Pharmacological and Mechanical Management of Chronic Stable Angina

Rafat F. Padaria, M.D.
Cardiovascular Medicine, PC.
What is Angina?

- It is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back or arm.
- Typically aggravated by exertion or emotional stress
- Relieved by nitroglycerin
Definition of Angina

- First described by William Heberden (1701-1801)
- Latin “angere” means “to choke or throttle”
- Pectoris- “pectus” means “chest”
- Severe crushing chest pain with a feeling beneath the sternum of pressure and suffocation
Chest Pain - Classification

- Typical Angina
  - Substernal discomfort with a characteristic quality and duration
  - Provoked by stress/exertion
  - Relieved by rest

- Atypical Angina
  - Meets 2 of the above characteristics

- Non cardiac chest pain
  - Meets one or none of the typical angina characteristics
Grading of Angina by the CCSCS

- **Class I**
  - Ordinary activity does not cause angina- occurs with strenuous, rapid, prolonged exertion

- **Class II**
  - Slight limitation of ordinary activity
Grading of Angina by the CCSCS

- **Class III**
  - Marked limitation of ordinary physical activity

- **Class IV**
  - Inability to carry on any physical activity without discomfort
  - Angina at rest
Stable Angina

- Chest pain in a patient who has already been diagnosed with ischemic heart disease that did not change its pattern in the preceding 2 months.
Unstable Angina

- **Rest Angina**
  - Occurring at rest
  - Usually prolonged >20 min occurring within a week of presentation

- **New onset Angina**
  - Severity is at least CCSC III with onset within 2 months of initial presentation

- **Increasing Angina**
  - Previously diagnosed angina that is distinctly more frequent, longer in duration.
Treatment of Stable Angina

Two major purposes

- Increase *quantity* of life
- Improve *quality* of life
Treatment of Stable Angina

- Pharmacological Therapy
- Mechanical Therapy
Pharmacological Treatment
Pharmacotherapy to prevent MI and Death

- Antiplatelet Agents
- Antithrombotic Agents
- Lipid lowering Agents
- ACE-Inhibitors
- Beta Blockers
Antianginal & Anti-ischemic Therapy

- Beta blockers
- Nitrates
- Calcium Channel Blockers
- Ranolazine
Antiplatelet Agents

- Aspirin
- Ticlid
- Plavix
Aspirin

- Inhibits cyclooxygenase and synthesis of platelet thromboxane A2
- Stable angina trial > 3000 pts had on average a 33% reduction in risk of CV events
Ticlid

- Inhibits platelet aggregation by binding with the ADP receptors
- Reduces blood viscosity by reduction in plasma fibrinogen and increase in red cell deformability
- Not been shown to decrease adverse CV events in pts with stable angina
Plavix

- Selectively and irreversibly inhibits the binding of ADP to its platelet receptors thereby blocking ADP mediated activation of GP IIb/IIIa complex
- CAPRIE trial plavix did slightly better than Aspirin in decreasing the combined risk of MI, vascular death or ischemic stroke
Antithrombotic Therapy

- LMW heparin – daily s/c administration
  - Decrease fibrinogen level
  - Improve clinical class and exercise time to 1 mm ST depression and peak ST depression
- Low intensity oral anticoagulation with warfarin - INR 1.47
  - Decrease risk of ischemic events in pts with CAD but no angina
Lipid Lowering Agents

- HMG-CoA reductase Inhibitor-
  - Significant reduction in non fatal and fatal MI
- Other Agents include
  - Fibric acid derivatives
  - Bile acid sequestrants
  - Niacin
Angiotensin Converting Enzyme Inhibitors

- Multiple trials have shown decrease in CV morbidity and mortality
- HOPE trial – Heart Outcomes Prevention Evaluation
  - Reduced CV death, MI & stroke in pts who were high risk for or had vascular disease in the absence of heart failure
- Should be used as routine secondary prevention for pts with known CAD
1867: Nitrates

19th century
Nitrate Therapy

- Endothelin independent vasodilators - reduce myocardial oxygen demand and improve perfusion
- Antithrombotic effects and anti platelet effect in pts with stable angina
- Improve exercise tolerance
- In combination with CCB and BB produce greater antianginal and anti ischemic effects
Selected Developments in the History of Antianginal Treatment

1867: Nitrates

1962: Beta-blockers

Beta Blockers

- They simultaneously improve symptoms and prevent SCD and MI
- Decrease myocardial oxygen demand
- Very effective with nitrates
- Vasospastic Angina- worsens with beta blocker
Selected Developments in the History of Antianginal Treatment

1867: Nitrates

1962: Beta-blockers

1967: CABG

1977: PCI

1981: CCBs

Calcium Channel Blockers

- Reduce the transmembrane flux of calcium via Ca channels
- Decrease coronary vascular resistance
- Increase coronary blood flow
- Decrease SVR and arterial pressure
- Very effective in vasospastic angina
Selected Developments in the History of Antianginal Treatment

19th century
- 1867: Nitrates

20th century
- 1962: Beta-blockers
- 1967: CABG
- 1977: PCI
- 1981: CCBs

21st century
- 2006: Ranolazine

Current Hypothesis of Ischemia at the Cellular Level

- Ischemia impairs cardiomyocyte sodium channel function
- Impaired sodium channel function contributes to:
  - Pathologic increased late sodium current
  - Sodium overload
  - Sodium-induced calcium overload
- Calcium overload causes impaired diastolic relaxation, which:
  - Increases diastolic wall tension
  - Increases myocardial oxygen demand
  - Reduces myocardial blood flow and oxygen supply (microvascular hypoperfusion)
  - Worsens ischemia and angina
Ranolazine

- Ranolazine is a novel antianginal agent.
- Mechanism of action is not fully elucidated
- Thought to act by inhibiting the late sodium current

Ranexa® (ranolazine extended-release tablets) PI. February 2006.
Ranolazine

- Ranolazine has antianginal and anti-ischemic effects that do not depend upon reductions in HR or BP
  - Does not increase the rate-pressure product at maximal exercise
  - Minimal changes in mean HR (<2 bpm) and systolic BP (<3 mm Hg)
  - BP increased by approximately 10 to 15 mm Hg in patients with severe renal impairment; BP should be monitored regularly in such patients

- Complementary to standard antianginal therapy
Ranexa: Indication

- Ranexa (ranolazine extended-release tablets) is indicated for the treatment of **chronic** angina

- Because Ranexa prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other antianginal drugs

- Ranexa should be used in combination with amlodipine, beta-blockers, or nitrates

- The effect on angina rate or exercise tolerance appeared to be smaller in women than in men
Ranolazine: Adverse Effects

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Placebo n=552 (%)</th>
<th>Ranolazine n=835 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>9 (2)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (1)</td>
<td>33 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>12 (2)</td>
<td>41 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (2)</td>
<td>22 (3)</td>
</tr>
</tbody>
</table>

- The incidence of dizziness with 1000 mg b.i.d. ranolazine was 6% (vs 2% placebo), while the incidence of syncope was 0.7% (vs 0% placebo).

Doses include 500 mg b.i.d., 750 mg b.i.d., and 1000 mg b.i.d.
The 750 mg dose of ranolazine is not approved.

Ranexa® (ranolazine extended-release tablets) PI. February 2006.
Safety in Older Patients

- Of the patients with chronic angina treated with ranolazine in controlled studies, 496 (48%) were ≥ 65 years of age and 114 (11%) were ≥ 75 years of age.

- A higher incidence of placebo-subtracted adverse events (23%) was observed in patients ≥ 75 years of age on ranolazine (constipation [19%], nausea [6%], dizziness [6%]).

- A higher incidence of placebo-subtracted discontinuations (11%) due to unacceptable AEs was observed in patients ≥ 75 years of age on ranolazine.

- Dose selection for an elderly patient should be cautious.
Safety: Dose-Related Increases in QT Interval Observed

- Ranolazine prolongs the QTc interval in a dose-related manner
  - Linear relationship: 2.6 msec/1000 ng/mL
- A mean effect of 6 msec on QTc was observed at the highest recommended dose of ranolazine
  - 5% of patients experienced QTc changes of at least 15 msec
- QT changes were not related to age, weight, gender, race, heart rate, CHF class, and diabetes
- While the clinical significance of QTc prolongation in the case of ranolazine is unknown, other drugs with this potential have been associated with torsades de pointes–type arrhythmias and sudden death

<table>
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<th>Mean change in QTc, msec (SD)</th>
<th>500 mg b.i.d.</th>
<th>1000 mg b.i.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>5.4</td>
<td>(14.7)</td>
</tr>
</tbody>
</table>

Ranolazine: NSTE-ACS

- MERLIN-TIMI 36 Trial
  - Not effective in reducing major CV events
  - 13% relative reduction in risk of recurrent ischemia
  - Significant reduction in the frequency of arrhythmias detected by Holter
  - No excess of arrhythmias or SCD during a median 1 yr f/u
  - More syncope with ranolazine
Other Therapies

- Fish oil and garlic: no current evidence to suggest a clinical benefit.
- Anti oxidant therapy: may be of benefit, but the benefits are still unresolved.
- Chelation therapy: 4 randomized trials found no benefit on progression of disease or clinical outcome.
Revascularization for Chronic Stable Angina

- CABG
- PCI
Alternative Therapies

- Enhanced External Counter Pulsation
- Spinal cord stimulation
- Surgical Laser Transmyocardial Revascularization
- Exercise Training - Cardiac Rehabilitation
Spinal Cord Stimulation

- Introduced in 1987
- Placement of a stimulating electrode in the dorsal epidural space C7-T1 level
- 2 small trials
- Paucity of data on intermediate and long term benefits
EECP

- Diastolic Augmentation of blood flow
- Pressure is applied via a series of cuffs on the LE in a sequence synchronized with the cardiac cycle
- Trials have shown improvement in angina symptoms in 75-80% pts
Laser TMR

- Create a series of transmural endomyocardial channels to improve myocardial revascularization
- Surgical TMR
- Percutaneous TMR
Surgical TMR

- Use a Carbon Dioxide or YAG laser
- Mechanism for improvement of symptoms
  - Denervation of myocardium
  - Increased myocardial perfusion
  - Stimulation of angiogenesis
- No data on long term effects
Percutaneous TMR

- A special catheter is used – holmium: YAG laser
- 2 randomized trials
  - Increase in exercise tolerance
  - Freedom from angina
- Not FDA approved
Exercise Training
Cardiac Rehabilitation

- Increases exercise tolerance
- Improve sense of well being
Conclusion

- Goal of therapy is to improve Quantity and Quality of life
- A- Aspirin and anti anginal therapy
- B- beta-blocker and blood pressure
- C- cigarette smoking and cholesterol
- D- diet and diabetes
- E- education and exercise