PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN

Robert B. Baron MD MS
Professor and Associate Dean
UCSF School of Medicine

Declaration of full disclosure: No conflict of interest

EXPLAINING THE DECREASE IN DEATHS FROM CHD

1980 to 2000:

• Death rate fell from:
  542.9 to 266.8 per 100K men
  263.3 to 134.4 per 100K women

• 341,745 fewer deaths from CHD in 2000

Ford ES, NEJM, 2007

EXPLAINING THE DECREASE IN DEATHS FROM CHD

• 47% from CHD treatments, 44% from risk factor modification

• Reductions in cholesterol: 24%

Ford ES, NEJM, 2007

Placebo-Controlled Statin Trials

Reductions in Major Coronary Events Relative to Placebo

[Graph showing reductions in major coronary events for different statin doses]
PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN

Placebo-Controlled Statin Trials – Celebrating Successes but Forgetting the Majority?

Remaining Major Coronary Events Relative to Placebo

Is there more we can do to identify and treat the non-responders?

A RISK-BASED APPROACH

The benefit from any given intervention is a function of:
1) The relative risk reduction conferred by the intervention, and
2) The native risk of the patient

A 40 year women, in good health. In for annual wellness visit. BMI, BP, diet and exercise all at ideal. What blood tests will you order to screen her for a lipid disorder?

1. Total cholesterol
2. LDL cholesterol and HDL cholesterol
3. LDL, HDL, and hs-CRP
4. LDL, HDL, hs-CRP, and Lp(a)
5. No screening blood tests for lipids

Prevention Of CVD in Women

- Overwhelming majority of recommendations are the same for women and for men
- Aspirin use is a notable exception
- But...“there may be gender differences in the magnitude of the relative and absolute potential benefits”

Mosca, Circulation 2011
PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN

USPSTF: Screening Recommendations

- Men:
  - age 35 and older, regardless of risk level
  - age 20 to 35, at increased risk
- Women:
  - age 20 and older at increased risk
  - If not at increased risk, no recommendation (I)
- Increased Risk:
  - tobacco use, diabetes, hypertension, obesity, and family history of premature CV disease.

ACC/AHA CVD Risk: Ideal

All of These

- Total cholesterol <200 mg/dL (untreated)
- BP <120/<80 mm Hg (untreated)
- Fasting blood glucose <100 mg/dL (untreated)
- Body mass index <25 kg/m2
- Abstinence from smoking
- Physical activity at goal for adults >20 y of age: 150 min/wk moderate intensity, 75 min/wk vigorous intensity, or combination
- Healthy (DASH-like) diet

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5. No screening blood tests for lipids

A 40 year women, in good health. Which of the following is the most effective intervention for primary prevention of CVD?

1. Aspirin
2. Folic acid
3. Estrogen
4. Vitamin E, C and beta carotene
5. Oily fish twice per week
6. All are effective
7. None are effective
Ineffective Interventions in Women

ACC/AHA 2011

- Hormone therapy should not be used for the primary or secondary prevention of CVD (Evidence A).
- Antioxidant vitamin supplements (e.g., vitamin E, C, and beta carotene) should not be used for the primary or secondary prevention of CVD (Evidence A).
- Folic Acid, with or without B6 and B12 supplementation, should not be used for the primary or secondary prevention of CVD (Evidence A).
- Routine use of aspirin in healthy women <65 years of age is not recommended to prevent MI (Evidence B).

Omega 3 Fatty Acids: Meta-analysis

- 48 RCTs of 36,913 participants; 41 cohort trials
- No significant effect of omega 3 fats on mortality, CV events, or cancer
- Analysis of diet only trials: also no benefit
- No reason to advise people to stop rich sources of omega 3 fats, but better trials needed

ORIGEN Trial

- RCT, 12,537 subjects; impaired FBS, IGT, or new diabetes, and high CV risk
- 900 mg n-3 fatty acids vs. placebo; 6.2 years
- Results: No difference in CV outcomes
  - 9.1% vs. 9.3% (p=0.72)

A 40 year women, in good health. Which of the following is the most effective intervention for primary prevention of CVD?

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2. Folic acid
3. Estrogen
4. Vitamin E, C and beta carotene
5. Oily fish twice per week
6. All are effective
7. None are effective
The best next step in lipid management is:

1. Continue current therapy
2. Begin a statin to goal LDL <100
3. Begin a statin to goal LDL <70
4. Begin a statin plus ezetimibe to LDL goal <70
5. Begin niacin

LDL Goal and Cutpoints in Patients with CHD and CHD Risk Equivalents (10-Year Risk >20%)

<table>
<thead>
<tr>
<th>LDL Level at Which to Initiate Diet</th>
<th>LDL Level at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg/dL Optional : &lt;70</td>
<td>≥100 mg/dL (&lt;100mg/dL: drug optional)</td>
</tr>
<tr>
<td>≥100 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Adult Treatment Panel III, 2004
PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN

Heart Protection Study: Vascular Events by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>Statin No. Events</th>
<th>Placebo No. Events</th>
<th>Risk Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td>Statin (10,269)</td>
<td>Placebo (10,267)</td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>285</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>≥100 &lt;130</td>
<td>670</td>
<td>881</td>
<td></td>
</tr>
<tr>
<td>≥130</td>
<td>1087</td>
<td>1365</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042</td>
<td>2606</td>
<td>24% reduction (p&lt;0.00001)</td>
</tr>
</tbody>
</table>

TREATING TO NEW TARGETS (TNT)

- RCT of 10,001 patients with stable CHD; 35-75 yr
- LDL <130 mg/dl
- Atorvastatin 10 vs atorvastain 80
- Followed for 4.9 years
- Research question: safety and efficacy of lowering LDL below 100 mg/dl

**TREATING TO NEW TARGETS (TNT)**

<table>
<thead>
<tr>
<th>LDL</th>
<th>Event %</th>
<th>Death %</th>
<th>LFTs %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorv 10</td>
<td>10.9</td>
<td>2.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Atorv 80</td>
<td>8.7</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td></td>
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SEARCH TRIAL

- RCT; 7 years; 10,064 patients with MI;
- Funded by Merck
- Simvastatin 80mg vs. 20mg
- Outcome: major vascular events (coronary death, MI, stroke, revascularization)
- Results: No difference (RR 0.94; CI 0.88 – 1.01)
SEARCH TRIAL

- Difference in myopathy risk
  - Muscle weakness + CK > 10x ULN
  - 80 mg: 22 patients
  - 20 mg: 0 patients
  - Risk 5x higher in year 1 compared with subsequent years

- Key drug interactions noted

SEARCH TRIAL

- Simvastatin contraindicated in users of
  - Antifungals
  - Macrolide antibiotics
  - Antiretrovirals
  - Gemfibrozil

- Do not exceed 10mg simvastatin if using
  - Verapamil
  - Diltiazem

- Do not exceed 20mg simvastatin if using
  - Amlodipine
  - Ranolazine
  - Amiodarone

LDL-Lowering Effects of Simvastatin

<table>
<thead>
<tr>
<th>Simvastatin</th>
<th>% Lowered LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>30%</td>
</tr>
<tr>
<td>20</td>
<td>38%</td>
</tr>
<tr>
<td>40</td>
<td>41%</td>
</tr>
<tr>
<td>80</td>
<td>47%</td>
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</table>

CURRENT USE OF SIMVASTATIN

- Myopathy risk may be higher with simvastatin than other statins

- Don’t routinely use higher than 40 mg (OK to use 80 if tolerated for more than 1 year)

- If inadequate response on simvastatin 40, consider atorvastatin or rosuvastatin
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STATINS AND FATIGUE
- Small RCT; 6 months; 1016 healthy patients
- Simvastatin 20mg vs pravastatin 40 vs placebo
- Outcome: self ratings of change in energy and fatigue with exertion on 5-point scale
- Results:
  - Statins worse than placebo
  - Simvastatin worse than pravastatin
  - Women more than men

The best next step in lipid management is:
1. Continue current therapy
2. Begin a statin to goal LDL <100
3. Begin a statin to goal LDL <70
4. Begin a statin plus ezetimibe to LDL goal <70
5. Begin niacin

63 yo woman; s/p MI. On atorvastatin 80.

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>LDL</td>
<td>95</td>
</tr>
<tr>
<td>HDL</td>
<td>40</td>
</tr>
<tr>
<td>TG</td>
<td>200</td>
</tr>
</tbody>
</table>

The best next step in lipid management is:
1. Continue current therapy
2. Switch to rosuvastatin
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe
Effects of Fibrates on Cardiovascular Outcomes

- 4 Recent meta-analyses
- 18 RCTs, 45,000 patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal coronary events</td>
<td>0.81</td>
<td>0.75-0.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total stroke</td>
<td>1.03</td>
<td>0.91-1.16</td>
<td>0.69</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.97</td>
<td>0.88-1.07</td>
<td>0.59</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.00</td>
<td>0.98-1.08</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Jun et al. The Lancet 2010

Fenofibrate plus statin vs. statin alone: ACCORD

- RCT of 5518 patients with type 2 DM
- CV events: 2.24 vs. 2.41, \( p = .32 \)
- Death: 1.47 vs. 1.61, \( p = .33 \)
- No difference in any secondary outcome
- Results do not support routine use of combination therapy in DM

ACCORD: NEJM 2010

NIACIN META-ANALYSIS OF RCTS

- 11 RCTS
- Coronary Drug Project (1970s) only large RCT
- Others very small

Berkert, Atherosclerosis 2010
PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN

Niacin Meta-Analysis: Summary of Results for Cardiovascular Events

AIM-HIGH Trial
- RCT of 3,414 patients with established CVD
- Simvastatin (or simvastatin + ezetimibe) to keep LDL at 40–80 mg/dl (mean 71).
- HDL 35 mg/dl, TG 161 mg/dl
- Randomized to receive sustained-release niacin or placebo

AIM-HIGH Trial
- Results: Study stopped early
  - No reduction in cardiovascular events, MI and stroke
  - Increase risk in ischemic stroke (28 vs 12)

Extended-release Niacin vs. Ezetimibe
- RCT of 208 patients with CHD or CHD risk-equivalent on statin at goal LDL
- Niacin 2000 vs Ezetimibe 10
- Outcome: carotid intima-media thickness (IMT)
- Results: Niacin better
  - Reduction in IMT
  - Major cardiovascular events, 1% vs 5%
Summary Lipid-Lowering Drugs

• Statins are treatment of choice to decrease risk

• No evidence to support adding niacin or fibrates to statins

• If statin-intolerant, niacin may reduce CVD risk (weak evidence)

• Fibrates appear to lower MI risk, but no other CVD endpoints

• Ezetimibe: just say no

The best next step in lipid management is:

1. Continue current therapy
2. Switch to rosuvastatin
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe

63 yo woman, no risk factors

LDL  155
HDL  55
TG   160
SBP  120
Nonsmoker

The best next step in lipid management is:

1. Continue current therapy
2. Begin a statin
3. Begin fenofibrate
4. Begin a statin plus ezetimibe
5. Begin niacin
Truth About CVD Risk Prevention
- Health professionals are not good at judging CV risk
- Counting risk factors is a “blunt instrument” and often leads to misclassification
- Calculate 10-year risk of hard CHD events (CHD death or non-fatal MI) using the Framingham Risk Score

Framingham Risk - Limitations
- Not accurate in patients under 30 or over 75
- Provide risk over 4-12 years only
- Relatively few patients with diabetes; no family history

BUT
- Good discrimination for future CHD events
- Validated in several populations and found to be relatively “transportable” for risk ordering but calibration varies

Examples of Proposed Novel Risk Markers
- C-reactive protein
- Fibrinogen
- vWF
- Factor VII
- Homocysteine
- Lipoprotein a
- LDL sub-fractions
- ST segment depression
- Heart rate variability
- Carotid Doppler
- Ankle-brachial index
- EBCT for coronary calcium
- Platelet activity

CRP AND Risk
- CRP does not change overall predictive ability of Framingham
- However, CRP (plus family history) may reclassify some patients (especially intermediate risk patients)
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C-reactive protein (CRP)

Hard to directly integrate into the Framingham risk....

Rough calculations:
CRP in top third increases risk by factor of 1.2-1.3

Average risk = x
Risk in top tertile = 1.3x
Risk in middle tertile = x
Risk in middle tertile = 0.7x

Coronary Calcium (CAC) and CV Prevention

- Broad population-based strategy not warranted
- CAC may reclassify intermediate risk patients
- Unknown if findings lead to improved outcomes

Bonow RO, NEJM 2009

63 yo woman, no risks

LDL 155
HDL 55
TG 160
SBP 120
Nonsmoker

10 yr risk: 2%...
Therefore no medication recommended

The best next step in lipid management is:

1. Continue current therapy
2. Begin a statin
3. Begin fenofibrate
4. Begin a statin plus ezetimibe
5. Begin niacin (sustained release)
Prevention of CVD Risk in Women: Aspirin

- Aspirin (81–325 mg/d) in women with CHD unless contraindicated (Evidence A).
- Aspirin in women >65 y of age (81 mg daily) if benefit for ischemic stroke and MI prevention is likely to outweigh risk of GI bleed and hemorrhagic stroke (Class IIa; Evidence B).
- Aspirin may be reasonable for women <65 y of age for ischemic stroke prevention (Class IIb; Level of Evidence B).

CONCLUSIONS

- Patients with CHD or CHD equivalent:
  - Treat aggressively with statin independent of LDL level (to LDL <70 in most cases)
  - Treat other risk factors aggressively as well, especially easy ones (HTN, Aspirin use)
  - Treat elevated non-HDL cholesterol and low HDL
  - Patients at high risk are undertreated. Maximize adherence and avoid clinical inertia

CONCLUSIONS

- Patients without CHD:
  - Assess lifetime CV risk with risk factors and 10-year CHD risk with Framingham Risk Score
  - Novel markers (hsCRP, coronary calcium score) may be useful for further discrimination among those with intermediate risk
  - Do a better job with what we have: HTN, ASA, smoking, weight, exercise, diet
  - Engage patient in shared decision making, especially if risk <10%

- Use medications at thresholds based on risk:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL goal</th>
<th>LDL drug threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk (&gt;20%)</td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
<tr>
<td>Mod high risk (10-20%)</td>
<td>&lt;100</td>
<td>≥130</td>
</tr>
<tr>
<td>Moderate risk (&lt;10%)</td>
<td>&lt;100</td>
<td>≥160</td>
</tr>
<tr>
<td>Low risk (no risk factors)</td>
<td>&lt;100</td>
<td>≥190</td>
</tr>
</tbody>
</table>
CONCLUSIONS

〜 Patients without CHD:

* Use medications at thresholds based on risk:

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>ASA</th>
<th>STATIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk (&gt;20%)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Mod high risk (10-20%)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Moderate risk (&lt;10%)</td>
<td>NO</td>
<td>Occasional YES</td>
</tr>
<tr>
<td>Low risk (no risk factors)</td>
<td>NO</td>
<td>Usually NO</td>
</tr>
</tbody>
</table>