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

ACC/AHA Guidelines
- 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 LDL-C Feature</th>
<th>No. Events Statin (10,269)</th>
<th>No. Events Placebo (10,267)</th>
<th>Risk Ratio and 95% CI Statin better than Placebo</th>
<th>24% reduction (p&lt;0.00001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>285</td>
<td>360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 &lt;130</td>
<td>670</td>
<td>881</td>
<td></td>
<td></td>
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<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>
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</tbody>
</table>

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
### ACC/AHA Guidelines

#### Importance of Lifestyle Recommendations
- Heart healthy diet
- Regular aerobic exercise
- Desirable body weight
- Avoidance of tobacco

### Heart Healthy Diet 2017
- Two dietary factors increase LDL:
  - Saturated fat
  - Total Calories
- Restriction of dietary cholesterol is no longer recommended (Dietary Guidelines 2015)

### Saturated Fat 2017
- 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

### 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
**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

**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)
Do the Pooled Cohort Risk Assessment Equations Overestimate Risk?

Baron Approach 2017

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

Mayo Clinic Statin Choice Decision Aid:

- http://statindecisionaid.mayoclinic.org/index.php/statin/index?PHPSESSID=0khk8nm14h9vubjm3423e6h6b2

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group.
63 yo woman; s/p MI

LDL 115
HDL 45
TG 160

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

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

LDL  95
HDL  40
TG   200

The best next step in lipid management is:

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

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

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.”

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

FOURIER TRIAL

- LDL reduced 59% (92 mmol/L 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

FOURIER TRIAL

- 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
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
63 yo man, no traditional risk factors

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

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 risks

LDL  155, HDL  55, TG  160
SBP  120, No BP meds
Nonsmoker, 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
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

Statin Use for Primary Prevention of CVD: USPSTF
- Age 40 – 75, no CVD, 1 or more CVD risk factor* and calculated risk of and 10% or greater

USPSTF B: Prescribe if no contraindications
- Treat with low to moderate dose statin

*Risk : dyslipidemia, diabetes, HTN, smoking

USPSTF 2016
Statin Use for Primary Prevention of CVD: USPSTF

- Age 40 – 75, no CVD, 1 or more CVD risk factor and calculated risk of and 7.5 – 10%

USPSTF C: Individualized decision

- Age 76 and older: USPSTF I

USPSTF 2016

USPSTF vs. ACA/AHA

- Recommendations modeled in NHANES primary prevention population.

- 3416 adults, 40-75. 21.5% already on statins.

- USPSTF: 15.8% additional
- ACA/AHA: 24.3% additional

- 55% of extra ACC/AHA group 40-59 years old.

Pagidipati, JAMA 2017

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)

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),

- 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)