Hypertension and Antihypertensive Agents

Edward JN Ishac, Ph.D.

Smith Building, Room 742
eishac@vcu.edu
8-2127 8-2126

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

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

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>Arhythmia</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>Calm-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CHF, Gingival hyperplasia, reflex lachrymation, constipation</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low GFR, renal insufficiency, diastolic, cough (ACEI), taste, Trenal mechanics</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low GFR, hypokalemia – CC: glucose intolerance → diabetes</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Many Rx interactions, low Tl, [K+] important, low K+→↑ toxicity</td>
</tr>
<tr>
<td>Vasoconstrictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flushing, dizziness, headache, reflex lachrymation, combo Rx</td>
</tr>
<tr>
<td>Nε-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, diarrhea, headache, reflex lachrymation</td>
</tr>
</tbody>
</table>

Systolic – Diastolic Blood Pressure

Figure 1. Location and orientation of arterial baroreceptors

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 (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

**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>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>&gt;160</td>
<td>or &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>140-109</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 2o 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: ↑ TBP, ↑ 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

**Rule of Ten**
10% Pheochromocytomas are:
- Malignant
- Bilateral
- Extra-renal
- 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

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
↓Na⁺ → ↑rise rate

Health Consequences – Cardiovascular Diseases

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 consumption (low dose ↓ BP)
- ↑ physical activity
- ↓ stress factors
- ↓ smoking
- ↓ caffeine intake

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

*Requires 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>

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

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

Sites of Action of Antihypertensive Agents

Sites of action of the major classes of antihypertensive drugs.

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
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</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>
</tbody>
</table>

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 (TTPR, reflex)

Chronic:

CO unchanged, ↓ TPR, ↓ NE → ↓ [Ca++]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

Nephron

Patients whose Hypertension is Controlled

Hypertension Is Largely Uncontrolled

<table>
<thead>
<tr>
<th>Percent</th>
<th>Whites (n=32.8 million)</th>
<th>African Americans (n=5.7 million)</th>
<th>Mexican Americans (n=1.3 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undiagnosed, unaware</td>
<td>Acknowledged, untreated</td>
<td>Treated, uncontrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>0</td>
<td>24</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>20</td>
<td>24</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>40</td>
<td>24</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>60</td>
<td>24</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

Hypertension Is Largely Uncontrolled

**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

**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

**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, diarrhea, 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

**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: rebound HT (can be very serious)

---

**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

- No reflex
  - BP (mmHg)
  - Reflex
  - 95
  - 100
  - 95
  - 55
  - 95
  - 100
  - 195
  - 105
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

Beta-Adrenergic Receptor Antagonists

Clinically a more useful class of drugs than α-adrenoceptor antagonists.
β-Adrenergic receptor 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)

Other Clinical Uses:
- Angina
- Congestive heart failure (CHF)
- Panic stress
- Hyperthyroidism (propranolol)
- Benign Prostate Hypertrophy (BPH)

Enlarged prostate leads to difficulty in urination
Alpha-receptor blocker (ie Prazosin) cause prostate relaxation
Relaxed prostrate improves urination
Propranolol - Hypertension

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

β-Blockers: Untoward Effects, Cautions

- Supersensitivity: Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal
- Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective agents preferred
- 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 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.

Mixed Alpha- and β-Receptor Blockers

- Labetalol
  - hypertensive crisis, chronic hypertension, CHF
  - 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, Congestive heart failure (CHF)

β-Blockers in CHF: 2002 Guideline

- Asymptomatic History of myocardial infarct or LVEF < 40%
- Stable heart failure
  - Any of
    - Current symptoms at rest
    - Evidence of fluid overload
    - Hypertension
  - Declining renal function
  - Recent exacerbations for worsening therapy
  - TT or S-TP at discharge
  - The following beta-blocker
  - If remains unstable, beta-blocker therapy not indicated
  - Unstable heart failure
- Persistent signs of heart failure
  - Persistent TT or S-TP maintained
  - Hospitalization
  - Consider beta-blocker
  - Unstable heart failure
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%

Beta-Blockers - Mechanism of Action

- ↓ cns sympathetic outflow
- ↓ BP

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

- 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

Calciuim blockers - Gingival Hyperplasia

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

Renin-Angiotensin-Aldosterone System

- 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

- ↓ 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, Lorsartan (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)

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)

ACE Inhibitors & ARBs - Adverse effects

- severe hypotension in hypovolemic patients, bilateral renal artery stenosis
- hyperkalemia ([K+])
- dry cough (ACEI), dry mouth, skin rashes, 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

Antihypertensive Market

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?
  - β-blockers efficacy may decrease as age increases
  - β-blockers are less effective in smokers
  - blacks respond less to β-blockers and ACE inhibitors
  - β-blockers and ACE inhibitors better in ↑ plasma renin
- use long-lasting drugs (Tcompliance)

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

Good Combotherapy: vasodilator with either β-blocker or diuretic
**Hypertension Treatment Chart**

**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;289:2560-2572.*

### 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></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></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;289:2560-2572.*