Antihypertensive Drugs

Nafrialdi
- **Parasympathetic:**
  - Heart rate ↓ → Cardiac output ↓ → BP ↓

- **Sympathetic:**
  - Heart rate ↑
  - Contractility ↑
  - Vascular tone ↑
  \[\rightarrow \text{BP} \uparrow\]

- **RAAS:**
  - Vascular tone ↑
  - Blood volume ↑
  \[\rightarrow \text{BP} \uparrow\]

- **Local factors:**
  - Vasodilator: EDRF, Prostacyclin (PGI2) → BP ↓
  - Vasocostrictor: Ang. II, Endothelin → BP ↑
# Blood Pressure Classification (JNC VI, 1997)

<table>
<thead>
<tr>
<th>Category</th>
<th>DBP</th>
<th>SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal</strong></td>
<td>&lt; 80</td>
<td>&lt; 120</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>&lt; 85</td>
<td>&lt; 130</td>
</tr>
<tr>
<td><strong>High normal</strong></td>
<td>85-89</td>
<td>130-139</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>90-99</td>
<td>140-159</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>100-109</td>
<td>160-179</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>&gt; 110</td>
<td>&gt; 180</td>
</tr>
<tr>
<td>Isolated systolic HT</td>
<td>&lt; 90</td>
<td>&gt; 140</td>
</tr>
</tbody>
</table>
Blood Pressure Classification (JNC VII, 2003)

<table>
<thead>
<tr>
<th>BP classification</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤ 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥ 160</td>
<td>≥ 100</td>
</tr>
</tbody>
</table>
Cardiovascular Risk Factors

- Hypertension
- Cigarette smoking
- Obesity (BMI $\geq 30$ kg/m$^2$)
- Physical inactivity
- Dyslipidemia
- Diabetes mellitus
- Microalbuminuria or estimated GFR $< 60$ ml/min.
- Age (>55 yrs for men, > 65 yrs for women)
- Family history of premature CV disease
  (men under age 55 or women under age 65)
Target Organ Damage

- **Heart**: left ventricular hypertrophy, heart failure, angina, myocardial infarction
- **Brain**: stroke
- **Kidney**: hypertensive nephropathy
- **Vessel**: atherosclerosis
- **Eye**: hypertensive retinopathy
## Treatment Strategy

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>Lifestyle Modification</th>
<th>Without Compelling Indication</th>
<th>With Compelling Indications (See Table 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Encourage</td>
<td>No antihypertensive drug indicated.</td>
<td>Drug(s) for compelling indications.†</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>Yes</td>
<td>Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.</td>
<td>Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>Yes</td>
<td>Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Algorithm for treatment of hypertension

**Lifestyle Modifications**

Not at Goal Blood Pressure (<140/90 mmHg)  
(<130/80 mmHg for patients with diabetes or chronic kidney disease)

**Initial Drug Choices**

Without Compelling Indications

- **Stage 1 Hypertension** (SBP 140–159 or DBP 90–99 mmHg)  
  Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.

With Compelling Indications

- **Stage 2 Hypertension** (SBP ≥160 or DBP ≥100 mmHg)  
  Two-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB).

Drug(s) for the compelling indications  
(See table 8)

- Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

**Not at Goal Blood Pressure**

Optimize dosages or add additional drugs until goal blood pressure is achieved. Consider consultation with hypertension specialist.
<table>
<thead>
<tr>
<th>Compelling Indication*</th>
<th>Recommended Drugs†</th>
<th>Clinical Trial Basis‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diuretic</td>
<td>BB</td>
</tr>
<tr>
<td>Heart failure</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Postmyocardial infarction</td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Diabetes</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>•</td>
<td>•</td>
</tr>
</tbody>
</table>
Non Pharmacologic Treatment

- Lifestyle modification
  - Weight reduction (if overweight/obese)
  - Adopt DASH eating plan (rich in fruit and vegetables, and lowfat diet)
  - Dietary sodium reduction
  - Moderation of alcohol consumption
  - Stop smoking
  - Regular physical activity
  - Stress avoidance
Sites of action of major classes of antihypertensive drugs.
Pharmacologic Treatment

• First line: 6 groups
  • Diuretics
  • Beta blockers
  • ACE-inhibitors
  • Ang II receptor blockers (ARB)
  • Ca antagonist
  • Alpha blockers* (considered first line in JNC VI but not in JNC VII)

• Second line: 3 groups
  • Adrenergic neuron inhibitors
  • Central $\alpha_2$- agonist
  • Direct vasodilator
I. DIURETICS

- Mechanisms of action:
  - Diuresis, natriuresis $\rightarrow$ blood volume $\downarrow$
    $\rightarrow$ cardiac output $\downarrow$ $\rightarrow$ BP $\downarrow$
  - Na$^+$ in serum & vascular smooth muscle $\downarrow$
    $\rightarrow$ vascular resistance $\downarrow$ $\rightarrow$ BP $\downarrow$

- 3 groups of diuretics:
  - I.a. Thiazide
  - I.b. Loop diuretics
  - I.c. Potassium sparing diuretics
I.a. THIAZIDE DIURETICS

Hydrochlorothiazide (HCT), Bendroflumethiazide, Chlortalidon, Indapamid

- Onset of anti hypertensive effect: 2-3 days
- Maximum effects: 2-4 weeks
- Drug of choice for mild to moderate HT, and HT with low renin activity (elderly)
- Much less effective in renal insufficiency
- Frequently used in combination with other anti HT drugs:
  - Prevents water retention by other anti HT drugs
  - Potentiation with other anti HT drugs
• **Adverse effects**
  • Hypokalemia \(\rightarrow\) digitalis toxicity \(↑\)
  • Hyponatremia, hypomagnesemia
  • Hyperuricemia \(\rightarrow\) precaution in gout arthritis
  • Hyperglycemia, hypercholesterolemia \(\rightarrow\) not ideal for DM and dyslipidemia
  • Hypercalcemia (rare) \(\rightarrow\) might be beneficial for retarding osteoporosis
  • Sexual dysfunction
• Caution: not effective in renal failure
• Interaction: NSAIDs reduces anti HT effects of diuretics
I.b. Loop Diuretics (high ceiling diuretics)

- FUROSEMIDE
  - Strong and rapid diuretic effect
  - Effective for HT with renal failure
  - First line drug for heart failure
  - Side effects:
    - $\approx$ Thiazide
    - Except Hypocalcemia
I.c. Potassium Sparing Diuretics

Spironolactone, Triamteren, Amiloride

- Weak diuretics
- Generally used in combination with other diuretic
- Reduces the risk of hypokalemia by other diuretic
- May risk hyperkalemia:
  - In renal failure
  - In combination with ACE-Inhibitor/ARB, NSAID
- Spironolactone is an aldosteron antagonist

→ Drug of choice for hyper aldosteronism
II. Beta-Blocker

- Mechanism: inhibition of b1 receptors
  - Heart $\rightarrow$ decreases cardiac output $\downarrow$
  - Juxtaglomerular cells $\rightarrow$ renin secretion $\downarrow$

- Clinical use:
  - Mild to moderate HT
  - HT with coronary artery disease
  - HT with supraventricular arrhythmia
  - HT with tachycardia
• Adverse effects
  • Bronchospasm
  • Bradycardia
  • Impotency
  • Peripheral vascular disturbances
  • Unfavourable effect on lipid profile
  • Masking hypoglycemic symptoms
  • Decrease renal function

• Contraindications
  • Asthma, COPD
  • Peripheral vascular disease
  • AV block grade 2-3
  • Sick sinus syndrome
III. ACE-inhibitor dan ARB

Angiotensinogen → Angiotensin I → Angiotensin II

ACE-inhibitor

Angiotensin II

AT1 receptor
• Vasoconstriction
• Aldosterone secretion
• Vascular/cardiac remodelling
• Sympathetic stimulation

AT2 receptor
• Vasodilatation
• Nitric oxide secretion
• Anti remodelling

Bradykinin → Inactive peptide

ACE
• ACE-Inhibition:
  • AngII ↓ : vasodilatation → BP ↓
    : aldosterone ↓ → Na⁺ and water retention ↓
  • Bradykinin ↑ → vasodilatation

• Clinical use:
  • First line drug for mild, moderate and severe HT
  • HT with heart failure
  • Hypertensive crisis
  • HT in diabetes, dyslipidemia, and DM nephropathy
  • Longterm use: cardioprotective, vasculoprotective
• **Adverse effects:**
  • Dry cough (10-20%)
  • Angio udem, *skin rash*, dysgeusia
  • Hypotension (*first dose phenomenon*)
  • Risk of Hyperkalemia:
    • In renal failure
    • If combined with K⁺ Sparing Diuretics or NSAID
  • Embryotoxic

• **Contraindication**
  • Pregnancy
  • Lactation → risk of renal failure in the fetus
  • Bilateral stenosis of Renal artery or unilateral stenosis in single kidney
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Prodrug/active</th>
<th>Active form</th>
<th>Hepatic Metabolism</th>
<th>Elimination</th>
<th>Daily Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Active</td>
<td>-</td>
<td>+</td>
<td>Kidney</td>
<td>2-3 x</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Active</td>
<td>-</td>
<td>-</td>
<td>Kidney</td>
<td>OD</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Prodrug</td>
<td>Perindoprilat</td>
<td>+</td>
<td>Kidney</td>
<td>OD</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Prodrug</td>
<td>Enalaprilat</td>
<td>+</td>
<td>Kidney</td>
<td>OD/ 2x</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Prodrug</td>
<td>Ramiprilat</td>
<td>+</td>
<td>Kidney</td>
<td>OD/ 2x</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Prodrug</td>
<td>Quinaprilat</td>
<td>+</td>
<td>Kidney</td>
<td>OD/ 2x</td>
</tr>
<tr>
<td>Silazapril</td>
<td>Prodrug</td>
<td>Silazaprilat</td>
<td>+</td>
<td>Kidney</td>
<td>OD</td>
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<tr>
<td>Benazepril</td>
<td>Prodrug</td>
<td>Benazeprilat</td>
<td>+</td>
<td>Kidney</td>
<td>OD/ 2x</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Prodrug</td>
<td>Fosinoprilat</td>
<td>+</td>
<td>Kidney + bilier</td>
<td>OD</td>
</tr>
</tbody>
</table>
IV. Angiotensin Receptor Blockers (ARB)

Losartan, Valsartan, Irbesartan, Candesartan, Telmisartan

- Mechanism of action:
  - Blockade of Ang II (AT1) receptor.
  - Vasodilatation
  - Aldosterone ↓
  - Decreasing Ang II-mediated sympathetic activation
  - Prevents vascular and cardiac hypertrophy (vasculo- and cardio protective)
Angiotensin Receptor Blocker (ARB)

- Side effects ≈ ACE-I, except:
  - No dry cough
  - No angio-edema
- Indications and contraindications = ACE-I
V. Calcium Channel Blocker

Inhibition of Ca\(^{++}\) influx

- Blood vessels $\rightarrow$ vasodilatation
- Heart $\rightarrow$ negative inotropism, negative dromotropism
- $\rightarrow$ not recommended in the presence of heart failure
Three groups of CCB

1. Dihydropyridine (DHP):
   - (nifedipine, amlodipine, nicardipine, felodipine, lasidipine, nitrendipine, …)
   - Vasculo selective:
     - Predominant vasodilatory effect
     - Minimal cardiac effects

2. Diphenylalkilamin: - verapamil
   - More cardioselective:
   - Decreases myocardial contractility and conduction

3. Benzothiazepin: - diltiazem
   - Cardioselective
   - Decreases myocardial contractility and conduction
Pharmacokinetics:

- **Nifedipine:**
  - Rapid oral absorption $\rightarrow$ rapid BP ↓
  - Short T1/2 $\rightarrow$ needs 3-4 x daily dosing

- **Amlodipine:**
  - Slow absorption
  - Long T1/2 $\rightarrow$ once daily

- First pass metabolism (all CCB)
- Extensive hepatic metabolism (>90%): all CCB $\rightarrow$ precaution in liver failure
- Minimal renal excretion $\rightarrow$ relatively save for renal failure
INDICATIONS

- Hypertension: dihydropiridine, verapamil, (diltiazem: rare)
- Hypertensive crisis: nifedipine (sublingual), nicardipine iv
- Angina pectoris: verapamil, diltiazem, nifedipine (short acting)
- Arrhythmia: verapamil, diltiazem

Note: Short acting Nifedipin is not recommended for maintenance therapy of HT
Adverse effects

- Nifedipine:
  - Hipotension → risk of myocardial and cerebral ischemia
  - Tachycardia
  - Head ache, flushing, peripheral edema

- Verapamil, diltiazem:
  - Bradicardia, constipation

Contraindication

- Heart failure (except amlodipine)
- Precaution in liver cirrhosis
VI. Alpha-blocker

Prazosin, terazosin, bunazosin, doxazosin

- Blockade of a-1 $\rightarrow$ vasodilatation
- Positive effect on lipid profile (LDL $\downarrow$, HDL $\uparrow$)
- Decreases insulin resistance

CLINICAL USAGE

- Mild to moderate HT
- Benign prostatic hypertrophy (HT or not)
- HT with DM /dyslipidemia
- HT with peripheral vascular disease
• **ADVERSE EFFECTS**
  - Orthostatic hypotension (first dose phenomenon: often w/ prazosin)
    → Start low dose, before bed time
  - Tachycardia
  - Head ache
  - Peripheral edema
• Prazosin, terazosin, bunazosin: short halflife → 2-3 x daily
• Doxazosin: longer half life → once daily
Second line drugs

I. ADRENERGIC BLOCKING AGENTS
(Reserpin, Guanetidin)

- **Mechanism:**
  - Reserpin: inhibits NE transport into nerve vesicles
  - Guanetidin: Shift NE out of vesicles
    - → depletion of NE vesicles
  - Low dose Reserpin + HCT: effective and very cheap

- **Side effects:**
  - Sedation, deppression
  - Nasal congestion
  - Peptic ulcer
II. Central $\alpha$-agonist

(Clonidin, methyldopa, guanfasin)

$\rightarrow$ sympathetic outflow $\downarrow$ $\rightarrow$ cardiac output $\downarrow$

- Methyldopa: D.O.C for pregnant women
- Side effects:
  - Dry mouth, sedation, dizziness
  - Sexual dysfunction
  - Fluid retention $\rightarrow$ decreased effects
  - Withdrawal effect can lead to hypertensive crisis
- Interaction: Tricyclic antidepressants, sympathomimetic drugs $\rightarrow$ reduces effects
III. DIRECT VASODILATORS

- **Hydralazin**: Mechanism?  
  - Indications:  
    - HT emergency  
    - HT in glomerulonephritis  
    - HT in eclampsia

- **Minoxidil & Diazoxide**: Potassium channel opener  
  - Malignant HT  
  - HT in glomerulonephritis  
  - Hypertensive encephalopathy

**Adverse effects**  
- **Hydralazin**: *lupus like syndrome*, tachycardia, flid retenton, angina pectoris  
- **Minoxidil**: hirsutism  
- **Diazoxide**: hyperglycemia → for insulinoma
Antihypertensive in special conditions

Pregnancy

- Methyldopa: choice
- Beta blocker: atenolol, metoprolol, labetalol (relatively safe)
- CCB: widely used in preeclampsia/ eclampsia, sinergisme with MgSO₄
- Hydralazin: preeclampsia/eclampsia
- ACE-I and ARB: contraindication
Antihypertensive in special conditions

Hypertensive emergency

- Oral drugs: captopril, nifedipine
- Parenteral drugs: clonidin, nitroglycerin, hydralazin, furosemide

Renal failure

- CCB, furosemide, clonidine, alpha blocker, hydralazine, NTG $\rightarrow$ safe
- ACE-I /ARB $\rightarrow$ CI if hyperkalemia, stop if creatinine increases
- B-blocker $\rightarrow$ tends to reduce renal function
Antihypertensive in special conditions

Liver cirrhosis
- CCB: not recommended

Asthma
- Beta-blocker: contraindicated

DM/dyslipidemia
- Choice: ACE-I /ARB
- B-blocker, thiazide: not recommended
- CCB. a-blocker, clonidine: safe