Hypertension and Antihypertensive Agents

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Agents used in HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hyper-tension</th>
<th>HF</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>HF (CI: unstable HF, bronchospasm, significant bradycardia, depression); Raynaud D. Caution in diabetes, asthma (use β1-)</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>HF, constipation, gingival hyperplasia, edema, reflex tachycardia</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td>Angioedema, hyperkalemia, cough (acei), tetrogenic, glossitis, taste</td>
</tr>
<tr>
<td>Diuretics</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td>GFR &gt;30, hypokalemia (CG); diabetes (↑glucose tolerance)</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td>Many Rx interactions, [K+], ↓use HF important, low K+↑toxicity,</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td>Flushing, dizziness, headache, nausea, reflex tachycardia</td>
</tr>
<tr>
<td>Na+ Channel blockers</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td>Effects enhanced in depolarized, damaged tissue, Phase 0, ↓CV</td>
</tr>
<tr>
<td>Nitrates</td>
<td>✔ ✔ ✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td>NO/cGMP, tolerance (off periods), flushing, dizziness, headache, reflex tachycardia, many forms</td>
</tr>
</tbody>
</table>
Leading Causes of Death in the U.S

Data NIH 2000

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 $\geq$ 140 mm Hg, or diastolic blood pressure $\geq$ 90 mm Hg
Introduction

Blood Pressure Regulation: Frank’s Formula

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

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

- 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

Figure 1: Location and innervation of arterial 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
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>and</td>
</tr>
<tr>
<td>Pre-Hypertension</td>
<td>120–139</td>
<td>or</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>or</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>or</td>
</tr>
</tbody>
</table>

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
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:** \( \uparrow \) synthesis, \( \uparrow \) release of NE & EPI into the circulation.

**Result:** \( \uparrow \) BP, \( \uparrow \) HR \( \rightarrow \) hypertensive crisis

**Treatment:**
- Surgical removal for solid tumor
- \( \alpha- / \beta \)-blocker ie. Labetatol
- \( \alpha \)-blocker ie, phenoxybenzamine or phentolamine
- Inhibit tyrosine hydroxylase ie. \( \alpha \)-methyl-p-tyrosine
- \( \beta \)-blocker only after \( \alpha \)-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
Hypertension (HT)

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- aldosterone overproduction: adrenal gland tumor hyperplasia
- renal artery stenosis or occlusion
- adrenal medulla tumor: pheochromocytoma

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- primary cause(s) unknown, possibly multi-factorial defects
  - genetics
  - smoking
  - stress
  - salt intake
  - obesity
  - age
  - alcohol
  - caffeine
  - others

BP Daily Fluctuation

BP Fluctuation Throughout a Day
Male 25 yr old college student

Systolic Blood Pressure
Diastolic Blood Pressure

Awakes, Arrives for class, Argues with girlfriend, ANS exam, Leaves campus, Dinner, Girlfriend is right, Sleeps

Morning, Afternoon
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.

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

Consequences/Complications of Hypertension:
- end organ damage, i.e. 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

Hypertension is a risk factor

TIA, stroke
Retinopathy
PAD/PVD
Renal failure
LVH, CHD, HF

Health Consequences - Age

USA
45-60 million HT

\(\downarrow\text{Na}^+ \rightarrow \downarrow\text{rise rate}\)
Health Consequences – Effective Treatment

Better understanding, better treatments, better results

Morse, M. Hypertension Treatment and the Prevention of Coronary Heart Disease in the Elderly. AFP; March 1, 1999.

Hypertension Treatment in the Elderly

Morse, M. Hypertension Treatment and the Prevention of Coronary Heart Disease in the Elderly. AFP; March 1, 1999.
Top Causes of Death (%), U.S.

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
## 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
Development of Antihypertensive Therapies

- 1940s: Vasodilator
  - Hydralazine
- 1950: Thiazides
- 1957: Ganglion blockers
  - Guanethidine
  - Reserpine
- 1960s: Peripheral sympatholytics
  - Guanethidine
- 1970s: Beta-blockers
  - Propranolol
- 1980s: Alpha1-blockers
  - Prazosin
- 1990s: Renin inhibitors
  - Aliskiren
- 2005: ARBs
  - Losartan

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>Class</th>
<th>% Selecting each class</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor / ARB</td>
<td>Cardiologist 71.6</td>
</tr>
<tr>
<td></td>
<td>GP/FP 57.5</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Cardiologist 57.9</td>
</tr>
<tr>
<td></td>
<td>GP/FP 50.2</td>
</tr>
<tr>
<td>Ca++-blocker</td>
<td>Cardiologist 51.5</td>
</tr>
<tr>
<td></td>
<td>GP/FP 35.6</td>
</tr>
<tr>
<td>Diuretics (thiazides)</td>
<td>Cardiologist 48.8</td>
</tr>
<tr>
<td></td>
<td>GP/FP 54.5</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>Cardiologist 16.4</td>
</tr>
<tr>
<td></td>
<td>GP/FP 17.2</td>
</tr>
<tr>
<td>Other class</td>
<td>Cardiologist 4.4</td>
</tr>
<tr>
<td></td>
<td>GP/FP 5.1</td>
</tr>
<tr>
<td>None (life-style)</td>
<td>Cardiologist 8.4</td>
</tr>
<tr>
<td></td>
<td>GP/FP 15.3</td>
</tr>
</tbody>
</table>
Hypertension Treatment by Drug Class

IMS Health NDTI, 1978-2002

Hypertension is largely uncontrolled

Patients whose Hypertension is Controlled

<table>
<thead>
<tr>
<th>Country</th>
<th>&lt; 140/90 mmHg</th>
<th>&lt; 160/95 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>27</td>
<td>20.5</td>
</tr>
<tr>
<td>Canada</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>England</td>
<td>6</td>
<td>22.5</td>
</tr>
<tr>
<td>France</td>
<td>24</td>
<td>17.5</td>
</tr>
<tr>
<td>Finland</td>
<td>20.5</td>
<td>19</td>
</tr>
<tr>
<td>Spain</td>
<td>20</td>
<td>17.5</td>
</tr>
<tr>
<td>Australia</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Germany</td>
<td>20</td>
<td>22.5</td>
</tr>
<tr>
<td>Scotland</td>
<td>17.5</td>
<td>19</td>
</tr>
<tr>
<td>India</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

USA: JNC VI. Arch Intern Med 1997
Canada: Joffres et al. Am J Hypertens 1997

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11. **Inhibit/reduce NE release**
    - eg. guanethidine, reserpine
12. **Ganglionic blockers**
    - eg. mecamylamine
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 \( \beta \)-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
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)
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 antihypertensive agents
- Commonly used in heart failure

Angiotensin Converting Enzyme (ACE) 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 Ag-I → active Ag-II (major effect)
- degrades bradykinin (a potent vasodilator)

ALSKIREN

ACE Inhibitors

Angiotensinogen (E. globulin in blood)

Angiotensin I (inactive)

Angiotensin II (active)

ACE

Output of sympathetic nervous system

Vasodilation of vascular smooth muscle

Retention of sodium and water

Levels of bradykinin

Decreased aldosterone production

Decreased angiotensin II

Decreased aldosterone secretion

ARBS

BP

Decreased blood pressure
**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 (tetrogenic)
- 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 a. 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

Angioedema

Often occurs in the deep layers of the skin, usually near the eyes and mouth.

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 →↓ TPR →↓ 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

<table>
<thead>
<tr>
<th>Non-dihydropyridines (non-DHPs):</th>
<th>Verapamil, Diltiazem, Bepridil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines (DHPs): [-dipine]</td>
<td>Nifedipine, Amlodipine, Nicardipine, Felodipine</td>
</tr>
</tbody>
</table>

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

**Verapamil:**
- significant cardiac depression, constipation
- caution in digitalized patients ($\uparrow$ digoxin levels)

**Diltiazem:**
- similar to Verapamil / Nifedipine (less)
- actions on cardiac and vascular beds
### Actions of Vasodilators

**Ca**²⁺ Antagonists
- Verapamil
- Diltiazem
- Nifedipine

**Open K⁺ Channels**
- Minoxidil
- Diazoxide

**Direct Vasodilation**
- Hydralazine

**Nitric oxide (NO)**
- β-natriuretic peptide
- Nitroprusside
- Nitrates

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### CCBs: Cardiovascular & renal actions:

<table>
<thead>
<tr>
<th></th>
<th>Diltiazem</th>
<th>Verapamil</th>
<th>Nifedipine (DHPs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>↓</td>
<td>↓↓</td>
<td>↓ or ↑ (reflex)</td>
</tr>
<tr>
<td>Nodal conduction</td>
<td>↓</td>
<td>↓↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Peripheral vasodilation</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
**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:

i. CNS effect to decrease sympathetic NS tone
ii. ↓renin secretion: beta1-receptors mediate renin release
iii. 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)
Beta-Adrenoceptor Blocking Agents (-olol)
(A-M β1-selective)

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th></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>Atenolol</td>
<td>β1</td>
<td>No</td>
<td>Yes</td>
<td>Low</td>
<td>3-4 hours</td>
<td>50</td>
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<tr>
<td>Betaxolol</td>
<td>β1</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14-22 hours</td>
<td>90</td>
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<tr>
<td>Bisoprolol</td>
<td>β1</td>
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<td>No</td>
<td>Low</td>
<td>9-12 hours</td>
<td>80</td>
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<tr>
<td>Carvedilol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85</td>
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<tr>
<td>Celiprolol</td>
<td>β1</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>4-5 hours</td>
<td>70</td>
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<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>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
<td>30</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>
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<tr>
<td>Penbutolol</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>High</td>
<td>31/2-6 hours</td>
<td>301</td>
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<tr>
<td>Sotalol</td>
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<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>90</td>
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<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>

1 Partial agonist effects at β1 receptors. 2 Labetalol also causes α1-selective blockade. 3 Bioavailability is dose-dependent.

Propranolol - Hypertension

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

![Graph showing changes in CO, TPR, and BP over days of treatment](attachment:image.png)
Mixed Alpha- and β-Receptor Blockers

- **Labetalol**
  - hypertensive crisis, chronic hypertension
  - competitive antagonist at both α- & β-ARs
  - $\beta_1 = \beta_2$ 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>MI</th>
<th>HF</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Non-selective $\beta_1/\beta_2$</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Carteolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; long acting; also for glaucoma</td>
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<tr>
<td>Carvedilol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>α-blocking activity</td>
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<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
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<td>Nadolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>long acting</td>
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<tr>
<td>Penbutolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; MSA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; prototypical beta-blocker</td>
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<tr>
<td>Sotalol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>K-channel blocker</td>
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<tr>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>primarily used for glaucoma</td>
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<tr>
<td>β₁-selective</td>
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<td></td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Betaxolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>MSA</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>short acting; operative arrhythmia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
</tr>
</tbody>
</table>
**β-Blockers: Untoward Effects, Cautions**

- **Supersensitivity:** Abrupt withdrawal $\rightarrow$ 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 alpha1-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)
  - Sympathetic activity increases
  - Constriction of great veins
  - Constriction of arteries (↑ TPR)
  - Increase in heart rate (> 20bpm)

- Reflex mediated

**Benign Prostate Hypertrophy (BPH)**

Enlarged prostate leads to difficulty in urination

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

Relaxed prostate improves urination
**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**

<table>
<thead>
<tr>
<th>Ca++ Antagonists</th>
<th>Open K+ Channels</th>
<th>Nitric oxide (NO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil, Diltiazem</td>
<td>Minoxidil, Diazoxide</td>
<td>β-natriuretic peptide</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Direct Vasodilation</td>
<td>Nitroprusside, Nitrates</td>
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<tr>
<td>Hydralazine</td>
<td></td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Ca++ channel blockers</th>
<th>ATP</th>
<th>β2-agonists</th>
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<tbody>
<tr>
<td>Ca channel blockers</td>
<td>CAMP</td>
<td>MLCK*</td>
</tr>
<tr>
<td>Ca^{2+}-calmodulin complex</td>
<td>MLCK-PO_{4}</td>
<td>MLC-PO_{4}</td>
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<td>MLC-PO_{4}</td>
<td>MLC</td>
<td>Myosin-LC</td>
</tr>
<tr>
<td>Myosin-LC</td>
<td>Actin</td>
<td>Contraction</td>
</tr>
<tr>
<td>Actin</td>
<td></td>
<td>Relaxation</td>
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</table>

<table>
<thead>
<tr>
<th>Nitrates</th>
<th>NO</th>
<th>Endothelial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Guanylyl-cyclase*</td>
<td>Guanylyl-cyclase</td>
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<tr>
<td></td>
<td>GTP</td>
<td>cGMP</td>
</tr>
<tr>
<td></td>
<td>MLC-PO_{4}</td>
<td>Myosin-LC</td>
</tr>
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<td></td>
<td>Myosin-LC</td>
<td>Actin</td>
</tr>
<tr>
<td></td>
<td>Actin</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relaxation</td>
</tr>
</tbody>
</table>
**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)

**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)
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 $\rightarrow$ ↑ cGMP)
- dilates both arterial (↓ TPR) and venous vessels
- ↓ venous return to the heart, reflex tachycardia

Adverse effects:
- reflex ↑ HR (arrhythmias), severe HT
- cyanide liberation $\rightarrow$ cyanide toxicity
- methemoglobinemia, metabolic acidosis

Nitroprusside vs Fenoldopam

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

![Graph comparing MAP over time for nitroprusside and fenoldopam](image-url)
Diazoxide

- used for acute hypertensive crisis
- opens K⁺-channels - stabilizes membrane potential
- dilates arteriolar vessels
  \[ \downarrow \text{TPR} \rightarrow \text{reflex} \uparrow \text{HR} \rightarrow \uparrow \text{CO} \]
- inhibits insulin release (via opening K⁺-channels on beta cell membrane)
- similar structure as thiazides but no diuretic effect

Pulmonary arterial hypertension

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

Endothelin pathway
- Pre-pro-ET → pro-ET
- Endothelin receptor antagonists
  - ETA
  - ETB

Nitric oxide pathway
- L-arginine → L-citrulline
- Nitric oxide
  - Vasodilation
  - Antiproliferation
  - Phosphodiesterase type 5 inhibitor

Prostacyclin pathway
- Arachidonic acid → PGI2
- Prostacyclin
  - Prostacyclin derivatives
  - Vasodilation
  - Antiproliferation

Reflex compensatory responses

eg. Calcium blockers, Hydralazine, Minoxidil

VASODILATOR
- Vasodilation
- Peripheral Resistance
- Arterial Pressure

DIURETIC
- Sodium Retention
- Fluid Volume
- Aldosterone
- Peripheral Resistance
- Renin Release
- Angiotensin
- Vasoconstriction
- Norepinephrine
- Heart Rate
- Sympathetic Activity
- Contraction
- Venous Compliance
- Cardiac Output

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.)
**Centrally acting sympatholytic agents**

Clonidine, \( \alpha \)-Methyldopa (prodrug \( \rightarrow \) \( \alpha \)-methyl-NE)
- good clinical value, useful but not frontline
- no metabolic side effects, does not interfere with exercise
- agonist central \( \alpha_2 \)-receptors \( \rightarrow \) \( \downarrow \) sympathetic outflow from vasomotor center
- \( \alpha \)-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, \( \downarrow \) 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
Adrenergic Neuron-Blocking Agents

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

Dwight Eisenhower
Sympathetic Nerve Terminal

\[ \text{Tyr} = \text{tyrosine}; \ TH = \text{tyrosine hydroxylase}; \ DD = \text{DOPA decarboxylase}; \ DA = \text{dopamine}; \ DBH = \text{dopamine } \beta\text{-hydroxylase}; \ NE = \text{norepinephrine} \]

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/Aliskerin contraindicated in pregnancy
- agents recommended for use in pregnancy include:
  a. alpha-methyl dopa
  b. Nifedipine
  c. Beta-blockers (not atenolol, Cl)
  d. Labetalol
  e. Prazosin
  f. Hydralazine

Basis for Combination Pharmacotherapy

a. Different MOA produce additive effect with ↓side effect
b. Alpha-receptor mediated functions are not affected (avoid postural 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
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

Drug Combinations

Diuretic Ca-Blocker

α₁-Blocker β-Blocker

ACE Inhibitor AT1-Blocker

Caution Not additive
No data/controversial Additive

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

SOURCE: MOSER AND PRISANT 1997
Algorithm for Treatment of Hypertension

Lifestyle Modifications

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

Initial Drug Choices

Without Compelling Indications

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

Drug(s) 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>

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 by Drug Class

IMS Health NDTI, 1978-2002

Hypertension Treatment Chart

CONCOMITANT DISEASE

DRUG CLASSES INDICATED IN TREATING HYPERTENSION

HIGH-RISK ANGINA PECTORIS

DIABETES

RECURRENT STROKE

HEART FAILURE

PREVIOUS MYOCARDIAL INFARCTION

CHRONIC RENAL DISEASE

Diuretics β-Blockers ACE Inhibitors ARBs Ca^{2+} channel blockers

Diuretics β-Blockers ACE Inhibitors ARBs Ca^{2+} channel blockers

Diuretics

Diuretics

Diuretics

Diuretics

β-Blockers

β-Blockers

β-Blockers

β-Blockers

ACE Inhibitors

ACE Inhibitors

ACE Inhibitors

ACE Inhibitors

Ca^{2+} channel blockers

Ca^{2+} channel blockers

Ca^{2+} channel blockers

Ca^{2+} channel blockers

Ca^{2+} channel blockers