Pharmacology of Antihypertensive Agents

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Nephrology and Hypertension
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Conflict of Interest Disclosure

Disclosure

I do not have any financial relationships to disclose.
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<th>Drug Class</th>
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<th>Mechanism of Action</th>
<th>Hemodynamic Effects</th>
<th>Adverse Drug Effects</th>
<th>Drug-Drug Interactions</th>
<th>Drug-Disease Interactions</th>
</tr>
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<tr>
<td><strong>ACE Inhibitors</strong></td>
<td>Captopril</td>
<td>Inhibits ACE - ↓ angiotensin II, ↑ bradykinin</td>
<td>↓ systemic vascular resistance and preload</td>
<td>HTN w/1st dose, Cough &amp; angioedema w/↑ kinin, renal impairment, hyperkalemia,</td>
<td>NSAIDS, Lithium</td>
<td>Pregnancy</td>
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<tr>
<td></td>
<td>Lisinopril</td>
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<td></td>
<td>Enalipiril</td>
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<tr>
<td><strong>Angiotensin II receptor</strong></td>
<td>Losartan</td>
<td>Blocks angiotensin II receptor binding</td>
<td>Vasodilation w/↓ preload ↓ afterload</td>
<td>no cough renal impairment, hyperkalemia,</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antagonists</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Calcium Channel</strong></td>
<td>Nifedipine</td>
<td>Bind Ca$^{2+}$ channels ↓ Ca$^{2+}$ for muscle contraction</td>
<td>Vasodilation</td>
<td>Constipation, peripheral edema, worsen CHF, headache,</td>
<td></td>
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<tr>
<td></td>
<td>Verapamil, diltiazem,</td>
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<tr>
<td><strong>Beta Antagonists</strong></td>
<td>Propranolol</td>
<td>Non-selective β receptor blockade Cardioselective β₁ receptor blockade</td>
<td>↓ Heart rate and contractility, ↑ systemic vascular resistance</td>
<td>Bad dreams, depression Cardio – worsen CHF and occlusive peripheral vascular disease (OPVD) Lungs – bronchospasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Diuretics</strong></td>
<td>Thiazides,</td>
<td>Negative salt and water balance, ↑ PGI$_2$ synthesis &amp; action, vasodilaton</td>
<td>Early drop in CO due to ↓ volume Peripheral vascular resistance decreased</td>
<td>Fluid and electrolyte imbalance, particularly hypokalemia with thiazides and loop diuretics, Hyperkalemia with spironolactone Furosemide mostly for fluid management</td>
<td>NSAIDS, Lithium</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td></td>
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<tr>
<td></td>
<td>Furosemide</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Ethacrynic acid,</td>
<td>Patients with Sulfa allergy</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td>Hydralazine</td>
<td>Relax vascular smooth muscle ?</td>
<td>↓ systemic vascular resistance</td>
<td>Immuno – lupus like Sx Cardio - ↑ HR use β block</td>
<td></td>
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<tr>
<td></td>
<td>Minoxidil</td>
<td>Vasodilation - ↑ K$^+$ channel hyperpolarize SM</td>
<td>↓ systemic vascular resistance</td>
<td>Cardio - ↑ HR use β block Fluid retention, Hypertrichosis</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Na$^+$ nitroprusside</td>
<td>Causes NO release, relaxes SM</td>
<td>↓ cardiac preload and afterload</td>
<td>Hypotension, cyanide and thiocyanate poisoning</td>
<td></td>
<td>Kidney or liver disease</td>
</tr>
<tr>
<td><strong>Central Agonists</strong></td>
<td>Clonidine</td>
<td>Central α$_{2a}$ receptor stimulation</td>
<td>↓ CO, ↓ systemic vascular resistance</td>
<td>Short ½life. Missed dose = rebound HTN</td>
<td></td>
<td>Depression, sexual dysfunction</td>
</tr>
<tr>
<td><strong>Alpha Antagonists</strong></td>
<td>Prazosin</td>
<td>Block peripheral α$_1$ adrenoreceptors</td>
<td>↓ systemic vascular resistance</td>
<td>Orthostatic HTN w/1st dose. Give 1st HS.</td>
<td></td>
<td>HF</td>
</tr>
<tr>
<td><strong>Dopamine Agonist</strong></td>
<td>Fenoldopam</td>
<td>Dopamine (DA) 1 agonant</td>
<td>↑ renal blood flow ↑ Na$^+$ excretion</td>
<td></td>
<td></td>
<td>IV only</td>
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</tbody>
</table>

**Mechanism of Action:**
- **ACE Inhibitors:** Inhibits ACE - ↓ angiotensin II, ↑ bradykinin
- **Angiotensin II receptor Antagonists:** Blocks angiotensin II receptor binding
- **Calcium Channel Antagonists:** Bind Ca$^{2+}$ channels ↓ Ca$^{2+}$ for muscle contraction
- **Beta Antagonists:** Non-selective β receptor blockade Cardioselective β₁ receptor blockade
- **Diuretics:** Negative salt and water balance, ↑ PGI$_2$ synthesis & action, vasodilaton
- **Vasodilators:** Relax vascular smooth muscle
- **Central Agonists:** Central α$_{2a}$ receptor stimulation
- **Alpha Antagonists:** Block peripheral α$_1$ adrenoreceptors
- **Dopamine Agonist:** Dopamine (DA) 1 agonant

**Hemodynamic Effects:**
- **ACE Inhibitors:** ↓ systemic vascular resistance and preload
- **Angiotensin II receptor Antagonists:** Vasodilation w/↓ preload ↓ afterload
- **Calcium Channel Antagonists:** Vasodilation
- **Beta Antagonists:** ↓ Heart rate and contractility, ↑ systemic vascular resistance
- **Diuretics:** Early drop in CO due to ↓ volume Peripheral vascular resistance decreased
- **Vasodilators:** ↓ systemic vascular resistance
- **Central Agonists:** ↓ CO, ↓ systemic vascular resistance
- **Alpha Antagonists:** ↓ systemic vascular resistance
- **Dopamine Agonist:** ↑ renal blood flow ↑ Na$^+$ excretion

**Adverse Drug Effects:**
- **ACE Inhibitors:** HTN w/1st dose, Cough & angioedema w/↑ kinin, renal impairment, hyperkalemia
- **Angiotensin II receptor Antagonists:** no cough renal impairment, hyperkalemia
- **Calcium Channel Antagonists:** Constipation, peripheral edema, worsen CHF, headache
- **Beta Antagonists:** Bad dreams, depression Cardio – worsen CHF and occlusive peripheral vascular disease (OPVD) Lungs – bronchospasm
- **Diuretics:** Fluid and electrolyte imbalance, particularly hypokalemia with thiazides and loop diuretics, Hyperkalemia with spironolactone Furosemide mostly for fluid management
- **Vasodilators:** Hypotension, cyanide and thiocyanate poisoning
- **Central Agonists:** Short ½life. Missed dose = rebound HTN
- **Alpha Antagonists:** Orthostatic HTN w/1st dose. Give 1st HS.
- **Dopamine Agonist:** ↑ renal blood flow ↑ Na$^+$ excretion

**Drug-Drug Interactions:**
- **ACE Inhibitors:** NSAIDS, Lithium
- **Angiotensin II receptor Antagonists:** NSAIDS, Lithium
- **Calcium Channel Antagonists:** Digoxin, β blockers = A-V block
- **Beta Antagonists:** Unstable angina, MI, HTN?
- **Diuretics:** NSAIDS, Lithium
- **Vasodilators:** Asthma, COPD, severe heart failure, OPVD, high° A-V block
- **Central Agonists:** Depression, sexual dysfunction
- **Alpha Antagonists:** HF
- **Dopamine Agonist:** IV only

**Drug-Disease Interactions:**
- **ACE Inhibitors:** Pregnancy
- **Angiotensin II receptor Antagonists:** Pregnancy
- **Calcium Channel Antagonists:** Nifedipine
- **Beta Antagonists:** Propranolol
- **Diuretics:** Thiazides, Spironolactone Furosemide
- **Vasodilators:** Hydralazine
- **Central Agonists:** Clonidine
- **Alpha Antagonists:** Prazosin
- **Dopamine Agonist:** Fenoldopam
Lower SBP and DBP Is Better

Ischemic Heart Disease Rates by SBP, DBP, and Age

Systolic Blood Pressure

Diastolic Blood Pressure

Age at risk:
- 80-89 years
- 70-79 years
- 60-69 years
- 50-59 years
- 40-49 years

Usual SBP (mm Hg)

Usual DBP (mm Hg)

Cl, confidence interval; IHD, ischemic heart disease

Adult aged > 18 years with hypertension

Set blood pressure goal and initiate blood pressure lowering-medication based on age, diabetes, and chronic kidney disease (CKD).

Implement lifestyle interventions (continue throughout management)

Blood Pressure Goal:
- SBP < 150 mmHg
- DBP < 90 mmHg

General Population (no diabetes or CKD)

- Age > 60 years
  - Blood Pressure Goal:
    - SBP < 150 mmHg
    - DBP < 90 mmHg
  - Nonblack
    - Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination

- Age < 60 years
  - Blood Pressure Goal:
    - SBP < 140 mmHg
    - DBP < 90 mmHg
  - Nonblack
    - Initiate thiazide-type diuretic or CCB, alone or in combination
  - Black
    - Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination

Diabetes or CKD present

- All ages
  - Diabetes present
    - No CKD
      - Blood Pressure Goal:
        - SBP < 140 mmHg
        - DBP < 90 mmHg
      - Initiate thiazide-type diuretic or CCB, alone or in combination
  - CKD present with or without diabetes
    - Blood Pressure Goal:
      - SBP < 140 mmHg
      - DBP < 90 mmHg
    - Initiate ACEI or ARB, alone or in combination with other drug class.

All races
All-Cause Mortality in Participants with a History of Diabetes Mellitus or FG 126+ mg/dL at Baseline

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/C</td>
<td>0.95 (0.86-1.05)</td>
<td>0.33</td>
</tr>
<tr>
<td>L/C</td>
<td>0.99 (0.89-1.09)</td>
<td>0.69</td>
</tr>
</tbody>
</table>
Development Of Antihypertensive Therapies

Effectiveness

Tolerability


Direct vasodilators

Peripheral sympatholytics

Ganglion blockers

Veratrum alkaloids

Thiazides diuretics

Central \( \alpha_2 \) agonists

Calcium antagonists

Calcium antagonists-DHPs

\( \beta \)-blockers

\( \alpha \)-blockers

ACE inhibitors

ARBs

SABs

Others

DRI
Cautions Regarding Antihypertensive Drug Therapy

Be careful that you do not climb aboard a bandwagon that is headed for a cliff.

- Reserpine causes breast cancer
- Diuretics increase heart attack risk
- CCBs cause GI hemorrhages and do not reduce CHD events
- ACE inhibitors should not be used in people with renal disease
- Diuretics cause ESRD
- B-blockers may no longer be indicated in the treatment of hypertension
Multiple Antihypertensive Agents Needed to Achieve Target BP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target BP (mm Hg)</th>
<th>No. of Antihypertensive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>DBP &lt;85</td>
<td>1</td>
</tr>
<tr>
<td>ABCD</td>
<td>DBP &lt;75</td>
<td>2</td>
</tr>
<tr>
<td>MDRD</td>
<td>MAP &lt;92</td>
<td>3</td>
</tr>
<tr>
<td>HOT</td>
<td>DBP &lt;80</td>
<td>4</td>
</tr>
<tr>
<td>AASK</td>
<td>MAP &lt;92</td>
<td>4</td>
</tr>
<tr>
<td>IDNT</td>
<td>&lt;135/85</td>
<td>4</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>&lt;140/90</td>
<td>4</td>
</tr>
</tbody>
</table>

Hypertension Education Program:

Treatment Approaches:
- Lifestyle
- Pharmacological
# Lifestyle Therapies in Hypertensive Adults: Summary

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Target</th>
</tr>
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<tbody>
<tr>
<td>Reduce foods with added sodium</td>
<td>&lt; 100 mmol/day</td>
</tr>
<tr>
<td>Weight loss</td>
<td>BMI &lt;25 kg/m(^2)</td>
</tr>
<tr>
<td>Alcohol restriction</td>
<td>Less or equal to 2 drinks/day</td>
</tr>
<tr>
<td>Exercise</td>
<td>at least 4 times/week</td>
</tr>
<tr>
<td>Dietary patterns</td>
<td>DASH diet</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Smoke free environment</td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>&lt; 102 cm for men</td>
</tr>
<tr>
<td></td>
<td>&lt; 88 cm for women</td>
</tr>
</tbody>
</table>
Patient Adherence

• Nonadherence of patients to prescribed medication is a challenge in all chronic conditions, with typical adherence rates at 1 year of
  • About 50% for drugs
  • About 5-10% for lifestyle changes

Antihypertensive Drugs

- **Diuretics:**
  - Thiazides: Hydrochlorothiazide, chlorthalidone
  - High ceiling: Furosemide
  - K+ sparing: Spironolactone, triamterene and amiloride

**MOA:** Acts on Kidneys to increase excretion of Na and H₂O – decrease in blood volume – decreased BP

- **Angiotensin-converting Enzyme (ACE) inhibitors:**
  - **Captopril, lisinopril,** enalapril, ramipril and fosinopril
  **MOA:** Inhibit synthesis of Angiotensin II – decrease in peripheral resistance and blood volume

- **Angiotensin (AT1) blockers:**
  - **Losartan,** candesartan, valsartan and telmisartan
  **MOA:** Blocks binding of Angiotensin II to its receptors
Antihypertensive Drugs

- **β-adrenergic blockers:**
  - Non selective: Propranolol (others: nadolol, timolol, pindolol, labetolol)
  - Cardioselective: Metoprolol (others: atenolol, esmolol, betaxolol)
  **MOA:** Bind to beta adrenergic receptors and blocks the activity

- **α – adrenergic blockers:**
  - Prazosin, terazosin, doxazosin, phenoxybenzamine and phentolamine
  **MOA:** Blocking of alpha adrenergic receptors in smooth muscles – vasodilatation

- **β and α – adrenergic blockers:**
  - Labetolol and carvedilol

- **Centrally acting:**
  - Clonidine, methyldopa
  **MOA:** Act on central α2A receptors to decrease sympathetic outflow – fall in BP
Antihypertensive Drugs

• Calcium Channel Blockers (CCB):
  • Verapamil, diltiazem, nifedipine, felodipine, amlodipine, nimodipine etc.
  **MOA:** Blocks influx of Ca++ in smooth muscle cells – relaxation of SMCs – decrease BP

• Vasodilators:
  • Arteriolar – Hydralazine (also CCBs and K+ channel activators)
  • Arterio-venular: Sodium Nitroprusside

• K+ Channel activators:
  • Diazoxide, minoxidil, pinacidil and nicorandil
  **MOA:** Leaking of K+ due to opening – hyper polarization of SMCs – relaxation of SMCs
What is the True Blood Pressure?

Daytime BP?  Dipping Pattern?  Nighttime BP?

Clinic BP?

Home BP?

24 Hr Average BP?

Morning Surge?

Variability of BP?
Angiotensin Converting Enzyme (ACE) Inhibitors

What is Renin - Angiotensin?
RAS Inhibition

- Renin is a proteolytic enzyme and also called angiotensinogenase
- It is produced by juxtaglomerular cells of kidney
- It is secreted in response to:
  - Decrease in arterial blood pressure
  - Decrease Na+ in macula densa
  - Increased sympathetic nervous activity
RAS Suppression when using ACE-Inhibitors, ARBs, or Diuretics

Angiotensinogen

↑ Renin activity

Angiotensin I

ACE-independent pathways

ACE

AECE

Angiotensin II

ARB

AT₁ Receptor

Harmful effects

AT₂ Receptor

Potential beneficial effects

Volume depletion

Compensatory feedback mechanisms

Diuretic
### Comparison of ACE inhibitors in duration of inhibition

<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th>Total half-life of binding (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>50-120*</td>
</tr>
<tr>
<td>Captopril</td>
<td>1.7*</td>
</tr>
<tr>
<td>Enalapril</td>
<td>11†</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>12†</td>
</tr>
<tr>
<td>Benazepril</td>
<td>10-11†</td>
</tr>
<tr>
<td>Quinapril</td>
<td>25*</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>15-24*</td>
</tr>
</tbody>
</table>

*Terminal elimination phase
†Effective half-life of accumulation

## ARBs: How Do They Compare

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (Diovan)</th>
<th>Losartan (Cozaar)</th>
<th>Eprosartan (Tevetan)</th>
<th>Telmisartan (Micardis)</th>
<th>Irbesartan (Avapro)</th>
<th>Olmesartan (Benicar)</th>
<th>Candesartan (Atacand)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Hypertension, Heart Failure</td>
<td>Hypertension Type II</td>
<td>Hypertension</td>
<td>Hypertension</td>
<td>Hypertension Type II</td>
<td>Hypertension</td>
<td>Hypertension CHF</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>25%</td>
<td>33%</td>
<td>13%</td>
<td>42% - 40mg 58% - 160mg</td>
<td>60-80%</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Peak Effect</strong></td>
<td>2-4 hours</td>
<td>L- 1 hour M – 3-4 hours</td>
<td>1-2 hours</td>
<td>0-1 hour</td>
<td>1.5-2 hours</td>
<td>1-2 hours</td>
<td>3-4 hours</td>
</tr>
<tr>
<td><strong>Half Life</strong></td>
<td>24 hours</td>
<td>L-2 hours M-6-9 hours</td>
<td>5-9 hours</td>
<td>24 hours</td>
<td>11-15 hours</td>
<td>13 hours</td>
<td>9-12 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Not Identified</td>
<td>CYP 450 2C9, 3A4</td>
<td>Primarily unchanged</td>
<td>Mostly unchanged</td>
<td>80% unchanged; 6% inactive metabolite</td>
<td>Not CYP 450</td>
<td>unchanged</td>
</tr>
<tr>
<td><strong>AT₁: AT₂ Receptor Affinity</strong></td>
<td>20,000:1</td>
<td>1,000:1</td>
<td>1,000:1</td>
<td>3,000:1</td>
<td>8,500:1</td>
<td>12,500:1</td>
<td>&gt;10,000:1</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>83% feces 13% urine</td>
<td>60% feces 35% urine</td>
<td>90% feces 7% urine</td>
<td>&gt;97% feces 1% urine</td>
<td>20% urine, remainder urine</td>
<td>50-65% feces 35-50% urine</td>
<td>67% feces 33% urine</td>
</tr>
</tbody>
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RAAS Blockade Can Be Considered A Foundation of Combination Therapy

<table>
<thead>
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<th>RAAS Blocker</th>
<th>+ CCB*</th>
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<tr>
<td></td>
<td><strong>Targets two key mechanisms of action:</strong></td>
</tr>
<tr>
<td></td>
<td>- Pressure</td>
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<tr>
<td></td>
<td>- Neurohormonal</td>
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<td><strong>Additive efficacy</strong></td>
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<td><strong>Excellent BP reduction in many demographic groups</strong></td>
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<td><strong>Potential safety/tolerability benefits</strong></td>
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<table>
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<th>+ Diuretic*</th>
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<td><strong>Targets two key mechanisms of action</strong></td>
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<tr>
<td>- Salt/volume</td>
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<td><strong>Additive efficacy</strong></td>
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RAAS=renin-angiotensin-aldosterone system  
CCB=calcium channel blocker; BP=blood pressure  
*Versus either drug alone

Calcium Channel Blockers – Classification
(Verapamil, Diltiazem, Nifedipine, Amlodipine)
**Ca ++ Channel Blockers**

Inhibit the inward movement of Ca ++ by blocking voltage-dependent Ca ++ channels located in cell membranes.

**Ca ++ channel antagonists**
**Ca ++ channel inhibitors**
**Ca ++ entry blockers**
etc......

Distinct families with diverse molecular structure:
Phenylalkylamines, Benzothiazepines, Dihydropyrididines

(Verapamil, Diltiazem, Nifedipine, Amlodipine)
Amlodipine Provides 24-Hour BP Efficacy

Ambulatory DBP after 4 weeks treatment

- Placebo
- Amlodipine 5mg

BP=blood pressure, DBP=diastolic blood pressure
n=108; mild-moderate primary hypertension; mean office baseline BP=162/101 mm Hg. Medication taken at same time in AM.
Calcium Channel Blockers

• Advantages:
  • Unlike diuretics no adverse metabolic effects but mild adverse effects like – dizziness, fatigue etc.
  • Do not compromise hemodynamics –
  • No sedation or CNS effect
  • Can be given to asthma, angina and PVD patients
  • No renal and limited male sexual function impairment
  • No adverse fetal effects and can be given in pregnancy [nifedipine]
  • Minimal effect on quality of life
General Effects and Side Effects - Continued

- Induce relaxation of arteriolar smooth muscle, but unlike other vasodilators, do not cause fluid retention.

- However, cause peripheral edema (increased hydrostatic pressure in lower extremities due to pre-capillary dilation). Often cause ankle edema.

- Headache, flushing, dizziness, nausea, peripheral edema (excessive vasodilation).

- Especially efficacious in low-renin hypertension (black patients, elderly).

- Efficacy is enhanced with concomitant use of diuretics and ACE inhibitors.

- SE generally reduced with slow release forms.
BP Response to instant-release Nifedipine

![Blood Pressure Graph]

Nifedipine 20 mg at 18:25

# Adverse events reported with instant-release nifedipine

<table>
<thead>
<tr>
<th>Study population</th>
<th>Nifedipine preparation</th>
<th>Adverse events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>166 hypertensive paediatric patients</td>
<td>Variable</td>
<td>Change in neurological status 3.6% (33% in those with acute CNS injury)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension 1.2%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Oxygen desaturation 9.6%</td>
<td></td>
</tr>
<tr>
<td>93 hypertensive patients, aged &gt;65 years, without coronary artery disease</td>
<td>5 mg sublingual</td>
<td>Myocardial ischaemia on ECG 7.5% (10.9% in those with LVH)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angina-like precordial tightness 2.2%</td>
<td></td>
</tr>
<tr>
<td>13 patients in the emergency department with a hypertensive crisis</td>
<td>10 mg sublingual</td>
<td>Reduction in middle cerebral artery flow velocity by 7.2%</td>
<td>8</td>
</tr>
<tr>
<td>30 adult patients with a hypertensive crisis</td>
<td>10 mg oral</td>
<td>Angina pectoris with ECG changes 6.7%</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rebound hypertension 13.3%</td>
<td></td>
</tr>
<tr>
<td>32 patients with pregnancy-induced hypertension</td>
<td>10–20 mg t.d.s. oral</td>
<td>34% increase in postpartum blood loss compared to controls</td>
<td>10</td>
</tr>
<tr>
<td>14 asymptomatic patients with hypertensive urgency</td>
<td>Single dose of 20 mg, short-acting</td>
<td>Transient cerebrovascular ischaemic attack 7.1%</td>
<td>11</td>
</tr>
</tbody>
</table>

Diuretics

- Drugs causing net loss of Na+ and water in urine
- Mechanism of antihypertensive action:
  - Initially: diuresis – depletion of Na+ and body fluid volume – decrease in cardiac output
  - Subsequently after 4 - 6 weeks, Na+ balance and CO is regained by 95%, but BP remains low!
  - Q: Why? Answer: reduction in total peripheral resistance (TPR) due to deficit of little amount of Na+ and water (Na+ causes vascular stiffness)
  - Similar effect is seen with sodium restriction (low sodium diet)
Diuretics

Thiazide diuretics – adverse effects

- Adverse Effects:
  - **Hypokalaemia** – muscle pain and fatigue
  - Hyperglycemia: Inhibition of insulin release due to K+ depletion (proinsulin to insulin) – precipitation of diabetes
  - **Hyperlipidemia**: rise in total LDL level – risk of stroke
  - **Hyperurecaemia**: inhibition of urate excretion
  - Sudden cardiac death – tosades de pointes (hypokalaemia)
  - All the above metabolic side effects – **higher doses (50 – 100 mg per day)**

- But, it's observed that these adverse effects are minimal with low doses (12.5 to 25 mg) - Average fall in BP is 10 mm of Hg
## Thiazides and Related Diuretics

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Dose (mg)</th>
<th>Frequency</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>12.5-50</td>
<td>1/day</td>
<td>24-72</td>
</tr>
<tr>
<td>HCTZ</td>
<td>12.5-50</td>
<td>1-2/day</td>
<td>12-18</td>
</tr>
<tr>
<td>Metolazone</td>
<td>0.5-5</td>
<td>1/day</td>
<td>18-24</td>
</tr>
<tr>
<td>Indapamide</td>
<td>1.25-5</td>
<td>1/day</td>
<td>18-24</td>
</tr>
</tbody>
</table>
Mean Office BSP and Change During the First 8-week Study Period

Mean Change From Week 0 To Week 8 In Average Hourly Ambulatory Systolic BP

Implications

- Chlorthalidone has a much longer elimination half-life (24 to 55 hours) than HCTZ (2.5-10 hours)

- This longer elimination half-life could help sustain a prolonged low level of diuresis or vasodilatations, resulting in lower mean nighttime BP, a finding which would not be readily observed in office BP measurements routinely obtained during daytime hours.
Diuretics

- Loop diuretics
  - **Furosemide**
    - Inhibit reabsorption of sodium and chloride ions
    - Proximal tubule
    - Distal tubule
  - **Loop of Henle**
    - Action at the distal tubule is independent of any inhibitory effect on carbonic anhydrase and aldosterone

- Loop diuretics
  - **Torsemide**
    - Acts within the lumen of the thick ascending portion of the loop of Henle
    - Inhibits the Na+/K+/2Cl⁻ carrier system
    - Half life is 3.5 hours
    - 80% hepatic metabolism, so caution in patients with liver disease
## Comparative pharmacokinetics of eplerenone and spironolactone

<table>
<thead>
<tr>
<th><strong>Spironolactone</strong></th>
<th><strong>Eplerenone ($$$)$</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake enhances the <em>bioavailability</em>, which is 60-70%</td>
<td><em>Absorption</em> approaches 100% and is not influenced by food.</td>
</tr>
<tr>
<td><em>Protein binding</em> $&gt; 90%$ and volume of distribution is $14 \pm 4$ liters.</td>
<td><em>Protein binding</em> is 50% with binding to $\alpha_1$-acid glycoproteins</td>
</tr>
<tr>
<td><em>Clearance</em> is $100 \pm 19\text{-ml} \cdot \text{min}^{-1} \cdot \text{kg}$ and is decreased in the elderly</td>
<td>Primary route of <em>clearance</em> is hepatic occurring by the CYP3A4 pathway</td>
</tr>
<tr>
<td>Primary route of elimination is metabolic as sulfur-containing products</td>
<td>The <em>elimination half-life</em> of eplerenone is 4-6 hrs and there are no active metabolites</td>
</tr>
<tr>
<td>$\beta$ Half-life of $1.4 \pm 0.5\text{-hrs}$ for spironolactone. Half-life ranging from 13 to 24-hrs for its active metabolites</td>
<td>Plasma <em>clearance</em> is approximately 10L/hr and is decreased in the elderly and hepatically impaired</td>
</tr>
</tbody>
</table>
Beta-adrenergic blockers

- **Non selective**: Propranolol (others: nadolol, timolol, *pindolol*, labetolol)
- **Cardioselective**: Metoprolol (others: atenolol, esmolol, betaxolol)

All beta-blockers similar antihypertensive effects – irrespective of additional properties

- Reduction in CO but no change in BP initially but slowly
- Adaptation by resistance vessels to chronically reduced CO – antihypertensive action
- Other mechanisms – decreased renin release from kidney (beta-1 mediated)
- Reduced NA release and central sympathetic outflow reduction
Beta-adrenergic blockers

- Advantages:
  - No postural hypotension
  - No salt and water retention
  - Low incidence of side effects
  - Low cost
  - Once a day regime
  - Preferred in young non-obese patients, prevention of sudden cardiac death in post infarction patients and progression of HF

- Drawbacks (side effects):
  - Fatigue, lethargy (low CO?) – decreased work capacity
  - Loss of libido – impotence
  - Cognitive defects – forgetfulness
  - Difficult to stop suddenly
  - Therefore cardio-selective drugs are preferred now
Centrally-Acting Sympatholytics

Clonidine

- 3rd or 4th choice for tx of hypertension. Mild- Severe hypertension.
- Cause less postural hypotension than other antihypertensive agents.
- May be used alone; often used in combination with diuretics.

- MOA

  - Pre and Post-synaptic $\alpha_2$ receptors agonist
  - CNS: Reduce outflow of SNS (activate inhibitory neuron in VLM).
  - Periphery: Only high doses of direct agonists. Induce vasoconstriction ($\alpha_2$ VSM).
General Effects

Lower BP by decreasing sympathetic outflow innervating the CV system.

Do not induce significant postural hypotension vs. peripheral sympatholytics (leave baroreceptor reflex intact).

Do not impair renal function. Suitable for patients with renal insufficiency

Decrease total cholesterol.

General Side Effects

Due to: central effects, sympathetic depression, unopposed parasympathetic.

Sedation, dry mouth, dizziness, nausea, headache, nasal stuffiness.

Sexual dysfunction.

Abrupt discontinuation causes dramatic rebound activity of sympathetic system (possibly due to development of adrenergic supersensitivity in VSM), causing hypertension, tachicardia, sweating. Can be avoided by gradual discontinuation.
Peripheral Receptors - $\alpha$ Blockers

Block the actions of NE in the periphery by competitively binding to $\alpha$ receptors.

$\alpha_1$-mediated constriction of arterial and venous SM.

**Postural hypotension is often a problem**

Diuretics and $\beta$ blockers increases their efficacy.
Vasodilators

Produce vasodilation and thus reduce PVR.

Generally act directly on VSM (their action does not depend on innervation of the VSM).

**Arterial Dilators**

- Hydralazine
- Minoxidil
- Diazoxide

**Arterial and venous dilators**

- Sodium nitroprusside
Arterial Dilators

**Hydralazine (Alazine, Apresoline)**

SE  Headache, nausea, flushing, nasal congestion (increased vasodilation).

Na⁺/fluid retention, tachicardia (sympathetic reflex).

**Immunological response that resembles systemic lupus (10% of patients, mainly caucasian women).**
Minoxidil (Loniten)

MOA  Increases permeability of cell membrane to potassium, resulting in cell hyperpolarization and thus reduced muscle contractions.

SE   Na⁺/fluid retention, tachicardia (sympathetic reflex).
     Significant hypertrichosis due to cutaneous blood flow (Rogaine).
Useful Dual Combinations

For additive hypotensive effect in add-on therapy
Combine an agent from
Column 1 with any in Column 2

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thiazide diuretic</td>
<td>• Beta adrenergic blocker</td>
</tr>
<tr>
<td>• Long-acting calcium channel blocker *</td>
<td>• ACE Inhibitor</td>
</tr>
<tr>
<td></td>
<td>• ARB</td>
</tr>
</tbody>
</table>

* Caution should be exercised when using a non DHP-CCB and a beta-blocker
Diuretics

Beta blockers

Alpha blockers

Angiotensin II antagonist

Calcium antagonist

ACE inhibitors
Fixed-Dose Combination

Lower Cost

Better Compliance

ACE inhibitors
+ HCTZ (12.5mg)

β- blockers
+ HCTZ (12.5mg)

AR II blockers
+ HCTZ (12.5mg)
Choice of Pharmacological Treatment for Hypertension

Individualized treatment

- Compelling indications:
  - Ischemic Heart Disease
  - Recent ST Segment Elevation-MI or non-ST Segment Elevation-MI
  - Left Ventricular Systolic Dysfunction
  - Cerebrovascular Disease
  - Left Ventricular Hypertrophy
  - Non Diabetic Chronic Kidney Disease
  - Renovascular Disease
  - Smoking
  - Diabetes Mellitus
    - With Diabetic Nephropathy
    - Without Diabetic Nephropathy
Adult aged > 18 years with hypertension

Implement lifestyle interventions (continue throughout management)

Set blood pressure goal and initiate blood pressure lowering-medication based on age, diabetes, and chronic kidney disease (CKD).

General Population (no diabetes or CKD)
- Age > 60 years
  - Blood Pressure Goal: SBP < 150 mmHg, DBP < 90 mmHg
  - Nonblack: Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination
  - Black: Initiate thiazide-type diuretic or CCB, alone or in combination

- Age < 60 years
  - Blood Pressure Goal: SBP < 140 mmHg, DBP < 90 mmHg

Diabetes or CKD present
- All ages
  - Diabetes present
    - No CKD
      - Blood Pressure Goal: SBP < 140 mmHg, DBP < 90 mmHg
      - Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination
  - CKD present with or without diabetes
    - Blood Pressure Goal: SBP < 140 mmHg, DBP < 90 mmHg
    - Initiate ACEI or ARB, alone or in combination with other drug class.
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Prototype Drug</th>
<th>Mechanism of Action</th>
<th>Hemodynamic Effects</th>
<th>Adverse Drug Effects</th>
<th>Drug-Drug Interactions</th>
<th>Drug-Disease Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td>Captopril, Lisinopril, Enalapril</td>
<td>Inhibits ACE - ↓ angiotensin II, ↑ bradykinin</td>
<td>↓ systemic vascular resistance and preload</td>
<td>HTN w/1st dose, Cough &amp; angioedema with↑ kinin, renal impairment, hyperkalemia,</td>
<td>NSAIDS, Lithium</td>
<td>Pregnancy</td>
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<tr>
<td>Angiotensin II</td>
<td>Losartan</td>
<td>Blocks angiotensin II receptor binding</td>
<td>Vasodilation w/↓ preload</td>
<td>no cough</td>
<td>NSAIDS, Lithium</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>receptor Antagonists</td>
<td></td>
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<tr>
<td>Calcium Channel</td>
<td>Nifedipine, Verapamil, diltiazem,</td>
<td>Bind Ca²⁺ channels ↓ Ca²⁺ for muscle contraction</td>
<td>Vasodilation</td>
<td>Constipation, peripheral edema, worsen CHF, headache</td>
<td>Digoxin, β blockers = A-V block</td>
<td>Unstable angina, MI, HTN?</td>
</tr>
<tr>
<td>Antagonists</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beta Antagonists</td>
<td>Propranolol, Metoprolol</td>
<td>Non-selective β receptor blockade Cardioselective β₁ receptor blockade</td>
<td>↓ Heart rate and contractility, ↑ systemic vascular resistance</td>
<td>Bad dreams, depression, Cardio – worsen CHF and occlusive peripheral vascular disease (OPVD) Lungs – bronchospasm</td>
<td>May interact w/CCBs or digoxin causing A-V block</td>
<td>Asthma, COPD, severe heart failure, OPVD, high° A-V block</td>
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<tr>
<td>Diuretics</td>
<td>Thiazides, Spironolactone, Furosemide, Ethacrynic acid,</td>
<td>Negative salt and water balance, ↑PGI₂ synthesis &amp; action, vasodilatlon</td>
<td>Early drop in CO due to ↓ volume Peripheral vascular resistance decreased</td>
<td>Fluid and electrolyte imbalance, particularly hypokalemia with thiazides and loop diuretics, Hyperkalemia with spironolactone Furosemide mostly for fluid management</td>
<td>NSAIDS, Lithium</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with Sulfa allergy</td>
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<tr>
<td>Vasodilators</td>
<td>Hydralazine</td>
<td>Relax vascular smooth muscle ?</td>
<td>↓ systemic vascular resistance</td>
<td>Immuno – lupus like Sx Cardio - ↑ HR use β block</td>
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<tr>
<td></td>
<td>Minoxidil</td>
<td>Vasodilation - ↑ K⁺ channel hyperpolarize SM</td>
<td>↓ systemic vascular resistance</td>
<td>Cardio - ↑ HR use β block Fluid retention, Hypertrichosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Na⁺ nitroprusside</td>
<td>Causes NO release, relaxes SM</td>
<td>↓ cardiac preload and afterload</td>
<td>Hypotension, cyanide and thiocyanate poisoning</td>
<td></td>
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<tr>
<td>Central Agonists</td>
<td>Clonidine</td>
<td>Central α₂a receptor stimulation</td>
<td>↓ CO, ↓ systemic vascular resistance</td>
<td>Short ½life. Missed dose = rebound HTN</td>
<td></td>
<td>Depression, sexual dysfunction</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Alpha Antagonists</td>
<td>Prazosin</td>
<td>Block peripheral α₁ adrenoreceptors</td>
<td>↓ systemic vascular resistance</td>
<td>Orthostatic HTN w/1st dose. Give 1st HS.</td>
<td></td>
<td>HF</td>
</tr>
<tr>
<td>Dopamine Agonist</td>
<td>Fenoldopam</td>
<td>Dopamine (DA) 1 agonist</td>
<td>↑ renal blood flow ↑Na⁺ excretion</td>
<td></td>
<td></td>
<td>IV only</td>
</tr>
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</tbody>
</table>
The inclusion of spironolactone with a thiazide diuretic in a regimen to treat hypertension is done to achieve which of the following?

A. Reduce hyperuricemia  
B. Reduce Mg+ loss  
C. Decrease the loss of Na+  
D. Reduce K+ loss

Which of the following drugs would be the best to treat moderate hypertension in a diabetic patient with mild proteinuria?

A. Enalapril  
B. Propranolol  
C. Hydrochlorothiazide  
D. Nifedipine

A 33-year-old man is diagnosed with essential hypertension. He is started on a blood pressure medication, and after 6 weeks, he notes fatigue, rash over his face, joint aches, and effusions. A serum antinuclear antibody (ANA) test is positive. Which of the following is the most likely agent?

A. Hydralazine  
B. Propranolol  
C. Thiazide diuretic  
D. Nifedipine  
E. Enalapril
A woman who is undergoing an endocrine work-up to diagnose the cause of a large multinodular goiter develops atrial fibrillation. Which of the following would be best to treat this arrhythmia?

A. Verapamil  
B. Propranolol  
C. Digitalis  
D. Bretylium  
E. Tocainide

A 16-year-old boy is brought to the hospital by ambulance following a car accident causing serious head injuries. His blood pressure is 220/170 mm Hg. Funduscropy reveals retinal damage, and you administer nitroprusside via infusion. Control of the hypertension requires 72 hours and you notice the patient becoming increasingly fatigued and nauseous. The mostly likely cause of these symptoms is

A. Production of thiocyanate from nitroprusside  
B. Negative inotropic activity of nitroprusside  
C. Renal precipitation of nitroprusside  
D. Accumulation of nitroprusside because of its long half-life  
E. Production of hydroxocobalamin.

A 66-year-old man presents to your office with a 5-month history of dry cough. He denies any other symptoms. His past medical history includes a recent myocardial infarction (MI), after which he was placed on several medications. He does not smoke, nor has he had a history of asthma. You decide that a medication side effect is the most likely cause of this patient’s symptoms. Which medication might this be?

A. Lisinopril  
B. Nitroglycerin  
C. Lovastatin  
D. Digoxin  
E. Quinidine
A 75-year-old woman, who is admitted for management of her recent stroke, develops increased blood pressure, up to 195/105, with a heart rate of 95. Her physician is worried about the possibility of cerebral hemorrhage into the preexisting infarct and decides to administer a **fast-acting antihypertensive drug**. Which of the following agent should be used for severe hypertension

A. Nitroprusside  
B. Furosemide  
C. Dobutamine  
D. Losartan  
E. Digoxin

Which of the following combination of drugs are best used together in order to cause synergistic anti-hypertensive effects?

A. Nifedipine-verapamil.  
B. Lisinopril-hydrochlorothiazide.  
C. Mannitol-spironolactone.  
D. Metoprolol-clonidine.  
E. Terazosin-lisinopril.

An 80 year-old woman is seen in Urgent Care for recent syncope. As part of the evaluation, you note the following vital signs: sitting BP 180/90 mmHg and HR 50 bpm, standing BP 110/40 mmHg and HR 110 bpm. Which of the following medications is most likely to have contributed to this finding?

A. Prazosin.  
B. Lisinopril.  
C. Verapamil.  
D. Metoprolol.  
E. Triamterene.