American Association of Clinical Endocrinologists and American College of Endocrinology

Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease

Writing Committee
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Co-Chair: Yehuda Handelsman, MD, FACP, FACE
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Reviewers:
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Farhad Zangeneh, MD
AACE Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease: Objectives and Structure

• This Clinical Practice Guideline aims to provide the following:
  • An evidence-based education resource
  • A practical tool for endocrinologists, other health care professionals and organizations, and regulatory agencies to use to reduce the risks and consequences of dyslipidemia
  
• 87 Recommendations
  • 45 are Grade A; 18 are Grade B; 15 are Grade C; 9 are Grade D

• Evidence Base
  • 695 citations: 203 are EL 1; 137 are EL 2; 119 are EL 3; 236 are EL 4
## AACE Clinical Practice Guidelines, Evidence Ratings, and Grades

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Evidence grade</th>
<th>Semantic descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>Meta-analysis of randomized controlled trials (MRCT)</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>Randomized controlled trial (RCT)</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT)</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>Nonrandomized controlled trial (NRCT)</td>
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<td>2</td>
<td>B</td>
<td>Prospective cohort study (PCS)</td>
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<td>2</td>
<td>B</td>
<td>Retrospective case-control study (RCCS)</td>
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<tr>
<td>3</td>
<td>C</td>
<td>Cross-sectional study (CSS)</td>
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<tr>
<td>3</td>
<td>C</td>
<td>Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database) (SS)</td>
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<tr>
<td>3</td>
<td>C</td>
<td>Consecutive case series (CCS)</td>
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<tr>
<td>3</td>
<td>C</td>
<td>Single case report (SCR)</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>No evidence (theory, opinion, consensus, review, or preclinical study) (NE)</td>
</tr>
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AACE Lipid Disorders Clinical Practice Guidelines
The following are questions based on the 87 Recommendations included in the CPGs

1. What are risk factors for ASCVD?
2. What risk categories does AACE recommend?
3. How is risk assessed?
4. How does T1DM affect risk?
5. Who should be screened for ASCVD risk and when?
6. What are secondary causes of dyslipidemia?
7. Which screening tests should be used?
8. What are lipid treatment goals?
9. What treatments are available for dyslipidemia?
10. What special considerations should be given to women?
11. What special considerations should be given to children and adolescents?
12. How does treatment of dyslipidemia affect ASCVD risk?
13. How are different drug categories used to treat dyslipidemia?
14. How should treatment be monitored?
15. Is the treatment of dyslipidemia and prevention of ASCVD cost-effective?

Abbreviations: AACE, American Association of Clinical Endocrinologists; ASCVD, atherosclerotic cardiovascular disease; CPGs, Clinical Practice Guidelines; T1DM, type 1 diabetes mellitus.

Question: What are risk factors for ASCVD?

The risk of ASCVD and ASCVD-related mortality is substantially greater in the presence of multiple risk factors. Since epidemiologic evidence indicates that ASCVD risk factors frequently cluster, it should be expected that many individuals have multiple risk factors.

Recommendations associated with this question:

R1. Identify risk factors that enable personalized and optimal therapy for dyslipidemia. (Grade A; BEL 1).

Abbreviation: ASCVD, atherosclerotic cardiovascular disease.

# Major Atherosclerotic Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Additional risk factors</th>
<th>Nontraditional risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>Obesity, abdominal obesity</td>
<td>† Lipoprotein (a)</td>
</tr>
<tr>
<td>† Total serum cholesterol level</td>
<td>Family history of hyperlipidemia</td>
<td>† Clotting factors</td>
</tr>
<tr>
<td>† Non–HDL-C</td>
<td>† Small, dense LDL-C</td>
<td>† Inflammation markers</td>
</tr>
<tr>
<td>† LDL-C</td>
<td>† Apo B</td>
<td>(hsCRP; Lp-PLA&lt;sub&gt;2&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>† LDL particle concentration</td>
<td>† Homocysteine levels</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Fasting/postprandial hypertriglyceridemia</td>
<td>Apo E4 isoform</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>† Uric acid</td>
</tr>
<tr>
<td>Stage 3 or 4 chronic kidney disease</td>
<td>PCOS</td>
<td>† TG-rich remnants</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Dyslipidemic triad</td>
<td></td>
</tr>
<tr>
<td>Family history of ASCVD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA<sub>2</sub>, lipoprotein-associated phospholipase; PCOS, polycystic ovary syndrome.

Question: How is risk assessed?

R4. The 10-year risk of a coronary event (high, intermediate, or low) should be determined by detailed assessment using one or more of the following tools (Grade C; BEL 4, upgraded due to cost-effectiveness):

- Framingham Risk Assessment Tool
- MESA 10-year ASCVD Risk with Coronary Artery Calcification Calculator
- Reynolds Risk Score, which includes hsCRP and family history of premature ASCVD
- UKPDS risk engine to calculate ASCVD risk in individuals with T2DM

R7. When the HDL-C concentration is greater than 60 mg/dL, one risk factor should be subtracted from an individual’s overall risk profile (Grade B; BEL 2).

R8. A classification of elevated TG should be incorporated into risk assessments to aid in treatment decisions (Grade B; BEL 2).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity CRP; MESA, Multi-Ethnic Study of Atherosclerosis; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Multi-Ethnic Study of Atherosclerosis

- **MESA investigated the correlates of subclinical CVD**\(^1\)
  - The study enrolled 6,814 patients between July 2000 and September 2002; at baseline, all patients were free of clinical CVD\(^2\)

- **10-year outcomes showed that CAC is an independent risk factor for CVD**\(^3\)
  - CAC predicts CVD risk in patients with or without traditional risk factors and in patients with family history of premature CHD\(^4-5\)
  - CAC was the strongest predictor of CVD in low-risk patients\(^6\)

- **The MESA risk score uses traditional risk factors and CAC to predict 10-year CHD risk**\(^7\)
  - The incorporation of CAC into this risk score has improved risk prediction\(^7\)

Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease; CVD, cardiovascular disease; MESA, Multi-Ethnic Study of Atherosclerosis.

MESA: CHD Event Rates With Increasing CAC Score and Based on Risk Factor Burden

*Hard events = MI, resuscitated cardiac arrest, CHD death

Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction

MESA: Cumulative CHD Incidence Across Coronary Artery Calcium Categories
ASCVD Risk Categories

<table>
<thead>
<tr>
<th>Low risk:</th>
<th>Extreme risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No risk factors</td>
<td>- Progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD with diabetes, stage 3 or 4 CKD, and/or HeFH, or in those with a history of premature ASCVD (&lt;55 years of age for males or &lt;65 years of age for females)</td>
</tr>
<tr>
<td>Moderate risk:</td>
<td>- This category was added in this CPG based on clinical trial evidence and supported by meta-analyses that further lowering of LDL-C produces better outcomes in individuals with ACS. IMPROVE-IT demonstrated lower rates of cardiovascular events in those with ACS when LDL-C levels were lowered to 53 mg/dL combining ezetimibe with statins.</td>
</tr>
<tr>
<td>- 2 or fewer risk factors and a calculated 10-year risk of less than 10%</td>
<td></td>
</tr>
<tr>
<td>High risk:</td>
<td></td>
</tr>
<tr>
<td>- An ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%</td>
<td></td>
</tr>
<tr>
<td>Very high risk:</td>
<td></td>
</tr>
<tr>
<td>- Established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CPG, clinical practice guideline; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial.
Question: For patients with diabetes, what risk categories does AACE recommend?

R2. Based on epidemiologic studies, individuals with T2DM should be considered as high, very high, or extreme risk for ACSVD (Grade B; BEL 3; upgraded due to high relevance).

R3. Based on epidemiologic and prospective cohort studies, individuals with T1DM and duration more than 15 years or with ≥2 major CV risk factors (e.g., albuminuria, stage 3 or 4 CKD, initiation of intensive control >5 years after diagnosis), poorly controlled hemoglobin A1C, or insulin resistance with metabolic syndrome should be considered to have risk-equivalence to individuals with T2DM (Grade B; BEL 2).

- T1DM is associated with increased ASCVD risk
- Individuals with T1DM should be screened annually for dyslipidemia
- Individuals with T1DM should be treated aggressively for dyslipidemia according to risk level recommendations

Abbreviations: A1C, glycated hemoglobin; AACE, American Association of Clinical Endocrinologists; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cerebrovascular; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Factors That May Increase Risk for Ischemic ASCVD in Patients With T1DM

Individuals with T1DM for >15 years or with ≥2 CV risk factors should be treated as if they had T2DM. Given the risks associated with T1DM, dyslipidemia in this population must not be overlooked and should be treated aggressively.

- Albuminuria\(^1\)
- Late-onset T1DM (>30 years of age) without nephropathy, but with:
  - Initiation of intensive control more than 5 years after diagnosis\(^2,3\)
  - Duration of disease greater than 15 years\(^4-8\)
- Previous history of MI or poorly controlled A1C\(^4\)
- Insulin resistance or MetS\(^9\) and an hsCRP concentration >3.0 mg/L\(^10\)

Abbreviations: A1C, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; CV, cerebrovascular; hsCRP, highly sensitive C-reactive protein; MetS, metabolic syndrome; MI, myocardial infarction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Systematic Review, Summary of Event Rates in Trial Participants With Diabetes, Stratified by Absence or Presence of Baseline Proteinuria

Randomized controlled trials (N=29), 116,790 patients with diabetes, ~518,611 patient-years of follow-up

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction.

Meta-Analysis: Hazard Ratios and 95% CIs for All-Cause and CV Mortality According to Estimated eGFR and Categorical Albuminuria

Question: Who should be screened for ASCVD risk and when?

Familial Hypercholesterolemia

- **R9.** Individuals should be screened for FH when there is a family history of:
  - Premature ASCVD (definite MI or sudden death before age 55 years in father or other male first-degree relative or before age 65 years in mother or other female first-degree relative) or
  - Elevated cholesterol levels (total, non-HDL, and/or LDL) consistent with FH (Grade C; BEL 4, upgraded due to cost-effectiveness).

Adults With Diabetes

- **R10.** Annually screen all adult individuals with T1DM or T2DM for dyslipidemia (Grade B; BEL 2).

Young Adults (Men Aged 20-45 Years, Women Aged 20-55 Years)

- **R11.** Evaluate all adults 20 years of age or older for dyslipidemia every 5 years as part of a global risk assessment (Grade C; BEL 4, upgraded due to cost-effectiveness).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Recommendations associated with this question:

**Question:** Who should be screened for ASCVD risk and when?

**Middle-Aged Adults (Men Aged 45-65 Years, Women Aged 55-65 Years)**

- **R12.** In the absence of ASCVD risk factors, screen middle-aged individuals for dyslipidemia at least once every 1 to 2 years. More frequent lipid testing is recommended when multiple global ASCVD risk factors are present (Grade A; BEL 1).
- **R13.** The frequency of lipid testing should be based on individual clinical circumstances and the clinician’s best judgment (Grade C; BEL 4, upgraded due to cost-effectiveness).

**Older Adults (Older Than 65 Years)**

- **R14.** Annually screen older adults with 0 to 1 ASCVD risk factor for dyslipidemia (Grade A; BEL 1).
- **R15.** Older adults should undergo lipid assessment if they have multiple ASCVD global risk factors (i.e., other than age) (Grade C; BEL 4, upgraded due to cost-effectiveness).
- **R16.** Screening for this group is based on age and risk, but not gender; therefore, older women should be screened in the same way as older men (Grade A; BEL 1).

**Children and Adolescents**

- **R17.** In children at risk for FH (e.g., family history of premature cardiovascular disease or elevated cholesterol), screening should be at 3 years of age, again between ages 9 and 11, and again at age 18 (Grade B; BEL 3, upgraded due to cost-effectiveness).
- **R18.** Screen adolescents older than 16 years every 5 years or more frequently if they have ASCVD risk factors, have overweight or obesity, have other elements of insulin resistance syndrome, or have a family history of premature ASCVD (Grade B; BEL 3, upgraded due to cost-effectiveness).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia.

Familial Hypercholesterolemia: Diagnosis

• FH diagnostic criteria include lipid levels and family history, physical symptoms (if any), and genetic analysis (if available)\(^1\)

• Three clinical diagnostic tools:\(^2\)\(^-\)\(^3\)
  • Simon Broome Register Diagnostic Criteria
  • Dutch Lipid Clinic Network Diagnostic Criteria
  • U.S. MEDPED

• Factors that lead to an FH diagnosis include:
  • Premature ASCVD, fasting LDL-C >190 mg/dL, the presence of tendon xanthomas, full corneal arcus in individuals <40 years of age, or a family history of high cholesterol and/or premature ASCVD\(^1\)

• While genetic testing may identify FH, it is not commonly used in the United States due to cost and lack of payer coverage\(^1\)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnoses Prevent Early Deaths Program Diagnostic Criteria.

Familial Hypercholesterolemia: Prevalence and Risk

- FH is caused by genetic mutations passed on by:
  - One parent (heterozygous, HeFH)\(^1\)
  - Both parents (homozygous, HoFH)\(^1\)
- **HoFH prevalence ranges from 1 in 160,000 to 1 in 250,000\(^2,3\)**
  - Individuals with HoFH have extremely high LDL-C levels (>500 mg/dL) and premature CV risk\(^4\)
  - Many with HoFH experience their first coronary event in childhood or adolescence\(^4\)
- **HeFH prevalence ranges from 1 in 200 to 1 in 250\(^3\)**
  - Individuals with HeFH can present with LDL-C levels 90 to 500 mg/dL and have premature CV risk\(^4\)
  - On average, individuals with HeFH experience their first coronary event at age 42 (about 20 years younger than the general population)\(^4\)
- **Early treatment is recommended for all individuals with FH, with a goal of reducing LDL-C levels by 50% from baseline\(^3\)**

Abbreviations: CV, cerebrovascular; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Question: Which screening tests should be used?

**Fasting Lipid Profile**

- **R19.** Use a fasting lipid profile to ensure the most precise lipid assessment; this should include total cholesterol, LDL-C, TG, and non-HDL-C (Grade C; BEL 4, upgraded due to cost-effectiveness).
- **R20.** Lipids, including TG, can be measured in the non-fasting state if fasting determinations are impractical (Grade D).

**LDL-C**

- **R21.** LDL-C may be estimated using the Friedewald equation: LDL-C = (total cholesterol – HDL-C) – TG/5; however, this method is valid only for values obtained during the fasting state and becomes increasingly inaccurate when TG levels are greater than 200 mg/dL, and becomes invalid when TG levels are greater than 400 mg/dL (Grade C; BEL 3).
- **R22.** LDL-C should be directly measured in certain high-risk individuals, such as those with fasting TG levels greater than 250 mg/dL or those with diabetes or known vascular disease (Grade C; BEL 3).

**HDL-C**

- **R23.** Measurement of HDL-C should be included in screening tests for dyslipidemia (Grade B; BEL 2).

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Question: Which screening tests should be used?

**Non-HDL-C**

- **R24.** Non-HDL-C (total cholesterol minus HDL-C) should be calculated to assist risk stratification in individuals with moderately elevated TG (200 to 500 mg/dL), diabetes, and/or established ASCVD (Grade B; BEL 2).

- **R25.** If insulin resistance is suspected, non-HDL-C should be evaluated to gain useful information regarding the individual’s total atherogenic lipoprotein burden (Grade D).

**Triglycerides**

- **R26.** TG levels should be part of routine lipid screening: moderate elevations (≥150 mg/dL) may identify individuals at risk for insulin resistance syndrome and levels ≥200 mg/dL may identify individuals at substantially increased ASCVD risk (Grade B; BEL 2).

**Apolipoproteins**

- **R27.** Apo B and/or an apo B/apo A1 ratio calculation and evaluation may be useful in at-risk individuals (TG ≥150, HDL-C <40, prior ASCVD event, T2DM, and/or insulin resistance syndrome [even at target LDL-C levels]) to assess residual risk and guide decision-making (Grade A; BEL 1).

- **R28.** Apo B measurements (reflecting the particle concentration of LDL and all other atherogenic lipoproteins) may be useful to assess the success of LDL-C–lowering therapy (Grade A; BEL 1).

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Additional Screening Tests

**Coronary artery calcification**

- **R33.** Coronary artery calcification measurement has been shown to be of high predictive value and is useful in refining risk stratification to determine the need for more aggressive treatment strategies *(Grade B; BEL 2)*.

**hsCRP**

- **R30.** Use hsCRP to stratify ASCVD risk in individuals with a standard risk assessment that is borderline, or in those with an intermediate or higher risk with an LDL-C concentration less than 130 mg/dL *(Grade B; BEL 2)*.

**Lp-PLA₂**

- **R31.** Measure lipoprotein-associated phospholipase A₂ (Lp-PLA₂), which in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify an individual’s ASCVD risk, especially in the presence of hsCRP elevations *(Grade A; BEL 1)*.

**Homocysteine**

- **R32.** The routine measurement of homocysteine, uric acid, plasminogen activator inhibitor-1, or other inflammatory markers is not recommended because the benefit of doing so is not sufficiently proven *(Grade D)*.

**Carotid intima media thickness**

- **R34.** Carotid intima media thickness may be considered to refine risk stratification to determine the need for more aggressive ASCVD preventive strategies *(Grade B; BEL 2)*.

Question: What special considerations should be given to women?

ASCVD is the leading cause of mortality in U.S. women. Women’s symptoms are often less overt and/or atypical than men’s. These differences can lead to delays in evaluation and diagnostic testing, decreased use of appropriate therapy, and increased mortality.

**Risk Assessment**

- **R5.** Special attention should be given to assessing women for ASCVD risk by determining the 10-year risk (high, intermediate, or low) of a coronary event using the Reynolds Risk Score or the Framingham (Grade C; BEL 4, upgraded due to cost-effectiveness).

**Treatment options**

- **R72.** Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient (Grade C; BEL 4; upgraded due to potential benefit).
- **R73.** Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended (Grade A; BEL 1).
- An HDL-C concentration <40 mg/dL is an established independent risk factor for ASCVD in both men and women. However, because HDL-C levels tend to be higher in women than in men, an HDL-C concentration <50 mg/dL in women is also considered a marginal risk factor.
- In stark contrast to findings in men, very low HDL-C (<40 mg/dL) is an independent risk factor for ASCVD development and mortality in women, even in the presence of total cholesterol concentrations less than 200 mg/dL or normal LDL-C and/or TG levels. Compared with women with high HDL-C, women with low HDL-C have a nearly 3-fold elevated risk of ASCVD.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
Question: What special considerations should be given to children and adolescents?

Risk Assessment

- **R6.** Dyslipidemia in childhood and adolescence should be diagnosed and managed as early as possible to reduce the levels of LDL-C that may eventually increase risk of CV events in adulthood (Grade A; BEL 1).

Screening

- **R17.** In children at risk for FH (e.g., family history of premature cardiovascular disease or elevated cholesterol), screening should be at 3 years of age, again between ages 9 and 11, and again at age 18 (Grade B; BEL 3, upgraded due to cost-effectiveness).

- **R18.** Screen adolescents older than 16 years every 5 years or more frequently if they have ASCVD risk factors, have overweight or obesity, have other elements of insulin resistance syndrome, or have a family history of premature ASCVD (Grade B; BEL 3, upgraded due to cost-effectiveness).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cerebrovascular; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Question: What are secondary causes of dyslipidemia?

Recommendations associated with this question:

**R29. Rule out secondary causes of dyslipidemia (Grade B; BEL 2).**

- Secondary causes of dyslipidemia must be excluded with a thorough medical and dietary history, as well as laboratory testing for glucose and thyroid, liver, and renal function levels.

# Common Secondary Causes of Dyslipidemia

<table>
<thead>
<tr>
<th>Affected lipids</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Total cholesterol and LDL-C</td>
<td>• Hypothyroidism&lt;br&gt;• Nephrosis&lt;br&gt;• Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma)&lt;br&gt;• Progestin or anabolic steroid treatment&lt;br&gt;• Cholostatic diseases of the liver due to abnormal lipoproteins, as in primary biliary cirrhosis&lt;br&gt;• Protease inhibitors for treatment of HIV infection</td>
</tr>
<tr>
<td>↑ Triglycerides and VLDL-C</td>
<td>• Chronic renal failure&lt;br&gt;• T2DM&lt;br&gt;• Obesity&lt;br&gt;• Excessive alcohol intake&lt;br&gt;• Hypothyroidism&lt;br&gt;• Antihypertensive medications (thiazide diuretics and b-adrenergic blocking agents)&lt;br&gt;• Corticosteroid therapy (or severe stress that increases endogenous corticosteroids)&lt;br&gt;• Orally administered estrogens, oral contraceptives, pregnancy&lt;br&gt;• Protease inhibitors for treatment of HIV infection</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; VLDL-C, very low-density lipoprotein cholesterol.

Cholesterol Treatment Trialists’ 2010: Efficacy of Intensive LDL-C Lowering in Patients With Low Baseline LDL-C

Meta-analysis of randomized controlled trials of major vascular events (coronary death, myocardial infarction, coronary revascularization, and ischemic stroke) with at least 1,000 patients and ≥2 years of more vs. less intense statin dosage (N=169,138)

For each 39 mg/dL reduction in LDL-C:

- Individuals with baseline LDL-C <77 mg/dL had a **29%** further reduction in major vascular events (*P*=0.007)
- Those with baseline LDL-C <70 mg/dL had a **37%** further reduction in major vascular events (*P*=0.004)

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosing): Patients Who Achieved Very Low LDL-C Levels Had Lower Risk for Major Cardiovascular Events

Adjusted* Hazard Ratio for Major CV Events

*adjusted for sex, age, smoking, diabetes, SBP, HDL-C, and trial

** >200 mg/dL for non-HDL-C

Cutoffs: LDL-C, ApoB, non-HDL-C

Achieved On-Trial Atherogenic Cholesterol and Lipoprotein Concentration, mg/dL

Abbreviations: apo, apolipoprotein; CV, cerebrovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

IMPROVE-IT: Improved Reduction of Outcomes, Vytorin Efficacy International Trial

**Trial design:** Patients with recent ACS were randomized 1:1 to either ezetimibe 10 mg + simvastatin 40 mg or simvastatin 40 mg and followed for a median of 6 years.

**Primary composite CV endpoint**

<table>
<thead>
<tr>
<th>Percent Reduction</th>
<th>Ezetimibe/simvastatin (n = 9,067)</th>
<th>Simvastatin (n = 9,077)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>32.7%</td>
<td>34.7%</td>
</tr>
<tr>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td><em>(P=0.016)</em></td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
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</tbody>
</table>

**Results**
- Primary endpoint (CV death/MI/UA/coronary revasc/stroke/moderate/severe bleeding) for ezetimibe/simvastatin vs. simvastatin: 32.7% vs. 34.7% (HR 0.94, 95% CI 0.89-0.99; *P*=0.016)
- MI: 13.1% vs. 14.8%, *P*=0.002; stroke: 4.2% vs. 4.8%, *P*=0.05; CVD/MI/stroke: 20.4% vs. 22.2%, *P*=0.003
- Median LDL follow-up average: 53.7 vs. 69.5 mg/dL

**Conclusions**
- In patients with high-risk ACS, ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing adverse CV events
- This is the first study powered for clinical outcomes to show a benefit with a non-statin agent
- Reaffirms the “lower is better” hypothesis with LDL-C

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

### Major Prespecified Subgroups: IMPROVE-IT

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Simva†</th>
<th>EZE/Simva†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean LDL 69.5</td>
<td>LDL 53.7 mg/dL</td>
</tr>
<tr>
<td>Male</td>
<td>34.9</td>
<td>33.2</td>
</tr>
<tr>
<td>Female</td>
<td>34.0</td>
<td>31.0</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>30.8</td>
<td>29.9</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>39.9</td>
<td>36.4</td>
</tr>
<tr>
<td>No diabetes</td>
<td>30.8</td>
<td>30.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.5</td>
<td>40.0</td>
</tr>
<tr>
<td>Prior LLT</td>
<td>43.4</td>
<td>40.7</td>
</tr>
<tr>
<td>No prior LLT</td>
<td>30.0</td>
<td>28.6</td>
</tr>
<tr>
<td>LDL-C &gt;95 mg/dL</td>
<td>31.2</td>
<td>29.6</td>
</tr>
<tr>
<td>LDL-C ≤95 mg/dL</td>
<td>38.4</td>
<td>36.0</td>
</tr>
</tbody>
</table>

†7-year event rates

*P-interaction=0.023, otherwise >0.05

Ezetimibe/Simva Better

Simva Better

Abbreviations: LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment 5/2013 to 1/2015) conducted at 197 academic and community hospitals in 6 continents, enrolling 968 patients (mean age 59.8 years, 27.8% female) with CAD. Patients with angiographic CAD were randomized to receive monthly evolocumab (420 mg) (n=484) or placebo (n=484) SQ for 76 weeks, in addition to statins.

Locally weighted polynomial regression (LOESS) plot demonstrates a linear continuous relationship between achieved LDL-C level and PAV progression/regression for levels of LDL-C ranging from 110 mg/dL to as low as 20 mg/dL.

Abbreviations: CAD, coronary artery disease; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody; LDL-C, low-density lipoprotein cholesterol; SQ, subcutaneous.

**GLAGOV: Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound**

**Primary Endpoint: Percent Atheroma Volume**

<table>
<thead>
<tr>
<th>Change in Percent Atheroma Volume (%)</th>
<th>Statin+Placebo</th>
<th>Statin+Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs. 0.05% in the placebo group ($P<0.001$ for between-group comparison)
- Patients with plaque regression: 64.3% with evolocumab vs. 47.3% with placebo ($P<0.001$)
- Major adverse cardiac events: 12.2% with evolocumab vs. 15.3% with placebo

**Conclusions**

- Among patients with angiographic evidence of CAD on chronic statin therapy, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression.

**Abbreviations:** CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous.

FOURIER Trial: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk

- This randomized, double-blind, placebo-controlled trial investigated the effects of adding evolocumab to high-intensity statin therapy compared with high-intensity statins alone.
- Participants were recruited from 12 prior evolocumab trials.
- Median patient follow-up was 2.2 years; study results included data for over 27,500 individuals with clinically evident atherosclerotic disease and baseline LDL-C levels ≥70 mg/dL and HDL-C levels ≥100 mg/dL.
- All study participants were receiving statin therapy with or without ezetimibe, and the evolocumab and placebo groups had the same baseline LDL-C (92 mg/dL).

Abbreviations: LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

FOURIER Evolocumab Study

LDL-C Levels Over time

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol.

FOURIER Primary and Secondary Endpoints

- At 26 months, extremely tight lipid control with evolocumab led to a 15% decrease in risk for the primary composite endpoint and 20% decrease in risk for a secondary composite endpoint
  - The primary endpoint included MI, cardiovascular death, stroke, coronary revascularization, or hospitalization for unstable angina
  - The secondary endpoint included cardiovascular death, MI, or stroke
- Beyond the second year of follow-up, the risk reduction increased to 20% for the primary endpoint and to 25% for the secondary endpoint
- For singular endpoints at 26 months, very tight lipid control reduced the risk of MI by 27%, stroke by 21%, and coronary revascularization by 22%

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

FOURIER Evolocumab Study Endpoints

Cumulative event rates for the primary efficacy endpoint
(Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

Cumulative rates for the key secondary efficacy endpoint (Composite of cardiovascular death, MI, or stroke)

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI, myocardial infarction.

EBBINGHAUS: Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects

N=1,974 patients from FOURIER Study, followed for 96 weeks

- EBBINGHAUS is the first prospectively designed study to evaluate the relationship between PCSK9 inhibition and changes in cognition, including memory, attention, and reaction time.

- The mean change in the primary endpoint of executive function, as measured by the Spatial Working Memory strategy index (from the Cambridge Neuropsychological Test Automated Battery), was -0.29 with placebo and -0.21 with evolocumab ($P<0.0001$ for noninferiority).

- All secondary outcomes were similar for placebo and evolocumab, including patient self-reports and investigator-reported cognitive adverse events.

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; PCSK9, proprotein convertase subtilisin/kexin type 9.

Question: What are lipid treatment goals?

**R35.** Treatment goals for dyslipidemia should be personalized according to levels of risk *(Grade A; BEL 1).*

**R36.** For individuals at **low risk** (i.e., with no risk factors), an LDL-C goal of less than 130 mg/dL is recommended *(Grade A; BEL 1).*

**R37.** For individuals at **moderate risk** (i.e., with 2 or fewer risk factors and a calculated 10-year risk of less than 10%), an LDL-C goal of less than 100 mg/dL is recommended *(Grade A; BEL 1).*

**R38.** For individuals at **high risk** (i.e., with an ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%), an LDL-C goal of less than 100 mg/dL is recommended *(Grade A; BEL 1).*

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol.

Question: What are lipid treatment goals?

**R39.** For individuals at very high risk (i.e., with established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH), an LDL-C goal of less than 70 mg/dL is recommended (Grade A; BEL 1).

**R40.** For individuals at extreme risk (i.e., with progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD in individuals with diabetes, stage 3 or 4 CKD, and/or HeFH, or in individuals with a history of premature ASCVD (<55 years of age for males or <65 years of age for females), an LDL-C goal of less than 55 mg/dL is recommended (Grade A; BEL 1).

**R41.** An LDL-C goal of <100 mg/dL is considered “acceptable” for children and adolescents, with 100 to 129 mg/dL considered “borderline” and 130 mg/dL or greater considered “high” (based on recommendations from the American Academy of Pediatrics) (Grade D).

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Question: What are lipid treatment goals?

**High-Density Lipoprotein Cholesterol**

- **R42.** HDL-C should be greater than 40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C (Grade A; BEL 1).

**Non–High-Density Lipoprotein Cholesterol**

- **R43.** For most individuals, a non–HDL-C goal (total cholesterol minus HDL-C) 30 mg/dL higher than the individual’s specific LDL-C goal is recommended (Grade D).
- **R44.** For individuals at extreme risk, a non–HDL-C goal 25 mg/dL higher than the individual-specific LDL-C goal is recommended (Grade A; BEL 1).

**Apolipoproteins**

- **R45.** For individuals at increased risk of ASCVD, including those with diabetes, an optimal apo B goal is less than 90 mg/dL, while for individuals with established ASCVD or diabetes plus 1 or more additional risk factor(s), an optimal apo B goal is less than 80 mg/dL, and for individuals at extreme risk, an optimal apo B goal is less than 70 mg/dL (Grade A; BEL 1).

**Triglycerides**

- **R46.** TG goals of less than 150 mg/dL are recommended (Grade A; BEL 1).

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

# ASCVD Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
</table>
| **Extreme risk** | – Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL  
– Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH  
– History of premature ASCVD (<55 male, <65 female) | <55 | <80 | <70 |
| **Very high risk** | – Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
– DM or stage 3 or 4 CKD with 1 or more risk factor(s)  
– HeFH | <70 | <100 | <80 |
| **High risk** | – ≥2 risk factors and 10-year risk 10%-20%  
– DM or stage 3 or 4 CKD with no other risk factors | <100 | <130 | <90 |
| **Moderate risk** | ≤2 risk factors and 10-year risk <10% | <100 | <130 | <90 |
| **Low risk** | 0 risk factors | <130 | <160 | NR |

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.
## Classification of Elevated Triglyceride Levels

TG levels that are even moderately elevated (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome. TG levels ≥200 mg/dL may indicate a substantial increase in ASCVD risk. Hypertriglyceridemia is also commonly associated with a procoagulant state and hypertension.

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

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; TG, triglycerides.

## Lipid Goals for Individuals at Risk for ASCVD

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;130 (low risk)</td>
</tr>
<tr>
<td></td>
<td>&lt;100 (moderate risk)</td>
</tr>
<tr>
<td></td>
<td>&lt;100 (high risk)</td>
</tr>
<tr>
<td></td>
<td>&lt;70 (very high risk)</td>
</tr>
<tr>
<td></td>
<td>&lt;55 (extreme risk)</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>30 above LDL-C goal; 25 above LDL-C goal (extreme risk individuals)</td>
</tr>
<tr>
<td>TG</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Apo B</td>
<td>&lt;90 (individuals at high risk of ASCVD, including those with diabetes)</td>
</tr>
<tr>
<td></td>
<td>&lt;80 (individuals at very high risk with established ASCVD or diabetes plus ≥1 additional risk factor)</td>
</tr>
<tr>
<td></td>
<td>&lt;70 (individuals at extreme risk)</td>
</tr>
</tbody>
</table>

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Classification of LDL-C Levels in Children and Adolescents

A body of evidence indicates that atherosclerosis begins early in life and that elevated lipid levels in adolescence predict elevated lipid levels well into adulthood. Dyslipidemia in childhood and adolescence should be diagnosed and managed as early as possible.

<table>
<thead>
<tr>
<th>Category</th>
<th>LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Borderline</td>
<td>100-129</td>
</tr>
<tr>
<td>High</td>
<td>≥130</td>
</tr>
</tbody>
</table>

Some pediatric lipid guidelines have an “Acceptable” LDL-C target of <110 mg/dL

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Question: What special considerations should be given to children and adolescents?

**Treatment goals**

- **R41.** An LDL-C goal of <100 mg/dL is considered “acceptable” for children and adolescents, with 100 to 129 mg/dL considered “borderline” and 130 mg/dL or greater considered “high” (based on recommendations from the American Academy of Pediatrics) (Grade D).

- **R53.** Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children (Grade A; BEL 1).

**Treatment**

- **R74.** Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria (Grade D; BEL 4):
  - LDL-C ≥190 mg/dL
  - LDL-C ≥160 mg/dL and the presence of 2 or more cardiovascular risk factors, even after vigorous intervention
  - Family history of premature ASCVD (before 55 years of age), or
  - Having overweight, obesity, or other elements of insulin resistance syndrome

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Question: What special considerations should be given to women?

ASCVD is the leading cause of mortality in U.S. women. Women’s symptoms are often less overt and/or atypical than men’s. These differences can lead to delays in evaluation and diagnostic testing, decreased use of appropriate therapy, and increased mortality.

Risk Assessment

- **R5.** Special attention should be given to assessing women for ASCVD risk by determining the 10-year risk (high, intermediate, or low) of a coronary event using the Reynolds Risk Score or the Framingham (Grade C; BEL 4, upgraded due to cost-effectiveness).

Treatment options

- **R72.** Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient (Grade C; BEL 4; upgraded due to potential benefit).
- **R73.** Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended (Grade A; BEL 1).
- An HDL-C concentration <40 mg/dL is an established independent risk factor for ASCVD in both men and women. However, because HDL-C levels tend to be higher in women than in men, an HDL-C concentration <50 mg/dL in women is also considered a marginal risk factor.
- In stark contrast to findings in men, very low HDL-C (<40 mg/dL) is an independent risk factor for ASCVD development and mortality in women, even in the presence of total cholesterol concentrations less than 200 mg/dL or normal LDL-C and/or TG levels. Compared with women with high HDL-C, women with low HDL-C have a nearly 3-fold elevated risk of ASCVD.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Question: What treatments are available for dyslipidemia?

Treatment categories for dyslipidemia:

- **Lifestyle changes**
  - Physical activity
  - Medical nutrition therapy
  - Smoking cessation

- **Pharmacologic therapy**
  - Statins
  - Fibrates
  - Omega-3 fish oil
  - Niacin
  - Bile acid sequestrants
  - Cholesterol absorption inhibitors
  - PCSK9 inhibitors
  - MTP inhibitor
  - Antisense apo B oligonucleotide
  - Combination therapies

**R47.** A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes *(Grade A, BEL 1)* and patient education with pharmacotherapy as needed to achieve evidence-based targets *(Grade A, BEL 1)*.

Abbreviations: apo, apolipoprotein; MTP, microsomal transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9.
Nonpharmacologic Dyslipidemia Treatments

Physical Activity

- **R48.** A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include at least 30 minutes of moderate-intensity physical activity [consuming 4-7 kcal/min] 4 to 6 times weekly, with an expenditure of at least 200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities (Grade A; BEL 1).
- **R49.** Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs (Grade A; BEL 1).
- **R50.** In addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week (Grade A; BEL 1).

Medical Nutrition Therapy

- **R51.** For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended (Grade A; BEL 1).
- **R52.** For adults, the intake of saturated fats, trans-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10-25 g/day) (Grade A; BEL 1).
- **R53.** Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children (Grade A; BEL 1).

Smoking Cessation

- **R54.** Tobacco cessation should be strongly encouraged and facilitated (Grade A; BEL 2; upgraded due to potential benefit).

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Question: How are different drugs used to treat dyslipidemia?

**Statins, Fibrates**

- **R55.** In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals *(Grade A, BEL 1).*

**Statins**

- **R56.** Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials *(Grade A; BEL 1).*
- **R57.** For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction *(Grade A, BEL 1).*
- **R58.** In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered *(Grade A, BEL 1).*
- **R59.** Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least 1 additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL *(Grade A, BEL 1).*
- **R60.** Extreme risk individuals should be treated with statins or with combination therapy to target an even lower LDL-C treatment goal of <55 mg/dL *(Grade A, BEL 1).*

**Fibrates**

- **R61.** Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL) *(Grade A; BEL 1).*
- **R62.** Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL *(Grade A; BEL 1).*

*Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.*

Question: How are different drugs used to treat dyslipidemia?

Bile acid sequestrants, omega-3 fish oil, combination therapy

**Bile Acid Sequestrants**

- **R66.** Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG (Grade A; BEL 1).

**Omega-3 Fish Oil**

- **R63.** Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose (Grade A, BEL 1).

**Combination Therapy**

- **R71.** Combination therapy of lipid-lowering agents should be considered when the LDL-C/ non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal (Grade A; BEL 1).

---

**Abbreviations:**
- apo, apolipoprotein
- FDA, Food and Drug Administration
- HDL-C, high-density lipoprotein cholesterol
- LDL-C, low-density lipoprotein cholesterol
- TG, triglycerides

Question: How are different drugs used to treat dyslipidemia?

PCSK9 inhibitors, cholesterol absorption inhibitors, niacin

### PCSK9 Inhibitors

- **R69.** Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH (Grade A; BEL 1).
- **R70.** PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals (Grade A; BEL 1).

### Cholesterol Absorption Inhibitors

- **R67.** Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals (Grade B, BEL 2).
- **R68.** Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk (Grade A; BEL 1).

### Niacin

- **R64.** Niacin therapy is recommended principally as an adjunct for reducing TG (Grade A, BEL 1).
- **R65.** Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefit with already well-controlled LDL-C (Grade A; BEL 1).

Question: How does treatment of dyslipidemia affect ASCVD risk?

R56. Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials (Grade A; BEL 1).

R58. In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered (Grade A, BEL 1).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Statins: Primary Metabolic Effects and Main Considerations

### Metabolic Effects
- Primarily ↓ LDL-C 21%-55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to upregulation of hepatic LDL receptors
- Effects on TG and HDL-C are less pronounced (↓ TG 6%-30% and ↑ HDL-C 2%-10%)

### Main Considerations
- Liver function test prior to therapy and as clinically indicated thereafter
- Myalgias and muscle weakness in some individuals
- Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, cyclosporine, warfarin, and protease inhibitors
- Myopathy/rhabdomyolysis in rare cases; increased risk with coadministration of some drugs (see product labeling)
- Simvastatin dosages should not exceed 40 mg in most individuals; dosages of 80 mg are no longer recommended except in those who have tolerated 80 mg for 12 months or more without muscle toxicity
- Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine
- Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups
- New-onset diabetes is increased in individuals treated with statins; however, it is dose-related, occurs primarily in individuals with MetS, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in ASCVD

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides.

### Lipid-Lowering Drug Therapies, Starting Dosages and Dosage Ranges

#### Statins

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20 mg</td>
<td>10-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg</td>
<td>10-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20-40 mg</td>
<td>5-80 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Oral</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40 mg</td>
<td>20-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-20 mg</td>
<td>10-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg</td>
<td>5-40 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2 mg</td>
<td>2-4 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

<sup>a</sup> Simvastatin, 80 mg, not approved for therapy unless individual has been on treatment for more than 1 year without myopathy.

Crestor (rosuvastatin calcium); [PI]; 2016; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lescol (fluvastatin sodium) [PI]; 2012 Lipitor (atorvastatin calcium) [PI]; 2015; Livalo (pitavastatin) [PI]; 2013; ; Mevacor (lovastatin) [PI]; 2014; Pravachol (pravastatin sodium) [PI]; 2016; Zocor (simvastatin) [PI]; 2015.
# Cholesterol Treatment Trialists’ Collaboration: Statin Benefits Across a Range of Baseline Levels

All Evaluated Trials Combined: LDL-C 90 to 130 mg/dL shows same benefit as LDL-C 50 to 90 mg/dL; 1 mmol/L = 38.6 mg/dL

<table>
<thead>
<tr>
<th>Baseline Levels</th>
<th>Events (% per annum)</th>
<th>RR(CI) per 1 mmol/L reduction in LDL-CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mmol/l (&lt;77 mg/dL)</td>
<td>Statin: 910 (4.1%)</td>
<td>Control: 1,012 (4.6%)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/l (77-96 mg/dL)</td>
<td>Statin: 1,528 (3.6%)</td>
<td>Control: 1,729 (4.2%)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/l (97-116 mg/dL)</td>
<td>Statin: 1,866 (3.3%)</td>
<td>Control: 2,225 (4.0%)</td>
</tr>
<tr>
<td>≥3.0 to &lt;3.5 mmol/l (117-135 mg/dL)</td>
<td>Statin: 2,007 (3.2%)</td>
<td>Control: 2,454 (4.0%)</td>
</tr>
<tr>
<td>≥3.5 mmol/l (&gt;136 mg/dL)</td>
<td>Statin: 4,508 (3.0%)</td>
<td>Control: 5,736 (3.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>Statin: 10,973 (3.2%)</td>
<td>Control: 13,350 (4.0%)</td>
</tr>
</tbody>
</table>

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

### Cholesterol Treatment Trialists’ Collaboration: Effect on CHD and Diabetes Primary Prevention

**1 mmol/L = 38.6 mg/dL**

<table>
<thead>
<tr>
<th>Previous Vascular Disease</th>
<th>Events (% per annum)</th>
<th>RR(CI) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous Vascular Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>Statin: 8,395 (4.5%)</td>
<td>Control: 10,123 (5.6%)</td>
</tr>
<tr>
<td>No- CHD, vascular</td>
<td>Statin: 674 (3.1%)</td>
<td>Control: 802 (3.7%)</td>
</tr>
<tr>
<td>None</td>
<td>Statin: 1,904 (1.4%)</td>
<td>Control: 2,425 (1.8%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Statin: 145 (4.5%)</td>
<td>Control: 192 (6.0%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Statin: 2,494 (4.2%)</td>
<td>Control: 2,920 (5.1%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>Statin: 8,272 (3.2%)</td>
<td>Control: 10,163 (4.0%)</td>
</tr>
</tbody>
</table>

Abbreviation: CHD: coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RR: relative risk.

Comparison of Statin Effects on Lipids After 6 Weeks of Treatment in Men and Women With LDL-C ≥160 mg/dL and ≤250 mg/dL (N=2,431)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage range, mg daily</th>
<th>TC (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>TG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20-80</td>
<td>↓ 21 to ↓ 36</td>
<td>↓ 29 to ↓ 48</td>
<td>↑ 4.6 to ↑ 8.0</td>
<td>↓ 12 to ↓ 13</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10-40</td>
<td>↓ 15 to ↓ 22</td>
<td>↓ 20 to ↓ 30</td>
<td>↑ 3.2 to ↑ 5.6</td>
<td>↑ 8 to ↓ 13</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10-80a</td>
<td>↓ 20 to ↓ 33</td>
<td>↓ 28 to ↓ 46</td>
<td>↑ 5.2 to ↑ 6.8</td>
<td>↓ 12 to ↓ 18</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20-40</td>
<td>↓ 13 to ↓ 19</td>
<td>↓ 17 to ↓ 23</td>
<td>↑ 0.9 to ↓ 3.0</td>
<td>↓ 5 to ↓ 13</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-80</td>
<td>↓ 27 to ↓ 39</td>
<td>↓ 37 to ↓ 51</td>
<td>↑ 2.1 to ↑ 5.7</td>
<td>↓ 20 to ↓ 28</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10-40</td>
<td>↓ 33 to ↓ 40</td>
<td>↓ 45 to ↓ 55</td>
<td>↑ 7.7 to ↑ 9.6</td>
<td>↓ 20 to ↓ 26</td>
</tr>
</tbody>
</table>

*Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

# Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

## PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCSK9 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alirocumab</td>
<td>75 mg every 2 weeks</td>
<td>75-150 mg every 2 weeks</td>
<td>SQ</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>140 mg every 2 weeks or 420 mg once monthly</td>
<td>Not applicable</td>
<td>SQ</td>
</tr>
</tbody>
</table>

### Metabolic Effects:
- ↓ LDL-C 48%-71%, ↓ non-HDL-C 49%-58%, ↓ TC 36%-42%, ↓ Apo B 42%-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels

### Main Considerations:
- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low
- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions with similar rates for drug vs. placebo were:
  - **Alirocumab**: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
  - **Evolocumab**: nasopharyngitis, back pain, and upper respiratory tract infection

---


Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SQ, subcutaneous injection; TC, total cholesterol.
Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

### Fibrates

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>48-145 mg</td>
<td>48-145 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>1,200 mg</td>
<td>1,200 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Fenofibric acid</td>
<td>45-135 mg</td>
<td>45-135 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Metabolic Effects:**

- Primarily ↓ TG 20%-35%, ↑ HDL-C 6%-18% by stimulating lipoprotein lipase activity
- Fenofibrate may ↓ TC and LDL-C 20%-25%
- Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size
- Fenofibrate ↓ fibrinogen level

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein, LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

Fibrates: Metabolic Effects and Main Considerations

Main Considerations:

- Gemfibrozil may ↑ LDL-C 10%-15%
- GI symptoms, possible cholelithiasis
- May potentiate effects of orally administered anticoagulants
- Gemfibrozil may ↑ fibrinogen level
- Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations
- May cause muscle disorders; myopathy/rhabdomyolysis when used with statin
- Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction
- Fenofibrate dose should be cut by two-thirds and gemfibrozil by one-half when eGFR is 15-60, and fibrates should be avoided when eGFR is <15
- Can improve diabetic retinopathy

Abbreviations: eGFR, estimated glomerular filtration rate; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol.
Helsinki Heart Study Analysis: Joint Effects of Serum Triglycerides, LDL-C and HDL-C on CHD Risk

Relative risk of cardiac events among placebo patients

<table>
<thead>
<tr>
<th>LDL/HDL</th>
<th>TG</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 mmol/L</td>
<td>&lt;200 mg/dL</td>
<td>1</td>
</tr>
<tr>
<td>&gt;5 mmol/L</td>
<td>&gt;200 mg/dL</td>
<td>3.5</td>
</tr>
<tr>
<td>&lt;5 mmol/L</td>
<td>&lt;200 mg/dL</td>
<td>1</td>
</tr>
<tr>
<td>&lt;5 mmol/L</td>
<td>&gt;200 mg/dL</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

FIELD: Fenofibrate Intervention in Event Lowering in Diabetes

Multinational, randomized controlled trial (N=9,795) of patients with T2DM currently taking statin therapy assigned to add-on treatment with fenofibrate or placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fenofibrate % (n)</th>
<th>Placebo % (n)</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary events</td>
<td>5% (256)</td>
<td>6% (288)</td>
<td>0.89</td>
<td>0.75-1.05</td>
<td>0.16</td>
</tr>
<tr>
<td>CHD mortality</td>
<td>2% (110)</td>
<td>2% (93)</td>
<td>1.19</td>
<td>0.90-1.57</td>
<td>0.22</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>3% (158)</td>
<td>4% (207)</td>
<td>0.76</td>
<td>0.62-0.94</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.
FIELD: Primary and Secondary Endpoints*

9,795 Patients With T2DM; Baseline cholesterol (mg/dL): TC 194; TG 154; HDL-C 42; LDL-C 119; Non-HDL 152

** Not corrected for large placebo-group statin drop-in rate.
** Nonfatal MI and CHD death.
† CHD events, stroke, CVD death, revascularizations.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides.

FIELD: Highest Therapeutic Benefit of Fenofibrate Seen in Patients With Elevated TG and Low HDL-C

### Risk reduction:

- Any MetS Criteria: 11%
- Low HDL <40 mg/dL (men) and <50 mg/dL (women): 14%
- TG >200: 23%
- Low HDL-C + TG >200 mg/dL: 27%

### Hazard ratio:

- Any MetS Criteria: 0.89
- Low HDL <40 mg/dL (men) and <50 mg/dL (women): 0.86
- TG >200: 0.77
- Low HDL-C + TG >200 mg/dL: 0.73

### (95%) CI:

- Any MetS Criteria: (0.80-0.99)
- Low HDL <40 mg/dL (men) and <50 mg/dL (women): (0.75-0.99)
- TG >200: (0.63-0.94)
- Low HDL-C + TG >200 mg/dL: (0.58-0.91)

### P-value:

- Any MetS Criteria: P<0.01
- Low HDL <40 mg/dL (men) and <50 mg/dL (women): P<0.01
- TG >200: P<0.01
- Low HDL-C + TG >200 mg/dL: P<0.05

*Not corrected for large placebo group statin drop-in rate

**HDL <40 mg/dL (men) and <50 mg/dL (women)

Abbreviations: CV, cerebrovascular; FIELD, SecondaryEndpoints from the Fenofibrate Intervention and Event Lowering in Diabetes trial; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides.

Bezafibrate Infarction Prevention (BIP) Study: Cumulative Probability of Primary Endpoints at 6.2 Years of Follow-up by Baseline Triglycerides and HDL-C Levels

<table>
<thead>
<tr>
<th>Triglycerides</th>
<th>Bezafibrate, n (%)</th>
<th>Placebo, n (%)</th>
<th>Reduction, %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 mg/dL</td>
<td>938 (12.6)</td>
<td>901 (13.7)</td>
<td>7.9</td>
<td>0.43</td>
</tr>
<tr>
<td>150 mg/dL</td>
<td>603 (16.3)</td>
<td>629 (17.1)</td>
<td>4.6</td>
<td>0.48</td>
</tr>
<tr>
<td>175 mg/dL</td>
<td>407 (15.9)</td>
<td>385 (20.3)</td>
<td>21.6</td>
<td>0.07</td>
</tr>
<tr>
<td>200 mg/dL</td>
<td>234 (12.0)</td>
<td>225 (19.7)</td>
<td>39.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL-C &lt;35 &amp; triglycerides:</th>
<th>Bezafibrate, n (%)</th>
<th>Placebo, n (%)</th>
<th>Reduction, %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 mg/dL</td>
<td>378 (13.5)</td>
<td>382 (15.5)</td>
<td>12.4</td>
<td>0.46</td>
</tr>
<tr>
<td>150 mg/dL</td>
<td>420 (18.5)</td>
<td>436 (19.4)</td>
<td>4.5</td>
<td>0.56</td>
</tr>
<tr>
<td>175 mg/dL</td>
<td>294 (17.2)</td>
<td>286 (22.2)</td>
<td>22.6</td>
<td>0.09</td>
</tr>
<tr>
<td>200 mg/dL</td>
<td>184 (13.0)</td>
<td>162 (22.3)</td>
<td>41.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL-C ≥35 &amp; triglycerides:</th>
<th>Bezafibrate, n (%)</th>
<th>Placebo, n (%)</th>
<th>Reduction, %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 mg/dL</td>
<td>560 (12.0)</td>
<td>518 (12.2)</td>
<td>1.6</td>
<td>0.77</td>
</tr>
<tr>
<td>150 mg/dL</td>
<td>183 (11.2)</td>
<td>193 (12.2)</td>
<td>8.5</td>
<td>0.59</td>
</tr>
<tr>
<td>175 mg/dL</td>
<td>113 (12.7)</td>
<td>99 (15.2)</td>
<td>16.8</td>
<td>0.45</td>
</tr>
<tr>
<td>200 mg/dL</td>
<td>50 (8.2)</td>
<td>63 (17.8)</td>
<td>35.9</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Abbreviation: HDL-C, high-density lipoprotein cholesterol.
ACCORD-LIPID: Primary Outcomes of the Prespecified Subgroups: High TG (≥204 mg/dL) and Low HDL-C (≤34 mg/dL) vs. All Others in Full Cohort

The benefit associated with fenofibrate treatment was confined to the high TG/low HDL-C subgroup, comprising <18% of ACCORD-LIPID trial population.

Major Fatal or Nonfatal CV Events

% Major Fatal or Nonfatal CV Events

31% lower event rate with simva; adjusted \( P=0.057 \)

![Graph showing event rates for different groups](image)

- Simva: 17.32%, 79/456, 31% lower event rate with simva; adjusted \( P=0.057 \)
- Simva + Fen: 12.37%, 60/485
- Simva: 10.11%, 231/2,284
- Simva + Fen: 10.11%, 229/2,264

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; CV, cerebrovascular; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Fibrates in HHS and VA-HIT

- HHS showed that fibrates are highly effective at lowering TG, and that reducing TG is associated with fewer ASCVD events and significantly reduces nonfatal MI\(^1\)
- Gemfibrozil use resulted in a 34% reduction in coronary heart disease endpoints (fatal and nonfatal MI or cardiac death)
- An 18-year HHS follow-up showed that TG reduction with fibrates significantly lowered the ASCVD mortality rate\(^2\)

- VA-HIT showed that increasing HDL-C and lowering TG in individuals with ASCVD whose primary lipid abnormality was low HDL-C significantly reduced the rate of coronary events, even without any change in LDL-C levels\(^3\)
- Gemfibrozil use resulted in a 22% reduction in the relative risk for nonfatal MI or coronary death and reduced nonfatal MI, coronary death, or stroke by 24%\(^3\)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglyceride; VA-HIT, Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial.

Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

Bile Acid Sequestrants

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>8-16 g</td>
<td>4-24 g</td>
<td>Oral</td>
</tr>
<tr>
<td>Colestipol</td>
<td>2 g</td>
<td>2-16 g</td>
<td>Oral</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>3.8 g</td>
<td>3.8-4.5 g</td>
<td>Oral</td>
</tr>
</tbody>
</table>

### Metabolic Effects:
- Primarily ↓ LDL-C 15%-25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDL-receptor upregulation)
- Colesevelam ↓ glucose and hemoglobin A1C (~0.5%); FDA-approved to treat T2DM

### Main Considerations:
- May ↑ serum TG
- Frequent constipation and/or bloating, which can reduce adherence
- Many potential drug interactions (decreased drug absorption), less so with colesevelam (see product labeling)
- May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K

Abbreviations: A1C, glycated hemoglobin; FDA, Food and Drug Administration; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; TG, triglyceride.

# Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

## Cholesterol Absorption Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>10 mg</td>
<td>10 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

### Combination therapies (single-pill)

| Ezetimibe/simvastatin        | 10/20 mg                               | 10/10 to 10/80 mg     | Oral                     |

### Metabolic Effects
- Primarily ↓ LDL-C 10%-18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver, leading to upregulation of hepatic LDL receptors
- ↓ Apo B 11%-16%
- In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34%-61%
- In combination with fenofibrate, ↓ LDL-C 20%-22% and ↓ apo B 25%-26% without reducing ↑ HDL-C

### Main Considerations
- Myopathy/rhabdomyolysis (rare)
- When coadministered with statins or fenofibrate, risks associated with those drugs remain (e.g., myopathy/rhabdomyolysis, cholelithiasis)

Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

**Omega-3 Fatty Acids**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omega-3-acid ethyl esters</strong> (Lovaza)</td>
<td>4 g per day</td>
<td>4 g per day</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Icosapent ethyl</strong> (Vascepa)</td>
<td>4 g per day</td>
<td>4 g per day</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Metabolic Effects:**
- ↓ TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apo B 4%, and non-HDL-C 8%-14% in individuals with severe hypertriglyceridemia most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased ß-oxidation; inhibition of acyl-CoA; 1,2-diacylglycerol acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity.
- Icosapent ethyl ↓ LDL-C 5%, whereas, omega-3-acid ethyl esters ↑ LDL-C 45%

Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

Omega-3 Fatty Acids: Main Considerations

- Assess TG levels prior to initiating and periodically during therapy.
- Omega-3-acid ethyl esters can increase LDL-C levels. Monitor LDL-C levels during treatment.
- May prolong bleeding time. Monitor coagulation status periodically in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation.
- Monitor ALT and AST levels periodically during treatment in patients with hepatic impairment. Some patients may experience increases in ALT levels only.
- Exercise caution when treating patients with a known hypersensitivity to fish and/or shellfish.

Abbreviation: AF, atrial fibrillation.
The effect of omega-3 fatty acids on cardiovascular morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia.

In patients with paroxysmal or persistent atrial fibrillation, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation.

Most common adverse events include arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%). May also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus.

Should be used with caution in nursing mothers and only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm.

Abbreviation: AF, atrial fibrillation.
# Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

## Niacin

<table>
<thead>
<tr>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release</td>
<td>250 mg</td>
<td>250-3,000 mg</td>
</tr>
<tr>
<td>Extended release</td>
<td>500 mg</td>
<td>500-2,000 mg</td>
</tr>
</tbody>
</table>

**Metabolic Effects:**
- ↓ LDL-C 10%-25%, ↓ TG 20%-30%, ↑ HDL-C 10%-35% by decreasing hepatic synthesis of LDL-C and VLDL-C
- ↓ Lipoprotein (a)
- Transforms LDL-C to less atherogenic form by increasing average particle size and also decreases LDL particle concentration

**Main Considerations:**
- Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatotoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation
- Deleterious effect on serum glucose at higher dosages
- Increases uric acid levels; may lead to gout

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol.

Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges

**MTP Inhibitor**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTP inhibitor</td>
<td>5 mg, with subsequent titration</td>
<td>5-60 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Metabolic Effects:**
- ↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in individuals with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL

**Main Considerations:**
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transaminases, which may be a risk for progressive liver diseases
- Also causes steatosis of the small intestine with resulting abdominal pain and steatorrhea unless a very-low-fat diet is followed; may also cause fat-soluble vitamin deficiency unless vitamin supplements are taken
- Caution should be exercised when used with other drugs with potential hepatotoxicity; because of hepatotoxicity risk, only available through REMS program

Abbreviations: ALT, aspartate amino transferase; AST, amino alanine transferase; FDA, Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MTP, microsomal transfer protein; REMS, Risk Evaluation and Mitigation Strategy; TG, triglycerides; VLDL, very low-density lipoprotein.

Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges
Mipomersen

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-sense apolipoprotein B oligonucleotide</td>
<td>200 mg once weekly</td>
<td>200 mg once weekly</td>
<td>SQ</td>
</tr>
<tr>
<td>Mipomersen (SQ injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Metabolic Effects**
- ↓ LDL-C 21%, TC 19%, apo B 24%, and non-HDL-C 22% in individuals with HoFH by degrading mRNA for apo B-100, the principal apolipoprotein needed for hepatic synthesis of VLDL (and subsequent intra-plasma production of IDL and LDL)

**Main Considerations:**
- Can cause increases in transaminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase, and total bilirubin before initiation, and of ALT and AST during treatment is recommended
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transaminases, which may be a risk for progressive liver diseases
- Caution should be exercised when used with other drugs with potential hepatotoxicity; because of hepatotoxicity risk, only available through REMS program

Abbreviations: ALT, aspartate amino transferase; apo, apolipoprotein; AST, amino alanine transferase; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger RNA; SQ, subcutaneous; VLDL, very low-density lipoprotein.

Question: How should treatment be monitored?

R75. Reassess individuals’ lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved (Grade D; BEL 4).

R76. While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals (Grade D; BEL 4).

R77. While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment (Grade C; BEL 4; upgraded due to potential benefit).

R78. More frequent lipid status evaluation is recommended in situations such as deterioration of diabetes control, use of a new drug known to affect lipid levels, progression of atherothrombotic disease, considerable weight gain, unexpected adverse change in any lipid parameter, development of a new ASCVD risk factor, or convincing new clinical trial evidence or guidelines that suggest stricter lipid goals (Grade C; BEL 4; upgraded due to potential benefit).

R79. Liver transaminase levels should be measured before and 3 months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g., semiannually or annually) (Grade C; BEL 4; upgraded due to potential benefit).

R80. Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle weakness on statin therapy (Grade C; BEL 4; upgraded due to potential benefit).

Abbreviation: ASCVD, atherosclerotic cardiovascular disease.
Question: Is the treatment of dyslipidemia and prevention of ASCVD cost-effective?

R81. Nonpharmacologic interventions, such as dietary management (Grade A; BEL 1) and smoking cessation, are the most cost-effective options available for ASCVD prevention (Grade A; BEL 2, upgraded due to potential health benefit).

R82. When nonpharmacologic interventions fail, pharmacologic intervention is a recommended cost-effective option for primary and secondary intervention among individuals at moderate to high risk (Grade B; BEL 2).

R83. Among otherwise healthy individuals at lower risk, the cost-effectiveness of primary pharmacologic intervention varies on the basis of age and sex (with this approach being least cost-effective among women at low risk) (Grade C; BEL 3).

R84. Statins have proven cost-effective in both secondary and primary prevention of ASCVD events in individuals at moderate to high risk, or in individuals at low risk whose LDL-C levels are very high (≥190 mg/dL) (Grade B; BEL 2).

R85. Treatment with fibrates has been found to be cost-effective as both monotherapy and combination therapy for lowering TG and raising HDL-C (Grade D; BEL 4), but not in reducing cardiovascular events, except in individuals with TG concentrations greater than 200 mg/dL and HDL-C concentrations less than 40 mg/dL (Grade D; BEL 4).

R86. Ezetimibe coadministered with statin therapy in individuals unable to meet target LDL-C levels has not been evaluated for cost-effectiveness in the U.S. Based on studies from Canada and the United Kingdom, ezetimibe may be a cost-effective strategy to achieve LDL-C goals, especially with price decreases for generic ezetimibe (Grade A; BEL 1).

R87. Bile acid sequestrants are generally not cost-effective alternatives to statin therapy despite generic availability; this is due to their low LDL-C lowering efficacy compared to statins (Grade B; BEL 2).


Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.
# ASCVD Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
</tbody>
</table>
| Extreme risk      | – Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL  
|                   | – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH  
|                   | – History of premature ASCVD (<55 male, <65 female)                                                                                                             | <55             | <80             | <70             |
| Very high risk    | – Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
|                   | – DM or stage 3 or 4 CKD with 1 or more risk factor(s)  
|                   | – HeFH                                                                                                                                                    | <70             | <100            | <80             |
| High risk         | – ≥2 risk factors and 10-year risk 10%-20%  
|                   | – DM or stage 3 or 4 CKD with no other risk factors                                                                                                           | <100            | <130            | <90             |
| Moderate risk     | ≤2 risk factors and 10-year risk <10%                                                                                                                         | <100            | <130            | <90             |
| Low risk          | 0 risk factors                                                                                                                                             | <130            | <160            | NR              |

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.