Learning Objectives:
Through the preparation for and participation in this lecture, a successful student should be able to:

- Explain the differences between Chronic stable angina (CSA), vasospastic angina, and acute coronary syndrome (ACS)
- Identify risk factors for the development of coronary artery disease (CAD)
- Categorize patients based on presenting symptoms to an appropriate Canadian Cardiovascular Society functional angina class
- Describe the goals of treatment for the management of CSA
- Evaluate and interpret the 2002 ACC/AHA and the 2006 ESC guidelines for the management of CSA
- Recognize the key principles of the 2006 AHA/ACC secondary prevention guidelines in patients with CAD or atherosclerotic vascular disease (AVD)
- Differentiate between the anti-ischemic and cardiovascular (CV) risk reduction pharmacotherapy for the management of CSA
- Recommend appropriate therapy, education, and monitoring for patients with CSA
- Describe the evidence based rational for the use of optimal CV risk reduction pharmacotherapy versus percutaneous coronary intervention (PCI) in the management of patients with CSA

Required Reading

Suggested Readings and References:
**Introduction**

**Ischemia**
- A condition where blood flow (and thus oxygen) is restricted to a part of the body
  - Cardiac ischemia
    - Lack of blood flow and oxygen to the heart muscle

**Coronary Artery Disease (CAD)**
- Also referred to as coronary heart disease (CHD) or ischemic heart disease (IHD)
- Leading cause of death in both men and women in the United States
- CAD encompasses:
  - Chronic stable angina (CSA)
  - Vasospastic angina
  - Acute coronary syndrome (ACS)
- Significant CAD:
  - At least a 70% diameter stenosis of at least one major epicardial artery segment
  - Or ≥ 50% stenosis of left main coronary artery

**Chronic Stable Angina (CSA)**
- Over 6 million Americans have angina
- Angina pectoris
  - Chest pain caused most often by myocardial anoxia as a result of occlusion of the coronary arteries from either atherosclerosis or spasm
- Stable angina
  - Chest pain or discomfort that occurs when the heart is working harder than usual and is relieved by rest or medication
- Clinical features of CSA:
  - Reversibility of symptoms
  - Repetitiveness of anginal attacks
  - Over months to years

**Vasospastic Angina**
- Also referred to as Prinzmetal’s or variant angina
- Spasm of the coronary artery causing ischemia
  - Possibly from endothelial dysfunction
  - Paradoxical response to agents that normally cause vasodilation
- Typically at rest in the early morning

**Acute Coronary Syndrome (ACS)**
- Myocardial Infarction (MI)
- Unstable Angina
  - Prolonged angina at rest (> 20 minutes)
  - Recent angina (within 2 months) marked limitations in activity
  - Increase in severity of Angina to CCS IV based on symptoms

**Heart Disease and Stroke Statistics (2007)**
- Prevalence of CHD (NHANES 1999-2004, % US population)
  - 20 – 39 y/o: ♂ 0.6 / ♀ 0.6
  - 40 – 59 y/o: ♂ 5.5 / ♀ 7.8
  - 60 – 79 y/o: ♂ 15.4 / ♀ 22.8
  - ≥ 80 y/o: ♂ 21.6 / ♀ 32.7
- Incidence of Angina Pectoris (per 1,000 person years)
  - 45 – 54 y/o: ♂ 1.1 / ♀ 4.8
  - 55 – 64 y/o: ♂ 4.0 / ♀ 8.9
  - 65 – 74 y/o: ♂ 5.6 / ♀ 9.9
  - 75 – 84 y/o: ♂ 6.2 / ♀ 13.0
• Cardiovascular Disease Mortality (United States, 2004)
  – CHD ~ 53%
  – Stroke ~ 17%
  – Hypertension~ 6%
  – Heart Failure ~ 6%

Pathophysiology

Atherosclerosis Development

Myocardial Oxygen Balance

Oxygen Supply

Oxygen Demand

Coronary Blood flow
Oxygen Extraction
Oxygen Availability

Heart Rate
Contractility
Wall Tension

Modifiable CV Risk Factors

- INTERHEART Study (Lancet 2004;364:937-52.)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Odds Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smoker</td>
<td>2.87 (2.58 – 3.19)</td>
</tr>
<tr>
<td>Current and former Smoker</td>
<td>2.04 (1.86 – 2.25)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.37 (2.07 – 2.71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.91 (1.74 – 2.10)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>1.62 (1.45 – 1.80)</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>2.67 (2.21 – 3.22)</td>
</tr>
<tr>
<td>Vegetables and fruits daily</td>
<td>0.70 (0.62 – 0.79)</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.86 (0.76 – 0.97)</td>
</tr>
<tr>
<td>Moderate alcohol intake</td>
<td>0.91 (0.82 – 1.02)</td>
</tr>
<tr>
<td>ApoB/Apo A-1 ratio (5:1)</td>
<td>3.25 (2.81 – 3.76)</td>
</tr>
</tbody>
</table>

Classification of Angina

General
- Typical (meets all 3 criteria)
  - Substernal chest discomfort with a characteristic quality and duration
  - Provoked by external or emotional stress
  - Relieved by rest or nitroglycerin
- Atypical (probable)
  - Meets 2 of the above characteristics
- Noncardiac
  - Meets 1 or none of the typical angina characteristics

Symptomatic

Canadian Cardiovascular Society Functional Angina Classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold or in wind, or under emotional stress, or only during the few hours after awakening.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.</td>
</tr>
<tr>
<td>IV</td>
<td>Inability to carry on any physical activity without discomfort, angina symptoms may be present at rest.</td>
</tr>
</tbody>
</table>

- Seattle Angina Questionaire
  - Physical limitation
  - Angina frequency
  - Angina stability
Quality of life

Scale (0 to 100)

- Minimal (75 to 100); 2 year Survival ~ 96%
- Mild (50 to 74); 2 year Survival ~ 93%
- Moderate (25 to 49); 2 year Survival ~ 89%
- Severe (0 to 24); 2 year Survival ~ 81%

Common Cardiac Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive Result</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treadmill Exercise</td>
<td>New horizontal or down-sloping [ST- segment depression (≥ 1mm)]</td>
<td>65 – 70</td>
<td>70 – 75</td>
</tr>
<tr>
<td>Exercise Stress Echocardiography</td>
<td>One or more new wall-motion abnormalities, LVD, or both</td>
<td>80 – 85</td>
<td>80 – 85</td>
</tr>
<tr>
<td>Dobutamine Stress Echocardiography</td>
<td>Inducible left ventricular wall-motion abnormalities, worsening of existing wall motion abnormalities, or LVD</td>
<td>80 – 85</td>
<td>85 – 90</td>
</tr>
<tr>
<td>Exercise Myocardial Perfusion SPECT</td>
<td>Inducible single or multiple perfusion abnormalities: LVD</td>
<td>85 – 90</td>
<td>85 – 90</td>
</tr>
<tr>
<td>Pharmacologic Myocardial Perfusion SPECT</td>
<td>Inducible single or multiple perfusion abnormalities: LVD</td>
<td>80 – 90</td>
<td>80 – 90</td>
</tr>
<tr>
<td>Electron-beam CT</td>
<td>Score &gt; 100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SPECT = single-photon emission computed tomography; CT = computed tomography; LVD = left ventricular dilation

Differential Diagnosis

Non-Atherosclerotic Causes of Chest Pain

**Cardiac**
- Aortic dissection
- Coronary artery vasospasm
- Pericarditis
- Valvular heart disease

**Non-cardiac**
- Anemia
- Anxiety
- Carbon monoxide poisoning
- Cocaine use
- Esophageal reflux/peptic ulcer disease
- Pleuritis
- Pneumonia
- Pneumothorax
- Pulmonary embolus
- Pulmonary hypertension
- Thyrotoxicosis
**Goals of Treatment**
- Reduce the frequency and severity of symptoms
- Prevent the progression of disease
- Reduce the risk of cardiovascular event
- Avoid or minimize adverse treatments effects

**ACC/AHA 2002 Stable Angina Treatment Guidelines**

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin in the absence of contraindications</td>
<td>A</td>
</tr>
<tr>
<td>Beta-blockers as initial therapy in the absence of contraindications in patients with prior MI or without prior MI</td>
<td>A (MI)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors (ACE-I) in all patients with CAD who also have diabetes and/or LV systolic dysfunction</td>
<td>B (w/o MI)</td>
</tr>
<tr>
<td>LDL-lowering therapy in patients with documented or suspected CAD and LDL-C greater than 130mg/dL with a target LDL-C of less than 100mg/dL</td>
<td>A</td>
</tr>
<tr>
<td>Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina</td>
<td>B</td>
</tr>
<tr>
<td>Calcium channel blockers (CCB) or long-acting nitrates as initial therapy for reduction of symptoms when beta-blockers are contraindicated</td>
<td>B</td>
</tr>
<tr>
<td>CCB’s or long-acting nitrates in combination with beta-blockers when initial treatment with beta-blockers is not successful</td>
<td>B</td>
</tr>
<tr>
<td>CCB’s or long-acting nitrates as a substitute for beta-blockers if initial treatment with beta-blockers leads to side effects</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIa/IIb Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel when aspirin is absolutely contraindicated</td>
<td>B</td>
</tr>
<tr>
<td>Long-acting nondihydropyridine CCB instead of beta-blockers as initial therapy</td>
<td>B</td>
</tr>
<tr>
<td>In patients with documented or suspected CAD and LDL-C 100 to 129 mg/dL, the following options:</td>
<td>B</td>
</tr>
<tr>
<td>a. Lifestyle and/or drug therapies to lower LDL-C to less than 100 mg/dL</td>
<td></td>
</tr>
<tr>
<td>b. Weight reduction and increased physical activity in persons with the metabolic syndrome</td>
<td></td>
</tr>
<tr>
<td>c. Institution of treatment of other lipid or non-lipid risk factors; consider use of niacin or fibrate for elevated triglycerides or low HDL-C</td>
<td></td>
</tr>
<tr>
<td>ACE-I’s in patients with CAD or other vascular disease</td>
<td>B</td>
</tr>
<tr>
<td>Low-intensity anticoagulation with warfarin in addition to aspirin</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class III Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole</td>
<td>B</td>
</tr>
<tr>
<td>Chelation Therapy</td>
<td>B</td>
</tr>
</tbody>
</table>
### ESC 2006 Stable Angina Treatment Guidelines

#### Recommendations to Improve Prognosis

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 75 mg daily in all patients without contraindications</td>
<td>A</td>
</tr>
<tr>
<td>Statin therapy for all patients with coronary disease</td>
<td>A</td>
</tr>
<tr>
<td>ACE-I’s in all patients with coincident indications (hypertension, heart failure, LV dysfunction, prior MI, or diabetes)</td>
<td>A</td>
</tr>
<tr>
<td>Oral beta-blocker in patients post MI or with heart failure</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIa Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I’s in all patients with angina and proven coronary disease</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel as an alternative agent in patients with stable angina who cannot take aspirin</td>
<td>B</td>
</tr>
<tr>
<td>High-dose statin therapy in high risk (&gt; 2% annual CV mortality) patients with proven coronary disease</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIb Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrate therapy in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome</td>
<td>B</td>
</tr>
</tbody>
</table>

#### Recommendations to Improve Symptoms and Reduce Ischemia

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide short acting nitroglycerin for acute symptom relief and situational prophylaxis</td>
<td>B</td>
</tr>
<tr>
<td>Test the effects of beta-blocker, and titrate to full dose; consider the need for 24 hour protection against ischemia</td>
<td>A</td>
</tr>
<tr>
<td>If intolerant to beta-blockers or poor efficacy attempt monotherapy with a CCB (A), long acting nitrate (C), or nicorandil (C)</td>
<td>A</td>
</tr>
<tr>
<td>If beta-blocker monotherapy insufficient then add a dihydropyridine CCB</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIa Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Try sinus node inhibition if beta-blocker intolerance</td>
<td>B</td>
</tr>
<tr>
<td>If CCB monotherapy or combination (CCB and beta-blocker) is unsuccessful, substitute CCB with a long-acting nitrate or nicorandil</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIb Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic agents (e.g., ranolazine) may be used where available as add on therapy, or as substitution therapy when conventional drugs are not tolerated</td>
<td>B</td>
</tr>
</tbody>
</table>
AHA/ACC Secondary Prevention Guidelines in Patients with CAD or AVD

Class I Recommendations

<table>
<thead>
<tr>
<th>LDL-C &lt; 100 mg/dL</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LDL-C &gt; 100 mg/dL initiate LDL-lowering therapy</td>
<td>A</td>
</tr>
<tr>
<td>ACE-I’s in all patients with the following indications (HTN, HF, LV dysfunction, s/p MI, or DM) and for all other patients (B)</td>
<td>A</td>
</tr>
<tr>
<td>Beta-blockers in patients (s/p MI, HF, ACS) unless contraindicated</td>
<td>A</td>
</tr>
</tbody>
</table>

Class IIa Recommendations

| At goal of LDL-C < 100 mg/dL, reasonable to treat to LDL-C < 70 mg/dL | A |
| Baseline LDL-C (70 -100 mg/dL), reasonable to treat to LDL-C < 70 mg/dL | B |
| Beta-blockers for all patients with CAD or AVD or DM unless contraindicated | C |

CAD = coronary artery disease; AVD = atherosclerotic vascular disease; LDL-C = low-density lipoprotein cholesterol; ACE-I = angiotensin converting enzyme inhibitor; HTN = hypertension; HF= heart failure; LV = left-ventricle; s/p MI = status post myocardial infarction; DM = diabetes mellitus

Pharmacotherapy

Anti-Ischemic Pharmacotherapy

- Hemodynamic Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heart Rate</th>
<th>Systolic Pressure</th>
<th>Left Ventricular Volume</th>
<th>Myocardial Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Nitrates</td>
<td>↑</td>
<td>↓</td>
<td>↓↓</td>
<td>↔</td>
</tr>
<tr>
<td>Dihydropyridine CCB</td>
<td>↑</td>
<td>↓↓</td>
<td>↔ or ↓</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Non-dihydropyridine CCB</td>
<td>↓↓</td>
<td>↓</td>
<td>↔ or ↓</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔ or ↑</td>
</tr>
</tbody>
</table>


- Beta-blockers
  - **First line for chronic stable angina**
  - Decrease myocardial oxygen consumption by ↓ HR, ↓ BP, ↓ myocardial contractility
  - Can use cardioselective or non-selective agents (prefer cardioselective)
    - Cardioselective: Metoprolol, atenolol, bisoprolol
    - Non-cardioselective: propranolol, nadolol
  - Never use agents with intrinsic sympathomimetic activity (ISA)
  - Key points of beta-blockade therapy
    - Need enough blockade to blunt the HR response when physiologically stressed
    - Sufficient blockade results in optimal ↓ cardiac demand
    - Side effects can limit the ability to titrate the dose
    - **Low doses are better than no doses**
• Calcium-channel blockers
  – **First line for vasospastic angina**
    – Dilate coronary and systemic arteries, \(↑\) coronary blood flow, \(↓\) myocardial oxygen consumption
  – Dihydropyridine
    • Can be safely used in combination with beta-blocker therapy
    • Do not use immediate release nifedipine for CSA
    • Medications: Nifedipine, amlodipine, felodipine
  – Non-dihydropyridine
    • Avoid use in combination with beta-blocker therapy (\(↓\) HR)
    • Medications: Diltiazem, verapamil

• Nitrates
  – **First line as needed for immediate relief of angina**
  – Second to Third line for chronic maintenance therapy for stable angina
  – Dilate systemic and coronary arteries resulting in venous pooling of blood (\(↓\) cardiac work and chamber size)
  – Contraindicated with PDE-5 inhibitors (e.g., sildenafil, vardenafil, tadalafil)
  – Key points of quick acting nitroglycerin (NTG)
    • Sublingual tablets most frequently used (buccal or sublingual spray available)
    • 75% have pain relief in 3 minutes
    • 15% have relief in 5 to 15 minutes
    • Directions
      - Dissolve 1 SL tablet (0.4 mg) under tongue or in buccal pouch at the first sign of an anginal attack
      - If symptoms have not improved **after 5 minutes** emergency medical services (EMS) should be contacted
      - Continue to take additional SL tablets until EMS arrives (1 tablet every five minutes up to a total of 3 tablets)
  – Key points of chronic maintenance NTG
    • Available in immediate release, sustained release, and transdermal products
    • Nitrate Tolerance
      • Develops with chronic use
      • Mechanism is debated
      • **All patients on chronic nitrate therapy need a nitrate free period of at least 8 hours (12 hours is best)**

– Dosing Table

<table>
<thead>
<tr>
<th>Nitrate Product</th>
<th>Route</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>SL tablet</td>
<td>0.4 mg q 5 min up to 3 doses</td>
<td>Acute Therapy</td>
</tr>
<tr>
<td>Buccal</td>
<td>1-3 mg q 5 min up to 3 doses</td>
<td>Acute Therapy</td>
<td></td>
</tr>
<tr>
<td>Spray</td>
<td>1-2 sprays q 5 min up to 3 doses</td>
<td>Acute Therapy</td>
<td></td>
</tr>
<tr>
<td>Ointment</td>
<td>0.5-2 inches BID to TID</td>
<td>ACS</td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>------</td>
<td>ACS</td>
<td></td>
</tr>
<tr>
<td>Transdermal patch*†</td>
<td>0.2-0.8 mg/hr q 24 hr</td>
<td>Chronic Therapy</td>
<td></td>
</tr>
<tr>
<td>Oral SR*</td>
<td>2.5-6.5 mg BID to TID</td>
<td>Chronic Therapy</td>
<td></td>
</tr>
<tr>
<td>Isosorbide Dinitrate</td>
<td>Oral*</td>
<td>10-40 mg BID to TID</td>
<td>Chronic Therapy</td>
</tr>
<tr>
<td>Oral SR*</td>
<td>80-120 mg daily to TID</td>
<td>Chronic Therapy</td>
<td></td>
</tr>
<tr>
<td>Isosorbide Mononitrate</td>
<td>Oral*</td>
<td>20 mg BID (7-8 hrs apart)</td>
<td>Chronic Therapy</td>
</tr>
<tr>
<td>Oral SR*</td>
<td>30-240 mg daily</td>
<td>Chronic Therapy</td>
<td></td>
</tr>
</tbody>
</table>

* 10 to 12 hour nitrate free period is recommended † Remove at Bedtime
• Ranolazine
  – Inhibits the late inward sodium channel
  – Trials
    • MARISA
      • Primary Outcome
        • Increase in exercise duration time
    • CARISA
      • Primary Outcomes
        • Increase in exercise duration time
        • Delayed time to angina symptoms
        • Delayed time to ST depression
      • Secondary Outcomes
        • Reduction in angina episodes per week
        • Reduction in nitroglycerin (NTG) use per week
    • ERICA
      • Angina Episodes per week
      • NTG use per week
    • MERLIN-TIMI-36
      • No difference in Primary CV composite endpoint
      • Recurrent Ischemia
        • 16.1% placebo vs. 13.9% ranolazine (p =0.03)
      • Arrhythmia on Holter monitor
        • 83.1% placebo vs. 73.1% ranolazine (p < 0.001)
    • ROLE
      • No significant ECG changes
      • Most common ADE’s: dizziness, constipation, peripheral edema
      – Indicated in patients who have CSA and are symptomatic despite being on beta-blockers and/or calcium channel blockers and nitrates
      • Optimal patients:
        • Intolerance to beta-blockers
        • Patients with low heart rates or blood pressures
      – Avoid use with concomitant medications known to prolong QTc Intervals
      – Dosing: 500 mg po BID (Max 1000 mg po BID)

CV Risk Reduction Pharmacotherapy
• Anti-platelet Therapy
  – ACC/AHA Recommendation:
    • ASA 75 – 325 mg daily for patients with CSA
  – American College of Chest Physicians Recommendation:
    • ASA 75 – 162.5 mg daily for patients with CSA
  – Antithrombotic Trialists’ Collaboration:
    • 7 clinical trials in CSA/CAD
    • 144/1448 (9.8%) vs. 208/1472 (14.1%) of vascular events in anti-platelet treated vs placebo, respectively
  – Monotherapy vs. Dual Therapy
Individual and Composite Endpoints

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure of RR</th>
<th>Overall composite endpoint</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE</td>
<td>Odds ratio</td>
<td>0.91 (0.84 – 0.99)</td>
<td>0.82 (0.70 – 0.97)</td>
<td>0.95 (0.82 – 1.08)</td>
</tr>
<tr>
<td>CURE</td>
<td>Hazard ratio</td>
<td>0.80 (0.72 – 0.90)</td>
<td>0.77 (0.67 – 0.89)</td>
<td>0.86 (0.63 – 1.18)</td>
</tr>
<tr>
<td>MATCH</td>
<td>Odds ratio</td>
<td>0.93 (0.84 – 1.05)</td>
<td>0.95 (0.66 – 1.36)</td>
<td>0.93 (0.79 – 1.10)</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>Odds ratio</td>
<td>0.93 (0.83 – 1.05)</td>
<td>0.92 (0.74 – 1.16)</td>
<td>0.82 (0.66 – 1.04)</td>
</tr>
</tbody>
</table>

CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; MATCH = Management of Atherothrombosis with Clopidogrel in High-risk Patients; CHARISMA = Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events; RR = relative risk

- Lipid-Lowering Therapy
  - All patients with CAD should be on LDL-C lowering therapy to reduce risk of CV events
  - Statin therapy is preferred
    - Intensity should be sufficient to attain a 30-40% LDL-C reduction
    - If baseline LDL-C is < 100 mg/dL still start statin therapy unless contraindicated

NCEP ATP III Goals (2004 Update)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk‡</td>
<td>&lt; 70 mg/dL</td>
<td>≥ 70 mg/dL</td>
<td>70 – 100 mg/dL consider drug options</td>
</tr>
<tr>
<td>High Risk (CHD* or CHD risk equivalent†)</td>
<td>&lt; 100 mg/dL</td>
<td>≥ 100 mg/dL</td>
<td>≥ 100 mg/dL (consider for &lt; 100 mg/dL)</td>
</tr>
</tbody>
</table>

NCEP ATP III = National Cholesterol Education Program, Adult Treatment Panel III; CHD = Coronary heart disease; TLC = Therapeutic lifestyle changes
*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia
†CHD risk equivalent includes peripheral arterial disease, abdominal aortic aneurysm, transient ischemic attack, stroke, > 50% obstruction of coronary artery, diabetes, or 2 + risk factors with a 10 year risk of hard CHD > 20%
‡Very high risk includes established CHD plus (1) multiple major risk factors (diabetes); (2) poorly controlled risk factors (smoking); (3) metabolic syndrome; (4) acute coronary syndrome

- ACE-Inhibitors
  - Inhibition of ACE results in
    - Vasodilation
    - Diuresis
    - Anti-remodeling
  - Two recent trials looking at ACE-I use in CAD and CSA since 2002 ACC/AHA guidelines
    - EUROPA only positive and PEACE negative study
  - Limitations of study comparisons based on the patient populations included in each study
    - PEACE greater utilization of lipid-lowering therapy than in HOPE and EUROPA
    - EUROPA and PEACE greater utilization of anti-platelet and beta-blocker medications than in HOPE
  - Myocardial tissue selectivity
    - Quinapril > benazepril > ramipril > perindopril > lisinopril > trandolapril > enalapril > fosinopril > captopril
## ACE Inhibitor Trials in CSA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design/Pts(N)/ Duration</th>
<th>ACE Inhibitor TDD</th>
<th>Primary Outcome</th>
<th>Primary Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE</td>
<td>R, PC 5 yr N = 9,297</td>
<td>Ramipril 10 mg</td>
<td>CV death, nonfatal MI, stroke</td>
<td>14.0% ramipril vs. 17.8% placebo (p &lt; 0.001)</td>
</tr>
<tr>
<td>EUROPA</td>
<td>R, PC 4.2 yr N = 13,655</td>
<td>Perindopril 8 mg</td>
<td>CV death, nonfatal MI, cardiac arrest with successful resuscitation</td>
<td>8.0% perindopril vs. 9.9% placebo (p = 0.003)</td>
</tr>
<tr>
<td>PEACE</td>
<td>R, PC 4.8 yr N = 8,290</td>
<td>Trandolapril 4 mg</td>
<td>CV death, nonfatal MI, revascularization</td>
<td>21.9% trandolapril vs. 22.5% placebo (p = 0.43)</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme; CSA = chronic stable angina; Pts = patients; TDD = target daily dose; R = randomized; PC = placebo-controlled; yr = year; CV = cardiovascular; MI = myocardial infarction

## Calcium-channel Blockers
- Three major clinical trials since 2002 guidelines:
  - ACTION
  - CAMELOT
  - INVEST
- Mechanism of action that explains the benefit of CCB therapy in decreasing atherosclerotic formation is not well developed
  - Thought to be related to improvement in endothelial nitric oxide release, resulting in the avoidance of atheroma formation in the vessels
- CAMELOT only positive study
- Limitations of study comparison secondary to patient populations included in each study and differences in primary endpoints
- Current guidelines reflect the appropriate level of ranking for the use of CCB’s in CSA.

## CCB Inhibitor Trials in CSA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design/Pts(N)/ Duration</th>
<th>ACE Inhibitor TDD</th>
<th>Primary Outcome</th>
<th>Primary Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTION</td>
<td>R, PC 4.9 yr N = 7,665</td>
<td>Nifedipine GITS 60 mg</td>
<td>Death, nonfatal MI, refractory angina, new overt HF, stroke, PVD</td>
<td>4.6% Nifedipine vs. 4.75% placebo (p = 0.54)</td>
</tr>
<tr>
<td>CAMELOT</td>
<td>R, PC 2 yr N = 1,991</td>
<td>Amlodipine 5 mg Enalapril 10 mg</td>
<td>CV death, nonfatal MI, resuscitated cardiac arrest, revascularization, stroke, TIA, hospitalization for angina, new PVD</td>
<td>16.6% Amlodipine vs. 23.1% placebo (p = 0.003)</td>
</tr>
<tr>
<td>INVEST</td>
<td>R, PC 2 yr N = 22,576</td>
<td>Verapamil 240 mg/ Trandolapril 2mg vs. Atenolol 50 mg/HCTZ 25 mg</td>
<td>Death, nonfatal MI, nonfatal stroke</td>
<td>9.93% Verapamil/Trandolapril vs. 10.17% Atenolol/HCTZ (p = 0.57)</td>
</tr>
</tbody>
</table>

CCB = calcium channel blocker; CSA = chronic stable angina; Pts = patients; TDD = target daily dose; R = randomized; PC = placebo-controlled; yr = year; GITS = gastrointestinal therapeutic system; CV = cardiovascular; MI = myocardial infarction; HF = heart failure; PVD = peripheral vascular disease; HCTZ = hydrochlorothiazide
• Other Therapies
  – Antioxidants
    • Oxidation of LDL-C is thought to play a role in the atherosclerotic process
    • Vitamin C and E protect LDL-C from oxidation
    • Multiple large randomized trials have shown no benefit with Vitamin E or other antioxidants in reducing CV events
  – Folic Acid
    • Elevated homocysteine concentrations have been associated with increased risk of CV disease
    • Folic acid is capable of lowering homocysteine levels
    • Mixed studies on benefit of supplementation with folic acid, B-12, and B-6 in reducing CV events

Optimal CV Risk Reduction Therapy vs. Percutaneous Coronary Intervention
• ACC/AHA/SCAI 2005 Percutaneous Coronary Intervention (PCI) guidelines
  – Recommend optimal medical therapy (intensive medical therapy, risk factor reduction, and lifestyle intervention) prior to utilization of PCI in stable CSA.
  – Patients with asymptomatic ischemia or CCS Class I or II angina
    • Class IIa: PCI is reasonable if patient has
      • 1 or more significant lesions in 1 or 2 coronary arteries suitable for PCI with viable myocardium and moderate to severe ischemia with noninvasive testing (level B)
      • Recurrent stenosis after PCI (level C)
      • Left main CAD (>50% stenosis), but not candidate for CABG (level B).
    • Class IIb: PCI in patients with 2-3 vessel disease
      • Proximal LAD CAD eligible for CABG with 1 arterial conduit and treated DM or LV dysfunction is not well established (level B)
      • Non-proximal LAD CAD with viable myocardium and ischemia on noninvasive testing (level C).
    • Class III: PCI is not recommended in patients who do not meet previous criteria or have 1 of the following
      • Small area of viable myocardium at risk (level C)
      • No objective ischemia (level C)
      • Lesions with a low likelihood of success (level C)
      • Mild symptoms not related to myocardial ischemia (level C)
      • Factors with increased risk of morbidity/mortality (level C)
      • Left main disease and eligible for CABG (level C)
      • Coronary stenosis < 50% (level C)
  – Patients with asymptomatic ischemia or CCS Class III
    • Class IIa: PCI is reasonable in single vessel or multi-vessel CAD who are undergoing medical therapy and who have
      • 1 or more significant lesions in 1 or more coronary arteries suitable for PCI with high success low morbidity/mortality (level B)
      • Focal saphenous vein graft lesions or multiple stenosis who are poor candidates for reoperative sugery (level C)
      • Significant CAD (>50%) who are candidates for revascularization but not CABG (level B).
    • Class IIb: PCI is reasonable in single vessel or multivessal CAD who are undergoing medical therapy and who have
      • 1 or more lesions to be dilated with a reduced likelihood of success (level B)
      • 2 or 3 vessel CAD with proximal LAD CAD and treated DM or LVD (level B)
• Class III: PCI is not recommended in patients who have no evidence of myocardial injury or ischemia, no trial of medical therapy, or who have 1 of the following
  • Small area of viable myocardium at risk (level C)
  • All lesions or the culprit lesion have morphology that conveys a low likelihood of success (level C)
  • High risk of procedure related morbidity or mortality (level C)
  • Left main disease and eligible for CABG (level C)
  • Coronary stenosis < 50% (level C)

• COURAGE
  – Treatment Arms:
    • PCI (+/- stent) + Optimal Medical Therapy (OMT)
    • OMT alone
  – Eligible patients:
    • Stable CAD
      • CCS I-III Angina
      • Stable post MI
      • Asymptomatic with objective myocardial ischemic findings
  – Primary Endpoint (Composite):
    • Composite
      • Nonfatal MI
      • All-cause mortality
    • 19.0% in the PCI group vs 18.5% in the OMT group (p = 0.34)
  – Median follow-up: 4.6 years
  – Optimal Medical Therapy
    • Antiplatelet therapy
      • ASA 81 – 325 mg/day or Clopidogrel 75 mg/day
    • Angina medications (Alone or in combination)
      • Metoprolol succinate
      • Amlodipine
      • Isosorbide mononitrate
    • Angiotensin blocking therapy
      • Lisinopril or Losartan
    • Lipid lowering therapy
      • Simvastatin +/- ezetimibe
      • Goal LDL-C level of 60 to 85 mg/dL
      • Following LDL-C goal achievement went to secondary goal of raising HDL-C (Exercise, niacin ER, and fibrate alone or combination)
  – Management of stable CAD patients with optimal CV risk reduction pharmacotherapy is appropriate and not worse than PCI (+/- stent)

Pharmaceutical Care for CSA
• ACC/AHA Initial Treatment 10-point plan:
  A = Aspirin and Antianginal therapy
  B = Beta-blocker and Blood pressure
  C = Cigarette smoking and Cholesterol
  D = Diet and Diabetes
  E = Education and Exercise
• Drug therapy monitoring to gage effectiveness of therapy
  – Vital Signs
  – Use of sublingual nitroglycerin
  – Adverse effects
  – Electrocardiogram if needed
  – Exercise tolerance testing has limited value
AS is a 64-year old male who was recently found to have two-vessel CAD with lesions of 50% and 65%. His past medical history is significant for hypertension and dyslipidemia. AS has been experiencing chest pain about 3 times a week when he does yard work and has to lift heavy objects.

Meds:  
- HCTZ 25mg po daily  
- Atorvastatin (Lipitor®) 10mg po daily  
- Aspirin 81mg po daily  

Exercise:  
None

FHx:  
- Father died of CHD at age 57  
- Mother died of MI at age 62

SHx:  
- 30 pack year history, no alcohol use

PE:  
- normal  
- wt = 180#  
- ht = 70”

VS:  
- BP = 144/92, 146/90 mm Hg  
- HR = 82

Fasting  
- 136 | 102 | 22 / 110  
Labs:  
- 4.0 | 29 | 1.0\  
- FLP:  
- TC = 160 mg/dL  
- HDL = 40 mg/dL  
- LDL = 95 mg/dL  
- TG = 230 mg/dL

1. What modifiable cardiovascular risk factors does AS have?

2. What is the most appropriate agent(s) to start in AS to treat his new diagnosis of Chronic Stable Angina?

3. Three weeks following initiation of propranolol (Inderal LA®) 80 mg po daily. AS presented to the clinic today with complaints of being short of breath on a daily basis. What in AS’s history would make you think it is related to the new initiation of a beta-blocker?

What would you change AS to for control of his Chronic Stable Angina?
HG is a 49-year-old female, has just undergone cardiac catheterization, which showed two-vessel CAD. She refuses to take nitrates because they cause severe headaches. Her medical history is significant for type 2 diabetes, hypertension, and dyslipidemia. She has been on a beta-blocker for her hypertension, but still is having angina symptoms at least 2 times weekly.

Meds:
- Metoprolol succinate (Toprol XL®) 50mg po daily
- HCTZ 25mg po daily
- Simvastatin (Zocor®) 40mg po qhs
- Metformin (Glucophage®) 1000mg po bid
- Nitroglycerin 0.4mg sl prn for chest pain

Exercise: Walks for 30 minutes 2x/week

FHx: Father died of old age at 82
Mother is still living at age 78

SHx: No tobacco or alcohol use

PE:
- Normal wt = 160#
- ht = 65”

VS:
- BP = 130/78, 132/82 mm Hg
- HR = 58

Fasting:
- 140 | 99 | 18 / 108
- A1C = 7.2%
- FLP:
- TC = 205 mg/dL
- HDL = 38 mg/dL
- LDL = 115 mg/dL
- TG = 210 mg/dL

1. What is the next appropriate medication to add to HG’s regimen to manage her symptoms of chronic stable angina?

2. What is an appropriate medication to add to HG’s regimen to prevent an MI or death?

3. Is HG appropriate for antiplatelet therapy? If so, what indicates HG for an antiplatelet agent?