Hypertension and Antihypertensive Agents

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Agents used in the treatment of HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hypertension</th>
<th>CHF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindication/Contrainol/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td>***</td>
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<td>***</td>
<td></td>
<td>Caution: CHF (unstable CHF, bronchoconstriction); or in diabetes, asthma (bronchoconstriction)</td>
</tr>
<tr>
<td>Ca+ Blockers</td>
<td>***</td>
<td>***</td>
<td></td>
<td></td>
<td>CHF, GFR (renal hypoproteinemia)</td>
</tr>
<tr>
<td>ACEI</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td></td>
<td>Low GFR, renal insufficiency, anemia</td>
</tr>
<tr>
<td>Diuretics</td>
<td>***</td>
<td>***</td>
<td></td>
<td></td>
<td>Low GFR, hyperkalemia, glucose intolerance, diabetes</td>
</tr>
<tr>
<td>Nitrates</td>
<td>**</td>
<td>***</td>
<td></td>
<td></td>
<td>Effects enhanced in depolarized tissue</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>***</td>
<td>***</td>
<td></td>
<td></td>
<td>Tolerance, flushing, dizziness, headache, reflex tachycardia</td>
</tr>
</tbody>
</table>

Introduction
Blood Pressure Regulation: Frank’s Formula
BP = Cardiac output (CO) x Total peripheral resistance (TPR)
CO = Stroke volume (SV) x Heart rate (HR)

Baroreceptor Reflex Arc
- oppose direct change in BP
- bidirectional, responds to T or Lin BP
- not concerned with HR
- not concerned with pulse pressure

Leading Causes of Death in the U.S

Data NIH 2000
**Definition of Hypertension (HT)**

Sustained elevation of systolic and/or diastolic BP above an arbitrarily defined level
- Systolic >139 mmHg and/or diastolic >89 mmHg

**General population (15-20%) hypertensive**

45 – 60 million in USA

**Secondary HT (10%):** can be cured by surgical procedures (early diagnosis of cause, ie renal stenosis, pheochromocytoma)

**Primary (essential) HT (90%):** is a lifelong disease, long-term control & treatment, cause unknown

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**Classification of Hypertension**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;130</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>High Normal</td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td>Stage 1 (mild)</td>
<td>140-150</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>180-203</td>
<td>110-119</td>
</tr>
<tr>
<td>Stage 4 (very severe)</td>
<td>&gt;209</td>
<td>&gt;119</td>
</tr>
</tbody>
</table>

*Requires three measurements (repeat visits)
BP lowest in the morning during the day

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**Hypertension (HT)**

**Secondary HTs (10%)**
- Neurogenic HT caused by brain damage
- Cortisol overproduction: hypophysis or adrenal gland tumor
- Aldosterone overproduction: adrenal gland tumor hyperplasia
- Renal artery stenosis or occlusion
- Adrenal medulla tumor: pheochromocytoma

**Primary (essential) HTs (90%)**
- Primary cause(s) unknown, possibly multi-factorial defects
  - Genetics
  - Smoking
  - Salt intake
  - Alcohol
  - Stress
  - Obesity
  - Age
  - Caffeine
  - Others

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**Renal Stenosis**

Decreased renal blood flow
- Renal BP
- Renin release
- Aldosterone
- Na+, water retention
- Systemic BP

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**Pheochromocytoma**

- Tumor:
- Synthesis, T release of NE & Epi into the circulation.
- Treatment:
- Surgical removal for solid tumor
- α- β-blocker ie. Labetalol
- α-blocker ie. Phenoxybenzamine or Phentolamine
- Inhibit tyrosine hydroxylase ie. α-methyl-p-tyrosine
- β-blocker only after α-blockade

**Rule of Ten**
- Malignant
- Bilateral
- Extra-adrenal
- In children
- Familial
- Recur (within 5 to 10 years)
- Present after stroke

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**Exam Stress**

- Normal BP: 120 / 80 mmHg HR: 72 bpm
- Before exam: 140 / 99 mmHg HR: 97 bpm
- During exam: 179 / 149 mmHg HR: 110 bpm
- End of exam: 111 / 74 mmHg HR: 76 bpm
Consequences of Sustained Hypertension

- failure in blood supply, renal failure (fibrinoid necrosis)
- loss of microcirculation
- aneurysms (rupture of blood vessels)
- myocardial and/or cerebral infarction
- increased risk of stroke
- increased risk of congestive heart failure

Health Consequences - Age

Health Consequences - Cardiovascular Diseases

Health Consequences - Effective Treatment

Better understanding, better treatments, better results

Health Consequences – Risk Factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>life expectancy Gain in Life Expectancy in Years for 25-Year-Old Individual</th>
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<tbody>
<tr>
<td>Reduce cholesterol level</td>
<td>Male: 0.4 Female: 0.4</td>
</tr>
<tr>
<td>To 200 mg/dl f 230-269 mg/dl</td>
<td>Male: 1.5 Female: 1.5</td>
</tr>
<tr>
<td>To 200 mg/dl f &lt;200 mg/dl</td>
<td>Male: 2 Female: 2</td>
</tr>
<tr>
<td>Reduce number of cigarette smoked</td>
<td>Male: 1.5 Female: 1.5</td>
</tr>
<tr>
<td>By 50%</td>
<td></td>
</tr>
<tr>
<td>Reduce systolic blood pressure:</td>
<td></td>
</tr>
<tr>
<td>To 130 mmHg f 140-159 mmHg</td>
<td>Male: 1.1 Female: 0.9</td>
</tr>
<tr>
<td>To 130 mmHg f &lt;140 mmHg</td>
<td>Male: 2 Female: 2</td>
</tr>
<tr>
<td>Reduce weight:</td>
<td></td>
</tr>
<tr>
<td>To ideal f &lt;5% over ideal</td>
<td>Male: 0.7 Female: 0.5</td>
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Non Drug Treatment – Life Style Modification

For mild – moderate hypertension
Less side effects, cheap

- ↓ salt intake (Japan, ↑ intake → ↑BP)
  2.5gm/day (250meq) → 1gm/day (100meq)
- ↓ calorie intake, weight loss
- ↓ alcohol consumption (low dose ↓BP)
- ↑ physical activity
- ↓ stress factors
- ↓ smoking
- ↓ caffeine intake
Classification of Hypertension

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For accurate determination: require three measurements (repeat visits)
BP in general is lowest in the morning and increases during the day

Antihypertensive Agents

1. Diuretics  
   - eg. hydrochlorothiazide
2. Central acting alpha2-agonists  
   - eg. clonidine, e-methyl dopa
3. Ganglionic blockers  
   - eg. mecamylamine
4. Inhibit NE release  
   - eg. guanethidine
5. Alpha-antagonists  
   - eg. prazosin
6. Beta-antagonists  
   - eg. propranolol
7. Vasodilators  
   - eg. hydralazine, nitroprusside
8. Renin / AII (ACEI)  
   - eg. captopril
9. Potassium sparing  
   - eg. spironolactone
10. Calcium-antagonists  
    - eg. nifedipine

Diuretics

Frontline class
- ↓ BP by body depletion of Na+ and reducing blood volume (BV)
- High clinical value as antihypertensive
- Effective in older patients (less β-blockers, ACEI)
- Less effective in lean individuals
- Used also in treatment of Congestive Heart Failure
- Often used in combination with β-blockers or vasodilators
- Effective when GFR > 30ml/min (normal: 125ml/min)

Diuretics - Mechanism of action

Initial:  
- ↓ body Na+ → ↓ BV → ↓ CO → ↓ BP (TPR, reflex)
Chronic:  
- CO unchanged, ↓ TPR, ↓ NE → ↓ [Ca2+]i → ↓ vascular tone
Direct vasodilation effect:  
- probably by opening K+ channels

Thiazides:  
- eg. hydrochlorothiazide
- act on early distal tubule
- inhibit Na+ reabsorption

Loop Diuretics:  
- eg. furosemide
- act on loop of Henle
- most potent
Diuretics - Adverse effects

- potassium depletion → hypokalemia; hazardous in persons taking digitalis → arrhythmia
- magnesium depletion → arrhythmia
- photosensitivity
- impair glucose tolerance → diabetes
- increase serum lipids (usually returns to normal)
- increase serum uric acid concentration → gout

Potassium Sparing Agents

- eg. Spironolactone
- aldosterone antagonist
- act on late distal tubule (collecting duct) to inhibit Na⁺ reabsorption and K⁺ secretion
- weak action
- hyperkalemia
- commonly used in combination therapy with other antihypertensive agents

Centrally acting sympatholytic agents

Useful class
- Act on central α₂-receptors → ↓ sympathetic outflow
- Good clinical value as antihypertensives.
  Clonidine, Guanfacine
  α-Methyldopa (converted to α-methyl-NE)
- do not interfere with exercise tolerance
- no metabolic effects

Adverse effects:
- sedation, mental depression, lactation, dry mouth
- withdrawal effect (can be very serious)

Ganglion-Blocking Agents

• block ganglionic nicotinic receptors (SNS, PNS)
• first effective antihypertensive class
• currently not used for chronic HT

Adverse effects (significant):
• Sympathoplegia:
  - excessive orthostatic hypotension, sexual dysfunction
• Parasympathoplegia:
  - constipation, ↓ urine, blurred vision, dry mouth
• Trimethaphan
  - i.v. injection, rapid, short half life (precise titration)
  - hypertensive crisis, controlled hypotension during surgery
• Mecamylamine: effective orally

Neurons of the ANS

Postural (Orthostatic) Hypotension

- Venous return falls
- Blood pressure falls
- Sympathetic activity increases
  - Constriction of great veins
  - Constriction of arteries (TPR)
  - Increase in heart rate

reflex mediated

reflex

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<tr>
<th>BP (mmHg)</th>
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<tbody>
<tr>
<td>95</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>95</td>
</tr>
<tr>
<td>195</td>
</tr>
<tr>
<td>100</td>
</tr>
</tbody>
</table>

reflex

no reflex
Adrenergic Neuron-Blocking Agents

Clinical value as antihypertensive is low
Guanethidine (last resort)
- inhibits release of NE from nerve terminals
- gradual depletion of NE stores
- neuronal uptake (uptake 1) is essential for action
- tricyclic antidepressants, cocaine decrease effectiveness
Adverse effects:
- marked postural hypotension
- diarrhea, impaired ejaculation

Reserpine
Clinical value as antihypertensive is low
Reserpine (last resort)
- inhibit uptake of NE into storage vesicle (also DA, 5-HT)
- leads to depletion of transmitter stores (peripheral & CNS action)
Adverse effects:
- sedation, mental depression, Parkinsonism syndrome
- increases gastric acid secretion

Alpha-Adrenoceptor Antagonists

Use low, but constant
Phenoxybenzamine (irreversible α1-receptor blocker)
- reflex tachycardia effect
- therapeutic value in pheochromocytoma, HT crisis
Prazosin (selective α1-receptor blocker)
- selective α1-receptor blocker in arterioles and venules (dilates both resistance and capacitance vessels)
- does not produce reflex tachycardia
- also used for benign prostate hyper trophy
Phentolamine (non-selective α-receptor blocker)
- reflex tachycardia effect
- diagnostic and therapeutic value in pheochromocytoma
Adverse effects:
- postural hypotension
- salt and fluid retention
- beneficiary effect on plasma lipids

Benign Prostate Hypertrophy (BPH)
Enlarged prostate leads to difficulty in urination
Alpha-receptor blocker (ie Prazosin) cause prostate relaxation
Relaxed prostate improves urination

Beta-Adrenoceptor Antagonists

Frontline as antihypertensive agents
Mechanism of action unknown
- central effect: inhibition of central sympathetic tone
- inhibition of renin secretion (beta1-receptors)
BUT: beta-blockers ↓ BP when plasma renin activity low
beta-blockers (like Pindolol) don’t plasma renin activity
- effect on cardiac beta1-receptors: ↓ HR → ↓ CO → ↓ BP
BUT: with continued treatment CO unchanged, ↑ TPR → ↓ BP
Other Clinical Uses:
- Angina
- Congestive heart failure (CHF)
- Panic stress
- Hyperthyroidism (propranolol)

Beta-Blockers - Mechanism of Action

Beta-Adrenergic Receptor Antagonists

Clinically a more useful class of drugs than α-adrenoceptor antagonists.

β-Adrenoceptor antagonists vary in respect to:

- Selectivity: Relative affinity for beta1- and beta2-adrenoceptors
  - propranolol (β1, β2) vs atenolol (β1)
- Intrinsic β-activity (ISA): also act as agonists at β-adrenoceptors, propranolol (no) vs pindolol (yes)
- Local anaesthetic activity (LA-action): their ability to stabilize excitable membranes
  - propranolol (yes) vs atenolol (no)
- Lipid solubility: propranolol (high) vs atenolol (low)

Propranolol - Hypertension

- Non-selective
- No partial agonist (ISA)
- Membrane stabilization (LA-action)
- Less effective in smokers, Afro-Americans, or elderly

Mixed Alpha- and β-Receptor Blockers

- Labetalol
  - hypertensive crisis, chronic hypertension, CHF
  - competitive antagonist at both α- & β-ARs
  - HR & CO unchanged; TPR ↓ → ↓ BP
  - some intrinsic β-adrenoceptor activity (ISA)

- Carvedilol
  - newest agent
  - chronic hypertension, Congestive heart failure (CHF)

β-Blockers: Untoward Effects, Contraindications

- Supersensitivity:
  - Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol).
  - Gradual withdrawal

- Asthma:
  - Blockade of pulmonary β2-receptors will increase airway resistance (bronchospasm)

- Diabetes:
  - Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred

- CNS: nightmares, mental depression, insomnia

β-Blockers: Heart Failure

- Old view (before 2002)
  - Contraindicated: β-blockers can precipitate latent heart failure by removing compensatory increase in sympathetic effects on heart. Pindolol has less of this effect due to intrinsic activity.

- New view
  - May be used for CHF with caution. Not suitable in unstable heart failure, or evidence of bronchospasm, fluid overload, significant bradycardia (decreased cardiac reserve) or depression.
**Beta-Blockers in CHF: 2002 Guideline**

- **MERIT-HF : Use of Metoprolol in CHF**
  - Metoprolol (n=1990) vs Placebo (n=2001)
  - β₁-selective, no ISA, LA-action
  - USA & 13 European countries
  - All received conventional medication
  - Monitored 1 – 1.5 years
  - Mortality ↓34%
  - Hospitalization ↓29%
  - Felt better ↑25%

- **Vasodilators**
  - relax smooth muscle of arterioles → ↓TPR
  - high clinical value (in combinations and hypertensive emergencies)

  - **Hydralazine**
    - EDRF / Nitric oxide (NO) / cGMP involvement
    - dilate arterioles but not veins
    - ↓TPR → BP reflex tachycardia

  - Adverse effects:
    - reflex sympathetic activation
    - headache, nausea, sweating, flushing
    - palpitations, ↑HR → angina
    - lupus reaction (mainly in slow acetylators)

- **Actions of Vasodilators**

- **Vasodilators - Minoxidil**
  - opens K⁺-channels in smooth muscle membranes
  - stabilization of membrane at its resting potential, contraction less likely
  - dilates arterioles but not veins

  - Adverse effects:
    - reflex sympathetic stimulation
    - fluid retention (value in combination therapy)
    - hypertrichosis (topical application as Rogaine)
Vasodilators – Sodium Nitroprusside
Sodium Nitroprusside
- activation of guanylylcyclase (direct and/or via release of NO)
- intracellular GTP → relaxation of vascular smooth muscle
- dilates both arterial (↓ TPR) and venous vessels
- venous return to the heart is decreased, reflex tachycardia
- hypertensive emergency, acute CHF
- i.v. administration, never oral toxicity

Adverse effects:
- cyanide liberation → cyanide toxicity
- thiocyanate elimination by the kidney (high dose / long infusion, insufficient sulfur donor, defect in cyanide metabolism)
- metabolic acidosis, arrhythmias, severe hypotension
- methemoglobinemia (non-reversible O₂ binding)

Vasodilators - Diazoxide
Diazoxide
- opens K⁺-channels - stabilizes membrane potential
- dilates arteriolar vessels
- i.v. administration
- ↓ TPR → reflex ↑ HR → ↑ CO
- inhibits insulin release (via opening K⁺-channels on beta cell membrane)
- similar structure as thiazide diuretics but no diuretic effect

Calcium Channel Blockers
Frontline class
- inhibition of calcium influx into arterial smooth muscle cells
- dilate arterioles → ↓ TPR, ↓ BP
- different effect on the heart and vessels
- contraindicated in CHF

Nifedipine:
- mainly arteriole vasodilation, little direct cardiac effect
- may cause reflex tachycardia, flushing, peripheral edema

Verapamil:
- some cardiac slowing, constipation
- caution in digitalized patients (↑ digoxin levels)

Diltiazem:
- similar to Verapamil / Nifedipine (less)
- both cardiac and vascular actions

Calcium blockers - Gingival Hyperplasia
- Calcium blockers – especially nifedipine (10%)
- Phenytoin (Dilantin) – for seizures (40%)
- Cyclosporine – immunosuppressant (30%)

Action of Vasodilators
eg. Calcium blockers, Hydralazine, Minoxidil

Renin-Angiotensin-Aldosterone System Inhibitors
Frontline class of antihypertensive agents
- inhibit action or production of angiotensin II
- AgII is a potent vasoconstrictor peptide
- decrease aldosterone production
- less effective in elderly, Afro-Americans

ACE is a peptidyl dipeptidase:
- converts AgI → active AgII (major effect)
- degrades bradykinin (a potent vasodilator)
Angiotensin-Converting Enzyme (ACE) Inhibitors

- Captopril: orally active
- Enalapril: for i.v. use, hypertensive emergency
- Benazepril, Fosinopril, Ramipril: longer acting agents

\( \downarrow \text{TPr}, \ CO \ \text{unchanged}, \ \text{HR} \ \text{unchanged} \)
- no reflex \( \uparrow \) HR, probably due to resetting \( \downarrow \) of baroreceptor reflex sensitivity
- improves intrarenal hemodynamics
- reverse cardiac hypertrophy seen in HT
- less effective with age and in Afro-Americans
- need to take before or after meals

Saralazin, Lorsarton (receptor antagonists)
- competitive inhibitor of AgII at its receptor
- has a weak agonist activity (depends on circulating AgII level)
- diagnostic value (AgII dependency of HT)

ACE Inhibitors - Adverse effects

- severe hypotension in hypovolemic patients, bilateral renal artery stenosis
- hyperkalemia \( [\text{K}^+] \)
- dry cough, dry mouth, skin rashes, glossitis
- altered sense of taste due to loss of Zinc (10-20%)
- contraindicated during the second and third trimester of pregnancy
- drug interactions with potassium-sparing diuretics, NSAID

ACEI - Glossitis

- Less than 5%
- Dry mouth
- Glossitis
- Oral ulceration (Stevens-Johnson Syndrome)
- Oral bleeding

ACE Inhibitors - Glossitis

Treatment of Hypertension

General considerations

Secondary HT (10%)
- can be cured by surgical procedures (early diagnosis of cause)
- renal artery stenosis, pheochromocytoma

Primary (essential) HT (90%)
- is a lifelong disease, long-term control & treatment
- HT often insidious, causes no symptoms
- conversely treatment can produce even serious

Adverse effects:
- patients compliance is very important
- treat the patient and not 'just' their BP (quality of life)

Treatment strategy

Initial step: Nonpharmacological
- sodium intake, weight loss, physical activity, alcohol, stress,
- overview of medication, other risk factors

IF NOT ENOUGH OR INITIALLY HIGHER STAGE OF HT

Drug therapy:
- continue or start with drug therapy (frontline agents)
- choose the proper medication?
- \( \beta \)-blockers efficacy may decrease as age increases
- \( \beta \)-blockers are less effective in smokers
- blacks respond less to \( \beta \)-blockers and ACE inhibitors
- \( \beta \)-blockers and ACE inhibitors better in \( \uparrow \) plasma renin
- use long-lasting drugs (\( \uparrow \) compliance)

Start with monotherapy:
- if necessary add second, or third agent (from different class)

Good Combotherapy: vasodilator with either \( \beta \)-blocker or diuretic

Antihypertensive Market
Hypertension Treatment Chart

Dental - General Considerations

- **Antihypertensive agents**
  - especially: α-blockers, ganglia-blockers, guanethidine
  - sit upright for 2 min before standing
  - limit Na-containing products i.e. saline

- **Respiratory**
  - asthma, CHF, patients on β-blockers
  - consider semisupine position

- **Dry mouth**
  - diuretics, β-blockers, α-blockers, clonidine, ACEI, calcium-blockers
  - advise patient avoid high EtOH mouth rinses
  - use sugar-free gum, frequent water sips

- **Photosensitivity**
  - thiazide diuretics, ACEI
  - avoid bright light during examination

CRL-Online

- Clinical Reference Library
- www.crlonline.com

- **Propranolol** - non-selective β-blocker
- **Metoprolol** - selective β1-blocker
- **Captopril** - ACE inhibitor
- **Verapamil** - Calcium blocker
- **Chlorothiazide** - Diuretic
- **Digoxin** - Cardiac glycoside

Hypertension Market Age and Sex Profile

Secondary Hypertension

Transmitter synthesis and release