NEW 2013 ACC/AHA GUIDELINES ON TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS

Jim Backes, PharmD
Professor - Department of Pharmacy Practice
University of Kansas School of Pharmacy
Assistant Director – Atherosclerosis and LDL-Apheresis Center
OBJECTIVES (Pharmacists)

• Describe the rationale for the recommendations involving the 2013 ACC/AHA Cholesterol Guidelines.

• Identify lifestyle changes recommended to reduce cardiovascular risk.

• Recognize the four major statin benefit groups.

• Differentiate between, high-dose, moderate-dose, and low-dose statin therapy.

• Explain the benefits/drawbacks of the 10-year Cardiovascular Risk Estimator.
OBJECTIVES (Technicians)

- Describe the purpose of the 2013 ACC/AHA Cholesterol Guidelines.
- Define lifestyle changes for reducing cardiovascular risk.
- List a patient type that would benefit from statin therapy.
- Identify the key statins used in clinical practice.
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Endorsed by the 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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Key Points

• Encourage adherence to a heart-healthy lifestyle.
• Statins are recommended for adults in groups demonstrated to benefit.
• Engage in a clinician-patient discussion before initiating statin therapy.
• Initiate the appropriate intensity of statin therapy to reduce ASCVD risk.
• Use Pooled Cohort Equations for estimating 10-year ASCVD risk.
• Evidence is inadequate to support specific LDL-C or non-HDL-C goals.
• Nonstatin drug therapy may be considered in selected individuals.
NHLBI Charge to the Expert Panel

Evaluate high quality \textbf{randomized controlled trial (RCT) evidence} to reduce ASCVD risk

- RCTs and systematic reviews/meta-analyses of RCTs independently assessed as fair-to-good quality
- Develop recommendations based on RCT evidence
- Less expert opinion than in prior guidelines
Principles (changes from ATP-III)

• Do not focus on LDL-C or non-HDL-C levels as treatment goals
  • Obtain a lipid panel to monitor adherence
• Use medications proven to reduce ASCVD risk
  • Moderate to high-intensity statin
• Four Statin-Benefit Groups
• Risk decisions in primary prevention
  • Optimal lifestyle emphasized
  • Clinician-patient discussion - shared decision-making
Evidence Review on Diet and Physical Activity (in the absence of weight loss) to be integrated with the recommendations of the Blood Cholesterol and High Blood Pressure Panels
LDL-C lowering – advise to:

• **Eat.…**
  - Vegetables, fruits, whole grains, some low-fat dairy, poultry, fish, legumes, olive oil, and nuts

• **Don’t eat as much.…**
  - Sweets, sugar-sweetened beverages, and red meats

• **Restrict** saturated and *trans* fats
Some Good News…

Dietary Cholesterol

There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C.
Physical Activity

• Advise patients to....
  • Perform moderate to vigorously intense aerobic activity
    • 3-4 sessions weekly
    • ~40 minutes per session
Physical Activity

• Aerobic physical activity
  • ↓ LDL-C 3.0-6.0 mg/dL (mean)
  • ↓ Non-HDL-C 6.0 mg/dL (mean)

• Resistance training
  • ↓ LDL-C, triglycerides, and Non-HDL-C by 3.0-6.0 mg/dL (mean)
4 Statin Benefit Groups

- **Clinical ASCVD***
  - Myocardial infarction, angina, revascularization
  - Stroke
  - Peripheral Vascular Disease
- **LDL-C ≥190 mg/dL (age ≥21 years)**
- **Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL**
- **Primary prevention**
  - Risk calculator: ≥7.5% 10-year ASCVD risk
    - No Diabetes
    - Age 40-75 years
    - LDL-C 70-189 mg/dL
Summary of Statin Initiation Recommendations to Reduce ASCVD Risk

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**
  - **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**
  - **No**
    - **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**
        - **LDL-C 70-189 mg/dL**
          - **Yes**
            - **Moderate-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%

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
(See Fig 5)
Summary of Statin Initiation Recommendations to Reduce ASCVD Risk

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

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†

<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)
**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>
<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 ≥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><strong>Atorvastatin (40†)−80 mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong></td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Rosuvastatin (5) 10 mg</strong></td>
<td>Pravastatin 10−20 mg</td>
</tr>
<tr>
<td></td>
<td><strong>Simvastatin 20–40 mg‡</strong></td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td><strong>Pravastatin 40 (80) mg</strong></td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td><strong>Lovastatin 40 mg</strong></td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td><strong>Fluvastatin XL 80 mg</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Fluvastatin 40 mg bid</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pitavastatin 2–4 mg</strong></td>
<td></td>
</tr>
</tbody>
</table>

*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.
Primary Prevention Global Risk Assessment

• ASCVD Risk Estimator
  • 10-year ASCVD risk (ages 40-79)
  • Lifetime ASCVD risk (ages 20-59)

*10-year ASVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke

• To estimate 10-year ASCVD* risk
  • Derived from 3 primary prevention RCTs
  • White and black men and women

• Identifies higher risk individuals for statin therapy (>7.5%)
Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

Risk Factors for ASCVD

- Gender
  - Male
  - Female

- Age
  - [ ] years

- Race
  - [ ] White
  - [ ] Other

- Systolic BP
  - [ ] mmHg

- Receiving treatment for high blood pressure (if SBP > 120 mmHg)
  - [ ] No
  - [ ] Yes

- Diabetes
  - [ ] No
  - [ ] Yes

- Smoker
  - [ ] No
  - [ ] Yes

- Total Cholesterol
  - [ ] mg/dL

- HDL Cholesterol
  - [ ] mg/dL

- [ ] Reset
- [ ] Calculate

http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx
Individuals Not in a Statin Benefit Group

• In those for whom a risk decision is uncertain, these factors may inform clinical decision making:

  • Family history of premature ASCVD
  • Elevated lifetime risk of ASCVD
  • LDL-C \( \geq 160 \text{ mg/dL} \)
  • hs-CRP \( \geq 2.0 \text{ mg/L} \)
  • CAC score \( \geq 300 \text{ Agaston units “calcium score”} \)
  • Ankle Brachial Index <0.9
Statin Therapy: Monitoring Response - Adherence

*Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C ≥ 220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥ 500 mg/dL, a fasting lipid panel is required.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C < 100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.
Monitoring Response-Adherence (cont.)

Anticipated therapeutic response?

No

- Reinforce improved adherence
  - Increase statin intensity‡
  - OR
  - Consider addition of nonstatin drug therapy

Follow-up 4-12 wk & thereafter as indicated

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

‡See guideline text
ASCVD Risk Estimator

Pooled Cohort Risk Assessment Equations
Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

Risk Factors for ASCVD

- **Gender**
  - Male
  - Female

- **Age**
  - years

- **Race**
  - White or other

- **Total Cholesterol**
  - mg/dL

- **HDL Cholesterol**
  - mg/dL

- **Systolic BP**
  - mmHg

- **Receiving treatment for high blood pressure**
  - No
  - Yes

- **Diabetes**
  - No
  - Yes

- **Smoker**
  - No
  - Yes

• **Primary prevention**
  - 5.0 to 7.4%
    (moderate intensity statin)
  - ≥7.5%
    (moderate - high intensity statin)

• **Diabetes Mellitus**
  - Moderate vs high-dose
CASE 1

62 year old AA Male no history of ASCVD

- Total cholesterol: 140
- Low HDL: 35
- SBP: 130 mmHg
- Not taking anti-hypertensive medications
- Non-diabetic
- Non-smoker
- Calculated 10-yr risk of ASCVD: 9.1%
Adults age >21 y and a candidate for statin therapy:

- Yes: 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

- No: LDL-C ≥190 mg/dL
  - Yes: High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

- No: Diabetes Type 1 or 2
  - Yes: Age 40-75 y
    - Yes: Estimated 10-y ASCVD risk ≥7.5% (High-intensity statin)
  - No: Moderate-intensity statin

- Yes: Estimate 10-y ASCVD Risk with Pooled Cohort Equations*
  - ≥7.5% estimated 10-y ASCVD risk and age 40-75 y
    - Moderate-to-high intensity statin
CASE 2

50 year old White Female no history of ASCVD

- Total cholesterol 180
- HDL: 50
- SBP: 130
- Taking HTN meds
- (+) Diabetes mellitus
- (+) smoker
- Calculated 10-yr ASCVD: 9.1%
CASE 3

48 yo White Female no history of ASCVD

• Total cholesterol 180
• HDL: 55
• SBP: 130
• No HTN meds
• (+) Diabetes mellitus
• Non-smoker
• Calculated 10-yr risk ASCVD: 1.8%; Lifetime risk: 39%
CASE 4

22 yo White Male no history of ASCVD

• Total cholesterol: 300
• HDL: 55
• LDL: 195
• SBP: 120
• No HTN meds
• No diabetes mellitus
• Non-smoker
• **Lifetime risk of ASCVD = 50%**
Adults age ≥21 y and a candidate for statin therapy

Clinical ASCVD

Yes

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%

LDL-C ≥190 mg/dL

Yes

No

Diabetes
Type 1 or 2
Age 40-75 y

Yes

No

Estimate 10-y ASCVD Risk with Pooled Cohort Equations

≥27.5% estimated 10-y ASCVD risk and age 40-75 y

Yes

No

Moderate-to-high intensity statin

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
CASE 5

66 yo White Female no history of ASCVD

• Total cholesterol: 230
• HDL: 55
• SBP: 150
• Taking HTN meds
• No diabetes mellitus
• Non-smoker
• Calculated 10-yr risk of ASCVD: 12.0 %
CASE 6

59 year old White Female recently hospitalized for CABG.

• Total cholesterol 175
• HDL: 55
• SBP: 150
• Taking HTN meds
• (-) Diabetes mellitus
• (-) smoker
• Calculated 10-yr ASCVD: **Not necessary**
Gaps in Care

- 35 yo Female with no history of ASCVD
  - LDL-C 180 mg/dL
  - Smoker
  - Hypertension
  - Poorly controlled DM
  - Low HDL-C
  - (+) Family history – mother and father have premature CHD
- **Not qualified** for statin therapy per ACC/AHA
A bit too much….

• 63 yo white Male
  • Total cholesterol = 170 mg/dL (optimal)
  • HDL-C = 50 mg/dL (optimal)
  • SBP = 110 mmHg (optimal)
  • Diet: Mediterranean
  • Exercise: aerobic and resistance training 4 hours/week
  • No family history of CHD – parents lived into their 90s
  • (-) tobacco
  • (-) DM
  • 10-Year ACVD Risk = 7.5% - moderate to high-dose statin
Safety

• RCTs & meta-analyses of RCTs used to identify safety considerations
• Allow estimation of net benefit from statin therapy
  • ASCVD risk reduction versus adverse effects
• Expert guidance on management of statin-associated adverse effects, including muscle symptoms
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
- Use of drugs affecting statin metabolism
- Age >75 years
- Asian ancestry
Statin Safety - Muscle

- Creatinine Kinase (CK) should not be routinely measured in individuals receiving statin therapy.
  - Exception: individuals believed to be at increased risk for adverse muscle events.

- During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, or weakness.
Statin Safety - Muscle

- It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients:
  - Obtain a history of prior or current muscle symptoms to establish a baseline before initiation of statin therapy.
  - If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis.
Statin Safety - Muscle

If mild to moderate muscle symptoms develop during statin therapy discontinue the statin until the symptoms can be evaluated.

- Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, rheumatologic disorders, or vitamin D deficiency).

- If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.
- Check hepatic function at baseline.
  - During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain).

- Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL.

- It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.
In individuals who are candidates for statin treatment but lack response or are completely statin intolerant

- Ensure adherence to lifestyle modifications
- It is reasonable to use nonstatin cholesterol-lowering drugs
Nonstatin Safety: Niacin

• **Monitor:** hepatic transaminases, fasting blood glucose or HbA1c, and uric acid.

• To reduce the frequency and severity of flushing:
  • Start low and go slow
  • Take niacin with food or **pre-medicate** with aspirin 325 mg 30 minutes before niacin

• **Clinical Update: utilization declining secondary to failed RCTs**
  • AIM-HIGH and HPS-THRIVE
Nonstatin Safety: BAS

- BAS should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL.

- Clinical Update
  - Used frequently for statin intolerance
  - Also lowers A1c
  - Watch drug interactions
Nonstatin Safety: Cholesterol-Absorption Inhibitors

• It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe.

• **Clinical Update**
  • Also used frequently for statin intolerance
  • Tablet splitting
  • Outcomes trial (IMPROVE-IT) involving ezetimibe set to be published in late 2014
Nonstatin Safety: Fibrates

- Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.

- Fenofibrate/fenofibric acid may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are ≥500 mg/dL.
Nonstatin Safety: Fibrates (cont.)

• Fenofibrate should not be used if moderate or severe renal impairment: eGFR <30 mL/min per 1.73 m²

• Modify dose if eGFR is between 30 and 59 mL/min per 1.73 m²

*Consult the manufacturer's prescribing information as there are several forms of fenofibrate available.

• Clinical Update
  • Utilization reduced after FIELD and ACCORD Trials (statin combo)
  • Generally reserved for hypertriglyceridemia
Nonstatin Safety: Omega-3 Fatty Acids

- If EPA and/or DHA are used for the management of severe hypertriglyceridemia (≥500 mg/dL)
  - Evaluate the patient for gastrointestinal disturbances and bleeding.

- Clinical Update
  - Supplements are effective and free of contaminants
  - Rx products are generally better tolerated
  - Overall RCTs show benefit but recent fails (ORIGIN)
  - Also used for cardioprotective doses (1000-2000 mg EPA/DHA daily)
Take Home Message

- ACC/AHA Guidelines use the intensity of statin therapy as the goal of treatment – instead of LDL-C and Non-HDL-C targets.

- Know the **4 Statin Benefit Groups**:
  1. Individuals with clinical **ASCVD**
  2. Individuals with primary elevations of **LDL–C ≥190 mg/dL**
  3. Individuals 40-75 yrs with **DM** & LDL–C 70 to 189 mg/dL w/o clinical ASCVD
  4. Individuals without clinical ASCVD or DM who are 40 to 75 years of age with LDL–C 70 to 189 mg/dL and have an **estimated 10-year ASCVD risk of 7.5% or higher.**

  *(using the Pooled Cohort Equations for ASCVD risk prediction)*