Hypertension and Antihypertensive Agents

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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>

* NIH: 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)

BP: 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

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 (20-25%) hypertensive
60 – 70 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

JNC VII Blood Pressure Classification (2003)

*Require three measurements (repeat visits)
BP lowest in the morning → ↑ during the day

<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>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>
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

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

BP Daily Fluctuation

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

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>

Sites of Action of Antihypertensive Agents

Main classes (‘frontline agents’)
- Diuretics (1st)
- Beta-blockers
- Calcium blockers
- ACE inhibitors / ARBs
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

Over 240 different drugs or combinations of drugs

Development of Antihypertensive Therapies

Hypertension Treatment by Drug Class

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>
<th>Cardiologist</th>
<th>GP/FP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor / ARB</td>
<td>71.6</td>
<td>57.5</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>57.9</td>
<td>50.2</td>
</tr>
<tr>
<td>Ca++-blocker</td>
<td>51.5</td>
<td>35.6</td>
</tr>
<tr>
<td>Diuretics (thiazides)</td>
<td>48.8</td>
<td>54.5</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>16.4</td>
<td>17.2</td>
</tr>
<tr>
<td>Other class</td>
<td>4.4</td>
<td>5.1</td>
</tr>
<tr>
<td>None (life-style)</td>
<td>8.4</td>
<td>15.3</td>
</tr>
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Over 240 different drugs or combinations of drugs

Hypertension is largely uncontrolled

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Over 240 different drugs or combinations of drugs
**Diuretics: Thiazides**

Frontline (1st): Hydrochlorothiazide, Metolazone

- early distal tubule, inhibit Na-Cl cotransporter 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)

**Thiazide Diuretics - Adverse effects**

- hypokalemia, hypercalcemia
- ↑ uric acid retention → gout
- can cause hyperglycemia/glucose intolerance; caution in diabetes
- photosensitivity
- excreted unchanged; caution with decreased renal function (need >30ml/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

**Potassium Sparing Diuretic Agents**

- Aldosterone antagonists: Spironolactone, Eplerenone
- Epithelial Na-channel blockers: Amiloride, 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 antihypertensivve agents
- commonly used in heart failure
- usually used to decrease edema

**Nephron**

ACE (Angiotensin Converting Enzyme) inhibitors

- Captopril, Lisinopril, Enalapril, Benazepril, Fosinopril [-pril]
- Frontline class: preferred class with diabetes
- 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 AT-I → active AT-II (major effect)
- degrades bradykinin (a potent vasodilator)
Angiotensinogen → Renin → Angiotensin I (ACE inhibitors) → Angiotensin II

- ACE inhibitors: (Lisinopril)
- Angiotensin IIA
- AT II
- Vasodilation
- Anti-proliferation
- ↑ Kinins
- ↑ NONO
- Vasoconstriction
- Cell growth
- Na+/H₂O retention
- SNS activation
- ↑ Aldosterone
- ↑ NO

**Actions of ACE Inhibitors**

- ↓ angiotensin II (AT-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**

- hypotension in hypovolemic patients
- angioedema, hyperkalemia
- dry cough (20-30%, ↑bradykinin)
- glossitis, oral ulceration, rash
- altered sense of taste (loss of zinc, 10-20%)
- contraindicated in pregnancy (tetrogenic)
- contraindicated in renal artery stenosis
- drug interaction with K-sparing diuretics (↑K+)
- NSAIDs (↓ effect)

**Angiotensin II Type I Receptor Blockers (ARBs)**

- 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

**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

- 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 $\rightarrow \downarrow$ TPR $\rightarrow \downarrow$ BP (less verapamil, more nifedipine)
- negative inotropic action on heart (more verapamil, less nifedipine)
- $T_1/2$: most 2-5 hrs, bepridil 42 hrs, amlodipine 30-50 hrs

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, $\downarrow$ HR, constipation
- caution in digitalized patients ($\uparrow$ digoxin levels)

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

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.

- 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)

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

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

Propranolol - Hypertension

Clinical use – Beta-blockers
**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, long acting
- reflex tachycardia effect, postural hypotension
- therapeutic value in pheochromocytoma, HT crisis

Prazosin (Terazosin, Doxazosin Tamsulosin, [-osin])
- 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)

**Postural (Orthostatic) Hypotension**

- Venous return falls, blood pressure falls (>20mmHg SBP, >10mmHg DBP)
- Sym pathetic activity increases
  - Constriction of great veins
  - Constriction of arteries (↑ TPR)
  - Increase in heart rate (> 20bpm)

**Actions of Vasodilators**

**Ca++ Antagonists**
Verapamil, Diltiazem
Nifedipine

**Open K+ Channels**
Minoxidil, Diazoxide

**Direct Vasodilation**
Hydralazine

**Nitric oxide (NO)**
β-natriuretic peptide
Nitroglycerin, Nitrates

**Benign Prostrate Hypertrophy (BPH)**

Enlarged prostate → urination difficulty

Alpha-receptor blockers (ie Prazosin, Terazosin, Doxazosin, Tamsulosin, [-osin]) cause prostrate relaxation → urination

Also 5α-reductase inhibitors: reduce levels of dihydrotestosterone (DHT, active hormone): Finasteride, Dutasteride

**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 arteries → ↓ 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-), phenoxybenzamine
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)

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

Diazoxide
- used for acute hypertensive crisis
- 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)

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:
- fluid retention (usually combo-therapy with diuretic)
- hypertrichosis (OTC, topical application as Rogaine)

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

Pulmonary Arterial Hypertension
a. Epoprostenol – prostacyclin (PGI₂)
b. Treprostenol – prostacyclin analogue
c. Bosentan – endothelin-1 antagonist (ETₐ +ET₈)
d. Sildenafil (Revatio, Viagra)
  – inhibit cGMP PDE5

• MAP >25mmHg (N=12-15)
• vessels constricted
• shortness of breath
• chest pain, fatigue
• tachycardia, syncope
Pulmonary arterial hypertension

Epoprostenol
Treprostenil
Sildenafil
Bosentan (ETA +ETB)
Ambrisentan (ETA)

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

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, urinary, 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

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- 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)

Neurons of the ANS

Cardiac smooth muscle, gland cells, nerve terminals

Antihypertensive clinical value is low, effective but agents of last resort

Guanethidine: (Bretylium used as antidysrhythmic, 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
**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

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**Fixed Combination Availability**

a. Thiazide diuretic and beta-blocker

b. Thiazide diuretic and ACE inhibitor

c. Thiazide diuretic and Ca-blocker

d. Thiazide diuretic and Angiotensin II receptor blocker

e. Thiazide diuretic and K-sparing diuretic

f. ACE inhibitor and Ca-blocker

g. Thiazide & Sympatholytic (other than beta-blocker)
   - Thiazide and alpha-methyl dopa
   - Thiazide and clonidine
   - Thiazide and prazosin
   - Thiazide and guanethidine
   - Thiazide and reserpine

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**Drug Combinations**

- Diuretic
- Ca-Blocker
- α-Blocker
- β-Blocker
- ACE Inhibitor
- AT1-Blocker

**Basis for Combination Pharmacotherapy**

a. Different MOA produce additive effect with ↓ side effect

b. Alpha-receptor mediated functions are avoided to minimize postural hypotension (HT)

c. Beta-blockers counter the reflex cardiac stimulation by vasodilators

d. Thiazides counter the fluid retention by sympatholytics and vasodilators

e. ACEIs/ARBs/K-sparing agents counter hypokalemia by thiazides

f. Fixed combinations – availability improves effect, cost & compliance

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**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/Aliskerin 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

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**Sympathetic Nerve Terminal**

Tyr = tyrosine; TH = tyrosine hydroxylase; DO = DOPA decarboxylase; DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine
Algorithm for Treatment of Hypertension

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

**Initial Drug Choices**
- Drug(s) for the compelling indications
- Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed

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

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

**With Compelling Indications**
- Drugs for the compelling indications
- Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed

**Not at Goal Blood Pressure**
- Optimize dosages/add additional drugs

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>

*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.