The New Lipid Guidelines
Myths and Facts

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## Disclosures: Vera Bittner, MD, MSPH

<table>
<thead>
<tr>
<th>Company</th>
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<th>Trial / Activity</th>
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<td>Pharmacovigilance</td>
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ARS 1: Audience Poll – Guideline Awareness

1. What lipid guidelines? 0%
2. I have heard about them, but don’t know any details. 0%
3. I have read a summary. 0%
4. I have read the entire document. 0%
5. I am using them consistently in my practice. 0%
Outline

◆ Background
  – How did the prevention guidelines come about?
  – Process determines content ….

◆ Rationale for the New Paradigm

◆ Approach to the Patient

◆ Case examples


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A Concise Summary:

This online-first version will be replaced with a final version when it is included in the issue. The final version may differ in small ways.

**Annals of Internal Medicine**

**Clinical Guideline**

**Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults: synopsis of the 2013 ACC/AHA Cholesterol Guideline**

Neil J. Stone, MD; Jennifer G. Robinson, MD, MPH; Alice H. Lichtenstein, ScD; David C. Goff Jr., MD, PhD; Donald M. Lloyd-Jones, MD, ScM; Sidney C. Smith Jr., MD; Conrad Blum, MD; and J. Sanford Schwartz, MD, for the 2013 ACC/AHA Cholesterol Guideline Panel*

**Description:** In November 2013, the American College of Cardiology and American Heart Association (ACC/AHA) released a clinical practice guideline on the treatment of blood cholesterol to reduce cardiovascular risk in adults. This synopsis summarizes the major recommendations.

**Methods:** In 2008, the National Heart, Lung, and Blood Institute convened the Adult Treatment Panel IV (ATP-IV) to update the 2001 ATP-III cholesterol guidelines using a rigorous process to systematically review randomized, controlled trials (RCTs) and meta-analyses of RCTs that examined cardiovascular outcomes. The panel commissioned independent systematic evidence reviews on low-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol goals in secondary and primary prevention and the impact of lipid drugs on atherosclerotic cardiovascular disease (ASCVD) events and adverse effects. In September 2013, the panel’s draft recommendations were transitioned to the ACC/AHA.

**Recommendations:** This synopsis summarizes key features of the guidelines in 8 areas: lifestyle, groups shown to benefit from statins, statin safety, decision making, estimation of cardiovascular disease risk, intensity of statin therapy, treatment targets, and monitoring of statin therapy.

*Ann Intern Med.*

For author affiliations, see end of text.
Background:
Process Determines Content
Institute of Medicine

Clinical Practice Guidelines We Can Trust.
NHLBI Charge To The Committee

- Evaluate higher quality RCT evidence for cholesterol-lowering drug therapy to reduce atherosclerotic cardiovascular disease (ASCVD) risk

- Use Critical Questions (CQ) to create the evidence search from which the guideline is developed
  - Cholesterol panel: 3 CQs
  - Risk assessment work group: 2 CQs
  - Lifestyle management work group 3 CQ’s

- Include RCT and systematic reviews/meta-analyses of RCT’s independently assessed as fair to good quality

- Develop recommendations based on these high quality publications 1995-2009 (2013)
Three Critical Questions

◆ **CQ1:** What is the evidence for LDL–C and non-HDL–C goals for the secondary prevention of ASCVD?

◆ **CQ2:** What is the evidence for LDL–C and non-HDL–C goals for the primary prevention of ASCVD?

◆ **CQ3:** For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?
The Guidelines

- Are not a comprehensive review of all available evidence
  - epidemiology / cell studies / animal studies / physiologic studies in humans / case reports / genetic data / subgroup analyses of trials / ..... 

- Are not a textbook of clinical lipidology

- Address only 3 critical questions – thus are not comprehensive treatment guidelines that cover all aspects of care of individuals with lipid disorders
June 2013: NHLBI → ACC / AHA
Guideline Authors

Chairs
- Neil J. Stone, MD, Chair - Cardiology
- Jennifer Robinson, MD, Vice Chair – Epidemiology, Internal Medicine
- Alice H. Lichtenstein, DSc, Vice Chair – Nutrition Research

Methodology Experts:
- Karen M. Eddleman, BS
- Nicole M. Jarrett
- Ken LaBresh, MD
- Lev Nevo, MD
- Janusz Wnek, PhD

NHLBI
- David Gordon, MD
- Susan T. Shero, MS, RN
- Daniel Levy, MD

Panel Members
- C. Noel Bairey Merz, MD – Cardiology
- Donald M. Lloyd-Jones, MD, ScM – Cardiology, Preventive Medicine and Epidemiology
- Conrad B. Blum, MD – Endocrinology
- Patrick McBride, MD, MPH – Family Practice
- Robert H. Eckel, MD – Endocrinology
- J. Sanford Schwartz, MD – Internal Medicine, Health Economics
- Anne C. Goldberg, MD – Endocrinology
- Sidney C. Smith, Jr, MD - Cardiology
- Karol Watson, MD, PhD – Cardiology
- Peter Wilson, MD – Endocrinology, Epidemiology
Rationale for the New Paradigm
Benefit-Based Strategy

(+ Estimate potential for benefits (e.g. ASCVD risk reduction)
(-) Estimate potential for harms (e.g. adverse effects)

Estimate net benefit

Clinically meaningful net benefit → Recommend therapy
Estimating Benefit

- **Absolute risk of a CVD event**
  - Estimate probability of an individual having a CVD event over a defined period of treatment (e.g., 5, 10, 30 years, lifetime) based on her or his risk factor levels

- **Relative reduction in CVD risk from treatment**
  - Identify the relative reduction in CVD risk with a specific treatment compared to no treatment

- **Number-needed-to-treat to benefit (NNT)**
  - Number treated to prevent one CVD event over defined period of treatment
  - Inverse of the reduction in absolute CVD risk from treatment
Estimating Harms

- **Absolute risk of an adverse event(s)**
  - Estimate probability of an individual having an adverse event over a defined period of treatment based on her/his characteristics predisposing to an adverse event or the type of treatment (e.g., agent or dose)

- **Relative risk of an adverse event**
  - If known
  - May vary by subgroup

- **Number-needed-to-treat to harm (NNH)**
  - Number treated to experience one adverse event over defined period of treatment
  - Inverse of the increase in absolute risk of harm from treatment
Estimating Benefit vs. Harm Based on RCTs

MODERATE INTENSITY STATIN TREATMENT
Assumes a 35% relative risk reduction in ASCVD from moderate intensity statin treatment
NNT to prevent 1 ASCVD event varies by baseline estimated 10-year ASCVD risk.

NNH based on 1 excess case of incident diabetes per 100 individuals* treated with statins for 10 years.
Clinician / Patient Discussion

The Expert Panel emphasizes that the guideline is “patient centered” in primary prevention. It is recommended that the potential for an ASCVD risk reduction benefit, adverse effects, and drug-drug interactions, along with patient preferences, must be considered before statins are initiated for the primary prevention of ASCVD. This gives clinicians and patients the opportunity for input into treatment decisions rather than a simplistic ‘one treatment fits all’ approach to drug therapy.

Quote from: 2013 Guidelines, Section 2.2 (Statin Benefit Groups)
Four Statin Benefit Groups

- Individuals with clinical ASCVD
  - ACS, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD presumed to be of atherosclerotic origin
  - Do not have NYHA Class II-IV heart failure
  - Do not receive hemodialysis.

- Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dl.

- Individuals 40-75 years of age with diabetes, LDL-C 70-189 mg/dl, but no clinical ASCVD.

- Individuals without clinical ASCVD or diabetes, who are 40-75 years of age with LDL-C 70-189 mg/dl, and have an estimated 10-year ASCVD risk of 7.5% or higher.
New Perspective on LDL-C and Non-HDL-C Goals

- Lack of RCT 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.

- Quantitative comparison of statin benefits with statin risk.

- Non-statin therapies: did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy.
Why Not Continue “Treat to Target”

- Current RCT data do not indicate what the target should be
- Unknown magnitude of additional ASCVD risk reduction with one target compared to another
- Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
- Thus, unknown net benefit from treat-to-target approach
Apo B Lipoproteins Are Causal in Atherosclerosis

- The members of the Expert Panel acknowledge the important contributions arising from decades of genetic and biochemical studies, observational epidemiologic and ecological studies, and *in vitro* and animal experiments that associated higher low-density lipoprotein cholesterol (LDL–C) levels with greater ASCVD risk.

- These studies provided the rationale for RCTs, which in turn demonstrated that lowering cholesterol levels reduced ASCVD events and thereby establish a central, causal role of atherogenic cholesterol-containing lipoprotein particles, particularly LDL, in the genesis of CHD and ASCVD.

Quote from: 2013 Guidelines, Section 1.3 (Scope of the Guideline)
Approach To The Patient
Role of Lifestyle Modification

- Lifestyle modification (i.e., adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol-lowering drug therapies.
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
- No

LDL–C ≥190 mg/dL

- Yes
- No

Diabetes
Type 1 or 2
Age 40-75 y

- Yes
- No

- Yes
- No

Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

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

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

Moderate-intensity statin

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%
ARS 2: Intensity of Statin Therapy

Question: Which of the following are considered “high intensity statin therapy”?

A. Simva 40 mg
B. Atorva 80 mg
C. Rosuva 10 mg
D. Fluva 80 mg
E. Pitava 4 mg

1. A and B  0%
2. B, C, and D  0%
3. B  0%
4. C and D  0%
5. B and E  0%
Intensity of Statin Therapy

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

<table>
<thead>
<tr>
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<th>Moderate-Intensity Statin Therapy</th>
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*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Note: Bolded doses were used in RCT’s reviewed by the panel
Treatment Algorithm (Part 2)

DM age <40 or >75 y

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

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

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

Clinic−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

No to statin

Yes to statin

Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence (See Fig 5)
The Pooled Cohort Risk Equation

- Excel Spreadsheet
  - http://my.americanheart.org/cvriskcalculator

- IOS App Store
- Android App Store
ASCVD Risk Estimator App

Gender
- Male
- Female

Age
- 20-79

Race
- White
- African American
- Other

HDL - Cholesterol (mg/dL)
- 20-100

Total Cholesterol (mg/dL)
- 130-320

Diabetes
- Yes
- No

Treatment for Hypertension
- Yes
- No

Systolic Blood Pressure
- 90-200

Smoker
- Yes
- No

*Intended for use if there is not ASCVD and the LDL-cholesterol is <190 mg/dL
**Optimal risk factors include: Total cholesterol of 170 mg/dL, HDL-cholesterol of 50 mg/dL, Systolic BP of 110 mm Hg, Not taking medications for hypertension, Not a diabetic, Not a smoker
Treatment Algorithm (Part 2)

DM age <40 or >75 y

Primary prevention
(No diabetes, LDL–C 70-189 mg/dL, and not receiving statin therapy)
Estimate 10-y ASCVD Risk every 4-6 years
Pooled Cohort Equations*

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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)
Individuals Not in a Statin Benefit Group

- For those in whom risk decision is uncertain, the following factors may inform clinical decision making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL–C $\geq 160$ mg/dL
  - hs-CRP $\geq 2.0$ mg/L
  - Coronary artery calcium (CAC) score $\geq 300$ Agatston units
  - Ankle brachial index (ABI)<0.9
Clinical ASCVD: Initiating 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).

- **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

- **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 >3X ULN

- **Monitor statin therapy** (Figure 5)
Monitoring Therapy and Adherence

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 & thereafter as indicated

Less than anticipated therapeutic response

Intolerance to recommended dose of statin therapy

Yes

Management of statin intolerance
(Table 8, Rec 8)

No

Reinforce medication adherence
Reinforce adherence to intensive lifestyle changes
Exclude secondary causes of hypercholesterolemia
(Table 6)

Follow-up 4-12 wk

No

Indicators of anticipated therapeutic response and adherence to selected statin intensity:
- High-intensity statin therapy† reduces LDL-C approx. 250% from the untreated baseline.
- Moderate-intensity statin therapy reduces LDL-C approx. 30% to <50% from the untreated baseline.
Case Examples
John

- 21 years old, healthy
- College student, plays intramural basketball, loves pizza, drinks 6-pack on weekend days
- Father and 2 uncles died of CHD at ages 41, 42, and 45
- Lipid profile: TC 311, HDL-C 39, LDL-C 260, TG 60
John

- Has heterozygous FH
- Thus falls into statin benefit group
- No indication to use risk calculator
- Needs lifestyle advice **AND** high intensity statin therapy
- If LDL-C remains high, consider adding a non-statin drug in addition
- Be sure to screen his siblings / family
**Intensity of Statin Therapy**

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‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Note: Bolded doses were used in RCT’s reviewed by the panel
Betty

- 78 yo, African American
- Stent in LAD 2 years ago; recent TIA
- Has diabetes, hypertension, and hypothyroidism
- CKD with eGFR of 50
- Lipid profile: TC 200, HDL-C 62, LDL-C 106, TG 160
Betty

- Has ASCVD and DM → falls into statin benefit group
- No indication to use risk calculator
- Is above age 75 and has co-morbidities that increase likelihood of adverse statin effects
- Choose moderate dose statin
Intensity of Statin Therapy

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<td>Lovastatin 40 mg</td>
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<td>Fluvasatin 40 mg bid</td>
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<td></td>
<td>*Pitavastatin 2–4 mg</td>
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Note: Bolded doses were used in RCT’s reviewed by the panel
Sam

- 68 yo, African American
- Hypertension for 10 years – BP 156/64 mmHg on HCTZ / Ramipril / Amlodipine
- Smokes ½ ppd, 40 pack year history
- Brother had MI at age 70
- Lipid profile: TC 219, HDL-C 42, LDL-C 148, TG 145
Sam’s Risk Calculation: 41.5% 10 y ASCVD Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Value</th>
<th>Acceptable range of values</th>
<th>Optimal values</th>
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<tbody>
<tr>
<td>Sex</td>
<td>M (for males) or F (for females)</td>
<td>M</td>
<td>M or F</td>
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<tr>
<td>Age</td>
<td>years</td>
<td>68</td>
<td>20-79</td>
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<td>Race</td>
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<td>AA</td>
<td>AA or WH</td>
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<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
<td>219</td>
<td>130-320</td>
<td>170</td>
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<tr>
<td>HDL-Cholesterol</td>
<td>mg/dL</td>
<td>42</td>
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<td>50</td>
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<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td>165</td>
<td>90-200</td>
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<td>Treatment for High Blood Pressure</td>
<td>Y (for yes) or N (for no)</td>
<td>Y</td>
<td>Y or N</td>
<td>N</td>
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<td>Diabetes</td>
<td>Y (for yes) or N (for no)</td>
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<td>Y or N</td>
<td>N</td>
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<td>Smoker</td>
<td>Y (for yes) or N (for no)</td>
<td>Y</td>
<td>Y or N</td>
<td>N</td>
</tr>
</tbody>
</table>

**Your 10-Year ASCVD Risk (%)**

41.5

**10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)**

8.1

**Your Lifetime ASCVD Risk (%)**

This calculator only provides lifetime risk estimates for individuals 20 to 58 years of age

**Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)**

6.0

*This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches. While 10-year risk estimates are derived from methods and data using continuous*
Patient is at high risk and potential for ASCVD risk reduction benefit is high

- No indicators of increased risk of adverse statin effects
- Stop smoking / treat BP / lifestyle recs
- Discuss statin therapy with patient – what intensity would you recommend?

**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
Andrea

- 41 yo, Caucasian
- Hypertension for 5 years – takes BP medications intermittently, currently off; BP 180/104 mmHg
- Obese, but not diabetic; smokes ½ ppd
- Brother had MI at age 50, sister has diabetes and had stent at age 47
- Lipid profile: TC 238, HDL-C 46, LDL-C 152, TG 200
Andrea’s Risk Calculation: 9.1% 10 y ASCVD Risk
Andrea

- 10 year risk is not that high, but she has 50% lifetime risk of ASCVD and very positive FH for CHD
- No indicators of increased risk of adverse statin effects
- Need to address adherence to BP meds (lack of adherence to BP meds predicts poor adherence to statins)
- Stop smoking
- Discuss statin therapy with patient – what would you recommend?
What about statin safety?

- To maximize the safety of statins, selection of the appropriate statin and dose should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects.

- Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
  - 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 (e.g. age >75 y) or concomitant use of drugs affecting statin metabolism.

- Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:
  - History of hemorrhagic stroke
  - Asian ancestry
Statin Safety Resource

National Lipid Association Task Force on Statin Safety – 2014 Update

http://www.lipidjournal.com/supplements
Summary

- 4 Statin Benefit Groups

- Treatment is guided by CV risk and likelihood of statin benefit vs. harm, not driven by LDL-C or non-HDL-C targets

- Discussion with the patient has a central role in determining course of treatment

- Use follow-up lipid levels to monitor adherence