**Approaches to Hypertension Treatment**

- Inhibit Sympathetic impulses
  - Inhibit contractility
  - Inhibit heart rate
  - Inhibit vasoconstriction
- Inhibit smooth muscle function
- Inhibit RAAS
- Inhibit Renal retention of water

**Antihypertensive Classes**

- Diuretics – Inhibit Renal Retention
- ACE inhibitors – inhibit RAAS
- Calcium channel blockers – inhibit cardiac and/or arterial muscle constriction
- ARBs – inhibit RAAS
- Beta blockers – inhibit heart sympathetic
- Alpha-1 blockers – inhibit artery sympathetic
- Alpha-2 agonist – inhibit both sympathetic
- Direct vasodilators – self explanatory

**RAAS Inhibitors**

- Renin inhibitors (DRAs)
- Angiotensin Converting Enzyme Inhibitors
- Angiotensin Receptor Blockers
- Aldosterone inhibitors

**Renin-Angiotensin Cascade**

- **Angiotensinogen**
- **Renin**
- **Angiotensin I**
- **Angiotensin II**
- **Bradykinin**
- **ACE**
- **Inactive peptides**

**Angiotensin Receptors**

- Type I receptor (AT₁)
  - Vasoconstriction
  - Increased catecholamine release
  - Cardiac and smooth muscle cell proliferation
  - Sodium and fluid retention (through aldosterone)
- Type II receptor (AT₂)
  - Vasodilation
  - Inhibition of muscle cell proliferation
  - Apoptosis

ACE Inhibitors

- **Action**
  - Inhibits Angiotensin II production
  - Inhibits Bradykinin breakdown
- **Therapeutic Uses**
  - Hypertension
  - Post MI, MI prevention
  - Nephropathy tx and prophylaxis
  - Heart Failure

Pass the Kleenex (Trivia)

- What’s the deal with “tissue ACE”?
  - 90% of ACE is found in or close to tissue
    - Vasculature
    - CNS
    - Adrenal
    - Heart
    - Kidney
    - Lung
    - Reproductive organs
  - Lipid soluble ACE inhibitors are distributed closer to the tissues than water soluble
    - Quinapril, Ramipril, Moexipril, Benazepril

ACE inhibitor Agents

- Captopril – generic, shorter half-life, no food
- Enalapril – generic, can be given IV
- Lisinopril – generic, does not require activation
- Quinapril – generic
- Benazepril
- Ramipril
- Trandolopril
- Perindopril
- Fosinopril – does not require renal dosing
- Moexipril – no food

Adverse events

- Bradykinin excess
  - Dry persistent cough
  - Angioedema
- First dose hypotension
- Hyperkalemia (supression of aldosterone)
- Renal Failure (only with renal stenosis)
- Fetal injury

Angiotensin Receptor Blockers

- Instead of blocking Angiotensin production
- Blocks Angiotensin II type 1 (AT1) receptors
- Adverse effects
  - No cough but still may cause angioedema
  - Hyperkalemia (supression of aldosterone)
  - Renal Failure
Aldosterone Receptor Blocker

- Eplerenone (more expensive, safer, more effective spironolactone)
- Approved for hypertension only
- Adverse events
  - hyperkalemia

Calcium Channel Blockers

- Inhibition of Calcium Channels
  - Arterial SMC: vasodilation
  - SA node: slowing of heart rate (chronotropic)
  - AV node: slowing of conduction (dromotropic)
  - Myocardium: reduction of contractility (inotropic)

- Calcium channels in heart are coupled to beta-1 receptors.

Nondihydropyridines

- Verapamil and Diltiazem
  - Dilation of arterioles
  - Reduction of heart rate
  - Reduction of AV conduction
  - Reduction of contractility
- Uses
  - Angina pectoris
  - Hypertension
  - Dysrhythmias

Calcium Channel Blockers

- Dihydropyridines act only on arterial SMC
  - Amlodipine – most popular in U.S.
  - Nifedipine – first (prototype)

- Nondihydropyridines act on arterial SMC and Cardiac calcium channels
  - Verapamil
  - Diltiazem

Nondihydropyridines

- Adverse Effects
  - Cardiac
    - Bradycardia
    - Partial or complete heart block
  - Non cardiac
    - Constipation
    - Dizziness
    - Edema of ankles and feet
    - Gingival Hyperplasia
- Drug interactions: digoxin and beta blockers
Dihydropyridines

- Effect only arteries at therapeutic doses
- May be used for angina pectoris and HTN
- Adverse effects
  - Hypotension
  - Ankle edema
  - Proteinuria
  - Gingival hyperplasia

Adrenergic Blockers

- Alpha-1 receptors
  - Arteries, bladder, urethra
  - Hypertension
  - BPH
  - Raynaud’s Disease
- Adverse effects
  - Orthostatic hypotension
  - Reflex tachycardia
  - Nasal congestion
  - Impotence

Adrenergic Antagonists

- Alpha-1 blockers
  - Prazosin (minipress)
  - Terazosin (hytrin)
  - Doxazosin (cardura)
  - Tamsulosin (flomax)
- Give at night to reduce orthostatic hypotension
- Education

Beta Blockers

- Inhibition of Beta-1 receptors (heart)
  - Reduction in heart rate
  - Reduced force of contraction
  - Reduced velocity of impulse conduction
- Uses
  - Angina pectoris
  - Hypertension
  - Cardiac dysrhythmias
  - MI
  - Heart Failure
  - Performance anxiety

Beta block Adverse Effects

- Bradycardia
- Reduced CO
- Heart Failure
- AV heart block
- Rebound cardiac excitation
- Blunts effects of epinephrine (stress)
- Bronchoconstriction (beta-2 inhibition)
- Decreased glycogenolysis (beta-2 inhibition)

Beta Blocker agents

- Cardioselective vs nonselective
  - Propranolol – non selective
  - Metoprolol – cardioselective
- Fat soluble vs insoluble
  - Atenolol fat insoluble
- Precautions
  - Severe allergy
  - Diabetes
### Vasodilators

- **Arterial vasodilation**
  - Decrease afterload: reducing workload
  - May increase perfusion esp of heart
- **Venous (capacitance) vasodilation**
  - Reduces venous return
  - Reduces preload \(\rightarrow\) contractility, possibly CO
- Selectivity is important

### Therapeutic uses
- HTN
- Angina pectoris
- Heart failure
- MI
- Shock (Preserve renal perfusion)

### Adverse effects
- Postural hypotension
- Reflex tachycardia
- Expansion of blood volume – combine with diuretic
- Headache

### Vasodilator agents

- **Arterial vasodilators**
  - Hydralazine
  - Minoxidil
  - Diazoxide
- **Venous and arterial**
  - Sodium nitroprusside
  - Organic Nitrates
    - Nitroglycerine (SL, IV, Transdermal)
    - Isosorbide dinitrate (PO)

### Previously Studied Agents

- **Alpha-1 Blockers**
  - Prazosin, Terazosin, Doxazosin
- **Beta Blockers**
  - Propanolol, Metoprolol, Atenolol, Labetalol
- **Indirect Adrenergic Antagonists**
  - Clonidine, Reserpine

### Hypertension Treatment

- **Diagnosis**
  - Confirm
  - Rule out secondary causes
  - Obtain baseline
  - Assess other risk factors
- **Education**
  - Disease, Diet, exercise, weightloss, smoking
- **Drugs**

- Treating HTN reduces
  - MI by 20 – 25%
  - Stroke 35 – 40%
  - Heart Failure >50%
Hypertension treatment

- Lifestyle Treatments
  - Weight loss
  - Sodium restriction
  - DASH Diet
  - Alcohol restriction
  - Exercise
  - Stop smoking
  - Potassium/Calcium intake

Medications

- Approach has changed
- Used to max one then switch or add
- Now use combinations early in lower doses
  - Reduces side effects
  - Attacks multiple pathophysiological mechanisms
- Particularly good combinations
  - Diuretics/beta blockers
  - ACE inhibitors/diuretics
  - ARB/diuretics
  - ACE inhibitors/calcium channel blockers

Special Considerations

- Renal disease: ACE inhibitor and/or ARB
- Diabetes: ACE inhibitor and/or ARB; caution with beta blockers and diuretics
- African Americans: ACE inhibitors less effective (BUT STILL WORK)
- Elderly: isolated systolic hypertension
  - Diuretics and vasodilators work best

Education

- Compliance/Adherence
  - Dizziness
  - Urination
  - Impotence
  - No magic pill
  - Self monitoring