Pharmacological Management of Chronic Coronary Artery Disease

Objectives

- Review the principles of myocardial oxygen supply and demand
- Review the mechanism of action, adverse effects, and clinical use of agents commonly utilized in the management of chronic coronary artery disease
- Review current guidelines regarding the pharmacological management of chronic coronary artery disease.

Katie Herndon is not speaking on behalf of Pfizer, but solely as a medical professional with an expertise in pharmacotherapy.

Epidemiology

- Coronary heart disease (CHD) is the single leading cause of death in America (one in every six deaths in 2006)
- An estimated 17.6 million American adults age 20 and older (7.9%) have CHD
- An estimated 10.2 million Americans suffer from angina, with approximately 500,000 new cases of stable angina occurring each year
- From 1996-2006, the death rate from CHD declined 36.4% and the actual number of deaths declined 21.9%
- The estimated direct and indirect 2010 cost of CHD is $177.1 billion


2006 Age-Adjusted Death Rates for CVD, CHD, and Stroke, Alabama

<table>
<thead>
<tr>
<th>Cause</th>
<th>Rank</th>
<th>Death Rate</th>
<th>% Change</th>
<th>Death Rate</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD*</td>
<td>51</td>
<td>33.9</td>
<td>-17.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rank</td>
<td>25</td>
<td>12.7</td>
<td>-30.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>51</td>
<td>15.5</td>
<td>-18.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rank includes District of Columbia and Puerto Rico


2006 Total Cardiovascular Disease Age-Adjusted Death Rates by State

Source: NCHS and AHA/B

Angina and Myocardial Ischemia

- Chronic coronary artery disease is most commonly due to obstruction of the coronary arteries by atherosclerotic plaque
- Angina pectoris is a discomfort in the chest or adjacent areas caused by myocardial ischemia
  - Retrosternal, but radiation is common
  - Often described as “viselike,” “constricting,” “crushing,” “heavy,” or “squeezing”
  - Brought on by exertion
  - Relieved by rest or nitroglycerin
- Ischemia is characterized by an imbalance between myocardial oxygen supply and demand

Regulation of Coronary Blood Flow

- The heart functions almost exclusively as an aerobic organ with little capacity for anaerobic metabolism
- Myocardial oxygen extraction is almost maximal at rest and may increase by only a slight margin upon maximal demand
- The main mechanism to bring more oxygen to the myocardium upon increased demand is to increase coronary blood flow

Coronary Blood Flow

- The normal coronary system consists of large epicardial or surface vessels that normally offer little intrinsic resistance to myocardial flow (conductance vessels)
- Conductance vessels give rise to intramyocardial arteries and arterioles (resistance vessels)
- The dense network of 4000 capillaries/mm² ensures that each myocyte is adjacent to a capillary
- Changes in myocardial oxygen requirement lead to rapid alterations in coronary vascular resistance
Factors Influencing Myocardial Oxygen Supply and Demand

- The myocardium is perfused mainly during diastole and shows a sharp decrease in perfusion during systole, which can be attributed to compression of intramyocardial vessels.
- The contracting heart obstructs its own blood supply.
- Extravascular compressive forces are greater in the subendocardium than in the subepicardial layer.

Extravascular Compressive Forces & Diastole

- Autoregulation: A mechanism by which the coronary artery can maintain a constant flow that matches the metabolic demand independently of the perfusion pressure.
- Coronary flow can increase up to five-fold between the resting state and maximal exercise (coronary flow reserve).
- Coronary flow reserve can be recruited to match coronary blood flow (supply) to energy needs (demand).

Coronary Blood Flow and Autoregulation

- Coronary stenosis obstructing at least 40% of vessel diameter results in a drop in perfusion pressure requiring a decrease in coronary resistance to maintain normal flow at rest.
- Coronary blood flow reserve has been partially recruited at rest. Exercise capacity is limited.
- When coronary stenosis occludes at least 80% of the vessel diameter, coronary reserve will be totally recruited at rest.
- Further obstruction will result in limitation of blood flow at rest.

Endothelial Control

- The endothelium plays a critical role in the maintenance of vascular homeostasis.
- In most healthy arteries, endothelium-dependent vasodilator mechanisms are predominant.
- Early atherosclerosis appears to attenuate these vasodilator mechanisms and result in the predominance of vasoconstrictor forces.
Myocardial Oxygen Demand (MVO₂)

- Ischemia most often results from increased demand in the face of a fixed oxygen supply.
- Alterations in MVO₂ are critically important for interventions intended to alleviate ischemia.
- Systolic Wall Tension: The force that the heart is required to develop and sustain during contraction.

\[ \text{Wall stress} = \text{pressure} \times \text{radius}^2 \times \text{wall thickness} \]

- MVO₂ reduced by:
  - Systolic pressure & afterload
  - Preload

- Heart Rate: Increased heart rate elevates MVO₂ by increasing the frequency of tension development per unit of time. Easy to alter pharmacologically.
- Contractility: Reflected in the rate of change of LV systolic pressure. Not a primary target for therapeutic intervention.

Goals of antianginal therapy:
- Reduce symptoms of cardiac ischemia
- Improve physical function and quality of life

Most effective agents for relieving ischemia and angina:
- Beta-adrenoreceptor blockers (β-blockers)
- Calcium antagonists
- Nitrates

Head-to-head comparative trials have not demonstrated greater antianginal efficacy among any single class of drugs.

**Pharmacotherapy to Reduce Ischemia and Relieve Symptoms**

**Beta-Blockers**

- Competitive inhibitors of the effects of neuronally released and circulating catecholamines on beta-adrenergic receptors.
- Nonselective beta-blocking drugs block both beta1 and beta2 receptors.
- Cardiodeselective beta blockers block beta1 receptors while having less effect on beta2 receptors.
- Cardiodeselectivity diminishes with increasing drug doses.

**Organ Receptor Response to Stimulus**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Receptor</th>
<th>Response to Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>SA node</td>
<td>Beta₁</td>
</tr>
<tr>
<td></td>
<td>Atria</td>
<td>Beta₂</td>
</tr>
<tr>
<td></td>
<td>AV node</td>
<td>Beta₁</td>
</tr>
<tr>
<td></td>
<td>His-Purkinje</td>
<td>Beta₁</td>
</tr>
<tr>
<td></td>
<td>Ventricles</td>
<td>Beta₁</td>
</tr>
<tr>
<td>Arteries</td>
<td>Peripheral</td>
<td>Beta₁</td>
</tr>
<tr>
<td></td>
<td>Coronary</td>
<td>Beta₁</td>
</tr>
<tr>
<td></td>
<td>Carotid</td>
<td>Beta₁</td>
</tr>
<tr>
<td>Other</td>
<td>Beta₁</td>
<td>Increased insulin release</td>
</tr>
<tr>
<td>Lungs</td>
<td>Beta₁</td>
<td>Dilation of bronchi</td>
</tr>
<tr>
<td>Uterus</td>
<td>Beta₂</td>
<td>Smooth muscle relaxation</td>
</tr>
</tbody>
</table>

**Drug Beta₁ Selectivity Alpha Blockade ISA Lipid Solubility t₁/₂ (hrs)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Beta₁ Selectivity</th>
<th>Alpha Blockade</th>
<th>ISA</th>
<th>Lipid Solubility</th>
<th>t₁/₂ (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>Low</td>
<td>3-4</td>
</tr>
<tr>
<td>Atenolol</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>6-9</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>14-24</td>
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<tr>
<td>Bisoprolol</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>9-12</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>High</td>
<td>6-10</td>
</tr>
<tr>
<td>Labetalol</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>Moderate</td>
<td>3-5</td>
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<tr>
<td>Metoprolol</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>3-4</td>
</tr>
<tr>
<td>Nadolol</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>14-24</td>
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<tr>
<td>Penbutolol</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>High</td>
<td>5</td>
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<tr>
<td>Pindolol</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>Moderate</td>
<td>3-4</td>
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<td>Propranolol</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>High</td>
<td>4-6</td>
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<tr>
<td>Timolol</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>3-4</td>
</tr>
</tbody>
</table>


**NEJM 2005;352: 2524-2533**

Beta-Blockers: Intrinsic Sympathomimetic Activity (ISA)

<table>
<thead>
<tr>
<th>Effector Organ</th>
<th>Physiologic Effect</th>
<th>Catecholamines</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO ANTAGONIST</td>
<td>full stimulation</td>
<td>Heart rate</td>
</tr>
<tr>
<td>BETA-BLOCKER WITHOUT AGONISM</td>
<td>weak stimulation</td>
<td>Decreased myocardial oxygen demand</td>
</tr>
<tr>
<td>BETA-BLOCKER WITH PARTIAL AGONISM</td>
<td>none</td>
<td>Increase in heart rate during exercise should not exceed 75% of the heart rate response associated with onset of ischemia</td>
</tr>
</tbody>
</table>

Mechanism of Action: Beta-Blockers

- Reduction in inotropic state and sinus rate
- Slowing of AV conduction
- Decreased myocardial oxygen demand, increased diastolic perfusion time
- Decrease myocardial oxygen demand

Side Effects of Beta-Blockers

- Fatigue, lethargy, inability to perform exercise
- CNS side effects: insomnia, sleep disturbance, nightmares, depression, memory disturbance, hallucinations
- Cardiac effects
  - Hypotension, sinus bradycardia, AV conduction abnormalities, left ventricular dysfunction
  - Bronchoconstriction (Beta2)
  - Peripheral vasoconstriction (Beta2)
- Altered glucose metabolism
  - Interference with insulin release (Beta2)
  - Mask the warning signs of hypoglycemia
- Gastrointestinal upset, sexual dysfunction

Calcium Antagonists

- A heterogeneous group of compounds that bind to L-type calcium channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue (SA and AV nodes)
- L-type calcium channels regulate the influx of calcium into muscle cells which stimulates smooth muscle contraction and cardiac myocyte contraction
- Noncompetitive blockade of voltage-sensitive L-type calcium channels causes:
  - Vascular smooth muscle relaxation (vasodilation)
  - Decreased myocardial force generation (negative inotropy)
  - Decreased heart rate (negative chronotropy)
  - Decreased conduction velocity within the heart (negative dromotropy)

Side Effects of Beta-Blockers

- Absolute Cardiac Contraindications
  - Severe bradycardia
  - Preexisting high degree of AV block and sick sinus syndrome
  - Severe/unstable LV dysfunction with severe heart failure symptoms
- Poor Candidates for Beta-Blocker Therapy
  - History of severe depression
  - Raynaud’s phenomenon, symptomatic peripheral vascular disease
  - Brittle diabetes
- Abrupt cessation of beta-blocking agents after prolonged administration can result in withdrawal symptoms
- Avoid use in Prazosin angina

Beta-Blockers in Angina

- Clinical Effectiveness
  - Improve the survival rate of patients with recent MI
  - Improve the survival rate and prevent stroke and CHF in patients with hypertension
- Not shown to reduce rate of coronary events or mortality specifically in patients with chronic stable angina
- Adjust the dose of β-blockers to reduce heart rate at rest to 55 to 60 bpm
- Increase in heart rate during exercise should not exceed 75% of the heart rate response associated with onset of ischemia
- Used in combination with long-acting nitrates and long-acting DHP calcium antagonists to produce greater efficacy
Mechanism of Action: Calcium Antagonists

- Alter myocardial oxygen supply:
  - Dilate epicardial coronary arteries
  - Dilate arterial resistance vessels
- Alter myocardial oxygen demand:
  - Reduce systemic vascular resistance & arterial pressure
  - Reduce contractility
  - Verapamil, Diltiazem
  - Nifedipine >> amlodipine and felodipine
- Decrease heart rate (Verapamil, Diltiazem)

Use of Calcium Antagonists

- Generally as effective as beta-blockers in relieving angina and improving exercise time in randomized trials
- Clinical effectiveness evident with both dihydropyridine and nondihydropyridine agents and various dosing regimens
- Shown to be effective in reducing the incidence of angina in patients with Prinzmetal (vasospastic) angina
- Relatively short-acting dihydropyridine calcium antagonists have the potential to enhance the risk of adverse cardiac events and should be avoided
- Long-acting DHP calcium antagonists enhance efficacy when used in combination with beta-blockers

Mechanism of Action: Nitroglycerin and Nitrates

- Organic nitrates are prodrugs and must be biodegraded to have therapeutic effects
- Biotransformation involves denitration of the nitrate through the action of mitochondrial aldehyde reductase, with subsequent liberation of nitric oxide (NO)
- Nitric oxide activates guanylyl cyclase, which leads to the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP)
- The second messenger cGMP reduces cytoplasmic calcium (Ca2+) by inhibiting inflow and stimulating mitochondrial uptake of calcium, thus mediating the relaxation of smooth muscle cells and causing vasodilation.

Calcium Antagonists

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Usual Dose</th>
<th>Duration of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting DHPs</td>
<td>Nitrendipine</td>
<td>Immediate release: 30-60 mg qd</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Slow release:</td>
<td>Long</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>Immediate release:</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Nitroprusside</td>
<td>5-10 mg/kg intravenously</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin</td>
<td>5-10 mg sublingually</td>
<td>Medium</td>
</tr>
<tr>
<td>Decreasing DHPs</td>
<td>Nifedipine</td>
<td>20-40 mg qd or tid</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>Slow release: 10-20 mg qd</td>
<td>Long</td>
</tr>
<tr>
<td></td>
<td>Isradipine</td>
<td>2.5-10 mg bid</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Amlodipine</td>
<td>5-10 mg qd</td>
<td>Long</td>
</tr>
</tbody>
</table>

Antianginal Effects: Nitroglycerin and Nitrates

- Endothelium-independent vasodilators
  - MV02:
    - Dilatation of capacitance veins reduces ventricular volume and preload
    - Dilatation of conductive arteries in combination with reduction of left ventricular volume lowers afterload
- Supply:
  - Dilate large epicardial coronary arteries, including stenotic segments
  - Dilate collateral vessels
  - Also reduces platelet adhesion and aggregation (EDRF)


Nitroglycerin and Nitrates

• Available in a variety of formulations with different routes of administration
• Improve exercise tolerance, time to onset of angina, and ST-segment depression during the treadmill exercise test
• Sublingual NTG tablets and spray are suitable for immediate relief of effort or rest angina and can also be used for prophylaxis to avoid ischemic episodes (2-5 minutes before planned exercise)
  – Replace NTG SL tablets every 3 months; Spray is stable for 3 years
• All long-acting nitrates appear to be equally effective when a sufficient nitrate-free interval is provided
• In combination with beta blockers or calcium antagonists, nitrates produce greater antianginal and anti-ischemic effects

Nitrate Tolerance

• Major limitation with long-term use of nitrates is the development of tolerance (loss of hemodynamic and antianginal effects during sustained therapy)
• Mechanism of nitrate tolerance is poorly understood
• Recent evidence supports the hypothesis that production of superoxide anion by the endothelium is central to the process (enhances NO degradation)
• Less frequent administration with an adequate nitrate-free interval (8 to 12 hours) appears to be the most effective method to prevent tolerance
  – Eccentric dosing regimens: 8 am + 2 pm; 7 am + 12 pm + 5 pm

Nitrate Side Effects

• Headache
• Hypotension
• Syncope
• Application Site Reactions
• Intermittent transdermal therapy associated with rebound angina and time-zero-effect
• The combination of nitrates and selective PDE-5 inhibitors may cause serious, prolonged, and potentially life-threatening hypotension
  – Nitrates increase production of cGMP; PDE-5 inhibitors decrease degradation of cGMP through inhibition of PDE-5
  – Avoid nitrates for at least 24 hours after sildenafil & vardenafil; 48 hours after tadalafil

Ranolazine

• A piperazine derivative indicated for the treatment of chronic angina
• Antianginal effect is achieved without clinically significant changes in heart rate or blood pressure
• Proposed mechanism of action is inhibition of the late inward sodium current (I Na) in cardiac cells
  – An increase in late I Na has been demonstrated in ischemic and failing hearts and leads to an increase in intracellular Na+
  – Intracellular Na+ triggers an increase in the influx of calcium through the reverse mode of the Na+-Ca2+ exchanger, resulting in Ca2+ overload
  – Ca2+ overload is associated with increased left ventricular diastolic tension (impaired relaxation during diastole) and electrical dysfunction
  – MVO2 increased and myocardial perfusion decreased by impaired relaxation and increased end diastolic pressure

Nitroglycerin and Nitrates

<table>
<thead>
<tr>
<th>Preparation of Agent</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal patch</td>
<td>0.06 mg/24 hr</td>
<td>24 hr continuous for 10-14 hr</td>
</tr>
<tr>
<td>Sublingual tablet</td>
<td>0.34 mg</td>
<td>As needed, up to 3 doses 3 min apart</td>
</tr>
<tr>
<td>Oral sustained release</td>
<td>2.5 mg</td>
<td>Two or three times daily</td>
</tr>
<tr>
<td>Intranasal instill</td>
<td>10 mg</td>
<td>Two or three times daily</td>
</tr>
<tr>
<td>Intranasal spray</td>
<td>50-150 mcg</td>
<td>Once or twice daily (eccentric schedule)</td>
</tr>
<tr>
<td>Intranasal instill</td>
<td>20 mcg</td>
<td>Twice daily (given 7-9 hr apart)</td>
</tr>
<tr>
<td>Intranasal sustained release</td>
<td>30-240 mcg</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

Nejm 1998;338:520-531


Pharmacotherapy 2007;27:1659-1676

Ranexa Package Insert

Drugs 2008;68:2483-2503
Ranolazine

**Consequences of ischemia**
- Electrical instability
- Myocardial dysfunction (↓ systolic function, ↑ diastolic stiffness)

**Conventional anti-ischemic medications**
- β blockers
- Nitrates
- Ca++ blockers

**Development of ischemia**
- O2 demand
  - Heart rate
  - Blood pressure
  - Preload
  - Contractility

- O2 supply
  - Conventional anti-ischemic medications
  - Ranolazine

- Compression of nutritive blood vessels

**Ischemia**
- ↑ Na+ overload
- ↓ Ca++ overload
- Diastolic relaxation failure (increased diastolic tension)
- Extravascular compression

**Late INa**
- Na+ overload

**Ranolazine**
- Inhibits the late inward Na current

**Ranolazine Pharmacokinetics**
- Extended-release formulation (do not crush, break, or chew)
- Tmax = 4-6 hours; t1/2 = 7 hours
- Bioavailability = 30-55%; Not affected by food
- Primarily metabolized by CYP 3A (70-85%) and to a lesser extent, CYP 2D6 (10-15%)
- A substrate of P-glycoprotein
- Less than 5% excreted unchanged by the kidneys
- Clearance reduced by renal insufficiency and clinically significant hepatic impairment

**Ranolazine Clinical Use**
- **Contraindications**
  - Use with strong CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin, nefazodone, neflunivir, ritonavir, indinavir, saquinavir)
  - Use with CYP3A inducers (rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, St. John’s wort)
  - Use in patients with clinically significant hepatic impairment
- Limit the dose to 500 mg twice daily in patients on moderate CYP3A inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, grapefruit juice
- Down-titrate ranolazine based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine
- Drugs transported by P-gp (e.g., digoxin) or metabolized by CYP2D6 (e.g., TCAs, antipsychotics) may need reduced doses

**Monotherapy with ranolazine increases exercise performance at trough and peak: MARISA**

**Combination regimen of ranolazine with:**
- Atenolol 50 mg qd, or
- Diltiazem 120 mg qd, or
- Amlodipine 5 mg qd

**Pharmacotherapy 2007;27:1659-1676**

Ranexa Package Insert

**Drugs 2008;68:2483-2503**
Ranolazine Clinical Use

- Most common adverse effects (>4% and more common than with placebo):
  - Dizziness, headache, constipation, nausea
- QT Interval Prolongation
  - Blocks $I_{Kr}$ and prolongs the QTc interval in a dose-related manner
  - Patients with preexisting QT prolongation, those taking agents known to prolong QT interval, and those with hepatic impairment were excluded from clinical trials
  - Expected increase in QTc is 2-5 msec
- 500 mg twice daily, increased to 1000 mg twice daily based on clinical symptoms

Recommended Drug Therapy in Patients with Angina and Other Medical Conditions

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Recommended Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Arhythmias or Conduction Disturbance</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Sympathetic Overactivity</td>
<td>Nortriptyline or amitriptyline</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Beta-blocker (verapamil)</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>Nortriptyline or amitriptyline</td>
</tr>
<tr>
<td>Rapid atrial fibrillation</td>
<td>Verapamil or beta-blocker</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Blunted Exercise Tolerance</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>Beta-blocker (calcium antagonist)</td>
</tr>
<tr>
<td>Severe pectoral discomfort</td>
<td>Beta-blocker (nitrates or diuretics)</td>
</tr>
<tr>
<td>COPD with bronchospasm or asthma</td>
<td>Nicardipine, amiodipine, verapamil, or diuretics</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Raynaud syndrome</td>
<td>Nortriptyline or amitriptyline</td>
</tr>
<tr>
<td>Claudication</td>
<td>Calcium antagonist</td>
</tr>
<tr>
<td>Severe depression</td>
<td>Calcium antagonist</td>
</tr>
</tbody>
</table>

Combination Therapy

- Anticipate the need for treatment with two or three agents in many patients
- Certain drug combinations are recommended and others should be avoided
- Recommended combination therapies:
  - Beta-Blocker + Dihydropyridine Calcium Channel Blocker
  - Beta-Blocker + Long-Acting Nitrate
- Not recommended:
  - Dihydropyridine Calcium Channel Blocker + Long-Acting Nitrate
  - Beta-Blocker + Non-Dihydropyridine Calcium Channel Blocker

ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina

- Beta-blockers as initial therapy in the absence of contraindications in patients with prior MI or without prior MI
- Calcium antagonists or long-acting nitrates as initial therapy for reduction of symptoms when beta-blockers are contraindicated
- Calcium antagonists or long-acting nitrates in combination with beta-blockers when initial treatment with beta-blockers is not successful
- Calcium antagonists and long-acting nitrates as a substitute for beta-blockers if initial treatment with beta-blockers leads to unacceptable side effects
- Long-acting calcium antagonists often preferable to long-acting nitrates because of sustained 24 hour effects

2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients with Chronic Stable Angina

- It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.