Cardiovascular Pharmacology

- Heart disease: leading cause of death in the U.S.
- ~ 80,000,000 people in the U.S. have some form of cardiovascular disease
  - HTN
  - Coronary disease
    - AMI
    - Angina
  - CVA
  - Heart failure
- CV disease is responsible for ~ 35.4% of all deaths (1:2.8 deaths)
Hyperlipidemia

**Cholesterol (CHO):**
- Risk of developing CHD is directly related to increased levels of blood cholesterol (LDL)
- Many *physiologic roles:*
  - Component of all cell membranes
  - Required for the synthesis of certain hormones
    - Estrogen
    - Progesterone
    - Testosterone
    - Corticosteroids
  - Required for the synthesis of bile salts (digestion and fat absorption)
  - Deposited in the stratum corneum of the skin (reduces evaporation of water and blocks transdermal absorption of water-soluble compounds)
- Total CHO = dietary (exogenous) + liver (endogenous: #1)

Lipoproteins

- Cholesterol and triglycerides
  - Carried in bloodstream by serum proteins (lipoproteins)
- 3 classes of lipoproteins are most relevant to CAD:
  - VLDL-C (*contain mostly triglycerides*)
  - LDL-C
    - *Transport cholesterol* from the liver to tissues/organs
    - Forms a platform for clot formation
    - 30% decrease in LDL-C will yield an ~ 30% decrease in CAD and stroke
  - HDL-C
    - Removes cholesterol from tissues to the liver
Pathogenesis of Plaque Rupture

Functions of the Endothelium:
- Not simply a barrier between the blood and smooth muscle as once thought
  1. Non-adhesive surface endures unimpeded blood flow
  2. In healthy people, exhibits antithrombotic and fibrinolytic properties
  3. Releases several vasoactive substances that regulate smooth muscle tone:
     - *Bradykinin* prompts the endothelium to synthesize and release nitric oxide → vasodilation

Functions of the Endothelium – continued:
- Controls cell proliferation
- Endothelial dysfunction → vasoconstriction, coagulation and cellular growth inhibition
- *Foam cells* form when LDL-C penetrates the damaged epithelial layer and becomes oxidized
- Need to focus on lipid core and stability of the fibrous cap
  - Statin drugs stabilize the cap
  - HDL-C: “The Paxil or Zoloft of foam cells!!”
Management of Hyperlipidemia

- Therapeutic Lifestyle Changes – FIRST!
  - TLC diet
    - 5-6% calories: Saturated fat
    - < 200 mg/day of cholesterol
    - Increase soluble fiber + plant stanols/sterols to enhance LDL reduction
  - Smoking cessation
  - Increase physical activity
  - Control HTN, diabetes and metabolic syndrome
  - Stress management
- 2013 Lifestyle Management Work Group Guideline

Lipid Levels

- When should cholesterol screening begin?
- Total Cholesterol
  - Desirable: < 200 mg/dL
- Triglycerides (VLDLs)
  - < 150 mg/dL
- HDL
  - > 40 mg/dL
- LDLs
  - < 100mg/dL: Optimal
  - [Consider values: < 130? < 100? < 70?]
### Goals & Cutpoints for TLC and Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>Initiate TLC</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents</td>
<td>&lt; 100 mg/dL</td>
<td>≥ 100 mg/dL</td>
<td>≥ 100 mg/dL</td>
</tr>
<tr>
<td>(10-yr risk &gt; 20%)</td>
<td>&lt; 70 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately high risk:</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td>2+ Risk Factors (10-yr risk of 10-20%)</td>
<td>&lt; 100 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate risk:</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
<tr>
<td>2+ Risk Factors (10-yr risk of &lt; 10%)</td>
<td>&lt; 160 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower risk:</td>
<td>&lt; 160 mg/dL</td>
<td>≥ 160 mg/dL</td>
<td></td>
</tr>
<tr>
<td>0-1 risk factor</td>
<td>160-189 mg/dL: LDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lowering drug optional</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Lipid Lowering Guidelines: 2013

**Four Major Statin Benefit Groups:**

1. Patients with clinical ASCVD
2. Primary elevations of LDL-C > 190 mg/dL
3. Diabetes aged 40-75 with LDL-C = 70-189 mg/dL without clinical ASCVD
4. Without clinical ASCVD or diabetes with LDL-C = 70-189 mg/dL and estimates 10-year ASCVD risk of 7.5% or higher
Lipid Lowering Guidelines: 2013

Risk Assessment In Primary Prevention:

- To estimate more closely the total burden of ASCVD, a comprehensive assessment of the estimated 10-year risk for an ASCVD event that includes both CHD and stroke

- Use the Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group to estimate the 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke) for the identification of candidates for statin therapy


Physiology Review: HMG-CoA Reductase

- **Cholesterol**: manufactured in the liver by a series of > 25 metabolic steps
- HMG-CoA reductase serves as the primary regulatory site for cholesterol biosynthesis
- Normally, this enzyme is controlled through negative feedback:
  - High levels of LDL will shut down production of HMG-CoA reductase, thus turning off the cholesterol pathway
- Statins act by inhibiting HMG-CoA reductase, which results in less cholesterol biosynthesis
- As the liver makes less cholesterol, it responds by making more LDL receptors on the surface of liver cells → enhancing removal of LDL and cholesterol
HMG-CoA Reductase Inhibitors

<table>
<thead>
<tr>
<th>Agents:</th>
<th>atorvastatin (Lipitor), fluvastatin, (Lescol), lovastatin (Pravachol), pitavastatin (Livalo), pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin (Zocor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Effects:</td>
<td>myopathy/myositis, hepatic dysfunction, N/V/D, abdominal pain, HA, insomnia, rhabdomyolysis, diabetes</td>
</tr>
<tr>
<td>Comments:</td>
<td>Many drug-drug interactions Monitor LFT’s Consider decreasing when 2 consecutive LDL-C &lt; 40 mg/dL</td>
</tr>
</tbody>
</table>

Lipid Lowering Guidelines: 2013

Secondary Prevention:

High-intensity statin therapy should be initiated/continued as first-line therapy in women and men ≤ 75 years of age who have clinical ASCVD, unless contraindicated

Moderate-intensity statin therapy should be used when high-intensity statin therapy is contraindicated/statin-associated adverse effects are present

In individuals with clinical ASCVD > 75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin
### Lipid Lowering Guidelines: 2013

#### Primary Prevention - elevations of LDL-C ≥ 190 mg/dL:
Adults ≥ 21 years of age with primary LDL-C ≥ 190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): Use high-intensity statin therapy unless contraindicated

Individuals unable to tolerate high-intensity statin therapy: use the maximum tolerated statin

Reasonable to intensify statin therapy to achieve at least a 50% LDL–C reduction

After the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C

---

#### Primary Prevention - with DM and LDL-C 70-189 mg/dL:
Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with DM

High-intensity statin therapy is reasonable for adults 40 to 75 years of age with DM with a ≥ 7.5% estimated 10-year ASCVD risk unless contraindicated

Adults with DM, who are < 40 or > 75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy
The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals with LDL-C 70 to 189 mg/dL without clinical ASCVD to guide initiation of statin therapy for the primary prevention of ASCVD.

Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥ 7.5% should be treated with moderate- to high-intensity statin therapy.

Reasonable to offer treatment with a moderate-intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk of 5% to < 7.5%.

**Lipid Lowering Guidelines: 2013**

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by &gt; 50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30 to &lt; 50%</td>
<td>Daily dose lowers LDL-C on average, by ≤ 30%</td>
</tr>
<tr>
<td>atorvastatin 40-80 mg</td>
<td>atorvastatin 10-20 mg</td>
<td>simvastatin 10 mg</td>
</tr>
<tr>
<td>rosuvastatin 20-40 mg</td>
<td>rosuvastatin 5-10 mg</td>
<td>pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>simvastatin 20-40 mg</td>
<td>lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>pravastatin 40-80 mg</td>
<td>fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>simvastatin 40 mg</td>
<td>pitavastatin 2-4 mg</td>
</tr>
<tr>
<td></td>
<td>fluvastatin 80 mg</td>
<td>pitavastatin 1 mg</td>
</tr>
</tbody>
</table>
### Bile Acid Sequestrants

<table>
<thead>
<tr>
<th>Agents</th>
<th>Cholestyramine (Questran), colesevelam (Welchol), colestipol (Colestid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Binds bile acids in gut; prevents reabsorption; increases cholesterol catabolism</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Constipation, dyspepsia, bloating, stomach cramps, abdominal distension, obstruction</td>
</tr>
<tr>
<td>Comments</td>
<td>Several drug-drug interactions Used as adjunct therapy Contraindicated when TG &gt; 300 mg/dL Malabsorption of vitamins A, D, E &amp; K</td>
</tr>
</tbody>
</table>

### Fibrates

<table>
<thead>
<tr>
<th>Agents</th>
<th>Gemfibrozil (Lopid), fenofibrate (Tricor), fenofibric acid (Trilipix)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Decrease secretion of very-low-density lipoproteins (VLDL); increases lipoprotein lipase activity</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Mild abdominal bloating, N/V/D, gallstones, altered taste, rash</td>
</tr>
<tr>
<td>Comments</td>
<td>Several drug-drug interactions Contraindicated severe hepatic/renal impairment Concurrent use with statins = increased risk of myositis, rhabdomyolysis and hepatotoxicity Monitor LFT’s</td>
</tr>
</tbody>
</table>
## Cholesterol Absorption Inhibitor

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Ezetimibe (Zetia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Decrease secretion of very-low-density lipoproteins (VLDL); increases lipoprotein lipase activity</td>
</tr>
<tr>
<td>Adverse Effects:</td>
<td>Diarrhea, abdominal pain, fatigue, arthralgia</td>
</tr>
<tr>
<td>Comments:</td>
<td>Primary role will be in combination with a statin in patients unable to achieve/sustain target LDL levels with statin alone OR in patients with contraindication/intolerance to statins. Outcome data ??</td>
</tr>
</tbody>
</table>

## Niacin

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Slo-Niacin, Niacor, Niacinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Inhibits lipolysis in adipose tissue; decreases hepatic production of VLDL; decreases serum triglycerides and LDL-C</td>
</tr>
<tr>
<td>Adverse Effects:</td>
<td>Flushing, pruritus, hyperglycemia, hyperuricemia, ulcers, HA, dizziness, nausea, hepatotoxicity</td>
</tr>
<tr>
<td>Comments:</td>
<td>Take aspirin 30 minutes before dose to reduce flushing. Monitor LFT’s. Combination therapy with statins or in patients intolerant of statins</td>
</tr>
</tbody>
</table>
Other Agents for Dyslipidemia

- B-vitamin supplementation (folate, B₆, and B₁₂)¹  
  No proven benefit
- Vitamin E²,³  
  No benefit in HOPE, GISSI trials
- Vitamin C, beta-carotene⁴  
  No proven benefit
- Macrolide antibiotic⁵  
  No benefit in ACADEMIC study
- Postmenopausal estrogen and progestin⁶  
  No benefit in HERS trial
- Vitamins C, E, selenium, and beta-carotene⁷  
  No benefit in HATS
- Fish oil (omega 3 fatty acids)  
  No formal AHA recommendation

Other Agents for Dyslipidemia References

Myocardial Infarction

- Zone of infarction
- Zone of injury
- Zone of ischemia

Clot stops flow of blood

Plaque buildup on vessel walls

Where the blockage occurs in the artery

Where the heart is affected
Myocardial Infarction: Symptoms

Symptoms:
- 1/3 patients history of alteration in typical anginal pain
- Most occur at rest
- Nitroglycerin has little effect

Myocardial Infarction

Physical Exam Findings:
- Dysrhythmias are common
- Presence of S4 very common
- Wheezing
- Pulmonary rales secondary to edema
- Low grade fever during 1st 48 hrs.
- Tachycardia
Myocardial Infarction

Lab/Diagnostics:

- ECG changes almost always
  - Peaked T waves, ST elevations, Q wave development
- Cardiac enzyme elevations
- Echocardiogram
- Leukocytosis

Myocardial Infarction

Management: What FIRST?

- IV
- O2 therapy
- 12 lead ECG and cardiac monitor
- Morphine 2-4 mg IVP
- Furosemide
- Sublingual nitrates
- ASA
- Metoprolol
- ACE inhibitors
- Thrombolytic therapy
- Angioplasty
- Heparin
Drugs for Hypertension

Hypertension

- Approximately 50 million people have HTN
- Most frequently encountered medical condition
- There is NO cure
- There are NO reliable symptoms: “Silent killer”
- Adverse effects of HTN:
  - Cardiovascular events: angina, MI, LV hypertrophy, heart failure
  - Cerebrovascular events: TIA, CVA
  - Retinopathy, papilledema
  - Nephropathy, renal failure
Hypertension

- **Sustained elevation…at least 3 times on 2 different occasions**
- **Primary/Essential**
  - 90-95%; onset usually < 55 years of age
- **Secondary**
  - 5-10%; secondary to known causes
- **Exacerbating factors**: smoking, obesity, alcohol intake, use of NSAIDS, herbal remedies

Hypertension

**Physiological regulation:**

1. **Adrenergic nervous system:**
   - Sympathetic outflow from CNS (catecholamine)
     - Stimulation: vasoconstriction & increase HR
     - Inhibition: decrease HR and vasodilation
2. **Vascular system**
   - Vasoactive substances synthesized by endothelium
     - Nitric oxide: vasodilation
     - Endothelin: vasoconstriction
Hypertension

Physiological regulation:
3. Rennin-angiotensin-aldosterone system (RAAS)
   - Renin (kidneys) → angiotensin I (angiotensin converting enzyme) → angiotensin II → aldosterone:
     - Increased peripheral resistance
     - Increased Na and H2O retention
4. Hormonal system
   - Vasopressin
   - Thyroid hormone

Hypertension: Labs/Diagnostics

- In uncomplicated disease, labs/diagnostics are usually normal
- Other tests to rule out particular causes:
  - Renovascular studies
  - CXR
  - Plasma aldosterone
  - a.m./p.m. cortisol levels
  - ECG
  - Thyroid studies
Hypertension Classifications: JNC-7

**Normal:**

< 120 and < 80

**Pre-hypertension:**

120-139 or 80-89

**Hypertension:**

- **Stage 1:** 140-159 or 90-99
- **Stage 2:** > 160 or > 100

Goal BP for Hypertension: JNC-8

- Systematic literature review restricted to RCT
- Definitions of hypertension and pre-hypertension not addressed

<table>
<thead>
<tr>
<th>Population</th>
<th>Goal BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>General &gt; 60</td>
<td>&lt; 150/90</td>
</tr>
<tr>
<td>General &lt; 60</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>&lt; 140/90</td>
</tr>
</tbody>
</table>
Hypertension: Management/ Nonpharmacologic = TLCs

◆ Weight reduction
◆ Low sodium diet
◆ Cessation of smoking
◆ Avoidance/reduction of alcohol intake
◆ Stress management
◆ Relaxation/exercise

Principles of Drug Therapy

◆ Initial therapy:
  ◆ One agent vs. two
  ◆ Individualize therapy (especially with the elderly)
    ◆ Start low and go slow
  ◆ Promote compliance
    ◆ Try to select an antihypertensive with 24 hour activity
    ◆ Consider at bedtime dosing, rather than a.m. dosing to protect against the a.m. catecholamine surge
  ◆ Select drug combinations that not only offer additive efficacy, but also decrease the toxicity of one or both drugs
Principles of Drug Therapy

- First, choose the class of drug, then choose an agent within the class
  - DO NOT assume that drugs within a class are interchangeable
- View claims of “receptor selectivity” with caution; significance may be influenced by drug dose, drug concentration, receptors and/or disease state
- Seek instances in which a single drug can positively impact more than one indication

Hypertension: Evidence-Based Treatment

- JNC 7 2003, JNC 8 2013
- AHA 2007
- ACC 2008
- European Society of Cardiology (ESC) & European Society of HTN (ESH) 2007, ESC & ESH 2013
- Canadian HTN education 2009, 2014
### Management of Hypertension: JNC-8

**Recommendation 1:**
In the **general population aged > 60 years**, initiate pharmacologic treatment to lower blood pressure at SBP ≥ 150 or DBP ≥ 90 and treat to a goal SBP < 150 and goal DBP < 90

IF pharmacologic treatment for high BP results in lower achieved SBP (< 140) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted (Expert Opinion)

**Recommendation 2:**
In the **general population < 60 years**, initiate pharmacologic treatment to lower BP at DBP ≥ 90 and treat to a goal DBP < 90

---

**Recommendation 3:**
In the **general population < 60 years**, initiate pharmacologic treatment to lower BP at SBP ≥ 140 and treat to a goal SBP < 140

**Recommendation 4:**
In the **population aged > 18 years with chronic kidney disease (CKD)**, initiate pharmacologic treatment to lower BP at SBP ≥ 140 or DBP ≥ 90 and treat to goal SBP < 140 and goal DBP < 90

**Recommendation 5:**
In the **population aged > 18 years with diabetes**, initiate pharmacologic treatment to lower BP at SBP ≥ 140 or DBP ≥ 90 and treat to goal SBP < 140 and goal DBP < 90
Management of Hypertension: JNC-8

**Recommendation 6:**
In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)

**Recommendation 7:**
In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB

**Recommendation 8:**
In the population aged > 18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes (applies to all CKD patients with HTN regardless of race or diabetes status)

Hypertension Management: Pharmacologic

- Diuretics
- ACE inhibitors
- A2 receptor antagonists
- Ca++ channel blockers
- Beta blockers
- Peripheral alpha1-blockers
- Centrally acting alpha2-agonists
- Arterial vasodilators
- Direct renin inhibitors
- Adrenergic antagonists
## Diuretics

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Thiazide diuretics: chlorothiazide (Diuril), chlorthalidone (Thalitone), hydrochlorothiazide (Microzide), indapamide (Lozol), metolazone (Zaroxolyn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Increase excretion of sodium and water</td>
</tr>
</tbody>
</table>
| Adverse Effects: | Hypokalemia, hypomagnesemia, hypo-natremia, rash, azotemia, hyperglycemia  
Rare: ototoxicity, pancreatitis, SLE |
| Comments: | First-line, drug of choice for HTN  
Reduce morbidity and mortality  
Screen for “sulfa” allergy  
May cause hypercalcemia |

## ACE-inhibitors

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Prinivil), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), trandolapril (Mavik)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Cause vasodilation and block sodium and water retention</td>
</tr>
<tr>
<td>Adverse Effects:</td>
<td>Cough, rash, taste disturbances, hyperkalemia, renal impairment, angioedema, neutropenia</td>
</tr>
</tbody>
</table>
| Comments: | Do not initiate if K > 5.5 mEq/L  
Contraindicated in pregnancy  
Generally considered first-line therapy  
Do not use in combination with ARB |
Angiotensin II - Receptor Blockers

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Azilsartan (Edarbi), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), losartan (Cozaar), olmesartan (Benicar), telmisartan (Micardis), valsartan (Diovan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Same as ACE inhibitors</td>
</tr>
<tr>
<td>Adverse Effects:</td>
<td>Cough (less than ACE inhibitor), hyperkalemia, headache, taste disturbances, renal impairment, angioedema, neutropenia</td>
</tr>
<tr>
<td>Comments:</td>
<td>Reserved for patients intolerant to ACE inhibitors. Do not initiate if K &gt; 5.5 mEq/L. Contraindicated in pregnancy. Do not use in combination with ACE inhibitor</td>
</tr>
</tbody>
</table>

Calcium Channel Blocking Agents

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Amlodipine (Norvasc), felodipine (Plendil), nicardipine (Cardene), nifedipine (Procardia, Adalat), isradipine (Dynacirc), nisoldipine (Sular), diltiazem (Cardizem), verapamil (Calan SR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Dihydropyridine: peripheral vasodilation. Diltiazem/verapamil: directly relax the heart</td>
</tr>
<tr>
<td>Adverse Effects:</td>
<td>Nifedipine - HA, flushing, peripheral edema. Diltiazem - HA, nausea, bradycardia. Verapamil - constipation, bradycardia</td>
</tr>
<tr>
<td>Comments:</td>
<td>Monitor: HR (verapamil, diltiazem). Other uses: angina, arrhythmias, migraine HA. Generally considered first-line therapy</td>
</tr>
</tbody>
</table>
# Beta-Blocking Agents

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Acebutolol (Sectral), atenolol (Tenormin), betaxolol (Kerlone), bisoprolol (Zebeta), carvedilol (Coreg), labetalol (Normodyne) metoprolol (Lopressor), nadolol (Corgard), nebivolol (Bystolic), pindolol (Visken), propranolol (Inderal), timolol (Blocadren)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Directly relaxes the heart</td>
</tr>
<tr>
<td>Adverse Effects:</td>
<td>Dizziness, bradycardia, 2nd or 3rd degree heart block, fatigue, insomnia, nausea</td>
</tr>
</tbody>
</table>
| Comments: | Many other applications: angina, arrhythmia  
Monitor: HR  
Avoid use in patients with asthma/COPD  
No longer recommended as first-line therapy |

# Peripheral Alpha\textsubscript{1}-Antagonists

<table>
<thead>
<tr>
<th>Agents:</th>
<th>Doxazosin (Cardura), prazosin (Minipress), terazosin (Hytrin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA:</td>
<td>Cause vasodilation</td>
</tr>
<tr>
<td>Adverse Effects:</td>
<td>First-dose syncope, dry mouth, orthostasis, dizziness, headache, nausea</td>
</tr>
</tbody>
</table>
| Comments: | Take first dose at bedtime  
Other applications: BPH  
Primarily adjunct therapy |
## Central Alpha$_2$-Agonists

<table>
<thead>
<tr>
<th>Agents</th>
<th>Clonidine (Catapres), methyldopa (Aldomet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Prevent vasoconstriction, cause vasodilation and slow heart rate</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Dry mouth, sedation, depression, headache, bradycardia, rebound HTN</td>
</tr>
<tr>
<td>Comments</td>
<td>Methylxymethyldopa is the drug of choice in pregnancy. Do not d/c abruptly: withdrawal, rebound HTN. Clonidine is available in a transdermal patch. Primarily adjunct therapy</td>
</tr>
</tbody>
</table>

## Arterial Vasodilators

<table>
<thead>
<tr>
<th>Agents</th>
<th>Hydralazine, (Apresoline), minoxidil (Loniten)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Directly relaxes vascular smooth muscle resulting in arterial vasodilation</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Nausea, flushing, dizziness, SLE, orthostatic hypotension, fluid retention, headache, palpitations, tachycardia</td>
</tr>
<tr>
<td>Comments</td>
<td>Reduce frequency in renal dysfunction. Causes reflex tachycardia. Available intravenously. Primarily adjunct therapy</td>
</tr>
</tbody>
</table>
## Direct Renin Inhibitors

<table>
<thead>
<tr>
<th>Agents</th>
<th>Aliskiren (Tekturna)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Inhibits renin which decreases plasma renin activity (PRA) and inhibits the conversion of angiotensinogen to angiotensin I</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Diarrhea, dizziness, headache, hyperkalemia, renal impairment, arrhythmia</td>
</tr>
<tr>
<td>Comments</td>
<td>Does not appear to offer any advantage over other currently available agents Teratogenic; avoid use in pregnancy</td>
</tr>
</tbody>
</table>

## Adrenergic Antagonists

<table>
<thead>
<tr>
<th>Agents</th>
<th>Reserpine (Resa), guanethidine (Ismelin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Depletes catecholamine stores to decrease blood pressure; depression of sympathetic nerve function</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Drowsiness, nasal stuffiness, depression, atrial fibrillation/arrhythmia</td>
</tr>
<tr>
<td>Comments</td>
<td>Reserpine reserved for third line therapy Contraindicated in renal failure: reserpine Adjust guanethidine dose in renal impairment Rarely used; numerous significant adverse effects and should be avoided</td>
</tr>
</tbody>
</table>
Isolated Systolic Hypertension

- Common with aging
  - ~ 65-75% of elderly HTN is ISH
- Arterial stiffness and PVR increases the amount of pump pressure required for circulation → increased SBP with no change or decrease in DBP
- Widening pulse pressure: good indicator
- Framingham Heart Study: systolic BP is a stronger predictor of patient outcomes
- Preferred treatment: dihydropyridine calcium channel blocker (amlodipine)

Special Patient Populations

- Uncomplicated → Diuretic, ACE inhibitor, CCB, ARB
- Asthma/COPD → Diuretic, CCB, ACE inhibitor
- Benign prostatic hypertrophy (BPH) → Alpha₁-blocker
Special Patient Populations

- **Congestive Heart Failure (CHF)**: ACE inhibitor, diuretic, beta-blocker, ARB
- **Coronary Artery Disease (CAD)**: Beta-blocker, ACE inhibitor, CCB
- **Peripheral Vascular Disease (PVD)**: Diuretic, ACE inhibitor, CCB, ARB

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Special Patient Populations

- **Post-MI**: Beta-blocker, ACE inhibitor
- **Diabetes**: ACE inhibitor, diuretic, ARB, CCB
- **Elderly**: Diuretic, ACE inhibitor, CCB, ARB
Special Patient Populations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>Diuretic, beta-blocker</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Hypertensive Urgency</td>
<td>Beta-blockers, ACE inhibitor, alpha₂-agonist</td>
</tr>
</tbody>
</table>

A Blurb on Herbs...

- **Ginseng**: Stimulates CNS resulting in increased BP
- **Ma Huang (ephrdra)**: Increases HR and BP
- **Yohimbe**: May cause CNS stimulation resulting in increased BP
- **Licorice**: High doses lead to sodium & water retention, potassium loss and increased BP
- **Hawthorne**: May dilate blood vessels
Hypertensive Crises: Emergencies and Urgencies

- Emergencies are characterized by severe elevations in BP (> 180/120 mm Hg) complicated by evidence of impending or progressive target organ dysfunction (TOD)
  - Require immediate BP reduction (not necessarily to normal) to prevent or limit target organ damage
- Urgencies are those situations associated with severe elevations in BP without progressive target organ dysfunction
  - BP reduction more gradual; lower BP within the next 24-48 hours

Hypertensive Crises: Emergencies

- Goal of therapy: reduce mean arterial BP by no more than 25% (within minutes to 1 hour), then, if stable, to < 160/100 to 110 within the next 2-6 hrs
- **AVOID** excessive falls in pressure as they may precipitate renal, cerebral or coronary ischemia
  - Short-acting nifedipine (PO/SL) NO longer considered acceptable
- Exception: ischemic stroke (keep BP elevated), aortic dissection (SBP < 100)
- Parenteral administration of an appropriate agent is necessary
## Hypertensive Crises: Emergencies

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol</td>
<td>Beta-blocking agent</td>
<td>Onset: 1-5 minutes Continuous infusion</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Peripheral vasodilator</td>
<td>Onset: 5-10 minutes Continuous infusion</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Venous/arterial vasodilator</td>
<td>Onset: 2-5 minutes Continuous infusion</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Arterial vasodilator</td>
<td>Onset: immediate Continuous infusion</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Arterial vasodilator</td>
<td>Onset: 10-30 minutes IV push</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Beta-blocker/ vasodilator</td>
<td>Onset: 5-10 minutes IV push</td>
</tr>
</tbody>
</table>

## Hypertensive Crises: Urgencies

- Treat with an oral, short-acting agent such as captopril, labetalol or clonidine followed by several hours of observation
- Oral loading doses of antihypertensive agents can lead to cumulative effects causing hypotension, sometimes following discharge from the ER/clinic
- Patients should not leave the ER/clinic without a confirmed follow-up visit within 1 to a few days
The End