Primary Prevention of Coronary Heart Disease: Using Traditional and Novel Risk Factors to Guide Effective Treatment

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Case Example

58 year old man in good health presents for regular health maintenance visit. He is concerned about heart disease and wants to know what can be done to reduce his risk.

• No diabetes, non-smoker, likes to walk
  – BMI 25
  – Blood pressure 124 / 82
  – Total cholesterol 210 mg/dl; HDL 41 mg/dl

• What would you recommend for CVD risk reduction?
Coronary heart disease

• Leading cause of morbidity and mortality
  – 600,000 first heart attacks each year in US
  – $156 billion direct and indirect costs annually
• Many (moderately strong) risk factors
• Most risk factors continuous and graded: no clear “cut-off” values

Reducing CHD risk

• Several therapies can reduce the risk of first CHD events (primary prevention):
  – Aspirin
  – Blood pressure reduction
  – Cholesterol-lowering therapies
  – Diet?
  – Exercise?
  – Smoking cessation
Risk-based treatment strategy

- Potential benefit from risk-reducing therapies is proportional to underlying CHD risk
- Treatment decisions require knowledge of underlying risk
  - Allows estimate of net benefit
- Recent treatment guidelines have emphasized use of global CHD risk for treatment decision making

What is global CHD risk?

- The overall chance that a patient will have a CHD event (non-fatal or fatal myocardial infarction, sudden death, or new onset angina) over some defined time period
- Estimated using risk factor data from large epidemiological studies like the Framingham Heart Study
AHA Recommendation

• All adults 40 years of age or older should know their absolute risk of developing CHD.
• Risk should be calculated every 5 years, or more frequently for patients with borderline risk levels

Circulation 2002; 106: 388-391

Physicians’ estimates of CHD risk are often inaccurate

• 6 published studies of physician estimation
  – 4 used hypothetical scenarios, 2 actual patients from primary care practices
• Compared with Framingham-calculated risk
• All found significant inaccuracy
  – Pignone 2003: 76% of MD estimates inaccurate (overestimates > underestimates)*

* Pignone et al BMC Health Serv Res 2003;3:13
Framingham Risk Equations

- Derived from large population of (mostly Caucasian) men and women ages 30-75 in Framingham, Massachusetts
- Uses information on age, sex, blood pressure, smoking, total / HDL cholesterol ± presence of diabetes, LVH on ECG
- For use in patients with no previous history of CHD, stroke, or PVD

http://www.framinghamheartstudy.org/risk

Framingham risk equations - Limitations

- Not accurate in patients under 30 or over 75
- Relatively few patients with diabetes
- Good discrimination for future CHD events: Area under ROC curve = 0.85
- Validated in several populations and found to be relatively “transportable” for risk ordering, but calibration varies

D’Agostino JAMA 2001;286:180-7
Framingham-based risk tools

- Several types of risk tools are available: paper charts, PDA programs, web tools
- Requires < 1 minute to perform calculation if clinical information is available
- Produces estimate of 10 year risk for:
  - total CHD events (death, MI, angina)
  - hard CHD events (death, MI) only
  - total CVD risk (adds stroke, HF, PVD)
- Best metric to use not clear

D’Agostino et al Circulation 2008; 117: 743-

Effect of giving patients
global CHD risk information

- 14 trials have examined impact of providing patients with global CHD risk information +/- other education
- Studies with repeated sessions and additional counseling produced modest reductions in predicted CHD risk
- Single sessions did not appear effective

Effect of giving providers global CHD risk information

• Few good studies
• Some increase in prescribing effective therapies for high-risk patients
• One trial found improved blood pressure (4.6 mm difference) in patients whose physicians received global risk information

Sheridan and Crespo BMC HSR 2008; 8: 60-

Using CHD risk to help patients and providers decide whether or not to use aspirin and statins for primary prevention
Statins for primary prevention

• Statins produce 30% reduction in major coronary events for primary prevention
  – Reduction proportional to the reduction in LDL cholesterol achieved
  – More evidence for men than women
• No trials have examined different “goal” lipid levels
• Moderate dose statin may be most efficient for primary prevention

Brugts et al BMJ 2009; 338: 2376-
Treatment threshold for statins

• Benefits: reduced CHD events and strokes
• Downsides: muscle pain, costs, need to take a pill daily
• Recent data on efficacy, long-term safety, and sharply reduced costs have reduced treatment threshold

Modeling

• Pletcher and colleagues recently examined thresholds for treating adults with elevated LDL (>130 mg/dl)
• They found treating adults with 10 year risk over 5% warranted at statin cost of $20 per month or less

Pletcher et al Annals Int Med 2009; 150: 243-54
Aspirin for primary prevention of CHD events in men

- Aspirin reduces relative risk of CHD events (nonfatal MI) in men by **23%**
- Aspirin causes gastrointestinal bleeding in 1-5 of 1000 users over 5 years
- Aspirin may also cause bleeding strokes in 1 of 1000 users over 5 years
- Determining benefit / harm ratio requires estimate of underlying CHD risk

**ATT Collaboration Lancet 2009; 373: 1849-60**

**Pignone et al Annals Internal Medicine 2002; 136: 161-72**

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Effects of aspirin in 1000 men over 5 years

<table>
<thead>
<tr>
<th>Events</th>
<th>Pt. with 2.5% CHD risk over 5 yrs</th>
<th>Pt. with 5% CHD risk over 5 yrs</th>
<th>Pt. with 10% CHD risk over 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI prevented</td>
<td>6</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>GI bleeds caused</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
</tr>
<tr>
<td>Bleeding stroke caused</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Implications

- When 10 yr. CHD risk < 5%, harms of aspirin are of similar magnitude to the benefits -- aspirin not routinely indicated
- When 10 yr. CHD risk >10%, benefits of aspirin likely exceed the harms -- aspirin should be considered for routine use
- For patients with intermediate risk, providers and patients should decide together, based on risk tolerance

Treatment Thresholds

<table>
<thead>
<tr>
<th>10 year CVD risk</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>No treatment</td>
</tr>
<tr>
<td>5-10%</td>
<td>Statin</td>
</tr>
<tr>
<td>10-15%</td>
<td>Consider Aspirin + Statin</td>
</tr>
<tr>
<td>&gt;15%</td>
<td>Aspirin + Statin</td>
</tr>
</tbody>
</table>
Assumptions

• Low-cost statin ($5 per month)
• Non-drug costs of statin therapy modest
  – Limited lipid, LFT, CK testing
  – Limited lipid-related visits
  – Adherence support not expensive
• No important adverse effects, apart from muscle pain
• No downside to daily medication usage

Case Example

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• No diabetes, non-smoker, likes to walk
  – BMI 25
  – Blood pressure 124 / 82
  – Total cholesterol 210 mg/dl; HDL 41 mg/dl
• What would you recommend for CVD risk reduction?
What is his risk of developing CHD over the next 10 years?

1. < 5%
2. 5-9%
3. 10-14%
4. 15-20%
5. > 20%

Framingham risk
10%- hard CHD events
13% total CHD events
Based on his risk of CHD, which of the following therapies would you offer?

1. Statin drug therapy only
2. Aspirin (81 mg daily) only
3. Both
4. Neither

Part 2: Using novel risk markers to better direct CHD prevention
Clinical scenario- continued

• The same 58 year old man we discussed earlier comes to your office 3 months later
• Concerned about possible medication side effects, he decided to try to eat better and get more exercise, but notes he has not been very successful
• Two weeks ago, while on a business trip to Texas, he decided to have a full body CT scan ($750) that included an analysis of coronary calcium

Novel risk markers

• C-reactive protein
• Fibrinogen
• vWF
• Factor VII
• Homocysteine
• Lipoprotein a
• LDL sub-fractions
• Platelet activity
• ST segment depression
• Heart rate variability
• Carotid Doppler
• Ankle-brachial index
• EBCT for coronary calcium
Can novel risk markers improve our ability to predict future CHD events?

- Goal is to improve outcomes through better risk prediction (compared with standard risk factor assessment), thus allowing better, targeted use of risk-based treatments
- No trials have examined effect on health outcomes
- Intermediate outcome = additional prognostic ability after accounting for traditional risk factors

How should we measure additional prognostic ability?

- Independent relative risk
- Discrimination: area under ROC curve
- Calibration
- Novel measures
  - Net reclassification index
  - Predictiveness curves
- Use of cost-effectiveness modeling
Novel risk factors - ARIC

- Compared standard risk factors vs. standard RF + series of 18 novel markers
- Outcome: area under the ROC curve
- Traditional RF: 0.80 women, 0.69 men
- Addition of single novel risk factors had little effect on area under ROC curve

Folsom Archives Int Med 2006; 166:1368-73

Electron beam CT scan for coronary calcium

- CT scan can detect coronary calcium, a marker for atherosclerotic plaque
- Plaque is a marker for atherosclerosis and coronary risk
- Downsides:
  - radiation risk
  - incidental findings
  - costs
Screening for Coronary Calcium

- No randomized trials of effect on health outcomes or treatment adoption
- 2 observational studies of effect on treatment use:
  - Wong 1996: CAC score > 0 associated with:
    - increase in aspirin, statin, Vitamin E use; decreased dietary fat consumption (RR range 1.5 – 3.5)
    - increased worry
  - O’Malley 2002/2003: no difference in smoking cessation among patients with positive vs. negative CT scans for coronary calcium

<table>
<thead>
<tr>
<th>CAC score</th>
<th>MESA Relative Risk</th>
<th>Meta-analysis Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1-100</td>
<td>3.6</td>
<td>2.1</td>
</tr>
<tr>
<td>101-400</td>
<td>7.7</td>
<td>5.4</td>
</tr>
<tr>
<td>&gt;400</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Pletcher et al Archives Internal Medicine 2004; 164: 1285-92
Clinical scenario, continued

His coronary calcium score was 74. Based on this result, what is his risk of having a CHD event over the next 10 years?
1. < 5%
2. 5-9%
3. 10-14%
4. 15-20%
5. > 20%

Determining the risk of CHD events after EBCT with CAC score = 74

- Pre-test probability = 12%
- CAC = 74 (table shows OR = 2.1)
- Use risk calculator*
- Calculated post-test probability: 7%

Based on his revised risk of CHD (7%), which therapies would you offer?

1. Statin drug therapy only
2. Aspirin (81 mg daily) only
3. Both
4. Neither

Compared with your treatment recommendations before you knew his calcium score, which of the following statements best describes your decision after knowing his calcium score?

1. I prescribed less aggressive treatment.
2. I prescribed the same treatment.
3. I prescribed more aggressive treatment.
Conclusions

• High burden of disease makes CHD prevention a high priority
• Current evidence and clinical guidelines support risk-based treatment approach
  – Calculate global risk
  – Use lower threshold for statins
• The role of novel risk markers such as EBCT remains unclear for now