Modern Management of Patients with Stable Coronary Artery Disease

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Scope of the Problem

- Prevalence of CAD: 17.6 million adults in US
  - 10.2 million have stable angina
- Incidence: 500,000 new cases of angina/year
- Angina is initial manifestation of ischemic heart disease in 50% of patients
- Incidence is expected to increase by 50% over the next 30 years
- Ischemic heart disease responsible for 1 out of every 4.8 deaths in US

Case

- 59 year old man h/o HTN presents with:
  - Having chest pain when climbing 2 flights of stairs or walking uphill
  - Symptoms disappear with rest
  - No family history of CAD
  - Medications include aspirin and HCTZ
- EKG (at rest): normal sinus rhythm, no ischemic changes
- Labs: Total cholesterol 187, LDL 132, HDL 44; other labs normal

Case

- Exercise stress echo:
  - completed 10 min on Bruce protocol
  - achieved 85% MPHR
  - test stopped by symptoms
  - 1 mm ST depression in the inferior leads
  - Echo: Small area of hypokinesis in the distal inferior wall
- What is your recommendation?
**Potential courses of action**

- Reassurance
- Risk factor modification (BP, lipids, smoking cessation) and counseling as appropriate
- Anti-anginal medications (nitrates, β-blockers)
- Pharmacological stress test with imaging
- Diagnostic cardiac catheterization only
- Diagnostic cardiac catheterization with possible PCI of any lesion(s) found
- Referral for CABG surgery

**Approach to Management of Stable CAD**

- Assess probability of CAD
- Risk stratification
- Treatment
  - Medical therapy
  - PCI
  - CABG

**Estimating the Probability of CAD: the Diamond and Forrester approach**

- Probability based on clinical observations
- Pain type, age, and gender were powerful predictors of the likelihood of CAD
  - e.g., a 64-year-old man with typical angina has a 94% likelihood of having significant CAD
  - e.g., a 32-year-old woman with nonanginal chest pain has a 1% chance of CAD

**Pretest Likelihood of CAD in Symptomatic Patients According to Age and Sex**

<table>
<thead>
<tr>
<th>Age</th>
<th>Nonanginal chest pain</th>
<th>Atypical chest pain</th>
<th>Typical angina</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>40-49</td>
<td>13</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>50-59</td>
<td>20</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>60-69</td>
<td>27</td>
<td>14</td>
<td>72</td>
</tr>
</tbody>
</table>
Duke Clinical Score

- Model from Duke also found age, gender and pain type were the most powerful predictors
- Added other significant predictors:
  - Smoking (≥ ½ ppd within last 5 years or at least 25 pack-years)
  - Q wave or ST-T-wave changes on EKG
  - hyperlipidemia (total cholesterol >250 mg/dL)
  - diabetes (glucose >140)
- Of these risk factors, diabetes had greatest influence on increasing risk

Pryor DB, Ann Intern Med 1993

Risk Stratification for Death or MI

- Goal: To identify high risk patients in whom coronary angiography and subsequent revascularization might improve survival
- Whenever possible, treadmill or bicycle exercise stress test should be used
  - Provides the most information concerning patient symptoms, cardiovascular function and hemodynamic response during usual forms of activity
  - Maximum exercise capacity strong predictor of death

Duke Treadmill Score

- Duke treadmill score
  = exercise time - (5 x ST deviation) - (4 x angina*)
  *angina score: 0=none, 1=nonlimiting, and 2=exercise-limiting.
- Classifies patients into low, intermediate, and high risk groups
- Accurate for predicting significant and severe CAD

**Risk of Significant CAD Based on Duke Treadmill Score**

<table>
<thead>
<tr>
<th>Risk category (score)</th>
<th>No stenosis ≥ 75%</th>
<th>1-vessel disease</th>
<th>2-vessel disease</th>
<th>3-vessel or LM disease</th>
<th>Annual mortality</th>
<th>5-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (≥ +5)</td>
<td>59.9%</td>
<td>16.4%</td>
<td>14.2%</td>
<td>9.5%</td>
<td>0.25%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Moderate risk (-10 to +4)</td>
<td>32.7%</td>
<td>12.3%</td>
<td>24.5%</td>
<td>30.6%</td>
<td>1.25%</td>
<td>9.5%</td>
</tr>
<tr>
<td>High risk (&lt; -10)</td>
<td>0.4%</td>
<td>5.9%</td>
<td>20.2%</td>
<td>73.5%</td>
<td>5%</td>
<td>35%</td>
</tr>
</tbody>
</table>


**Risk Stratification: High Risk Stress Tests**

- Severe resting or exercise-induced LV dysfunction (LVEF < 35%)
- High-risk treadmill score (score < -10)
- Stress-induced large perfusion defect (particularly if anterior) or multiple perfusion defects of moderate size
- Moderate or large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
- Echocardiographic wall motion abnormality (involving > 2 segments) developing at low dose of dobutamine (≤ 10 mg/kg/min) or at low heart rate (< 120 beats/min)
- Stress echocardiographic evidence of extensive ischemia

**Use of Exercise Test Results in Patient Management**

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Predicted average annual mortality</th>
<th>Recommended initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤1% per year</td>
<td>Medical therapy</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1% to 3%</td>
<td>Cardiac catheterization</td>
</tr>
<tr>
<td>High</td>
<td>≥3% per year</td>
<td>Imaging study</td>
</tr>
</tbody>
</table>

<5% pt with low-risk treadmill score will be identified as high risk after imaging
Those with known LV dysfunction should have cardiac catheterization

**Treatment for Stable CAD**
Goals of Treatment

- Decrease risk of future MI and death
- Elimination of anginal chest pain
- Return to normal activities
- Good patient compliance - minimal side effects of therapy, cost-effective
- Goal must be modified in light of the clinical characteristics and preferences of each patient

Components of Optimal Medical Therapy

- Cigarette smoking cessation
- Blood pressure control
- Lipid management to goal
- Physical activity
- Weight management to goal
- Diabetes management to goal
- Antiplatelet agents
- Renin angiotensin aldosterone system blockers
- Beta blockers

Antiplatelet therapy

- Aspirin 75-325 mg/day
  - Decreases risk of cardiovascular event by 33%
  - Recommended for all patients without contraindications

- Clopidogrel 75 mg
  - In patients with previous MI, stroke and peripheral vascular disease, clopidogrel may be more effective than aspirin in decreasing the combined risk of MI, vascular death or ischemic stroke (CAPRIE Trial)
  - Recommended for patients who are intolerant of aspirin

β-blockers

- Mainstay of anti-anginal therapy
- Improves survival in post-MI patients and patients with HTN
- Titrate β-blocker to goal resting HR 55-60 bpm
- For patients intolerant of β-blockers, consider calcium channel blockers
  - Dilate epicardial arteries, decrease myocardial oxygen demand
  - Nondihydropyridines can slow HR
  - Long-acting dihydropyridines decrease cardiac contractility

**β-blocker Evidence**

Summary of Secondary Prevention Trials of β-blocker Therapy

<table>
<thead>
<tr>
<th>Phase of Treatment</th>
<th>Total # Patients</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Treatment</td>
<td>28,970</td>
<td>0.87 (0.77–0.98)</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>24,298</td>
<td>0.77 (0.70–0.84)</td>
</tr>
<tr>
<td>Overall</td>
<td>53,268</td>
<td>0.81 (0.75–0.87)</td>
</tr>
</tbody>
</table>

RR=Relative risk, CI=Confidence interval


**Intensive Lipid Lowering Therapy**

**Recommended LDL-C treatment goals**

- ATP III Update 2004:
  - <100 mg/dL: Patients with CVD or CVD risk equivalents (10 year risk >20%)
  - <100 mg/dL: Therapeutic option for high risk patients

- AHA/ACC guidelines for patients with CAD:
  - <100 mg/dL: Goal for all patients with CVD
  - <70 mg/dL: A reasonable goal for all patients with CVD


**HMG-CoA Reductase Inhibitor Therapy**

**Relationship between LDL-C Levels and Event Rates in Secondary Prevention Trials of Patients with Stable CHD**

- Statin
- Placebo


**ACE-I in Stable CAD: HOPE trial**

- Statin Placebo
- Ramipril


22% Reduction in Events P=.0001*

15% Reduction in Events at 1 year
**HOPE Trial: Benefits of ACE-I**

- **Effects Beyond Baseline Therapy**
  - Aspirin
  - Beta-blockers
  - Lipid-lowering agents
  - Diuretics
  - Other Antiplatelets
  - Calcium Channel Blockers

- **Results**
  - Stroke: 32%*
  - CV Death: 26%*
  - Nonfatal MI: 20%*
  - All Cause Mortality: 16%**

*P = 0.0001
**P = 0.005

NEJM 2000; 342:145-153

**ACE-I/ARB in Stable CAD**

- ACE-I decrease MI, CV death, and stroke in patients with vascular disease
- ACE-I are recommended in all patients with LVEF ≤ 40%, and CAD patients with diabetes or CKD
- Use ARBs in patients with heart failure or post-MI with LVEF ≤ 40% who are intolerant of ACE-I
- Consider ACE-I or ARB for all other patients

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**Other anti-anginal therapy**

- **Nitrates**
  - Improve exercise tolerance, time to onset of angina
  - No mortality benefit
  - Greater effect in combination with β-blocker or CCB
- **Calcium channel blockers**
  - Short-acting dihydropyridines increase CV events!
  - Long-acting dihydropyridines and nondihydropyridines can improve symptoms
- **Ranolazine**
  - Increases exercise tolerance, time to angina, decreases anginal episodes compared

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**Staged Drug Therapy for Chronic Angina**

1. **B Blocker**
2. If symptoms persist, add LA nitrates
3. If symptoms persist, add Ca++ Blocker
4. If symptoms persist, add LA nitrates

*Depending on clinical characteristics
† Provided no contraindication

ACCF/AHA angina guidelines, J Am Coll Cardiol 2002; 39:15-48
Impact of pharmacological treatment

- None: 6% event rate (RRR 25%)
- Aspirin: 0% event rate (RRR 25%)
- Aspirin β-blocker: 4.5% event rate (RRR 25%)
- Aspirin β-blocker Statin: 3% event rate (RRR 30%)
- Aspirin β-blocker Statin ACEI: 2.3% event rate (RRR 30%)

*CV death, AMI or stroke

Yusuf S. Lancet 2002;360:2

Revascularization

Indications for Revascularization

- Left main CAD
- Major 3 vessel CAD
- Two vessel disease with LAD involvement
- High risk features on non-invasive testing
- Persistent symptoms despite adequate medical therapy
- Symptomatic patients refusing anti-anginal drug therapy

Percutaneous coronary interventions

- Over 1 million procedures done in US/year, most elective (85%)
- > 60% of patients undergoing revascularization have PCI
- MDs recommend PCI more than CABG in patients who are eligible for both
  - But...how does PCI compare to optimal medical therapy and CABG?
Summary of PCI vs Med therapy trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mortality</th>
<th>Prevent MI</th>
<th>Short-term anginal relief</th>
<th>Short-term QoL</th>
<th>Long-term QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITA-2</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI</td>
<td>PCI</td>
<td>No diff</td>
</tr>
<tr>
<td>ACME</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI</td>
<td>PCI</td>
<td>N/A</td>
</tr>
<tr>
<td>ACME-2</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI</td>
<td>No diff</td>
<td>N/A</td>
</tr>
<tr>
<td>MASS</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MASS-II</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI</td>
<td>PCI</td>
<td>N/A</td>
</tr>
<tr>
<td>AVERT</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI</td>
<td>No diff</td>
<td>No diff</td>
</tr>
<tr>
<td>TIME</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI</td>
<td>PCI</td>
<td>No diff</td>
</tr>
<tr>
<td>COURAGE</td>
<td>No diff</td>
<td>No diff</td>
<td>PCI*</td>
<td>PCI</td>
<td>No diff</td>
</tr>
</tbody>
</table>

* No difference at 5 years

Adapted from Kereiakes, JACC 2007;50:1598-1603

Meta-analysis: PCI vs Conservative Medical Management

Meta-analysis of 11 randomized trials

<table>
<thead>
<tr>
<th></th>
<th>Favors PCI</th>
<th>Favors Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk ratio (95% CI)</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>


Trials of Aggressive Medical Therapy vs PCI

AVERT (Pitt et al): Atorvastatin superior to routine PCI in preventing ischemic events (p<0.04)

Hambrecht et al: Exercise training superior to PCI in preventing ischemic events (6 v 15; p <0.02)

COURAGE: Study design

AHA/ACC Class I/II indications for PCI, suitable coronary artery anatomy and ≥70% stenosis in ≥1 proximal epicardial vessel + objective evidence of ischemia or ≥80% stenosis + class III angina without provocation testing

Optimal medical therapy* + PCI (n = 1149) Randomized Optimal medical therapy (n = 1138)

Primary outcome: All-cause mortality, nonfatal MI

Follow-up: Median 4.6 years

*Intensive pharmacologic therapy + lifestyle intervention

COURAGE: Optimal Medical Therapy +/- PCI

Survival free of primary outcome

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>1138</td>
<td>1017</td>
<td>939</td>
<td>834</td>
<td>658</td>
<td>468</td>
<td>317</td>
<td>200</td>
</tr>
<tr>
<td>PCI + medical therapy</td>
<td>1149</td>
<td>1013</td>
<td>952</td>
<td>833</td>
<td>637</td>
<td>417</td>
<td>200</td>
<td>35</td>
</tr>
</tbody>
</table>

HR 1.05* (0.87-1.27) P = 0.62


All-cause death, MI

Boden et al. NEJM 2007;356:1503-16

COURAGE: Cumulative event rates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCI + OMT (%)</th>
<th>Medical therapy (%)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI</td>
<td>19</td>
<td>18.5</td>
<td>1.05</td>
<td>0.87-1.27</td>
<td>0.62</td>
</tr>
<tr>
<td>Death, MI, stroke</td>
<td>20</td>
<td>19.5</td>
<td>1.05</td>
<td>0.87-1.27</td>
<td>0.62</td>
</tr>
<tr>
<td>Death</td>
<td>7.6</td>
<td>8.3</td>
<td>0.87</td>
<td>0.65-1.16</td>
<td>0.38</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>13.2</td>
<td>12.3</td>
<td>1.13</td>
<td>0.89-1.43</td>
<td>0.33</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.1</td>
<td>1.8</td>
<td>1.56</td>
<td>0.80-3.04</td>
<td>0.19</td>
</tr>
<tr>
<td>Hospitalization for ACS</td>
<td>12.4</td>
<td>11.8</td>
<td>1.07</td>
<td>0.84-1.37</td>
<td>0.56</td>
</tr>
<tr>
<td>Revascularization (PCI or CABG)</td>
<td>21.1</td>
<td>32.6</td>
<td>0.60</td>
<td>0.51-0.71</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Boden et al. NEJM 2007;356:1503-16

COURAGE: Freedom from angina

<table>
<thead>
<tr>
<th>Time point</th>
<th>PCI (%) + OMT</th>
<th>Medical therapy (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>1 year</td>
<td>66</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 years</td>
<td>72</td>
<td>67</td>
<td>0.02</td>
</tr>
<tr>
<td>5 years</td>
<td>74</td>
<td>72</td>
<td>NS</td>
</tr>
</tbody>
</table>

Boden et al. NEJM 2007;356:1503-16

Effect of Stents on Outcomes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Death*</th>
<th>MI*</th>
<th>Revascularization p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCA vs medical</td>
<td>0.91 (0.70-1.18)</td>
<td>1.23 (0.89-1.70)</td>
<td>0.92 (0.74-1.14)</td>
</tr>
<tr>
<td>BMS vs medical</td>
<td>0.90 (0.70-1.16)</td>
<td>1.24 (0.88-1.75)</td>
<td>0.71 (0.58-0.87)</td>
</tr>
<tr>
<td>DES vs medical</td>
<td>0.96 (0.60-1.52)</td>
<td>1.15 (0.73-1.82)</td>
<td>0.58 (0.38-0.88)</td>
</tr>
<tr>
<td>BMS vs PTCA</td>
<td>0.99 (0.76-1.30)</td>
<td>1.01 (0.83-1.23)</td>
<td>0.68 (0.60-0.77)</td>
</tr>
<tr>
<td>DES vs PTCA</td>
<td>1.05 (0.66-1.69)</td>
<td>0.94 (0.65-1.35)</td>
<td>0.30 (0.17-0.51)</td>
</tr>
<tr>
<td>DES vs BMS</td>
<td>1.06 (0.71-1.58)</td>
<td>0.93 (0.68-1.26)</td>
<td>0.44 (0.35-0.56)</td>
</tr>
</tbody>
</table>

*Combined estimates from both direct and indirect comparisons from 61 RCTs and 25,388 total patients.

Trikalinos et al. Lancet 2009;373:911-18
Subgroups who may benefit from PCI

- Patients with moderate to severe ischemia (≥ 10%) on stress testing with nuclear imaging
- Patients whose symptoms are not relieved with medical therapy

Revascularization in patients with DM: BARI-2D

- About 2400 patients with diabetes randomized to prompt or delayed revascularization
- All patients received intensive medical therapy

<table>
<thead>
<tr>
<th>% Pts Meeting Target Values</th>
<th>Baseline</th>
<th>Three Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycated HbA1c &lt;7.0%</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>LDL cholesterol &lt;100 mg/dl</td>
<td>60</td>
<td>83</td>
</tr>
<tr>
<td>BP ≤130/80 mm Hg</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td>% that smoked in prior year</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>All 3 at target values</td>
<td>13</td>
<td>28</td>
</tr>
</tbody>
</table>

Change in QOL score on SAQ after PCI

Spertus JA et al., Circulation 2004; 110:3789-94

BARI Revascularization in patients with DM: BARI-2D

- About 2400 patients with diabetes randomized to prompt or delayed revascularization
- All patients received intensive medical therapy

NEJM 2009; 360:2503-15

Cumulative Rate of First Revascularization
BARI-2D Conclusions

- No difference overall in event rates between prompt vs delayed or no revascularization

- In higher risk patients selected for CABG, prompt revascularization reduces CV events compared with delayed/no revascularization ($p=0.01$)

- In lower risk patients selected for PCI, no difference in event rates in prompt vs delayed/no revascularization
Multi-vessel Disease: A meta-analysis of mortality for PTCA vs CABG

Hoffman et al. JACC 2003

Conclusions: PCI in stable CAD

- Single vessel disease: PCI does not reduce mortality, and is not cost-effective (> $200,000/QALY)
- Multivessel disease: CABG is superior to PCI in reducing mortality, angina and repeated revascularization
- Diabetes: CABG is superior revascularization strategy in higher risk patients; PCI shows no difference from medical therapy

Summary: Management of Stable CAD

- Risk Stratification is important
  - Clinical history: age, sex, angina description
  - Exercise testing is best if possible
  - Low risk patients have low overall mortality
- Medical therapy is very effective
- Revascularization should be reserved for high risk patients, and patients who are symptomatic despite optimal medical therapy

Summary

Treatment for Stable CAD

- A = Antiplatelet, ACE-I, and Antianginal therapy
- B = Beta-blocker and Blood pressure
- C = Cigarette smoking and Cholesterol
- D = Diet and Diabetes
- E = Education and Exercise