Response mediated by the sympathetic nervous system

- Sympathetic activity
  - Activation of $\beta_1$ adrenoceptors on the heart
  - Activation of $\alpha_1$ adrenoceptors on smooth muscle
  - Activation of $\beta_1$ adrenoceptors on kidney

  - Cardiac output
  - Increased venous return
  - Peripheral resistance

Decrease in blood pressure

- Renal blood flow
  - Renin
  - Angiotensin II

  - Aldosterone
  - Glomerular filtration rate
  - Sodium, water retention
  - Blood volume

Increase in blood pressure

Response mediated by the renin–angiotensin–aldosterone system
Renin-angiotensin-aldosterone system

- Angiotensinogen → Angiotensin I → Angiotensin II → Aldosterone secretion

- Decrease in renal perfusion (juxtaglomerular apparatus) → Renin

- Lungs

- Kidney

- Surface of pulmonary and renal endothelium: ACE

- Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion. H₂O retention

- Adrenal gland: cortex

- Arteriolar vasoconstriction. Increase in blood pressure

- ADH secretion

- Pituitary gland: posterior lobe

- Collecting duct: H₂O absorption

- Na⁺ K⁺ Cl⁻ Na⁺ K⁺

- Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Hypertension

<table>
<thead>
<tr>
<th>Normal</th>
<th>Systolic mm Hg</th>
<th>Diastolic mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;120 and &lt;80</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Prehypertension</th>
<th>120–139 or 80–89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>140–159 or 90–99</td>
</tr>
<tr>
<td>Stage II</td>
<td>≥160 or ≥100</td>
</tr>
</tbody>
</table>
Antihypertensive Strategies

• The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality.

• For most patients, the blood pressure goal when treating hypertension is a pressure less than 140/90 mmHg.

• In patients with diabetes, goal of less than 140/80 mm Hg.

• Chronic kidney disease and proteinurin, lower goals of less than 130/80 mm Hg may be considered.

• Elderly patients may have less than 150/90 mm Hg)
Patient Compliance in Antihypertensive Therapy

• Lack of patient compliance is the most common reason for failure of antihypertensive therapy.

• Therapy is generally directed at preventing future disease sequelae rather than relieving current discomfort.

• The adverse effects associated with the hypertensive therapy may influence the patient more than the future benefits.

• Thus, it is important to enhance compliance by selecting a drug regimen that reduces adverse effects and also minimizes the number of doses required daily.

• Combining two drug classes in a single pill, at a fixed-dose combination, has been shown to improve patient compliance and the number of patients achieving goal blood pressure.
• Mild hypertension can sometimes be controlled with monotherapy,
• But most patients require more than one drug to achieve blood pressure control.
• Current recommendations are to initiate therapy with a:
  ❖ Thiazide diuretic, ACE inhibitor, Angiotensin receptor blocker (ARB) or Calcium Channel Blocker.
• If blood pressure is inadequately controlled, a second drug should be added, with the selection based on minimizing the adverse effects of the combined regimen and achieving goal blood pressure.
• Patients with systolic blood pressure greater than 160/100mm Hg should be started on two antihypertensives simultaneously.
CONCOMITANT DISEASE

HIGH CORONARY DISEASE RISK
- Diuretics
- β-Blockers
- ACE inhibitors
- Ca$^{2+}$ channel blockers

DIABETES
- Diuretics
- ACE inhibitors
- ARBs
- Ca$^{2+}$ channel blockers

RECURRENT STROKE
- Diuretics
- ACE inhibitors

HEART FAILURE
- Diuretics
- β-Blockers
- ACE inhibitors
- ARBs
- Aldosterone-receptor antagonists

PREVIOUS MYOCARDIAL INFARCTION
- β-Blockers
- ACE inhibitors
- Aldosterone-receptor antagonists

CHRONIC RENAL DISEASE
- ACE inhibitors
- ARBs
Diuretics

- Thiazide diuretics can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent.
- Regardless of class, the initial mechanism of action of diuretics is based upon decreasing blood volume, which ultimately leads to decreased blood pressure.
- Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and heart failure.
- Routine serum electrolyte monitoring should be done for all patients receiving diuretics.
Thiazide diuretics

- **Hydrochlorothiazide**
- **Chlorthalidone**

- Lower blood pressure initially by **increasing sodium and water excretion**.
- This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow.
Thiazide diuretics

• Thiazide diuretics can induce hypokalemia, hyperuricemia and, to a lesser extent, hyperglycemia in some patients.

• With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance.

• Thiazides are useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics.

• With the exception of metolazone thiazide diuretics are not effective in patients with inadequate kidney function.
Loop Diuretics

- The loop diuretics
  - Furosemide
  - Torsemide
  - Bumetanide
  - Ethacrynic acid

- Act promptly by blocking sodium and chloride reabsorption in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics.

- Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.
Diuretics

• Like thiazides, they can cause hypokalemia.
• Unlike thiazides, loop diuretics increase the Ca\textsuperscript{2+} content of urine, whereas thiazide diuretics decrease it.
• These agents are rarely used alone to treat hypertension.
• But they are commonly used to manage symptoms of heart failure and edema.
Potassium-sparing Diuretics

- Amiloride.
- Triamterene.

✓ inhibitors of epithelial sodium transport at the late distal and collecting ducts
- Eplerenone.
- Spironolactone.

✓ aldosterone receptor antagonists reduce potassium loss in the urine.

- Aldosterone antagonists have the additional benefit of diminishing the cardiac remodeling that occurs in heart failure.

- Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.
β-Adrenoceptors Blockers

- β-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure.
- Actions
- The β-blockers reduce blood pressure primarily by decreasing cardiac output.
- They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone.
- The prototype β-blocker is propranolol which acts at both β₁ and β₂ receptors.
- Selective blockers of β₁ receptors, such as metoprolol and atenolol are among the most commonly prescribed β-blockers.
- **Nebivolol** is a selective blocker of β₁ receptors, which also increases the production of nitric oxide, leading to vasodilation.
Mechanism of Action

β-Adrenoceptor blockers

Activation of β₁ adrenoceptors on the heart → Cardiac output

Activation of β₁ adrenoceptors on kidney

Renin → Angiotensin II

Peripheral resistance

Aldosterone

Sodium, water retention → Blood volume

Decrease in blood pressure
• Selective β-blockers may be administered cautiously to hypertensive patients who also have asthma.

• The nonselective β-blockers, such as propranolol and nadolol, are contraindicated in patients with asthma due to their blockade of β2-mediated bronchodilation.

• β-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.
• The primary **therapeutic benefits** of β-blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia (for example, atrial fibrillation), previous myocardial infarction, angina pectoris, and chronic heart failure.

• Conditions that **discourage the use** of β-blockers include reversible bronchospastic disease such as asthma, second- and third-degree heart block, and severe peripheral vascular disease.
Pharmacokinetics

• The β-blockers are orally active for the treatment of hypertension.
• Oral β-blockers may take several weeks to develop their full effects.
• Esmolol, metoprolol, and propranolol are available in intravenous formulations.
Adverse Effects

1. Common effects:
   • The β-blockers may cause bradycardia, hypotension, and CNS side effects such as fatigue, lethargy, and insomnia.
   • The β-blockers may decrease libido and cause erectile dysfunction, which can severely reduce patient compliance.

2. Alterations in serum lipid patterns: Noncardioselective β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.

3. Drug withdrawal: Abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease.
   ❖ Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease.
ACE Inhibitors

• **Enalapril**
• **Lisinopril**

First-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease

• The ACE inhibitors lower blood pressure by reducing **peripheral vascular resistance** without reflexively increasing cardiac output, heart rate, or contractility.

• These drugs block the enzyme ACE which cleaves angiotensin I to form the potent vasoconstrictor angiotensinII.
• ACE is also responsible for the breakdown of **bradykinin**, a peptide that increases the production of **nitric oxide and prostacyclin** by the blood vessels.

• Both nitric oxide and prostacyclin are **potent vasodilators**.
  
  ➢ ACE inhibitors decrease angiotensin II and increase bradykinin levels.
  
  ❖ Vasodilation of both arterioles and veins occurs as
  
  ✓ a result of decreased vasoconstriction (from diminished levels of angiotensin II)

  ✓ enhanced vasodilation (from increased bradykinin).

  ➢ By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

• ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing cardiac work.
• All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.
• Like the ARBs, ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy.
• Beneficial effects on renal function may result from decreasing intraglomerular pressures, due to efferent arteriolar vasodilation.
• ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction.
• Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a myocardial infarction.
• ACE inhibitors are first-line drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease.
Pharmacokinetics

• All of the ACE inhibitors are orally bioavailable as a drug or **prodrug**.
• All but **Captopril** and **Lisinopril** undergo hepatic conversion to active metabolites, so these agents may be preferred in patients with severe hepatic impairment.
• **Fosinopril** is the only ACE inhibitor that is not eliminated primarily by the kidneys and does not require dose adjustment in patients with renal impairment.
• **Enalapril** is the only drug in this class available intravenously.
Adverse Effects

• Common side effects include dry cough, rash, fever, altered taste, hypotension and hyperkalemia
• The **dry cough**, which occurs in up to 10% of patients, is thought to be due to **increased levels of bradykinin** and **substance P** in the pulmonary tree and resolves within a few days of discontinuation.
• The cough occurs more frequently in women.
• **Angioedema** is a rare but potentially life-threatening reaction that may also be due to **increased levels of bradykinin**.
• Potassium levels must be monitored while on ACE inhibitors, and potassium supplements and potassium-sparing diuretics should be used with caution due to the risk of hyperkalemia.
• Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease.
• ACE inhibitors can induce **fetal malformations** and should not be used by **pregnant women**.
Angiotensin II Receptor Blockers

- **ARBs**, are alternatives to the ACE inhibitors
- **Losartan**
- **Irbesartan**

These drugs block the AT1 receptors, decreasing the activation of AT1 receptors by angiotensin II.

Their pharmacologic effects are similar to those of ACE inhibitors in that they produce **arteriolar and venous dilation** and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention.

- ARBs do not increase **bradykinin** levels.
- They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease.
- Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased.
- ARBs should not be combined with an ACE inhibitor for the treatment of hypertension due to similar mechanisms and adverse effects.
- These agents are also **teratogenic** and should not be used by pregnant women.
Renin Inhibitor

- **Aliskiren**, selective renin inhibitor.
- Directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs.
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- Aliskiren should not be routinely combined with an ACE inhibitor or ARB.
- Aliskiren can cause diarrhea, especially at higher doses, and can also cause **cough** and angioedema, but probably less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, Aliskiren is contraindicated during pregnancy.
Calcium channel blockers

- Calcium channel blockers are a recommended treatment option in hypertensive patients with diabetes or angina.
- High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.
Classes of calcium channel blockers

- Three chemical classes
- Different pharmacokinetic properties and clinical indications

1. Diphenylalkylamines: **Verapamil**
   - Verapamil is the least selective of any calcium channel blocker and has significant effects on both cardiac and vascular smooth muscle cells.
   - It is also used to treat angina and supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.

2. Benzothiazepines: **Diltiazem**.
   - Like verapamil, diltiazem affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared to that of verapamil.
   - Diltiazem has a favorable side effect profile.
### A  Dilation of coronary vessels

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Weak action</th>
<th>Strong action</th>
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<tbody>
<tr>
<td>Nifedipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### B  AV Conduction

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>Little effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
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</tbody>
</table>

### C  Frequency of adverse effects

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Nifedipine</td>
<td>18%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>9%</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>2%</td>
</tr>
</tbody>
</table>

3. Dihydropyridines: This class of calcium channel blockers

- **Nifedipine** (the prototype)
- **Amlodipine**.
- **Felodipine**.
- **Isradipine**.
- **Nicardipine**.
- **Nisoldipine**.

- These agents differ in pharmacokinetics, approved uses, and drug interactions.
- All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart.
- They are, therefore, particularly beneficial in treating hypertension.
- The dihydropyridines have the advantage in that they show **little interaction** with other cardiovascular drugs, such as digoxin or warfarin, which are often used concomitantly with calcium channel blockers.
Mechanism of Action

- The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium.
- Calcium enters muscle cells through special voltage sensitive calcium channels.
- This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.
- Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature.
- This causes vascular smooth muscle to relax, dilating mainly arterioles.
- Calcium channel blockers do not dilate veins.
Therapeutic Uses

• In the management of hypertension, CCBs may be used as an initial therapy or as add-on therapy.

• They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease.

• Because unlike β-blockers, they do not have the potential to adversely affect these conditions.

• All CCBs are useful in the treatment of angina.

• In addition, diltiazem and verapamil are used in the treatment of atrial fibrillation.
Pharmacokinetics

- Most of these agents have short half-lives (3 to 8 hours) following an oral dose.
- **Sustained-release** preparations are available and permit once-daily dosing.
- Amlodipine has a very long half-life and does not require a sustained-release formulation.

**Adverse effects**

- First-degree atrioventricular block and constipation are common dose dependent side effects of verapamil.
- Verapamil and diltiazem should be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects.
- Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines. Peripheral edema is another commonly reported side effect of this class.
- Nifedipine and other dihydropyridines may cause gingival hyperplasia.
α-adrenoceptor-blocking receptor

- Prazosin
- Doxazosin
- Terazosin

- Produce a competitive block of $\alpha_1$-adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.
- These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.
- Therefore, long-term tachycardia does not occur, but salt and water retention does.

- **Reflex tachycardia and postural hypotension** often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses.

- Due to **weaker outcome** data and their **side effect profile**, α-blockers are **no longer recommended as initial treatment for hypertension**, but may be used for refractory cases.

- Other $\alpha_1$-blockers with greater selectivity for prostate muscle are used in the treatment of benign prostatic hyperplasia.
α β- adrenoceptor- blocking receptor

- **Labetalol**
- **Carvedilol**
  - block α1, β1, and β2 receptors.
  - Carvedilol, although an effective antihypertensive, is mainly used in the treatment of heart failure.
  - Carvedilol, as well as metoprolol succinate, and bisoprolol have been shown to reduce morbidity and mortality associated with heart failure.
  - Labetalol is used in the management of gestational hypertension and hypertensive emergencies.
Centrally Acting Adrenergic Drugs

- **Clonidine.**
  - $\alpha_2$ agonist: inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery.
  - This leads to reduced total peripheral resistance and decreased blood pressure.
  - Clonidine is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs.
  - Clonidine does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.
  - Clonidine is absorbed well after oral administration and is excreted by the kidney.
Clonidin

✔️ It is also available in a **transdermal patch**.

➢ **Adverse effects include**

❖ following abrupt withdrawal of clonidine.

✔️ sedation, dry mouth, and constipation.

✔️ Rebound hypertension occurs

❖ The drug should, therefore, be withdrawn slowly if discontinuation is required.
Methyldopa

- **Methyldopa** is an $\alpha_2$ agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS.
- The most common **side effects** of methyldopa are sedation and drowsiness.
- Its use is **limited** due to adverse effects and the need for multiple daily doses.
- It is mainly used for management of **hypertension in pregnancy**, where it has a record of safety.
Vasodilators

- Hydralazine.
- Minoxidil.

✓ are not used as primary drugs to treat hypertension.
✓ producing relaxation of vascular smooth muscle, primarily in arteries and arterioles.

❖ Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption.

❖ Vasodilators also increase plasma renin concentration, resulting in sodium and water retention.

✓ These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker.
✓ **Hydralazine** is an accepted medication for controlling blood pressure in **pregnancy induced hypertension**.

➢ **Adverse effects of hydralazine include**
  - Headache.
  - Tachycardia.
  - Nausea, sweating.
  - Arrhythmia, and precipitation of angina.
  - A lupus-like syndrome can occur with high dosages, but it is reversible upon discontinuation of the drug.

➢ **Minoxidil** treatment causes hypertrichosis (the growth of body hair). This drug is used topically to treat male pattern baldness.