MANAGEMENT OF HYPERLIPIDEMIA AND CARDIOVASCULAR RISK: Balancing Benefits and Harms

Robert B. Baron, MD MS
Professor and Associate Dean
UCSF School of Medicine
baron@medicine.ucsf.edu

EXPLAINING THE DECREASE IN DEATHS FROM CVD

1980 to 2000: death rate fell by approximately 50% in both men and women

2000 to 2010: Death still falling: down 31%
- About 1/2 from acute treatments, 1/2 from risk factor modification:
  - Predominantly cholesterol (1/4), BP, smoking

Placebo-Controlled Statin Trials

Reductions in Major Coronary Events Relative to Placebo
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

2013 ACC/AHA Guidelines
What is New?
- 4 groups of patients who benefit from statins
- Identifies high and moderate intensity statins
- No LDL treatment targets
- Non-statin therapies no not provide acceptable risk reduction
- Estimate 10-year ASCVD risk with new equation

Heart Protection Study: Vascular Events by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>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>
</tr>
<tr>
<td>&lt;100</td>
<td>285</td>
<td>360</td>
</tr>
<tr>
<td>≥100 &lt;130</td>
<td>670</td>
<td>881</td>
</tr>
<tr>
<td>≥130</td>
<td>1087</td>
<td>1365</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
</tr>
</tbody>
</table>

24% reduction (p<0.00001)

2013 ACC/AHA Guidelines
Four Groups of Patients Who Benefit From Statins
- Individuals with clinical ASCVD
- Individuals with primary elevations of LDL ≥190
- Individuals age 40-75 with diabetes and LDL ≥70
- Individuals without ASCVD or diabetes, age 40-75, with LDL ≥70, and 10 year risk 7.5% or higher
2013 ACC/AHA Guidelines
Importance of Lifestyle Recommendations

- Heart healthy diet
- Regular aerobic exercise
- Desirable body weight
- Avoidance of tobacco

Heart Healthy Diet 2016

- Two dietary factors increase LDL:
  - Saturated fat
  - Total Calories
- Restriction of dietary cholesterol is no longer recommended (Dietary Guidelines 2015)

Saturated Fat 2016

- Observational studies: no association between sat fat and CVD
- But: RCTs that replace sat fat with unsat fat reduce total and LDL cholesterol and CVD events and mortality
- And: replacing sat fat with carb reduces total and LDL cholesterol but increases triglycerides and HDL and does not lower CVD events

2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals with clinical ASCVD:
  - Treat with: high intensity statin, or moderate intensity statin if > age 75
- Individuals with primary elevations of LDL ≥190:
  - Treat with: high intensity statin
2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals 40-75 with diabetes and LDL ≥ 70:
  - Treat with: moderate intensity statin, or high intensity statin if risk over 7.5%
- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - Treat with: moderate-to-high intensity statin

2013 ACC/AHA Guidelines
High Intensity vs. Moderate Intensity Statin

- High Intensity: lowers LDL by >50%
  - Atorvastatin 40 - 80
  - Rosuvastatin 20 - 40
- Moderate Intensity: lowers LDL by 30-50%
  - Atorvastatin 10 - 20
  - Rosuvastatin 5 – 10
  - Simvastatin 20 - 40
  - Pravastatin 40 – 80
  - Lovastatin 40

How Best To Calculate 10 Year Risk?

Pooled Cohort Risk Assessment Equations: hard CHD events and stroke

- http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

Pooled Cohort Risk Assessment Equations

- Age
- Gender
- Race (White/African American)
- Total cholesterol (170 mg/dl)
- HDL cholesterol (50 mg/dl)
- Systolic BP (110 mmHg)
- Yes/no meds for BP
- Yes/no DM
- Yes/no cigs
- Outcome: 10-year risk of total CVD (fatal and non-fatal MI and stroke)
Management of Hyperlipidemia and Cardiovascular Risk

Do the Pooled Cohort Risk Assessment Equations Overestimate Risk?

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group.

How Best To Calculate 10 Year Risk?  
Baron Approach Fall 2016

- Use both CHD (hard end points) calculator and new CV risk calculator
- Include both in shared decision-making discussion

How Best To Calculate 10 Year Risk?  
Mayo Clinic Statin Choice Decision Aid:

- http://statindecisionaid.mayoclinic.org/index.php/statin/index?PHPSESSID=0khk8nm14h9vubjm3423e6h6b2
63 yo woman; s/p MI

<table>
<thead>
<tr>
<th>LDL</th>
<th>115</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL</td>
<td>45</td>
</tr>
<tr>
<td>TG</td>
<td>160</td>
</tr>
</tbody>
</table>

The best next step in lipid management is:

1. Atorvastatin 40 mg
2. Rosuvastatin 10 mg
3. Pravastatin 40 mg
4. Simvastatin 40 mg
5. Lovastatin 40 mg
6. Whatever works to get her LDL below 70 mg/dl

2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals with clinical ASCVD:
  - Treat with: high intensity statin, or moderate intensity statin if > age 75

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6. Whatever works to get her LDL below 70 mg/dl
63 yo woman; s/p MI. On atorvastatin 80.

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

The best next step in lipid management is:

1. Continue current therapy
2. Switch to rosvastatin 40 mg
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe

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Summary Lipid-Lowering Drugs

- Statins are treatment of choice based on RCT to decrease risk
- No evidence to support adding niacin or fibrates to statins
- If completely statin-intolerant, niacin may reduce CVD risk (weak evidence)
- Fibrates appear to lower MI risk, but no other CVD endpoints

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Summary Lipid-Lowering Drugs

- Ezetimibe study: (IMPROVE-IT)
  - 18,000 ACS patients (40% from North America)
  - RCT: Simvastatin vs simvastatin + ezetimibe. Took 7 years. Death, MI, Stroke
  - Simvastatin: 34.7% vs Simva/ezetimibe 32.7% (270 fewer events over 7 years)
PCSK9 Inhibitors
- Evolocumab (Repatha) and alirocumab (Praluent)—monoclonal antibodies that reduce liver LDL-receptor degradation
- Reduce LDL by 50%. Injectable Q2 – 4 weeks
- Approved for FH or patients with CVD “who need additional LDL lowering.”
- Unproven cardiovascular benefits

The best next step in lipid management is:
1. Continue current therapy
2. Switch to rosuvastatin 40 mg (Also potentially correct, but medication still on patent)
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe

63 yo woman, no traditional risk factors
LDL 155
HDL 55
TG 160
SBP 120
No BP meds
No DM
Non smoker

The best next step in lipid management is to calculate 10 year risk and:
1. Continue current therapy (no meds)
2. Begin atorvastatin 40
3. Begin atorvastatin 10
4. Begin simvastatin 20
5. Begin sustained release niacin
6. Begin red yeast rice
63 yo woman, no risks

LDL  155, HDL  55, TG  160
SBP  120, No BP meds
Non smoker, No DM

10 yr CHD risk (old calculator): 2%
10 yr CV risk (new calculator): 4.5%

Therefore no medication recommended

The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds)
2. Begin atorvastatin 40
3. Begin atorvastatin 10
4. Begin simvastatin 20
5. Begin sustained release niacin
6. Begin red yeast rice

63 yo man, no traditional risk factors

LDL  155
HDL  55
TG  160
SBP  120
No BP meds
No DM
Non smoker

63 yo man, no risks

LDL  155, HDL  55, TG  160
SBP  120, No BP meds
Non smoker, No DM

10 yr CHD risk (old calculator): 10%
10 yr CV risk (new calculator): 10.8%

“Toss-up.” Shared decision making. If start statin (per new guidelines), can start with moderate intensity statin
Management of Hyperlipidemia and Cardiovascular Risk

Robert Baron MD, MS

The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds)- old (but toss-up)
2. Begin atorvastatin 40-new (but still close call)
3. Begin atorvastatin 10-new (but still close call)
4. Begin simvastatin 20-new (but still close call)
5. Begin sustained release niacin
6. Begin red yeast rice

Key is shared decision-making

Other Factors That Could Affect Treatment Decisions

- LDL ≥ 160 mg/dl or evidence of genetic disorder
- Family history of premature ASCVD (<55 in first degree male relative, <65 in first degree woman)
- hs-CRP ≥2mg/dl
- CAC score ≥ 300 (or ≥75% for age, sex, ethnicity
- Ankle brachial index <0.9
- Elevated lifetime risk of ASCVD

The Good and The Controversial of the ACC/AHA Cholesterol Guidelines

- Focus on healthy lifestyle is good
- Focus to use statins (and not other agents) is good
- Focus to treat patients at high risk is good
- Focus to treat all patients with LDL <190 mg/dl and treat patients with DM/existing CV disease is good
- Not having target LDL is controversial
- Adults with no DM or heart disease and 10-year calculated risk >7.5% (using new risk calculator) to be treated – controversial
**NSAIDS and CVD**
- Danish national study, 97,698 patients with prior MI. 44% received NSAIDS.
- NSAIDS associated with 42% increase in CV death (CI 1.36 – 1.49)
- Diclofenac 96% and rofecoxib 66% increase
- Ibuprofen 34% and naproxen 27% increase

**Competing Risks**
- Example: women with 10-year risk 10%
- Reduce risk by 30% with statins. Risk now 7%.
- Add NSAID. Increase risk by 50%
- Total risk now back to 10%

**Aspirin and CVD**
- Aspirin reduces nonfatal MI by about 20%; no benefit on non-fatal stroke.
- Also reduces incidence of colorectal cancer.
- Has definable off-setting harms: GI bleed, hemorrhagic stroke

**Aspirin and CVD**
- Age 50 – 59 and 10% 10-yr risk: USPSTF B (Prescribe if no contraindications)
- Age 60 – 69 and 10% 10-yr risk: USPSTF C (Individualized decision)
- Less than age 50, over age 70: USPSTF I (Insufficient evidence)

USPSTF 2016
### Conclusions I
- Statins are effective and cost effective in selected groups of patients
- Optimal screening age not known.
  - ACC/AHA age 21 (to identify those > LDL 190)
  - USPSTF age 35 men and 45 women for most, age 20 if increased risk.
- Use statins in patients with ASCVD, LDL ≥190 and diabetes

### Conclusions II
- For those without ASCVD and diabetes, calculate 10 year risk, and treat those with risk greater than 7.5% (or 10% or maybe even 15%). Use shared decision making.
- Use appropriate intensity statin (high and moderate)
- Monitor adherence, but do not treat to specific LDL goal

### Conclusions III
- Do not treat those over age 75 (unless ASCVD), on dialysis or moderate/severe CHF
- Do not treat with other lipid-modifying drugs in addition to statins (but may need if truly statin intolerant)
- Avoid other factors that raise risk (i.e. NSAIDS) and use those that lower it (i.e. aspirin)