Quick Facts

Risk factors

- Type 2 diabetes mellitus (T2DM): T2DM can decrease levels of good cholesterol (HDL) and increase levels of bad cholesterol (LDL), which increases chance for a cardiovascular (CV) event, such as stroke.
- Lifestyle choices: eating a diet high in saturated and trans fats, physical inactivity, obesity
- Family history
- Age: Risk increases with advancing age
- Gender: men typically have lower HDL levels than women; women typically have lower LDL levels than men (until age 55)

Complications

Over time, high cholesterol levels can lead to the following:

- Artery damage
- Hardening of the arteries (atherosclerosis)
- Heart disease
- Increased risk of stroke
- Chest pain caused by decreased lack of oxygen-rich blood
- Peripheral artery disease (PAD) caused by decreased blood flow to arteries in arms, stomach, legs, and feet

Prevalence and incidence

- About 1 in 6 adult Americans has high cholesterol.2
- Anyone can develop high cholesterol, including children.
- 42.2% of US adults are at moderate risk of developing high cholesterol, 13.1% are at high risk, and another 6.2% are thought to be undiagnosed.3

Cost of disease burden

- Among patients in the US with hyperlipidemia, the direct clinical and economic annual costs associated with new cardiovascular event (including up to 3 years post-event) are approximately US$195.6 billion.

REFERENCES

No clear definition of dyslipidemia exists; however, there is a linear relationship between lipid levels and benefits of pharmacologic and non-pharmacologic treatments.

A diagnosis of dyslipidemia can include any (or a combination) of the following:

- Elevated chylomicrons
- Elevated triglycerides (TG)
- Elevated total cholesterol (TC)
- Elevated low-density lipoproteins (LDL-C)
- Decreased high-density lipoproteins (HDL-C)

Cholesterol Transport and Removal

- Chylomicrons take in dietary lipids in the intestines, travel through the bloodstream, where muscle and adipose tissue convert it into Chylomicron remnants.
- Chylomicron remnants travel to the liver where they are converted into Very Low-Density Lipoprotein (VLDL) particles.
- VLDL particles travel through the bloodstream where they are broken down into a final product known as LDL particles and taken up into the muscles and adipose tissue, and if in excess, deposited along artery walls.
- HDL particles can be protective against this process by removing cholesterol from the artery walls and returning it to the liver; this is known as reverse cholesterol transport.

Atherosclerosis occurs as a compensatory response to excess lipids, and this process is the basis of most acute coronary syndromes:

- LDL particles with a cholesterol and triglyceride core enter the arterial wall. Macrophages consume these lipids and trigger inflammation.
- The resulting lipid core/macrophage infiltration/inflammation is clinically referred to as plaque.
- As the plaque grows, the arterial wall expands into the artery lumen.
- Blood flow becomes progressively restricted and will continue to do so until the artery becomes clotted off altogether, causing ischemia.
- As plaques enlarge, they may burst, which allows the plaque components to enter the blood stream and cause full occlusions in smaller blood vessels.

**FIGURE 1: Excess lipids; Atherosclerosis**
Etiology

Causes

- Genetic mutation of receptors or apolipoproteins
- Overproduction of lipids or beta-apolipoproteins (LDL)
- Underproduction of alpha-apolipoproteins (HDL)

Medications that can elevate LDL-C or TG³

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>TG</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolic steroids</td>
<td>Oral estrogen</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Danazol</td>
<td>Tamoxifen, Raloxifene</td>
<td>Thiazides</td>
</tr>
<tr>
<td>Progestins</td>
<td>Retinoids</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Sirolimus</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Interferon</td>
<td>(TG = rosiglitazone only)</td>
</tr>
<tr>
<td>Fibrates or omega-3 fatty acids (if patient has severely elevated TG and atherogenic dyslipidemia)</td>
<td>Beta-blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atypical antipsychotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bile acid sequestrants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L-asparaginase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
</tr>
</tbody>
</table>

Early detection and screening

Fasting lipoprotein profile should include the following:
- Total cholesterol (TC)
- Low-density lipoprotein (LDL-C; calculated)
- High-density lipoprotein (HDL-C)
- Triglycerides (TG)

Non-HDL-C can be calculated by the following formula:
\[
\text{non-HDL-C} = \text{TC} - \text{HDL-C}
\]

REFERENCES

Guidelines and Landmark Trials

Guidelines


Table 1: Guidelines for Hyperlipidemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 2013 American College of Cardiology/American Heart Association blood cholesterol guideline | Initiation of statin therapy | - Focus on prevention of atherosclerotic cardiovascular disease (ASCVD; eg, MI, angina, stroke, PAD, revascularization).  
- Recommend primary and secondary intervention in individuals without New York Heart Association (NYHA) class II–IV heart failure and/or not receiving hemodialysis.  
- Guideline organized by statin benefit groups.  
- Risk assessment conducted using Pooled Cohort Equations, which predicts a 10-year risk of ASCVD.  
- No specific numeric goals of treatment, but rather proportional benefit is seen as compared to the patient baseline.  
- In patients without clear indications, risk and benefit should be weighed for statin therapy.  
- Statin therapy is the only therapy recommended by this guideline owing to a lack of randomized controlled trials supporting other medications for reducing atherosclerotic cardiovascular disease and mortality.  
- Guideline recommends moderate- to high-intensity statins for most patients. |
| Statin benefit groups | Patients ≥ 21 years of age for whom the ASCVD risk reduction clearly outweighs the risk of adverse events  
- Secondary prevention in individuals with clinical ASCVD  
- Primary prevention in individuals with LDL-C ≥ 190 mg/dL  
- Primary prevention in individuals with diabetes (but no ASCVD), 40 to 75 years of age, with LDL-C 70 to 189 mg/dL  
- Primary prevention in individuals 40 to 75 years of age with LDL-C 70 to 189 mg/dL without diabetes or ASCVD but with estimated 10-year ASCVD risk ≥ 7.5% |
| Statin benefit group for whom moderate evidence supports the use of statins | Primary prevention in individuals with 5–7.5% 10-year ASCVD risk and 40–75 years of age with LDL-C 70–89 mg/dL  
- < 5% 10-year ASCVD risk, or < 40 years old or > 75 years old  
- Patients and providers should discuss ASCVD risk reduction benefits, adverse effects of statin therapy, drug interactions, drug-disease interactions and patient preference. |
## Importance of numeric treatment goals

- Historically useful for both health care providers and patients to monitor progress.
- Ensure that aggressive lowering of atherogenic cholesterol is matched to absolute risk of an event.
- Avoid undertreatment.

### Risk assessment

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Low           | 0 or 1 major ASCVD risk factors  
|               | Equates to $<5\%$ 10-year risk of an ASCVD event using any available risk assessment calculator |
| Moderate      | 2 major ASCVD risk factors in the absence of conditions that place individuals in higher risk categories  
|               | Is approximately equated to $5-10\%$ 10-year risk for an ASCVD event using any available risk assessment calculator |
| High          | T1DM or T2DM and $\leq1$ major ASCVD risk factor  
|               | CKD stage 4  
|               | LDL-C $\geq190\text{ mg/dL}$  
|               | Presence of $\geq3$ major ASCVD risk factors |
| Very high     | Clinical evidence of ASCVD  
|               | T1DM or T2DM and $\geq2$ major ASCVD risk factors  
|               | Evidence of end-organ damage  
|               | End stage chronic kidney disease (CKD; however, data have consistently not shown benefit) |

### Major ASCVD risk factors

- Age (male 45 years or older, female 55 years or older)
- Family history of early heart disease (male $<55$ years, female $<65$ years)
- Cigarette smoking
- High blood pressure (on medication or at least $140/90\text{ mmHg}$)
- Low HDL-C (male $<40\text{ mg/dL}$, female $<50\text{ mg/dL}$)

### Statin initiation

- Initiate treatment with statin at the dose required to reach goal.
- Each doubling of statin dose is estimated to result in an additional $6\%$ of LDL-C lowering.
- If treatment goals are not met, especially in high- and very high-risk individuals, a second or third agent can be considered.
- Therapies to be considered include ezetimibe, niacin, gemfibrozil, and cholestyramine.

### Non-statin therapy projected LDL-C lowering

- Bile acid sequestrants: 15–30%
- Nicotinic acid: 5–25%
- Fibric acids: 5–20%
- Cholesterol absorption inhibitors: 13–20%
- Long chain omega-3 fatty acid drugs: 6–25%

### 2015 NLA Part 2 Guidelines

- Primary emphases of these guidelines include lifestyle therapies and special populations.
- Mirror recommendations in NLA Part 1 including risk assessment and goals of therapy, but include guidance for patient populations not included in NLA Part 1 (or ACC/AHA).  
- Provide additional guidance for use of non-statin therapies.  
- Stresses the importance of team-based care (including pharmacists).
<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 2017 Update on ACC Expert Consensus Decision Pathway on Use of Non-Statins | - Statin benefit groups  
  - Addresses the concern that the 2013 ACC/AHA guidelines did not include any non-statin recommendations.  
  - Statins remain cornerstone of dyslipidemia management.  
  - Recommendations organized by statin benefit groups as in the 2013 ACC/AHA guideline:  
    - Group 1: Adults ≥ 21 years of age with clinical ASCVD on statin for secondary prevention  
    - Group 2: Adults ≥ 21 years of age with baseline LDL-C > 190 mg/dL (not caused by secondary modifiable causes) on statin for primary prevention  
    - Group 3: Adults 40–75 years of age without clinical ASVD but with diabetes and baseline LDL-C 70–189 mg/dL, on statin for primary prevention  
    - Group 4: Adults 40–75 years of age without clinical ASCVD or diabetes with baseline LDL-C 70–189 mg/dL with an estimated 10-year risk of an ASCVD event ≥ 7.5% and on statin for primary prevention |
| Risk assessment | Other factors should be considered when deciding whether to add on additional therapy to a statin:  
  - Adherence to medication and lifestyle  
  - Statin intolerance  
  - Control of other risk factors  
  - Clinical-patient discussion on potential benefits and risks and patient preference  
  - Projected percentage of LDL-C reduction with add-on therapy  
  - Monitoring of response to therapy, adherence, and lifestyle  
  - Additional therapies to be considered only if a ≥ 50% LDL-C reduction is not achieved with maximally tolerated high-intensity statin |
| Interventions to consider |  
  - Referral to lipid specialist/registered dietitian  
  - Ezetimibe  
  - Bile-acid sequestrants in ezetimibe-intolerant patients (cholestyramine)  
  - PCSK9 inhibitors (evolocumab or alirocumab)  
  - Mipomersen, lomitapide, LDL apheresis may be considered by lipid specialist for familial hypercholesterolemia |

**Guideline comparisons**

<table>
<thead>
<tr>
<th>ACC/AHA guidelines</th>
<th>NLA parts 1 and 2</th>
<th>ACC non-statin consensus pathway</th>
</tr>
</thead>
</table>
| ➤ Intended for general practitioners  
  ➤ Designed for easy use  
  ➤ Focus on ASCVD risk reduction  
  ➤ Does not include specific goals for lipid lowering, but rather includes approximate proportion-al decrease in lipid levels that might be expected  
  ➤ Only recommends statins because no randomized controlled trial data exists that shows additional ASCVD risk lowering with further therapies  
  ➤ Introduces the concept of “statin benefit groups” | ➤ Intended for medical specialists seeing higher-risk patients (e.g., cardiologists, lipid specialists)  
  ➤ Designed for more individualized risk assessment and treatment targets  
  ➤ Includes specific numeric lipid goals based on comorbidities or the condition of the patient  
  ➤ Has co-primary targets of LDL-C and non-HDL-C  
  ➤ Part 2 recommendations for special populations not addressed by ACC/AHA  
  ➤ Includes recommendations for non-statin | ➤ Addresses barriers to appropriate use of statin therapy  
  ➤ Gives specific and hierarchical recommendations for additional therapies for patients in need of additional lipid lowering that are receiving maximally tolerated dosing of high-intensity statins |
**Landmark trials**

<table>
<thead>
<tr>
<th>Landmark trial</th>
<th>Description</th>
</tr>
</thead>
</table>
| PROVE-IT TIMI 22<sup>1</sup> | Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial.  
*Summary* Examined the effects of intensive vs. moderate statin therapy after acute coronary syndromes (ACS).  
*Importance* This trial heavily influenced subsequent guidelines to recommend higher-intensity statin therapy in high-risk patients. |
| JUPITER<sup>2</sup> | Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein.  
*Summary* Analyzed the benefits of statins in patients without hyperlipidemia but with elevated inflammatory markers.  
*Importance* This trial demonstrated the efficacy of statins in reducing clinical outcomes even when used in primary prevention. |
| HPS2-THRIVE<sup>3</sup> | Effects of extended-release niacin with laropiprant in high-risk patients.  
*Summary* Define the role of niacin therapy (in combination with a statin) in reducing cardiovascular events.  
*Importance* Niacin therapy does not add additional benefit to a statin in regard to clinical outcomes, despite beneficial effects on lipids. |
| IMPROVE-IT<sup>4</sup> | Ezetimibe added to statin therapy after acute coronary syndromes  
*Summary* Define the role of ezetimibe therapy (in combination with a statin) in reducing cardiovascular events.  
*Importance* This trial formed the basis of current recommendations to prioritize ezetimibe as the first-line non-statin therapy when further lipid lowering is desired. |
| FOURIER<sup>5</sup> | Evolocumab and clinical outcomes in patients with cardiovascular disease.  
*Objective* Examine the effect of PCSK9 inhibitors on cardiovascular outcomes.  
*Importance* PCSK9 inhibitors have positive benefits on clinical outcomes in high-risk patients even when added to a statin. |

**REFERENCES**

DYSLIPIDEMIA

Patient Presentation

Symptoms

- Usually patients present symptom-free.
- Certain modifiable and non-modifiable factors can increase risk for high cholesterol.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Effect on cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Lowers HDL-C and raises LDL-C</td>
</tr>
<tr>
<td>Diet</td>
<td>High trans and saturated fat diets (high TC)</td>
</tr>
<tr>
<td></td>
<td>Low physical activity</td>
</tr>
<tr>
<td></td>
<td>Obesity (high TG, high LDL-C, low HDL-C)</td>
</tr>
<tr>
<td>Age</td>
<td>Increased risk with age</td>
</tr>
<tr>
<td></td>
<td>Inability to clear cholesterol from our blood as we get older</td>
</tr>
<tr>
<td>Gender</td>
<td>Women (&lt; 55 years of age) have lower LDL-C than men.</td>
</tr>
<tr>
<td></td>
<td>Women tend to have higher HDL-C than men at any age.</td>
</tr>
<tr>
<td>Family history</td>
<td>Family history of high cholesterol combined with poor lifestyle choices increases risk for high cholesterol.</td>
</tr>
<tr>
<td></td>
<td>Inherited genetic high cholesterol “familial hypercholesterolemia” starts young and worsens with age.</td>
</tr>
<tr>
<td></td>
<td>Familial hypercholesterolemia often cannot be treated or controlled with lifestyle changes alone.</td>
</tr>
</tbody>
</table>

All patients should be screened regardless of symptoms (age ≥ 20 years old).
- Repeat screening should be done every 5 years.
- Rescreen earlier than 5 years if clinically indicated.
  - Changes in ASCVD risk factors
  - ASCVD event in close relative
  - Secondary cause of dyslipidemia
- Screen patients early with family history of ASCVD.

Clinical evaluation

- Family history
  - Early family ASCVD increases patient risk
- Rule out secondary causes of dyslipidemia
  - Diet (malabsorption)
  - Hypothyroidism
  - Obstructive liver disease
  - Medication-related causes
- ASCVD risk factors
  - Age (male 45 years or older, female 55 years old)
  - Family history of early heart disease (male < 55 years, female < 65 years)
  - Cigarette smoking
  - High blood pressure (on medication or at least 140/90 mmHg)
  - Low HDL-C (male < 40 mg/dL, female < 50 mg/dL)

Risks of uncontrolled dyslipidemia

- ASCVD events
  - Acute coronary syndrome
  - Myocardial infarction
  - Stable or unstable angina
  - Transient ischemic attack
  - Peripheral arterial disease
- Cardiovascular mortality
**Diagnostic tests**

- Fasting lipid panel (9 to 12 hours without food) should be obtained at baseline.

<table>
<thead>
<tr>
<th>Total cholesterol (TC)</th>
<th>&lt; 200 mg/dL</th>
<th>Desirable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200–239 mg/dL</td>
<td>Borderline</td>
</tr>
<tr>
<td></td>
<td>≥ 240 mg/dL</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDL cholesterol (LDL-C)</th>
<th>&lt; 100 mg/dL</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100–129 mg/dL</td>
<td>Near optimal</td>
</tr>
<tr>
<td></td>
<td>130–159 mg/dL</td>
<td>Borderline</td>
</tr>
<tr>
<td></td>
<td>160–189 mg/dL</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>≥ 190 mg/dL</td>
<td>Very high</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL cholesterol (HDL-C)</th>
<th>&lt; 40 mg/dL</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 60 mg/dL</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triglycerides (TG)</th>
<th>&lt; 150 mg/dL</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150–199 mg/dL</td>
<td>Borderline</td>
</tr>
<tr>
<td></td>
<td>200–499 mg/dL</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>≥ 500 mg/dL</td>
<td>Very high</td>
</tr>
</tbody>
</table>

- Lipoprotein lipid levels should be used in conjunction with ASCVD risk assessment to determine treatment goals and therapies.
- Test, at minimum, total cholesterol and HDL.
- Non-HDL-C = total cholesterol minus HDL-C

**REFERENCES**


**Treatment Goals**

Treatment goals for dyslipidemia vary between the available guidelines. Overall, the American College of Cardiology and the American Heart Association aim for ASCVD prevention instead of numeric treatment targets; the National Lipid Association guidelines provide specific numeric goals based on risk stratification. The 2017 ACC/AHA Non-Statin Expert Consensus Pathway recommends treatment thresholds above which non-statin therapy should be considered, which does include an absolute LDL-C reduction percentage that varies by statin benefit group. Therefore, the ultimate treatment goal for each patient should be individualized and dependent upon an in-depth and ongoing assessment of risks vs. benefits, drug interactions, drug-disease interactions, and patient preference.

### National Lipid Association Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HDL-C (mg/dL)</td>
<td>LDL-C (mg/dL)</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 130</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt; 130</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>High</td>
<td>&lt; 130</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Very high</td>
<td>&lt; 100</td>
<td>&lt; 70</td>
</tr>
</tbody>
</table>
The ACC does not provide numeric goals of therapy for dyslipidemia, but in its Expert Consensus Decision Pathway on the Role of Non-Statin Therapies, treatment thresholds are recommended above which providers can consider the use of non-statin in addition to maximally tolerated statin therapy. These thresholds are based on statin benefit group as described in the 2013 ACC/AHA Blood Cholesterol Guidelines.

<table>
<thead>
<tr>
<th>Statin benefit group</th>
<th>Threshold for considering non-statin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
<tr>
<td>Group 1 (secondary prevention in patients with ASCVD)</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Group 2 (primary prevention in patients with LDL-C ≥ 190 mg/dL)</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Group 3 (primary prevention in individuals with diabetes [but no ASCVD], 40 to 75 years of age, with LDL-C 70 to 189 mg/dL)</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Group 4 (primary prevention in individuals 40 to 75 years of age with LDL-C 70 to 189 mg/dL without diabetes or ASCVD but with estimated 10-year ASCVD risk ≥ 7.5%)</td>
<td>&lt; 100</td>
</tr>
</tbody>
</table>

REFERENCES

Disease State Management

Nonpharmacologic Management of Dyslipidemia

- Results in an expected total cholesterol reduction of 3–7%
- Heart-healthy diet
  - Emphasizes intake of vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts
  - Limits intake of sweets, sugar-sweetened beverages, and red meats (as culturally accepted)
  - Dietary cholesterol < 200 mg/day
  - 5–6% of calories from saturated fat and minimal to no calories from trans fat
  - Options include DASH diet, USDA Food Pattern, or AHA Diet
  - ≥ 150 minutes/week of moderate or higher intensity exercise
  - Plant sterols/stanols (2 g/day)
  - Dietary viscous soluble fiber (10–25 g/day)
  - Weight reduction (5-10% of body weight)
  - Smoking cessation
  - VERY low-fat diet for high TG (to prevent pancreatitis)
  - Per NLA, individuals in low and moderate risk groups should be given a 3-month trial to implement lifestyle modifications before initiation of drug therapy
Pharmacologic Management of Dyslipidemia\(^2\text{--}^5\)

All guidelines recommend initiating a statin as first-line therapy for dyslipidemia, with intensity of therapy based on degree of LDL-C reduction.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (in mg/day)</th>
<th>High intensity (lowers LDL-C (\geq 50%) from baseline)</th>
<th>Moderate intensity (lowers LDL-C 30–50% from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>40–80</td>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>–</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>–</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>–</td>
<td>2–4</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>–</td>
<td>40–80</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20–40</td>
<td>5–10</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>–</td>
<td>20–40</td>
<td></td>
</tr>
</tbody>
</table>

If non-statin therapies are considered, the LDL-C lowering varies by drug class.

American College of Cardiology/American Heart Association

The 2013 ACC/AHA Blood Cholesterol Guidelines recommend statin therapy as the first-line therapy (the only medication therapy recommended by these guidelines) based on statin benefit group.\(^2\)

The 2017 ACC Non-Statin Expert Consensus Decision Pathway provides additional considerations for what agents are appropriate when maximally tolerated statin therapy does not decrease LDL-C by \(\geq 50\%\) from baseline or when treatment thresholds are not met (see treatment goals section above).\(^5\)

A compilation of both sets of recommendations is depicted in the following algorithm in figure 2.

**FIGURE 2: Adapted from 2013 ACC/AHA Blood Cholesterol Guidelines and 2017 ACC Non-Statin Expert Consensus Decision Pathway.\(^2\text{--}^5\)**

Patient in a statin benefit group?

- **Statin Benefit Group 1**
  - High intensity statin (moderate if > 75 yrs)
  - LDL-C NOT decreased by 50% with maximally tolerated statin?
    - If no comorbidities, ezetimibe first, then PCSK9i second
    - If no comorbidities, ezetimibe OR PCSK9i (add the other agent second)

- **Statin Benefit Group 2**
  - High intensity statin
  - LDL-C NOT decreased by 50% with maximally tolerated statin?
    - Ezetimibe OR PCSK9i (add the other agent second)

- **Statin Benefit Group 3**
  - Moderate intensity statin (high intensity if 10-yr ASCVD risk \(\geq 7.5\%\))
  - Increase to high-intensity statin if not previously done?
    - LDL-C NOT decreased by 50% with maximally tolerated statin?
      - Ezetimibe OR PCSK9i (add the other agent second)

- **Statin Benefit Group 4**
  - Moderate-to-high intensity statin based on risk-benefit analysis
  - Increase to high-intensity statin if not previously done?
    - LDL-C NOT decreased by 50% with maximally tolerated statin?
      - Ezetimibe OR PCSK9i (add the other agent second)
Statin benefit groups (patients ≥ 21 years of age for whom the ASCVD risk reduction clearly outweighs the risk of adverse events)\(^2,5\)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Secondary prevention in individuals with clinical ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Primary prevention in individuals with LDL-C ≥ 190 mg/dL</td>
</tr>
<tr>
<td>Group 3</td>
<td>Primary prevention in individuals with diabetes (but no ASCVD), 40 to 75 years of age, with LDL-C 70 to 189 mg/dL</td>
</tr>
<tr>
<td>Group 4</td>
<td>Primary prevention in individuals 40 to 75 years of age with LDL-C 70 to 189 mg/dL without diabetes or ASCVD but with estimated 10-year ASCVD risk ≥ 7.5%</td>
</tr>
</tbody>
</table>

**Comorbidities influencing use of non-statin in statin benefit group 15**

- Diabetes
- ASCVD event within 3 months
- ASCVD event while taking statin
- Poorly controlled ASCVD risk factors
- Elevated Lp(a)
- Chronic kidney disease +/- hemodialysis
- Heart failure
- Baseline LDL-C ≥ 190 mg/dL without secondary causes
- Age ≥ 65 years
- Prior myocardial infarction (MI) or non-hemorrhagic stroke
- Current smoking
- Symptomatic peripheral artery disease with prior MI or stroke
- Revascularization
- Residual coronary artery disease after revascularization
- Low HDL-C
- Elevated hsCRP
- Metabolic syndrome

**High-risk markers influencing use of ezetimibe in statin benefit group 4\(^5\)**

- 10-yr ASCVD risk ≥ 20%
- LDL-C ≥ 160 mg/dL at baseline
- Poorly controlled ASCVD risk factors
- Family history of premature ASCVD
- Evidence of subclinical atherosclerosis
- Elevated hsCRP
- Inflammatory comorbidities (chronic kidney disease, HIV, rheumatoid arthritis)

**Considerations**

- Adherence to medication and lifestyle modifications, along with control of ASCVD risk factors, should be assessed at every visit.
- Bile acid sequestrants can be used as alternative to ezetimibe if patient is ezetimibe-intolerant and triglycerides < 300 mg/dL.
- Mipomersen and lomitapide can be used in coordination with a lipid specialist for patients with familial hypercholesterolemia.

**National Lipid Association**

The National Lipid Association Guidelines Parts 1 and 2 also recommend statin therapy as first-line treatment, with intensity based on LDL-C reduction needed to achieve numeric lipid targets. If treatment goals are not met, especially in high-risk and very-high-risk patients, a second or third agent can be considered.\(^3,4\)
### Table adapted from the 2015 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia Parts 1 and 2.3,4

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
<th>Statin intensity</th>
<th>Non-statin therapy (if goal not achieved)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HDL-C LDL-C (mg/dL)</td>
<td>Non-HDL-C LDL-C (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0–1 major ASCVD risk factors</td>
<td>&lt; 130 &lt; 100</td>
<td>≥ 190 ≥ 160</td>
<td>Drug and dose selected based on reduction needed to achieve goal.</td>
</tr>
<tr>
<td></td>
<td>2 major ASCVD risk factors</td>
<td>&lt; 130 &lt; 100</td>
<td>≥ 160 ≥ 130</td>
<td>Use high-intensity statin as required.</td>
</tr>
<tr>
<td>High</td>
<td>T1DM or T2DM and ≤ 1 major ASCVD risk factor</td>
<td>&lt; 130 &lt; 100</td>
<td>≥ 130 ≥ 100</td>
<td>Titrate patient to maximally tolerated statin.</td>
</tr>
<tr>
<td></td>
<td>CKD stage 4</td>
<td></td>
<td></td>
<td>Consider PCSK9i for ASCVD + LDL-C ≥ 100; HeFH without ASCVD but LDL-C ≥ 130; statin-intolerance (off-label)</td>
</tr>
<tr>
<td></td>
<td>LDL-C ≥ 190 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence of ≥ 3 major ASCVD risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>Clinical evidence of ASCVD</td>
<td>&lt; 100 &lt; 70</td>
<td>≥ 100 ≥ 70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1DM or T2DM and ≥ 2 major ASCVD risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of end-organ damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>End stage chronic kidney disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Major ASCVD risk factors³

- Age (male 45 years or older, female 55 years or older)
- Family history of early heart disease (male < 55 years, female < 65 years)
- Cigarette smoking
- High blood pressure (on medication or at least 140/90 mmHg)
- Low HDL-C (male < 40 mg/dL, female < 50 mg/dL)

### Considerations⁴

- Elderly patients with one major ASCVD risk factor should receive formal risk stratification using the Framingham Risk Score or the Pooled Cohort Equations.
- Patients ≥ 80 years old should be initiated on a moderate-intensity statin for secondary prevention regardless of LDL-C reduction needed based on increased risk of adverse effects.
- HIV and rheumatoid arthritis can be considered major ASCVD risk factors.
Hypertriglyceridemia (TG ≥ 500 mg/dL)³

- Intensive lifestyle interventions, including a very low-fat diet, are the mainstay of therapy.
- ASCVD risk reduction is secondary to preventing pancreatitis until TG is lowered.
- Goal of therapy is TG < 500 mg/dL.
- Blood glucose control must be achieved.
- Pharmacologic therapy is indicated with potent TG lowering effects (no preference), including fibrates, niacin, and omega-3 fatty acids:
  - Add second (and third) non-statin TG lowering agent until target achieved.

**Medications and Clinical Pearls**

<table>
<thead>
<tr>
<th>HMG CoA reductase inhibitors</th>
<th>Because of differing half-lives, some statins may be taken at different times of the day to increase efficacy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Simvastatin and fluvastatin should be taken at bedtime.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Lovastatin should be taken with the evening meal.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Altoprev® (extended-release lovastatin) should be taken at bedtime.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Atorvastatin (Lipitor®), rosvastatin (Crestor®), pitavastatin (Livalo®), and pravastatin (Pravachol®) can be taken at any time of day.</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Myopathy is a common adverse event in the use of statin therapy.1</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>It is often overlooked in the elderly because of comorbid conditions (such as osteoarthritis) and polypharmacy.</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Myopathy can progress to rhabdomyolysis if left unrecognized in patients.</td>
</tr>
<tr>
<td>Atorvastatin/amlodipine</td>
<td>Chances of developing myopathy can be increased owing to drug-drug interactions or duplicate therapies that may increase statin levels.</td>
</tr>
<tr>
<td>Simvastatin/sitagliptin</td>
<td>Myopathy is a dose-dependent adverse statin event.2</td>
</tr>
</tbody>
</table>

Percent LDL-C reduction listed in the package insert for each statin dose applies to statin-naïve patients only; once a patient is already receiving a statin, each doubling of the dose results in an incremental 6% LDL-C reduction.

<table>
<thead>
<tr>
<th>Bile acid resins³</th>
<th>Is less potent than other classes and not always well-tolerated because of increased GI side effects (flatulence, bloating, diarrhea, or constipation).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>Can increase triglycerides.</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Can bind to vitamins, hormones, or other medications in the intestines and result in subtherapeutic levels.</td>
</tr>
<tr>
<td>Colesevelam</td>
<td></td>
</tr>
</tbody>
</table>
### Cholesterol absorption inhibitor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>When used as monotherapy or in addition to statin therapy, significantly decreases TG, LDL-C, and non-HDL-C cholesterol and favorably affects HDL-C levels.</td>
</tr>
<tr>
<td>Ezetimibe/atorvastatin</td>
<td>Does not interfere with the absorption of TG, fatty acids, bile acids, or fat-soluble vitamins (unlike bile acid resins).</td>
</tr>
<tr>
<td>Ezetimibe/simvastatin</td>
<td>Is well tolerated, with safety profiles similar to placebo.</td>
</tr>
</tbody>
</table>

### Fibrates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline fenofibrate (fenofibric acid)</td>
<td>Concomitant use of fibrates may significantly reduce CV risk in patients whose LDL-C is controlled by statin therapy.</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Most effective at decreasing plasma triglyceride-rich lipoproteins (TRLs).</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Considered to be well tolerated with an excellent safety profile.</td>
</tr>
<tr>
<td></td>
<td>Increases tubular secretion of creatinine but does not affect renal function.</td>
</tr>
<tr>
<td></td>
<td>Can interact with other medications:</td>
</tr>
<tr>
<td></td>
<td>♦ Rhabdomyolysis with HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td></td>
<td>♦ Decreased anticoagulant effect of warfarin derivatives may cause increased bleeding.</td>
</tr>
</tbody>
</table>

### Omega-3 acids (fish oils)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 acid ethyl esters</td>
<td>Considered as treatment for severe hypertriglyceridemia and high-risk patients with atherogenic dyslipidemia.</td>
</tr>
<tr>
<td>Icosapent ethyl</td>
<td>Prescription-strength omega-3 fatty acids (4 grams per day) have been shown to lower TG levels.</td>
</tr>
<tr>
<td></td>
<td>Adding omega-3 fatty acids to statin therapy has been shown to help patients reach non-HDL cholesterol goals.</td>
</tr>
<tr>
<td></td>
<td>Concomitant use has been shown to decrease the risk of major coronary events by 19% when compared to treatment with statin plus a placebo.</td>
</tr>
<tr>
<td></td>
<td>Unfavorable GI side-effect profile, including belching, bad (fish) breath, heartburn, nausea, and loose stools</td>
</tr>
<tr>
<td></td>
<td>♦ Freezing capsules before administration and taking with meals can decrease GI side effects.</td>
</tr>
</tbody>
</table>

### PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>Fully human monoclonal antibodies used to lower LDL-cholesterol levels.</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Given by injection only.</td>
</tr>
<tr>
<td></td>
<td>♦ Side-effect profile: swelling or rash at injection site, limb pain, and fatigue</td>
</tr>
<tr>
<td></td>
<td>♦ Long-term side effects are unknown.</td>
</tr>
<tr>
<td></td>
<td>♦ Target patient populations are adults with primary nonfamilial or heterozygous familial hypercholesterolemia; patients with mixed dyslipidemia, including patients with T2DM; and patients unable to tolerate statins.</td>
</tr>
</tbody>
</table>

### Niacin (IR/SR/ER)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Has been proven to lower total cholesterol, LDL-C, and TG and increase HDL-C.</td>
</tr>
<tr>
<td></td>
<td>ER Niacin is associated with increased lowering effect on LDL-C and TG, whereas immediate release has shown greater increases in HDL-C.</td>
</tr>
<tr>
<td></td>
<td>Both ER and immediate release have unattractive side-effect profiles, including flushing and palpitations.</td>
</tr>
<tr>
<td></td>
<td>Has also been associated with decreased control of diabetes and exacerbations of PUD, gout, and hepatitis.</td>
</tr>
</tbody>
</table>
References


Complementary and Integrative Health Approaches (CIHA)

Many therapies have been studied for treatment of hyperlipidemia. Given the complex disease state that is greatly affected by lifestyle (diet and physical activity), it is difficult for many studies using complementary and integrative health approaches to have strong external validity. Many current therapies considered CIHA options are understudied or have variable results.

There are several studies ongoing in current animal models for the treatment of hyperlipidemia. Gastrodia elata blume (EGB), acupuncture, and traditional Chinese herbs (Chaihu-Shugan-San) have shown favorable results in animal models but have been limited to no standardized testing in humans. Listed next are a variety of CIHA therapy options with current human evidence for their use.

<table>
<thead>
<tr>
<th>CIHA</th>
<th>Efficacy</th>
<th>Evidence for Efficacy</th>
</tr>
</thead>
</table>
| Plant stanols and sterols | Safe     | ➤ Guidelines recommend 2–3 g/day.  
➤ Doses > 2g showed no additional benefit.  
➤ 8.7% greater reduction in LDL-C vs placebo.  
➤ Competitively inhibits absorption of dietary and biliary cholesterol by competing for space in micelles |
| Fibers             | Safe     | ➤ Guidelines recommend 2–10 g/day.  
➤ Reduction 1.7 mg/dl per gram of fiber.  
➤ 7.2 g of fiber showed reduction in TG of 4% and LDL-C of 7% compared to placebo.  
➤ Affect hepatic cholesterol, lipoprotein metabolism, and increase bile acid loss resulting in decreased hepatic cholesterol concentrations and upregulation of LDL-C receptors |
| Soy protein        | Safe     | ➤ Upregulate LDL-C receptors; Variable range of doses used in studies.  
➤ **Study 1**: 47 g/day average resulted in TC reduction of 9.3%, LDL-C 12.9%, and TG 10.5%.  
➤ **Study 2**: meta-analysis reduction in TC of 3.8%, LDL-C 5.3%, TG 5.3%, and increase HDL-C of 3.0% vs placebo.  
➤ Recent studies showed mixed results inconsistent with previous studies. |
<p>| Garlic             | Safe     | Unclear mechanism of action, theorized to contain sulfur constituents, which inhibit hepatic cholesterol synthesis |</p>
<table>
<thead>
<tr>
<th>CIHA</th>
<th>Efficacy</th>
<th>Evidence for Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guggul</td>
<td>Inadequately studied, but safe</td>
<td>Contains guggulsterones E/Z, which antagonize bile acid receptors.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Study:</strong> RCT with 1000-2000 mg guggul extract TID for 8 weeks showed no LDL-C reduction vs placebo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Study contradicts smaller studies, which showed benefit.</td>
</tr>
<tr>
<td>Red yeast rice</td>
<td>Effective, but with some danger</td>
<td>➤ Fermented rice produces monacolin K.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Monacolin K contains lovastatin, sterols, and monounsaturated fatty acids.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Inhibits endogenous synthesis of cholesterol.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Lovastatin dose per capsule of red yeast rice is variable and manufacturing underregulated.</td>
</tr>
<tr>
<td>Policosanol</td>
<td>Inadequately studied, but safe</td>
<td>➤ Cuban product from sugarcane; is not available in the US.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ 10 mg/day showed LDL-C reduction of 23.7%, TC 16.2%, and HDL-C increase of 10.6% in Cuban studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Inhibit hepatic cholesterol synthesis with theorized effect on LDL binding, uptake, and degradation</td>
</tr>
<tr>
<td>Vaccinium arctostaphylos³</td>
<td>Inadequately studied, but safe</td>
<td>➤ 52 patients randomized to fruit extract (45 mg BID) vs placebo for 4 weeks showed reduction in TC, LDL-C, and TG and no change in HDL-C.</td>
</tr>
<tr>
<td>Co-enzyme Q10</td>
<td>Safe</td>
<td>➤ Current phase 3 study under investigation: Co-Q10 + Vitamin E vs Co-Q10 vs placebo examining effects on lipid profiles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Addition of Co-Q10 (200 mg/day) to statin therapy reduced the intensity of statin adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Improve cholesterol efflux from macrophages.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➤ Antioxidant helps prevent statin-induced adverse events (myopathy).</td>
</tr>
</tbody>
</table>

**REFERENCES**

At every visit, health care providers should reinforce adherence to therapeutic lifestyle changes and pharmacologic therapy for dyslipidemia.

**Monitoring**

**Efficacy**

- Fasting lipid panel (including total cholesterol, HDL-C, triglycerides, and calculated LDL-C) at baseline
- Repeat 4–12 weeks after initiation of drug therapy, then every 3–12 months as clinically indicated.
- If numeric lipid targets included as part of treatment plan, monitor frequently until goal achieved, then every 4–12 months to assess maintenance of goal lipid levels and adherence.

**Safety**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Timeline for Monitoring</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>3 months after initiation</td>
</tr>
<tr>
<td>Statins*</td>
<td>LFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>LFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>LFT Blood glucose Uric acid</td>
<td>LFT Blood glucose Uric acid</td>
<td>LFT Blood glucose Uric acid</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Renal function</td>
<td>Renal function</td>
<td>Renal function</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Lipid panel (TG)</td>
<td>Lipid panel (TG)</td>
<td>Lipid panel (TG)</td>
</tr>
</tbody>
</table>

Abbreviations: LFT = liver function tests (hepatic transaminases); TG = triglycerides
*Check creatine kinase if muscle symptoms develop.

**Refer to lipid specialist**
- Patients with LDL-C ≥ 190 mg/dL
- Children and adolescents
- Pregnancy
- Heterozygous or homozygous familial hypercholesterolemia
- Statin intolerance (after rigorous assessment)

**Assessing Adherence**

- Evaluate health literacy.
- Establish a comfortable relationship between the patient and provider.
- Monitor prescription refill data (eg, electronic medical record, pharmacy records, insurance billing).
- Conduct direct discussion with patient.
  - How many missed doses in the last month?
  - What adverse effects have you experienced from your medication?
  - What are some of the reasons you do not take your medication? (Address cost if necessary.)
- Administer validated questionnaire, such as the 8-item Morisky Medication Adherence Scale (MMAS-8).

**Strategies to Improve Adherence**

- A multidisciplinary health care team, including pharmacists, is optimal for maximizing medication adherence through identification of and solutions to barriers to adherence.

  SIMPLE:
  - Simplify the regimen.
  - Impart knowledge.
  - Modify patient beliefs and behavior.
  - Provide communication and trust.
  - Leave the bias.
  - Evaluate adherence (bring all medications to each visit, ask direct questions, technological intervention).
Practical Clinical Management Tips

Statin intolerance\(^1\)

- Muscle-related side effects are common with statin therapy, but true statin intolerance is uncommon.
- Rule out other causes of myalgia (recent exercise, hypothyroidism, and vitamin D deficiency) to determine true statin intolerance.
- Drug-drug interactions that can increase statin levels in the body must also be evaluated.
- Women, patients of Asian descent, and the elderly may be at increased risk for statin-related myalgias.
- Testing for true tolerance:
  - discontinue the offending statin therapy until muscle-related side effects have subsided
  - rechallenge with at least two to three alternate statin medications, preferably those with differing metabolic pathways and half-lives. Dosing regimens that have been studied include every other day and twice weekly (with statins that have long half-lives such as rosuvastatin).
- The American College of Cardiology Statin Intolerance App is available for free for both Apple and Android devices, along with a web-based version.\(^2\)
  - The app is based on 2013 ACC/AHA Blood Cholesterol Guidelines\(^3\) and evaluates statin intolerance to work through steps to manage and treat the patient, and to complete basic risk assessment.
  - Non-statin medications should not be considered for therapy until statin intolerance has been thoroughly evaluated and documented.

REFERENCES

Guideline changes

- Recent changes in hyperlipidemia treatment guidelines have shifted from a treat-to-target approach to new treatment goals based on a percentage decrease from baseline readings.
- Guidelines now separate patients into four groups for primary and secondary prevention of hyperlipidemia, with each group having a recommendation for statin intensity.

Current treatment guideline recommendations include the following:

- Statin therapy is considered first-line treatment for lowering cholesterol.
- Other agents, such as niacin, bile acid resins, and fibrates, are reserved for statin-intolerant patients or for those not reaching their target goals on statins alone.

REFERENCES


Pharmacogenomics Implications

<table>
<thead>
<tr>
<th>Drug: Simvastatin; Gene: SLCO1B1</th>
<th>Informative PGx</th>
<th>CPIC Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with 1 copy of the variant SLCO1B1 gene where cytosine replaces thymine at position 521 of the coding region of the gene (c.521T&gt;C) are considered to have an “intermediate function” phenotype, and individuals with 2 copies of this variant form are considered to have a “low function” phenotype.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As compared with individuals with a “normal function” SLCO1B1 phenotype, intermediate function and poor function phenotype individuals are at intermediate and high risk of simvastatin-induced myopathy, respectively.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SLCO1B1 Phenotype and related recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low function</td>
</tr>
<tr>
<td>Potential toxicity:</td>
</tr>
<tr>
<td>Use lower dose of drug or choose an alternative.</td>
</tr>
</tbody>
</table>

REFERENCES

Impact on specific populations

- Racial and ethnic minority populations in the United States, excepting blacks, have been found to have a higher incidence of elevated triglycerides compared with non-Hispanic whites. Additionally, most minority groups, except for blacks and Japanese Americans, have a higher incidence of low HDL cholesterol, and the incidence of elevated LDL is increased among Asian Indians, Filipinos, Japanese, and Vietnamese individuals when compared with non-Hispanic whites.1
- Among minority populations, Hispanics, Asian Indians and Filipinos are at the highest risk for dyslipidemia and have higher coronary heart disease mortality rates.2
- Older adults have a higher incidence of dyslipidemia versus younger age groups and premenopausal women tend to have lower rates of elevated LDL cholesterol versus their male counterparts.3

Barriers to care

- In households of lower socioeconomic position, diets tend to be higher in saturated fats, which can lead to increased cholesterol levels.4
- Lack of education can hinder understanding of the relationship between food and cholesterol.
- One survey of black teens and young adults in Phoenix Arizona showed that 70% had knowledge of the relationship between cholesterol and heart disease, but only 49% had awareness that reducing intake of animal products could lower CHD risk.5

Black and Hispanic adolescent females tend to have lower rates of physical activity compared with their white counterparts.6

- Blacks and Hispanics have been shown to receive vascular care at health care facilities that perform a lower volume of procedures and have higher mortality rates after coronary bypass surgery and myocardial infarction.7
- Mexican Americans tend to be less likely to be aware of or treated for dyslipidemia, while blacks have lower rates of medication adherence compared with non-Hispanic whites.7

Cultural Considerations

- Food choices and physical activity are greatly influenced by culture (beliefs, values, and attitudes).7
  - Economic factors are closely linked to food availability.
  - Recent immigrants and individuals of lower socioeconomic position may not have easy access to healthy foods.
  - Low-cost foods can often be high in fat and oils.
  - Cultures with diets high in saturated fat can have an increased risk of dyslipidemia.
- The Seven Countries Study compared food habits in the US, Japan, Northern Europe, and Southern Europe. The study confirmed that high blood cholesterol increased risk for heart disease. In this study, patients who ate a Mediterranean diet had reduced risk of coronary heart disease.8

Cultural Sensitivities and Health Disparities
Traditional Hispanic diets have been shown to include high levels of fiber. Studies show that the diets of US-born Hispanics include higher levels of fat and sugar when compared to traditional diets because of less access to good quality, nutritious foods. Latin American immigrants often adopt poor eating habits in the United States, consuming higher fat meals, larger portions, and fewer fruits and vegetables.

Traditional East Asian diets are lower in total and saturated fats when compared to traditional western and Asian Indian diets.

Chinese immigrants living in the United States for prolonged periods of time have been shown to consume diets containing unhealthy foods and to have less physical activity in their daily routines.

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Traditional East Asian diets are lower in total and saturated fats when compared to traditional western and Asian Indian diets.

Chinese immigrants living in the United States for prolonged periods of time have been shown to consume diets containing unhealthy foods and to have less physical activity in their daily routines.

Discontinue all lipid-lowering therapies (except bile acid sequestrants) when a woman becomes pregnant or during attempts to become pregnant.

Hypercholesterolemia during pregnancy and lactation may be treated with bile acid sequestrants.

Screen for dyslipidemia before pregnancy or as soon as possible once pregnancy is determined.

Avoid pregnancy if possible while taking lipid-lowering therapies (except bile acid sequestrants).

Part 2 of the 2015 National Lipid Association (NLA) Guidelines focuses on several major patient populations that were omitted from the 2013 ACC/AHA Guidelines and only briefly addressed (if at all) in Part 1 of the NLA Guidelines.

Pregnancy

Special Populations

Pregnancy

Screen for dyslipidemia before pregnancy or as soon as possible once pregnancy is determined.

Avoid pregnancy if possible while taking lipid-lowering therapies (except bile acid sequestrants).

Hypercholesterolemia during pregnancy and lactation may be treated with bile acid sequestrants.

Diet, increased physical activity, and other lifestyle modifications should be recommended in children and adolescents when overweight or obese; diet should be guided by a dietitian or nutritionist when possible.

Discontinue all lipid-lowering therapies (except bile acid sequestrants) when a woman becomes pregnant or during attempts to become pregnant.

Hypercholesterolemia during pregnancy and lactation may be treated with bile acid sequestrants.

Diet, increased physical activity, and other lifestyle modifications should be recommended in children and adolescents when overweight or obese; diet should be guided by a dietitian or nutritionist when possible.

References

Consider screening children 2 years of age and older for dyslipidemia if one or both biological parents have hypercholesterolemia or are taking cholesterol-lowering medications, the child has an expanded first-degree relative with a premature ASCVD event, or family history is unknown.

Consider regular screening for children with ASCVD risk factors and conditions associated with increased ASCVD risk (no valid screening methods in patients < 20 years of age).

Children ≥ 8 years of age should be considered for pharmacologic lipid-lowering therapy if LCL-C is ≥ 190 mg/dL and/or non-HDL-C is ≥ 220 mg/dL.

Moderate evidence of efficacy and safety exists for statins and bile acid sequestrants in children and adolescents; minimal evidence exists to support use of cholesterol absorption inhibitors.

Potential side effects of all pharmacologic lipid-lowering therapy should be closely monitored.

**Ethnic groups**

ASCVD risk burden varies greatly depending on country of origin or descent.

Overall, treatment is largely the same with additional considerations for risk assessment (incidence and risk for each ethnic group is in comparison to non-Hispanic white patients).

Hispanic/Latino patients

- Hispanics/Latinos have a greater prevalence of high TG and low HDL-C.
- LDL-C levels tend to be higher in Hispanic men.
- Hispanics/Latinos have a higher prevalence of T2DM, obesity, and metabolic syndrome.
- Some risk assessment tools may overestimate risk in Hispanic/Latino individuals.
- Hispanics/Latinos should be treated according to the NLA part 1 guidelines with special considerations.

African American patients

- African Americans are at increased risk of ASCVD; however, ASCVD risk is less driven by dyslipidemia.
- Caution should be used when assessing non-lipid risk factors such as HTN, overweight or obesity, and physical inactivity when determining ASCVD risk.
- African Americans have a lower incidence of metabolic syndrome and lower TG and higher HDL-C.
- Incidence of T2DM is higher in African Americans.
- African American individuals should generally be treated according to NLA Part 1 guidelines.

South Asian patients

- Patients of South Asian descent have a higher incidence of insulin resistance and accompanying metabolic disturbances.
- South Asians have an increased incidence of metabolic syndrome and have different waist circumference for defining obesity.
- In general, South Asian patients should be treated according to NLA Part 1 guidelines.
- Monitoring for statin-induced diabetes is indicated because South Asians are at increased risk.

American Indian and Alaska Native patients

- American Indians and Alaska Natives have higher prevalence and incidence of ASCVD and some risk factors including obesity, metabolic syndrome, diabetes mellitus, and cigarette smoking.
- Clinicians should screen for and manage dyslipidemia according to NLA Part 1 guidelines with strong emphasis on lifestyle therapy.

**High-risk patients**

Human immunodeficiency virus (HIV)

- HIV-infected individuals are at increased risk for ASCVD.
- Fasting lipid panel should be obtained in all newly diagnosed individuals with HIV before and after starting antiretroviral therapy (ART).
- For primary ASCVD prevention, HIV should be considered an additional risk factor for risk assessment.
- Non-HDL-C and LDL goals per the NLA Part 1 guidelines should be followed for HIV-infected patients.
Statin therapy is first-line therapy for lipid lowering in patients with HIV.
Caution with drug-drug interactions between lipid-lowering therapy and ART.

Rheumatoid arthritis (RA)
Patients with rheumatoid arthritis are at increased risk for ASCVD.
For primary prevention of ASCVD, RA may be counted as a separate risk factor for risk assessment.
Statins are generally the first-line treatment for lipid lowering in patients with RA.
Lipid panels may not be reliable if obtained during a flare and should be re-checked once patient is stable.
Patients with RA should generally be treated according to NLA Part 1 guidelines.

Residual risk (patients who need additional lipid lowering after maximally tolerated statin)
First-line adjunctive therapy: ezetimibe
Second-line adjunctive therapy: colesevelam
Third-line adjunctive therapy: extended release niacin

REFERENCES

Interprofessional Collaborative Practice

Pharmacist counseling can play a significant role in managing patients with hyperlipidemia. Important counseling points include the following:

- Initial evaluation and explanation of hyperlipidemia, including assessment of LDL-C, HDL-C, triglycerides, and overall cholesterol levels
- Explanation and patient understanding of the importance of modifiable factors such as diet and exercise, discussing issues such as the following:
  - Difference between good and bad fats
  - Motivation to read product labels and limit the intake of saturated fats
  - Importance of healthy diet and exercise to aid in reaching cholesterol goals
  - Importance of maintaining a healthy weight
  - Tobacco cessation
- Review of baseline readings and percentage targets, as well as consequences of high cholesterol such as:
  - Heart attack
  - Stroke
  - Vascular disease
  - Atherosclerosis
- Recommend and emphasize regular cholesterol level evaluation, starting at age 35 for men and age 45 for women
- Patients working with pharmacists have been shown to achieve greater reductions in LDL compared with patients treated by teams without clinical pharmacists.
- Reduction in LDL for patients managed by multidisciplinary teams including clinical pharmacists was shown to be between 5% and 22% greater than those teams without, even for inpatient populations who presented with higher risk factors for hyperlipidemia.
- These short-term outcomes can likely be extrapolated to show fewer CV events, improved quality of life and lower healthcare related costs for patients with dyslipidemias, showing again the importance of interprofessional collaborative practice.

REFERENCES