Hypertension and Antihypertensive Agents

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NO/cGMP, tolerance (off periods), flushing, dizziness, headache, reflex tachycardia, many forms

Nitrates
Effects enhanced in depolarized, damaged tissue, Phase 0, ↓ CV

Na+-Channel blockers
Flushing, dizziness, headache, nausea, reflex tachycardia

Vasodilators
Many Rx interactions, [K+], ↓ use HF important, low K+ → ↑ toxicity

Cardiac glycosides
GFR >30, hypokalemia (CG); diabetes (↓ glucose tolerance)

Diuretics
Angina, edema, renal failure, tetrogenic, glossitis, taste

ACEI / ARBs
HF, constipation, gingival hyperplasia, edema, reflex tachycardia

Beta-Blockers
Contraindications/Cautions/Notes
Angina
Arrhythmia
HF
Hyper tension
Drug Class

Leading Causes of Death in the U.S

Prevalence of Common Cardiovascular and Lung Diseases, U.S., 2005

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Diseases*</td>
<td>80,700,000</td>
</tr>
<tr>
<td>Hypertension**</td>
<td>73,000,000</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>16,800,000</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>5,300,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>5,800,000</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Asthma</td>
<td>22,000,000</td>
</tr>
<tr>
<td>COPD</td>
<td>24,000,000</td>
</tr>
</tbody>
</table>

* Includes hypertension, CHD, heart failure, and stroke.
** Hypertension is defined as systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg

Introduction
Blood Pressure Regulation: Frank’s Formula
BP = Cardiac output (CO) X Total peripheral resistance (TPR)
CO = Stroke volume (SV) X 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
**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

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**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
CV mortality risk x2 each 20/10 mmHg ↑BP

**Secondary HT (10%):** can be treated 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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**JNC VII Blood Pressure Classification (2003)**

<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>or 80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>or ≥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>BP Classification</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- 99</td>
</tr>
<tr>
<td>stage 1 (mild)</td>
<td>140-159</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>180-209</td>
<td>110-119</td>
</tr>
<tr>
<td>stage 4 (very severe)</td>
<td>&gt;209</td>
<td>&gt;119</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

---

**Renal Stenosis**
Primary cause of 2o HT

- Decreased renal blood flow
  - renal BP
  - ↑ renin release
  - ↑ aldosterone
  - ↑ Na⁺, water retention
  - ↑ systemic BP
**Rule of Ten**

10% Pheochromocytomas are:

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

**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. Labetalol
- α-blocker ie. phenoxybenzamine or phentolamine
- Inhibit tyrosine hydroxylase ie. α-methyl-p-tyrosine
- β-blocker only after α-blockade

**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

**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
  - Salt intake
  - Alcohol
  - Stress
  - Obesity
  - Age
  - Others

**BP Daily Fluctuation**

**CV Mortality Risk Doubles with Each 20/10 mm Hg BP Increment**

*Individuals aged 40-70 years, starting at BP 115/75 mm Hg.
CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Franklin Roosevelt (1882-1945)**

FDR died unexpectedly, April 12, 1945 - less than six months after being elected to a fourth term. His arteries were so atherosclerotic that embalmers could not get a needle into them.
Consequences/Complications of Hypertension:
- End organ damage, e.g., retinopathy
- Failure in blood supply, renal failure (fibrinoid necrosis)
- Loss of microcirculation, PAD/PVD
- Aneurysms (rupture of blood vessels)
- Myocardial and/or cerebral infarction
- Increased risk of stroke, congestive heart failure

Health Consequences - Age

Health Consequences – Effective Treatment
Better understanding, better treatments, better results

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 (low dose ↓ BP)
- ↑ physical activity
- ↓ stress factors
- ↓ smoking
- ↓ caffeine intake
## Exercise, Diet & Lifestyle

"Unbelievable. Smoking a cigarette while shoveling snow. Can he lose a note?"

## Hypertension Lifestyle Modification

<table>
<thead>
<tr>
<th>Modification</th>
<th>SBP reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5 – 20 mmHg/10 kg wt loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8 – 14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2 – 8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4 – 9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2 – 4 mmHg</td>
</tr>
</tbody>
</table>

## Antihypertensive Agents (JNC VII, 2003)

1. Diuretics (1st) eg. hydrochlorothiazide
2. Renin / AgII (ACEI, ARBs) eg. lisinopril, losartan
3. Calcium-antagonists eg. nifedipine, verapamil
4. Beta-antagonists eg. propranolol
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. Renin inhibitor eg. aliskiren (newest agent)
10. Dopamine agonist eg. fenoldopam (acute HT)
11. Inhibit/reduce NE release eg. guanethidine, reserpine
12. Ganglionic blockers eg. mecamylamine

## Antihypertensive Usage (ACC, 2001)

For untreated 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>% Selecting each class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiologist</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>ACE inhibitor / ARB</td>
</tr>
<tr>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Ca&quot;-blocker</td>
</tr>
<tr>
<td>Diuretics (thiazides)</td>
</tr>
<tr>
<td>Alpha-blocker</td>
</tr>
<tr>
<td>Other class</td>
</tr>
<tr>
<td>None (life-style)</td>
</tr>
</tbody>
</table>

## Sites of Action of Antihypertensive Agents

- **Main classes**
  - "Frontline agents"
  - Diuretics (1st)
  - Beta-blockers
  - Calcium blockers
  - ACE inhibitors / ARBs

## Development of Antihypertensive Therapies

- 1940s
  - Vasodilator
  - Thiazides/Chlorothiazide
  - Peripheral sympatholytic
  - Ganglion blockers
  - Hexamethonium
- 1950
  - AA Spironolactone
  - Beta-blockers
  - Propranolol
- 1957
  - Alpha-blockers
  - Phenoxycyanazine
  - Phenotiamine
  - Alpha2-agonists
  - Clonidine
  - Non-DHP CCBs
  - Diltiazem
  - Verapamil
- 1960s
  - ACEI Captopril
  - Metoprolol
  - Amlodipine
  - Losartan
- 1970s
  - Beta-blockers
  - Nifedipine
  - Labetalol
  - Alpha-beta blockers
  - Lisinopril
  - Losartan

- 1990s
  - DHP CCBs
  - Nifedipine
  - Amlodipine
- 2005
  - ARBs
  - Losartan
  - Lisinopril
  - Lisinopril
  - Amlodipine
  - Labetalol

- 2005
  - ARBs
  - Losartan
  - Lisinopril
  - Lisinopril
  - Amlodipine
  - Labetalol

**Figure 31-2. Sites of action of the major classes of antihypertensive drugs.**
Hypertension Treatment by Drug Class

IMS Health NDTI, 1978-2002

Patient's whose Hypertension is Controlled

Antihypertensive Agents (JNC VII, 2003)

1. Diuretics (1st) eg. hydrochlorothiazide
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Diuretics: Thiazides

Frontline (1st): Hydrochlorothiazide, Metolazone
- early distal tubule, inhibit Na-Cl symporter to inhibit water/Na+ reabsorption
- ↓ BP by depletion body of Na+ → ↓ blood volume (BV)/plasma volume (PV)
- also vasodilator action via K+ channel opening
- high clinical value as antihypertensive & combination therapy, inexpensive
- retains effectiveness with elderly
- often used in combination with β-blockers or vasodilators
- effective when GFR > 30ml/min (normal: 125ml/min)
Mean arterial pressure (MAP), total peripheral resistance (TPR), cardiac output (CO) & plasma volume (PV) during thiazide treatment of HT.

Initial:
- ↓ body Na+ → ↓ BV → ↓ CO → ↓ BP (TPR, reflex)

Chronic:
- CO unchanged, ↓ TPR, ↓ NE → ↓ [Ca++]i → ↓ TPR

Initial: ↓ body Na+ → ↓ BV → ↓ CO → ↓ BP (TPR, reflex)

Potassium Sparing Diuretic Agents
- Aldosterone antagonists: Spironolactone, Eplerenone
- Epithelial Na-channel blockers: Amlodilide, Triamterene
- act on late distal tubule & collecting duct to inhibit Na+ reabsorption and K+ secretion
- weak action, least potent
- hyperkalemia
- commonly used in combination therapy with other agents (esp. thiazide & loop diuretics)

Loop diuretics:
- Not used as antihypertensive agents
- Commonly used in heart failure

Angiotensin Converting Enzyme (ACE) Inhibitors
Captopril, Lisinopril, Enalapril, Benazepril, Fosinopril
- inhibit ACE to ↓ production of angiotensin II
- Ag-II is a potent vasoconstrictor peptide, aldosterone, ADH
- less effective in elderly, Afro-Americans

ACE is a peptidyl dipeptidase:
- converts AgI → active Ag-II (major effect)
- degrades bradykinin (a potent vasodilator)

Renin-Angiotensin-Aldosterone System (RAAS)

Thiazide Diuretics - Adverse effects
- hypokalemia, hypercalcemia
- ↑ uric acid retention → gout
- can cause hyperglycemia/glucose intolerance; caution in diabetes
- excreted unchanged; caution with decreased renal function (need >30ml/min)
**Actions of ACE Inhibitors**
- ↓ angiotensin II production
- decrease activity of sympathetic NS
- ↓ TPR, CO unchanged, HR unchanged
- no reflex ↑ HR, probably due to resetting (↓) of baroreceptor reflex sensitivity
- ↓ aldosterone production → ↓ Na/water retention
- ↑ bradykinin level (inhibit metabolism)
- improves intrarenal hemodynamics
- less effective in elderly and Afro-Americans

**Adverse effects: ACE Inhibitors**
- severe hypotension in hypovolemic patients
- angioedema, hyperkalemia
- dry cough (associated with ↑ bradykinin)
- glossitis, oral ulceration, rash
- altered sense of taste (loss of zinc, 10-20%)
- contraindicated in pregnancy (tetragenic)
- contraindicated in renal artery stenosis
- drug interaction with K-sparing diuretics (↑ K+)
- NSAIDs (↓ effect)

**Angiotensin II Type I Receptor Blockers (ARBs)**
Losartan, Valsartan, Irbesartan [-sartan]
- competitive antagonists of angiotensin II Type I receptors
- Type I receptors mediate: ↑ aldosterone, ↑ ADH, ↑ TPR, ↑ SNS
- Type II receptors mediate: vasodilation (↓ TPR), ↑ NO
- use increasing, no generic, used if cannot tolerate ACEI
- actions similar to ACEI (no dry cough, no ↑ bradykinin)
- less angioedema, glossitis, oral ulceration, rash
- also contraindicated in pregnancy and renal artery stenosis
- slight weak agonist activity (depends on [angiotensin II])
- most likely will overtake ACEIs with generic availability

**ACEI – Angioedema; Glossitis**
- Angioedema (<1%)
- Dry mouth (only ACEIs)
- Glossitis (<5%)
- Oral ulceration
- Oral bleeding

**Calcium Channel Blockers**
- frontline class, oral and generally well absorbed
- bind to L-type calcium channels in cardiac and vascular smooth muscle
- inhibition of calcium influx into cardiac and arterial smooth muscle cells
- minimal effect on venous capacitance vessels.
- dilate arterioles → ↓ TPR → ↓ BP (less verapamil, more nifedipine)
- negative inotropic action on heart (more verapamil, less nifedipine)
- T½: most 2-5 hrs, bepridil 42 hrs, amlodipine 30-50 hrs

**Renin Inhibitor: Aliskiren**
- newest agent, introduced 2005
- direct renin inhibitor → ↓ angiotensin I
- actions similar to ACEI (no cough, no ↑ bradykinin)
- less angioedema, glossitis, oral ulceration, rash
- adverse effects/CIs similar to ACEIs/ARBs
- used if cannot tolerate ACEIs or ARBs
- poor bioavailability < 5%
- may ↓ [furosemide], (MOA unknown)
Calcium Channel Blockers

Non-dihydropyridines (non-DHPs):
- Verapamil, Diltiazem, Bepridil

Dihydropyridines (DHPs): [-dipine]
- Nifedipine, Amlodipine, Nicardipine, Felodipine

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

Verapamil:
- significant cardiac depression, constipation
- caution in digitalized patients (↑ digoxin levels)

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

Actions of Vasodilators

Ca++ Antagonists
- Verapamil, Diltiazem, Nifedipine

Open K+ Channels
- Minoxidil, Diazoxide

Nitric oxide (NO)
- Nitroprusside, Nitrates

Open K+ Channels
- Minoxidil, Diazoxide

Nitric oxide (NO)
- Nitroprusside, Nitrates

Calcium Blockers: Adverse effects

- constipation (more likely with non-DHPs, ie. verapamil)
- non-DHPs: cardiac depression, bradycardia, AV block
- non-DHPs are contraindicated with beta-blockers
- mostly DHPs: hypotension, reflex tachycardia, flushing, headache, edema
- hypotension (more likely with DHPs ie. nifedipine)
- gingival hyperplasia (nifedipine, 10%)
- CHF non-DHPs contraindicated, DHPs not recommended
- CYP3A4 inhibitors: grapefruit, verapamil, diltiazem
- CYP3A4 substrates: amlodipine, verapamil

Calcium blockers - Gingival Hyperplasia

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

Beta-Adrenoceptor Antagonists

Frontline, high clinical value as antihypertensives
- delayed hypotensive action
- ↑ response elderly, Afro-Americans, smokers

Multiple possible mechanisms of action:
1. CNS effect to decrease sympathetic NS tone
2. ↑renin secretion: beta1-receptors mediate renin release
3. block cardiac beta1-receptors: ↓HR → ↓CO → ↓BP
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)

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Beta-Adrenoceptor Blocking Agents (-olol)

<table>
<thead>
<tr>
<th>(A-M β1-selective) Properties of several beta-receptor blocking drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selectivity</strong></td>
</tr>
<tr>
<td>Phenotypic</td>
</tr>
<tr>
<td>Beta-</td>
</tr>
<tr>
<td>Beta-</td>
</tr>
<tr>
<td>Pressure</td>
</tr>
<tr>
<td>Pressure</td>
</tr>
<tr>
<td>Pressure</td>
</tr>
<tr>
<td>Pressure</td>
</tr>
</tbody>
</table>

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Propranolol - Hypertension

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

Mixed Alpha- and β-Receptor Blockers

- **Labetalol**
  - hypertensive crisis, chronic hypertension
  - competitive antagonist at both α- & β-ARs
  - β1 = β2 activity > α-activity (3:1)
  - HR & CO unchanged; ↓TPR → ↓BP
  - some intrinsic β-adrenoceptor activity (ISA)

- **Carvedilol**
  - newest agent
  - chronic hypertension, CHF

---

Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>M</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective β/β2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carazolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; long acting; also for glaucoma</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>α-blocking activity</td>
</tr>
<tr>
<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA, α-blocking activity</td>
</tr>
<tr>
<td>Nadolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>long acting</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA, MSA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; prototypical beta-blocker</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>X</td>
<td></td>
<td></td>
<td>K-channel blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>primarily used for glaucoma</td>
</tr>
<tr>
<td>β1-selective</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Acebutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>MSA</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>X</td>
<td></td>
<td></td>
<td>short acting; operative arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>MSA</td>
</tr>
</tbody>
</table>

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β-Blockers: Untoward Effects, Cautions

- **Supersensitivity**: Abrupt withdrawal → Rebound HT, less with β-blockers with partial agonist (ie. pindolol).
- **Cardiac**: ↓reserve, fatigue, dizziness
- **Asthma**: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective better
- **Diabetes**: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred
- **Raynaud D**: Decreased peripheral circulation
- **CNS**: Nightmares, mental depression, insomnia
- **Elderly**: ↓Effectiveness, ↑adverse effects (ie. depression)
Alpha-Adrenoceptor Antagonists

Not frontline, use low, but constant

Phenoxybenzamine:
- irreversible α1-receptor blocker
- reflex tachycardia effect, postural hypotension
- therapeutic value in pheochromocytoma, HT crisis

Prazosin (Terazosin, Doxazosin [-azosin])
- selective α1-receptor blocker
- does not produce reflex tachycardia
- also for benign prostrate hypertrophy (common use)

Phentolamine (non-selective α-receptor blocker)
- reflex tachycardia, not used for HT

Adverse effects:
- postural hypotension (all)
- salt and fluid retention
- impotence (phenoxybenzamine)

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Benign Prostate Hypertrophy (BPH)

Enlarged prostrate leads to difficulty in urination

Alpha-receptor blockers (ie Prazosin, Terazosin, Doxazosin, Tamsulosin) cause prostrate relaxation

Relaxed prostrate improves urination

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Vasodilators

- all vasodilators relax arteriolar smooth, some also relax veins
- various MOA: NO/cGMP, direct relaxation or opening of K-channel
- relax smooth muscle of arterioles → ↓ TPR → reflex ↑ HR
- general adverse effects of vasodilators include: headache, nausea, palpitations, sweating, flushing, fluid retention
- good clinical value (in combinations and hypertensive emergencies)

a. CCBs: ↓Ca through L-type channels (ie. verapamil, nifedipine)
b. Open K-channels: minoxidil, diazoxide (acute HT)
c. Direct vasodilator: mainly arterioles, hydralazine (may ↓Ca release)
d. Coupled to NO/cGMP: dilate veins also, Na nitroprusside, nitrates
e. Dopamine agonist: Fenoldopam (D-1A subtype) for acute HT
f. Alpha-antagonists: Prazosin (alpha1-)

---

Actions of Vasodilators

Ca++ Antagonists
- Verapamil, Diltiazem
- Nifedipine

Open K+ Channels
- Minoxidil, Diazoxide

Direct Vasodilation
- Hydralazine

Nitric oxide (NO)
- β-natriuretic peptide

Ca++ antagonist

Hydralazine
- direct muscle relaxation (may ↓ Ca++ release)
- dilate arterioles but not veins
- ↓ TPR → reflex tachycardia
- bioavailability: 25% (slow and rapid acetylators)

Adverse effects:
- reflex tachycardia, ↑ HR can provoke angina
- headache, nausea, palpitations
- sweating, flushing, fluid retention
- lupus reaction (slow acetylators chronic inflammatory condition)

---

Postural (Orthostatic) Hypotension

- Venous return falls, blood pressure falls (>20mmHg SBP, >10mmHg DBP)
- Reflex mediated
- Increase in heart rate (> 20bpm)

BP (mmHg)

Normal

BPH
**Minoxidil (Rogaine)**

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

**Adverse effects:**
- reflex sympathetic stimulation (used with β-blocker)
- fluid retention (usually combo-therapy with diuretic)
- hypertrichosis (OTC, topical application as Rogaine)

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**Sodium Nitroprusside**

- used for acute emergency hypertension and CHF
- used i.v., (cyanide toxicity via oral administration)
- activation of guanylyl cyclase (direct and/or via release of NO → cGMP)
- dilates both arterial (↓ TPR) and venous vessels
- ↓ venous return to the heart, reflex tachycardia

**Adverse effects:**
- reflex ↑ HR (arrhythmias), severe HT
- cyanide liberation → cyanide toxicity
- methemoglobinemia, metabolic acidosis

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**Nitroprusside vs Fenoldopam**

- used for acute hypertensive crisis
- fenoldopam: dopamine-1A agonist → ↓ TPR
- nitroprusside: nitric oxide (NO) → ↑ cGMP

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**Diazoxide**

- used for acute hypertensive crisis
- opens K⁺-channels - stabilizes membrane potential
- dilates arteriolar vessels
- ↓ TPR → reflex ↑ HR → ↑ CO
- inhibits insulin release (via opening K⁺-channels on beta cell membrane)
- similar structure as thiazides but no diuretic effect

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**Pulmonary arterial hypertension**

a. Epoprostenol – prostacyclin (PGI₂)
b. Treprostenol – prostacyclin analogue
c. Bosentan – endothelin-1 antagonist
d. Sildenafil (Revatio, Viagra) – inhibit cGMP PDE5

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**Pulmonary arterial hypertension**

- Enoximone pathway
- Nitric oxide pathway
- Prostacyclin pathway
- Endothelin-1 antagonist
- Phosphodiesterase 5 inhibitor
Reflex compensatory responses
eg. Calcium blockers, Hydralazine, Minoxidil

Centrally acting sympatholytic agents
Clonidine, α-Methyldopa (prodrug → α-methyl-NE)
- good clinical value, useful but not frontline
- no metabolic side effects, does not interfere with exercise
- agonist central α₂-receptors ↓ sympathetic outflow from vasomotor center
- α-methyldopa is preferred agent for HT in pregnancy
- clonidine used in opiate & nicotine withdrawal treatment

Adverse effects:
- dry mouth, drowsiness, lightheadedness, dizziness, impotence
- abrupt withdrawal effect (rebound HT, esp. clonidine)

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

Adrenergic Neuron-Blocking Agents
Antihypertensive clinical value is low, effective but agents of last resort

Guanethidine: (Bretylium used as antidyshrhythmic, saved ET)
- ↓ release of NE from nerve terminals → gradual depletion of NE stores
- neuronal uptake is essential for action (TCAs or cocaine ↓ effect)
Adverse effects:
- marked postural hypotension,
- diarrhea, impaired ejaculation

Reserpine (significant adverse effects)
- Antihypertensive clinical value is low, effective but agent of last resort
- inhibit uptake of NE into storage vesicle (also DA, 5-HT)
- leads to depletion of transmitter stores (peripheral & CNS action)
Adverse effects:
- severe sedation, mental depression, Parkinsonism
- increases gastric acid secretion

Sympathetic Nerve Terminal

Tyr = tyrosine; TH = tyrosine hydroxylase; DD = DOPA decarboxylase;
DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine
**Hypertension: General considerations**

- **Age**: Beta-blocker and ACEI/ARB efficacy may decrease with age (>70 yrs)
- **Race**: Beta-blockers and ACEI/ARBs less effective in blacks than whites
- **Renin**: Patients with ↑ renin may respond better with beta-blockers, ACEI/ARBs/Aliskiren
- **Smokers**: Beta-blockers less effective
- **Diabetes**: ACEI/ARBs/Aliskiren improve renal function
- **Chronic NSAIDs**: ↓ response - diuretics, ACEI, beta-blockers
- **Compliance**: treat patient not just BP, quality of life
- **Lifestyle**: smoking, overweight, exercise, alcohol intake

**Hypertension and Pregnancy**

- HT in pregnancy is among the leading cause of maternal mortality
- about 1% of pregnancies are complicated by chronic HT, 5% by gestational HT
- Important: ACEI/ARBs/Aliskiren contraindicated in pregnancy
- agents recommended for use in pregnancy include:
  a. alpha-methyl dopa
  b. Nifedipine
  c. Beta-blockers (not atenolol, CI)
  d. Labetalol
  e. Prazosin
  f. Hydralazine

**Basis for Combination Pharmacotherapy**

- Different MOA produce additive effect with ↓ side effect
- Alpha-receptor mediated functions are not affected (avoid postural HT)
- Beta-blockers counter the reflex cardiac stimulation by vasodilators
- Thiazides counter the fluid retention by sympatholytics and vasodilators
- ACEIs/ARBs/K-sparing agents counter hypokalemia by thiazides
- Fixed combinations – availability improves effect, cost & compliance

**Fixed Combination Availability**

- Thiazide diuretic and beta-blocker
- Thiazide diuretic and ACE inhibitor
- Thiazide diuretic and Ca-blocker
- Thiazide diuretic and Angiotensin II receptor blocker
- Thiazide diuretic and K-sparing diuretic
- ACE inhibitor and Ca-blocker
- Thiazide & Sympatholytic (other than beta-blocker)
  - Thiazide and alpha-methyl dopa
  - Thiazide and clonidine
  - Thiazide and prazosin
  - Thiazide and guanethidine
  - Thiazide and reserpine

**Drug Combinations**

- AT1-blockers=angiotensin receptor blocker; ACE=angiotensin converting enzyme inhibitor

**Algorithm for Treatment of Hypertension**

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

  **Stage 1 Hypertension**
  - SBP 140–159 or DBP 90–99 mmHg
  - May consider ACEI, ARB, BB, or combination.

  **Stage 2 Hypertension**
  - SBP >160 or DBP >100 mmHg
  - Thiazide-type diuretic + ACEI, or ARB, or BB, or CCB

  **Not at Goal Blood Pressure**
  - Optimize dosages/add additional drugs
  - Diuretics: thiazides, CCB
  - ACEI, ARB
  - BB

  **With compelling indications**
  - Other antihypertensive drugs (diuretics, ACEI, ARB, CCB) as needed

**Without compelling indications**

- Thiazide-type diuretic
  - SBP, DBP not controlled
  - May consider ACEI, ARB, BB, or combination.

- Thiazide-type diuretic + ACEI, or ARB, or BB, or CCB
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.

Hypertension Treatment Chart

<table>
<thead>
<tr>
<th>Concomitant Disease</th>
<th>Drug Classes Indicated in Treating Hypertension</th>
</tr>
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<tbody>
<tr>
<td>High-Risk AMI History</td>
<td>Diuretics, β-Blockers, ACE inhibitors, ARBs, CCBs</td>
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<tr>
<td>Diabetics</td>
<td>Diuretics, β-Blockers, ACE inhibitors, ARBs, CCBs</td>
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<tr>
<td>Recurrent Stroke</td>
<td>Diuretics, β-Blockers, ACE inhibitors, ARBs, CCBs</td>
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<td>Pre-Hypertension</td>
<td>β-Blockers, ACE inhibitors, ARBs, CCBs</td>
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<tr>
<td>Chronic Renal Disease</td>
<td>β-Blockers, ACE inhibitors, ARBs, CCBs</td>
</tr>
</tbody>
</table>

Hypertension Treatment by Drug Class

- Calcium Channel Blockers
- β-Blockers
- Diuretics
- ACE Inhibitors
- ARBs
- Alpha Blockers

IMS Health NDTI, 1978-2002