Update on Lipid Management

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Medical College of Wisconsin
The stats on heart disease

- Over the past 10 years for which statistics are available, the death rate from heart disease has fallen about 39 percent – but the burden and risk factors remain alarmingly high.

- Heart disease strikes someone in the U.S. about once every 34 seconds.

- Heart disease is the No. 1 cause of death in the United States, killing almost 380,000 people a year.

- Heart disease is the No. 1 killer of women, taking more lives than all forms of cancer combined.

- Over the past 10 years for which statistics are available, the death rate from heart disease has fallen about 39 percent.

Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012

Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012
Age-Adjusted Death Rates for CHD‡ by Race/Ethnicity & Sex, U.S., 1999–2008

Deaths/100,000 population

Green - Black, Purple - White, Blue - Hispanic, Red - American Indian, Orange - Asian

Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012
The statistics, continued

- Over 39,000 African-Americans died from heart disease in 2010, the most recent year for which statistics are available.

- Cardiovascular operations and procedures increased about 28 percent from 2000 to 2010, according to federal data, totaling about 7.6 million in 2010.

- About 720,000 people in the U.S. have heart attacks each year. Of those, about 122,000 die.

- About 620,000 people in the U.S. have a first-time heart attack each year, and about 295,000 have recurrent heart attacks.

Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012

Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, NHLBI, February 2012
What accounts for the decline in CV deaths?

Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000


ABSTRACT

Mortality from coronary heart disease in the United States has decreased substantially in recent decades. We conducted a study to determine how much of this decrease could be explained by the use of medical and surgical treatments as opposed to changes in cardiovascular risk factors.
Explaining decrease in CV deaths

Figure 1. Estimated and Observed Reductions in Deaths from Coronary Heart Disease in the United States between 1980 and 2000, Stratified According to Age and Sex.

The bars show the observed decrease in deaths in each age group, and the vertical lines the extreme minimum and maximum estimates in the sensitivity analysis.

Figure 2. Percentage of the Decrease in Deaths from Coronary Heart Disease Attributed to Treatments and Risk-Factor Changes in Our Study Population and in Other Populations.

In the New Zealand study, 1974 to 1981 (Beaglehole et al.), the analysis focused on specific treatments and inferred contribution from risk factors. In the Finland study, 1972 to 1992 (Vartiainen et al.), the analysis focused on risk factors and inferred contribution from treatments.
Decrease in CV deaths

- Reductions in major risk factors accounted for about ½ of the decrease in deaths from coronary heart disease

- The largest contributions for medical therapies came for secondary prevention, treatments for ACS and heart failure

- Revascularization by means of CABG or angioplasty accounted for 7% of overall drop in deaths
Evolution of Lipid Guidelines

- NCEP ATP-I 1988
- NCEP ATP-III 2001
- ACC/AHA 2013
- NCEP ATP-II 1993
- NCEP ATPIII Update 2004
The previous guidelines
ATP III (2001)

Primary goal for treatment: LDL

- <100  Optimal
- 100-129  Near Optimal/Above Optimal
- 130-159  Borderline High
- 160-189  High
- 190  Very high
### ATP III

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>HDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Desirable</td>
<td>Low</td>
</tr>
<tr>
<td>200-239</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Borderline</td>
<td>High</td>
</tr>
<tr>
<td>&gt;240</td>
<td>&gt;60</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>
### Assessment of risk

<table>
<thead>
<tr>
<th>CHD equivalents</th>
<th>Major risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical CHD</td>
<td>Smoking</td>
</tr>
<tr>
<td>Symptomatic carotid artery disease</td>
<td>Hypertension (BP 140/90 mmHg or on antihypertensive medication)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>Low HDL cholesterol (&lt;40 mg/dl)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>Family history of premature CHD (CHD in male first degree relative &lt;55 years; CHD in female first degree relative &lt;65 years)</td>
</tr>
<tr>
<td></td>
<td>Age (men 45 years; women 55 years)</td>
</tr>
</tbody>
</table>
**LDL cholesterol goals and cutpoints for TLC and drug therapy**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL goal</th>
<th>When to initiate TLC</th>
<th>When to consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk &gt; 20% 10 year risk</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
<td>➢ 130</td>
</tr>
<tr>
<td>CHD, and equivalents</td>
<td></td>
<td></td>
<td>➢ (100-129 – drug optional)</td>
</tr>
<tr>
<td>2+ risk factors</td>
<td>&lt; 130</td>
<td>&gt; 130</td>
<td>10-20% risk - &gt; 130</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 20% risk - &gt; 160</td>
</tr>
<tr>
<td>0-1 risk factors</td>
<td>&lt;160</td>
<td>&gt; 160</td>
<td>➢ 190</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>➢ (160-189 – drug optional)</td>
</tr>
</tbody>
</table>
ATP-III update 2004

- Option to lower LDL-C levels to less than 70 mg/dL in high risk patients


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Bacon Good For You, Reports Best Scientist Ever

RADIO NEWS · Science & Technology · ISSUE
45·35 · Aug 26, 2007
New cholesterol guidelines

- The ACC and AHA in collaboration with the NHLBI of the NIH formed an expert panel in 2008 to draft new cholesterol guidelines

- They used evidence from RCTs, reviews and meta-analyses and the predetermined outcomes of these trials (not post-hoc analyses)

- The NHLBI removed itself from the process, and other members removed themselves because of disagreement

- The guidelines and the new cardiovascular risk calculator were released in late 2013 without a preliminary period for discussion or criticism

- No attempt to harmonize the guidelines with previous versions of guidelines or with international guidelines
What’s new?

- Elimination of targets
- High intensity statin therapy emphasized and low intensity statin therapy eliminated
- ASCVD is now inclusive of stroke
- Non-statin therapies markedly de-emphasized
- No guidelines for triglycerides
- Four treatment groups identified
Group 1: Individuals with Clinical ASCVD

- CAD
- PAD
- Cerebrovascular Disease
### Group 1 recommendation

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Potential Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins are recommended in the highest tolerated doses in this high risk group</td>
<td>Follow up LDL levels irrelevant</td>
</tr>
<tr>
<td>Without targets, treatment is simpler and requires less monitoring</td>
<td>Less individualized approach to minimize residual risk</td>
</tr>
<tr>
<td>Cerebrovascular disease is included</td>
<td>Patients no longer have a goal -discourages self-management</td>
</tr>
<tr>
<td></td>
<td>Eliminate consideration of multi-drug consideration</td>
</tr>
<tr>
<td></td>
<td>This undermines potential development of new therapies</td>
</tr>
</tbody>
</table>
Group 2: People with LDL > 190

- These patients should receive statins in maximally tolerated doses
- New guidelines suggest consideration of additional agents if LDL remains above 190 with maximally tolerated statin therapy
Group 3: Diabetics

- **Who:**
  - Age 40-75
  - LDL-C 70-189
  - No Clinical ASCVD

- **How much:**
  - If 10 year risk > 7.5% - high intensity therapy
  - If 10 year risk < 7.5%, then moderate intensity statin

- **Disadvantages**
  - Does not address patients younger than 40 or older than 75
  - Some patients may be overtreated
  - These patients have high residual risk and may require more aggressive LDL lowering or non-LDL targets for therapy

- **Advantages**
  - Aggressive treatment of a high risk group
Statin dosing

**High Intensity**
- Atorvastatin 40-80 mg
- Rosuvastatin 20 mg – 40 mg

**Moderate Intensity**
- Atorvastatin 10-20 mg daily
- Rosuvastatin 5-10 mg daily
- Simvastatin 20-40 mg daily
- Pravastatin 40-80 mg daily
- Lovastatin 40 mg daily

**Lowers LDL-C ≥ 50%**

**Lowers LDL-C 30-50%**
Group 4: Patients with 10 year risk > 7.5%

- Age 40-75
- LDL 70-189
- No ASCVD
- 10 year risk of >7.5% by new risk calculator

There’s an app for it!
Risk Calculator

ASCVD Risk Estimator*

10-Year ASCVD Risk

8.7% calculated risk
0.4% risk with optimal risk factors**

Lifetime ASCVD Risk

50% calculated risk
8% risk with optimal risk factors

Recommendation Based On Calcul...

Age

42

Race

White
African American
Other

Total Cholesterol (mg/dL)

190

HDL - Cholesterol (mg/dL)

42

Systolic Blood Pressure

138

Treatment for Hypertension

Y  N

Diabetes

Y  N

Smoker

Y  N

*Intended for use if there is not ASCVD and
Risk Calculator

Based on the data entered (assuming no clinical ASCVD and LDL-C 70-189 mg/dL):

- Gender: Female
- Age: 42
- Race: African American
- Total Cholesterol: 190
- HDL-Cholesterol: 42
- Systolic Blood Pressure: 138
- Hypertension Treatment: Yes
- Diabetes: No
- Smoker: Yes

Moderate to High-Intensity Statin Recommended

Before initiating statin therapy, it is reasonable for clinicians and patients to engage in a discussion.
Statins in Primary Prevention

- Recommendation that statins be initiated in primary prevention patients with a 10 year risk of events ≥ 7.5%
- Consideration of statin therapy recommended in patients with 10 year risks of 5-7.5%
- In patients with Diabetes Mellitus, the threshold of greater than or equal to 7.5% is used to determine whether high intensity or moderate intensity statin therapy recommended
- In the guidelines, the new criteria could result in more than 45 million middle aged Americans who do not have cardiovascular disease being recommended for statin therapy
- This is about 1:3 adults (many of which are already on statin)
Primary prevention trials

- Reduction of MI and stroke in those with increased LDL (WOSCOPS, MEGA)
- Reduced HDL cholesterol (AFCAPS/TexCAPS)
- Raised concentrations of CRP (JUPITER), Diabetes (CARDS) or HTN (ASCOT-LLA)
Primary Prevention

- Between 1995-2008 six major primary prevention trials, which included greater than 55,000 men and women showed that statins were effective in primary prevention of MI, CVA among those with elevated LDL, reduced HDL, increased CRP, DM, or HTN.

- No trial of statin therapy has used a global risk prediction score as enrollment criterion

- Statins CANNOT be recommended simply based on high risk without regard for individuals and specific clinical conditions
Special Populations: CORONA trial

- Daily treatment with 10 mg of rosuvastatin did not reduce the composite outcome of death from cardiovascular causes or nonfatal myocardial infarction or stroke in vulnerable, elderly patients with ischemic, systolic heart failure who had already received extensive treatment with drugs for cardiovascular disease.

- However, rosuvastatin reduced the number of hospitalizations for cardiovascular causes, in addition to effectively reducing levels of LDL cholesterol and high-sensitivity C-reactive protein.
Special populations: AURORA trial

- In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level.

- However, there was no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
Special Populations:

- **Expert panel does not make a recommendation in patients with ischemic HF or in patients on maintenance HD.**
The risk calculator is controversial

“It is in the realm of primary prevention that the new guidelines are likely to be more controversial.”

www.thelancet.com, Volume 382, November 30, 2013
Which of these two patients would be considered for statin therapy?

- 55 year old male
- Smoker
- HTN, untreated
- LDL 75, HDL 50
- 9.6% 10 year risk

- 60 year old female
- No HTN
- Non-smoker
- LDL 180, HDL 50
- 3.8% 10 year risk

The context is KEY
More important than absolute risk is the projected treatment effect for the INDIVIDUAL.
Overestimation of risk?

- The predicted 10 year risks of atherosclerotic events using the ACC/AHC algorithm were compared to observed event rates in three large primary prevention cohorts:
  - The Women’s Health Study
  - The Physicians’ Health Study
  - Women’s Health Initiative Observational Study

- The ACC/AHA risk prediction calculatory systematically overestimated observed risks by 75-150%
Does the risk predictor correctly assess vascular risk?
Comparison of observed event rates with predicted event rates in two external validation cohorts
On the basis of the date from five external validation cohorts, it is possible that 40-50% of 33 million Americans targeted by new ACC/AHA guidelines do not have risk thresholds that are greater than 7.5%
Application of New Cholesterol Guidelines to a Population-Based Sample

Michael J. Pencina, Ph.D., Ann Marie Navar-Boggsan, M.D., Ph.D., Ralph B. D’Agostino, Sr., Ph.D., Ken Williams, M.S., Benjamin Neely, M.S., Allan D. Sniderman, M.D., and Eric D. Peterson, M.D., M.P.H.

ABSTRACT

BACKGROUND
The 2013 guidelines of the American College of Cardiology and the American Heart Association (ACC-AHA) for the treatment of cholesterol expand the indications for statin therapy for the prevention of cardiovascular disease.

METHODS
Using data from the National Health and Nutrition Examination Surveys of 2005 to 2010, we estimated the number, and summarized the risk-factor profile, of persons for whom statin therapy would be recommended (i.e., eligible persons) under the new ACC-AHA guidelines, as compared with the guidelines of the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program, and extrapolated the results to a population of 115.4 million U.S. adults between the ages of 40 and 75 years.
Application of New Cholesterol Guidelines to a Population-Based Sample

- Pencina, MJ, et al used data from NHANES (National Health and Nutrition Examination Surveys) 2005-2010, estimated the number and summarized risk factor profile of persons from whom statin therapy would be recommended under new guidelines compared to ATP III.

- New guidelines would increase the number of US adults receiving or eligible for statin therapy from 37.5% (43.2 million) to 48.6% (56 million).

- Effect would largely be driven by increased number of adults who would be classified solely on their 10 year risk.
Extrapolation of the NHANES Sample to All U.S. Adults, According to Two Guidelines for the Management of Cholesterol.

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

All statin recommendations must be made with LIFESTYLE counseling!!

“Lifestyle counseling should occur at the initial and follow-up visits as the foundation for statin therapy and may improve the overall risk factor profile”

Lunch in Milwaukee 😊
ASCVD Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

- **Adults age >21 y and a candidate for statin therapy**

  - **Clinical ASCVD**
    - Yes
    - **LDL-C ≥190 mg/dL**
      - Yes
      - **High-intensity statin**
        - (Moderate-intensity statin if not candidate for high-intensity statin)
      - No
      - **Diabetes**
        - Yes
        - **Estimated 10-y ASCVD risk ≥7.5%**
          - **High-intensity statin**
          - No
          - **Age >75 y OR if not candidate for high-intensity statin**
            - **Moderate-intensity statin**
        - No
        - **Age ≤75 y**
          - **High-intensity statin**
          - (Moderate-intensity statin if not candidate for high-intensity statin)
    - No

**Definitions of High- and Moderate-intensity Statin Therapy (See Table 5)**

- **High**
  - Daily dose lowers LDL-C by approx. ≥50%
- **Moderate**
  - Daily dose lowers LDL-C by approx. 30% to <50%

**Notes**

- LDL-C: Low-Density Lipoprotein-Cholesterol
- ASCVD: Atherosclerotic Cardiovascular Disease
- Statin: A class of cholesterol-lowering drugs
Diabetes
Type 1 or 2
Age 40-75 y

Yes
No

Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*

Yes
No

≥7.5% estimated
10-y ASCVD risk
and age 40-75 y

Yes
No

Moderate-intensity statin

High-intensity statin

Moderate-to-high intensity statin

ASCVD prevention benefit of statin therapy may be less clear in other groups
In selected individuals, consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment
Clinical ASCVD

Not currently on statin therapy
Initial evaluation prior to statin initiation
- Fasting lipid panel*
- ALT
- CK (if indicated)
- Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

Evaluate and Treat Laboratory Abnormalities
1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes (Table 6)
3. Unexplained ALT >3X ULN

Aged ≤75 y without contraindications, conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance
Initiate high-intensity statin therapy
Counsel on healthy lifestyle habits

Aged >75 y† OR with conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance
Initiate moderate-intensity statin therapy
Counsel on healthy lifestyle habits

Monitor statin therapy
(Figure 5)
No history of Clinical ASCVD
No clinical History of ASCVD
Additional factors to consider in treatment decisions

Primary LDL–C >160 mg/dL or other evidence of genetic hyperlipidemias,

- Family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative,

- Elevated C-reactive protein >2 mg/L

- ABI <0.9, or lifetime risk of ASCVD.
Safety Considerations

- In patients recommended for high intensity therapy, consider moderate intensity therapy if patients have characteristics that predispose individuals to statin adverse effects.
  - Multiple or serious comorbidities, including impaired renal or hepatic function.
  - History of previous statin intolerance or muscle disorders.
  - Unexplained ALT elevations >3 times ULN.
  - Patient characteristics or concomitant use of drugs affecting statin metabolism.
  - >75 years of age.
Safety and Monitoring

- Other patients that may warrant consideration to decrease statin intensities may include, but are not limited to:
  - History of hemorrhagic stroke.
  - Asian ancestry.
Safety Considerations (continued)

- CK levels should not be routinely measured – Class III (no benefit)

- Can consider checking CK level in individuals with personal history of muscle events, increased risk for myopathy

- ALT levels should be monitored prior to initiation, but no further follow up levels unless concern for hepatotoxicity

- Should not initiate simvastatin at 80 mg or increase to 80 mg – Class III (harm)
Monitoring and reassessment

- Assess medication and lifestyle adherence
  - Fasting lipid panel

  **Anticipated therapeutic response?**
  - Yes: Reinforce continued adherence
    - Follow-up 3-12 mo
    - Anticipated therapeutic response?
      - Yes: Reinforce improved adherence
        - Increase statin intensity
        - OR Consider addition of nonstatin drug therapy
        - Follow-up 4-12 wk 
        - therefrom as indicated
      - No: Reinforce medication adherence
        - Reinforce adherence to intensive lifestyle changes
        - Exclude secondary causes of hypercholesterolemia
        - (Table 6)
        - Follow-up 4-12 wk
  - No: Less-than-anticipated therapeutic response
    - Intolerance to recommended dose of statin therapy
      - Yes: Management of statin intolerance
        (Table 6, Rac 6)
      - No: Reinforce therapeutic response

Indicators of anticipated therapeutic response and adherence to selected statin intensity:
- High-intensity statin therapy† reduces LDL-C approx. ≥50% from the untreated baseline.
- Moderate-intensity statin therapy reduces LDL-C approx. 30% to <50% from the untreated baseline.
In summary….

- Despite ongoing decline in cardiovascular death rates, the burden of CV disease remains alarmingly high.

- Reduction of CV death rates is in part due to advancement of medical therapies, including statins for both primary and secondary prevention.

- The new guidelines are a departure from old guidelines in that there is no treatment targets.

- Four treatment groups were identified, including: those with ASCVD; individuals with LDL > 190; diabetics age 40-75; and individuals without ASCVD who have estimated 10 year risk of events.

- It has been suggested that risk calculator may overestimate risk in certain patients, and that the number of patients eligible for statin therapy increases especially in the older patients.

- Guidelines guide therapy, and do not mandate it and you still need to have individualized approach in treatment decisions.
Thank You!!!

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