PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN:
Integrating New Data and New Guidelines

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No relevant financial relationships

EXPLAINING THE DECREASE IN DEATHS FROM CVD

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

2000 to 2010: Death still falling: down 31%

- About 1/2 from acute treatments, 1/2 from risk factor modification:
  - Predominantly cholesterol, BP, smoking

Placebo-Controlled Statin Trials

Reductions in Major Coronary Events Relative to Placebo
Heart Protection Study: Vascular Events by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>Statin (10,269)</th>
<th>Placebo (10,267)</th>
<th>Risk Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;100</td>
<td>285</td>
<td>360</td>
<td>Statin better</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>
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<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td>24% reduction (p&lt;0.00001)</td>
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</tbody>
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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
- Based only on RCT data
- Healthy lifestyle for all
- 4 groups of patients who benefit from statins
- Identifies high and moderate intensity statins
- No LDL treatment targets
- Non-statin therapies do not provide acceptable risk reduction
- Estimate 10-year ASCVD risk with new equation

2018 ACC/AHA Guidelines
- Based on RCT data plus other lines of evidence
- Healthy lifestyle for all
- 4 groups of patients who benefit from statins
- Identifies high, moderate and low intensity statins
- Some LDL treatment targets
- Non-statin therapies do provide acceptable risk reduction in some patients
- Estimate 10-year ASCVD risk with same equation
### 2013 and 2018 ACC/AHA Guidelines

**Four Groups of Patients Who Benefit From Statins**

- Individuals with clinical ASCVD
- Individuals with primary elevations of LDL \( \geq 190 \)
- Individuals age 40-75 with diabetes and LDL \( \geq 70 \)
- Individuals without ASCVD or diabetes, age 40-75, with LDL \( \geq 70 \), and 10 year risk 7.5% or higher

**Importance of Lifestyle Recommendations**

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

### 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

### 2018 ACC/AHA Guidelines

**What Approach for Each Group?**

- Individuals with clinical ASCVD:
  - Treat with: high intensity statin, or maximally tolerated statin
  - Reduce LDL by 50%
  - In very high risk ASCVD (multiple events, major event and other risks), use 70 mg/dl to consider adding non-statins (ezetemibe and PCSK inhibitor)
2013 ACC/AHA Guidelines
What Statin for Each Group?

• Individuals with primary elevations of LDL ≥190:
  • Treat with: high intensity statin

2018 ACC/AHA Guidelines
What Statin for Each Group?

• Individuals with primary elevations of LDL ≥190:
  • Treat with: high intensity statin
  • If over LDL >100, consider ezetemibe or PCSK9

2013 ACC/AHA Guidelines
What Approach 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%

2018 ACC/AHA Guidelines
What Approach for Each Group?

• Individuals 40-75 with diabetes and LDL ≥ 70:
  • Treat with: moderate intensity statin
  • If multiple risk factors or 50 - 75 years old use high intensity statin to reduce LDL by 50%
2013 ACC/AHA Guidelines
What Statin for Each Group?
- 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

2018 ACC/AHA Guidelines
What Approach for Each Group?
- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - Have a clinician-patient risk discussion before starting statins
  - Risk factors, risk enhancing factors, potential benefits and harms, costs, and patient preferences and values (shared decision-making)

2018 ACC/AHA Guidelines
Risk Enhancing Factors That Favor Statin
- Family history
- LDL ≥ 160
- Metabolic syndrome
- Chronic kidney disease
- Hx of preeclampsia or premature menopause
- Chronic inflammatory disorders (RA, HIV, psoriasis)
- High risk ethnic groups (South Asian)
- Elevated triglycerides ≥ 175
- ApoB, hsCRP, ABI, lp(a)
2018 ACC/AHA Guidelines
Coronary Artery Calcium
- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - If risk uncertain consider CAC
  - Score 0: withhold treatment
  - Score 1-99: favors statin
  - Score >100: statin indicated

2018 ACC/AHA Guidelines
Borderline Risk
- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 5.0 - 7.5% or higher:
  - Risk enhancing factors may favor statin

2013 and 2018 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

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)
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 Do Shared Decision Making?

Mayo Clinic Statin Choice Decision Aid:

http://statindecisionaid.mayoclinic.org/index.php/statin/index?PHPSESSID=0khk8n m14h9vubjm3423e6h6b2
Other Lipid-Lowering Drugs

• Statins are treatment of first choice based on RCTs
• No evidence to support adding niacin or fibrates to statins
• Niacin has harmful affects in combination with statins and uncertain benefits when used alone (weak evidence)
• Fibrates appear to lower MI risk, but no other CVD endpoints.

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.”

FOURIER TRIAL

• 27,564 patients, CV disease, on statin, LDL >70, 2.2 years
• Evolocumab vs placebo (SQ injections)
• Primary composite CV endpoint: death, MI, stroke, ACS revascularization
• Secondary endpoint: CV death, MI, stroke

Sabatine MS, NEJM, 2017
FOURIER TRIAL

- LDL reduced 59% (92 mg/dl to 30)
- Primary composite endpoint:
  - 1344 (9.8%) vs 1563 (11.3%)
  - 15% reduction
- Secondary endpoint: CV death, MI, stroke
  - 816 (5.9%) vs 1013 (7.4%)
  - 20% reduction

Sabatine MS, NEJM, 2017

- NNT 66 over 2 years
- No reduction in death
- No obvious safety concerns

Reflections:
- Evolocumab reduces risk
- Risk reduction less than hoped/thought
- $14,000 per year

ODYSSEY Outcomes

- 18,924 patients, ACS in last 12 months, on statin, LDL >70, 2.8 years
- Alirocumab vs placebo (SQ injections Q 2 weeks)
- Primary composite CV endpoint: CHD death, MI, unstable angina, or stroke
- Secondary endpoint: CHD death, CV death, MI, stroke

ACC, 2018

- LDL reduced 55% (101 mg/dl to 53)
- Primary composite endpoint:
  - 9.5% vs 11.1%
  - 14% reduction
- Secondary endpoints:
  - All cause mortality: 3.5% vs 4.1% (15% reduction)
  - CHD Death: NS
  - CV death: NS

ACC, 2018
**PCSK9 Inhibitors 2018 Value Statement**

- “May be considered”
- Long-term safety (>3 years) is uncertain
- Economic value low is low at current prices

**Final Thoughts**

- Statins are effective and cost effective in selected groups of patients
- Use statins in patients with ASCVD, LDL ≥190 and diabetes
- Use statins for most patients with risk ≥20%

**Final Thoughts**

- For those without ASCVD, diabetes or LDL ≥190, calculate 10-year risk and treat those interested (shared decision-making)
- For patients with 5% - 20% risk, enhancing factors may help decide
- In very high risk ASCVD patients, consider second medication (ezetimibe or PCSK9 inhibitor)