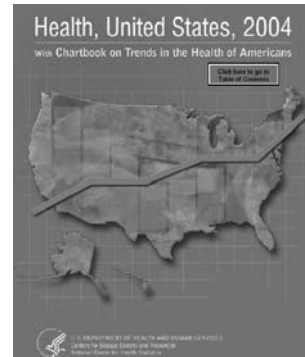


Treatment of Hypertension

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<http://www.cdc.gov/nchs/data/hus/hus04trend.pdf#067>

Hypertension

- ◆ 50 million Americans may have HTN
– YOU have a 90% lifetime risk of developing hypertension
- ◆ Hypertension is *not a disease*, it is an *asymptomatic risk factor!*
- ◆ **Major** contributor to the development of CHF

Hypertension

Table 2. Trends in awareness, treatment, and control of high blood pressure in adults ages 18–74*

	NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, PERCENT			
	II (1976–80)	III (PHASE 1) 1988–91	III (PHASE 2) 1991–94	1999–2000
Awareness	51	73	68	70
Treatment	31	55	54	59
Control†	10	29	27	34

Benefits of Treating HTN

- ◆ Significant reductions in morbidity and mortality due to cardiovascular disease (CHD, MI, CHF) and cerebrovascular disease (stroke)

HTN

- ◆ Systolic and Diastolic Pressure
- ◆ $BP = CO \times TPR$
» $CO = HR \times SV$
- ◆ Preload
- ◆ Afterload
- ◆ Venous dilation and constriction
- ◆ Arteriolar dilation and constriction

Non-Compliance with Anti-Hypertensive Therapy

- ◆Cost
- ◆Adverse Effects
- ◆Complexity of Dosing
- ◆Inadequate follow-up
- ◆Lack of understanding of disease state
- ◆PATIENT BELIEF!

Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII)

- ◆National High Blood Pressure Education Program
- ◆NIH-NHLBI
- ◆ <http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm>

JNC-VII Classification

- ◆Normal: <120/<80
- ◆Pre-hypertension: 130-139/80-89
- ◆Stage 1 (Mild): 140-159/90-99
- ◆Stage 2 (Moderate): >160/>100
- ◆Stage 3 (Severe): Eliminated

Risk Stratification

- | | |
|--|-----------------------|
| ◆Risk factors: | ◆Target organ damage: |
| » smoking, | » heart disease |
| » dyslipidemia | » stroke or TIA |
| » diabetes | » nephropathy |
| » age >60 | » retinopathy |
| » sex (males and post-menopausal females), | |
| » family hx in male < 55 or female < 65 | |

Goals of Therapy

- ◆Diagnose properly
- ◆Identify 2° causes
- ◆Identify risk factors
- ◆Identify target organ damage
- ◆Identify compelling indications
- ◆Select best agent

Goals of Therapy

- ◆General: 140/90
- ◆Diabetes or renal insufficiency: 130/80
- ◆Renal failure and proteinuria: 125/75

Other Considerations

- ◆ Young, no other CHD risk factors: 160/100
- ◆ White Coat Hypertension
- ◆ J-curve phenomenon: DBP <85 in CHD
- ◆ Isolated Systolic Hypertension
 - Diuretic or long-acting DHP CCA
- ◆ Non-pharmacologic measures (6-12 mos)
only: nl or pre w/o CI

Pharmacotherapy of Hypertension

- ◆ Thiazide Diuretics
- ◆ β -blockers
- ◆ ACE Inhibitors/A-II Antagonists
- ◆ Calcium Channel Blockers
- ◆ α blockers
- ◆ α - β Blockers
- ◆ Centrally acting agents
- ◆ Direct Vasodilators
- ◆ Combination Therapy

JNC-VII Recommendations

- ◆ “Stepped care is out”
- ◆ “Long-acting” drugs preferred
- ◆ Low-dose combinations may be appropriate
- ◆ Preferred 1st line drugs
 - Thiazide Diuretics
 - β -blockers
 - ACE-I, ARB, CCB

JNC-VII Recommendations

- ◆ Monotherapy for Stage 1 HTN
- ◆ Not good 1st line drugs:
 - Direct-acting vasodilators (hydralazine, minoxidil)
 - α_2 agonists (clonidine, guanfacine)
 - Peripherally acting adrenergic antagonists (Guanadrel, guanethidine)
 - Short-acting calcium channel antagonists

JNC-VII Recommendations

- ◆ In most cases, HTN does not need to be controlled acutely!
- ◆ If inadequate response (1-3 months)
 - Increase the dose
 - Switch to another class
 - Add another drug
 - » HCTZ is a good 2nd choice

Diuretics

- | | |
|---------------------------|-------------------|
| ◆ Thiazides: HCTZ, et al. | ◆ Loop Diuretics: |
| ◆ Chlorthalidone | – furosemide, |
| ◆ Metolazone | – bumetanide, |
| ◆ Indapamide | – torsemide |
| ◆ “Potassium Sparing” | – ethacrynic acid |
| – triamterene | |
| – amiloride | |
| – spironolactone | |

HCTZ

- ◆ My Pick
- ◆ Best for blacks, elderly, mild HTN
- ◆ Synergistic with ACE, β -blockers
- ◆ Dose: 12.5 - 50 mg (usually not > 25 mg)
- ◆ Protective against Hip Fractures
 - decreases urinary Ca^{++} excretion
 - increases BMD

Potassium Sparing Diuretics

- ◆ Potassium sparing - in combo with HCTZ
 - Do not work well alone in tx of HTN
 - Caution use with ACE-I
 - Caution use in Renal Insufficiency
 - Spironolactone
 - » hyperaldosteronism
 - » CHF, ascites
 - Hyperkalemia

Other Diuretics

- ◆ Chlorthalidone ---> Hypokalemia
- ◆ Metolazone, Indapamide - better in renal insufficiency

Loop Diuretics

- ◆ MOA:
 - Block reabsorption of Cl^- in ascending LOH
- ◆ Short acting
- ◆ Reserved for renal insufficiency
- ◆ Equivalencies exist between drugs
- ◆ Cross-sensitivity with sulfa drugs

Diuretics Adverse Effects

- | | |
|--------------------------------------|----------------------------|
| ◆ Hypokalemia/natremia | ◆ \uparrow LDL/TG |
| ◆ Hyperkalemia (K^+ -spar) | ◆ Sexual dysfunction |
| ◆ Hyperuricemia(T)(L) | ◆ Hyper(T)/hypocalcemia(L) |
| ◆ Glucose intolerance | ◆ Ototoxicity(L) |
| ◆ Postural hypotension | ◆ Hypomagnesemia |
| ◆ Phototoxicity (L) | |

Beta Blockers

- ◆ MOA:
 - \downarrow HR
 - \downarrow contractility
 - \downarrow renin output
- ◆ Patient selection:
 - whites, young, CHD, A-fib, migraine, post-MI, anxious, tachycardic
- ◆ Properties
 - Cardioslectivity
 - Intrinsic sympathomimetic activity (ISA)
 - Lipophilicity/Hydrophilicity

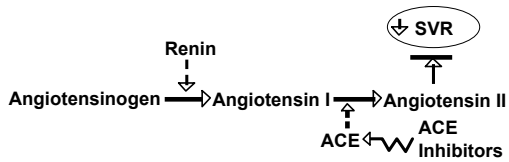
Adverse Effects

- ◆ Bradycardia
- ◆ Dizziness
- ◆ Bronchial constriction
- ◆ Fatigue
- ◆ Insomnia/bizarre dreams
- ◆ Depression
- ◆ Postural hypotension
- ◆ ↓ HDL, ↑ TG
- ◆ AV block
- ◆ Sexual dysfunction
- ◆ ↑ PVD
- ◆ Abrupt cessation

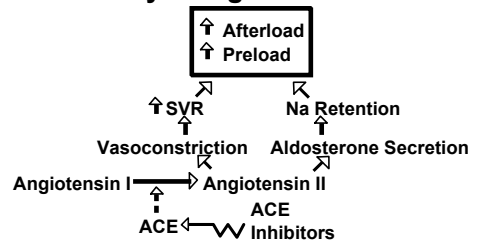
Beta Blockers

- ◆ Effect on Lipids
- ◆ Effect on sexual function
- ◆ Caution use in:
 - CHF, COPD, Asthma, IDDM
- ◆ My pick: Atenolol
 - Generic, inexpensive, hydrophilic, cardioselective, once-a-day

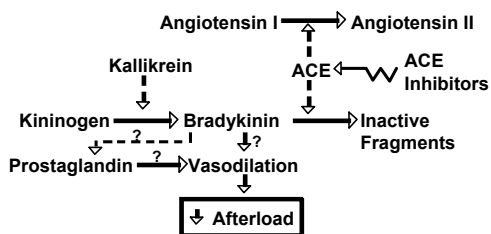
ACE Inhibitors Mechanism of Action



ACE Inhibitors Physiologic Effects



ACE Inhibitors Other Effects



ACE Inhibitors

- ◆ Response: Whites > Blacks
- ◆ DOC if concomitant DM, CHF
- ◆ Synergistic with HCTZ
- ◆ Most are once-a-day (Captopril BID-TID)

ACE Inhibitors

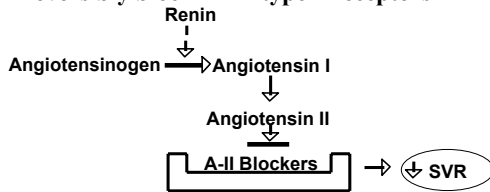
- ◆ DC diuretic prior to starting ACE (or start at very low dose and watch carefully)
- ◆ Caution use in: renal insufficiency, RAS
- ◆ Cough
- ◆ Hyperkalemia
- ◆ My pick: they're all about the same
 - Differences in pharmacokinetics
 - Effects on “tissue” ACE ?

Adverse Effects

- ◆Angioedema
- ◆Rash
- ◆Neutropenia
- ◆Metallic taste
- ◆Concurrent diuretic
- ◆Cough
- ◆Proteinuria
- ◆Hyperkalemia
- ◆Postural hypotension
- ◆Renal artery stenosis

Angiotensin II Receptor Antagonists

- ◆ Mechanism of Action: Competitively, reversibly block AT-2 type 1 receptors



Angiotensin II Antagonists

- ◆ Efficacy equal to ACE-I
- ◆ Indication: ACE-I is indicated but unable to tolerate
- ◆ ACE-I's without the cough?
- ◆ Comparably priced to ACE-I's
- ◆ A lot more on the way

Combination ACE-I and ARB

- ◆ Combination tx appears to be more effective in reducing BP and proteinuria than either drug alone
- ◆ More “complete” inhibition of A-II effects

Calcium Channel Blockers

- ◆ Verapamil (Calan, Verelan, Covera-HS)
- ◆ Diltiazem (Cardizem, Dilacor, Cartia XT)
- ◆ Dihydropyridines (the “-ipines”)
 - 1st generation - e.g., nifedipine
 - 2nd generation - e.g., amlodipine

Calcium Channel Blockers

- ◆ MOA:
 - blocks Ca channels in myocardium and vasculature → vasorelaxation → ↓ SVR
- ◆ Patient selection
 - elderly, blacks = whites, angina, PVD, migraine px
- ◆ Caution: CHF, 2° or 3° heart block
- ◆ Anti-anginal
- ◆ Differ in side effect profiles
- ◆ Diuretic additive
- ◆ NOT protective post-MI
- ◆ Increase mortality ????

Adverse Effects

- ◆ Headache
- ◆ Bradycardia (V/D)
- ◆ Dizziness
- ◆ Constipation (V)
- ◆ Postural hypotension
- ◆ GERD (DHP)
- ◆ Flushing
- ◆ Edema (DHP)
- ◆ Reflex tachycardia (DHP)
- ◆ AV conduction disturbances (V/D)

Calcium Channel Blockers

- ◆ Good in elderly, blacks = whites
- ◆ Anti-anginal
- ◆ Differ in side effect profiles
- ◆ Diuretic additive
- ◆ NOT protective post-MI
- ◆ Increase mortality ????
- ◆ My pick: Adalat CC, amlodipine

Alpha-1 Blockers

- ◆ Doxazosin (Cardura), Terazosin (Hytrin) are once-daily
- ◆ Prazosin (Minipress) - rarely used
- ◆ Lipid-lowering
- ◆ Also used for BPH
- ◆ First dose syncope (give HS)
- ◆ Caution: orthostatic hypotension
- ◆ Rather expensive
- ◆ Avoid in CHF (ALLHAT)

Alpha-1 Blockers

- | | |
|-----------------------|------------------------|
| ◆ Patient Selection | ◆ Adverse effects |
| – Good add on agents | – Syncope |
| – Lipid abnormalities | – Dizziness |
| – HTN and BPH | – Headache |
| | – Postural hypotension |
| | – Sexual dysfunction |
| | – ↑ HDL, ↓ LDL |

Central Alpha-2 Agonists

- | | |
|--------------|------------|
| ◆ Methyldopa | Clonidine |
| Guanabenz | Guanfacine |
- ◆ MOA: see classification of drug
 - ◆ 7-day patches (clonidine)
 - Rebound hypertension, may precipitate CVA, MI
 - ◆ CNS effects in elderly
 - ◆ Xerostomia a big reason for noncompliance
 - ◆ Patient selection:
 - compliance, add on therapy, cost, pregnancy

Others

- ◆ Direct Vasodilators
 - Hydralazine
 - Minoxidil
- ◆ Adverse effects
 - hypertrichosis
 - reflex tachycardia
- ◆ Adrenergic Inhibitors
 - Reserpine
 - Guanethidine
 - Guanadrel
- ◆ Adverse effects
 - postural hypotension
 - sexual dysfunction
 - depression

Alpha-Beta Blockers

- ◆ Products
 - Labetalol (Trandate, Normodyne)
 - Carvedilol (Coreg)
- ◆ Not used frequently in routine tx of HTN
- ◆ Severe, renovascular HTN?

Combinations

- ◆ Lotrel: amlodipine + benazepril
- ◆ Lexxel: felodipine + enalapril
- ◆ Teczem: diltiazem + enalapril
- ◆ Tarka: verapamil + trandolapril
- ◆ Not indicated as initial treatment
- ◆ Superior to either agent alone
- ◆ Niche yet to be defined
 - ACEI+CCA: less edema, reduces proteinuria

Special Situations

- ◆ Blacks
 - Best: diuretic, CCB
 - Avoid: ACEI, β -blockers
- ◆ Women: ? thiazide
- ◆ Pregnancy
 - Best: methyldopa, hydralazine
 - Avoid: ACEI, β -blockers (1st trim)

Special Situations

- ◆ Elderly
 - Best: diuretic, β -blocker
 - Avoid: vasodilators, central α_2 agonists, α -blockers
- ◆ CAD: β -blockers (non-ISA), CCB
- ◆ CHF
 - Best: ACE-I, vasodilators, β -blockers
 - Avoid: CCB, alpha-blockers

Special Situations

- ◆ LVH: Avoid vasodilators
- ◆ Renal dz: loops, caution with ACEI
- ◆ DM
 - Best: ACEI (+/- A-II blocker)
 - Avoid: β -blockers (if hypoglycemia is a concern)
- ◆ COPD / Asthma
 - Best: CCB (but may aggravate hypoxia)
 - Avoid: β -blockers

Drugs That Can Exacerbate HTN

- ◆ Oral contraceptives
- ◆ NSAIDs
- ◆ Caffeine, Nicotine
- ◆ Sympathomimetics
- ◆ MAO Inhibitors/Tyramine
- ◆ Licorice (glycyrrhizic acid)
- ◆ Steroids
- ◆ Cyclosporine
- ◆ Etoh
- ◆ Street drugs

HTN CRISES: Emergencies & Urgencies

- | | |
|-------------------------------|---------------------------|
| ◆ Emergencies | ◆ Urgencies |
| - Hypertensive encephalopathy | - Upper stage 3 HTN |
| - Intracranial hemorrhage | - HTN w/ optic disk edema |
| - Unstable angina | - Perioperative HTN |
| - Acute MI | |
| - Eclampsia | |

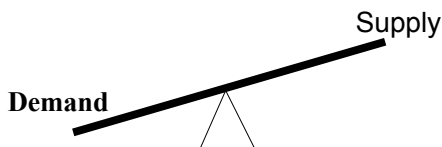
Emergencies & Urgencies

- | | |
|-------------------------|--------------------|
| ◆ Emergencies | ◆ Urgencies |
| - ↓ by 25% max | - Clonidine usage |
| - then: 160/100 | - Captopril usage |
| - Avoid excessive falls | - Goal <110 DBP |
| | - Avoid nifedipine |
- (See table 10 for agents used)

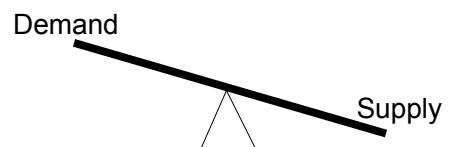
Treatment of Coronary Artery Disease

Michael A. Oszko, Pharm. D.

Myocardial Ischemia



Myocardial Ischemia Treatment Principle



Myocardial Ischemia

Demand

Heart Rate
Contractility
Blood Pressure

Supply

Arterial pO₂
Hemoglobin
Coronary Blood Flow

Coronary Artery Disease Primary Prevention

- ◆ Cessation of Cigarette Smoking
- ◆ Control of Blood Pressure
- ◆ Control of Cholesterol Levels
- ◆ Exercise
- ◆ Weight Control
- ◆ ? Hormone replacement therapy (HRT)

Coronary Artery Disease Secondary Prevention

- ◆ Hormone Replacement Therapy
 - HERS trial: no decrease in cardiac mortality
 - WHI: some evidence of *increased risk* in first two years, then no difference in cardiac mortality
- ◆ Post-menopausal women should not receive HRT for CVD prevention only

Coronary Artery Disease Treatment Options

- ◆ Nitrates
- ◆ Beta Blockers
- ◆ Calcium Channel Blockers
- ◆ ASA
- ◆ HRT (?)

Nitrates Mechanism of Action

- ◆ Reduce Cardiac Preload
- ◆ Dilate Coronary Arteries

Nitrates Chemical Entity

- ◆ Nitroglycerin
- ◆ Isosorbide Dinitrate
- ◆ Isosorbide Mononitrate

**Nitrates
Method of Administration**

- Sublingual
- Immediate Release
- Sustained Release
- Paste
- Patch
- Intravenous

**Nitrates
Key Features**

- ◆ Nitrate Free Interval (8-12 hrs)
- ◆ Cost

Sublingual Nitroglycerin

- ◆ First Line Agent
- ◆ Acute Pain/Prophylaxis
- ◆ Patient Education Is Critical
- ◆ Must Keep Fresh Supply

Nitrate Free Interval

- ◆ ISDN: 0700; 1200; 1500
- ◆ ISMN: 7 hours apart (BID)
- ◆ Paste: 0700; 1200; 1500
- ◆ Patch: 12 hr. on; 12 hr. off

**Beta Blockers
Mechanism of Action**

- ◆ Decrease Heart Rate
- ◆ Reduce Blood Pressure
- ◆ Decrease Contractility

**Beta Blockers
Differences**

- ◆ β Selectivity
- ◆ ISA
- ◆ α Blocking Activity

**Beta Blockers
Limitations**

- ◆ Adverse Effects
- ◆ Contraindications

**Beta Blockers
Withdrawal of Treatment**

- ◆ Unstable Angina – Exercise Caution
- ◆ Limit Physical Activity
- ◆ Taper Over 10-14 Days

**Calcium Channel Blockers
Distinctly Different**

- ◆ Verapamil
- ◆ Diltiazem
- ◆ Nifedipine
- ◆ Bepridil

**Calcium Channel Blockers
Concerns**

Verapamil

Diltiazem

CHF
Bradycardia
Constipation

CHF
Bradycardia

**Nifedipine, et al
Concerns**

- ◆ Flushing
- ◆ Dizziness
- ◆ Peripheral Edema
- ◆ Avoid - short-acting

**Aspirin
Should be administered to all
Patients with at least one risk
factor unless an allergy to it exists!**



Effect of Agents on Myocardial Oxygen Demand

	Heart Rate	Contractility	BP
Nitrates	↑	○	↓
β Blockers	↓↓	↓	↓
Nifedipine	↑	○	↓
Verapamil	↓	↓	↓
Diltiazem	↓	↓	↓

Coronary Artery Disease Treatment Plan

1. Initiate Aspirin
2. Sublingual NTG
3. NTG vs. CCB vs. βB
4. Maximize Single Agent
5. Combination Treatment

Anti-Oxidants

- ◆ α -tocopherol (Vitamin E)
–No evidence of benefit
- ◆ Ascorbic acid (Vitamin C)
- ◆ Beta-carotene
- ◆ Ubiquinone (Coenzyme-Q)

Coronary Artery Disease Agent Selection

- CHF ?
- PVD ?
- COAD ?
- DM ?
- Conduction Problems ?
- Age?