LDL-Cholesterol

How Low is Too Low?

Benjamin J. Hirsh, M.D., F.A.C.C., F.N.L.A.
Director, Preventive Cardiology
Sandra Atlas Bass Heart Hospital
Assistant Professor
Northwell/Hofstra School of Medicine
CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

COURSE NAME: Medicine RSS eLearning Modules

CME eLEARNING ACTIVITY NAME: LDL-Cholesterol: How Low is Too Low?
2018 Cholesterol Guidelines

PROGRAM DESCRIPTION, EDUCATIONAL GOAL AND RATIONALE:
Evidence based guidelines are constantly changing and being updated for several core areas of Internal Medicine throughout the year. It is important for physicians to practice the most up-to-date standard of care in all specialties to promote patient health and well-being. Our series of lectures at the medicine regularly scheduled series promotes continuing education for the practicing internist and highlights important updates in medical practice in these core areas. Physicians in general practice often and do not have the time to keep themselves up-to-date with medical advances as they are busy seeing patients in the clinical setting. The Medicine Regularly Scheduled Series gives these physicians the opportunity to learn these advances in an academic setting.
CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

TARGET AUDIENCE:
Physician Partners and Premium Network community-based providers

LEARNING OBJECTIVES:
• To Understand the Recent Data Regarding Treatment to Low LDL-Cholesterol and Effect on Cardiovascular Outcomes.
• To Recognize the Safety Data Regarding Cellular and Physiologic Effects Among Patients Treated to Low LDL Cholesterol.
• To Understand How Recent Studies Have Advanced Our Understanding of the Role of LDL Cholesterol Physiology.
• Identify how personal care guidelines have become more specific since 2013.
• Conduct a detailed risk assessment and identify new lipid lowering options for patients with highest ASCVD risk.
• New lipid lowering options for patients with highest ASCVD risk.
• Learn how to utilize Risk Enhancing Factors.
• Identify benefits of therapy v. side effects.
• Review risk factors.
CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

FACULTY PRESENTER/AUTHOR:

Guy L. Mintz M.D., FACP, FACC, FNLA
Director of Cardiovascular Health & Lipidology, Sandra Atlas Bass Heart Hospital
Associate Professor of Medicine, Zucker School of Medicine

Benjamin J. Hirsh, M.D., F.A.C.C., F.N.L.A.
Director, Preventive Cardiology
Sandra Atlas Bass Heart Hospital
Assistant Professor
Northwell/Hofstra School of Medicine

Sandy Balwan, MD
Executive Director & Chief Medical Officer
Northwell Health IPA

Course Director:
George Boutis, MD
Attending Physician
Department of Medicine
Northwell Health

Planners:
John Raimo, MD
Division of Hospital Medicine
Site Director, Internal Medicine Residency Program

Sean LaVine, MD
Site Director, Division of Hospital Medicine
Long Island Jewish Medical Center
CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

ACCREDITATION:
Northwell Health is accredited by the Accreditation Council for Continuing Medical Education to provide Continuing Medical Education for physicians.

CREDIT DESIGNATION:
Northwell Health designates this Continuing Medical Education activity for a maximum of 1 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

METHOD OF PHYSICIAN PARTICIPATION:
To receive credit the participants must:
Read/view the entire educational activity.
Input name and credentials to gain CME credit.
CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

COURSE HOST:
Department of Medicine
Northwell Health

ESTIMATED TIME TO COMPLETE ACTIVITY:
90 minutes

ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT:
An announcement of program support will be made to all attendees at the beginning of each educational activity.
CME ACCREDITED UPDATES IN MEDICINE ELEARNING SERIES

DISCLOSURE POLICY:
Northwell Health adheres to the ACCME’s Standards for Commercial Support. Any individuals in a position to control the content of a CME activity, including faculty, planners, reviewers or others are required to disclose all relevant financial relationships with commercial interests. All relevant conflicts of interest will be resolved prior to the commencement of the activity.

FACULTY DISCLOSURES:
Drs. Thomas McGinn, Dr. Sandy Balwan, George Boutis, John Raimo and Sean LaVine have nothing to disclose. Dr. Hirsh’s disclosures are on the next slide.

RELEASE DATE: 2/5/19
REVIEW DATE: 2/5/19
PROGRAM EXPIRATION: 7/30/19
Relevant Disclosures:
Consultanship: Sanofi-Regeneron
Advisory Board: AstraZeneca, Regeneron
Objectives

1. To Understand the Recent Data Regarding Treatment to Low LDL-Cholesterol and Effect on Cardiovascular Outcomes.

2. To Recognize the Safety Data Regarding Cellular and Physiologic Effects Among Patients Treated to Low LDL Cholesterol.

3. To Understand How Recent Studies Have Advanced Our Understanding of the Role of LDL Cholesterol Physiology.
In your opinion, what directly measured LDL-C is considered too low?

A. 60 mg/dL
B. 40 mg/dL
C. <25 mg/dL
D. <15 mg/dL
E. There is no lower limit
Treatment of LDL-Cholesterol to Lower CHD Events
Lessons from 3 Decades of Cholesterol Treatment Trials

**LDLc and ASCVD: Primary and Secondary Prevention**

- In Absence of RFs, LDLc -ASCVD Directly-Related; Observed EVEN at ‘Normal’ Levels
- In Presence of Plaque, Regression is Directly-Related to LDL-C Level

---

**Bioimage: Atherosclerosis (Low-Risk)**
CAC, Iliofemoral, Carotid, Abdominal Aorta

**Plaque Regression Directly Related to LDLc Lowering**

---

PCSK9 Inhibitor Therapy & LDL-Cholesterol Levels
Greater Potency, Lower LDLc, And Questions Regarding Safe & Optimal LDLc Levels

Very Low Levels of [LDL-C] Safety & Efficacy
### Very Low [LDLc] & Adverse Events

**[LDLc] <20 – 25 mg/dL and Adverse Events in The FOURIER & ODYSSEY RCTs**

### FOURIER Adverse Events

- **[LDLc] < 20mg/dL (n=2669)**

<table>
<thead>
<tr>
<th>% pts</th>
<th>Neurocog</th>
<th>AST/ALT↑</th>
<th>CK↑</th>
<th>Non-CV death</th>
<th>Hem stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
</tr>
<tr>
<td>10</td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
<td><img src="Image" alt="" /></td>
</tr>
</tbody>
</table>

- Analyzed 5 groups by achieved LDL-C at 4 wks
  1. <20 mg/dL, N=2669
  2. 20-49 mg/dL, N=8003
  3. 50-69 mg/dL, N=3444
  4. 70-99 mg/dL, N=7471
  5. ≥100 mg/dL, N=4395 (referent)

### ODYSSEY Adverse Events

- **[LDLc] < 25 mg/dL (n=839)**

#### **CENTRAL ILLUSTRATION: Low-Density Lipoprotein Cholesterol Levels <25 mg/dl Following Alirocumab Treatment: Associated Factors, Exposure, and Safety**

- **LDL-C Achieved With Alirocumab Treatment**
  - n = 3,440
  - Median Duration: 43.3 weeks

- **Factors Associated With LDL-C <25 mg/dl**
  - Lower baseline LDL-C and Lp(a)
  - Higher triglycerides, lower HDL-C
  - Being male and older, with a lower BMI
  - Not having HeFH
  - Having cardiovascular disease
  - Having type 2 diabetes and higher HbA1c
  - Use of 150 mg Q2W alirocumab dose and baseline LDL-C <160 mg/dl

- **Adverse Events**
  - Overall similar AE rates including neurological and neurocognitive events in patients achieving LDL-C <25 vs. 25 mg/dL
  - Higher rates of cataracts with LDL-C <25 vs. ≥25 mg/dL (2.6% vs. 0.8%) although no difference between overall alirocumab and control group.

Ultra Low [LDLc]: Lower is Better for Reduction in MACE

Efficacy & Safety for Patients with On-Treatment [LDLc] of < 10 mg/dL

FOURIER Efficacy
[LDLc] < 10 mg/dL (n=504); Median = 7 mg/dL

**Ultra-Low LDL-C at 1 Month**
504 Pts: Achieved LDL-C at 4 weeks < 10 mg/dL
Median LDL-C = 7 mg/dL, IQR: 5-9 mg/dL

Neurocognitive Outcomes
Ebbinghaus: Cognitive Function in a Randomized Trial of Evolocumab.

2000 Fourier Patients
- Neurocognitive Testing
- Working Memory
- Spatial Processing
- Language Fluency
- Reaction Time
- Psychomotor Speed
- Baseline
- 6 Months
- Yearly
- 5 Years

STRATIFIED by the lowest-attained LDLc level:
- After Randomization: No associations between LDLc level and adverse cognitive outcomes.
- Including among 661 patients who underwent cognitive testing with LDLc levels below 25 mg/dL.

Addressing the Concerns with Treatment to Low Levels of LDLc
Addressing the concerns with treatment to very low [LDL]

Could profound reduction of LDLc deplete cholesterol stores and compromise essential functions of cholesterol, including:

- Hormone Synthesis
- Fat-Soluble Vitamin Synthesis
- Myelin Sheath Formation
- Cell-membrane Integrity
- Bile-Acid Synthesis

Addressing the concerns with treatment to very low [LDL]

Is LDL necessary to supply cholesterol to peripheral tissues?

Intra cellular [cholesterol] is predominantly
- Synthesized de novo or
- Acquired from HDL (significantly less is acquired from LDL)
- LDL is an Insignificant Source of Cholesterol for Steroid Synthesis

Addressing the concerns with treatment to very low [LDL] Does Cholesterol-lowering therapy affect adrenal and gonadal hormone synthesis?

Statins (FDA). Despite Reducing LDL, Statins Do Not Alter Hormone Synthesis

- **Cortisol**
  - Males: Before statin therapy (800), After statin therapy (600)
  - Females: Before statin therapy (400), After statin therapy (300)

- **DHEA-S**
  - Males: Before statin therapy (1200), After statin therapy (1000)
  - Females: Before statin therapy (900), After statin therapy (700)

- **SHBG**
  - Males: Before statin therapy (600), After statin therapy (400)
  - Females: Before statin therapy (300), After statin therapy (200)

- **Testosterone**
  - Males: Before statin therapy (1100), After statin therapy (900)
  - Females: Before statin therapy (700), After statin therapy (500)

PCSK9 (FDA). Despite Reducing LDL to Very Low Levels, PCSK9 Inhibitors Do Not Alter Hormone Synthesis

- **Cortisol**
  - Placebo: Baseline (383.3), Week 52 (394.5)
  - Evolocumab: Baseline (377.2), Week 52 (404.1)

- **KTH**
  - Placebo: Baseline (4.9), Week 52 (5.2)
  - Evolocumab: Baseline (4.9), Week 52 (5.4)

- **Cortisol/ACTH Ratio**
  - Placebo: Baseline (131.6), Week 52 (103.0)
  - Evolocumab: Baseline (113.6), Week 52 (103.0)

Addressing the predominant concerns with very low [LDL]
Is the CNS Affected by Reduced [LDL] or the use of PCSK9 Antibodies?

The CNS Predominantly Synthesizes Cholesterol De Novo. HDL Crosses Blood Brain Barrier. LDL Does Not.

- Cholesterol is a major component of the CNS\(^1,2\)
  - The CNS predominantly synthesizes cholesterol de novo\(^1,2\)
  - The blood-brain barrier (BBB) prevents the uptake of systemic lipoprotein cholesterol from atherogenic lipoproteins\(^2,3\)
  - However, HDL does appear to cross the BBB\(^3\)
- This segregation ensures that cholesterol metabolism within the brain is isolated from changes in the circulating lipid levels due to diet or medication\(^2\)

Concerns with regard to PCSK9 Monoclonal Antibodies in the Central Nervous System

- PCSK9 Monoclonal Antibodies are too large to cross the blood brain barrier.
- No increased neurocognitive risk in a pooled analysis of 14 trials on PCSK9 inhibitors even after attaining an extremely low LDL-C level.
- Loss of function of PCSK9 is not associated with any signs of neurocognitive deficits.

1. Figure Adapted from Katsuno M, et al. Nature Med 2009.
Addressing the predominant concerns with very low [LDL]
Inaccurate Measures of Calculated LDLc at low LDL-c levels and high triglycerides.

Calculated LDLc Underestimation of Actual LDLc Increases More as LDLc < 70; TG > 150

- At LDL-C levels < 100 mg/dL, calculating LDL-C by the Friedewald Equation results in a negative bias which becomes progressively more pronounced at lower LDL-C levels, with a percent difference as high as -27.6% at LDL-C levels ≤ 25 mg/dL, compared with LDL-C levels analyzed by the reference method (PUC)

- Further, as TG levels increase in patients within these low LDL-C ranges, the negative bias seen with calculated LDL-C increased to as high as 66%

As LDL-C decreased, underestimation of LDL-C by Friedewald increased

General Principles in Cholesterol Management

1. Early Identification of FH is Essential!
2. Higher-Risk Patients with Higher LDLc Benefit the Most
3. Risk Reduction Continues to Accrue Over Time
   i.e., Treatment Should be Sustained
Early Recognition of Familial Hypercholesterolemia is Essential!

Hidden in Plain Sight

Arcus Senilis

FH is more common than many well known genetic diseases

- 1:300 – 1:500 worldwide
- 620,000 FH patients in US
- Average LDL is 220 mg/dl
- 20 fold increased risk of coronary heart disease
- Causes 20% of MIs before age 45 and 5% before age 60

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

Goldberg et al. J. Clinical Lipidology. 2011

Northwell Health™
Higher-Risk Patients Benefit Most from Cholesterol Reduction

Risk & Benefit

- CTT Statin Meta-analyses
- Reduction in CVD risk is proportionally similar in patients at all levels of risk
- Greatest absolute number of events avoided in patients at highest risk
- Similar to Statins, the recent nonstatin therapies reduce ASCVD risk by extent of absolute LDL-C lowering (highest levels) & Achieved LDL-C Level

Duration of Therapy

LDL-Reduction Leads to Even Greater ASCVD Risk Reduction…if Sustained.

Perspectives on Serum [LDL-C]
Past & Present
Key Opinion Leaders
And
The Bigger Picture
Lessons from the Past & Present
Treatment of LDL-Cholesterol – From 1984 to 2018

A Receptor-Mediated Pathway for Cholesterol Homeostasis
Michael S. Brown and Joseph L. Goldstein

The LDL receptor studies lend experimental support to the epidemiologists’ suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (9). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (28). In view of the 10 to 1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (118). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16 and ref. 119). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25-60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings.


LDL Cholesterol Treatment in the PCSK9 Era
Getting Back on Target
Marc S. Sabatine and Robert P. Giugliano

> LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 40 mg/dL)
> Lowering LDL-C with evolocumab (while on statin) safely reduced CV events in a variety of high risk patients, mostly by reducing MI and ischemic stroke
> No excess in safety events, including new DM, even at very low achieved LDL-C <20 mg/dL at 2.2 years

Based on the totality of the data, we would advocate targeting an LDL-C level of 20-25 mg/dL (0.5-0.6 mmol/L) or lower in secondary prevention in high-risk pts

Adapted from Editorial on FOURIER Trial JAMA Cardiol 2018; 2:935-936.
Cardiovascular Prevention

Keeping Sight of the Big Picture
Lifestyle Remains the Cornerstone of Therapy

We Are Evolving in the Wrong Direction
Lifestyle Remains the Cornerstone of Therapy
We Are Evolving in the Wrong Direction


LYON-HEART Study: Mediterranean Diet

MI Prior 6 Mos – Mediterranean vs Western
Reduction of Nonfatal MIs
Reduction in Overall Mortality
Subsequent studies decreased inflammation
Lifestyle Remains the Cornerstone of Therapy
We Are Evolving in the Wrong Direction

“Exercise can be viewed as a preventive medical treatment, like a ‘pill’ that should be taken on an almost daily basis.”
Nanette Wenger, M.D., M.A.C.P., M.A.C.C.
2013 American Heart Association Scientific Statement

Potential Cardioprotective Effects of Regular Physical Activity

<table>
<thead>
<tr>
<th>Anti-atherosclerotic</th>
<th>Psychologic</th>
<th>Anti-Thrombotic</th>
<th>Anti-Ischemic</th>
<th>Anti-Arrhythmic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved lipids</td>
<td>↓ Depression</td>
<td>↓ Platelet adhesiveness</td>
<td>↓ Myocardial O₂ demand</td>
<td>↑ Vagal tone</td>
</tr>
<tr>
<td>Lower BPs</td>
<td>↓ Stress</td>
<td>↑ Fibrinolysis</td>
<td>↑ Coronary flow</td>
<td>↓ Adrenergic activity</td>
</tr>
<tr>
<td>Reduced adiposity</td>
<td>↑ Social support</td>
<td>↓ Fibrinogen</td>
<td>↓ Endothelial dysfunction</td>
<td>↑ HR variability</td>
</tr>
<tr>
<td>↑ Insulin sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑ Blood viscosity | ↑ EPCs and CACs | ↑ Nitric Oxide

Wrap Up

- Recent trials demonstrate that reducing LDLc to very low levels are safe with ezetimibe and PCSK9 inhibitors (with 5 years of data).
- Cholesterol is mostly derived through de novo synthesis and HDL.
- LDL is an insignificant source of cholesterol for steroid synthesis.
- There may be no lower limit to LDL cholesterol.
- Identifying FH and high-risk patients EARLY is essential, as is long-term treatment.
- Cholesterol is one of many modifiable risk factors leading to accelerated atherosclerosis.
- Lifestyle remains the cornerstone of therapy to reduce atherosclerosis.

**LIPID CENTER:**

Dr. Mintz and Dr. Hirsh will be starting a lipid treatment program at North Shore.

In the meantime, feel free to reach out with questions.

Thank you!

Benjamin J Hirsh MD, FACC, FNLA  
bhirsh@northwell.edu

Guy L Mintz, MD, FACP, FACC, FNLA  
gmintz@northwell.edu
2018 Cholesterol Guidelines

Guy L. Mintz M.D., FACP, FACC, FNLA
Director of Cardiovascular Health & Lipidology
Sandra Atlas Bass Heart Hospital
North Shore University Hospital
Associate Professor of Medicine
Zucker School of Medicine
Atherosclerosis Timeline

- Foam Cells
- Fatty Streak
- Intermediate Lesion
- Atheroma
- Fibrous Plaque
- Complicated Lesion/Rupture

Endothelial Dysfunction

- From first decade: Growth mainly by lipid accumulation
- From third decade: Smooth muscle and collagen
- From fourth decade: Thrombosis, hematoma

Myocardial Infarction
Stenosis Severity and Risk

<table>
<thead>
<tr>
<th>Degree Stenosis prior to MI</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>68%</td>
</tr>
<tr>
<td>50%-70%</td>
<td>18%</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Guidelines New Emphasis

1. More personalized care than 2013 guidelines

2. Detailed risk assessment

3. New lipid lowering options for patients with highest ASCVD risk

4. Utilize Risk Enhancing Factors

5. Class I Recommendation: Patient-Physician discussion
   • Benefits of therapy v. side effects
   • Potential drug-drug interaction
   • Review risk factors
   • Financial cost
Emphasis on Heart Healthy Lifestyle

• Reduces development of risk factors

• Foundation for ASCVD risk reduction

• Primary intervention for Metabolic syndrome

• Assess lifetime risk in young adults (20-39 years of age)
Life Style Discussion

• In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages.

• In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of life-time risk facilitates the clinician–patient risk discussion and emphasizes intensive lifestyle efforts.

• In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
### ATP-III Guidelines for LDL-C Goals, Levels for Lifestyle Changes, and Levels for Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>LDL-C Level for Initiation of TLC (mg/dL)</th>
<th>LDL-C Level to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥130 (100–129: drug optional)</td>
</tr>
<tr>
<td>≥2 risk factors (10-year risk ≤20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10%–20%: ≥130 10-year risk &lt;10%: ≥160</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190 (160–189: LDL-C-lowering drug optional)</td>
</tr>
</tbody>
</table>

**LDL-C**

- **LDL-C Goals**: Refer to ATP-III Guidelines.
- **Levels for Lifestyle Changes**: Refer to ATP-III Guidelines.
- **Levels for Drug Therapy**: Refer to ATP-III Guidelines.

**TLC** (therapeutic lifestyle changes)

Four Statin Benefit Groups

1. Primary Prevention Over Lifespan

2. Diabetes Mellitus In Adults
   - Age 40 - 75 years of Age
   - LDL-C of 70mg/dl-189 mg/dl
   - Risk Enhancers independent of other risk factors

3. Severe Hypercholesterolemia: LDL> 190 mg/dl

4. Secondary Atherosclerotic Heart Disease Prevention
Primary Prevention for ASCVD

- 40-75 years of age
- Lifestyle modification to reduce risk factors
- Review Risk Factors: LDL-C, HBA1C, Smoking cessation, Weight loss, Hypertension
- Calculate 10 years ASCVD risk
  - AHA/ACC Pooled Cohort Risk Calculator
  - Reynolds Risk Score
  - Framingham Risk Score

Shared decision making with patient including statin side effects & cost
ASCVD Risk Calculators

• AHA/ACC Pooled Cohort

• Reynolds Risk Score (includes hs-CRP & family history)

• Framingham Risk Score

• MESA (Multi Ethnic Study of Atherosclerosis)
  10 year ASCVD Risk with Coronary Calcium calculated
# Cardiovascular Risk Calculators

<table>
<thead>
<tr>
<th>AHA/ ACC Pooled Cohort: 10 year ASCVD Risk (NFMI, CHD DEATH OR CVA)</th>
<th>Framingham Calculator: 10 year MI Risk</th>
<th>Reynolds Risk Score: 10 year Risk: MI, CVA, other Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
<td>Gender</td>
<td>Gender</td>
</tr>
<tr>
<td>RACE (B/W/OTHER) Under mate: Am Indians, South Asia, Hispanics--PR Over mate: East Asia, Mexican Americans</td>
<td></td>
<td>HIGH SENSITIVITY CRP (HS--CRP)</td>
</tr>
<tr>
<td>TOTAL CHOLESTEROL</td>
<td>TOTAL CHOLESTEROL</td>
<td>TOTAL CHOLESTEROL</td>
</tr>
<tr>
<td>HDL--C</td>
<td>HDL--C</td>
<td>HDL--C</td>
</tr>
<tr>
<td>SYSTOLIC BP</td>
<td>SYSTOLIC BP</td>
<td>SYSTOLIC BP</td>
</tr>
<tr>
<td>HTN TREATMENT: Y/N</td>
<td>HTN TREATMENT: Y/N</td>
<td>MOTHER OR FATHER MI &lt; 60 YRS</td>
</tr>
<tr>
<td>DIABETES: Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMOKER: Y/N</td>
<td>SMOKER: Y/N</td>
<td></td>
</tr>
</tbody>
</table>
AHA-ACC ASCVD Risk Calculator

The ACC and the American Heart Association (AHA), in collaboration with the National Heart, Lung, and Blood Institute and other specialty societies, have released four guidelines focused on the assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk and management of elevated blood cholesterol and body weight in adults.

In order to support the implementation of these guidelines the ACC and AHA have jointly published a new mobile application (app).

The ASCVD Risk Estimator application helps health care providers and patients estimate 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD) using the Pooled Cohort Equations and lifetime risk prediction tools. The ASCVD Risk Estimator provides easy access to recommendations specific to calculated risk estimates. Additionally, the app includes readily accessible guideline reference information for both providers and patients related to therapy, monitoring, and lifestyle.

The app is available on both iTunes (iPhones, iPads) and Google Play (Galaxy, Nexus, other Android devices). Use the links below from your mobile device to download the app.

Download the App From iTunes
Download the App From Google Play
Launch the Web Version
Entered Data (tap to edit):

<table>
<thead>
<tr>
<th>Entered Data (tap to edit):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Race</strong></td>
</tr>
<tr>
<td><strong>Total Cholesterol</strong></td>
</tr>
<tr>
<td><strong>HDL Cholesterol</strong></td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure</strong></td>
</tr>
<tr>
<td><strong>HBP Treatment</strong></td>
</tr>
<tr>
<td><strong>Diabetic</strong></td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>60 Years Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
<td>White/Other</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>210 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>42 mg/dL</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>131 mmHg</td>
</tr>
<tr>
<td>HBP Treatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetic</td>
<td>No</td>
</tr>
<tr>
<td>Smoker</td>
<td>No</td>
</tr>
</tbody>
</table>
Restart Wizard
Guidelines

Estimated 10-year ASCVD Risk

12.3%

Elevated Risk
10-year optimal risk: 5.7%

Estimated Lifetime Risk (Y), N/A
Optimal Lifetime Risk, N/A

Recommendation

Entered Data (tap to edit):

Age
60 Years Old

Gender
Male

Race
White/Other

Northwell Health™
<table>
<thead>
<tr>
<th>ASCVD PLUS CALCULATOR</th>
<th>INFORMATION OFFERED</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>CURRENT 10 YEAR RISK OF ASCVD</td>
</tr>
<tr>
<td>GENDER</td>
<td>OPTIMAL ASCVD RISK</td>
</tr>
<tr>
<td>RACE (B/W/ OTHER)</td>
<td>VIEW ADVICE: LIFESTYLE CHANGE, LDL--C THERAPY INTENSITY, (70--189 MG/DL), REVIEW RISK ENHANCERS</td>
</tr>
<tr>
<td>SYSTOLIC BLOOD PRESSURE</td>
<td></td>
</tr>
<tr>
<td>DIASTOLIC BLOOD PRESSURE</td>
<td></td>
</tr>
<tr>
<td>TOTAL CHOLESTEROL</td>
<td></td>
</tr>
<tr>
<td>HDL CHOLESTEROL</td>
<td></td>
</tr>
<tr>
<td>LDL CHOLESTEROL</td>
<td></td>
</tr>
<tr>
<td>DIABETES Y/N</td>
<td></td>
</tr>
<tr>
<td>SMOKER Y/N</td>
<td></td>
</tr>
<tr>
<td>HYPERTENSION THERAPY Y/N</td>
<td></td>
</tr>
<tr>
<td>STATIN Y/N</td>
<td></td>
</tr>
<tr>
<td>ASPIRIN Y/N</td>
<td></td>
</tr>
<tr>
<td>REFINE RISK USING PREVIOUS DATA</td>
<td></td>
</tr>
</tbody>
</table>
Utilization of Ten Year ASCVD Risk Score

Characteristics:
• 40-75 years of age
• Non Diabetic & LDL-C ≥ 70 mg/dl

Low Risk: < 5 %
• Therapeutic lifestyle Change

Borderline Risk: 5 - < 7.5 %
• Risk discussion for statin benefit; risk enhancers

Intermediate: Moderate Risk: > 7.5 % & < 20 %
• Evaluate Risk enhancers & Coronary artery calcification if uncertain
• Moderate intensity statin, LDL-C reduction 30-50%

High Risk: > 20 %
• 10 year ASCVD Risk ≥ 20%
• High Intensity statin, Reduce LDL-C by 50%
Primary Prevention: Assessment

• Age 40-75 years of age
• No Diabetes
• LDL-C > 70mg/dl
• 10 year ASCVD risk of > 7.5 %

• Start moderate or high intensity statin therapy

• Presence of Risk Enhancing Factors Favor Statin Therapy
Ten Year ASCVD Risk: ≥7.5-19.9%

• 40-75 years of age; non-diabetic
• LDL-C ≥ 70 mg/dl – 189 mg/dl
• Intermediate Risk

Coronary Calcium Score: if risk uncertain

• CAC of zero: statins withheld or delayed unless diabetic, smoker, or strong family history of premature ASCVD
• CAC score: 1-99 : statin therapy especially ≥ 55 years old
• CAC score ≥ 100 or ≥ 75th percentile: statin therapy
## Risk-Enhancing Factors for Clinician–Patient Risk Discussion

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of premature ASCVD (males, age &lt;55 y; females, age &lt;65 y)</td>
</tr>
<tr>
<td>Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*</td>
</tr>
<tr>
<td>Metabolic syndrome (increased waist circumference, elevated triglycerides [&gt;175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 in women mg/dL] are factors; tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td>Chronic kidney disease (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)</td>
</tr>
<tr>
<td>Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS</td>
</tr>
<tr>
<td>History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia</td>
</tr>
<tr>
<td>High-risk race/ethnicities (e.g., South Asian ancestry)</td>
</tr>
</tbody>
</table>
## Risk Enhancing Factors: Biomarkers & Clinical Assessment

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid/biomarkers:</strong> Associated with increased ASCVD risk</td>
</tr>
<tr>
<td>- Persistently* elevated, primary hypertriglyceridemia ($\geq 175$ mg/dL);</td>
</tr>
<tr>
<td>- If measured:</td>
</tr>
<tr>
<td>- Elevated high-sensitivity C-reactive protein ($\geq 2.0$ mg/L)</td>
</tr>
<tr>
<td>- Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) $\geq 50$ mg/dL or $\geq 125$ nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).</td>
</tr>
<tr>
<td>- Elevated apoB $\geq 130$ mg/dL: A relative indication for its measurement would be triglyceride $\geq 200$ mg/dL. A level $\geq 130$ mg/dL corresponds to an LDL-C $&gt;160$ mg/dL and constitutes a risk-enhancing factor</td>
</tr>
<tr>
<td>- ABI $&lt; 0.9$</td>
</tr>
</tbody>
</table>
## Selected Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

<table>
<thead>
<tr>
<th>CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score Is Zero</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Parents reluctant to initiate statin therapy who wish to understand their risk and potential for benefit more precisely</td>
</tr>
<tr>
<td>• Parents concerned about need to reinstate statin therapy amid discontinuation for statin-associated symptoms</td>
</tr>
<tr>
<td>• Older parents (men, 55-80 y of age; women, 60-80 y of age) with low burden of risk factors who question whether they would benefit from statin therapy</td>
</tr>
<tr>
<td>• Middle-aged adults (40-55 y of age) with PCE-calculated 10-year risk of ASCVD 5% to &lt;7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group</td>
</tr>
</tbody>
</table>
Coronary Calcium Score

1. Add to risk assessment in asymptomatic patients at intermediate risk, 10-20% if decision regarding statins is uncertain
2. Score of zero reasonable to withhold statin therapy & reassess in 5-10 years
3. Score: 1-99 Agaston units may support statin use age > 55 years
4. Score: > 100 Agaston units or 75th percentile by age & gender- start statin therapy
5. Result: > 300 Agaston units-High risk scan which requires high intensity statin therapy
6. Low dose radiation with newer scanners about 1 mSv, (Chest Cat Scan 7 mSv, mammogram 0.4 mSv; CXR-0.1 mSv, people in U.S. exposed to average of 3 mSv from natural surroundings)
Coronary Artery Calcification
<table>
<thead>
<tr>
<th>Coronary Calcium Score</th>
<th>10 Year Risk of NFMI or CHD Death</th>
<th>Risk Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Less than 1 %</td>
<td>Lower</td>
</tr>
<tr>
<td>1--99</td>
<td>4 %</td>
<td>Lower to Moderate</td>
</tr>
<tr>
<td>100 --399</td>
<td>13 %</td>
<td>Moderate</td>
</tr>
<tr>
<td>400 &amp; Greater</td>
<td>24 %</td>
<td>High</td>
</tr>
</tbody>
</table>
MESA: Cumulative CHD Incidence Across Coronary Artery Calcium Categories
# Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

<table>
<thead>
<tr>
<th>Checklist Item</th>
<th>RecommendaSon</th>
</tr>
</thead>
</table>
| ASCVD risk assessment           | • Assign to sta@n treatment group; use ASCVD Risk Es@mator Plus.*  
                                  |   o In lower--risk primary--preven@on adults 40--75 y of age with LDL--C ≥70 mg/dL (≥1.8 mmol/L).                                         
                                  |   o Not needed in secondary preven@on, in those with LDL--C ≥190 mg/dL (≥4.9 mmol/L), or in those 40--75 y of age with diabetes mellitus.  |
|                                 | • Assess other pa@ent characteris@cs that influence risk. See Risk--Enhancing Factors (Sec@on 4.4.1.3. and Table 6)                       |
|                                 | • Assess CAC (Sec@on 4.4.1.4.) if risk decision is uncertain and addi@onal informa@on is needed to clarify ASCVD risk.                   |
|                                 |   o Use decision tools to explain risk (e.g., ASCVD Risk Es@mator Plus,* Mayo Clinic Sta@n Choice Decision Aid).                        |
| Lifestyle modifica@on s         | • Review lifestyle habits (e.g., diet, physical ac@vity, weight or body mass index, and tobacco use).                                  |
|                                 | • Endorse a healthy lifestyle and provide relevant advice, materials, or referrals. (e.g., CardioSmart, AHA Life’s Simple 7, NLA Pa@ent Tear Sheets, PCNA Clinicians’ Lifestyle Modifica@on Toolbox, cardiac rehabilita@on, die@@an, smoking cessa@on program). |
AHA SIMPLE 7

1. Manage Blood Pressure
2. Control Cholesterol
3. Reduce Blood Sugar
4. Get Active
5. Eat Better
6. Lose Weight
7. Stop Smoking
Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

<table>
<thead>
<tr>
<th>Checklist Item</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential net clinical benefit of pharmacotherapy</td>
<td>• Recommend statins as first-line therapy.</td>
</tr>
<tr>
<td></td>
<td>• Consider the combination of statin and nonstatin therapy in selected patients.</td>
</tr>
<tr>
<td></td>
<td>• Discuss potential risk reduction from lipid-lowering therapy.</td>
</tr>
<tr>
<td></td>
<td>• Discuss the potential for adverse effects or drug–drug interactions.</td>
</tr>
</tbody>
</table>
# Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

<table>
<thead>
<tr>
<th>Checklist Item</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost considerations</td>
<td>• Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, co-pay, copayment).</td>
</tr>
</tbody>
</table>
| Shared decision-making                | • Encourage the patient to verbalize what was heard (e.g., patient’s personal ASCVD risk, available options, and risks/benefits).  
  • Invite the patient to ask questions, express values and preferences, and state ability to adhere to lifestyle changes and medications.  
  • Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions.  
  • Collaborate with the patient to determine therapy and follow-up plan. |
### Recommendations for Older Adults

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In adults 75 years of age or older with an LDL--C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), iniSasng a moderate--intensity staSn may be reasonable.</td>
</tr>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In adults 75 years of age or older, it may be reasonable to stop staSn therapy when funcSonal decline (physical or cogniSve), mulSmorbidity, frailty, or reduced life--expectancy limits the potenSal benefits of staSn therapy.</td>
</tr>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In adults 76 to 80 years of age with an LDL--C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid staSn therapy.</td>
</tr>
<tr>
<td>COR</td>
<td>LOE</td>
<td>RecommendaSons for Older Adults</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In adults 75 years of age or older with an LDL--C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiaSing a moderate--intensity staSn may be reasonable.</td>
</tr>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In adults 75 years of age or older, it may be reasonable to stop staSn therapy when funcSonal decline (physical or cogniSve), mulSmorbidity, frailty, or reduced life--expectancy limits the potenSal benefits of staSn therapy.</td>
</tr>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In adults 76 to 80 years of age with an LDL--C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid staSn therapy.</td>
</tr>
</tbody>
</table>
Diabetes Is a Significant Risk Factor for MI

Incidence of MI Over 7 Years: Diabetic vs. Non-Diabetic Patients

<table>
<thead>
<tr>
<th>Events/100 Person Year</th>
<th>Type 2 Diabetes</th>
<th>No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>45.0*</td>
<td></td>
</tr>
<tr>
<td>No prior MI</td>
<td>20.2*</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>18.8*</td>
<td></td>
</tr>
<tr>
<td>No Prior MI</td>
<td>3.5*</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001
Diabetic Patients

- 40-75 years of age
- LDL ≥ 70 mg/dl
- Begin moderate intensity statin therapy without calculating 10 year risk

HIGHER RISK:
- Multiple ASCVD risk factors
- 50-75 years of age
- High Intensity Statin therapy to reduce LDL ≥ 50%
Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes

- Long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 ml/min/1.73 m²
- Retinopathy
- Neuropathy
- ABI <0.9
Endocrine Society: ASCVD–Diabetes Risk Categories

- **Low risk:**
  - No risk factors
- **Moderate risk:**
  - 2 or fewer risk factors and a calculated 10-year risk of less than 10%
- **High risk:**
  - 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%
- **Very high risk:**
  - 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
- **Extreme risk:**
  - 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 (<55 years of age for males or <65 years of age for females)
  - 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.

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.
## Endocrine: 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>LDL-C (mg/dL)</td>
<td>Non--HDL-C (mg/dL)</td>
</tr>
<tr>
<td>Extreme risk</td>
<td>&lt;55</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Very high risk</td>
<td>&lt;70</td>
<td>&lt;100</td>
</tr>
<tr>
<td>High risk</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

### Definitions:
- 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

### Notes:
- Progressive ASCVD includes 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)
- 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)
- DM or stage 3 or 4 CKD with no other risk factors
- HeFH

### References:
Familial Heterozygous Hypercholesterolemia

• LDL $\geq$ 190 mg/dl

• Initiate high intensity therapy statin therapy without calculating 10 year ASCVD Risk

• LDL remains $\geq$ 100 mg/dl - adding ezetimibe is reasonable

• If LDL remains $\geq$ 100 mg/dl on high intensity statin and ezetimibe therapy consider PCSK9 therapy if multiple risk factors for ASCVD exist
### Recommendations for Primary Severe Hypercholesterolemia [LDL-C ≥190 mg/dL (≥4.9 mmol/L)]

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.</td>
</tr>
<tr>
<td>Ila</td>
<td>B-R</td>
<td>2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable.</td>
</tr>
<tr>
<td>Iib</td>
<td>B-R</td>
<td>3. In patients 20 to 75 years of age with a baseline LDL-C ≥190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≥300 mg/dL (≥3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.</td>
</tr>
<tr>
<td>Iib</td>
<td>B-R</td>
<td>4. In patients 20 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.</td>
</tr>
<tr>
<td>Iib</td>
<td>C-LD</td>
<td>5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.</td>
</tr>
</tbody>
</table>

**Value Statement:** Uncertain Value (B-NR)

6. Among patients with FH with no evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 US list prices.
Thrombosis of a disrupted atheroma, the cause of most acute coronary syndromes, results from:

- Weakening of the fibrous cap
- Thrombogenicity of the lipid core
Secondary Prevention: Major ASCVD Events

• Recent acute coronary syndrome (≤ 12 months)

• Myocardial Infarction (≥ 12 months)

• Ischemic stroke history

• Symptomatic peripheral arterial disease
  • Claudication: ABI ≤ 0.85
  • Previous Revascularization or amputation
# High-Risk for Future ASCVD Events

## Major ASCVD Events
- Recent acute coronary syndrome (within the past 12 months)
- History of myocardial infarction (other than recent acute coronary syndrome event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)

## High-Risk Conditions
- Age ≥65 years
- Heterozygous familial hypercholesterolemia
- History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
- Diabetes Mellitus
- Hypertension
- Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)
- Current smoking
- Persistently elevated LDL-C (LDL-C ≥100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe
- History of congestive heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.*
Secondary Prevention: Very High Risk ASCVD

• Multiple major ASCVD events OR

• One major ASCVD event and multiple high risk conditions:
  - Age: ≥ 65 years old
  - Diabetes
  - Hypertension
  - CKD (GFR: 15-59 cc/min +/- albuminuria)
  - Smokers
  - Persistently elevated LDL-C ≥ 100 mg/dl
  - Prior CABG or PCI, CHF
  - Heterozygous FH
Secondary Prevention for ASCVD

• High intensity statin therapy

• Maximally tolerated statin therapy

• Decrease coronary artery disease risk

• GOAL: reduce LDL by ≥ 50%
Treatment of Very High Risk ASCVD Patients

• Reasonable to add Ezetimibe to maximally tolerated statin therapy if LDL ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl

• Reasonable to add PCSK-9 therapy if LDL ≥ 70 mg/dl on maximally tolerated statin and Ezetimibe therapy
Recommendations for Statin Therapy Use in Patients With ASCVD

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>B--R</td>
<td>In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences.</td>
</tr>
<tr>
<td>IIA</td>
<td>C--LD</td>
<td>In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences.</td>
</tr>
</tbody>
</table>
### Recommendations for StaSn Therapy Use in Patients With ASCVD

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In patients with clinical ASCVD who are receiving maximally tolerated staSn therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe.</td>
</tr>
<tr>
<td>IIb</td>
<td>B--R</td>
<td>In patients with heart failure (HF) with reduced ejecSon fracSon attributable to ischemic heart disease who have a reasonable life expectancy (3 to 5 years) and are not already on a staSn because of ASCVD, clinicians may consider iniSaSon of moderate--intensity staSn therapy to reduce the occurrence of ASCVD events.</td>
</tr>
</tbody>
</table>
Secondary Prevention Treatment

- Patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

- The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

- Use a maximally tolerated statin to lower LDL-C levels by ≥50%.
**Intensity of Statin Therapy**

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

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg</td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>LDL-C Lowering†</th>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td></td>
<td>30% to 49%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Primary Statins</td>
<td>Atorvastatin (40 mg) 80 mg Rosuvastatin 20 (40 mg)</td>
<td>Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20-40 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Other Statins</td>
<td>–</td>
<td>Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1-4 mg</td>
<td>Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg</td>
</tr>
</tbody>
</table>
Secondary Prevention in ASCVD Patients

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk

Age ≤75 yrs

High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)

If high-intensity statin not tolerated, use moderate-intensity statin (Class I)

If on maximal statin & LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIa)

Initiation of moderate or high-intensity statin is reasonable (Class IIa)

Continuation of high-intensity statin is reasonable (Class IIa)

Age >75

Very high-risk ASCVD

High-intensity or maximal statin (Class I)

If on maximal statin Rx & LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)

If clinically judged-maximal LDL-C lowering Rx & LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective

Northwell Health™
Non-Statin Lipid Therapy In Guidelines

• 1. Ezetimibe

• 2 PCSK-9 Inhibitors
**IMPROVE-IT: Improved Reduction on 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.

**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.

Impact of an PCSK9 mAb on LDL Receptor Expression

- LDL particle
- LDL Receptor
- Endocytosis
- Recycling of LDL-R
- Clathrin-coated vesicle
- Endosome
- PCSK9 Apparatus
- Golgi apparatus
- Endoplasmic reticulum
- Hepatocyte
- Nucleus
- SREBP
- Lysosome
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
- 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

Main Considerations:
- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuations on 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.

**PCSK9 Therapy Issues**

- Long term safety $\geq 3$ years uncertain

- Economic cost
### Recommendations for Statin Safety and Statin-Associated Side Effects

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No</td>
<td>B--R</td>
<td>Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS.</td>
</tr>
<tr>
<td>Benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III: No</td>
<td>C--LD</td>
<td>In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.</td>
</tr>
<tr>
<td>Benefit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evaluate Successful Statin Therapy

• Compliance with medical therapy and lifestyle

• Repeat lipid panel 4-12 weeks after statin begins

• Dose adjusted every 3-12 months as needed

• Consider addition of non-statin drugs if LDL $\geq 70$ mg/dl, or non-HDL-C $> 100$ mg/dl
Bempedoic Acid

- Once-daily, oral pill
- 30% LDL-C lowering
  - Incremental 20%+ on top of statins, including high-intensity statins
  - Incremental 30% on top of PCSK9i
- 40% hsCRP reduction alone; 48% hsCRP reduction with the combination of bempedoic acid / ezetimibe + atorvastatin 20 mg
- Potential for lower occurrence of muscle-related side effects
- Safe and well-tolerated
**CLEAR Outcomes Study**
Northwell Investigators: Dr. Guy Mintz & Dr. Ben Hirsh

**Primary Objective:**

To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of major adverse cardiovascular events (MACE) in patients with, or at high risk for, cardiovascular disease (CVD) who are statin intolerant.

This will be assessed with a composite primary efficacy endpoint that includes time to first occurrence of:

- cardiovascular (CV) death
- nonfatal myocardial infarction (MI)
- nonfatal stroke, or
- coronary revascularization.
Secondary Objectives:

• To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of other clinical endpoints of CV morbidity and mortality and all-cause mortality.

• To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hsCRP).

• To evaluate the long-term safety and tolerability of bempedoic acid 180 mg/day compared to placebo.
"But that’s the beauty of it, Rita! I don’t have to worry about my fat intake today. I’m having a quadruple bypass tomorrow!"
Expected Changes in Therapeutic Approaches to Cardiovascular Disease in the Future

Treatment Modes

- Cure
- Palliation
- Prevention

21st Century and Beyond

Top 10 Take-Home Messages

2018 Cholesterol Guidelines
Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of life-time risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
Top 10 Take Home Messages

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by \( \geq 50\% \).
Top 10 Take Home Messages

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

• Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

• In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).

• In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.
4. In patients with severe primary hypercholesterolemia (LDL-C level $\geq 190 \text{ mg/dL} [\geq 4.9 \text{ mmol/L}])$ without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

- If the LDL-C level remains $\geq 100 \text{ mg/dL} (\geq 2.6 \text{ mmol/L}),$ adding ezetimibe is reasonable.

- If the LDL-C level on statin plus ezetimibe remains $\geq 100 \text{ mg/dL} (\geq 2.6 \text{ mmol/L})$ & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety ($>3$ years) is uncertain and economic value is low at mid-2018 list prices.
Top 10 Take Home Messages

5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

- the presence of risk-enhancing factors (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.
Top 10 Take Home Messages

7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include:

- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- metabolic syndrome;
- chronic kidney disease;

- history of preeclampsia or premature menopause (age <40 yrs)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L);
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include

and, if measured in selected individuals

• apolipoprotein B ≥130 mg/dL
• high-sensitivity C-reactive protein ≥2.0 mg/L
• ankle-brachial index <0.9 and 1
• lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk)
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels $\geq 70$ mg/dL–189 mg/dL ($\geq 1.8$–4.9 mmol/L), at a 10-year ASCVD risk of $\geq 7.5\%$ to $19.9\%$, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those $\geq 55$ years of age.
- For any patient, if the CAC score is $\geq 100$ Agatston units or $\geq 75$th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.
10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after starting or dose adjustment, repeated every 3 to 12 months as needed.

• Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
• In ASCVD patients at very high-risk, triggers for adding non-statin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).
Secondary Prevention

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk*  

Age ≤75 y

High-intensity statin  
(Goal: ↓ LDL-C ≥50%)  
(Class I)

If high-intensity statin not tolerated, use moderate-intensity statin  
(Class I)

If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable  
(Class IIb)

Initiation of moderate- or high-intensity statin is reasonable  
(Class IIa)

Continuation of high-intensity statin is reasonable  
(Class IIa)

Age >75 y

High-intensity or maximal statin  
(Class I)

If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable  
(Class IIa)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I  
(Class I)

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable  
(Class IIa)

Very high-risk* ASCVD

Dashed arrow indicates RCT-supported efficacy, but is less cost effective
### Table 6. Risk-Enhancing Factors for Clinician–Patient Risk Discussion

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Family history of premature ASCVD (males, age &lt;55 y; females, age &lt;65 y)</td>
</tr>
<tr>
<td>• Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L]*)</td>
</tr>
<tr>
<td>• Metabolic syndrome (increased waist circumference, elevated triglycerides [&gt;175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 in women mg/dL] are factors; tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td>• Chronic kidney disease (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplant)</td>
</tr>
<tr>
<td>• Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS</td>
</tr>
<tr>
<td>• History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia</td>
</tr>
<tr>
<td>• High-risk race/ethnicities (e.g., South Asian ancestry)</td>
</tr>
</tbody>
</table>
### Table 6 continued

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Lipid/biomarkers</strong>: Associated with increased ASCVD risk</td>
</tr>
<tr>
<td>o Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);</td>
</tr>
<tr>
<td>o If measured:</td>
</tr>
<tr>
<td>▪ <strong>Elevated high-sensitivity C-reactive protein</strong> (≥2.0 mg/L)</td>
</tr>
<tr>
<td>▪ <strong>Elevated Lp(a)</strong>: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).</td>
</tr>
<tr>
<td>▪ <strong>Elevated apoB</strong> ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C &gt;160 mg/dL and constitutes a risk-enhancing factor</td>
</tr>
<tr>
<td>▪ <strong>ABI</strong> &lt;0.9</td>
</tr>
</tbody>
</table>