

The Management of Hypertension

Allison A. Torbert, Pharm.D.
Roberta M. Skoronski, Pharm.D.

*Clinical Instructors
UW School of Pharmacy*

Objectives

- Explain the classification and goals of therapy in the treatment of hypertension based on JNC VI recommendations
- Describe nonpharmacologic and pharmacologic treatment approaches
- Recognize patients with hypertension and comorbid conditions in order to optimize therapy
- Develop an approach to manage hypertensive patients

Prevalence

- Approximately 50-60 million Americans have HTN defined as:
 - systolic BP (SBP) 140 mm Hg or >
 - diastolic BP (DBP) 90 mm Hg or >
- Incidence increases with age
- Blacks > whites
- Men > women
- Greater in less educated, lower socioeconomic groups

Classification of Blood Pressure for Adults Age 18 & Older*

Category	Systolic (mm Hg)	&	Diastolic (mm Hg)
Optimal+	< 120	&	< 80
Normal	< 130	&	< 85
High-normal	130-139	&	85-89
Hypertension++			
Stage 1	140-159	&	90-99
Stage 2	160-179	&	100-109
Stage 3	≥ 180	&	≥ 110

*Not taking antiHTN drugs & not acutely ill. When SBP & DBP fall into different categories, highest classification should be used. Isolated systolic HTN defined as SBP ≥ 140 and DBP < 90 and staged appropriately. In addition to classifying accordingly, clinicians should specify presence or absence of target organ disease & additional risk factors

+ Optimal BP with respect to CV risk is < 120/80; unusually low BP's should be evaluated for clinical significance.

++Based on avg. of 2 or > readings taken at each of 2 or > visits.

Why treat hypertension?

- Increased risk of the following with increased BP
 - CVD (nonfatal and fatal)
 - CHD
 - Stroke
 - Renal disease
 - All cause mortality

THE HIGHER THE BP THE HIGHER THE RISK

Why treat hypertension?

- Major risk factor for CHD
 - Accelerates atherosclerosis
 - Atimulates LVH
 - Increasing risk three to ten fold for CHF
 - Associated with ventricular arrhythmias
- To decrease/prevent target organ disease (TOD)

Goals of Therapy

- General goal is < 140/90
- Reduce mortality
- Improve quality of life
 - Long term: avoid HTN morbidity
 - Short term: can we make these patients feel good?
- Goal BP is <130/85 in hypertensive diabetics
- Goal for pts with renal insufficiency is < 135/85; for pts with > 1 gm/day of urinary protein, goal is ≤ 125/75

Target Organ Disease

- Risks of CVD at any level of elevated BP are increased several fold for patients with TOD
- Manifestations of TOD
 - Cardiac
 - Clinical, electrocardiograph, or radiologic evidence of CAD
 - LVH or “strain” by ECG or LVH by echo
 - Left ventricular dysfunction or cardiac failure

Target Organ Disease

- Manifestations of TOD (cont'd)
 - Cerebrovascular
 - TIA or stroke
 - Peripheral vascular
 - Absence of 1 or more major pulses in extremities (except dorsalis pedis) with or without intermittent claudication; aneurysm

Target Organ Disease

- Manifestations of TOD (cont'd)
 - Renal
 - Serum creatinine ≥ 1.5 mg/dL
 - Proteinuria (1+ or >)
 - Microalbuminuria
 - Retinopathy
 - Hemorrhages or exudates, with or without papilledema

White Coat Hypertension

- BP repeatedly higher in physician office or clinic setting than at home or outside office
- Can affect 20% of patients
- Encourage home BP monitoring if suspected

Isolated Systolic Hypertension (ISH)

- SBP ≥ 140 mm Hg and DBP < 90 mm Hg (per JNC VI guidelines)
- Generally in older patients > 65 years old
- Structural changes in vasculature cause rigid arteries
- High stroke risk
- SHEP trial

Diagnosis and Treatment Goals

- Routine initial evaluation
 - Diagnosis of HTN should be based on average of 2 or more readings taken at 2 or more visits
 - Baseline labs
 - Cardiovascular risk factors
- Goals of therapy
 - Prevent morbidity and premature mortality; decrease CV risk

Diagnosis and Treatment Goals

- Goals of therapy (cont'd)
 - Prevent or reverse end-organ damage
 - BP goal less than 140/90 mm Hg
 - J-curve phenomenon
 - Attaining BP goal and minimizing adverse effects and drug toxicity

Non-Pharmacologic Treatment

- Lifestyle modifications
- Used as adjunctive therapy to antiHTN meds
- Can lower BP and reduce CVD risk at minimal cost and risk to patient
- Attempt for 3 to 6 months before initiating drug therapy if patients in early stage of HTN and free of end-organ damage
- Diet modification (DASH, sodium restriction)
 - Please see Appendix I

Lifestyle Modifications for Hypertension Prevention and Management

- Lose weight if overweight
- Limit alcohol intake to no more than 1 oz. ethanol per day or 0.5 oz. ethanol per day for women and lighter weight people
- Increase aerobic physical activity (30-45 minutes most days of the week)
- Reduce sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride)
- Maintain adequate intake of dietary potassium (≥ 90 mmol/day)
- Maintain adequate intake of dietary calcium and magnesium for general health
- Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health

Treatment Algorithm

Please see Appendix II (Figure 8 from JNC VI)

Risk Stratification*

BP Stages (mm Hg)	Risk Group A (No risk factors, no TOD/CCD)*	Risk Group B (At least 1 risk factor, not including diabetes, no TOD/CCD)	Risk Group C (TOD/CCD and/or diabetes, with/without other risk factors)
High-normal (130-139/85-89)	Lifestyle modifications	Lifestyle modifications	Drug therapy ^M
Stage 1 (140-159/90-99)	Lifestyle modifications (up to 12 months)	Lifestyle modifications** (up to 6 months)	Drug therapy
Stages 2 and 3 ($\geq 160/\geq 100$)	Drug therapy	Drug therapy	Drug therapy

*Lifestyle modification should be adjunctive therapy for all patients getting drug therapy

**TOD/CCD indicates target organ disease/clinical cardiovascular disease

***For patients with multiple risk factors, consider drugs as initial therapy plus lifestyle modifications

^MFor those with heart failure, renal insufficiency, or diabetes

Special Populations

- African Americans
 - Carefully evaluate Beta Blockers and ACEI
 - Addition of diuretics improve response
- Women
 - OCP's
 - Small but detectable increase in SBP and DBP
 - DO NOT SMOKE
 - BP normalizes a few months after d/c
 - Pregnancy
 - DO NOT USE ACEI
 - Methyldopa is most extensively evaluated
 - Post Menopausal Estrogen Replacement

Special Populations

- Angina
 - Beta Blockers, CCBA
- Myocardial Infarction
 - Non-ISA Beta Blockers, ACEI
- CHF
 - ACEI, diuretics
- Renal Disease
 - ACEI, diuretics
- Reactive Airway Disease
 - Avoid Beta Blockers
- Gout
 - Avoid diuretics

Special Populations

- Diabetes
 - Beta Blockers may worsen glucose intolerance and mask hypoglycemia
 - ACEI, alpha blockers or CCBA may be D.O.C.
- Dyslipidemia
 - Thiazides and loops may increase Tc, TGs, LDL
 - Beta Blockers may increase TGs, lower HDL
 - Alpha blockers have been shown to improve lipids
- SEE JNC VI FOR FURTHER DETAIL

Trends in Recommendations

JNC I and II: Diuretics
↓
JNC III: Diuretics and β -blockers
↓
JNC IV: Diuretics, β -blockers, ACEIs, & CCBs
↓
JNC V: Diuretics and β -blockers
↓
JNC VI: Diuretics and β -blockers in uncomplicated HTN; consider comorbid conditions

Pharmacologic Treatment

- Diuretics
- Beta blockers
- ACE inhibitors
- Angiotensin receptor blockers
- Calcium channel blockers
- Alpha-1 blockers
- Centrally-acting alpha-2 agonists
- Direct vasodilators
- Peripherally acting adrenergic antagonists

Diuretics

- Classes
 - Thiazide and thiazide-like diuretics
 - Loop diuretics
 - Potassium-sparing diuretics

Diuretics

- Thiazide and thiazide-like
 - Most effective anihypertensive agent
 - Use in patients with CrCl > 30 ml/min or Cr < 2.0 mg/dL

Diuretics

- Thiazide and thiazide-like
 - Examples:
 - Hydrochlorothiazide (HCTZ)
 - Chlorothiazide
 - Chlorthalidone
 - Indapamide
 - Metolazone
 - Combinations
 - HCTZ 25mg/triamterene 37.5 mg (25 mg/50 mg; 50 mg/75 mg)
 - HCTZ 25 mg/spironolactone 25mg (50 mg/50 mg)
 - HCTZ 50 mg/amiloride 5 mg

Diuretics

- Dosing of thiazides and thiazide-like
 - Please see Appendix III (table 7 and 8 from JNC VI)

Diuretics

- Possible side effects of thiazides and thiazide-like diuretics
 - Hypokalemia, hypomagnesemia, hyponatremia, hyperuricemia, hypercalcemia, hyperglycemia, hypercholesterolemia (less with indapamide), hypertriglyceridemia, sexual dysfunction, weakness, pancreatitis, rashes/allergic reaction, photosensitivity reactions

Diuretics

- Precautions/Special Considerations of thiazides and thiazide-like
 - Hypokalemia predisposes patients to cardiac arrhythmias (digitalis, LVH)
 - May precipitate gout
 - Ineffective in renal failure (Cr > 2 mg/dL) except for metolazone or indapamide
 - Metolazone effective in decreasing GFR (<40ml/min) - high doses required

Diuretics

- Loop diuretics
 - Potent diuresing agent
 - Use in patients with CrCl < 30 ml/min or Cr > 2.0 ml/dL
 - Examples
 - Furosemide
 - Bumetanide
 - Torsemide
 - Ethacrynic acid (nonsulfonamide)

Diuretics

- Dosing of loop diuretics
 - Please see Appendix III (table 7 and 8 from JNC VI)

Diuretics

- Possible side effects of loop diuretics
 - Dehydration, hypokalemia, hyponatremia, hypomagnesemia, hyperglycemia, hyperuricemia, metabolic alkalosis, circulatory collapse, hyperlipidemia, blood dyscrasias, rash, ototoxicity (furosemide)

Diuretics

- Precautions/Special Considerations of loop diuretics
 - Effective in renal failure
 - Higher doses of loop diuretics may be needed in CHF/edematous or renally impaired patients
 - Ethacrynic acid - alternative for thiazide and sulfa containing diuretics

Diuretics

- Potassium-sparing diuretics
 - Weak diuretics alone, additive antiHTN effects with loops or thiazides
 - Use in combination with other diuretics to avoid or reverse hyperkalemia
 - Avoid use in patients with Cr > 2.5 mg/dL
 - Examples
 - Spironolactone
 - Amiloride
 - Triamterene
 - Combinations

Diuretics

- Dosing of potassium sparing diuretics
 - Please see Appendix III (table 7 and 8 from JNC VI)

Diuretics

- Possible side effects of K+ sparing diuretics
 - Hyperkalemia, gynecomastia, GI disturbances, rash, headache (amiloride), nephrolithiasis (triamterene), menstrual irregularities, decreased libido in males (spironolactone)
 - Precautions/Special Considerations of K+ sparing diuretics
 - Hyperkalemia may be exaggerated when combined with ACEIs, K+ supplements, NSAIDs, and pts with renal failure

Diuretics

- Drug Interactions
 - Increase efficacy of diuretics
 - Diuretics that act at different sites in the nephron
 - Decrease efficacy of diuretics
 - Resin-binding agent - decrease absorption
 - NSAIDs
 - Steroids
 - Effects on other drugs
 - Lithium - can raise levels
 - ACE inhibitors - potassium sparing diuretics may exacerbate hyperkalemia

Diuretics

- Monitoring parameters
 - Blood pressure (orthostasis)
 - Electrolytes
 - Renal function
 - Volume depletion/weight gain
 - Periodic lipid profiles

Beta Blockers

- Reduce BP in patients with combined systolic and diastolic HTN or ISH
- Indicated for patients with concomitant diseases (angina, post-MI, atrial fibrillation or tachycardia, migraine, hyperthyroidism)

Beta Blockers

- Dosing
 - Please see Appendix III (table 7 and 8 from JNC VI)

Beta Blockers

- Cardioselectivity (β_1 selectivity)
 - At low doses, affect the heart > extracardiac tissue
 - May still cause bronchospasm (inhibit β_2) in patients with bronchospastic disease/chronic airway obstruction in low & high doses
 - Use with caution in patients with asthma, hypoglycemia, or PVD
 - First choice in hypertensive patients post-MI

Beta Blockers

- Intrinsic Sympathomimetic Activity (ISA) or Partial Agonist Activity
 - Produce less bradycardia (at rest and with exercise)
 - Reduce PVR and cause less depression of AV conduction
 - Less effect in reducing incidence of MI, sudden death, and total mortality post-MI

Beta Blockers

- Alpha-adrenergic activity
 - Reserved for more severe HTN
 - Alpha activity reduces PVR & maintains CO
 - May cause more postural effects

Beta Blockers

- Membrane-stabilizing activity (MSA)
 - “Quinidine-like” effect
 - MSA can manifest with massive β -blocker intoxication

Beta Blockers

- Lipid solubility
 - Controversy whether this relates to CNS adverse effects
 - May be related to cardioprotection (unproven)
 - Water soluble agents tend to have less variable bioavailability and longer half-lives (qd dosing)

Beta Blockers

- Side effects
 - Bradycardia
 - Fatigue
 - Insomnia
 - Mask symptoms of hypoglycemia
 - Increase TG and decrease HDL
 - Decrease exercise tolerance
 - Increase peripheral arterial insufficiency
 - CNS effects: depression, sedation, nightmares, flat affect
 - May exacerbate CHF

Beta Blockers

- Precautions & special considerations
 - Contraindicated in bronchospastic disease and 2nd- or 3rd-degree heart block
 - Use with caution in depression, diabetes mellitus (Type 1 and 2), dyslipidemia (non-ISA), heart failure (except carvedilol), PVD
 - Do not discontinue abruptly in patients with CAD or ischemic heart disease

Beta Blockers

- Drug interactions
 - Increase efficacy of β -blocker
 - Cimetidine
 - Quinidine
 - Food
 - Decrease efficacy of β -blocker
 - NSAIDs
 - Rifampin
 - Phenobarbital
 - Withdrawal of clonidine

Beta Blockers

- Drug interactions (cont'd)
 - Effect on other drugs
 - Propranolol induces hepatic enzymes to increase clearance of drugs with similar metabolic pathway
 - May mask and prolong symptoms of insulin-induced hypoglycemia
 - Heart block may occur with nondihydropyridine CCB's

Beta Blockers

- Drug interactions (cont'd)
 - Effect on other drugs
 - Sympathomimetics cause unopposed alpha-adrenoreceptor-mediated vasoconstriction
 - Beta-blockers increase angina-inducing potential of cocaine

Beta Blockers

- Monitoring parameters
 - Blood pressure
 - Heart rate
 - Side effects

ACE Inhibitors

- JNC VI recommends considering use in the following indications unless contraindicated
 - Type 1 Diabetes with proteinuria
 - CHF
 - MI with systolic dysfunction/LVH

ACE Inhibitors

- Examples
 - Benazepril
 - Captopril
 - Enalapril
 - Fosinopril
 - Lisinopril
 - Moexipril
 - Quinapril
 - Ramipril
 - Trandolapril
 - Combinations
 - With diuretics
 - With CCBAs

ACE Inhibitors

- Dosing of ACE Inhibitors
 - Please see Appendix III (table 7 and 8 from JNC VI)

ACE Inhibitors

- Possible side effects of ACE Inhibitors
 - Cough, hyperkalemia, hypotension, metallic or loss of taste, rash, acute renal failure in patients with renal artery stenosis, rarely: neutropenia and angioedema

ACE Inhibitors

- Special Considerations and Precautions
 - Bilateral artery stenosis/renal vascular disease
 - Pregnancy
 - May reduce GFR in the presence of renal impairment

ACE Inhibitors

- Drug Interactions
 - Increase efficacy of ACE Inhibitors
 - Chlorpromazine, clozapine
 - Decrease efficacy of ACE Inhibitors
 - NSAIDs, antacids,
 - ACE Inhibitors may raise serum lithium levels
 - ACE Inhibitors may exacerbate hyperkalemic effect of potassium sparing diuretics

ACE Inhibitors

- Monitoring parameters
 - Blood pressure
 - Potassium levels
 - Renal function
 - Cough

Angiotensin II receptor blockers

- Examples
 - Losartan
 - Valsartan
 - Irbesartan
 - Combinations
 - Losartan 50 mg/ HCTZ 12.5 mg
- Dosing of Angiotensin II receptor blockers
 - Please see Appendix III (table 7 and 8 from JNC VI)

Angiotensin II receptor antagonists

- May be useful in patients that don't tolerate ACE Inhibitor due to cough
- Special considerations/precautions
 - Hepatic dysfunction
 - Renal vascular disease
 - Pregnancy

Calcium Channel Blockers

- Classes
 - Nondihydropyridines
 - Verapamil
 - ↓ in HR & slows AV node conduction
 - Diltiazem
 - ↓ in HR & SA node conduction
 - Mibefradil
 - Slight ↓ in HR and acts as a peripheral arterial vasodilator

Calcium Channel Blockers

- Classes
 - Dihydropyridines
 - Potent vasodilators leading to ↑ in HR
 - Examples:
 - Nifedipine
 - Amlodipine
 - Felodipine
 - Isradipine
 - Nisoldipine
 - Nicardipine

Calcium Channel Blockers

- Dosing
 - Please see Appendix III (table 7 and 8 from JNC VI)

Calcium Channel Blockers

- Side effects
 - Verapamil
 - Constipation, bradycardia, 1st-degree heart block, anorexia, nausea, peripheral edema, hypotension
 - Diltiazem
 - Bradycardia, 1st-degree heart block, anorexia, nausea, peripheral edema, hypotension, some constipation

Calcium Channel Blockers

- Side effects (cont'd)
 - Dihydropyridines
 - Headache, dizziness, peripheral edema, flushing, gingival hyperplasia, tachycardia, GI complaints

Calcium Channel Blockers

- Precautions and special considerations
 - Nondihydropyridines contraindicated in 2nd- or 3rd-degree heart block
 - Mibefradil contraindicated with terfenadine, astemizole, cisapride, lovastatin, and simvastatin and in sick sinus syndrome or 2nd- or 3rd-degree heart block without a pacemaker
 - Use with caution in heart failure (except amlodipine, felodipine)

Calcium Channel Blockers

- Drug interactions
 - Increase efficacy of CCB
 - Grapefruit juice (some dihydropyridines)
 - Cimetidine or ranitidine
 - Beta-blockers (↓↓ in HR with nondihydropyridines)
 - Decrease efficacy of CCB
 - Rifampin
 - Phenobarbital

Calcium Channel Blockers

- Drug interactions (cont'd)
 - Effect on other drugs
 - Cyclosporine levels increase with diltiazem, verapamil, mibefradil, or nicardipine
 - Nondihydropyridines increase levels of other drugs metabolized by same hepatic enzyme system, including digoxin, quinidine, sulfonyleureas, & theophylline

Calcium Channel Blockers

- Drug interactions (cont'd)
 - Effect on other drugs
 - Verapamil may lower serum lithium levels
 - Prazosin may decrease clearance of verapamil

Calcium Channel Blockers

- Monitoring
 - Blood pressure
 - Heart rate
 - Peripheral edema
 - Constipation

Alpha-1 Blockers

- “Two-for one” agent in treating men with benign prostatic hyperplasia and hypertension
- Lipid-neutral agent

Alpha-1 Blockers

- Dosing
 - Please see Appendix III (table 7 and 8 from JNC VI)

Alpha-1 Blockers

- Side effects
 - Dizziness
 - Syncope
 - Headache
 - Orthostatic hypotension
 - Flushing
 - Reflex tachycardia
 - Fluid retention

Alpha-1 Blockers

- Drug interactions
 - Prazosin may decrease clearance of verapamil
 - Increased risk of orthostatic hypotension when used with other antihypertensive agents

Alpha-1 Blockers

- Monitoring
 - Blood pressure
 - Signs and symptoms of orthostatic hypotension
 - Improvement in symptoms of BPH, if applicable

Central Alpha-2 Agonists

- Smooth, intact postural reflexes
- Useful for withdrawal-states from depressants
- Wide dose range for wide range of blood pressures
- Lipid neutral

Central Alpha-2 Agonists

- Examples:
 - Clonidine
 - Methyldopa
 - Guanfacine
 - Guanabenz
- Dosing of Central Alpha-2 Agonists
 - Please see Appendix III (table 7 and 8 from JNC VI)

Central Alpha-2 Agonists

- Possible side effects
 - Sedation, dry mouth, bradycardia, impotence, withdrawal hypotension, skin rash, depression, hepatic dysfunction (methyldopa), hemolytic anemia (methyldopa)
 - Monitoring parameters
 - Blood pressure
 - Side effects

Central Alpha-2 Agonists

- Drug interactions with central alpha-2 agonists
 - Decrease efficacy of central alpha-2 agonists
 - TCA, MOA-Is
 - Methyldopa may increase serum lithium levels
 - Beta-blockers may increase the severity of withdrawal hypertension
 - Many agents used in anesthesia are potentiated by clonidine

Direct Vasodilators

- Dosing
 - Please see Appendix III (table 7 and 8 from JNC VI)

Direct Vasodilators

- Side effects
 - Hydralazine
 - Fluid retention, tachycardia, headache, worsening angina, drug-induced lupus, dermatitis, drug fever, peripheral neuropathy, hepatitis
 - Minoxidil
 - Fluid retention, tachycardia, worsening angina, hypertichosis, pericardial effusion

Direct Vasodilators

- Monitoring
 - Blood pressure
 - Side effects

Peripherally Acting Adrenergic Antagonists

- Generally restricted for use in patients with refractory hypertension
- Examples:
 - Reserpine
 - Guanadrel
 - Guanethidine
- Dosing
 - Please see Appendix III (table 7 and 8 from JNV VI)

Peripherally Acting Adrenergic Antagonists

- Possible side effects
 - Guanadrel and guanethidine:
 - Postural hypotension, syncope, explosive diarrhea, impotence, weight gain
 - Reserpine:
 - Nasal congestion, increases gastric acid secretion, diarrhea, bradycardia, depression, withdrawal hypertension
- Monitoring parameters
 - Blood pressure
 - Side effects

Causes for Lack of Responsiveness to Therapy

- Pseudoresistance
 - “White coat hypertension”
 - Pseudohypertension in elderly
 - Wrong cuff size
- Noncompliance
- Volume overload
 - Excess salt intake
 - Progressive renal damage
 - Fluid retention from reduction of blood pressure
 - Inadequate diuretic therapy
- Associated conditions
 - Smoking
 - Increasing obesity
 - Sleep apnea
 - Insulin resistance
 - Ethanol intake of more than 1 oz per day
 - Anxiety/panic attacks
 - Chronic pain
 - Intense vasoconstriction
 - Organic brain syndrome
- Identifiable causes of HTN

Causes for Lack of Responsiveness to Therapy (Cont'd)

Drug Related Causes

- Doses too low
- Wrong type of diuretic
- Inappropriate combinations
- Rapid activation
- Drug interactions
 - Sympathomimetics
 - Nasal decongestants
 - Appetite suppressants
 - Cocaine/illicit drugs
- Drug interactions (cont'd)
 - Caffeine
 - Oral contraceptives
 - Adrenal steroids
 - Licorice
 - Cyclosporine
 - Tacrolimus
 - Erythropoietin
 - Antidepressants
 - NSAIDs

Pharmacist Monitoring

- Patient education
 - What high blood pressure is
 - Why are they being treated
 - Risk factors and complications
 - Symptoms of high BP
 - May require treatment for life
 - Should be monitored for life
 - Name, dose, & schedule of medication(s)
 - Side effects
 - Everyone responds differently

Pharmacist Monitoring

- Compliance
 - Is patient taking meds correctly
 - Are they likely to be noncompliant
 - Get feedback on side effects that may cause noncompliance
 - Monitor for noncompliance
 - Provide mechanisms to improve compliance
