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>Rank</th>
<th>Death Rate</th>
<th>% Change 1996-2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>330.9</td>
<td>−17.2</td>
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<tr>
<td>CHD</td>
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<td></td>
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<tr>
<td>25</td>
<td>121.7</td>
<td>−32.4</td>
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<tr>
<td>Stroke</td>
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</tbody>
</table>


2006 Total Cardiovascular Disease Age-Adjusted Death Rates by State

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

**Extravascular Compressive Forces & Diastole**
- 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.

Coronary Blood Flow and Autoregulation

- 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).

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 this vasodilator mechanism 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

Pharmacotherapy to Reduce Ischemia and Relieve Symptoms

- 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

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
- Cardioselective beta blockers block beta1 receptors while having less effect on beta2 receptors
- Cardioselectivity diminishes with increasing drug doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Beta Selectivity</th>
<th>Alpha Blockade</th>
<th>ISA</th>
<th>Lipid Solubility</th>
<th>t₁/₂ (hrs)</th>
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<tbody>
<tr>
<td>Acebutolol</td>
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<td>0</td>
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<td>Low</td>
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<td>0</td>
<td>0</td>
<td>Low</td>
<td>3-4</td>
</tr>
</tbody>
</table>

Organ Receptor Response to Stimulus

| Heart       | SA node | Beta₁ | Increased heart rate |
|            | Atria   | Beta₁ | Increased contractility & conduction velocity |
|            | AV node | Beta₁ | Increased automaticity & conduction velocity |
|            | His-Purkinje | Beta₁ | Increased automaticity & conduction velocity |
|            | Ventricles | Beta₁ | Increased automaticity, contractility, conduction velocity |

| Arteries    | Peripheral | Beta₂ | Dilatation |
|            | Coronary   | Beta₂ | Dilatation |
|            | Carotid    | Beta₂ | Dilatation |

| Other       | Beta₂ | Increased insulin release and muscle glycogenolysis |
| Lungs       | Beta₂ | Dilatation of bronchi |
| Uterus      | Beta₂ | Smooth muscle relaxation |

Beta-Blockers: Intrinsic Sympathomimetic Activity (ISA)

**NO ANTAGONIST**
- Catecholamines
- Physiologic Effect
  - full stimulation

**BETA-BLOCKER WITHOUT AGONISM**
- BETA-BLOCKER WITH PARTIAL AGONISM
  - weak stimulation

**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

**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

**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)
  - 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)

**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**
- Asthma or reversible airway component in chronic lung disease patients
- 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 Prinzmetal angina

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**Clinical Antagonists**
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  - Decreased heart rate (negative chronotropy)
  - Decreased conduction velocity within the heart (negative dromotropy)
Mechanism of Action: Calcium Antagonists

- Alter myocardial oxygen supply:
  - Dilate epicardial coronary arteries
  - Dilate arterial resistance vessels
- Alter oxygen demand:
  - Reduce systemic vascular resistance & arterial pressure
  - Reduce contractility
    - Verapamil, Diltiazem
    - Nifedipine >> amiodipine 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
- 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>
</table>
| Dihydropyridines
  - Nifedipine
    - Immediate release: 30-60 mg daily orally
    - Slow release: 30-180 mg daily orally
  - Amlodipine
    - Immediate release: 10-20 mg daily orally
    - Slow release: 12.5-25 mg daily orally
  - Felodipine
    - Immediate release: 5-10 mg daily orally
    - Slow release: 5-10 mg daily orally
  - Nifedipine
    - Immediate release: 20-40 mg daily orally
    - Slow release: 20-40 mg daily orally
  - Nitrendipine
    - Immediate release: 10-20 mg daily orally
| Short       | Short      | Short              | Hypotension, dizziness, flushing, nausea, edema |
| Nitroglycerin
  - Nitroglycerin
    - Immediate release: 3-10 mg every 3-5 minutes
| Short       | Short      | Short              | Hypotension, dizziness, flushing, nausea, edema |

**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)

**Endothelium-dependent vasodilators**

- Amlodipine
  - Common adverse effects
    - Overt decompensated heart failure - although amlodipine / felodipine are generally as effective as beta-blockers in relieving angina
    - Bradycardia, sinus node dysfunction, and AV nodal block (with heart rate-modulating calcium antagonists)
- Side Effects
  - Hypotension, depression of cardiac function and worsening heart failure
  - Peripheral edema and constipation
  - Headache, flushing, dizziness and nonspecific central nervous system symptoms
  - Bradycardia, AV dissociation, AV block, and sinus node dysfunction (with heart rate-modulating calcium antagonists)

**Nitrates**

- Decrease heart rate
- Reduce systemic vascular resistance
- Decrease peripheral vascular resistance
- Decrease oxygen consumption
- Alter myocardial oxygen supply
- Alter myocardial oxygen demand

**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
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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
- Hypotension
- Dizziness
- 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
  - Narrows 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 tadalafl

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+
  - Increase in intracellular Na+ triggers an increase in the influx of calcium through the reverse mode of the Na+-Ca2+ exchanger, resulting in intracellular 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
Ranolazine

**Development of ischemia**

- **O**₂ demand
  - Heart rate
  - Blood pressure
  - Preload
  - Contractility
- **O**₂ supply

**Consequences of ischemia**

- Electrical instability
- Myocardial dysfunction
  - (systolic function/ diastolic stiffness)

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

Ranolazine

Compression of nutritive blood vessels

**Consequences of ischemia**

- Ischemia
  - Late INa
  - Na⁺ overload
- Diastolic relaxation failure
  - (increased diastolic tension)
  - Extravascular compression

**Late INa**

**Na⁺ overload**

**Diastolic relaxation failure**

*Increased diastolic tension*

**Extravascular compression**

**Development of ischemia**

- **O**₂ demand
  - O**₂** supply

**Consequences of ischemia**

- Electrical instability
- Myocardial dysfunction
  - (systolic function/ diastolic stiffness)

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

Ranolazine

Compression of nutritive blood vessels

**Ranolazine Pharmacokinetics**

- Extended-release formulation (do not crush, break, or chew)
- Tmax = 4-6 hours; t½ = 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, neflinavir, ritonavir, indinavir, saquinavir)
  - Use with CYP3A inducers (rifampin, rifabutin, phenobarbitral, 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,
- Diltiazem 120 mg qd, or
- Amlodipine 5 mg qd

**CARISA**

Change from baseline, sec

Placebo

750 mg bid

1000 mg bid

1500 mg bid

n=791

*p<0.05; **p<0.01; ***p<0.001 vs placebo.

**Ranolazine (MARISA)**

Placebo

500 mg bid

1000 mg bid

1500 mg bid

n=175

*p<0.01 vs placebo; ***p<0.001 vs placebo

Chaitman et al. JACC 2004;43:1375

Chaitman et al. JAMA 2004;291:309
**Ranolazine Clinical Use**

- Most common adverse effects (>4% and more common than with placebo):
  - Dizziness, headache, constipation, nausea
- QT Interval Prolongation
  - Blocks If 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>
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<tbody>
<tr>
<td>Cardiac Arrhythmias or Conduction Disturbance</td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td></td>
</tr>
<tr>
<td>Severe left ventricular and diastolic dysfunction</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Beta-blocker (verapamil)</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>Nitrates or antiadenine</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Widening of QRS complexes</td>
<td>Beta-blocker</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.