Lipid Update
AHA/ACC 2013 Guidelines

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Goals

• Overview
• Focus on ASCVD risk reduction:
  • 4 statin benefit groups
• A new perspective on LDL-C and/or Non-HDL C treatment goals
• Global risk assessment for primary prevention: 10 year ASCVD risk
• Case applications
• Safety recommendations
• Role of Biomarkers and noninvasive tests
NHANES Top Sins for CVD mortality in Population-Attributable Fractions

• 1. BP (aPAF of 39.2%) with or without treatment >120/80
  • Every 10% increase in hypertension treatment, an estimated 14 000 deaths would be prevented annually

• 2. Current Smoking (14.3)
  • Every 5% increase in smoking cessation would prevent 7000 deaths annually

• 3. Lack of healthy diet of < or =2 healthy diet score (13.2)

• 4. BMI >30 (11.3)

• 5. HbA1c >5.7 (8.2)

• 6. Cholesterol >240 (3.7)
NHANES <2% of Americans met 7 ideal measures

NHANES ’88-’94, ’99-’04, ’05-’10
Y-axis segments shown in blue indicate range from 0 to 0.2. CVD indicates cardiovascular disease; IHD, ischemic heart disease; NHANES, National Health and Nutrition Examination Survey.
NHANES III Linked Mortality File cohort

- 14.5 years of follow-up, participants who met 6 or more vs 1 or fewer cardiovascular health metrics had:
  - 51% lower risk of all-cause mortality
  - 76% lower risk of CVD mortality
  - 70% lower risk of IHD mortality.
Figure 1. Estimated effects of population-wide shifts in systolic BP distributions on mortality.

Table:

<table>
<thead>
<tr>
<th>Reduction in BP (mmHg)</th>
<th>% Reduction in Mortality Stroke</th>
<th>% Reduction in Mortality CHD</th>
<th>Total % Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-6</td>
<td>-4</td>
<td>-3</td>
</tr>
<tr>
<td>3</td>
<td>-8</td>
<td>-5</td>
<td>-4</td>
</tr>
<tr>
<td>5</td>
<td>-14</td>
<td>-9</td>
<td>-7</td>
</tr>
</tbody>
</table>

Why we care about lipids...

Figure 1 Estimate of number of events avoided for every 1.29 mmol/L reduction in cholesterol concentration in 1000 patients

James Shepherd

Resource management in prevention of coronary heart disease: optimising prescription of lipid-lowering drugs

The Lancet, Volume 359, Issue 9325, 2002, 2271 - 2273

http://dx.doi.org/10.1016/S0140-6736(02)09299-1
What’s new in the 2013 AHA Lipid Guidelines

• Focus on ASCVD risk reduction: 4 statin benefit groups
• A new perspective on LDL-C and/or Non-HDL C treatment goals
  • Not a SINGLE RTC to support treatments specific target, i.e. LDL <70, 100
  • NON statin therapy should NOT be used to reduce ASCVD risk, as the benefits are out weighed by risk and the superiority in statin performance
• Global risk assessment for primary prevention: 10 year ASCVD risk
• Safety recommendations
• Role of Biomarkers and noninvasive tests
• Future updates...
Resources to use

• Websites
  • http://my.americanheart.org/cvriskcalculator

• Apps ASCVD Risk estimator (a favorite at the UMHC)
  • FREE in the app store
  • Also gives summaries, lifestyle recommendations, how to initiate, safety recs and external links to guidelines
  • Patient resources and links as well
Population group application

• Estimates of 10-year risk for ASCVD are applicable to:
  • African-American men and women 40 through 79 years of age
  • Non-Hispanic white men and women 40 through 79 years of age

• Other ethnic groups, it is recommended to use the equations for non-Hispanic whites,
  • Though these estimates may **Underestimate** the risk for persons from some race/ethnic groups, especially
    • American Indians,
    • Some Asian Americans (e.g., of south Asian ancestry)
    • Some Hispanics (e.g., Puerto Ricans)
  • **Overestimate** the risk for others, including:
    • Some Asian Americans (e.g., of east Asian ancestry)
    • Some Hispanics (e.g., Mexican Americans)
Targeted Treatment Groups

1. Clinical ASCVD (secondary). No need to risk assess this group
   - Defined by:
     1. ACS,
     2. History of MI,
     3. Stable or unstable angina,
     4. Coronary or other arterial revascularization,
     5. Stroke, or
     6. Peripheral arterial disease presumed to be of atherosclerotic origin.

2. Primary elevations of LDL-C at or > 190 mg/dL

3. Diabetes aged 40-75 with LDL-C 70-189 mg/dL and **without** clinical ASCVD

4. Without clinical ASCVD or diabetes with LDL-C 70 to 189 mg/dL AND estimated 10 yr ASCVD risk of 7.5% or higher
Patient perceptions:
What my doctor wants,
What I actually do
Heart-healthy lifestyle habits are the foundation of ASCVD prevention (See 2013 AHA/ACC Lifestyle Management Guideline)

**Age ≥21 y and a candidate for statin therapy**

- **Clinical ASCVD**
  - Yes
    - **Age ≤75 y**
      - High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
    - No
      - **Age >75 y OR if not candidate for high-intensity statin**
        - Moderate-intensity statin

**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%

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments (See Fig 5)

**LDL-C ≥190 mg/dL**

- Yes
  - High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
- No

**Diabetes**

- **LDL-C 70-189 mg/dL**
  - Yes
    - **Age 40-75 y**
      - Estimated 10-y ASCVD risk ≥7.5%
        - High-intensity statin
    - No
      - Moderate-intensity statin
  - No
    - **DM age <40 or ≥75 y or Primary prevention** (No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)

Primary prevention

(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)
Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)
Estimate 10-y ASCVD risk every 4-6 y using Pooled Cohort Equations†

DM age <40 or >75 y or LDL-C <70 mg/dL

<5%
10-y ASCVD risk†

Age <40 or >75 y and LDL-C <190 mg/dL†

≥7.5%
10-y ASCVD risk (Moderate- or high-intensity statin)

5% to <7.5%
10-y ASCVD risk (Moderate-intensity statin)

In selected individuals, additional factors may be considered to inform treatment decision making§

Clinician-Patient Discussion
Prior to initiating statin therapy, discuss:
1. Potential for ASCVD risk-reduction benefits
2. Potential for adverse effects and drug–drug interactions
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥2 mg/L§

Emphasize adherence to lifestyle
Manage other risk factors
Monitor adherence

No to statin

Yes to statin

Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence* (See Fig 5)
Why statins?

• Statins prevent both nonfatal and fatal ASCVD events
  • (esp. strokes which women bear the brunt of disability in non-lethal strokes)
• STRONG evident to reduce mortality in patients with prior ASCVD
• Moderate evidence without known ASCVD to reduce total mortality with increased risk
How I feel about my patients
A new perspective on LDL-C and/or Non-HDL C treatment goals

• NO LONGER set targets just say no to <70 or <100!
• AIM-HIGH: the additional reduction in non-HDL-C in addition to apo-B, Lp(a) and TGs in addition to HDL-C increases with niacin did NOT reduce ASCVD when pts were treated to LDL-C 40-80 mg/dL (!)
• ACCORD: futility in adding fenofibrate in patients with DM, BUT a subgroup showed in those with high TG and low HDL-C suggested that fenofibrate may reduce ASCVD in pts with DM
Statins in patients with known ASCVD

• All pts <75 yrs with known ASCVD
• If on a statin, go from low or moderate to high-intensity statin if possible
  • High intensity is >50% reduction in LDL-C. Moderate is 30-50%, lower <30% reduction
  • Atorvastatin 40-80mg (IDEAL trial only if not able to handle 80) reduced ASCVD risk more than moderate-intensity with atorvastatin 10, pravastatin 40 or simvastatin 20-40 mg
• if >75 yrs of age
  • no clear evidence of benefit of high dose statin
  • Obvious benefit of moderate intensity.
Statin initiation in ASCVD

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)
   - If primary, screen family for FH
3. Unexplained ALT ≥3 times ULN

Age ≤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

Age >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)
# Statin Dosing

**AHA 2013/AHA Blood Cholesterol Update, Stone et al**

## Table 5. High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C, on average, by approximately $\geq$50%</td>
<td>Daily dose lowers LDL-C, on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C, on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg‡</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>
A rule of thumb for comparing statin doses that lower LDL–C approximately 30% to 35% is:

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>80 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20 mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5 mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

Each doubling of the statin dose usually results in an additional 5% to 7% reduction in LDL–C (i.e. the 6% rule).
Case 1. Kristoff

A 63-year-old man is seen in the office 2 weeks after a ST-elevation myocardial infarction (MI). A former smoker with hypertension, he was discharged on atorvastatin 80mg daily, dual anti-platelet therapy, long-acting metoprolol, and an ACE inhibitor. One year before the acute MI, he was prescribed simvastatin 40 mg which was then increased to simvastatin 80 mg. He stopped the simvastatin 80 mg 2 weeks after developing muscle cramps in his legs. Although he has no muscle symptoms since he started the atorvastatin 80 mg, he is concerned about having had muscle cramps in the past on a statin and would like to decrease the atorvastatin to 20 mg daily. What is the best answer?

1. Randomized trials of high intensity statin therapy versus moderate intensity statin therapy have not shown a significant difference in outcomes. He should decrease the atorvastatin to 20 mg to minimize adverse effects.

2. Systematic meta-analyses of randomized clinical trials support using an intensive statin dose such as atorvastatin 80 mg/day over a moderate intensity statin. He should stay on atorvastatin 80 mg.

3. He should be followed with creatine kinase (CK) values when his lipids are checked at each visit for the first year.

4. Although his liver panel was normal in the hospital, he should have ALT done at each subsequent visit.
Other pearls from Kristoff

- CKs are not needed for screening
- CK obtain if muscle aches or consider in previous muscle aches
- If you have myalgias, do a stop statin and washout
- If after 2 weeks statin free and STILL with myalgic, go after NON-statin cause
- Try a dose reduction or a different statin, i.e. simvastatin to atorvastatin
- In Kristoff, a SLC01B1 deficiency may explain the simvastatin 80 and CCB leading to the muscle aches
  - Simvastatin 80 not rec’d any longer
  - If your pt is on simvastatin 80 for 12 mo. or longer without muscle injury, that’s ok, but don’t initiate or up to that dose
Kristoff’s back... 3 yrs later

• He was on artovastatin 80mg for >2.5 yrs without muscle symptoms. He recently developed progressive myalgias and weakness over weeks. He can’t do 3 squats and 6 mo. prior to was doing many at the local gym. He’s been off statins for 2.5 weeks and still symptomatic. Which is the best answer?

• 1. He should be switched to red yeast rice
• 2. Stay off statin until he’s eval’d for other causes
• 3. Switch to rosuvastatin 40 mg and given CoQ10
• 4. He should be re-challenged with atorvastatin 80
• If he’s AA, CK levels are not useful in evaluating muscle symptoms
Myalgias are not always statin!

• Off >2 weeks, look elsewhere:
  • PMR, etoh use, hypothyroidism, primary muscle disease
  • CK, ESR, etc.

• In Kristoff,
  • CK WNL
  • ESR >100
  • Treated for PMR and then had statin re-instated

• Xuezhikang, red yeast rice extract
Lifestyle... Yes, I am serious... You should be too

- Low fat vegetarian diet
- NO STATIN
- Meditation/Yoga
- Exercise
- Eating/ cooking
- Induction
- Less LDL decreased, but MORE reduction in atherosclerosis load and events... just sayin’
- >50-54% adherence

**Table 5: Univariate and Multivariate analysis of various parameters in regression of CAD**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt_d≥3.0</td>
<td>8.71</td>
<td>1.81</td>
<td>41.76</td>
<td>0.006</td>
<td>12.96</td>
<td>0.43</td>
</tr>
<tr>
<td>Tc_d≥15.8</td>
<td>2.10</td>
<td>0.69</td>
<td>6.37</td>
<td>0.190</td>
<td>0.07</td>
<td>0.009</td>
</tr>
<tr>
<td>LdL_d≥11.0</td>
<td>2.18</td>
<td>0.74</td>
<td>6.40</td>
<td>0.155</td>
<td>0.52</td>
<td>0.007</td>
</tr>
<tr>
<td>HDL_d≥0.9</td>
<td>2.97</td>
<td>0.98</td>
<td>9.03</td>
<td>0.054</td>
<td>2.47</td>
<td>0.072</td>
</tr>
<tr>
<td>Tg_d≥29.1</td>
<td>3.90*</td>
<td>1.13</td>
<td>13.37</td>
<td>0.030</td>
<td>144.22</td>
<td>0.966</td>
</tr>
<tr>
<td>Exercise ≥60%</td>
<td>4.69*</td>
<td>1.52</td>
<td>14.43</td>
<td>0.007</td>
<td>0.07</td>
<td>0.0006</td>
</tr>
<tr>
<td>Diet ≥60%</td>
<td>7.08*</td>
<td>2.23</td>
<td>22.44</td>
<td>0.0009</td>
<td>3.72</td>
<td>0.096</td>
</tr>
<tr>
<td>Rajyoga ≥40%</td>
<td>164.0*</td>
<td>17.94</td>
<td>1498</td>
<td>0.0000</td>
<td>34773*</td>
<td>2.63</td>
</tr>
<tr>
<td>Program ≥54%</td>
<td>72.0*</td>
<td>8.58</td>
<td>604</td>
<td>0.0001</td>
<td>33.38</td>
<td>0.509</td>
</tr>
</tbody>
</table>

**Table 6: Cardiac events over a mean followup period of 6.48 ± 1.56 (range 0.35 - 8.34 yrs). Values are Mean ± SD**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of Coronary Events</th>
<th>Most, Vs Least adherence</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA requiring hospital admission</td>
<td></td>
<td></td>
<td>3.59</td>
<td>0.96 - 13.59</td>
<td>0.06</td>
</tr>
<tr>
<td>Myocardial Infarction (Non Fatal)</td>
<td></td>
<td></td>
<td>1.15</td>
<td>0.10 - 13.26</td>
<td>0.909</td>
</tr>
<tr>
<td>Requirement of CABG</td>
<td></td>
<td></td>
<td>6.82</td>
<td>0.83 - 56.09</td>
<td>0.074</td>
</tr>
<tr>
<td>Requirement of PCI</td>
<td></td>
<td></td>
<td>1.16</td>
<td>0.20 - 6.73</td>
<td>0.899</td>
</tr>
<tr>
<td>Cardiac Mortality (Fatal MI)</td>
<td></td>
<td></td>
<td>1.009</td>
<td>0.27 - 3.75</td>
<td>0.094</td>
</tr>
<tr>
<td>Any event</td>
<td></td>
<td></td>
<td>4.32</td>
<td>1.69 - 11.05</td>
<td>0.022</td>
</tr>
<tr>
<td>No. of persons suffering cardiac events</td>
<td></td>
<td></td>
<td>1.96</td>
<td>0.76 - 5.02</td>
<td>0.163</td>
</tr>
<tr>
<td>Average event per person</td>
<td></td>
<td></td>
<td>0.225</td>
<td>0.305 - 0.70</td>
<td></td>
</tr>
<tr>
<td>Average follow up in yrs (Range)</td>
<td></td>
<td></td>
<td>6.91 (0.96)</td>
<td>5.64 (1.37)</td>
<td>6.20 (1.88)</td>
</tr>
<tr>
<td>Person years of observation</td>
<td></td>
<td></td>
<td>214.30</td>
<td>236.47</td>
<td>334.58</td>
</tr>
</tbody>
</table>

*Indian Heart J. 2011; 63:461-469
Satish K Gupta et al.*
Table 4: Changes in coronary artery lesions as per program adherence. Value are Mean ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>Overall adherence</th>
<th>p</th>
<th>Most adherence</th>
<th>p</th>
<th>Medium adherence</th>
<th>P</th>
<th>Least adherence</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Diameter Stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>73</td>
<td></td>
<td>22</td>
<td></td>
<td>26</td>
<td></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>No. of lesions</td>
<td>306</td>
<td></td>
<td>102</td>
<td></td>
<td>118</td>
<td></td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65.40 ± 14.11</td>
<td>70.06 ± 8.09</td>
<td>64.64 ± 12.36</td>
<td>62.47 ± 13.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 m</td>
<td>59.13 ± 19.95</td>
<td>59.00 ± 13.84</td>
<td>52.78 ± 17.48</td>
<td>71.03 ± 17.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change at 24 m</td>
<td>6.10 ± 17.23</td>
<td>18.23 ± 12.94</td>
<td>11.85 ± 11.38</td>
<td>-10.96 ± 13.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative change at 24 m</td>
<td>7.05 ± 35.04</td>
<td>29.05 ± 15.12</td>
<td>19.10 ± 20.22</td>
<td>-23.03 ± 38.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trends in % Diameter Stenosis

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>No. of patients</th>
<th>No. of patients</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>21</td>
<td>0</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>28.77%</td>
<td>0.00%</td>
<td>7.69%</td>
<td>76.00%</td>
</tr>
<tr>
<td>No change</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>8.22%</td>
<td>9.89%</td>
<td>3.85%</td>
<td>12.00%</td>
</tr>
<tr>
<td>Regression</td>
<td>46</td>
<td>20</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>63.01%</td>
<td>90.91%</td>
<td>88.46%</td>
<td>12.00%</td>
</tr>
</tbody>
</table>

Overall Chi Square = 40.5, p<0.0001

Trends in Coronary Lesion Severity

<table>
<thead>
<tr>
<th></th>
<th>No. of lesions</th>
<th>No. of lesions</th>
<th>No. of lesions</th>
<th>No. of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression &gt; 10%</td>
<td>40</td>
<td>1</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>12.90%</td>
<td>3.20%</td>
<td>5.08%</td>
<td>33.68%</td>
</tr>
<tr>
<td>No change &lt; 10%</td>
<td>159</td>
<td>36</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>50.00%</td>
<td>45.80%</td>
<td>54.24%</td>
<td>60.20%</td>
</tr>
<tr>
<td>Regression &gt; 10%</td>
<td>119</td>
<td>48</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>37.40%</td>
<td>40.68%</td>
<td>40.68%</td>
<td>6.12%</td>
</tr>
</tbody>
</table>

Overall Chi Square = 102.57, p<0.000
Lipid metabolism
Triglycerides

• Clear increase risk of ASCVD with increased TG, female > men
• 25% undiagnosed DM
• Consider familial if > 95\textsuperscript{th} percentile
  • >1000 FCHL
  • FHTG, Apo C II def, Apo-A5, GP1HBP1
• If high after diet, exercise, glucose control and removal of offending drugs, toxins (ETOH) consider genetic. See handout
• Lipodystrophy

| Table 1. Triglyceride Classification Revisions Between 1984 and 2001 |
|-------------------------|-------------------|-------------------|
| Desirable               | <250               | <200               | <150               |
| Borderline-high         | 250–499            | 200–399            | 150–199            |
| High                    | 500–999            | 400–999            | 200–499            |
| Very high               | >1000              | >1000              | ≥500               |
Screen With Nonfasting Triglycerides

- **<200**
  - Follow-up as required

- **≥200**
  - Fasting lipoprotein panel

<table>
<thead>
<tr>
<th>Optimal</th>
<th>Normal</th>
<th>Borderline</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>&lt;150</td>
<td>150–199</td>
<td>200–499</td>
<td>≥500*</td>
</tr>
</tbody>
</table>

**Recommendations**

- **Weight loss**: Up to 5%
- **Carbohydrates**: 50%–60%
  - Added sugars: <10%
  - Fructose: <100 g
- **Protein**: 15%
- **Fat**: 25%–35%
  - TFA: Avoid
  - SFA: <7%
  - MUFA: 10%–20%
  - PUFA: 10%–20%
  - EPA/DHA: 0.5–1 g
- **Aerobic activity**: at least 2x weekly

**Pharmacologic therapy**
Triglycerides

- If statin candidate, statin first, then...
- Fibrate, if primary and then 2-4 grams EPA (VA-HIT)
- Fibrate esp. if DM not at goal and TG > 204 and HDL low <34 (ACCORD)
- JELIS high risk group (TG >180 and HDL<40) statin and EPA had reduced 53% ASCVD risk

**Table 11. Effects of Nutrition Practices on Triglyceride Lowering**

<table>
<thead>
<tr>
<th>Nutrition Practice</th>
<th>TG-Lowering Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (5% to 10% of body weight)</td>
<td>20</td>
</tr>
<tr>
<td>Implement a Mediterranean-style diet vs a low-fat diet</td>
<td>10–15</td>
</tr>
<tr>
<td>Add marine-derived PUFA (EPA/DHA) (per gram)</td>
<td>5–10</td>
</tr>
<tr>
<td>Decrease carbohydrates</td>
<td></td>
</tr>
<tr>
<td>1% Energy replacement with MUFA/PUFA</td>
<td>1–2</td>
</tr>
<tr>
<td>Eliminate trans fats</td>
<td></td>
</tr>
<tr>
<td>1% Energy replacement with MUFA/PUFA</td>
<td>1</td>
</tr>
</tbody>
</table>
Case 2. Sven

- 48 yr man with FH and hx of CABG x3 7 years ago for statin intolerance. Max dose he tolerates is rosuvastatin 10 mg twice a week. If taken more than this, he has diffuse aching without weakness and a normal CK. Most recent FLP showed: LDL-C of 168, TG 138, and HDL-C of 46. Initial LDL-C was 240. Which is the best answer?

- 1. Ezetimibe has been shown to further reduced ASCVD events when added to statin therapy. Continue statin and add ezetimibe 10 mg

- 2. Gemfibrozil has been shown to reduce the ASCVD events when used as monotherapy in men with CAD. Continue statin, add gemfibrozil

- 3. Bile acid sequestrants have been shown to reduce ASCVD events when used as monotherapy in men with primary hypercholesterolemia. Continue statin, add cholestyramine 4 g packets BID

- 4. DC the rosuvastatin and begin the lovastatin 40 mg daily
Sven pearls

• Didn’t get 50% reduction, but STAY on statin. Even the 72 decrease means 40% reduction in ASCVD risk for him
• If used as monotherapy, niacin and bile acid sequestrants reduce ASCVD events, but AIM-HIGH showed 0 benefit to adding either niacin or ezetimibe to statin.
• IMPROVE-IT showed ezetimibe with simvastatin with CKD reduced ASCVD events
• While gemfibrozil reduced ASCVD events in men with CAD, CAN’T use with statin due to HIGH risk of myopathy and rhabdomyolysis. Consider if absolutely no statin possible.
• Rosuvastatin has the best LDL-C reduction for dose
Case 3. Elsa

- 26 yr woman with an LDL-C 260 mg/dL, TG 102, since her teens has tried lots of diets. Dad died of MI at 38, and dad’s brother diet of stroke at 32. Both were smokers. She’s on a second gen OCT and is wondering if she should get off. She wants to conceive. She “social smokes”. BP 110/60, BMI 24. Bl inferior pole cornea arcus, no xanthelasma, thickened Achilles tendon. CV exam WNL. Which is the best answer?

- 1. She’s likely heterozygous for familial hypercholesterolemia and should start high-intensity statin
- 2. if her partner has normal cholesterol, the likelihood of her child having her genetic condition is an icy 1 in 4
- 3. Cigarette smoking should be stopped because of desired pregnancy
- Stop oct and start high dose statin
- Estimate 10 yr risk of ASCVD and then consider statin
Elsa

- She’s heterozygous for FH
- HIGH statin BY THE AGE OF 21
- Continue contraception while on statin. It’s class X
- Once planned for pregnancy, stop 2-3 mo in advance, resume after lactation complete. Use non-estrogen.
- Autosomal Dominant, so 1:2
- These folks should NEVER smoke
- Counsel other lifestyle
Primary prevention

- LDL-C >190 mg/dL
- Reduction in risk: diet, exercise, meditation, stress reduction, health awareness
- Look for secondary causes when LDL-C >190mg/dL and TG >500mg/dL if not clear to be FH
- If no secondary causes, screen for genetic source, then do family testing and counseling
- Screen for alt >3 times ULN
Secondary causes

- If TG non-fasting >500 get fasting, if >500 fasting, genetic testing (if not uncontrolled DM)
- Most common:
  - Excess ETOH
  - Uncontrolled DM
  - Overt albuminuria
- Pregnancy and lactation
  - **Normal** progressive rise of cholesterol and TG
  - Contraindicated statins, ezetimibe, niacin

### Table 6. Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL-C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Saturated or <em>trans</em> fats, weight gain, anorexia nervosa</td>
<td>Weight gain, very-low-fat diets, high intake of refined carbohydrates, excessive alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, rapaloxifene, tamoxifen, beta blockers (not carvedilol), thiazides</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hypothyroidism, obesity, pregnancy*</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy*</td>
</tr>
</tbody>
</table>
Starts before birth and in childhood....
Primary prevention

• For each 39 mg/dL reduction in LDL-C by statin, reduced ASCVD risk by about 20%
• AFCAPS-TEXCAPS and MEGA trials looked at target # goal, no benefit to LDL-C <100 vs % reduction
• If LDL-C >190 mg/dL, high dose statin regardless or 10 yr risk
• GOAL: at least 50% reduction in LDL-C
• If can’t tolerate, highest dose tolerable
• May add other drugs to achieve greater reduction, but this is “expert opinion”
• However, add a drug when 50% reduction didn’t occur
No Clinical ASCVD
Not currently on cholesterol-lowering drugs
Initial evaluation prior to statin initiation
- Fasting lipid panel*
- ALT
- Hemoglobin A1c (if diabetes status unknown)
- 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)
   - If primary, screen family for FH
3. Unexplained ALT ≥3 times ULN

Assign to statin benefit group
(Figure 2)
Counsel on healthy-lifestyle habits

Diabetes and age 40-75 y†
OR
LDL-C ≥190 mg/dL

No diabetes, age 40-75 y, and
LDL-C 70-189 mg/dL

Yes

Estimate 10-y ASCVD risk using
Pooled Cohort Equations†
Yes

Estimate 10-y ASCVD risk using Pooled Cohort Equations†

≥7.5% 10-y ASCVD risk

Clinicians and patients should engage in a discussion of the potential for:
1. ASCVD risk-reduction benefits§
2. Adverse effects§
3. Drug–drug interactions
4. Patient preferences

Initiate statin therapy (Figure 2)
Re-emphasize healthy-lifestyle habits

<5% 10-y ASCVD risk

<5% 10-y ASCVD risk

Age <40 or >75 y and LDL-C <190 mg/dL

In selected individuals, additional factors may be considered to inform treatment decision making‡
Case 4. Anna

- 60 yr AA female here to inquire about starting a statin, but worried about it causing DM. Her mom had DM and a stroke at 62. She’s a non-smoker, BP 142/88 on 2 BP meds and BMI is 31. FLP shows total cholesterol of 200, HDL-C 55, TG 100, LDL-C 125. fasting BG is 109 and HbA1C 5.9%. What’s her 10 Yr ASCVD risk? Which is the best answer?

- 1. She should focus on lifestyle change to improve her risk because lifestyle has been show to reduce risk > than statins
- 2. Risk of progression to DM with a statin outweighs any ASCVD risk reduction from statins. No statin
- 3. She should start a moderate or high-intensity statin
- 4. A high-sensitivity CRP >2 would be needed to help decide to start a statin
Anna

- Risk >7.5% 10 yr moderate or high based on evidence (AFCAPS/TexCAPS, MEGA, JUPITER)
- AA women have higher risk that similarly aged non-hispanic white women
- She is not DM... YET, LIFESTYLE CHANGE. MetS = metformin
- JUPITER showed women >60 with a CRP >2 had a reduction of ASCVD events with rosuvastatin 20
- Moderate intensity statin results in 1 new DM, while preventing 5.4 ASCVD events per 1000 individuals/1 year
- High intensity statin resulted in 3 new DM while preventing 5.9 ASCVD events per 1000 individuals/1 year
- However this happened within the first 6 weeks, so may have been natural progression in metabolic syndrome
- Would only get hsCRP if ASCVD risk <7.5% and considering statin
Case 5. Hans

- 35 yr man with a strong FMH of premature CAD with both dad and bro having MI <55. He’s a non-smoker, non-DM, exercising 150m minutes/week. He’s gained 10 lbs since 18 yrs age. BP 140/90, wt 170 lb, ht 70 in, BMI 24.4. FLP showed LDL-c 160mg/dL, HDL-C 45 mg/dL, TG 100. He also eats a heart healthy diet. His wife wants to discuss statin option given FMH.

Which would be the most helpful in making a statin decision?

- 1. Strong FMH of premature ASCVD
- 2. CAC score of 300 units or more
- 3. hs- CRP > or equal to 2.0 mg/L
- 4. Lifetime risk of ASCVD
- 5. LDL-C at or >160
- 6. All of these can be considered
All things considered...

• Primary LDL-C at or more than 160 mg/dL or other evidence or genetic hyperlipidemias
• FMH of premature ASCVD first degree relative <55 in male, <65 female in first degree female relative
• High CRP > or equal to 2 mg/dL
• CAC of at least 300 Agaston units or at or > 75 percentile for age, sex and ethnicity
• ABI <0.9
• Elevated lifetime risk of ASCVD (5-7.5%), or still consider if have any above AND <5% 10 yr risk.

• For Hans, consider atorvastatin 10/day, simvastatin 20-40, or rosuvastatin 10. Reinforce good habits. Offer low fat vegetarian diet, exercise, meditation, stress reduction, and limit “crap” in diet. TALK. TALK.
Case 6. Olafa

- A 44 yr woman has a 10 year hx of type 2 DM. She is a non-smoker with well-controlled DM and microalbuminuria. She is on dietary management, metformin, and takes one omega-3 fatty acid capsule with 840 mg EPA and DHA, lisinopril/HCTZ for BP. FMH of DM, but not premature ASCVD. She has BP of 134/78, BMI 36, FLP LDL-C 95, TG 350, and HDL-C 38, HbA1c 7.5%. **What is the best answer?**

- 1. Her LDL-C is under 100 so she at goal and doesn’t require a statin
- 2. She should start simvastatin 20 mg and fenofibrate 160 mg a day
- 3. To reduce her risk of ASCVD event, the dose of omega-3 should be increased to 4 capsules daily to lower her TGs
- 4. If she does not want a statin, a bile acid Sequestrant is the next best choice for her
- 5. Her 10 yr ASCVD risk should be calculated to determine if she needs a high or moderate intensity statin
No Clinical ASCVD
Not currently on cholesterol-lowering drugs
Initial evaluation prior to statin initiation
- Fasting lipid panel*
- ALT
- Hemoglobin A1c (if diabetes status unknown)
- CK (if indicated)
- Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1)

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(Figure 2)
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1. ASCVD risk-reduction benefits§
2. Adverse effects§
3. Drug–drug interactions
4. Patient preferences

Initiate statin therapy
(Figure 2)
Re-emphasize healthy-lifestyle habits

Monitor statin therapy
(Figure 5)

5% to <7.5% 10-y ASCVD risk

<5% 10-y ASCVD risk

Age <40 or >75 y and LDL-C <190 mg/dL

In selected individuals, additional factors may be considered to inform treatment decision making‡
The real problem
Olafa Pearls

• She is DM, 40-75 with and LDL 70-189= statin benefit
• CARDS trial showed women and men with DM, no ASCVD, had reduced ASCVD events with just moderate atorvastatin 10 mg a day
• JUPITER rosuvastatin 20 reduced ASCVD events
• If 10 yr ASCVD risk >7.5% HIGH intensity
• Don’t need to know APO B or LDL particle number
• ACCORD showed no benefit adding fenofibrate to women with TG and love HDL-C. Statins help no matter the LDL #
• JELIS show 1800 mg EPA added to low dose statin in Japanese women, no primary benefit seen, EXCEPT 53% ASCVD risk reduction in high risk group
• Bile acid sequestrants can lower HbA1c, but elevate TG. Only start when TG <250-300 mg/dL
• LIFESTYLE: consider low fat vegetarian, low-fat vegan with supplements, Mediterranean diet, NO processed foods. Why?
• NO HDL-C increasing drugs are shown (YET) to reduce ASCVD events in statin tx’d patients
• AHA recs 2-4 grams EPA and DHA daily for TG lowering, marine preferable (need RCT)
How times change
Practical application From the Canada

Install a desktop calculator having characteristics congruent with your practice

• CCS algorithms using FRS might be most appropriate for Canada
• Quantification of dietary, exercise, and statin interventions are helpful
• Tool should include the following: real-time display of changes in risk factors and interventions that are turned on and off;
• graphics capability to display effects of risk factor changes on CVD risk;
• ability to generate cardiovascular age, which might improve patients’ understanding and
• decision support option for age thresholds, diabetes, and family history

Use 10-y CVD risk as threshold for treatment in place of LDL level

• LDL levels are referenced only as extremes of the primary prevention spectrum and are no longer used as thresholds for intervention

Abandon treatment goals

• In place of treatment goals ...maximize change in dietary pattern with patient input;
• maximize exercise interventions with patient input;
• optimize exercise and assess myalgia before statin introduction;
• use statin therapy according to degree of FRS; and
• consider dispensing with LDL follow-up unless you think it will motivate the patient. This concept might have to be introduced gradually
## Implementation take home

<table>
<thead>
<tr>
<th>Use statin dosing according to level of FRS and patient tolerance</th>
<th>If intolerant, remember that a low-dose statin can give two-thirds of maximal lipid lowering. High-risk patients require high-intensity dosing or maximally tolerated dosing. Myalgia might respond to changes in dosing, timing, statin type, or dosing intensity.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abandon hsCRP measurement as part of risk assessment</td>
<td>No longer part of treatment decision.</td>
</tr>
<tr>
<td>Treat all patients with diabetes aged 40 to 75 y according to recommendations</td>
<td>Treat with moderate-intensity statin if no risk factors are present. Treat with high-intensity statin if risk factors are present or the 10-y CVD risk is ≥ 7.5%.</td>
</tr>
<tr>
<td>Treat all adults with LDL ≥ 5.0 mmol/L according to recommendations</td>
<td>Consider a secondary cause or familial hyperlipidemia. Consider consultation.</td>
</tr>
<tr>
<td>Make the patient part of the intervention decision</td>
<td>A lifestyle commitment can modify risk and reduce need for drug use. Patients’ understanding of absolute risk reduction using statins might influence treatment threshold. A 10-y CVD risk treatment threshold of 7.5% is always negotiable.</td>
</tr>
</tbody>
</table>
Questions?

KEEP CALM AND ASK ME QUESTIONS