Hypertension

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EPIDEMIOLOGY

• Approximately 31% of the population (72 million Americans) have high BP (≥140/90 mm Hg).

• Data indicate that of the population of Americans with hypertension,
  – 68.9% are aware that they have hypertension
  – only 58.4% are on some form of antihypertensive treatment
  – only 34% of all patients have controlled BP
EPIDEMIOLOGY

• In the population age >60 years, the prevalence of hypertension in 2000 was estimated at 65.4%, which is significantly higher than the 57.9% prevalence estimated in 1988.

• The percentage of men with high BP is higher than that of women before the age of 45 years.

• After age 55 years, a much higher percentage of women have high BP than men.
ARTERIAL BLOOD PRESSURE

• Arterial BP is the pressure in the arterial wall measured in millimeters of mercury (mm Hg).
  
• **SBP** is achieved during cardiac contraction and represents the peak value.
  
• **DBP** is achieved after contraction when the cardiac chambers are filling, and represents the nadir value.
DBP and SBP

- Clinically, it is important to note that incremental elevations in SBP are more predictive of CV disease than elevations in DBP for patients older than 50 years of age.
- Within this population, elevated SBP is often the primary BP abnormality.
- Therefore, SBP is the target of evaluation and intervention for most patients with hypertension.
- In younger patients with hypertension, elevated DBP may be the only BP abnormality present.
Pulse pressure & MAP

• The difference between SBP and DBP is called the pulse pressure and is a measure of arterial wall tension.

• Mean arterial pressure (MAP) is the average pressure throughout the cardiac cycle of contraction.

• It is sometimes used clinically to represent overall arterial BP, especially in hypertensive emergency
Blood pressure

- Arterial BP is hemodynamically generated by the interplay between blood flow and the resistance to blood flow.
- It is mathematically defined as the product of cardiac output and total peripheral resistance according to the following equation:
  $$BP = \text{cardiac output} \times \text{total peripheral resistance (SVR)}$$
- cardiac output = $SV \times HR$
- $SV$
  - Contractility
  - Venus return
<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Diastolic Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 and</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</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>

Superscript:

*a*Classification determined based on the average of two or more properly measured seated blood pressure measurements from two or more clinical encounters. If systolic and diastolic blood pressure values yield different classifications, the highest category is used for the purpose of determining a classification.

*b*For patients with diabetes mellitus, significant chronic kidney disease, known coronary artery disease (myocardial infarction, stable angina, unstable angina), noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease, abdominal aortic aneurism), or a Framingham risk score of 10% or greater, values ≥130/80 mm Hg are considered above goal; patients with left ventricular dysfunction have a blood pressure goal of less than 120/80 mm Hg.
Pathogenesis

• Increased sympathetic neural activity, with enhanced beta-adrenergic responsiveness
• Increased angiotensin II activity and mineralocorticoid excess
• Genetic factors account for approximately 30 percent of the variation in blood pressure in various populations
• Reduced adult nephron mass may be related to:
  – genetic factors
  – Intrauterine developmental disturbance (eg, hypoxia, drugs, nutritional deficiency)
  – post-natal environment (eg, malnutrition, infections)
ETIOLOGY; type of HTN

• Essential or primary hypertension
  – In most patients (More than 90%),
  – results from an unknown pathophysiologic etiology
  – cannot be cured, but it can be controlled

• Secondary hypertension
  – A small percentage of patients
  – specific cause of their hypertension.
  – There are many potential secondary causes:
    • concurrent medical conditions or are endogenously induced.
  – If the cause can be identified, hypertension in these patients has the potential to be cured.
SECONDARY HYPERTENSION

• Fewer than 10% of patients have secondary hypertension

• When a secondary cause is identified, removing the offending agent be the first step in management.
Secondary Causes of Hypertension

- Chronic kidney disease
- Cushing’s syndrome
- Coarctation of the aorta
- Obstructive sleep apnea
- Parathyroid disease
- Pheochromocytoma
- Primary aldosteronism
- Renovascular disease
- Thyroid disease
- Drugs
Table 8-3
Causes of Secondary Hypertension

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchymal disease</td>
<td>3</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>0.1</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>0.1</td>
</tr>
<tr>
<td>Primary hyperaldosteronism</td>
<td>0.1</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>0.1</td>
</tr>
<tr>
<td>Estrogens</td>
<td>0.4</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.2 or more</td>
</tr>
</tbody>
</table>
Drugs that Causes of Secondary Hypertension

- **Adrenal steroids**
  - (e.g., prednisone, fludrocortisone, triamcinolone)
- **Anabolic steroids** (nandrolone)
- **Amphetamines/anorexiants**
  - (e.g., sibutramine, diethylpropion)
- **Estrogens**
  - (usually oral contraceptives)
- **Calcineurin inhibitors**
  - (cyclosporine and tracolimus)
- **Decongestants**
  - (phenylpropanolamine and analogs)
- **Erythropoiesis stimulating agents**
  - (erythropoietin)
- **NSAIDSs, COX-2 inhibitors**
Drugs that Causes of Secondary Hypertension cont

• Others:
  – venlafaxine, bromocriptine, bupropion, buspirone, carbamazepine, clozapine, desulfrane, ketamine, metoclopramide

• Situations:
  – β-blocker or centrally acting α-agonists (when abruptly discontinued);
  – β-blocker without α- blocker first when treating pheochromocytoma
• Street drugs and other natural products
  – Cocaine and cocaine withdrawal
  – Ephedra alkaloids (e.g., Ma-huang), “herbal ecstasy,” other phenylpropanolamine analogs
  – Nicotine withdrawal, anabolic steroids, narcotic withdrawal, methylphenidate, phencyclidine, ketamine, ergotamine and other ergot-containing herbal products, St. John’s wort

• Food substances
  – Sodium
  – Ethanol
  – Licorice
  – Tyramine-containing foods if taking a monoamine oxidase inhibitor
Potential Mechanisms of Pathogenesis

• HUMORAL MECHANISMS
  – Natriuretic Hormone
  – The Renin–Angiotensin–Aldosterone System
  – Insulin Resistance and Hyperinsulinemia

• NEURONAL REGULATION

• VASCULAR ENDOTHELIAL MECHANISMS

• ELECTROLYTES AND OTHER CHEMICALS
HUMORAL MECHANISMS

The Renin–Angiotensin–Aldosterone System

• The RAAS is a complex endogenous system that is involved with most regulatory components of arterial BP

• The RAAS regulates sodium, potassium, and fluid balance Consequently,

• This system significantly influences vascular tone and sympathetic nervous system activity and is the most influential contributor to the homeostatic regulation of BP.
Angiotensin II Formation

Angiotensinogen

Bloodstream

Renin

Angiotensin I

Angiotensin converting enzyme

Angiotensin II

Vasoconstriction

Increased aldosterone secretion

Increased ADH Secretion

Increased thirst
Renin-angiotensin-aldosterone system

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
HUMORAL MECHANISMS

• Insulin Resistance and Hyperinsulinemia

1. increased renal sodium retention
2. enhanced sympathetic nervous system activity
3. insulin has growth hormonelike actions that can induce hypertrophy of vascular smooth muscle cells.
4. Insulin also may elevate BP by increasing, which leads to increased vascular intracellular calcium resistance
ELECTROLYTES AND OTHER CHEMICALS

• Epidemiologic and clinical data have associated excess sodium intake with hypertension.

• Altered calcium homeostasis also may play an important role in the pathogenesis of hypertension.

• Potassium depletion may increase peripheral vascular resistance,
Hypertension is termed the “silent killer” because most patients do not have symptoms.

The primary physical finding is elevated BP.

The diagnosis of hypertension cannot be made based on one elevated BP measurement.

The average of two or more measurements taken during two or more clinical encounters should be used to diagnose hypertension.

Most important symptom = asymptomatic
Measuring Blood Pressure

- Auscultatory Method
- BP Monitoring Outside the Office
  - Ambulatory Blood Pressure Monitoring
  - Self Blood Pressure Monitoring
Ambulatory Blood Pressure Monitoring Indications

1. suspected white coat hypertension to differentiate white coat from essential hypertension
2. apparent drug resistance
3. hypotensive symptoms while on antihypertensive therapy
4. Episodic hypertension
5. Autonomic dysfunction
6. to identify “nondippers” whose BP does not decrease by >10% during sleep and which may portend increased risk of BP-related complications.
Limitations Ambulatory and Self Blood Pressure Monitoring

1. lack of validated devices
2. complexity of use, costs
3. lack of prospective outcomes data describing normal ranges for these measurements.
Ambulatory and Self Blood Pressure Monitoring normal value

- The upper limit for normal ambulatory BP is
- 140/90 mm Hg during the day
- 125/75 mm Hg at night
- 135/85 mm Hg during 24 hours.
Self Blood Pressure Monitoring

• Although self-monitoring of BP at home is less complicated and less costly than ambulatory monitoring, patients may omit or fabricate readings.

• Thus, devices that have a memory or printouts are recommended
BP measurement

• Patient should be seated for 5 minutes with arm bared, unrestricted by clothing, and supported at heart level.

• Smoking or food ingestion should not have occurred within 30 minutes before the measurement.
Lab test

• All patients with hypertension should have the following measured prior to initiating therapy:
  – 12-lead electrocardiogram
  – blood glucose and hematocrit
  – serum potassium
  – creatinine (with estimated glomerular filtration rate [GFR])
  – calcium
  – fasting lipid panel.
Approach

A. identify secondary causes

B. identify other CV risk factors or comorbid conditions that may define prognosis and/or guide therapy

C. assess for the presence or absence of hypertension-associated target-organ damage
Target-Organ Damage

CV Risk Factor
Target-Organ Damage

- Clinical CV events (e.g., MI, stroke, kidney failure) are clinical end points of target-organ damage.
- They are the primary causes of CV morbidity and mortality in patients with hypertension.
- The primary organs involved are the eye, brain, heart, kidneys, and peripheral blood vessels.
- The probability of CV events and CV morbidity and mortality in patients with hypertension is directly correlated with the severity of BP elevation and additional CV risk factors.
Heart

- Clinical manifestations include left ventricular hypertrophy, coronary heart disease (angina, prior MI, and prior coronary revascularization), and heart failure.
- These complications may lead to cardiac arrhythmias, angina, MI, and sudden death.
- Coronary disease (also called coronary heart disease or coronary artery disease) and associated CV events are the most common causes of death in patients with hypertension.
Brain

• Stroke can result from
  – thrombotic occlusion of small vessels
  – intracerebral hemorrhage resulting from ruptured microaneurysms.

• Transient ischemic attacks (TIA) secondary to atherosclerotic disease in the carotid arteries
Eye

- retinal hemorrhages and exudates, and disk edema.
- Focal arteriolar narrowing, retinal infarcts, and flame-shaped hemorrhages usually are suggestive of accelerated or malignant phase of hypertension.
- Papilledema is swelling of the optic disk and is caused by a breakdown in autoregulation of capillary blood flow in the presence of high pressure.
- It is usually only present in hypertensive emergencies.
kidney

• it is an important cause of end-stage kidney disease
Cardiovascular (CV) Risk and BP

• based primarily on epidemiologic data. Beginning at a benchmark BP of 115/75 mmHg, the risk of CV disease doubles with every increment of 20/10 mmHg.

• There is a significant increase in risk of CV events in patients with prehypertension BP values versus normal BP values.
Framingham Risk Scoring

• Estimating individual risk for CV disease is essential for all patients with hypertension.
• Framingham risk scoring is considered an appropriate way to predict individual 10-year risk for coronary artery disease (CAD), also referred to as coronary heart disease (CHD)
Framingham Risk Scoring

- Age
- Total cholesterol
- Smoker
- HDL cholesterol
- Systolic blood pressure
- 10-year risk
  - low or moderate risk (<10%)
  - moderately high risk (10%–20%)
  - high risk (>20%).
Indication

• All patients with hypertension who do not have a history of hypertension-associated complications or diabetes should have Framingham risk scoring.
• Identifying patients with Framingham risk scores ≥10% is clinically relevant because more aggressive antihypertensive treatment is needed in this population according to 2007 AHA guidelines.

• For patients with hypertension-associated complications or diabetes, Framingham risk scoring is not needed because 10-year risk of CAD is assumed to be >20%.
Major CV Risk Factors

• Advanced age (>55 yr for men, >65 yr for women)
• Cigarette smoking
• Diabetes mellitus
• Dyslipidemia
• Family history of premature atherosclerotic vascular disease (men <55 yr or women <65 yr)
• Hypertension
• Kidney disease (microalbuminuria or estimated GFR <60 mL/min)
• Obesity (BMI ≥30 kg/m²)
• Physical inactivity
Overall Goal of Therapy

• The overall goal of treating hypertension is to reduce hypertension associated morbidity and mortality.

• This morbidity and mortality is related to target-organ damage (e.g., CV events, heart failure, and kidney disease).

• Reducing risk remains the primary purpose of hypertension therapy and the specific choice of drug therapy is significantly influenced by evidence demonstrating such risk reduction.
Goal of Therapy

• Most patients have a goal BP of less than 140/90 mm Hg for the general prevention of CV events or CV disease (e.g., coronary artery disease)

• However, this goal is lowered to less than 130/80 mm Hg for patients with
  – diabetes
  – significant chronic kidney disease
  – Known coronary artery disease (myocardial infarction, stable angina, unstable angina)
  – noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease, abdominal aortic aneurism)
  – Framingham 10-year risk moderately high risk (10%–20%), or high risk (>20%)

• patients with left ventricular dysfunction (heart failure) have a BP goal of less than 120/80 mm Hg
Goal BP determination based on patient specific history and cardiovascular risk assessment

Past Medical History

Primary Prevention
- None of the conditions listed below

Diabetes Mellitus

Chronic Kidney Disease

Coronary Artery Disease (CAD)
- Chronic – chronic stable angina, prior MI
- Acute – unstable angina, acute MI

CAD Risk Equivalent
- Carotid artery disease (prior ischemic stroke, transient ischemic attack)
- Peripheral arterial disease
- Abdominal aortic aneurysm

BP Goal

Framingham Risk Score

<10%
- <140/90 mmHg

>\geq 10%
- <130/80 mmHg

Left Ventricular Dysfunction
- <120/80 mmHg
GOAL BLOOD PRESSURE VALUES RECOMMENDED BY THE AMERICAN HEART ASSOCIATION IN 2007²

- Most patients for general prevention \(<140/90\) mm Hg
- Patients with diabetes (referred to as coronary artery disease risk equivalent), significant chronic kidney disease, known coronary artery disease (myocardial infarction, stable angina, unstable angina), noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease, abdominal aortic aneurism [referred to as coronary artery disease risk equivalents]), or a Framingham risk score of 10% or greater
- Patients with left ventricular dysfunction \(<120/80\) mm Hg (heart failure)
GENERAL APPROACH TO TREATMENT

• lifestyle modifications
• drug therapy

• Lifestyle modification alone is considered appropriate therapy for patients with prehypertension.

• However, lifestyle modifications alone are not considered adequate for patients with stage 2 and hypertension with additional CV risk factors, especially patients with BP goals of less than 130/80 mm Hg (e.g., diabetes, coronary artery disease, chronic kidney disease) or less than 120/80 mm Hg (i.e., left ventricular dysfunction), who have not attained this goal BP.
NONPHARMACOLOGIC THERAPY

• lifestyle modifications.
  – Weight reduction
  – physical activity
  – DASH-type dietary patterns
  – Reduced salt intake
  – Moderation of alcohol intake
  – Smoking cessation
Duration

• Previous JNC guidelines recommended lifestyle modifications for 6 to 12 months before starting drug therapy in patients with few to no risk factors and no hypertension-associated complications, and no compelling indications (i.e., primary prevention patients with Framingham risk scores of <10%).
Duration

• lifestyle modifications alone to treat hypertension for only “several weeks” before starting drug therapy in patients with stage 1 hypertension who have “moderate” CV risk (i.e., one to two risk factors), and

• for “several months” in patients with stage 1 hypertension who are at “low” CV risk (i.e., no additional risk factors).
'CHRISTMAS IS COMING, THE GOOSE IS GETTING FIT.'
Weight reduction

• Weight loss in obese individuals can lead to a significant fall in blood pressure.
• The decline in BP induced by weight loss can occur in the absence of dietary sodium restriction
• For most patients, an average weight loss of 10 kg can reduce SBP by 5 to 20 mmHg
How to stop over-consuming

Chris Haldane
The Dietary Approaches to Stop Hypertension (DASH)

• The Dietary Approaches to Stop Hypertension (DASH) eating plan is a diet that is rich in
  – fruits
  – Vegetables
  – low-fat dairy products with a reduced content of saturated and total fat.

• This diet can substantially reduce BP (8-14 mmHg in SBP for most patients) and yield similar results to single drug therapy
Reduced salt intake

- Intake of sodium should be minimized as much as possible, ideally to 1.5 g/day, although an interim goal of less than 2.3 g/day may be reasonable considering the difficulty in achieving these low intakes.
- Patients should be aware of the multiple sources of dietary sodium (e.g., processed foods, soups, table salt) so that they may follow these recommendations.
- Evidence from clinical trials has shown that sodium restriction provides mean reductions in BP of 5/2.7 mmHg in patients with hypertension.
- Practical recommendation
Excessive alcohol use can either cause or worsen hypertension.

Patients with hypertension who drink alcoholic beverages should restrict their daily intake.
physical activity

• Regular physical activity for at least 30 minutes most days of the week is recommended for all adults

• Studies show that aerobic exercise can reduce BP, even in the absence of weight loss.

• Patients should consult their physicians before starting an exercise program, especially those with CV and/or target-organ disease.

• Regular physical activity can reduce SBP by 4 to 9 mmHg in most patients
Smoking cessation

• Cigarette smoking is a major, independent, modifiable risk factor for CV disease.
• Patients with hypertension who smoke should be counseled regarding the additional health risks that result from smoking.
Potassium

• Potassium intake should be encouraged through fruits and vegetables with high content (ideally 4.7 g/day) in those with normal kidney function
### Lifestyle modifications in the management of hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate systolic BP reduction, range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI, 18.5 to 24.9 kg/m²)</td>
<td>5-20 mmHg per 10-kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8 to 14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 meq/day (2.4 g sodium or 6 g sodium chloride)</td>
<td>2 to 8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)</td>
<td>4 to 9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks per day in most men and no more than 1 drink per day in women and lighter-weight persons</td>
<td>2 to 4 mmHg</td>
</tr>
</tbody>
</table>

For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be higher for some individuals; they are not all additive. BMI: body mass index; BP: blood pressure; DASH: Dietary Approaches to Stop Hypertension. Adapted from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, JAMA 2003; 289:2560.
PHARMACOTHERAPY

• The choice of initial drug therapy depends on the degree of BP elevation and presence of compelling indications.

• Most patients with stage 1 hypertension should be initially treated with a thiazide-type diuretic, ACE inhibitor, ARB, or CCB.

• For patients with more severe BP elevation (stage 2 hypertension), combination drug therapy, with one of the agents being preferably a thiazide type-diuretic, is recommended.

• There are six compelling indications where specific antihypertensive drug classes have evidence showing unique benefits in patients with the compelling indication.
Initial Drug Therapy Choices

No Compelling Indications

Stage 1 Hypertension
(SBP 140–159 or DBP 90–99 mm Hg)

- Thiazide-type diuretics [A-1];
- ACE inhibitor, ARB, CCB, or combination [A-2].

Compelling Indications
(see Fig. 15–3)

Stage 2 Hypertension
(SBP >160 or DBP >100 mm Hg)

- Two-drug combination for most [A-3].
  Usually a thiazide-type diuretic with an ACE inhibitor, or ARB, or CCB [A-2].
PHARMACOTHERAPY

- A diuretic (primarily a thiazide-type), ACE inhibitor, angiotensin II receptor blocker (ARB), or calcium channel blocker (CCB) are considered primary antihypertensive agents that are acceptable firstline options.

- β-Blockers are now preferred either to treat a specific compelling indication, or in combination with one of the aforementioned primary antihypertensive agents for...
Pharmacotherapy recommendations

Past Medical History
(see Figure 13-2)

Primary Prevention

First Line

ACEI (or ARB), or CCB, or thiazide diuretic, or combination

Sequential Therapy

Compelling Indication

Diabetes Mellitus

ACEI, or ARB

Thiazide diuretic

CCB, or β-blocker

Chronic Kidney Disease

ACEI, or ARB

Thiazide diuretic for BP control

CCB for ischemia control

Chronic or Acute CAD

β-blocker and ACEI (or ARB)

Prior Ischemic Stroke

ACEI and thiazide diuretic, or ARB

Aldosterone antagonist if severe heart failure

Left Ventricular Dysfunction

ACEI (or ARB) and thiazide (or loop) diuretic, and β-blocker

Hydralazine and isosorbide dinitrate if black
Drug selection

• Which drug
  – Compelling indications
  – Contraindications
  – Favorable effect on symptoms in comorbid conditions
  – May have adverse effect on comorbid conditions

• First line drug
  – Cost
  – ADR
Likely to have a favorable effect on symptoms in comorbid conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign prostatic hypertrophy</td>
<td>Alpha blocker</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>Beta blocker (noncardioselective)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>Migraine</td>
<td>Beta blocker, calcium channel blocker</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Thiazide diuretic</td>
</tr>
<tr>
<td>Perioperative hypertension</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>Raynaud's syndrome</td>
<td>Dihydropyridine calcium channel blocker</td>
</tr>
</tbody>
</table>
May have adverse effect on comorbid conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Beta blocker, central alpha agonist</td>
</tr>
<tr>
<td>Gout</td>
<td>Diuretic</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Aldosterone antagonist, ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Thiazide diuretic</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>ACE inhibitor or ARB</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Medication</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Angioedema</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Bronchospastic disease</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>Depression</td>
<td>Reserpine</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>ACE inhibitor, ARB (includes women likely to become pregnant)</td>
</tr>
<tr>
<td>Second or third degree heart block</td>
<td>Beta blocker, nondihydropyridine calcium channel blocker</td>
</tr>
</tbody>
</table>
Combination therapy

• Ideal Combinations
  – combination of an ACEI or ARB with a CCB
  – Thiazide diuretics are very effective in lowering BP when used in combination with most other antihypertensive agents

• Certain nondiuretic antihypertensive agents (i.e., aliskiren, reserpine, arterial vasodilators, and centrally acting agents) can eventually cause significant sodium retention and increased fluid volume thus should ideally be given in combination with a diuretic to maximize BP lowering.
Less Efficacious Combinations

– The combination of an ACEI or ARB with a β-blocker provides less additional BP lowering compared with other combination regimens
– Use of a dihydropyridine CCB in combination with a nondihydropyridine CCB may lower BP, but the overlapping mechanism of action results in less than ideal reductions in BP
– Combinations of ACE and ARB???
BP Reduction with drug therapy

• When using a standard dose of a first-line antihypertensive agents (an ACEI, ARB, CCB, or thiazide diuretic), and even with β-blockers, the average reduction in SBP/DBP is only 10/5 mmHg.

• This has been termed by some as the “10 over 5” rule.
Monitoring

• Blood pressure control should be evaluated 1 to 4 weeks after starting or modifying therapy for most patients.

• BP usually begins to fall within 1 to 2 weeks of starting an agent, but steady-state antihypertensive effects typically take up to 4 weeks.
Special Populations

- Very Elderly Patients
- Isolated Systolic Hypertension
Very Elderly Patients

• Older patients with hypertension (>65 years of age) have the lowest rates of BP control, and this rate decreases in even older populations.

• Very elderly patients (>75 years of age), similar to black patients, respond best to thiazides and CCBs and less to ACEIs, ARBs, and β-blockers.

• However they should be viewed as medical myths rather than definitive realities.
Isolated Systolic Hypertension

- Isolated systolic hypertension (ISH) is defined as an elevated SBP (>140 mmHg) with a “normal” DBP (<90 mmHg)
- Exceptions include:
  - lower doses should be used when first starting therapy
  - initial drug therapy, even with stage 2 hypertension, should only be started with monotherapy
- In earlier JNC recommendations, thiazide diuretics and long-acting dihydropyridine CCB were preferred
- The JNC7 recommends that selection of pharmacotherapy in elderly patients be according to the same general treatment philosophies as for other patients with hypertension
White-Coat Hypertension

• White-coat hypertension describes patients who have consistently elevated BP values measured in a clinical environment in the presence of a health care professional, yet when measured elsewhere or with 24-hour ambulatory monitoring, BP is not elevated.

• Home BP monitoring or 24-hour ABPM is warranted in patients suspected of having white-coat hypertension to differentiate this from true hypertension.
White-Coat Hypertension: definition

- The commonly used definition is a persistently elevated average office blood pressure of $>140/90$ mmHg and an average awake ambulatory reading of $<135/85$ mmHg.
- The label white-coat hypertension applies only to patients without target-organ disease who are not on antihypertensive therapy.
- It is estimated to be present in 15% to 20% of people with stage 1 hypertension.
White-Coat Hypertension and Cardiovascular (CV) Risk

• patients with white-coat hypertension are at risk for developing clinically relevant hypertension.

• Moreover, data suggest that patients with white-coat hypertension are at a higher risk for CV disease than normotensive patients.
White-Coat Hypertension decision to treat

• The decision to treat or not treat white-coat hypertension is controversial.
• many studies demonstrated reductions in CV morbidity and mortality with antihypertensive therapy had white-coat hypertension.
• At minimum, patients with white-coat hypertension should be treated with:
  – lifestyle modifications
  – closely monitored with a device that can measure BP outside the clinic
Discontinuing therapy

• between 5 and 55 percent of patients remain normotensive for at least one to two years a larger fraction of patients do well with a decrease in the number and/or dosage of medications taken

• **Gradual** discontinuation of therapy is most likely to be effective in **mild and well controlled HTN** and who can often be maintained on **nonpharmacologic** therapy such as weight loss and sodium restriction

• More gradual tapering of drug dosage is indicated in well-controlled patients taking multiple drugs
Diuretics

• first-line agents for hypertension
• when combination therapy is needed in hypertension to control BP, a diuretic is recommended to be one of the agents used
Diuretics

• There are four subclasses of diuretics that are used in the treatment of hypertension:
  – thiazides
  – loops
  – potassium-sparing agents
  – and aldosterone antagonists
Potassium-sparing & Aldosterone antagonists diuretics

• Potassium-sparing diuretics are weak antihypertensive agents but provide an additive effect when used in combination with a thiazide or loop diuretic.

• Moreover, they counteract the K and Mg-losing properties of the other diuretic agents

• Aldosterone antagonists (spironolactone and eplerenone) may be technically considered potassium-sparing agents, but are more potent antihypertensives.

• However, they are viewed by the JNC7 as an independent class because of evidence supporting compelling indications
mechanisms of action

• The drop in BP seen when diuretics are first started is caused by an initial diuresis.

• initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance.

• With chronic diuretic therapy, extracellular fluid and plasma volume return to near pretreatment values.

• peripheral vascular resistance decreases to values that are lower than the pretreatment baseline.

• This reduction in peripheral vascular resistance is responsible for chronic antihypertensive effects.
diuretic of Choice

• **Thiazides** are the preferred type of diuretic for treating hypertension.

• **loop diuretic**: In patients requiring diuresis to treat concurrent edema, such as in heart failure

• **Aldosterone antagonist** is indicated in patients with advanced HF who have relatively preserved renal function and for the treatment of hypokalemia
Thiazides

- Hydrochlorothiazide and chlorthalidone are the two most frequently used thiazide diuretics.
- Chlorthalidone is 1.5 to 2.0 times more potent than hydrochlorothiazide.
- This is attributed to a longer half-life (45 to 60 hours vs. 8 to 15 hours) and longer duration of effect (48 to 72 hours vs. 16 to 24 hours) with chlorthalidone.
- These differences in BP lowering do not appear to result in differences in CV outcomes.
Administration

• Diuretics should ideally be dosed in the morning if given once daily to minimize risk of nocturnal diuresis.

• with chronic use, thiazide-type diuretics, potassium sparing diuretics, and aldosterone antagonists rarely cause a pronounced diuresis.
ADR

• Side effects of thiazide-type diuretics include
  – hypokalemia
  – hypomagnesemia
  – hypercalcemia
  – hyperuricemia
  – hyperglycemia
  – dyslipidemia
  – sexual dysfunction
Many of these side effects were identified when high-doses of thiazides were used in the past (e.g., hydrochlorothiazide 100 mg/day).

Current guidelines recommend limiting the dose of hydrochlorothiazide or chlorthalidone to 12.5 to 25 mg/day, which markedly reduces the risk for most metabolic side effects.

Loop diuretics may cause the same side effects, although the effect on serum lipids and glucose is not as significant, and hypocalcemia and ototoxicity may occur.
Potassium-sparing diuretics

- Potassium-sparing diuretics can cause hyperkalemia, especially in patients with:
  - chronic kidney disease
  - diabetes
  - in patients receiving concurrent treatment with an ACE inhibitor, nonsteroidal antiinflammatory drugs, or potassium supplements.
Eplerenone and spironolactone

• eplerenone is a very selective aldosterone antagonist
• Although spironolactone may cause gynecomastia in up to 10% of patients, this occurs rarely with eplerenone
• its propensity to cause hyperkalemia is greater than with the other potassium sparing agents, and even spironolactone.
• Because of this increased risk of hyperkalemia, eplerenone is contraindicated in patients with impaired kidney function or type 2 diabetes with proteinuria.
Interaction

• Diuretics can be used safely with most other agents.
• However, concurrent administration with lithium may result in increased lithium serum concentrations.
• This interaction can predispose patients to lithium toxicity.
ACEI, mechanism

• ACE inhibitors block the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion.

• ACE inhibitors also block the degradation of bradykinin and stimulate the synthesis of other vasodilating substances including prostaglandin E2 and prostacyclin.

• The fact that ACE inhibitors lower blood pressure in patients with normal plasma renin activity suggests that bradykinin and perhaps tissue production of ACE are important in hypertension.
Dosing

• Starting doses of ACE inhibitors should be low with slow dose titration.

• Acute hypotension may occur at the onset of ACE inhibitor therapy, especially
  – in patients who are sodium- or volume-depleted
  – in heart failure exacerbation
  – very elderly
  – on concurrent vasodilators or diuretics.

• Patients with these risk factors should start with half the normal dose followed by slow dose titration (e.g., 6-week intervals).
ACEI; drugs

- All ACE inhibitors can be dosed once daily for hypertension except captopril, which is usually dosed 2 or 3 times daily.
- The absorption of captopril (but not enalapril or lisinopril) is reduced by 30% to 40% when given with food.
### Table 13-13 ACEI in Hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Starting Dose(^a) (mg/day)</th>
<th>Usual Dosage Range (mg/day)</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril (Lotensin)</td>
<td>10</td>
<td>20-40</td>
<td>Daily to BID</td>
</tr>
<tr>
<td>Captopril (Capoten)</td>
<td>25</td>
<td>50-100</td>
<td>BID to TID</td>
</tr>
<tr>
<td>Enalapril (Vasotec)</td>
<td>5</td>
<td>10-40</td>
<td>Daily to BID</td>
</tr>
<tr>
<td>Fosinopril (Monopril)</td>
<td>10</td>
<td>20-40</td>
<td>Daily</td>
</tr>
<tr>
<td>Lisinopril (Prinivil, Zestril)</td>
<td>10</td>
<td>20-40</td>
<td>Daily</td>
</tr>
<tr>
<td>Moexipril (Univasc)</td>
<td>7.5</td>
<td>7.5-30</td>
<td>Daily to BID</td>
</tr>
<tr>
<td>Perindopril (Aceon)</td>
<td>4</td>
<td>4-16</td>
<td>Daily</td>
</tr>
</tbody>
</table>
Compelling indication

• ACE inhibitors are considered first-line therapy in all patients who have
  – HF or asymptomatic LV dysfunction,
  – in all patients who have had an ST elevation MI,
  – in patients with a non-ST elevation MI who have had an anterior infarct, diabetes, or systolic dysfunction,
  – proteinuric chronic renal failure

• Combination therapy with an ARB appears to be beneficial in patients with HF and proteinuric chronic renal failure.
The most serious adverse effects of the ACE inhibitors are neutropenia and agranulocytosis, proteinuria, glomerulonephritis, and acute renal failure; these effects occur in less than 1% of patients.

Bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders patients dependent on the vasoconstrictive effect of angiotensin II on efferent arterioles, making these patients particularly susceptible to acute renal failure.
ADR

• The GFR decreases in patients receiving ACE inhibitors because of inhibition of angiotensin II vasoconstriction on efferent arterioles.

• Serum creatinine concentrations often increase, but modest elevations (e.g., absolute increases of less than 1 mg/dL) do not warrant changes.

• Therapy should be stopped or the dose reduced if larger increases occur.
ADR

- ACE inhibitors decrease aldosterone and can increase serum potassium concentrations.
- Hyperkalemia occurs primarily in patients with chronic kidney disease or diabetes and in those also taking ARBs, NSAIDs, potassium supplements, or potassium-sparing diuretics.
Angioedema is a serious potential complication that occurs in less than 2% of patients. It may be manifested as lip and tongue swelling and possibly difficulty breathing. Drug withdrawal is appropriate for all patients with angioedema, and some patients may also require drug treatment and/or emergent intubation. Cross-reactivity between ACE inhibitors and ARBs has been reported.
ADR

• A persistent dry cough occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.

• If an ACE inhibitor is indicated because of compelling indications, patients should be switched to an ARB.
Contraindication

- ACE inhibitors are absolutely contraindicated in pregnancy because serious neonatal problems, including renal failure and death in the infant, have been reported when mothers took these agents during the second and third trimesters.
ARBs

• ACE inhibitors block only the renin-angiotensin pathway, whereas ARBs antagonize angiotensin II generated by either pathway.

• The ARBs directly block the angiotensin type 1 (AT1) receptor that mediates the known effects of angiotensin II
bradykinin

• Unlike ACE inhibitors, ARBs do not block the breakdown of bradykinin.

• While this accounts for the lack of cough as a side effect, there may be negative consequences because some of the antihypertensive effect of ACE inhibitors may be due to increased levels of bradykinin.
efficacy

• All drugs in this class have similar antihypertensive efficacy and fairly flat dose-response curves.
• The addition of low doses of a thiazide diuretic can increase efficacy significantly.
Indications

• In patients with type 2 diabetes and nephropathy, ARB therapy has been shown to significantly reduce progression of nephropathy.

• For patients with systolic heart failure, ARB therapy has also been shown to reduce the risk of cardiovascular events
Performance to ACEI

• In at least one setting, severe hypertension with ECG evidence of left ventricular hypertrophy (LIFE trial), trials demonstrating benefit of an ARB have not been performed with ACE inhibitors.

• An ARB can thus be used instead of an ACE inhibitor in such patients

• we would not switch a patient who is already receiving and tolerating an ACE inhibitor to an ARB (since it is highly likely that an ACE would be similarly effective).
side effects

• ARBs appear to have the lowest incidence of side effects compared with other antihypertensive agents.
• Cough is very uncommon.
• Like ACE inhibitors, they may cause renal insufficiency, hyperkalemia, and orthostatic hypotension.
• Angioedema is less likely to occur than with ACE inhibitors, but cross-reactivity has been reported.
• ARBs should not be used in pregnancy
β blockers

• The exact hypotensive mechanism of β blockers is not known but may involve decreased cardiac output through negative chronotropic and inotropic effects on the heart and inhibition of renin release from the kidney
• Even though there are important pharmacodynamic and pharmacokinetic differences among the various β blockers, there is no difference in clinical antihypertensive efficacy.
Indication

• A beta blocker without intrinsic sympathomimetic activity should be given
  – after an acute myocardial infarction
  – stable patients with heart failure or asymptomatic left ventricular dysfunction (beginning with very low doses to minimize the risk and degree of initial worsening of myocardial function).

• The use of beta blockers in these settings is in addition to the recommendations for ACE inhibitors in these disorders

• Beta blockers are also given for rate control in patients with atrial fibrillation, for control of angina
pharmacokinetic differences

• There are pharmacokinetic differences among β blockers in first-pass metabolism, serum half-lives, degree of lipophilicity, and route of elimination.

• Propranolol and metoprolol undergo extensive first-pass metabolism.

• Atenolol and nadolol have relatively long half-lives and are excreted renally; the dosage may need to be reduced in patients with moderate to severe renal insufficiency.

• Even though the half-lives of the other β blockers are much shorter, once-daily administration still may be effective.

• β Blockers vary in their lipophilic properties and thus CNS penetration.
ADR

• Side effects from β blockade in the myocardium include bradycardia, atrioventricular (AV) conduction abnormalities, and acute heart failure.

• Pulmonary β2 blockade may cause acute exacerbations of bronchospasm in patients with asthma or COPD.

• Blocking β2 receptors in arteriolar smooth muscle may cause cold extremities and aggravate intermittent claudication or Raynaud's phenomenon because of decreased peripheral blood flow.
ADR

• Increases in serum lipids and glucose appear to be transient and of little clinical importance.

• β Blockers increase serum triglyceride levels and decrease HDL cholesterol levels slightly.

• β Blockers with alfa-blocking properties (carvedilol and labetalol) do not affect serum lipid concentrations.
Abrupt cessation

• Abrupt cessation of β-blocker therapy may produce unstable angina, myocardial infarction, or even death in patients predisposed to ischemic myocardial events.

• In patients without coronary artery disease, abrupt discontinuation of β-blocker therapy may be associated with sinus tachycardia, increased sweating, and generalized malaise.

• For these reasons, it is always prudent to taper the dose gradually over 1 to 2 weeks before discontinuation.
Calcium Channel Blockers

- The calcium channel blockers (CCBs) cause relaxation of cardiac and smooth muscle by blocking voltage-sensitive calcium channels, thereby reducing the entry of extracellular calcium into cells.
- Vascular smooth muscle relaxation leads to vasodilation and a corresponding reduction in blood pressure.
- Dihydropyridine calcium channel antagonists may cause reflex sympathetic activation, and all agents (except amlodipine) may demonstrate negative inotropic effects.
Non Dihydropyridine CCB

- Verapamil decreases heart rate, slows AV nodal conduction, and produces a negative inotropic effect that may precipitate heart failure in patients with borderline cardiac reserve.
- Diltiazem decreases AV conduction and heart rate to a lesser extent than verapamil.
Indication

• they can be given for rate control in patients with atrial fibrillation or for control of angina.

• Calcium channel blockers may be preferred in patients with obstructive airways disease
ADR

- Nifedipine rarely may cause an increase in the frequency, intensity, and duration of angina in association with acute hypotension.
- This effect may be obviated by using sustained-released formulations of nifedipine or other dihydropyridines.
ADR

• Other side effects of dihydropyridines include dizziness, flushing, headache, gingival hyperplasia, peripheral edema, mood changes, and gastrointestinal complaints.

• Side effects due to vasodilation such as dizziness, flushing, headache, and peripheral edema occur more frequently with dihydropyridines than with verapamil or diltiazem.
• Diltiazem and verapamil can cause cardiac conduction abnormalities such as bradycardia, AV block, and heart failure. Both can cause anorexia, nausea, peripheral edema, and hypotension.

• Verapamil causes constipation in about 7% of patients
• Dihydropyridines cause a baroreceptor-mediated reflex increase in heart rate because of their potent peripheral vasodilating effects.

• Dihydropyridines usually do not decrease AV node conduction
alfa-Receptor Blockers

• Prazosin, terazosin, and doxazosin are selective alfa-receptor blockers that inhibit catecholamine uptake in smooth muscle cells of the peripheral vasculature, resulting in vasodilation.
ADR

• A potentially severe side effect is a first-dose phenomenon characterized by orthostatic hypotension accompanied by transient dizziness or faintness, palpitations, and even syncope within 1 to 3 hours of the first dose or after later dosage increases.

• These episodes can be obviated by having the patient take the first dose, and subsequent first increased doses, at bedtime.

• Occasionally, orthostatic dizziness persists with chronic administration.
• Sodium and water retention can occur with higher doses and sometimes with chronic administration of low doses.

• These agents are most effective when given with a diuretic to maintain hypotensive efficacy and minimize potential edema.
Place in therapy

• Because data suggest that doxazosin (and probably other alfa-receptor blocker blockers) are not as protective against cardiovascular events as other therapies, their use should be reserved for unique cases such as men with benign prostatic hyperplasia if they are already receiving other standard antihypertensive therapy (diuretic, blocker, or ACE inhibitor).
Hypertensive Crises

- Hypertensive crises are situations when measured BP values are markedly elevated, typically in the upper range of stage 2 hypertension (>180/110 mmHg).

- They are classified as either a hypertensive emergency (with acute or progressive target-organ damage) or urgency (without acute or progressive target-organ damage).
Hypertensive emergencies

- Hypertensive emergencies require hospitalization for immediate BP lowering using intravenous (IV) medications and intraarterial BP monitoring.

- Examples of acute target-organ damage include
  - Encephalopathy
  - myocardial infarction (MI)
  - unstable angina
  - pulmonary edema
  - Eclampsia
  - Stroke
  - head trauma
  - life-threatening arterial bleeding
  - aortic dissection
  - severe retinopathy
  - acute kidney failure
• Thank you for your attention