACEI) and potassium supplements.
- Very low incidence of persistent cough and angioedema (much lower than ACEI).
- Diarrhea

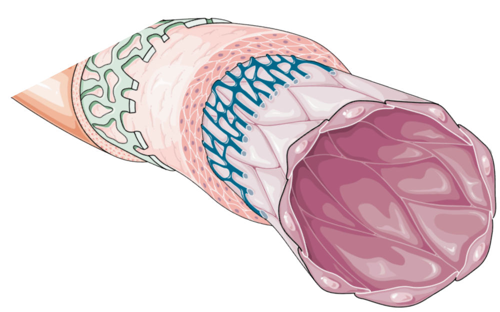
Calcium Channel Blockers

- Calcium channels bring calcium from outside the cell to inside the cell.
- In the heart and smooth muscle that surrounds arteries, calcium is essential for contraction.
- Therefore the activity of calcium channels plays an important role for contraction of the heart and smooth muscle that surrounds the arteries and arterioles.
- Calcium channel blockers block the entry of calcium into heart cells and smooth muscle cells, therefore decreasing contraction.
- Calcium channel blockers are classified into two categories:

1. Dihydropyridine calcium channel blockers
2. Non-dihydropyridine calcium channel blockers

1. Dihydropyridine calcium channel blockers

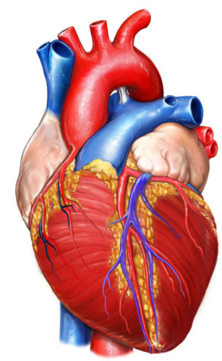
- Dihydropyridine calcium channel blockers significantly decrease calcium influx into smooth muscle of arteries.
- This results in relaxation of the muscle around the arteries and causes vasodilation.
- At therapeutic doses they do not act on the heart.
- Suffix of drug names is always "dipine". For example, nifedipine, felodipine etc.



Adverse Effects

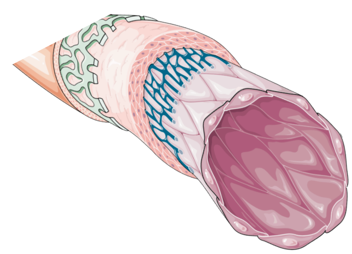
- Flushing
- Dizziness
- Headache
- Peripheral edema
- Reflex tachycardia
- Rash

2. Non-dihydropyridine calcium channel blockers



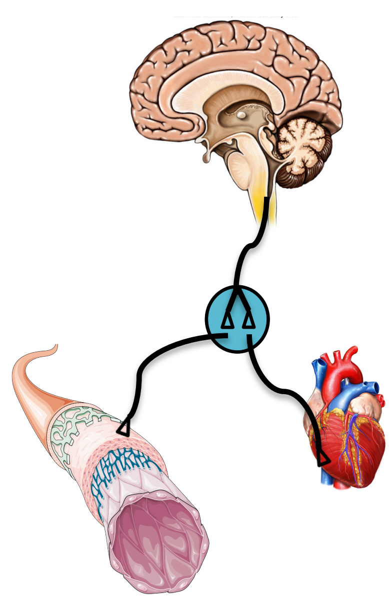
- These drugs block calcium channels in both the heart and smooth muscle of the arteries.
- Therefore, in addition to producing vasodilation of arteries, non-dihydropyridine calcium channel blockers also decrease cardiac output.

Adverse Effects



- Constipation
- Dizziness
- Flushing
- Headache
- Edema
- May compromise cardiac function. Should be used with caution in patients with cardiac failure.

Centrally Acting Alpha 2 Agonists



- These drugs bind to and activate alpha 2 receptors in the brainstem.
- Activation of these receptors decreases sympathetic outflow to the heart and blood vessels.
- Sympathetic activity normally causes increased cardiac output and vasoconstriction.
- By inhibiting sympathetic outflow, centrally acting alpha 2 receptor agonists decrease cardiac output and peripheral resistance.

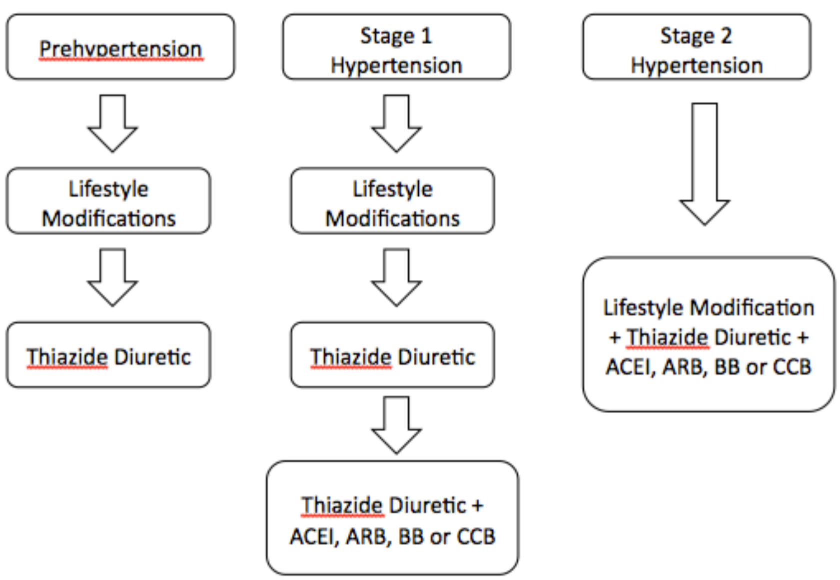
Adverse Effects

- Drowsiness
- Dry mouth
- Rebound hypertension if withdrawn abruptly.

13.5 Treatment Algorithms

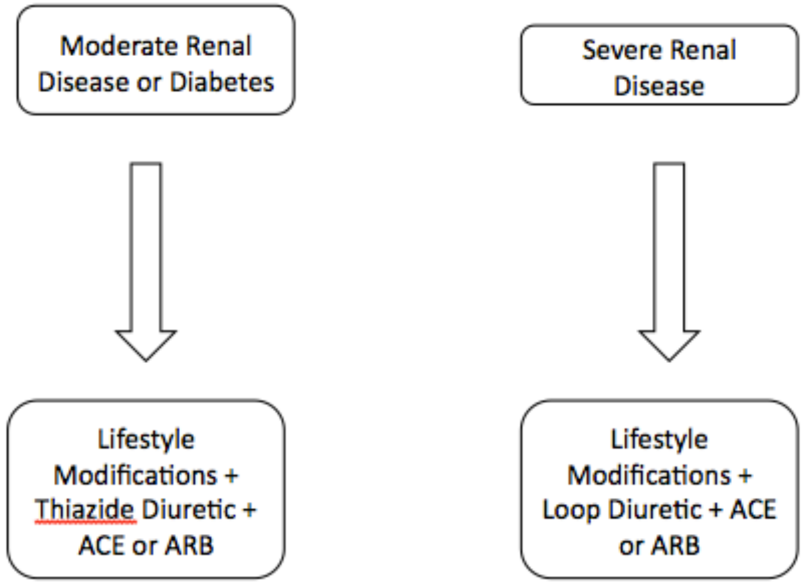
- Deciding how to treat patients with hypertension can be difficult.
- The target blood pressure that most patients should achieve is less than 140/90 mmHg.
- Patients with diabetes or chronic kidney disease should achieve a blood pressure less than 130/80 mmHg.
- Keeping blood pressure below 130/80 mmHg in patients with chronic kidney disease slows the progression of kidney damage. In patients with severe renal disease, thiazide diuretics are ineffective so loop diuretics should be used.
- Treatment algorithms exist for patients with just hypertension and for patients with hypertension plus diabetes or kidney disease.
- These algorithms help guide dosing.

Treatment Algorithm – Hypertension only



NOTE other classes may be substituted if patients don't respond.

Treatment Algorithm – Diabetes and Renal Disease



NOTE other classes may be substituted if patients don't respond.