Confusion about guidelines: How should we treat lipids?

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Disclosures

- Board and committee membership—National Lipid Association, Foundation of National Lipid Association
- Guideline development—ACC/AHA 2013 Cholesterol Guideline, Endocrine Society Triglyceride Clinical Practice guideline, National Lipid Association Familial Hypercholesterolemia Recommendations
- Research contracts—Merck, Genzyme/ISIS, Genzyme/Sanofi-Aventis, Glaxo-Smith-Kline, Regeneron/Sanofi-Aventis, Amarin, Amgen, Pfizer, Genentech/Roche, IONIS, Regeneron (all grants to medical school)
- Consulting—Sanofi-Aventis, OptumRx, uniQure
- Editorial—Merck (Merck Manual)
Questions

- Who should be treated to lower cardiovascular risk?
- Where do guidelines agree?
- Where do guidelines disagree?
- Should we treat to a goal?
- Should men and women be treated differently?
- What about young patients, older patients?
- What medications should we use?
- Should we use more than one medication?
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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2013 ACC/AHA Cholesterol Guideline to Reduce ASCVD Risk Focused on Net Benefit from Treatment

Major recommendations for *initiating* statin therapy

Heart healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

- Adults 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)

- Yes
  - Age >75 y OR if not candidate for high-intensity statin
    - Moderate-intensity statin

LDL–C ≥190 mg/dL

- Yes
  - High-intensity statin
    (Moderate-intensity statin if not candidate for high-intensity statin)

- No
  - Yes
    - Diabetes
      - Type 1 or 2
      - Age 40-75 y
        - Yes
          - Estimated 10-y ASCVD risk ≥7.5%*
            - High-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%
2013 ACC/AHA Cholesterol Guideline to Reduce ASCVD Risk Focused on Net Benefit from Treatment

Major recommendations for *initiating* statin therapy (cont)

**Clinician-Patient Discussion**
Prior to initiating statin therapy, discuss:
1. Potential for ASCVD risk reduction benefit
2. 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
3. Potential for adverse effects and drug-drug interactions
4. Healthy lifestyle
5. Management of other risk factors
6. Patient preferences

**Emphasize adherence to lifestyle**
Manage other risk factors
Monitor adherence

**Encourage adherence to lifestyle**
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence (See Fig 5)
Overview of 2013 ACC/AHA cholesterol guideline

1. Treat blood cholesterol to reduce ASCVD risk
2. Healthy lifestyle is the foundation for ASCVD risk reduction
   • Background therapy for all randomized controlled trials
   • ACC/AHA 2013 Lifestyle and Obesity Guidelines
3. Use appropriate intensity of statin therapy to reduce ASCVD risk in those most likely to benefit
   • Quantitative comparison of statin ASCVD risk reduction versus adverse effects
   • Emphasis on 4 statin benefit groups (Strong evidence)
     • Other groups may benefit from statins (Less evidence)
   • Use Pooled Cohort Equations to estimate 10-year ASCVD risk in primary prevention LDL-C 70-189 mg/dl
     • Regularly monitor adherence to lifestyle & drug therapy – including LDL-C
4. Only consider nonstatin therapy for additional LDL-C lowering after maximizing lifestyle & statin therapy in high risk patients

Where do most guidelines agree?

- Treat according to risk—the higher the risk, the more intensive the therapy
- Start with lifestyle modification
- Secondary prevention
  - Patients with ASCVD are at high risk
  - Some patients are very high risk
- Primary prevention
  - Most controversial
  - Assess risk and treat more intensively if at higher risk
Emphasis on healthy lifestyle

- Initial treatment for everyone
- Risk estimator provides lifetime risk estimate for patients 20 to 59
- This helps to drive discussions of greater adherence to heart-healthy lifestyle and improved risk factors
- Can be helpful in the decision process in people with lower short-term risk but high lifetime risks
Lifestyle Recommendations Include:
Advise Adults Who Would Benefit from LDL-Cholesterol Lowering to:

- Consume a dietary pattern that emphasizes
  - Intake of vegetables, fruits, and whole grains
  - Includes low-fat dairy products, poultry, fish, legumes
  - Non-tropical vegetable oils and nuts

And limits intake of:
- sweets, sugar-sweetened beverages & red meats.

- Aim for a dietary pattern that achieves 5%–6% of calories from saturated fat.

Low Saturated Fat Foods

- Skim milk and low-fat dairy products
- Margarine and unsaturated vegetable oils (soybean, corn, canola) **NOT COCONUT OIL**
- Lean meat, poultry, and fish
- Whole-grain breads and cereals
- Most fruits and vegetables
Clinician – Patient Discussion before Statin Therapy

- Estimate 10-year ASCVD risk
- Review other risk factors and risk factor control
- Review potential for benefit from heart-healthy lifestyle
- Review potential for benefit from statins and potential for adverse effects and drug-drug interactions
- Consider patient preferences
Additional factors to consider when evaluating risk

- For those patients where a risk decision is uncertain, these factors may inform clinical decision making in the context of the clinician-patient discussion:
  - LDL-C $\geq 160$ mg/dL
  - Family history of premature ASCVD
  - Increased lifetime risk
  - Hs-CRP $\geq 2$
  - Coronary calcium score $\geq 300$
  - Ankle-brachial index $< 0.9$

NOTE: Guidelines do not supersede clinical judgment. Treatment thresholds and goals without consideration of risk makes less sense than personalizing therapy to the patient’s risks and preferences
Monitoring and follow up

- Adherence to a heart healthy lifestyle
  - Optimal adherence to help improve lipids, affect other risk factors
- Each visit review adherence to statin
  - Maximally tolerated statin intensity and lifestyle to keep LDL-C low
- Measure lipids regularly
  - 3-12 weeks after start, then 4-12 months as appropriate to check adequacy of statin therapy
  - If not taking statin—why?
  - Consider secondary causes of LDL-C elevation (e.g. hypothyroidism)
  - If high risk and inadequate response, consider non-statin therapy
  - There are biologic differences in response (e.g. FH patients)
- Review safety issues at each visit with history, and labs if appropriate
  - For example: some may need CK, fasting glucose, hemoglobin A1c
Where guidelines disagree: targets

- No targets/goals—intensity of statin therapy
  - ACC/AHA
  - ACC non statins
- Yes targets/goals—LDL-C, non-HDL-C, apo B—stratified by risk
  - National Lipid Association
  - American Association of Clinical Endocrinologists
# NLA: Treatment Goals and Levels to Consider Drug Therapy According to Risk Category

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy Non-HDL-C (LDL-C) mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;130 (&lt;100)</td>
<td>≥190 (≥160)</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;130 (&lt;100)</td>
<td>≥160 (≥130)</td>
</tr>
<tr>
<td>High</td>
<td>&lt;130 (&lt;100)</td>
<td>≥130 (≥100)</td>
</tr>
<tr>
<td>Very High</td>
<td>&lt;100 (&lt;70)</td>
<td>≥100 (≥70)</td>
</tr>
</tbody>
</table>

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Goals versus Intensity of Therapy

- Lack of randomized trial evidence to support titration of drug therapy to specific LDL-C and/or non-HDL-C goals
- Strong evidence that appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit
- Randomized trial data allows quantitative comparison of statin benefits with statin adverse effects
  - Important in discussions regarding benefit/risk of diabetes with statin therapy
  - Number-needed-to-treat compared with number-needed-to-harm
Treat Patients With the Greatest Absolute Risk the Most Aggressively

Why stop at 100 or 70 mg/dl?
No lower LDL-C limit for ASCVD risk reduction

Relative reduction CVD Risk by Achieved LDL-C level (mg/dl)

-56
-49
-44
-42
-36
-29

*Individual level meta-analysis adjusted for sex, age, smoking, diabetes, SBP, HDL-C

Individual meta-analysis 26 Statin RCTs (n=170,000)

Similar relative risk reduction per 1 mmol/l reductions in LDL-C across all subgroups.

CTT 2010 meta-analysis 26 statin trials

CTT Collaboration. Lancet 2010; 376: 1670-81:

<table>
<thead>
<tr>
<th>Event Rate (n)</th>
<th>Statin/more</th>
<th>Control/less</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Heterogeneity/trend test</th>
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<tbody>
<tr>
<td></td>
<td>Previous vascular disease</td>
<td></td>
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</tr>
<tr>
<td>CHD</td>
<td>8395 (4.5%) 10123 (5.6%)</td>
<td>7995 (4.5%) 10168 (5.7%)</td>
<td>0.79 (0.75-0.82)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Non-CHD vascular</td>
<td>674 (3.1%) 802 (3.7%)</td>
<td>674 (3.1%) 802 (3.7%)</td>
<td>0.81 (0.71-0.92)</td>
<td>p=0.1</td>
</tr>
<tr>
<td>None</td>
<td>1904 (4.4%) 2425 (1.8%)</td>
<td>1904 (4.4%) 2425 (1.8%)</td>
<td>0.75 (0.69-0.82)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>145 (4.5%) 192 (6.0%)</td>
<td>145 (4.5%) 192 (6.0%)</td>
<td>0.77 (0.58-1.01)</td>
<td>p=0.3</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>2014 (4.2%) 2920 (5.1%)</td>
<td>2014 (4.2%) 2920 (5.1%)</td>
<td>0.80 (0.74-0.86)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>No diabetes</td>
<td>8272 (3.2%) 10163 (4.0%)</td>
<td>8272 (3.2%) 10163 (4.0%)</td>
<td>0.78 (0.75-0.81)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>8712 (3.5%) 10725 (4.4%)</td>
<td>8712 (3.5%) 10725 (4.4%)</td>
<td>0.77 (0.74-0.80)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Female</td>
<td>2261 (2.5%) 2625 (2.9%)</td>
<td>2261 (2.5%) 2625 (2.9%)</td>
<td>0.83 (0.76-0.90)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>6086 (2.9%) 7455 (3.6%)</td>
<td>6086 (2.9%) 7455 (3.6%)</td>
<td>0.78 (0.75-0.82)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>&gt;65 to ≤75</td>
<td>4032 (3.7%) 4908 (4.6%)</td>
<td>4032 (3.7%) 4908 (4.6%)</td>
<td>0.78 (0.74-0.83)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>&gt;75</td>
<td>485 (4.8%) 917 (5.4%)</td>
<td>485 (4.8%) 917 (5.4%)</td>
<td>0.84 (0.73-0.97)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>6176 (3.7%) 7350 (4.5%)</td>
<td>6176 (3.7%) 7350 (4.5%)</td>
<td>0.80 (0.76-0.84)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>4543 (2.7%) 5707 (3.5%)</td>
<td>4543 (2.7%) 5707 (3.5%)</td>
<td>0.76 (0.72-0.80)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;140</td>
<td>5470 (3.2%) 6500 (3.8%)</td>
<td>5470 (3.2%) 6500 (3.8%)</td>
<td>0.80 (0.77-0.85)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>≥140 to &lt;160</td>
<td>3145 (3.0%) 4049 (3.9%)</td>
<td>3145 (3.0%) 4049 (3.9%)</td>
<td>0.75 (0.70-0.80)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>≥160</td>
<td>2067 (3.6%) 2473 (4.5%)</td>
<td>2067 (3.6%) 2473 (4.5%)</td>
<td>0.79 (0.73-0.85)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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<tr>
<td>&lt;80</td>
<td>4558 (3.5%) 5366 (4.2%)</td>
<td>4558 (3.5%) 5366 (4.2%)</td>
<td>0.81 (0.76-0.85)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>≥80 to &lt;90</td>
<td>3690 (3.0%) 4587 (3.8%)</td>
<td>3690 (3.0%) 4587 (3.8%)</td>
<td>0.77 (0.73-0.82)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>≥90</td>
<td>2452 (3.0%) 3128 (3.9%)</td>
<td>2452 (3.0%) 3128 (3.9%)</td>
<td>0.77 (0.72-0.82)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
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</tr>
<tr>
<td>&lt;25</td>
<td>3030 (3.0%) 3688 (3.7%)</td>
<td>3030 (3.0%) 3688 (3.7%)</td>
<td>0.79 (0.74-0.84)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>≥25 to &lt;30</td>
<td>5033 (3.3%) 6772 (4.1%)</td>
<td>5033 (3.3%) 6772 (4.1%)</td>
<td>0.78 (0.74-0.83)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>≥30</td>
<td>2732 (3.3%) 3331 (4.1%)</td>
<td>2732 (3.3%) 3331 (4.1%)</td>
<td>0.78 (0.73-0.84)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>≥1.0</td>
<td>5256 (4.0%) 6165 (5.0%)</td>
<td>5256 (4.0%) 6165 (5.0%)</td>
<td>0.78 (0.75-0.82)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>&gt;1.0 to ≤1.3</td>
<td>3666 (3.1%) 4452 (3.9%)</td>
<td>3666 (3.1%) 4452 (3.9%)</td>
<td>0.77 (0.73-0.82)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>&gt;1.3</td>
<td>2199 (2.4%) 2633 (2.9%)</td>
<td>2199 (2.4%) 2633 (2.9%)</td>
<td>0.80 (0.74-0.87)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Smoking status</td>
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<td></td>
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<td></td>
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<tr>
<td>Current smokers</td>
<td>2268 (3.6%) 2896 (4.7%)</td>
<td>2268 (3.6%) 2896 (4.7%)</td>
<td>0.78 (0.73-0.84)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>8703 (3.1%) 10452 (3.9%)</td>
<td>8703 (3.1%) 10452 (3.9%)</td>
<td>0.78 (0.75-0.82)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Estimated GFR (mL/min per 1.73m²)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>2712 (4.1%) 3354 (5.1%)</td>
<td>2712 (4.1%) 3354 (5.1%)</td>
<td>0.77 (0.72-0.83)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>≥60 to &lt;90</td>
<td>6101 (3.2%) 7540 (4.0%)</td>
<td>6101 (3.2%) 7540 (4.0%)</td>
<td>0.78 (0.75-0.82)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>≥90</td>
<td>1315 (2.5%) 1571 (3.0%)</td>
<td>1315 (2.5%) 1571 (3.0%)</td>
<td>0.77 (0.69-0.85)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Total</td>
<td>19773 (3.2%) 23350 (4.0%)</td>
<td>19773 (3.2%) 23350 (4.0%)</td>
<td>0.78 (0.76-0.80)</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

Figure 3: Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol, by baseline prognostic factors

Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups, and are weighted per 1.0 mmol/L LDL cholesterol (LDL-C) difference at 1 year. Missing data are not plotted. RRs are shown with horizontal lines denoting 95% CIs or with open diamonds showing 95% CIs. CHD=coronary heart disease. GFR=glomerular filtration rate.
### CTT 2010 meta-analysis 26 statin trials: women

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Heterogeneity/trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
<td></td>
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<td>Non-CHD vascular</td>
<td>674 (3.1%)</td>
<td>802 (3.7%)</td>
<td>0.81 (0.71–0.92)</td>
</tr>
<tr>
<td>None</td>
<td>1904 (1.4%)</td>
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<td>Diabetes</td>
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<tr>
<td>Type 1 diabetes</td>
<td>145 (4.5%)</td>
<td>192 (6.0%)</td>
<td>0.77 (0.58–1.01)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>2494 (4.2%)</td>
<td>2920 (5.1%)</td>
<td>0.80 (0.74–0.86)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>8272 (3.2%)</td>
<td>10163 (4.0%)</td>
<td>0.78 (0.75–0.81)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8712 (3.5%)</td>
<td>10725 (4.4%)</td>
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<td>Female</td>
<td>2261 (2.5%)</td>
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</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>6056 (2.9%)</td>
<td>7455 (3.6%)</td>
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</tr>
<tr>
<td>&gt;65 to ≤75</td>
<td>4032 (3.7%)</td>
<td>4908 (4.6%)</td>
<td>0.78 (0.74–0.83)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>885 (4.8%)</td>
<td>987 (5.4%)</td>
<td>0.84 (0.73–0.97)</td>
</tr>
</tbody>
</table>

Similar relative risk reduction per 1 mmol/l (~40 mg/dL) reductions in LDL-C across all subgroups.

CTT Collaboration. Lancet 2010; 376: 1670-81: Individual meta-analysis 26 Statin RCTs (n=170,000)
CTT 2010 meta-analysis 26 statin trials: age

Similar relative risk reduction per 1 mmol/l (~40 mg/dL) reductions in LDL-C across all subgroups.

CTT Collaboration. Lancet 2010; 376: 1670-81: Individual meta-analysis 26 Statin RCTs (n=170,000)
After maximizing statin therapy, there is a role for non-statins

- Prefer non-statins shown to reduce ASCVD events
  - Added to statin
    - Ezetimibe (IMPROVE-IT)
    - Fenofibrate (ACCORD – low HDL-C + high triglycerides—harm to women?—microvascular benefit)
  - As monotherapy
    - Niacin (Coronary Drug Project)
    - Gemfibrozil (VA-HIT)
    - Fenofibrate (FIELD)
    - Bile acid sequestrants (Lipid Research Clinics)
Typical percent LDL-C reduction by statin and dose

<table>
<thead>
<tr>
<th>Treatment (drug/dose)</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>-40</td>
<td>-46</td>
<td>-52</td>
<td>-55</td>
<td>------</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>------</td>
<td>-37</td>
<td>-43</td>
<td>-48</td>
<td>-51</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-26</td>
<td>-30</td>
<td>-38</td>
<td>-41</td>
<td>-47*</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>------</td>
<td>-21</td>
<td>-27</td>
<td>-31</td>
<td>-40</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>------</td>
<td>-20</td>
<td>-24</td>
<td>-30</td>
<td>-36</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>------</td>
<td>------</td>
<td>-22</td>
<td>-25</td>
<td>-35</td>
</tr>
<tr>
<td>Pitavastatin (1 mg)</td>
<td></td>
<td></td>
<td>(1 mg)</td>
<td>-32</td>
<td>(2 mg)</td>
</tr>
<tr>
<td>Pitavastatin (2 mg)</td>
<td></td>
<td></td>
<td>(2 mg)</td>
<td>-36</td>
<td>(4 mg)</td>
</tr>
</tbody>
</table>

*Simvastatin 80 mg only in patients already taking for > 1 year and no other contraindications (higher risk of rhabdomyolysis)

Compiled from various clinical trials and package inserts
2016 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

JACC 68: 92-125 2016
The Panel was convened by the ACC to answer the following questions regarding use of non-statin therapies:

1) In what patient populations should non-statin therapies be considered?

2) In what situations should non-statin therapies be considered, such as, when the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) is less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?

3) If non-statin therapies are to be added, which agents or therapies should be considered and in what order?
Figure 1.
Patient Populations Addressed and Factors and Interventions to Consider

Figure 2A. Patients ≥21 Years of Age with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

Figure 2B. Patients ≥21 Years of Age with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention

Figure 2C. Patients ≥21 Years of Age with Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Secondary Prevention

Figure 3. Patients ≥21 Years of Age without Clinical ASCVD and with Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Primary Prevention

Figure 4. Patients Aged 40-75 years without Clinical ASCVD and with Diabetes and Baseline LDL-C 70-189 mg/dL, on Statin for Primary Prevention

Figure 5. Patients aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and 10-Year ASCVD Risk ≥7.5%, on Statin for Primary Prevention

LDL-C and Lipid Changes

Simva 40 vs. Simva 40/Ezetimibe 10
7 years’ F/U

Differences between groups

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Change (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>-15</td>
</tr>
<tr>
<td>Total Chol</td>
<td>-17</td>
</tr>
<tr>
<td>Trig</td>
<td>-9</td>
</tr>
<tr>
<td>HDL</td>
<td>+0.5</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-0.5</td>
</tr>
</tbody>
</table>
**IMPROVE-IT: Primary Endpoint**

Cardiovascular Death, MI, Stroke, documented Unstable Angina requiring rehospitalization, or coronary revascularization (>30 days)

<table>
<thead>
<tr>
<th></th>
<th>Eze/Simva (N=9067)</th>
<th>Simva (N=9077)</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>32.7%</td>
<td>34.7%</td>
<td>0.936</td>
<td>(0.89, 0.99)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

**Diabetes: 27% of patients  Hazard Ratio: 0.856 (0.779, 0.939)**

Kaplan-Meier event rates to 7 years
Median follow-up 57 months
Total patient years follow-up for primary endpoint  = 80,286

PCSK9 monoclonal antibodies

- PCSK9 monoclonal antibodies reduce atherogenic lipoproteins
- Indicated in patients with familial hypercholesterolemia and patients with cardiovascular disease—both groups needing addition LDL lowering not obtained with statins and other lipid lowering therapy
- Safety data look good to date
- Alirocumab and evolocumab approved but costly
- Long term outcome studies are in progress
Effects of PCSK9 Antibodies in Adults with Hypercholesterolemia

- Systematic review and meta-analysis. Evaluated 24 trials with 10,159 patients. Mean follow up 44.6 months
- LDL-C reduced by 47.5% with therapy and Lp(a) reduced by 25%
- All-cause mortality reduced (OR 0.45) and non-fatal MI reduced (OR 0.49)
- There were no serious adverse events, and no mention of neurocognitive differences

Annals Intern Med 2015;163:40
Impact of PCSK9 Inhibitors on Lipids and Outcomes: A Network Meta-analysis

- Evaluated 17 trials with 13,083 patients
- Baseline mean LDL-C was 122 mg/dL, and was reduced by 57% to 51 mg/dL
- Therapy reduced all-cause mortality (OR 0.43) however the incidence of neurocognitive AEs was higher (OR 2.34)

Eur Heart J 2016;37:536
### PCSK9 Inhibitor CVD Outcomes Trials

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab</th>
<th>Alirocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Amgen</td>
<td>Sanofi / Regeneron</td>
<td>Pfizer</td>
</tr>
<tr>
<td><strong>Trial</strong></td>
<td>FOURIER</td>
<td>ODYSSEY Outcomes</td>
<td>SPIRE I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SPIRE II</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>27,500</td>
<td>18,000</td>
<td>17,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9,000</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>MI, stroke or PAD</td>
<td>4-52 wks post-ACS</td>
<td>High risk of CV event</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>Atorva ≥20 mg or equiv</td>
<td>Evid-based med Rx</td>
<td>Lipid-lowering Rx</td>
</tr>
<tr>
<td><strong>LDL-C mg/dL (mmol/L)</strong></td>
<td>≥70 (≥1.8)</td>
<td>≥70 (≥1.8)</td>
<td>70-99 (1.8-2.6)</td>
</tr>
<tr>
<td><strong>PCSK9i Dosing</strong></td>
<td>Q2W or Q4W</td>
<td>Q2W</td>
<td>Q2W</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>1°: CV death, MI, stroke, revasc or hosp for UA, Key 2°: CV death, MI, or stroke</td>
<td>CHD death, MI, ischemic stroke, or hosp for UA</td>
<td>CV death, MI, stroke, or urgent revasc</td>
</tr>
<tr>
<td><strong>Recruitment Status</strong></td>
<td>Completed June 2015</td>
<td>Still recruiting</td>
<td>Still recruiting</td>
</tr>
<tr>
<td><strong>Completion</strong></td>
<td>2017</td>
<td>1/2018 (possibly sooner)</td>
<td>8/2017</td>
</tr>
</tbody>
</table>
Primary prevention: gaps in the evidence

- Patients not well represented in randomized outcomes trials
  - Younger patients (<40)
  - Older patients (>75)
Other questions

- What about triglycerides?
- Should we treat HDL?
General agreement:

No evidence but clinical standard
Treat Triglycerides >500 mg/dl to reduce risk of pancreatitis

Less agreement:

Adding medication to lower triglycerides when they are less than < 500 mg/dL
HDL

- Lack of evidence for HDL-C targets
- Lack of evidence for pharmacologic treatment in the statin era
  - AIM-HIGH, HPS2 THRIVE
  - Failure of CETP inhibitors
Summary

- ACC/AHA 2013 guidelines
  - Assess and treat according to risk of ASCVD
  - Focus on statins
  - Not treating to a goal

- ACC non statin update
  - Consider non statins as additional therapy
  - Ezetimibe, bile acid sequestrants, PCSK9 monoclonal antibodies

- Areas requiring more outcomes research include:
  - Triglycerides, HDL, primary prevention
Thank you!