Antihypertensive Drugs
Pharmacotherapy of HTN

- Rationale for reducing arterial pressure
  - Reduce cardiac output
  - Reduce heart rate
  - Reduce stroke volume

- Reduce system vascular Resistance
  - Dilate systemic vasculature
Major Categories - Drugs

- Four major drug categories
  - Sympathetic nervous system suppressors:
    - α1 and β1 antagonists
    - α2 agonists
  - Direct vasodilators:
    - Calcium channel antagonists
    - Potassium channel agonists
  - Renin-angiotensin system targeting drugs:
    - ACE inhibitors
    - Angiotensin II receptor antagonists
  - Diuretics:
    - Thiazides
    - Loop diuretics
    - K+ - sparing diuretics
Classification of Drugs Used in Hypertension

- Diuretics
  - Osmotic
  - Thiazide
  - Loop
  - K⁺ sparing

- Cardioinhibitory drugs
  - β-blockers
  - Ca⁺⁺ channel blockers

- Centrally Acting Sympatholytics

- Vasodilators
  - α-blockers
  - ACEi
  - ARB
  - Ca⁺⁺ channel blockers
  - Direct acting arterial dilators
  - Ganglionic blockers
  - Nitrodiilators
  - K⁺ channel openers
Diuretics
• Thiazides freely filtered and secreted in proximal tubule
• Bind to the electroneutral NaCl cotransporter
• Thiazides impair Na\(^+\) and Cl\(^-\) reabsorption in the early distal tubule: “low ceiling”
Diuretics

- **Thiazide**
  - chlorthalidone, hydrochlorothiazide (HCTZ), indapamide, metolazone

- **Loop**
  - bumetanide, furosemide, torsemide

- **Potassium-sparing**
  - amiloride, triamterene

- **Aldosterone antagonists**
  - eplerenone, spironolactone
Osmotic diuretics generally consist of molecules which are small enough to pass through the ultrafiltration barrier and enter the nephron.

However, the molecules that form osmotic diuretics either block the reabsorption of solutes from the nephron (especially sodium) or are not easily absorbed from the nephron themselves (mannitol).

Consequently solutes remain within the filtrate and exert an osmotic effect that inhibits the reabsorption of water.

- This effect can also be seen if blood plasma levels of glucose become very high (e.g. in hyperglycaemic episodes experienced by individuals with diabetes mellitus). The glucose that remains unabsorbed inhibits the reabsorption of water and larger volumes of urine are typically produced, initially.
Thiazide Diuretics

- Dose in morning to avoid nocturnal diuresis
- Adverse effects:
  - hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, hyperlipidemia, sexual dysfunction
  - lithium toxicity with concurrent administration
- More effective antihypertensives than loop diuretics unless CrCl < 30 mL/min
- Chlorthalidone 1.5 to 2 times as potent as HCTZ
Loop Diuretics

- Dose in AM or afternoon to avoid nocturnal diuresis
- Higher doses may be needed for patients with severely decreased glomerular filtration rate or heart failure
- **Adverse effects:**
  - hypokalemia, hypomagnesemia, hypocalcemia, hyperuricemia,
Potassium-sparing Diuretics

- Dose in AM or afternoon to avoid nocturnal diuresis
- Generally reserved for diuretic-induced hypokalemia patients
- Weak diuretics, generally used in combination with thiazide diuretics to minimize hypokalemia

Adverse effects:
- may cause hyperkalemia especially in combination with an ACE inhibitor, angiotensin-receptor blocker or potassium supplements
- avoid in patients with CKD or diabetes
Aldosterone antagonists

- Dose in AM or afternoon to avoid nocturnal diuresis
- Due to increased risk of hyperkalemia, eplerenone contraindicated in CrCl < 50 mL/min & patients with type 2 diabetes & proteinuria
- Adverse effects:
  - may cause hyperkalemia especially in combination with ACE inhibitor, angiotensin-receptor blocker or potassium supplements
  - avoid in CKD or DM patients
  - Gynecomastia: up to 10% of patients taking spironolactone
Summary: Sites of Diuretic Action
Cardioinhibitory Drugs
**β-Blockers**

- Inhibit renin release
  - weak association with antihypertensive effect
- Negative chronotropic & inotropic cardiac effects reduce CO
  - β-blockers with intrinsic sympathomimetic activity (ISA)
    - do not reduce CO
    - lower BP
    - decrease peripheral resistance
  - Membrane-stabilizing action on cardiac cells at high enough doses
**β-Blockers**

- **Adverse effects:**
  - bradycardia
  - atrioventricular conduction abnormalities
  - acute heart failure
  - abrupt discontinuation may cause rebound hypertension or unstable angina, myocardial infarction, & death in patients with high coronary disease risk
  - bronchospastic pulmonary disease exacerbation
  - may aggravate intermittent claudication, Raynaud’s phenomenon
**β-Receptors**

- Distributed throughout the body
  - concentrate differently in certain organs & tissues

- **β1 receptors:**
  - heart, kidney
  - stimulation increases HR, contractility, renin release

- **β2 receptors:**
  - lungs, liver, pancreas, arteriolar smooth muscle
  - stimulation causes bronchodilation & vasodilation
  - mediate insulin secretion & glycogenolysis
Cardioselective β-Blockers

- Greater affinity for β1 than β2 receptors
  - inhibit β1 receptors at low to moderate dose
  - higher doses block β2 receptors
- Safer in patients with bronchospastic disease, peripheral arterial disease, diabetes
  - may exacerbate bronchospastic disease when selectivity lost at high doses
  - dose where selectivity lost varies from patient to patient
- Generally preferred β-blockers for HTN
**β-Blockers**

- **Cardioselective**
  - atenolol, betaxolol, bisoprolol, metoprolol, nebivolol

- **Nonselective**
  - nadolol, propranolol, timolol

- **Intrinsic sympathomimetic activity**
  - acebutolol, carteolol, penbutolol, pindolol

- **Mixed α- and β-blockers**
  - carvedilol, labetolol
Nonselective $\beta$-Blockers

- Inhibit $\beta_1$ & $\beta_2$ receptors at all doses
- Can exacerbate bronchospastic disease
- Additional benefits in:
  - essential tremor
  - migraine headache
  - thyrotoxicosis
Intrinsic sympathomimetic activity

- Partial β-receptor agonists
  - do not reduce resting HR, CO, peripheral blood flow
- No clear advantage except patients with bradycardia who must receive a β-blocker
- Contraindicated post-myocardial infarction & for patients at high risk for coronary disease
- May not be as cardioprotective as other β-blockers
- Rarely used
Clinical Controversy

- Meta-analyses suggest β-blocker based therapy may not reduce CV events as well as other agents
- Atenolol $t^{1/2}$: 6 to 7 hrs yet it is often dosed once daily
  - IR forms of carvedilol & metoprolol tartrate have 6- to 10- & 3- to 7-hour half-lives respectively: always dosed at least BID
- Findings may only apply to atenolol
  - may be a result of using atenolol daily instead of BID
## Properties Of β-Blockers

<table>
<thead>
<tr>
<th>Name</th>
<th>β-1 Selective</th>
<th>α-blockade</th>
<th>Lipophilic</th>
<th>Increases ISA</th>
<th>Other ancillary properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>Disputed</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Bisoprolol</td>
<td>Yes</td>
<td>No</td>
<td>Weak</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Bucindolol</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Disputed</td>
<td>Vasodilator action</td>
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<tr>
<td>Carvedilol</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Antioxidant, effects on endothelial function</td>
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<tr>
<td>Celiprolol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>β-2 only</td>
<td>No</td>
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<tr>
<td>Metoprolol</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>Vasodilation through nitric oxide</td>
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<tr>
<td>Propranolol</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Membrane stabilizing Effect</td>
</tr>
<tr>
<td>Timolol</td>
<td>No</td>
<td>No</td>
<td>Weak</td>
<td>No</td>
<td>Anti-platelet effects</td>
</tr>
</tbody>
</table>
Mixed α-β-blockers

Carvedilol reduces mortality in patients with systolic HF treated with diuretic & ACE inhibitor

Adverse effects:
- additional blockade produces more orthostatic hypotension
Calcium Channel Blockers
CCBs

- **Calcium Channel Blockers**
  - Inhibit influx of $\text{Ca}^{2+}$ across cardiac & smooth muscle cell membranes
    - muscle contraction requires increased free intracellular $\text{Ca}^{2+}$ concentration
    - CCBs block high-voltage (L-type) $\text{Ca}^{2+}$ channels resulting in coronary & peripheral vasodilation

- **dihydropyridines vs non-dihydropyridines**
  - different pharmacologically
  - similar antihypertensive efficacy
CCBs

- **Dihydropyridines:**
  - Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, clevidipine

- **Non-dihydropyridines:**
  - Diltiazem, verapamil

- **Adverse effects of non-dihydropyridines:**
  - Bradycardia
  - Atrioventricular block
  - Systolic HF
CCBs

- **Dihydropyridines:**
  - baroreceptor-mediated reflex tachycardia due to potent vasodilating effects
  - do not alter conduction through atrioventricular node
    - not effective in supraventricular tachyarrhythmias

- **Non-dihydropyridines:**
  - decrease HR, slow atrioventricular nodal conduction
  - may treat supraventricular tachyarrhythmias
Non-dihydropyridine CCBs

- ER products preferred for HTN
- Block cardiac SA & AV nodes: reduce HR
- May produce heart block
- Not AB rated as interchangeable/equipotent due to different release mechanisms & bioavailability
- Additional benefits in patients with atrial tachyarrhythmia
Dihydropyridine CCBs

- Avoid short-acting dihydropyridines
  - particularly IR nifedipine, nicardipine
- Dihydropyridines more potent peripheral vasodilators than nondihydropyridines
  - may cause more reflex sympathetic discharge: tachycardia, dizziness, headaches, flushing, peripheral edema
- Additional benefits in Raynaud’s syndrome
- Effective in older patients with isolated systolic HTN
## CCBs: Pharmacokinetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Oral Absorption (%)</th>
<th>Bioavailability (%)</th>
<th>Protein Bound (%)</th>
<th>Elimination Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>&gt;90</td>
<td>10-35</td>
<td>83-92</td>
<td>2.8-6.3*</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>&gt;90</td>
<td>41-67</td>
<td>77-80</td>
<td>3.5-7</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>&gt;90</td>
<td>45-86</td>
<td>92-98</td>
<td>1.9-5.8</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>-100</td>
<td>35</td>
<td>&gt;95</td>
<td>2-4</td>
</tr>
<tr>
<td>Isradipine</td>
<td>&gt;90</td>
<td>15-24</td>
<td>&gt;95</td>
<td>8-9</td>
</tr>
<tr>
<td>Felodipine</td>
<td>-100</td>
<td>20</td>
<td>&gt;99</td>
<td>11-16</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>&gt;90</td>
<td>64-90</td>
<td>97-99</td>
<td>30-50</td>
</tr>
</tbody>
</table>

**CCBs**: Calcium Channel Blockers
Centrally Acting Sympatholytics
- **Sympatholytic drugs**
  - Peripheral sympatholytic drugs such as alpha-adrenoceptor and beta-adrenoceptor antagonists block the influence of norepinephrine at the effector organ (heart or blood vessel)
  - Ganglionic blockers that block impulse transmission at the sympathetic ganglia
  - Block sympathetic activity within the brain. These are called centrally acting sympatholytic drugs

- clonidine, guanabenz, guanfacine, α-methyldopa
ACE Inhibitors

- 2\textsuperscript{nd} line to diuretics for most patients
- Block angiotensin I to angiotensin II conversion
- ACE (\textbf{A}ngiotensin \textbf{C}onverting \textbf{E}nzyme) distributed in many tissues
  - primarily endothelial cells
  - blood vessels: major site for angiotensin II production
- Block bradykinin degradation; stimulate synthesis of other vasodilating substances such as prostaglandin \(E_2\) & prostacyclin
- Prevent or regress left ventricular hypertrophy by reducing angiotensin II myocardial stimulation
ANGIOTENSINOGEN

Renin Secretion
- Macula densa signal
- Renal artery pressure/blood flow
- Sympathetic stimulation

Renin

ANGIOTENSIN I

Converting Enzyme

ANGIOTENSIN II

Adrenal Cortex
Kidney
Intestine
CNS
Peripheral Nervous System
Vascular Smooth Muscle
Heart

Aldosterone synthesis

Sodium/Water Reabsorption

Vasopressin

Blood Volume

Total Peripheral Resistance

Blood Pressure

Vasoconstriction

Contractility

Cardiac Output


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ACE Inhibitors

- Monitor serum \( K^+ \) & SCr within 4 weeks of initiation or dose increase

**Adverse effects:**

- cough
  - up to 20% of patients
  - due to increased bradykinin
- angioedema
- hyperkalemia: particularly in patients with CKD or DM
- neutropenia, agranulocytosis, glomerulonephritis, acute renal failure
ARBs

• Angiotensin II Receptor Blockers
• Angiotensin II generation
  ◦ renin-angiotensin-aldosterone pathway
  ◦ alternative pathway using other enzymes such as chymases
• Inhibit angiotensin II from all pathways
  ◦ directly block angiotensin II type I (AT1) receptor
  ◦ ACE inhibitors partially block effects of angiotensin II
ARBs

- Do not block bradykinin breakdown
  - less cough than ACE Inhibitors
- **Adverse effects:**
  - orthostatic hypotension
  - renal insufficiency
  - hyperkalemia
# AT II Receptor -Types

<table>
<thead>
<tr>
<th>AT₁ Receptor</th>
<th>AT₂ Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Cell growth &amp; Proliferation</td>
<td>Anti-growth</td>
</tr>
<tr>
<td>Promotes Reabsorption of Na &amp; Water</td>
<td>Natriuresis</td>
</tr>
<tr>
<td>Produces Free radicals</td>
<td>Produces Nitric oxide (Vasodilation)</td>
</tr>
<tr>
<td>Induces growth factors, Endothelin and Plasminogen Activator Inhibitor 1 (PAI-1)</td>
<td></td>
</tr>
</tbody>
</table>
Pathological role of AT–II

Angiotensin II

- Endothelin Catecholamines
- PAI-1, Platelet Aggregation Tissue Factor
- VCAMICAM Cytokines
- Proteolysis Inflammation
- Growth Factors Cytokines matrix

- Cardiac Contraction Vasoconstriction
- Thrombosis
- Inflammation
- Plaque Rupture
- Cardiac Vascular Remodeling
Angiotensin Receptor Blockers (ARBs)

- Block activation of angiotensin II AT1 receptors
- Effects include:
  - Vasodilation
  - Reduced secretion of vasopressin
  - Reduced production and secretion of aldosterone
  - Reduction in blood pressure
**MOA of ARB**

- **Angiotensinogen** → Renin → Angiotensin I → ACE → Angiotensin II (AT II) → AT

  - Increased AG II levels

- Non ACE Pathway:
  - Chymase
  - Trypsin
  - Cathepsin, Peptidase, Tonin

- **Telmisartan**
  - AT
    - Vasoconstriction
    - Renal sodium reabsorption
    - Cell growth and proliferation (remodelling)
  - AT
    - Vasodilation
    - Natriuresis
    - Antiproliferation

- **Bradykinin**
  - No cough

- **Active peptides**
  - ACE

- **Inactive peptides**
Side Effects of ARBs

- Usually well-tolerated
- Dizziness
- Headache
- Hyperkalemia

- Infrequent ADRs
- First dose orthostatic hypotension
- Rash
- Diarrhea
- Dyspepsia
- Abnormal liver function
- Muscle cramp, back pain
- Insomnia,
- Decreased Hb
- Renal impairment
- Pharyngitis/nasal congestion
ACE I / ARBs
Preferred agent in Diabetic HTN

- Offer Reno protection

<table>
<thead>
<tr>
<th>AT II</th>
<th>ACEI / ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase Intra-renal Pr &amp; Constricts Efferent Arteriole</td>
<td>Decreases</td>
</tr>
<tr>
<td>Thickening of Glomerular basement membrane: Stimulates Renal fibrosis &amp; Stimulates TGF beta (Hypertrophy, collagen syn.); Stimulates MCP (Inflammation)</td>
<td>Corrects</td>
</tr>
<tr>
<td>Endothelial dysfn</td>
<td>Improvement in Endothelial fn</td>
</tr>
</tbody>
</table>
New Antihypertensive Drugs

- Vasodilator beta-blockers
- Renin inhibitors
- Endothelin receptor antagonists
- Dual-acting angiotensin-plus endothelin-receptor antagonist
- Angiotensin-targeting vaccines
Renin Inhibitors

- **Aliskiren**
  - Aliskiren is the first in a new class of potent, orally effective renin inhibitors.
  - Whereas all of the other drugs act by inhibiting certain aspects of the ultimate step in the reninangiotensin system (RAS), ie, angiotensin II, aliskiren targets the first and rate-limiting step - namely, renin.