Hypertension and Antihypertensive Agents

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Leading Causes of Death in the U.S

Data NIH  2000
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>Contraindications/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>Caution: CHF (unstable CHF, bronchospasm, significant bradycardia); or in diabetes, asthma (use β1-selective), depression</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>CHF, Gingival hyperplasia, reflex tachycardia, constipation</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>Low GFR, renal stenosis, glossitis, tetrogenic, cough (ACEI), taste, ↑renal mechanics</td>
</tr>
<tr>
<td>Diuretics</td>
<td>✔️ ✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>Low GFR, hypokalemia → CG; glucose intolerance → diabetes</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>Many Rx interactions, low Ti, [K+] ; important, low K+↑toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>Flushing, dizziness, headache, reflex tachycardia, combo Rx</td>
</tr>
<tr>
<td>Na+-Channel blockers</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>✔️ ✔️ ✔️</td>
<td>✔️</td>
<td>Effects enhanced in depolarized tissue, damaged tissue. Phase 0</td>
</tr>
<tr>
<td>Nitrates</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

\[ BP = \text{Cardiac output (CO)} \times \text{Total peripheral resistance (TPR)} \]

\[ \text{CO} = \text{Stroke volume (SV)} \times \text{Heart rate (HR)} \]

120/80 mmHg

70 bpm

Fast acting

Long acting
Baroreceptor Reflex Arc

- oppose direct change in BP
- bidirectional, responds to ↑ or ↓ in BP
- not concerned with HR
- not concerned with pulse pressure

Increase stretch → increase firing of baroreceptors

Systolic – Diastolic Blood Pressure
**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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**New Blood Pressure Classification – JNC VII**

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</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>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

*Require three measurements (repeat visits)
BP lowest in the morning → ↑ during the day
**Previous Classification of Hypertension (<2003)**

<table>
<thead>
<tr>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;130</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139</td>
</tr>
<tr>
<td>Stage 1 (mild)</td>
<td>140-159</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>160-179</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>180-209</td>
</tr>
<tr>
<td>Stage 4 (very severe)</td>
<td>&gt;209</td>
</tr>
</tbody>
</table>

*Require three measurements (repeat visits)*

BP lowest in the morning → ↑ during the day

---

**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
  - stress
  - salt intake
  - obesity
  - age
  - alcohol
  - caffeine
  - others
Renal Stenosis

Primary cause of 2° HT

Decreased renal blood flow
- ↓ renal BP
- ↑ renin release
- ↑ aldosterone
- ↑ Na*, water retention
- ↑ systemic BP

Pheochromocytoma

Tumor: ↑ synthesis, ↑ release of NE & EPI into the circulation.
Result: ↑ BP, ↑ HR → hypertensive crisis
Treatment: - surgical removal for solid tumor
- α- / β-blocker ie. Labetatol
- α-blocker ie, phenoxybenzamine or phentolamine
- inhibit tyrosine hydroxylase ie. α-methyl-p-tyrosine
- β-blocker only after α-blockade

Rule of Ten
10% Pheochromocytomas are:

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

BP Daily Fluctuation

Fluctuation Throughout a Day
(Case: Male, 35 years of age)

Systolic Blood Pressure
Diastolic Blood Pressure

6AM  12  6PM  12
Morning  Afternoon  Evening

Gets up  Arrives at the company  Discussion on the telephone  Argument in a meeting  Leaves the company  Dinner  Sleeps
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

USA
45-60 million HT

\[ \downarrow \text{Na}^+ \rightarrow \downarrow \text{rise rate} \]
Health Consequences – Cardiovascular Diseases

Health Consequences – Effective Treatment

Better understanding, better treatments, better results
Health Consequences – Risk Factors

↓ Risk factors → ↑ life expectancy

<table>
<thead>
<tr>
<th>Gains in Life Expectancy in Years for 35-Year-Old Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Reduce cholesterol level:</td>
</tr>
<tr>
<td>To 200 mg/dl if 200–239 mg/dl</td>
</tr>
<tr>
<td>To 200 mg/dl if ≥240–299 mg/dl</td>
</tr>
<tr>
<td>Reduce number of cigarettes smoked:</td>
</tr>
<tr>
<td>By 50%</td>
</tr>
<tr>
<td>Eliminate smoking</td>
</tr>
<tr>
<td>Reduce diastolic blood pressure:</td>
</tr>
<tr>
<td>To 88 mm Hg if 90–94 mm Hg</td>
</tr>
<tr>
<td>To 88 mm Hg if ≥95–104 mm Hg</td>
</tr>
<tr>
<td>Reduce weight:</td>
</tr>
<tr>
<td>To ideal if &lt;30% over ideal</td>
</tr>
<tr>
<td>To ideal if ≥30% over ideal</td>
</tr>
</tbody>
</table>


Non Drug Treatment – Life Style Modification

For mild – moderate hypertension
Less side effects, cheap, improved lifestyle

- ↓ 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
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<td>&gt;209</td>
</tr>
</tbody>
</table>

For accurate determination: requires three measurements (repeat visits)
BP in general is lowest in the morning and increases during the day
Antihypertensive Agents (JNC VII, 2003)

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

Main classes  
(‘frontline agents’)

Beta-blockers  
Diuretics (1st)  
Calcium blockers  
ACE inhibitors / ARBs

Sites of Action of Antihypertensive Agents
Antihypertensive Usage (ACC, 2001)

For untreated patients patients with BP of 140-159/90-99 mmHg and no other risk factors, indicate which class(es) of medications you would use:

<table>
<thead>
<tr>
<th>Medication</th>
<th>% Selecting each class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiologist</td>
</tr>
<tr>
<td>ACE inhibitor / ARB</td>
<td>71.6</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>57.9</td>
</tr>
<tr>
<td>Ca-blocker</td>
<td>51.5</td>
</tr>
<tr>
<td>Diuretics</td>
<td>48.8</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>16.4</td>
</tr>
<tr>
<td>Other class</td>
<td>4.4</td>
</tr>
<tr>
<td>None (life-style)</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Hypertension Is Largely Uncontrolled

Patients whose Hypertension is Controlled

<table>
<thead>
<tr>
<th>&lt; 140/90 mmHg</th>
<th>&lt; 160/95 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA: JNC VI. Arch Intern Med 1997</td>
<td></td>
</tr>
<tr>
<td>Canada: Joffres et al. Am J Hypertens 1997</td>
<td></td>
</tr>
</tbody>
</table>

USA 27 |
Canada 16 |
England 6 |
France 24 |
Finland 20.5 |
Spain 20 |
Australia 19 |
Germany 22.5 |
Scotland 17.5 |
India 9 |

> 65 years

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:
\[ \downarrow \text{body Na}^+ \rightarrow \downarrow \text{BV} \rightarrow \downarrow \text{CO} \rightarrow \downarrow \text{BP} \left( \uparrow \text{TPR, reflex} \right) \]

Chronic:
\[ \text{CO unchanged, } \downarrow \text{TPR, } \downarrow \text{NE} \rightarrow \downarrow \text{[Ca}^{++}\text{j]} \rightarrow \downarrow \text{vascular tone} \]

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

---

Nephron
### Diuretics - Adverse effects

**(Thiazide & Loop)**

- 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

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### Potassium Sparing Diuretic 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 $\alpha_2$-receptors $\rightarrow$ ↓sympathetic outflow
- Good clinical value as antihypertensives.
  
  Clonidine, Guanfacine
  $\alpha$-Methyldopa (converted to $\alpha$-methyl-NE)
- do not interfere with exercise tolerance
- no metabolic effects

Adverse effects:
- sedation, mental depression, lactation, dry mouth
- withdrawal effect: rebound HT (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 (CNS-mediated), controlled hypotension during surgery

- Mecamylamine: effective orally
Neurons of the ANS

- Venous return falls
- Blood pressure falls

Postural (Orthostatic) Hypotension

- Sympathetic activity increases
  - Constriction of great veins
  - Constriction of arteries (↑ TPR)
  - Increase in heart rate

BP (mmHg)

<table>
<thead>
<tr>
<th>No reflex</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 100 95</td>
<td>100 100 195 105</td>
</tr>
</tbody>
</table>

reflex mediated
Adrenergic Neuron-Blocking Agents

Clinical value as antihypertensive is low

Guanethidine (last resort), bretylium
- 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 → ulcer
Alpha-Adrenoceptor Antagonists

- Use low, but constant

Phenoxybenzamine (irreversible $\alpha_1$-receptor blocker)
- reflex tachycardia effect
- therapeutic value in pheochromocytoma, HT crisis

Prazosin (selective $\alpha_1$-receptor blocker)
- selective alpha1-receptor blocker in arterioles and venules (dilates both resistance and capacitance vessels)
- does not produce reflex tachycardia
- also used for benign prostrate hypertrophy

Phentolamine (non-selective $\alpha$-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 Prostrate Hypertrophy (BPH)

- Enlarged prostrate leads to difficulty in urination
- Alpha-receptor blocker (ie, Prazosin) cause prostrate relaxation
- Relaxed prostrate improves urination
Beta-Adrenoceptor Antagonists

Frontline as antihypertensive agents

Mechanism of action unknown
- central effect: inhibition of central sympathetic tone
  BUT: beta-blockers (like Nadolol, Sotalol don't cross CNS)
- 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 - Arrhythmias
- Congestive heart failure (CHF) - Glaucoma (Timolol)
- Panic stress - Migraine
- Hyperthyroidism (propranolol) - Tremor

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

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

Beta-Adrenoceptor Blocking Agents (-olol)
(A-M β1-selective)

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
<th>Approximate Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β1</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3-4 hours</td>
<td>50%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6-9 hours</td>
<td>40%</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>β1</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14-22 hours</td>
<td>90%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9-12 hours</td>
<td>80%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85%</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>β1</td>
<td>Yes¹</td>
<td>No</td>
<td>Low</td>
<td>4-5 hours</td>
<td>70%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
<td>...</td>
</tr>
<tr>
<td>Labetalol</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
<td>80%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>50%</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14-24 hours</td>
<td>33%</td>
</tr>
<tr>
<td>Peroxolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>90%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>30%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>90%</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4-5 hours</td>
<td>50%</td>
</tr>
</tbody>
</table>

¹Partial agonist effects at β1 receptors.  *Labetalol also causes α1-selective blockade.  Bioavailability is dose-dependent.
Mixed Alpha- and β-Receptor Blockers

• **Labetalol**
  - hypertensive crisis, chronic hypertension, CHF
  - competitive antagonist at both α- & β-ARs
  - $\beta_1 = \beta_2$ activity $>\alpha$-activity (3:1)
  - HR & CO unchanged; $\downarrow$ TPR $\rightarrow$ $\downarrow$ BP
  - some intrinsic $\beta$-adrenoceptor activity (ISA)

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

β-Blockers: Untoward Effects, Cautions

• **Supersensitivity**: Rebound effect with $\beta$-blockers, less with $\beta$-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal

• **Asthma**: Blockade of pulmonary $\beta_2$-receptors leads to increase in airway resistance. $\beta_1$-selective agents preferred

• **Diabetes**: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of $\beta_2$-ARs in liver. $\beta_1$-selective agents preferred

• **Raynaud D**: Decreased peripheral circulation

• **CNS**: nightmares, mental depression, insomnia

• **Elderly**: Effectiveness is decreased, more CNS effects (ie. depression)
**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.

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**Beta-Blockers in CHF: 2002 Guideline**

![Beta-Blockers in CHF: 2002 Guideline](image-url)
MERIT-HF: Use of Metoprolol in CHF

- Metoprolol (n=1990) vs Placebo (n=2001)
- $\beta_1$-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%

Beta-Blockers - Mechanism of Action

Diagram showing the mechanism of action of beta-blockers, including:
- Decrease in CNS sympathetic outflow
- Decrease in blood pressure
- Decrease in cardiac output
- Decrease in Peripheral resistance
- Decrease in Angiotensin II
- Decrease in Aldosterone
- Decrease in Sodium, water retention
- Increase in Blood volume
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:
- reflectory sympathetic activation
- headache, nausea, sweating, flushing
- palpitations, ↑ HR → angina
- lupus reaction (mainly in slow acetylators)

Actions of Vasodilators

<table>
<thead>
<tr>
<th>Ca++ Antagonists</th>
<th>Open K+ Channels</th>
<th>Nitric Oxide (NO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>Minoxidil</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Diazoxide</td>
<td>Nitroprusside</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrates</td>
</tr>
</tbody>
</table>

Diagram showing the actions of vasodilators, including Ca++ antagonists, open K+ channels, and nitric oxide (NO) pathways.
Vasodilators - Minoxidil

Minoxidil (Rogaine)
- 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 guanylyl cyclase (direct and/or via release of NO
- intracellular ↑ cGMP → 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 Congestive heart failure (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

Primary and secondary effects of vasodilator therapy in essential hypertension and the manner by which diuretic and beta-adrenergic blocker therapy can overcome the undesirable secondary effects. (From Koch-Weser J. Vasodilator drugs in the treatment of hypertension. Arch Intern Med 1974;133:1017-1027, copyright 1974, American Medical Association.)
Renin-Angiotensin-Aldosterone System

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)

actions of Angiotension converting enzyme

Angiotensinogen

Angiotensin II

Vasoconstriction
- Increased TPR
- Increased BP

Aldosterone secretion
- Increased NA & H₂O retention

Increased PG synthesis

Kininogen

Bradykinin

Inactive

Vasodilation
- Decreased TPR
- Decrease BP
Angiotensin-Converting Enzyme (ACE) Inhibitors

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

↓ TPR, CO unchanged, HR unchanged

- no reflex ↑ HR, probably due to resetting (↓) 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 (ARBs, 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 & ARBs - Adverse effects

- severe hypotension in hypovolemic patients, bilateral renal artery stenosis
- hyperkalemia (↑[K⁺])
- dry cough (ACEI), dry mouth, skin rushes, glossitis
- altered sense of taste due to loss of Zinc (10-20%)
- tetrogenic, 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

Treatment of Hypertension (> 139/89mmHg)

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 ↑ plasma renin
- use long-lasting drugs (↑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

U.S. ANTIHYPERTENSIVE MARKET TOTAL Rx’S

![Graph showing changes in antihypertensive market from 1986 to 1992](image-url)
Hypertension Treatment Chart

**CONCOMITANT DISEASE**

- ANGINA PECTORIS
- DIABETES (ORIGIN INDEPENDENT)
- HYPERLIPIDEMIA
- CONGESTIVE HEART FAILURE
- PREVIOUS MYOCARDIAL INFARCTION
- CHRONIC RENAL DISEASE
- ASTHMA, CHRONIC RESPIRATORY DISEASE

**DRUGS COMMONLY USED IN TREATING HYPERTENSION**

- Diuretics
- Beta-Blockers
- ACE Inhibitors
- CCB Channel Blockers

**KEY:**
- Drug class
- Commonly used drugs
- Alternate drugs

*Based on benefits from outcome studies or existing guidelines, the compelling indication is managed in parallel with the BP. JNC 7. JAMA. 2003;289:2560-2672.

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**JNC 7: HT - Compelling Indications for Individual Drug Classes**

<table>
<thead>
<tr>
<th>High-Risk Condition With Compelling Indication*</th>
<th>Recommended Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diuretic</td>
</tr>
<tr>
<td>Heart failure</td>
<td>x</td>
</tr>
<tr>
<td>Post-MI</td>
<td>x</td>
</tr>
<tr>
<td>High CAD risk</td>
<td>x</td>
</tr>
<tr>
<td>Diabetes</td>
<td>x</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>x</td>
</tr>
<tr>
<td>Stroke prevention</td>
<td>x</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; CAD = coronary artery disease; Aldo Ant = aldosterone antagonist.

*Based on benefits from outcome studies or existing guidelines, the compelling indication is managed in parallel with the BP. JNC 7. JAMA. 2003;289:2560-2672.