AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice.

Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied. These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. Medical professionals are encouraged to use this information in conjunction with, and not as a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual circumstances.

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Abbreviations:
4S = Scandinavian Simvastatin Survival Study; **A1C** = glycated hemoglobin; **AACE** = American Association of Clinical Endocrinologists; **AAP** = American Academy of Pediatrics; **ACC** = American College of Cardiology; **ACE** = American College of Endocrinology; **ACS** = acute coronary syndrome; **ADMIT** = Arterial Disease Multiple Intervention Trial; **ADVENT** = Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial; **AFCAPS/TexCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **AHA** = American Heart Association; **AHRQ** = Agency for Healthcare Research and Quality; **AIM-HIGH** = Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides trial; **ASCVD** = atherosclerotic cardiovascular disease; **ATP** = Adult Treatment Panel; **apo** = apolipoprotein; **BEL** = best evidence level; **BIP** = Bezafibrate Infarction Prevention trial; **BMI** = body mass index; **CABG** = coronary artery bypass graft; **CAC** = coronary artery calcification; **CARDS** = Collaborative Atorvastatin Diabetes Study; **CDP** = Coronary Drug Project trial; **CI** = confidence interval; **CIMT** = carotid intimal media thickness; **CKD** = chronic kidney disease; **CPG(s)** = clinical practice guideline(s); **CRP** = C-reactive protein; **CTT** = Cholesterol Treatment Trialists; **CV** = cerebrovascular; **CVA** = cerebrovascular accident; **EL** = evidence level; **FH** = familial hypercholesterolemia; **FIELD** = Secondary Endpoints from the Fenofibrate Intervention and Event Lowering in Diabetes trial; **FOURIER** = Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; **HATS** = HDL-Atherosclerosis Treatment Study; **HDL-C** = high-density lipoprotein cholesterol; **HeFH** = heterozygous familial hypercholesterolemia; **HHS** = Helsinki Heart Study; **HIV** = human immunodeficiency virus; **HoFH** = homozygous familial hypercholesterolemia; **HPS** = Heart Protection Study; **HPS2-THRIVE** = Treatment of HDL to Reduce the Incidence of Vascular Events trial; **HR** = hazard ratio; **HRT** = hormone replacement therapy; **hsCRP** = high-sensitivity CRP; **IMPROVE-IT** = Improved Reduction of Outcomes: Vytorin Efficacy International Trial; **IRAS** = Insulin Resistance Atherosclerosis Study; **JUPITER** = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; **LDL-C** = low-density lipoprotein cholesterol; **Lp-PLA2** = lipoprotein-associated phospholipase A2; **MACE** = major cardiovascular events; **MESA** = Multi-Ethnic Study of Atherosclerosis; **MetS** = metabolic syndrome; **MI** = myocardial infarction; **MRFIT** = Multiple Risk Factor Intervention Trial; **NCEP** = National Cholesterol Education Program; **NHLBI** = National Heart, Lung, and Blood Institute; **PCOS** = polycystic ovary syndrome; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **Post CABG** =

Post Coronary Artery Bypass Graft trial; **PROSPER** = Prospective Study of Pravastatin in the Elderly at Risk trial; **QALY** = quality-adjusted life-year; **ROC** = receiver-operator characteristic; **SOC** = standard of care; **SHARP** = Study of Heart and Renal Protection; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus; **TG** = triglycerides; **TNT** = Treating to New Targets trial; **VA-HIT** = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; **VLDL-C** = very low-density lipoprotein cholesterol; **WHI** = Women's Health Initiative

ABSTRACT

Objective: The development of these guidelines is mandated by the American Association of Clinical Endocrinologists (AACE) Board of Directors and American College of Endocrinology (ACE) Board of Trustees and adheres with published AACE protocols for the standardized production of clinical practice guidelines (CPGs).

Methods: Recommendations are based on diligent reviews of the clinical evidence with transparent incorporation of subjective factors, according to established AACE/ACE guidelines for guidelines protocols.

Results: The Executive Summary of this document contains 87 recommendations of which 45 are Grade A (51.7%), 18 are Grade B (20.7%), 15 are Grade C (17.2%), and 9 (10.3%) are Grade D. These detailed, evidence-based recommendations allow for nuance-based clinical decision-making that addresses multiple aspects of real-world medical care. The evidence base presented in the subsequent Appendix provides relevant supporting information for Executive Summary Recommendations. This update contains 695 citations of which 203 (29.2 %) are EL 1 (strong), 137 (19.7%) are EL 2 (intermediate), 119 (17.1%) are EL 3 (weak), and 236 (34.0%) are EL 4 (no clinical evidence).

Conclusion: This CPG is a practical tool that endocrinologists, other health care professionals, health-related organizations, and regulatory bodies can use to reduce the risks and consequences of dyslipidemia. It provides guidance on screening, risk assessment, and treatment recommendations for a range of individuals with various lipid disorders. The recommendations emphasize the importance of treating low-density lipoprotein cholesterol (LDL-C) in some individuals to lower goals than previously endorsed and support the measurement of coronary artery calcium scores and inflammatory markers to help stratify risk. Special consideration is given to individuals with diabetes, familial hypercholesterolemia, women, and youth with dyslipidemia. Both clinical and cost-effectiveness data are provided to support treatment decisions. **(Endocr Pract. 2017:Suppl2;23:1-87)**

I. INTRODUCTION

In 2016, approximately 660,000 U.S. residents will have a new coronary event (defined as a first hospitalized myocardial infarction [MI] or atherosclerotic cardiovascular disease [ASCVD] death), and approximately 305,000 will have a recurrent event. The estimated annual incidence of MI is 550,000 new and 200,000 recurrent attacks. The average age at first MI is 65.1 years for men and 72.0 years for women (1 [EL 4; NE]). Dyslipidemia is a primary, major risk factor for ASCVD and may even be a prerequisite for ASCVD, occurring before other major risk factors come into play. Epidemiologic data also suggest that hypercholesterolemia and perhaps coronary atherosclerosis itself are risk factors for ischemic cerebrovascular accident (CVA) (2 [EL 4; NE]). According to data from 2009 to 2012, >100 million U.S. adults ≥20 years of age have total cholesterol levels ≥200 mg/dL; almost 31 million have levels ≥240 mg/dL (1 [EL 4; NE]). Increasing evidence also points to insulin resistance—which results in increased levels of plasma triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) and a decreased concentration of high-density lipoprotein cholesterol (HDL-C)—as an important risk factor for peripheral vascular disease (3 [EL 2; PCS]), CVA, and ASCVD (4 [EL 2; PCS]).

Analysis of 30-year national trends in serum lipid levels shows improvements in total cholesterol and LDL-C levels. This may in part be explained by the steady increase in the use of lipid-lowering drug therapy (self-reported rate of lipid-medication use, 38%). However, 69% of U.S. adults have LDL-C concentrations above 100 mg/dL. Furthermore, the doubling in prevalence of individuals who have obesity, the high percentage with elevated TG levels (33%), and the correlation between obesity and elevated TG point to the need for continued vigilance on the part of physicians to reduce ASCVD risk (5 [EL 3; SS]).

This clinical practice guideline (CPG) is for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. The mandate for this CPG is to provide a practical guide for endocrinologists to reduce the risks and consequences of dyslipidemia. This CPG extends and updates existing CPGs available in the literature, such as the American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Dyslipidemia and Prevention of Atherosclerosis (6 [EL 4; NE]), and complements the AACE Diabetes Mellitus Comprehensive Care Plan CPG (7 [EL 4; NE]). The landmark National Cholesterol Education Program (NCEP) guidelines (8 [EL 4; NE]) serve as the backbone of these lipid recommendations.

This CPG is unique in that it supports the use of apolipoprotein (apo) B level and/or LDL particle concentration to refine efforts to achieve effective LDL-C lowering, provides screening recommendations for individuals of different ages, and identifies special issues for children

and adolescents. This CPG also discusses the challenges associated with atherosclerosis and heart disease that are specific to women. It continues to emphasize the importance of LDL-C lowering and supports the measurement of inflammatory markers to stratify risk in certain situations. Finally, this CPG presents an evaluation of the cost-effectiveness of lipid-lowering management.

This document is organized based on discrete clinical questions, with an Executive Summary of key recommendations followed by the supporting evidence base. The objectives of this CPG are to provide:

- An overview of the screening recommendations, assessment of risk, and treatment recommendations for various lipid disorders;
- Special consideration for individuals with diabetes, women, and children/adolescents with dyslipidemia; and
- Cost-effectiveness data to support therapeutic decision-making.

II. METHODS

This CPG was developed in accordance with the AACE Protocol for Standardized Production of Clinical Practice Guidelines (9 [EL 4; NE]). Reference citations in the text of this document include the reference number, numerical descriptor (EL 1-4), and semantic descriptor (explained in Table 1) (9 [EL 4; NE]).

All primary writers have made disclosures regarding multiplicities of interests and have attested that they are not employed by industry. In addition, all primary writers are AACE members and credentialed experts. Primary writers submitted contributions to specific clinical questions, which were subsequently reviewed, discussed, and integrated into the final document. This valuable input provides the basis for the recommendations herein. The

format of this CPG is based on specific and relevant clinical questions (labeled "Q").

Recommendations (labeled "R") are assigned Grades that map to the best evidence level (BEL) ratings based on the highest quality supporting evidence level (EL) (Tables 1 and 2; Figure 1) (9 [EL 4; NE]), all of which have also been rated based on scientific substantiation (Table 3) (9 [EL 4; NE]). Recommendation Grades are designated "A," "B," or "C" when there is scientific evidence available, or "D" when there is only expert opinion or a lack of conclusive scientific evidence. Technically, the BEL follows the recommendation Grade in the Executive Summary. Briefly, there are 4 intuitive levels of evidence: 1 = strong, 2 = intermediate, 3 = weak, and 4 = no evidence (Table 3). Comments may be appended to the recommendation Grade and BEL regarding any relevant subjective factors that may have influenced the grading process (Table 4) (9 [EL 4; NE]). Details regarding each recommendation may be found in the upcoming corresponding section of the CPG Evidence Base Appendix and will include a complete list of supporting References. Thus, the process leading to a final recommendation and grade is not rigid, but rather incorporates complex expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making, options, and individualization of care. This document is a guideline, and since individual circumstances and presentations differ, ultimate clinical management is based on what is in the best interest of the individual and involves his or her input ("patient-centered care") and reasonable clinical judgment by treating clinicians.

This CPG was reviewed and approved by the primary writers, other invited experts, the AACE Publications Committee, the AACE Board of Directors, and the ACE Board of Trustees before submission for peer review by *Endocrine Practice*. The efforts of all those involved are greatly appreciated.

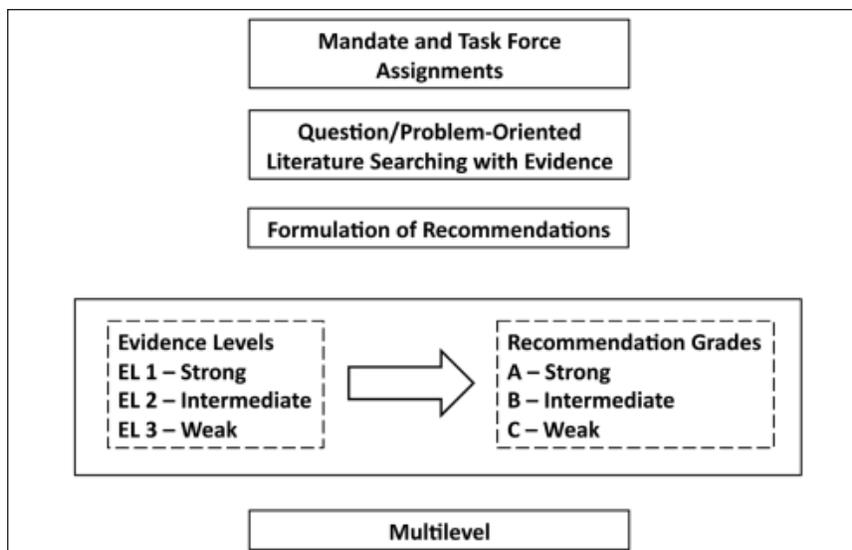| Table 1 2014 American Association of Clinical Endocrinologists Protocol for Production of Clincal Practice Guidelines - Step I: Evidence Rating[a]	
Numerical descriptor (evidence level)[b]	**Semantic descriptor**
1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trial (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling or database) (SS)
3	Consecutive case series (CCS)
3	Single case report (SCR)
4	No evidence (theory, opinion, consensus, review, or preclinical study) (NE)
[a] Adapted from: Endocr Pract. 2014;20:692-702 (9 [EL 4; NE]). [b] 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; 4 = no evidence.	

Fig. 1. 2014 American Association of Clinical Endocrinologists Clinical Practice Guideline Methodology. Current American Association of Clinical Endocrinologists Clinical Practice Guidelines have a problem-oriented focus that results in a shortened production timeline, middle-range literature searching, emphasis on patient-oriented evidence that matters, greater transparency of intuitive evidence rating and qualifications, incorporation of subjective factors into evidence level to recommendation grade mapping, cascades of alternative approaches, and an expedited multilevel review mechanism (9 [EL 4; NE]).

Table 2
2014 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step II: Evidence Analysis and Subjective Factors[a]

Study design	Data analysis	Interpretation of results
Premise correctness	Intent-to-treat	Generalizability
Allocation concealment (randomization)	Appropriate statistics	Logical
Selection bias		Incompleteness
Appropriate blinding		Validity
Using surrogate endpoints (especially in "first-in-its-class" intervention)		
Sample size (beta error)		
Null hypothesis vs. Bayesian statistics		
[a] Reprinted from: *Endocr Pract*. 2014;20:692-702 (9 [EL 4; NE]).		

Table 3
2014 American Association of Clinical Endocrinologists Protocol for
Production of Clinical Practice Guidelines—
Step III: Grading of Recommendations; How Different
Evidence Levels Can Be Mapped to the Same Recommendation Grade[a,b]

Best evidence level	Subjective factor impact	Two-thirds consensus	Mapping	Recommendation grade
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1, 2, 3, 4	NA	No	Adjust down	D

[a] Starting with the left column, best evidence levels (BELs), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA, not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).
[b] Reprinted from *Endocr Pract.* 2014;20:692-702 (9 [EL 4; NE]).

Table 4
2014 American Association of Clinical Endocrinologists
Protocol for Production of Clinical Practice Guidelines—
Step IV: Examples of Qualifiers That
May Be Appended to Recommendations[a]

Cost-effectiveness

Risk-benefit analysis

Evidence gaps

Alternative physician preferences (dissenting opinions)

Alternative recommendations ("cascades")

Resource availability

Cultural factors

Relevance (patient-oriented evidence that matters)

[a] Reprinted from *Endocr Pract.* 2014;20:692-702 (9 [EL 4; NE]).

III. EXECUTIVE SUMMARY

In this update, there are 87 Recommendations of which 45 are Grade A (51.7%), 18 are Grade B (20.7%), 15 are Grade C (17.2%), and 9 (10.3%) are Grade D. There is a greater percentage of Recommendations that are Grade A or B (72%) compared with those that are Grade C and Grade D (28%). The evidence base presented here provides relevant information for the recommendations in the Executive Summary.

3Q1. HOW SHOULD INDIVIDUALS BE SCREENED FOR THE DETECTION OF DYSLIPIDEMIA?

3Q1.1. Global Risk Assessment

- **R1.** Identify risk factors that enable personalized and optimal therapy for dyslipidemia (Table 5) (**Grade A; BEL 1**).

- **R2.** Based on epidemiologic studies, individuals with type 2 diabetes (T2DM) should be considered as high, very high, or extreme risk for ASCVD (Table 6) (**Grade B; BEL 3; upgraded due to high relevance**).

- **R3.** Based on epidemiologic and prospective cohort studies, individuals with type 1 diabetes (T1DM) and duration more than 15 years or with 2 or more major cardiovascular (CV) risk factors (e.g., albu-minuria, chronic kidney disease [CKD] stage 3/4, initiation of intensive control >5 years after diagnosis), poorly controlled hemoglobin A1C (A1C) or insulin resistance with metabolic syndrome should be considered to have risk-equivalence to individuals with T2DM (Table 7, see online Appendix/Evidence Base) (**Grade B; BEL 2**).

- **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 (Table 8) (**Grade C; BEL 4, upgraded due to cost-effectiveness**):
  - Framingham Risk Assessment Tool (https://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php)
  - Multi-Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD Risk with Coronary Artery Calcification Calculator (https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx)
  - Reynolds Risk Score, which includes high-sensitivity CRP (hsCRP) and family history of premature ASCVD) (http://www.reynoldsriskscore.org)
  - United Kingdom Prospective Diabetes Study (UKPDS) risk engine to calculate ASCVD risk in individuals with T2DM) (https://www.dtu.ox.ac.uk/riskengine)

Table 5 Major Atherosclerotic Cardiovascular Disease Risk Factors		
Major risk factors	**Additional risk factors**	**Nontraditional risk factors**
Advancing age[a-d] ⇧ Total serum cholesterol level[a,b,d] ⇧ Non–HDL-C[d] ⇧ LDL-C[a,d] Low HDL-C[a,d,e] Diabetes mellitus[a-d] Hypertension[a-d] Chronic kidney disease 3,4[h] Cigarette smoking[a-d] Family history of ASCVD[a,d,g]	Obesity, abdominal obesity[c,d] Family history of hyperlipidemia[d] ⇧ Small, dense LDL-C[d] ⇧ Apo B[d] ⇧LDL particle concentration Fasting/post-prandial hypertriglyceridemia[d] PCOS[d] Dyslipidemic triad[f]	⇧Lipoprotein (a) ⇧ Clotting factors ⇧ Inflammation markers (hsCRP; Lp-PLA$_2$) ⇧Homocysteine levels Apo E4 isoform ⇧ Uric acid ⇧ TG-rich remnants

Abbreviations: apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase; PCOS = polycystic ovary syndrome.
[a] Risk factors identified in the Framingham Heart study.
[b] Risk factors identified in the MRFIT study (Multiple Risk Factor Intervention Trial).
[c] Risk factors identified in the INTERHEART study.
[d] Risk factors identified in guidelines and position statements (National Cholesterol Education Program Adult Treatment Panel III, American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Position Statement, American Association of Clinical Endocrinologists Insulin Resistance Syndrome Position Statement, American Diabetes Association Standards of Care 2009, American Diabetes Association/American College of Cardiology Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk, National Lipid Association, Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing).
[e] Elevated HDL-C is a negative risk factor.
[f] Hypertriglyceridemia; low HDL-C; and an excess of small, dense LDL-C.
[g] Definite myocardial infarction 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.
[h] Based on a pooled analysis of community-based studies (N = 22,634).

- **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 (http://www.reynoldsriskscore.org) or the Framingham Risk Assessment Tool (http://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php) (Table 8) (**Grade C; BEL 4, upgraded due to cost-effectiveness**).

- **R6.** Dyslipidemia in childhood and adolescence should be diagnosed and managed as early as pos-

sible to reduce the levels of LDL-C that may eventually increase risk of CV events in adulthood (Table 9) (**Grade A; BEL 1**).

- **R7.** When the HDL-C concentration is >60 mg/dL, 1 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 (Table 10) (**Grade B; BEL 2**).

Table 6 Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals				
		Treatment goals		
Risk category	**Risk factors[a]/10-year risk[b]**	**LDL-C (mg/dL)**	**Non-HDL-C (mg/dL)**	**Apo B (mg/dL)**
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, 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% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 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; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not recommended; UKPDS = United Kingdom Prospective Diabetes Study. [a] Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C. [b] Framingham risk scoring is applied to determine 10-year risk. Reproduced with permission from Garber et al. *Endocr Pract.* 2017;23:207-238.				

3Q1.2. Screening
Familial Hypercholesterolemia
- **R9.** Individuals should be screened for familial hypercholesterolemia (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 dwyslipidemia (**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**).

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**).

Table 8 Key Cardiovascular Risk Scoring Tools: Framingham, MESA, Reynolds, and UKPDS		
Framingham Global Risk Risk factors included/questions	**Risk group/ Framingham Global Risk (10-year absolute ASCVD risk)**	**Clinical examples**
Risk assessment tool for calculating 10-year risk of having a heart attack for adults 20 and older who do not have heart disease or diabetes (using data from the Framingham Heart Study): Age: ☐ years Sex: ◯ Female ◯ Male Total cholesterol: ☐ mg/dL HDL cholesterol: ☐ mg/dL Smoker (in last month): ◯ No ◯ Yes Systolic blood pressure: ☐ mm Hg Are you currently on any medication to treat high blood pressure: ◯ No ◯ Yes [Calculate]	High >20%	• Established coronary artery disease • Cerebrovascular disease • Peripheral arterial disease • Abdominal aortic aneurysm • Diabetes mellitus • Chronic kidney disease
	Intermediate 10-20%	• Subclinical coronary artery disease • MetS • Multiple risk factors[a] • Markedly elevated levels of a single risk factor[b] • First-degree relative(s) with early onset coronary artery disease
	Lower <10%	• May include women with multiple risk factors, MetS, or 1 or no risk factors
	Optimal <10%	• Optimal levels of risk factors and heart-healthy lifestyle

- **High risk:** A greater than 20% risk that you will develop a heart attack or die from coronary disease in the next 10 years.
- **Intermediate risk:** A 10-20% risk that you will develop a heart attack or die from coronary disease in the next 10 years.
- **Low risk:** Less than 10% risk that you will develop a heart attack or die from coronary disease in the next 10 years.

[a] Patients with multiple risk factors can fall into any of the 3 categories by Framingham scoring.
[b] Most women with a single, severe risk factor will have a 10-year risk ≤10%.

Multi-Ethnic Study of Atherosclerosis (MESA) Risk factors included/questions	**Risk calculation outcomes**
MESA 10-Year ASCVD risk with coronary artery calcification: Sex: Male ◯ Female ◯ Age (45-85 years): ☐ years Coronary artery calcification: ☐ Agatston Race/ethnicity (choose one): ◯ Caucasian ◯ Chinese ◯ African American ◯ Hispanic Diabetes: Yes ◯ No ◯ Currently smoke: Yes ◯ No ◯ Family history of heart attack: Yes ◯ No ◯ Total cholesterol: ☐ mg/dL HDL cholesterol: ☐ mg/dL Systolic blood pressure: ☐ mm Hg Lipid-lowering medication: Yes ◯ No ◯ Hypertension medication: Yes ◯ No ◯ [Calculate 10-year ASCVD risk]	• External validation provided evidence of very good discrimination and calibration • Harrell's C-statistic ranged from 0.779 to 0.816 in validation against existing studies • The difference in estimated 10-year risk between events and nonevents was approximately 8-9%, indicating excellent discrimination • Mean calibration found average predicted 10-year risk within 1/2 of a percent of the observed event rate • The test predicts 10-year risk of a ASCVD event

- **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 sex; 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 ele-

Table 8 *Continued*	
Reynolds Risk Score **Risk factors included/questions**	**Risk calculation outcomes**
Reynolds Risk Score predicts 10-year risk of heart attack, CVA, or other major heart diseases in healthy people without diabetes. Age [____] Years (≤80) Currently smoke? ◯ Yes ◯ No Systolic blood pressure [____] mm Hg Total cholesterol [____] mg/dL or [____] mmol/L HDL cholesterol [____] mg/dL or [____] mmol/L hsCRP [____] mg/L Mother or father have heart attack ◯ Yes ◯ No before age 60? [Calculate 10-year risk]	• Compared to ATP III/Framingham 10-year risk categorization: ○ Very little change in categorization of individuals with very low (<5%) risk ○ 30% reclassification of those classified as 5% to <10% risk according to ATP III ○ 29% reclassification of those classified as 10% to <20% risk according to ATP III ○ 25% reclassification of those classified as ≥20% risk according to ATP III • Risk is classified as low (<5%), low to moderate (5% to <10%), moderate to high (10% to <20%), and high (≥20%) ASCVD Risk
UKDPS Risk Score **Risk factors included/questions**	**Risk calculation outcomes**
UKPDS risk engine is a model for estimating risk of ASCVD in persons with T2DM (this risk is up to 3x greater than for the general population) Age [____] years Weight [____] kg Height [____] cm Sex ◯ Male ◯ Female HDL cholesterol [____] mmol/L Total cholesterol [____] mg/L Systolic blood pressure [____] mm Hg Smoker ◯ Yes ◯ No Afro-Caribbean ethnicity? ◯ Yes ◯ No A1C [____] % Time period (duration of [____] years: (4, 5, 6, 7, 8, 9, 10, 15, 20) diabetes) Regular exercise per week: [____] # of times (1, 2, 3, 4, >5) [Calculate risk]	• Survival rates predicted by UKPDS Risk Score model were similar to rates observed in the UKPDS trial, well within non-parametric confidence intervals • Predicted survival rates adjust for A1C, blood pressure, and lipid risk factors • The UKPDS Risk Engine provides risk estimates and 95% confidence intervals in individuals with T2DM not known to have heart disease for: - Nonfatal and fatal coronary heart disease - Fatal coronary heart disease - Nonfatal and fatal CVA - Fatal CVA
Abbreviations: A1C = hemoglobin A1C; ATP III = Adult Treatment Panel III; ASCVD = atherosclerotic cardiovascular disease; A1C = glycated hemoglobin; CVA = cerebrovascular accident; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; ln = natural logarithm; MetS = metabolic syndrome; MI = myocardial infarction; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study.	

Table 9
Classification of LDL-C Levels in
Children and Adolescents

Category	LDL-C, mg/dL
Acceptable	<100
Borderline	100-129
High	≥130
Abbreviation: LDL-C = low-density lipoprotein cholesterol	

Table 10
Classification of Elevated TG Levels

TG category	TG concentration, mg/dL	Goal
Normal	<150	
Borderline-high	150-199	<150 mg/dL
High	200-499	
Very high	≥500	
Abbreviation: TG = triglycerides		

ments of the insulin resistance syndrome, or have a family history of premature ASCVD (**Grade B; BEL 3, upgraded due to cost-effectiveness**).

3Q2. WHICH SCREENING TESTS ARE RECOMMENDED FOR THE DETECTION OF CARDIOVASCULAR RISK?

3Q2.1. 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**).

3Q2.2. 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 and invalid when TG levels are greater than 200 mg/dL and 400 mg/dL, respectively (**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**).

3Q2.3. HDL-C
- **R23.** Measurement of HDL-C should be included in screening tests for dyslipidemia (**Grade B; BEL 2**).

3Q2.4. Non-HDL-C
- **R24.** The non-HDL-C (total cholesterol – 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, the non-HDL-C should be evaluated to gain useful information regarding the individual's total atherogenic lipoprotein burden (**Grade D**).

3Q2.5. TG
- **R26.** TG levels should be part of routine lipid screening: moderate elevations (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome and levels ≥200 mg/dL may identify individuals at substantially increased ASCVD risk (**Grade B; BEL 2**).

3Q2.6. 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 the 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**).

3Q2.7. Secondary Causes of Dyslipidemia
- **R29.** Rule out secondary causes of dyslipidemia (Table 11) (**Grade B; BEL 2**).

3Q2.8. Additional Tests
- **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 <130 mg/dL (**Grade B; BEL 2**).

- **R31.** Measure lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$), 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**).

- **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**).

- **R33.** Coronary artery calcification (CAC) measurement has been shown to be of high predictive value and is useful in refining risk stratification to deter-

Table 11 Common Secondary Causes of Dyslipidemia	
Affected lipids	**Conditions**
↑ Total cholesterol and LDL-C	• Hypothyroidism
	• Nephrosis
	• Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma)
	• Progestin[a] or anabolic steroid treatment
	• Cholostatic diseases of the liver due to abnormal lipoproteins, as in primary biliary cirrhosis
	• Protease inhibitors for treatment of HIV infection[b]
↑ TG and VLDL-C	• Chronic renal failure
	• T2DM[c]
	• Obesity
	• Excessive alcohol intake
	• Hypothyroidism
	• Antihypertensive medications (thiazide diuretics and β-adrenergic blocking agents)
	• Corticosteroid therapy (or severe stress that increases endogenous corticosteroids)
	• Orally administered estrogens[d], oral contraceptives, pregnancy
	• Protease inhibitors for treatment of HIV infection[b]

Abbreviations: HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; T2DM = type 2 diabetes mellitus; TG = triglycerides
[a] Progestational agents, especially those with androgenic activity, can increase LDL-C and decrease HDL-C.
[b] Protease inhibitors can induce peripheral lipodystrophy, increased visceral fat, insulin resistance, and diabetes. Protease inhibitor-induced dyslipidemia may include elevated LDL-C and/or the atherogenic dyslipidemia pattern of high TG; small, dense, LDL-C; and low HDL-C. However, newer generation protease inhibitors may have improved lipid profiles.
[c] Diabetic dyslipidemia is often similar to atherogenic dyslipidemia: high TG, small, dense LDL-C, and low HDL-C.
[d] Transdermally administered estrogens are not associated with increased TG levels.

mine the need for more aggressive treatment strategies (**Grade B; BEL 2**).

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

3Q3. WHAT ARE THE TREATMENT RECOMMENDATIONS IN INDIVIDUALS WITH DYSLIPIDEMIA AND ASCVD RISK?

3Q3.1. Treatment Goals
• **R35.** Treatment goals for dyslipidemia should be personalized according to levels of risk (Tables 6 and 11) (**Grade A; BEL 1**).

• *3Q3.1.1. Risk Categories and LDL-C Goals (Table 6)*
• **R36.** For individuals at __low risk__ (i.e., with no risk factors), an LDL-C goal <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 <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 <100 mg/dL is recommended (**Grade A; BEL 1**).

• **R39.** For individuals at __very high risk__ (i.e., with established or recent hospitalization for acute coronary syndrome (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 heterozygous familial hypercholesterolemia [HeFH]), an LDL-C goal <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 <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 <55 mg/dL is recommended (**Grade A; BEL 1**).

- **R41.** An LDL-C goal <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) (Table 9) (**Grade D**).

- *3Q3.1.2. HDL-C*
  - **R42.** HDL-C should be >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**).

- *3Q3.1.3. Non-HDL-C*
  - **R43.** For most individuals, a non-HDL-C goal (total cholesterol – HDL-C) 30 mg/dL higher than the individual's specific LDL-C goal is recommended (Table 12) (**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 (Table 12) (**Grade A; BEL 1**).

- *3Q3.1.4. Apolipoproteins*
  - **R45.** For individuals at increased risk of ASCVD, including those with diabetes, an optimal apo B goal is <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 <80 mg/dL, and for individuals at extreme risk, an optimal apo B goal is <70 mg/dL (Table 12) (**Grade A; BEL 1**).

- *3Q3.1.5 TG*
  - **R46.** TG goals <150 mg/dL are recommended (Table 12) (**Grade A; BEL 1**).

3Q3.2. Treatment Recommendations
  - **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**).

- *3Q3.2.1. 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

Table 12 Lipid Goals for Patients at Risk for Atherosclerotic Cardiovascular Disease[a]	
Lipid parameter	**Goal (mg/dL)**
TC	<200
LDL-C	<130 (low risk) <100 (moderate risk) <100 (high risk) <70 (very high risk) <55 (extreme risk)
Non-HDL-C	30 above LDL-C goal; 25 above LDL-C goal (extreme risk patients)
TG	<150
Apo B	<90 (patients at high risk of ASCVD, including those with diabetes) <80 (patients at very high risk with established ASCVD or diabetes plus ≥1 additional risk factor) <70 (patients at extreme risk)
Abbreviations: apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides [a] See text for references and evidence levels.	

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**).

- *3Q3.2.2. 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**).

- *3Q3.2.3. Smoking Cessation*
  - **R54.** Tobacco cessation should be strongly encouraged and facilitated (**Grade A; BEL 2; upgraded due to potential benefit**).

- *3Q3.2.4. Pharmacologic Therapy*
  - **R55.** In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals (Table 13) (**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 to target an even lower LDL-C treatment goal of <55 mg/dL (Table 6) (**Grade A, BEL 1**).

Fibrates

- **R61.** Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL) (Table 13) (**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 are <40 mg/dL (**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**).

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 benefits with well-controlled LDL-C (**Grade A; BEL 1**).

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**).

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**).

Table 13 Primary Lipid-Lowering Drug Classes		
Drug class	**Metabolic effect[a]**	**Main considerations[b]**
HMG-CoA reductase inhibitors (statins: lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, pitavastatin)	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%)	Liver function test prior to therapy and as clinically indicated thereafter. Myalgias and muscle weakness in some patients 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 co-administration of some drugs (see product labeling). Simvastatin dosages of 80 mg are no longer recommended. 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 patients treated with statins; however, it is dose-related, occurs primarily in patients 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.
Cholesterol absorption inhibitors (ezetimibe)	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	Myopathy/rhabdomyolysis (rare) Myopathy/rhabdomyolysis (rare) When co-administered with statins or fenofibrate, risks associated with those drugs remain (e.g., myopathy/rhabdomyolysis, cholelithiasis)
PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors (alirocumab, evolocumab)	↓LDL-C 48-71%, ↓ non-HDL-C 49-58%, ↓Total-C 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	Requires subQ self-injection, and refrigeration is generally needed. Adverse reactions resulted in discontinuation in 2.2% overall, 1.2% more than placebo for evolocumab, and 5.3% overall, 0.2% more than placebo for alirocumab. Overall levels of adverse reactions and discontinuation very low. Adverse reactions with significantly different rates between drug and placebo were local injection site reactions (1.9% greater for alirocumab vs. placebo, 0.7% greater for evolocumab vs. placebo) and influenza (1.2% greater for alirocumab vs. placebo, 0.2% for evolocumab vs. placebo). The most common adverse reactions with similar rates for drug vs. placebo were for the following: Alirocumab (4-12%; most common to least common): nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia; Evolocumab (2-4%; most common to least common): Nasopharyngitis, back pain, and upper respiratory tract infection.

Table 13 *Continued*		
Fibric acid derivatives (gemfibrozil, fenofibrate, fenofibric acid)	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	Gemfibrozil may ↑ LDL-C 10-15%. GI symptoms, possible cholelithiasis. May potentiate effects of orally administered anticoagulants. Gemfibrozil may ↑ fibrinogen level[c]. Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations[d]. Myopathy/rhabdomyolysis when used with statin (uncommon with gemfibrozil, but increased risk with all statins except fluvastatin); interaction less likely with fenofibrate or fenofibric acid (no apparent difference by statin). Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction. Fenofibrate dose should be cut by two-thirds and gemofibrozil by one-half when eGFR is 15-60, and fibrates should be avoided when eGFR is <15. May cause muscle disorders. Can improve diabetic retinopathy.
Niacin (nicotinic acid)	↓ 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	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.
Bile acid sequestrants (cholestyramine, colestipol, colesevelam hydrochloride)	Primarily ↓ LDL-C 15-25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDLR upregulation) Colesevelam ↓ glucose and hemoglobin A1C (~0.5%); is FDA approved to treat T2DM	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
MTP inhibitor (lomitapide)	↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in patients with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL	Can cause increases in transaminases (ALT, AST). Monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to initiation, and of ALT and AST during treatment, is required per FDA REMS. 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.

Table 13 *Continued*		
Antisense apolipoprotein B oligonucleotide (mipomersen via subQ injection)	↓ LDL-C 21%, TC 19%, apo B 24%, and non-HDL-C 22% in patients with HoFH by degrading mRNA for apo B-100, the principal apolipoprotein needed for hepatic synthesis of VLDL (and subsequent intraplasma production of IDL and LDL)	Can cause increases in transaminases (ALT, AST). Monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to 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.
Omega-3 fatty acids (icosapent ethyl, omega-3-acid ethyl esters)	↓ 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-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity Icosapent ethyl ↓ LDL-C 5%, whereas omega-3-acid ethyl esters ↑ LDL-C 45%	TG levels should be carefully assessed prior to initiating therapy and periodically during therapy. Omega-3-acid ethyl esters can increase LDL-C levels. Monitoring of LDL-C levels during treatment is recommended. May prolong bleeding time. Periodic monitoring of coagulation status should be undertaken in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation. Periodic monitoring of ALT and AST levels during treatment is recommended for patients with hepatic impairment. Some patients may experience increases in ALT levels only. Caution should be exercised when treating patients with a known hypersensitivity to fish and/or shellfish. 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 AF, 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. The most common adverse events in patients receiving omega-3 fatty acids included arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%). Patients may also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus. Omega-3 fatty acids should be used with caution in nursing mothers and should only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm.

Abbreviations: AF = atrial fibrillation; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; apo = apolipoprotein; eGFR = estimated glomerular filtration rate; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; HMG-CoA = hydroxymethylglutaryl-coenzyme A; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; MTP = microsomal triglyceride transfer protein; REMS = Risk Evaluation and Mitigation Strategies; subQ = subcutaneous; TC = total cholesterol; TG = triglycerides; VLDL-C, very low-density lipoprotein cholesterol

[a] Percentage of change varies depending on baseline lipid variables and dosages. Statin potency and dosages vary.
[b] Most frequent or serious; See prescribing information for complete contraindications, warnings, precautions, and side effects.
[c] Results vary. Gemfibrozil has been shown to decrease, have no effect on, or increase fibrinogen depending on the study.
[d] Results vary. Gemfibrozil has been shown to have no effect on or increase homocysteine.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) Inhibitors

- **R69.** 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**).

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**).

Special Considerations: Women

- **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**).

Special Considerations: Children and Adolescents

- **R74.** Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, 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 the insulin resistance syndrome

3Q3.3. Follow-up and Monitoring

- **R75.** Re-assess 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**).

3Q4. IS TREATMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE 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, co-administered 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**).

IV. APPENDIX: EVIDENCE BASE

In this update, there are 695 citations of which 203 (29.2 %) are EL 1 (strong), 137 (19.7%) are EL 2 (intermediate), 119 (17.1%) are EL 3 (weak), and 236 (34.0%) are EL 4 (no clinical evidence). There is a greater percentage

of references that are EL 1 or 2 in the 2017 update: 340/695 (49%), which is 8% higher compared with 246/606 (41%) in the 2012 AACE CPG (6 [EL 4; NE]). The evidence base presented here provides relevant information for the recommendations in the Executive Summary.

4Q1. HOW SHOULD INDIVIDUALS BE SCREENED FOR THE DETECTION OF DYSLIPIDEMIA?

4Q1.1. Global Risk Assessment

The third report of the NCEP ATP (Adult Treatment Panel) categorizes ASCVD risk based on a system of risk factor counting and 10-year risk according to Framingham risk scoring (10 [EL 4; NE]). In addition, the American Diabetes Association (ADA)/American College of Cardiology (ACC) 2008 Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk establishes risk categorization for individuals with diabetes (11 [EL 4; NE]). An overview of accepted ASCVD risk categories and factors is outlined in Table 5 (10 [EL 4; NE]; 11 [EL 4; NE]; 12 [EL 2; PCS]; 13 [EL 2; PCS]; 14 [EL 4; NE]; 15 [EL 4; NE]; 16 [EL 4; NE]; 17 [EL 2; MNRCT]; 18 [EL 2; PCS]; 19 [EL 4; NE]; 20 [EL 3; SS]; 21 [EL 1; MRCT]; 22 [EL 4; NE]) and Table 6 (10 [EL 4; NE]; 11 [EL 4; NE]; 17 [EL 2; MNRCT]; 23 [EL 4; NE]; 24 [EL 3; SS]; 25 [EL 1; RCT]; 26 [EL 1; RCT]; 27 [EL 1; RCT]; 28 [EL 4; NE]; 29 [EL 2; PCS]; 30 [EL 1; RCT]; 31 [EL 4; NE]; 32 [EL 4; NE]; 33 [EL 3; SS]; 34 [EL 1; MRCT]; 35 [EL 1; RCT]; 36 [EL 3; SS]). Several risk calculators are presented in Table 8 (229 [EL 3; SS]; 30 [EL 2; PCS]; 33 [EL 3; SS]; 36 [EL 3; SS]; 37 [EL 4; NE]; 38 [EL 4; NE]; 39 [EL 4; NE]; 40 [EL 4; NE]; 41 [EL 4; NE]). The remainder of this section will review these major ASCVD risk factors, as well as important nontraditional risk factors.

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 (42 [EL 4; NE]; 43 [EL 3; SS]). The Framingham Heart Study and the MRFIT trial (Multiple Risk Factor Intervention Trial) showed that approximately 85% of excess risk for premature ASCVD is due to 1 or more major risk factor(s) (12 [EL 2; PCS]; 14 [EL 4; NE]). The INTERHEART trial, which gathered data on 29,972 individuals in 52 countries, identified 9 ASCVD risk factors that, taken together, accounted for 90% of MI risk. However, 5 of those risk factors (smoking, lipids, hypertension, diabetes, and obesity) constituted a full 80% of observed risk (18 [EL 2; PCS]). Guidelines and position statements such as the American College of Endocrinology (ACE) Position Statements on polycystic ovary syndrome

(PCOS) and the insulin resistance syndrome (available at http://www.aace.com) also identify other risk factors as having significant associations with ASCVD (15 [EL 4; NE]; 19 [EL 4; NE]). Based on available evidence, Table 5 outlines the most important, current major, additional, and nontraditional ASCVD risk factors.

Advancing Age

Men 45 years and older and women 55 years and older have an increased risk of ASCVD; ASCVD occurs most commonly among individuals 65 years and older (10 [EL 4; NE]).

High LDL-C and Total Cholesterol

The association between high serum cholesterol levels, especially high LDL-C, and ASCVD is causal and independent of other risk factors (44 [EL 4; NE]; 45 [EL 2; PCS]; 46 [EL 4; NE]; 47 [EL 2; PCS]). The CARE trial (Cholesterol and Recurrent Events) determined that LDL-C-attributable risk is not linear and increases sharply within higher ranges (48 [EL 1; RCT]). The MRFIT study found a strong and progressive relationship between elevated total cholesterol levels and death of ASCVD (13 [EL 2; PCS]).

Since multiple studies have demonstrated that lowering LDL-C results in decreased ASCVD risk (25 [EL 1; RCT]; 26 [EL 1; RCT]; 27 [EL 1; RCT]; 49 [EL 1; RCT]; 50 [EL 1; RCT]; 51 [EL 1; RCT]; 52 [EL 1; RCT]; 53 [EL 1; RCT]; 54 [EL 1; RCT]; 55 [EL 1; RCT]; 56 [EL 2; PCS]), the focus of risk prediction and reduction has shifted toward LDL-C management in ASCVD and primary prevention in individuals with multiple risk factors (10 [EL 4; NE]).

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is caused by genetic mutations passed on by one (heterozygous, HeFH) or both parents (homozygous, HoFH) (57 [EL 4; NE]). A parental history of heart disease or MI has been established as an independent risk factor for ASCVD (58 [EL 3; CSS]; 59 [EL 3; CSS]; 60 [EL 3; SS]). It has been estimated that 77% of individuals with ASCVD and 54% of their first- and second-degree relatives express genetically linked dyslipidemia. Moreover, ASCVD risk is approximately 50% in siblings of individuals with premature ASCVD (61 [EL 4; NE]). In addition, studies of asymptomatic individuals indicate that a positive family history of ASCVD increases the risk of subclinical atherosclerosis (CAC and CIMT) compared with risk of individuals without a positive family history (62 [EL 3; CSS]; 63 [EL 3; CSS]; 64 [EL 3; CSS]).

HoFH is quite uncommon; although it was previously thought to affect 1 in 1 million people, recent prevalence estimates are between 1 in 160,000 and 1 in 250,000 (65 [EL 4; NE]; 66 [EL 4; NE]). Individuals with HoFH

have extremely high LDL-C levels, above 500 mg/dL, and premature cardiovascular risk; many individuals with HoFH experience their first coronary event as children or adolescents (68 [EL 4; NE]). HeFH is more common and also more frequently occurring than once believed. Recent data indicate that HeFH prevalence is 1 in 200 or 1 in 250, as opposed to 1 in 500 as previously reported (66 [EL 4; NE]). Individuals with HeFH can present with LDL-C levels ranging from 90 to 500 mg/dL. HeFH is also associated with premature ASCVD; on average, individuals with HeFH experience their first coronary event at age 42, which is about 20 years younger than the general population (68 [EL 4; NE]).

FH diagnostic criteria include lipid levels and family history, physical symptoms (if any), and genetic analysis (if available) (66 [EL 4; NE]). Three of the clinical diagnostic tools that are available are: the Simon Broome Register Diagnostic Criteria, the Dutch Lipid Clinic Network Diagnostic Criteria, and the US Make Early Diagnoses Prevent Early Deaths Program Diagnostic Criteria (MEDPED) 67 [EL 4; NE], 68 [EL 4; NE]). 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 younger than 40 years of age, or a family history of high cholesterol and/or premature ASCVD (66 [EL 4; NE]). Although it is an important risk factor, familial history is often overlooked during evaluations of individual cardiovascular risk. A family history of ASCVD, however, is both highly predictive and typically easy to determine by direct inquiry. While genetic testing may identify FH, it is not commonly used in the U.S. due to cost and lack of payer coverage (66 [EL 4; NE]).

FH is due to mutations causing partial or full dysfunction of LDL receptor activity; this results in increased plasma LDL-C levels and increased ASCVD risk (69 [EL 4; NE]). Individuals with HoFH often present with LDL-C levels >500 mg/dL, while individuals with HeFH typically present with LDL-C levels between 155 and 500 mg/dL (66 [EL 4; NE]). Early treatment is recommended for all individuals with FH, with a goal of reducing LDL-C levels by 50% from baseline (66 [EL 4; NE]).

Clinical trial data indicate that the use of PCSK9 inhibitors can significantly lower LDL-C compared to placebo, by up to 61% in individuals with HeFH and 39% in individuals with HoFH (69 [EL 4; NE]; 70 [EL 1; RCT]) The use of PCSK9 inhibitors in combination with statins is recommended to lower LDL-C in individuals with HF (70 [EL 1; RCT]; 71 [EL 1; RCT]; 72 [EL 4; NE]). Individuals with HeFH and a history of ASCVD or with a first-degree relative with premature ASCVD are considered at extreme risk and should have an LDL-C goal <55 mg/dL. (35 [EL 1; RCT])

Low HDL-C

Low HDL-C is associated with hypertriglyceridemia, T2DM, having overweight or obesity, physical inactivity, cigarette smoking, very high carbohydrate intake, certain drugs (beta-adrenergic blockers, anabolic steroids, progestational agents), and genetic factors (10 [EL 4; NE]). Low HDL-C can act synergistically with other lipid risk factors to increase ASCVD risk. For example, the ratio of total cholesterol or LDL-C to HDL-C may be a clinically valuable and potentially sensitive marker of ASCVD risk (73 [EL 4; NE]; 74 [EL 2; PCS]; 75 [EL 2; PCS]). A re-analysis of data from the Treating to New Targets (TNT) trial found that both ratios of total cholesterol to HDL-C and LDL-C to HDL-C were highly predictive of major cardiovascular event risk (76 [EL 1; RCT]), while a clinical study of 258 normotensive, nondiabetic individuals with overweight determined that a TG to HDL-C ratio 2.4 or higher was predictive of the presence of insulin resistance (77 [EL 3; CSS]). In addition, low HDL-C was a significant predictor of cardiovascular risk in all treatment groups, including individuals with the lowest (<70 mg/dL) LDL-C levels (76 [EL 1; RCT]).

The atherogenicity of low HDL-C can depend on both genetic and environmental factors. For example, the apo AI Milano trait, first isolated in a small community in Northern Italy, is marked by very low HDL-C and high TG levels. Carriers of this trait do not show signs of atherosclerosis typically associated with this lipid profile (78 [EL 3; SS]; 79 [EL 3; SS]). In fact, a normal apo AI level in an individual with low HDL-C may be an indication of less risk, as this suggests the presence of an adequate number of HDL-C particles that contain less cholesterol (80 [EL 4; NE]).

High HDL-C as a Negative Risk Factor

An HDL-C concentration greater than 60 mg/dL is an independent negative risk factor in both sexes, and when HDL-C is greater than 60 mg/dL, 1 risk factor can be subtracted from an individual's overall risk profile (10 [EL 4; NE]; 81 [EL 2; PCS]; 82 [EL 2; MNRCT]; 83 [EL 2; PCS]). An analysis of 4 large epidemiologic studies suggests that each 1 mg/dL increase in HDL-C is associated with a decrease in ASCVD risk of 2% in men and 3% in women (82 [EL 2; MNRCT]). The cardioprotective effect of HDL-C may be due to its role in reverse cholesterol transport and other mechanisms such as the ability of HDL-C to prevent LDL oxidation (84 [EL 4; NE]; 85 [EL 4; NE]).

Research shows a strong predictive link between HDL-C levels and longevity; healthy older individuals tend to have higher HDL-C levels than younger individuals, regardless of the younger individuals' ASCVD status (86 [EL 2; PCS]; 87 [EL 3; CSS]; 88 [EL 3; CSS]; 89 [EL 4; NE]). These results apply to the general population, though a high HDL-C concentration may not confer cardioprotection for every individual (90 [EL 4; NE]).

T2DM

The presence of T2DM is considered an ASCVD risk equivalent; therefore, individuals with diabetes are considered to be at high, very high, or extreme risk. Approximately 65% of diabetes-related mortality is due to heart disease and CVA. In comparison with individuals who do not have diabetes, individuals with T2DM have a significantly increased risk of ASCVD. For example, individuals with diabetes plus a previous MI have been shown to have a 2.5-fold greater risk of subsequent ASCVD events than individuals with ASCVD but no diabetes (91 [EL 4; NE]; 92 [EL 4; NE]). Epidemiologic data from Finland similarly suggest that individuals with T2DM and no history of MI have cardiovascular risk (fatal MI, nonfatal MI, CVA, or overall cardiovascular mortality) equivalent to those without diabetes and a history of MI. This same study found that individuals with T2DM and previous MI were at the highest risk, with a 7-year fatal or nonfatal MI incidence of 45% (93 [EL 3; CSS]). The Emerging Risk Factors Collaboration (94 [EL 3; CSS]) is a larger, more recent study showing similar evidence of diabetes as a CV risk equivalent.

In addition to hyperglycemia, individuals with T2DM commonly have other risk factors including hypertension; low HDL-C; hypertriglyceridemia; small, dense LDL-C; a procoagulant state; and/or a pro-inflammatory milieu (22 [EL 4; NE]; 92 [EL 4; NE]; 95 [EL 4; NE]; 96 [EL 4; NE]; 97 [EL 2; PCS]; 98 [EL 3; CSS]; 99 [EL 4; NE]). Based on this level of increased risk, the NCEP ATP III and ADA/ACC Consensus Statement consider individuals with T2DM to manifest an ASCVD equivalent (a 10-year risk of ASCVD events that is equal to that of individuals with established ASCVD) and therefore be at high risk (10 [EL 4; NE]; 11 [EL 4; NE]). Furthermore, the ADA/ACC categorizes individuals with diabetes and 1 or more additional risk factor as "very high risk" (11 [EL 4; NE]). Individuals with prediabetes (impaired fasting glucose and/or impaired glucose tolerance), especially those with MetS, are considered to be at increased risk for ASCVD. Lipid treatment goals for these individuals should be the same as those with diabetes (100 [EL 4; NE]).

T1DM

Approximately 90% of individuals with diabetes have T2DM; therefore most data on lipid disorders and diabetes relate to those with T2DM. However, T1DM is also associated with increased ASCVD risk, especially after 15 years' duration (101 [EL 3; CSS]; 102 [EL 2; PCS]; 103 [EL 2; PCS]; 104 [EL 2; PCS]; 105 [EL 2; PCS]; 106 [EL 4; NE]). Individuals with T1DM often do not have insulin resistance or its features such as a low HDL-C level or high TG. In fact, their HDL-C levels are typically higher than those in the general population (107 [EL 4; NE]; 108 [EL 4; NE]). Nonetheless, individuals with T1DM tend to develop atherosclerosis earlier than otherwise healthy indi-

viduals; have accelerated progression of coronary events, CVA, and peripheral arterial disease; and have higher associated mortality (109 [EL 3; CSS]; 110 [EL 3; SS]; 111 [EL 2; RCCS]; 112 [EL 3; SS]; 113 [EL 3; CCS]; 114 [EL 3; CSS]; 115 [EL 4; NE]). The Pittsburgh Epidemiology of Diabetes Complications Study and EURODIAB study found a similarly high prevalence of ASCVD among individuals with T1DM in both the U.S. (8.0% in men, 8.5% in women) and Europe (8.6% in men, 7.4% in women) (103 [EL 2; PCS]; 104 [EL 2; PCS]; 113 [EL 3; CSS]). Several studies of individuals with T1DM have suggested other factors that may increase risk for ischemic ASCVD:

- Albuminuria (117 [EL 2; PCS]),
- Late-onset T1DM (older than 30 years) without nephropathy, but with:
  - Initiation of intensive control more than 5 years after diagnosis (102 [EL 2; PCS]; 118 [EL 2; PCS]),
  - Duration of disease greater than 15 years (101 [EL 3; CSS]; 102 [EL 2; PCS]; 103 [EL 2; PCS]; 104 [EL 2; PCS]; 105 [EL 2; PCS]; 106 [EL 4; NE]),
  - Previous history of MI, *or*
  - Poorly controlled A1C (101 [EL 3; CSS]),
- Insulin resistance or MetS (119 [EL 3; SS]), and
- An hsCRP concentration greater than 3.0 mg/L (120 [EL 3; CSS])

Given the risks associated with T1DM and ASCVD, dyslipidemia in this population must not be overlooked and should be treated aggressively. Recommended optimal lipid levels for these individuals are outlined in Table 12 (11 [EL 4; NE]; 17 [EL 2; MNRCT]; 25 [EL 1; RCT]; 26 [EL 1; RCT]; 27 [EL 1; RCT]; 30 [EL 1; RCT]; 31 [EL 4; NE]; 34 [EL 1; MRCT]; 35 [EL 1; RCT]; 121 [EL 1; MRCT]).

Individuals with T1DM for more than 15 years or with 2 or more CV risk factors should be treated as if they had T2DM (101 [EL 3; CSS]; 102 [EL 2; PCS]; 103 [EL 2; PCS]; 104 [EL 2; PCS]; 105 [EL 2; PCS]; 106 [EL 4; NE]).

For a more comprehensive review of the treatment of diabetes, see the 2015 AACE and ACE Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (122 [EL 4; NE]).

Hypertension

Hypertension increases ASCVD risk independently of other risk factors, and this risk increases as blood pressure rises (16 [EL 4; NE]). Available evidence strongly suggests that insulin resistance predisposes individuals to hypertension (28 [EL 4; NE]), and epidemiologic studies show a very high correlation between hypertension and dyslipidemia (10 [EL 4; NE]).

Even mild elevations in blood pressure can increase risk. In individuals aged 40 to 70 years with a blood pressure starting at 115/75 mm Hg, ASCVD risk doubles with each increase of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure (16 [EL 4; NE]). Blood pressure-lowering therapy has been associated with significant decreases in the incidence rates of MI (20-25%), CVA (35-40%), and heart failure (>50%) (16 [EL 4; NE]); however, hypertension may remain an ASCVD risk factor even when normalized with treatment (123 [EL 4; NE]; 124 [EL 2; PCS]; 125 [EL 3; SS]; 126 [EL 2; PCS]). A thorough evaluation of blood pressure, either through 24-hour or home blood pressure monitoring, provides the most accurate results and may be warranted for certain individuals (16 [EL 4; NE]; 28 [EL 4; NE]; 83 [EL 2; PCS]; 127 [EL 2; PCS]).

Cigarette Smoking

Cigarette smoking is a powerful risk factor, especially for MI, peripheral artery disease, and CVA. Smoking accelerates coronary plaque development and may lead to plaque rupture; it is particularly dangerous in individuals with advanced coronary atherosclerosis (14 [EL 4; NE]). The risk of ASCVD mortality for individuals who smoke cigarettes is about double that of lifetime nonsmokers. However, within 1 year of smoking cessation, this risk is reduced by about 50%, and continues to decline with time (128 [EL 4; NE]).

One possible explanation for the ASCVD risk associated with cigarette smoking may be related to its effect on HDL-C. Numerous studies have shown that smoking has a substantial, negative effect on HDL-C levels and the LDL-C to HDL-C ratio. Smoking also appears to have a negative effect on postprandial lipids, including TG (129 [EL 3; SS]; 130 [EL 2; NRCT]; 131 [EL 3; SS]; 132 [EL 2; PCS]; 133 [EL 2; NRCT]; 134 [EL 3; SS]). However, smoking cessation significantly increases HDL-C, with improvements noted as early as 30 days (135 [EL 2; MNRCT]).

Obesity and Overweight

Approximately two-thirds of the adults in the U.S. have overweight (body mass index [BMI] 25 to 29.9 kg/m^2) or obesity (BMI ≥30 kg/m^2) (136 [EL 4; NE]; 137 [EL 3; SS]). It is well documented that individuals who have overweight also have a high prevalence of risk factors such as hypertension, T2DM, and dyslipidemia (138 [EL 2; PCS]; 139 [EL 2; PCS]). In particular, excess visceral or intra-abdominal fat increases and independently predicts ASCVD risk (18 [EL 2; PCS]; 136 [EL 4; NE]; 140 [EL 2; SS]; 142 [EL 2; PCS]). Elevated intra-abdominal fat is highly and independently correlated with insulin resistance (142 [EL 3; CSS]; 143 [EL 3; CSS]) and is also associated with prothrombotic/pro-inflammatory states; increased TG, total cholesterol, LDL-C, small dense LDL-C and apo

B; and decreased HDL-C (10 [EL 4; NE]; 142 [EL 3; CSS]; 143 [EL 3; CSS]).

Intra-abdominal obesity is one of the most reliable markers of the insulin resistance syndrome (143 [EL 3; CSS]). Existing U.S. guidelines indicate that a waist circumference greater than 102 cm (40 in) in men or greater than 88 cm (35 in) in women is considered "categorical abdominal obesity" (10 [EL 4, NE]). However, other organizations have adopted a more stringent definition. For example, the International Diabetes Federation defines abdominal obesity as ≥94 cm (≥37 in) for men and ≥80 cm (≥31.5 in) for women; for Asians and Central/South Americans the cutoffs are ≥90 cm (≥35 in) for men and ≥80 cm (≥31.5 in) for women (144 [EL 4, NE]).

LDL Particle Number

The genetically influenced small, dense LDL-C particle is believed to be especially atherogenic, perhaps due in part to its oxidative susceptibility (145 [EL 4; NE]; 146 [EL 4; NE]; 147 [EL 3; CSS]; 148 [EL 4; NE]; 149 [EL 4; NE]; 150 [EL 4; NE]). Several studies point to increased ASCVD risk associated with small, dense LDL-C (151 [EL 2; RCCS]; 152 [EL 3; SS]; 153 [EL 1; RCT]). In addition, evidence from the Framingham Offspring Cohort indicates that primary consideration should be given to measuring and adjusting risk based on particle number (measured directly or as apo B). Specifically, researchers found that compared with LDL-C or non-HDL-C assessments, LDL particle number was a more sensitive indicator of ASCVD risk (20 [EL 3; SS]). The Cardiovascular Health Study and MESA both demonstrated that although LDL-C and LDL particle size are associated with atherogenicity, LDL particle number is a more potent measure of ASCVD risk than either of these 2 measures (154 [EL 2; PCS]; 155 [EL 3; CSS]).

Small, Dense LDL

Small, dense LDL-C is found in 50% of men with ASCVD and is also referred to as LDL pattern B (61 [EL 4; NE]). This pattern is often observed in individuals with elevated TG and low HDL-C, a combination known as the dyslipidemic triad, as well as in individuals with T2DM, the insulin resistance syndrome, and/or chronic anovulation or PCOS (150 [EL 4; NE]; 156 [EL 3; CSS]; 157 [EL 2; CSS]; 158 [EL 2; PCS]; 159 [EL 3; CSS]). Elevated non-HDL-C (i.e., total serum cholesterol – HDL-C) and apo B levels are also clinical markers for the presence of small, dense LDL (80 [EL 4; NE]). Approximately 25% of individuals with small, dense LDL particles inherit this abnormality and do not have hypertriglyceridemia. Measurement of apo B will identify these individuals (156 [EL 3; CSS]). Elevated non-HDL-C (i.e., total serum cholesterol – HDL-C) and apo B levels are also clinical markers for the presence of small, dense LDL (80 [EL 4; NE]).

Fasting and/or Postprandial Hypertriglyceridemia

TG levels are an important component of risk evaluation in both men and women (10 [EL 4; NE]). Historically, the clinical significance of fasting hypertriglyceridemia as an independent risk factor weakened or disappeared when LDL-C and HDL-C concentrations were considered. However, abundant clinical evidence indicates that elevated TG levels may be an independent risk factor (10 [EL 4; NE]; 47 [EL 2; PCS]; 45 [EL 2; PCS]; 132 [EL 2; PCS]; 160 [EL 4; NE]; 161 [EL 2; PCS]; 162 [EL 4; NE]; 163 [EL 2; PCS]; 164 [EL 2; MNRCT]; 165 [EL 2; PCS]; 166 [EL 3; SS]; 167 [EL 3; CSS]; 168 [EL 2; MNRCT]). TG levels that are even moderately elevated (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome (15 [EL 4; NE]). TG levels 200 mg/dL or higher may indicate a substantial increase in ASCVD risk (10 [EL 4; NE]). Although hypertriglyceridemia can be an independent genetic disorder, it is widely accepted as a marker of insulin resistance (15 [EL 4; NE]; 169 [EL 4; NE]). Hypertriglyceridemia is also commonly associated with a procoagulant state and hypertension (170 [EL 4; NE]).

As TG levels increase with age, the importance of hypertriglyceridemia as an ASCVD risk factor also appears to increase (160 [EL 4; NE]; 161 [EL 2; PCS]; 162 [EL 4; NE]). Furthermore, research suggests that like low HDL-C, high serum TG levels may act synergistically with other lipid abnormalities to increase ASCVD risk. For example, the Prospective Cardiovascular Münster (PROCAM) study demonstrated that hypertriglyceridemia increased the incidence of ASCVD by approximately 2.5-fold in men and women with LDL-C levels greater than 155 mg/dL (47 [EL 2; PCS]). Serum TG levels may also predict coronary risk when they are associated with a high LDL-C to HDL-C ratio (>5) or when HDL-C levels are low (45 [EL 2; PCS]; 47 [EL 2; PCS]; 171 [EL 4; NE]; 172 [EL 2; PCS]; 173 [EL 4; NE]).

Because hypertriglyceridemia is interrelated with so many other lipid and nonlipid risk factors, the benefit of lowering TG directly remains uncertain (15 [EL 4; NE]). Furthermore, several studies indicate that postprandial, or nonfasting, TG may be an equally or more potent ASCVD risk factor than fasting TG. Two major prospective studies, the Women's Health Study (N = 26,509, 11.4-year follow-up) and the Copenhagen City Heart Study (N = 13,981, 26-year follow-up), both found that nonfasting TG were independently associated with MI and ischemic heart disease (174 [EL 2; PCS]; 175 [EL 2; PCS]). In the Women's Health Study, the association between both fasting and nonfasting TG and cardiovascular events was significant in univariate analysis (P<.001 for trend across tertiles). The relationship of fasting TG lost statistical significance after adjustment for total cholesterol and HDL-C and weakened further with adjustment for markers of insulin resistance (diabetes, BMI, and hsCRP). However, the association for nonfasting TG levels remained significant with adjustment (P =.006 for trend) (174 [EL 2; PCS]). In addition, an elevated postprandial TG was the only variable independently associated with cardiovascular events among women with normal (≥50 mg/dL) HDL-C levels (176 [EL 3; CCS]).

Proposed explanations for the association between postprandial TG and ASCVD risk include increased postprandial production of TG-rich lipoprotein remnants, which are highly atherogenic, and an abnormal response to an oral fat load, which indicates insulin resistance (174 [EL 2; PCS]; 175 [EL 2; PCS]; 176 [EL 3; CCS]; 177 [EL 4; NE]; 178 [EL 2; PCS]; 179 [EL 3; CCS]; 180 [EL 1; RCT]; 181 [EL 4; NE]; 182 [EL 4; NE]). Data also suggest that in individuals with normal glucose tolerance, postprandial TG levels are useful in assessing cardiovascular risk but provide no extra prognostic value in those with dysglycemia (183 [EL 4; NE]).

PCOS

PCOS is well established as a manifestation of the insulin resistance syndrome and/or the compensatory hyperinsulinemia that may precede any glucose abnormality. Reports indicate that 75% or more women who have PCOS also fulfill the criteria for the insulin resistance syndrome (19 [EL 4; NE]; 184 [EL 2; PCS]). Studies indicate that individuals with PCOS have greater than average levels of CAC and CIMT (19 [EL 4; NE]; 185 [EL 2; PCS]; 186 [EL 2; PCS]), as well as significantly higher rates of ASCVD and ASCVD risk factors such as T2DM and hypertension (19 [EL 4; NE]; 185 [EL 2; PCS]; 187 [EL 3; SS]; 188 [EL 3; CSS]; 189 [EL 3; CSS]).

The Dyslipidemic Triad

Individuals who have the common dyslipidemic triad (hypertriglyceridemia, low HDL-C, and small dense LDL-C [also called the atherogenic lipoprotein profile or atherogenic dyslipidemia]) are at high risk for ASCVD (61 [EL 4; NE]; 151 [EL 2; RCCS]; 156 [EL 3; CSS]). This type of dyslipidemia is one of the components of the high-risk insulin resistance syndrome (Table 7) (15 [EL 4; NE]) and is also common among individuals with T2DM (10 [EL 4; NE]). The relative contribution of each element of the dyslipidemic triad cannot be determined; therefore, the dyslipidemic triad should be viewed as an independent risk factor (10 [EL 4; NE]). The presence of the dyslipidemic triad alongside elevated LDL-C significantly enhances risk, and each condition should be addressed.

Other Risk Factors

Increased Lipoprotein (a)

Production of the LDL variant lipoprotein (a) is largely genetically determined, and its pathogenic mechanism remains unclear; however, elevated plasma concentrations are independently associated with ASCVD risk (190 [EL

4; NE]; 191 [EL 4; NE]). Data on the level of risk associated with lipoprotein (a) are inconsistent (192 [EL 2; PCS]; 193 [EL 1; RCT]; 194 [EL 2; PCS]; 195 [EL 2; MNRCT]; 196 [EL 2; PCS]; 197 [EL 2; PCS]; 198 [EL 1; RCT]; 199 [EL 2; PCS]); however, a prospective analysis of Women's Health Study participants indicated that increased risk was observed only among participants with extremely high lipoprotein (a) levels (≥90th percentile) and above-average LDL-C levels (200 [EL 2; PCS]).

Risk associated with elevated lipoprotein (a) appears to vary by ethnic group; for example, data from the Coronary Artery Risk Development in Young Adults (CARDIA) study showed that mean and median lipoprotein (a) concentrations in African American participants (13.0 and 11.6 mg/dL, respectively) were almost 2 to 3 times that in white participants (6.9 and 3.7 mg/dL, respectively) (201 [EL 2; PCS]). However, lipoprotein (a) elevation appeared to confer a stronger risk for white participants than for African American participants (201 [EL 2; PCS]). Moreover, any interpretation is complicated by a lack of standardized measurement procedures, as well as data indicating that population lipoprotein (a) levels can range from less than 0.1 mg/dL to greater than 100 mg/dL (191 [EL 4; NE]; 195 [EL 2; MNRCT]). Some evidence suggests that statin-induced LDL-C reduction may attenuate the risk associated with lipoprotein (a) (202 [EL 1; RCT]).

Testing for lipoprotein (a) is therefore not generally recommended, although it may provide useful information to ascribe risk in Caucasians with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals.

Factors Related to Blood Clotting

Available data suggest that plasminogen activator inhibitor 1 is related to intra-abdominal obesity, insulin resistance, and in individuals with diabetes, hyperinsulinemia and hyperproinsulinemia. Consequently, elevated plasminogen activator inhibitor 1 may be a risk factor for ASCVD (203 [EL 4; NE]; 204 [EL 4; NE]; 205 [EL 2; PCS]; 206 [EL 4; NE]). However, assays for plasminogen activator inhibitor 1 are not standardized. For these reasons, plasminogen activator inhibitor 1 screening is not generally recommended.

Fibrinogen is a clotting factor that, when elevated, may lead to a prothrombotic state (207 [EL 3; CSS]). An increased fibrinogen level is a strong, established marker of ASCVD risk in men and women (208 [EL 4; NE]; 209 [EL 4; NE]; 210 [EL 4; NE]; 211 [EL 4; NE]). However, as with lipoprotein (a), screening in the general population is not recommended because fibrinogen levels can vary among ethnic groups.

Furthermore, factors unrelated to ASCVD may affect fibrinogen levels (208 [EL 4; NE]; 209 [EL 4; NE]; 211 [EL 4; NE]), and no standard measurement assay exists (210 [EL 4; NE]; 211 [EL 4; NE]). Nonetheless, prospective studies consistently show that adding fibrinogen to lipid evaluations significantly improves ASCVD risk prediction (212 [EL 4; NE]). Fibrinogen may also be a marker of inflammation (207 [EL 3; CSS]).

Markers of Inflammation

ASCVD risk can be indicated by markers of systemic inflammation such as hsCRP (213 [EL 1; RCT]; 214 [EL 2; PCS]): hsCRP concentrations less than 1.0 mg/L are considered normal, 1.0 to 3.0 mg/L intermediate, and greater than 3.0 mg/L high risk (215 [EL 4; NE]). Including hsCRP measurements with standard lipid testing has been shown to add predictive value in determining risk for future ASCVD events (214 [EL 2; PCS]; 216 [EL 2; PCS]). Even after adjustment for standard ASCVD risk factors, elevated hsCRP levels have a progressive association with increased MI and CVA among men aged 40 to 84 years (213 [EL 1; RCT]). Elevated hsCRP levels (≥1.9 mg/L) also correspond to increased ASCVD risk in healthy, postmenopausal women with LDL-C levels less than 130 mg/dL (214 [EL 2; PCS]). Furthermore, significantly elevated hsCRP in combination with significantly elevated Lp-PLA$_2$ (e.g., both in the highest tertile) constitutes very high risk in individuals with low or moderately elevated LDL-C (217 [EL 2; PCS]; 218 [EL 2; PCS]).

Lp-PLA$_2$ is a blood enzyme that hydrolyzes oxidized phospholipids, causing atherogenic vascular inflammation (217 [EL 2; PCS]). In particular, the accumulation of macrophages and lymphocytes in atherosclerotic inflammation is accompanied by increased expression of Lp-PLA$_2$ in atherosclerotic plaques, especially complex plaques (219 [EL 4; NE]; 220 [EL 3; CCS]; 221 [EL 4; NE]; 222 [EL 4; NE]). Lp-PLA$_2$ has been identified as a strong and independent predictor of ASCVD events and CVA in individuals with and without manifest ASCVD (223 [EL 2; PCS]; 224 [EL 3; CSS]; 225 [EL 2; PCS]), as well as in individuals with low LDL-C (217 [EL 2; PCS]). Best evidence available indicates that an Lp-PLA$_2$ level less than 200 ng/mL is normal, ≥200 and <223 ng/mL is intermediate, and ≥223 ng/mL is high (217 [EL 2; PCS]; 223 [EL 2; PCS]). Lp-PLA$_2$ appears to act synergistically with CRP (measured as hsCRP), such that risk is substantial when both are elevated (218 [EL 2; PCS]; 217 [EL 2; PCS]). However, while CRP is a marker of general inflammation, Lp-PLA$_2$ appears to specifically indicate vascular inflammation and is not influenced by obesity (213 [EL 1; RCT]; 219 [EL 4; NE]; 220 [EL 2; CCS]).

Hyperhomocysteinemia

Homocysteine, a precursor of methionine, is highly reactive, and elevated levels may damage vessel walls and induce intimal fibrosis (226 [EL 4; NE]; 227 [EL 4; NE]). Prospective clinical studies of individuals with ASCVD or ASCVD risk factors have consistently demonstrated increased levels of serum homocysteine (>15 μmol/L)

alongside cardiovascular events and mortality (226 [EL 4; NE]; 228 [EL 2; PCS]; 229 [EL 4; NE]). However, the link between homocysteine levels and cardiovascular event risk is much stronger after disease onset (212 [EL 4; NE]; 226 [EL 4; NE]; 229 [EL 4; NE]; 230 [EL 2; PCS]; 231 [EL 3; CCS]; 232 [EL 2; PCS]; 233 [EL 3; CCS]; 234 [EL 2; PCS]; 235 [EL 2; PCS]). Evaluation of homocysteine levels in individuals with established ASCVD (including ischemia) may help explain the ASCVD etiology (226 [EL 4; NE]). Data from the National Health and Nutrition Examination Survey III (236 [EL 3; SS]) and MESA (237 [EL 3; SS]) have shown that the addition of homocysteine is a powerful tool when used in conjunction with the Framingham Risk Score to identify individuals with ASCVD at high risk who might otherwise be classified as being at intermediate risk.

Elevated homocysteine levels appear to be mediated by deficiencies in folic acid and vitamins B6 and B12 (238 [EL 4; NE]). Although treatment with these supplements lowers plasma homocysteine levels, research to date does not indicate that such therapy reduces ASCVD risk (239 [EL 1; RCT]; 240 [EL 1; RCT]; 241 [EL 1; RCT]; 242 [EL 1; RCT]; 243 [EL 4; NE]). Therefore, homocysteine measurement is not recommended as part of routine screening.

Elevated Uric Acid

Increased serum uric acid levels are linked to insulin resistance syndrome, obesity, dyslipidemia, and hypertension (244 [EL 3; SS]). Data from the First National Health and Nutrition Examination Survey and the National Health and Nutrition Examination Survey 1 Epidemiologic Follow-up Study showed a significant increase in ASCVD mortality among the highest uric acid quartile (>6.99 mg/dL for men and >5.6 mg/dL for women), suggesting that uric acid may be an independent risk factor (244 [EL 3; SS]). However, Framingham research evaluating the impact of uric acid lowering has not shown a positive effect on reducing CV events (245 [EL 2; PCS]). Therefore, available evidence indicates that the role of uric acid in ASCVD risk remains undefined (245 [EL 2; PCS]; 246 [EL 4; NE]).

ASCVD Risk and the Insulin Resistance Syndrome

Individuals who have insulin resistance are at increased risk for developing a cluster of abnormalities known as the insulin resistance syndrome (15 [EL 4; NE]). Although this is sometimes referred to as MetS or dysmetabolic syndrome, the AACE prefers the term *insulin resistance syndrome*, as this more accurately pinpoints the underlying pathophysiology of insulin resistance and compensatory hyperinsulinemia that unites these conditions (15 [EL 4; NE]). The components of the insulin resistance syndrome, outlined in Table 7, include important risk factors for ASCVD. Thus, individuals with the insulin resistance syndrome are at increased risk for developing ASCVD. Likewise, individuals who do not have diabetes but have a diagnosis of ASCVD have a greater prevalence of the insu-

lin resistance syndrome than those without ASCVD (15 [EL 4; NE]). Individuals who are insulin resistant will not necessarily develop all of the abnormalities that comprise the insulin resistance syndrome; however, the identification of even 1 component raises the likelihood of an insulin resistance syndrome diagnosis (15 [EL 4; NE]).

Elevated blood glucose is a late and possibly terminal manifestation of insulin resistance. Before the development of hyperglycemia, diagnosing insulin resistance syndrome may be difficult, with no simple, single clinically measurable test available (15 [EL 4; NE]). However, the components of the insulin resistance syndrome are frequently identifiable. Individuals who exhibit nonhyperglycemic signs of insulin resistance should undergo further assessment, with consideration given to performing a 2-hour, 75-g oral glucose tolerance test (15 [EL 4; NE]).

CKD

Growing evidence suggests that individuals with CKD, who represent a growing population, have increased risk for ASCVD (17 [EL 2; MNRCT]). It appears that the increased risk of ASCVD does not occur only in individuals with end-stage renal disease, but also in those with mild-to-moderate chronic renal dysfunction. These findings led the National Kidney Foundation in 2002 to consider CKD as an ASCVD equivalent (247 [EL 4; NE]).

Chronic Inflammatory Conditions

Individuals with chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematous, and ankylosing spondylitis appear to have an increased risk of ASCVD. In the Nurses' Health Study, individuals who had had rheumatoid arthritis for more than 10 years appeared to have an increased risk for ASCVD compared with individuals without rheumatoid arthritis (relative risk, 3.1; confidence interval [CI], 1.64-5.87) (248 [EL 2; PCS]). Also in the Nurses' Health Study that included 119,332 female nurses, systemic lupus erythematous was eventually diagnosed in 148 women. The age-adjusted relative risk of ASCVD was 2.25 (95% CI, 1.77-4.27), while after adjustment for other traditional risk factors, the hazard ratio (HR) remained greater than 2 for the group of women with systemic lupus erythematous (249 [EL 2; PCS]). Increased prevalence of ASCVD has been also reported in individuals with ankylosing spondylitis (250 [EL 3; CSS]).

Human Immunodeficiency Virus (HIV)

Individuals with HIV appear to have increased risk of ASCVD. It is not well established whether the increased risk for ASCVD is secondary to traditional or nontraditional risk factors, such as changes in body composition (lipoatrophy/lipodystrophy) or inflammation, effect of antiretroviral medications, or direct effects of HIV on the vasculature (251 [EL 4; NE]).

4Q1.2. Screening

Screening guidelines for dyslipidemia vary by age group; however, the decision to screen should always be based on clinical judgment. Specific indications exist to alert physicians to conduct screenings.

Young Adults (≥20 Years of Age)

A number of studies have shown that atherosclerosis can be present early in life, well before symptoms occur (252 [EL 3; CSS]; 253 [EL 3; CSS]; 254 [EL 3; CSS]). Although ASCVD risk in young adults is low, adults older than 20 years should be evaluated for dyslipidemia every 5 years as part of a global risk assessment (10 [EL 4; NE]). More frequent assessments are warranted for young individuals with a family history of premature ASCVD (definite MI or sudden death before age 55 years in father or other first-degree male relative, or before age 65 years in mother or other first-degree female relative) (10 [EL 4; NE]). Consideration of more frequent testing should also be given to individuals with ASCVD risk factors (10 [EL 4; NE]; 11 [EL 4; NE]; 12 [EL 2; PCS]; 13 [EL 2; PCS]; 14 [EL 4; NE]; 15 [EL 4; NE]; 16 [EL 4; NE]; 17 [EL 2; MNRCT]; 18 [EL 2; PCS]; 19 [EL 4; NE]; 20 [EL 3; SS]; 21 [EL 1; MRCT]; 22 [EL 4; NE]). All young adults with diabetes should be screened with a lipid profile at the time of diagnosis. If LDL-C values are within the accepted risk level (<100 mg/dL), a lipid profile repeated every 3 to 5 years is reasonable, (22 [EL 4; NE]) but can be conducted more frequently based on individual clinical considerations.

Middle-Aged Adults (Men ≥45 Years of Age, Women ≥55 Years of Age)

Intervention trials involving middle-aged men and women have shown that treatment of dyslipidemia is beneficial in individuals at high risk (e.g., those with established ASCVD, diabetes, or hypertension) (25 [EL 1; RCT]; 27 [EL 1; RCT]; 49 [EL 1; RCT]; 51 [EL 1; RCT]; 255 [EL 1; MRCT]). However, the benefits of primary prevention using lipid-lowering treatment in individuals at low risk are not as well established (255 [EL 1; MRCT]).

This information must be considered in the context of existing risk in the U.S. population. Despite substantial increases in the use of lipid-lowering therapy, less than one-third of Americans have LDL-C levels below 100 mg/dL, while two-thirds have elevated TG (5 [EL 3; SS]). The MESA study, which had a multicenter cohort of individuals aged 45 to 84 years with no ASCVD at baseline (N = 6,814), found a 29.3% prevalence of dyslipidemia (256 [EL 3; CSS]). Moreover, several community-based, population screening studies of middle-aged individuals described as "typically health-conscious" found dyslipidemia prevalence ranging from 21 to 49% (257 [EL 3; SS]; 258 [EL 3; SS]; 259 [EL 3; SS]). Given these high prevalence rates, even when no ASCVD risk factors are present, it is recommended that middle-aged individuals should be screened for dyslipidemia at least every 1 to 2 years. More frequent lipid testing is recommended when multiple ASCVD risk factors are present (10 [EL 4; NE]; 15 [EL 4; NE]; 22 [EL 4; NE]). The frequency of testing should be based on individual clinical circumstances and the clinician's best judgment. All individuals with diabetes should be screened with a lipid profile at the time of diagnosis (22 [EL 4; NE]) and annually thereafter. Based on individual clinical considerations, some individuals with diabetes can be screened less frequently.

Older Adults (≥65 Years of Age)

The AACE advocates screening for dyslipidemia in all adults up to age 75 years regardless of ASCVD risk status and in adults older than age 75 years who have multiple ASCVD risk factors. Although the association between high LDL-C and ASCVD weakens with age (10 [EL 4; NE]), increased serum cholesterol in older individuals (men ≥65 years, women ≥75 years) is associated with a greater absolute number of acute coronary events compared with middle-aged or younger populations (1 [EL 4; NE]; 260 [EL 3; SS]; 261 [EL 4; NE]). In individuals older than 70 years, the 5,804-participant Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial demonstrated a secondary, but not primary, prevention ASCVD event benefit for the group treated with pravastatin (26 [EL 1; RCT]).

Because many older individuals may benefit from lipid-lowering therapy, those with 0 to 1 ASCVD risk factors should be screened for dyslipidemia annually (10 [EL 4; NE]; 25 [EL 1; RCT]; 26 [EL 1; RCT]; 52 [EL 1; RCT]; 262 [EL 1; RCT]). In addition, older individuals should undergo lipid assessment if they have multiple ASCVD risk factors (i.e., risk factors other than age) (10 [EL 4; NE]). Consideration should also be given to the fact that treatment to lower lipid levels and attenuate atherosclerosis may potentially decrease CVA and transient ischemic attack incidence in this population (25 [EL 1; RCT]; 26 [EL 1; RCT]; 49 [EL 1; RCT]; 54 [EL 1; RCT]; 262 [EL 1; RCT]; 263 [EL 1; RCT]).

Women

ASCVD is the leading cause of mortality in women in the U.S., killing nearly 400,000 women in 2013 (1 [EL 4; NE]). Minority women, in particular African-American women, have higher death rates than Caucasian women because of both ASCVD and CVA (1 [EL 4; NE]). Diagnosis of ASCVD in women can be particularly problematic. Approximately one-half of women presenting with symptoms suggestive of ischemia have angiographically normal or near-normal coronary arteries. Furthermore, women's symptoms are often less overt and/or are atypical compared with those of men. These differences can lead to delays in evaluation and diagnostic testing, decreased use of appro-

priate therapy, and increased mortality (264 [EL 4; NE]; 265 [EL 4; NE]). In addition, traditional diagnostic methods such as imaging, electrocardiography, and exercise testing may be less accurate in women whose anatomy, hormonal milieu, age at ASCVD onset, and age-related comorbidities are unique (266 [EL 4; NE]). ASCVD risk assessment for women may be aided by using the Reynolds Risk Score or Framingham Risk Assessment Tool (Table 8).

In light of the diagnostic challenges that present when trying to identify ASCVD in women, prevention and treatment of dyslipidemia is an essential consideration in this population. However, efforts to manage dyslipidemia in women have often been inadequate. While lipid-lowering treatments are used routinely for men, they are frequently underprescribed for women (267 [EL 1; MRCT]). Furthermore, although lowering LDL-C significantly reduces ASCVD risk in women, the unique roles of hormonal change on cardiovascular risk, HDL-C, and TG must also be addressed.

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 (252 [EL 3; CSS]; 268 [EL 4; NE]; 269 [EL 3; CCS]; 270 [EL 4; NE]; 271 [EL 4; NE]). Furthermore, studies show that the presence and severity of atherosclerotic lesions in children and young adults are related to serum lipid levels and are associated with the extent of atherosclerosis and ASCVD rates in adulthood (270 [EL 4; NE]; 271 [EL 4; NE]; 272 [EL 3; CSS]; 273 [EL 2; PCS]; 274 [EL 3; CCS]; 275 [EL 3; CCS]) Although there is consensus that early intervention is warranted, even in very young individuals (271 [EL 4; NE]; 276 [EL 4; NE]; 277 [EL 4; NE]; 278 [EL 4; NE]; 279 [EL 4; NE]; 280 [EL 4; NE]; 281 [EL 2; PCS]; 282 [EL 3; CCS]), the most effective diagnostic and treatment approaches for pediatric dyslipidemia are far from clear. The original guidelines addressing the management of cholesterol in pediatric and adolescent subjects were published by the National Cholesterol Education Program (NCEP) in 1992 and focused primarily on identifying children with elevated LDL-C (277 [EL 4; NE]). Since that time, recognizing that patterns of dyslipidemia in children and adolescents have evolved to include those with combined dyslipidemia with the associated features of obesity, moderate- to-severe elevations in TGs, normal-to-mild LDL-C elevations, and decreased HDL-C levels. (271 [EL 4; NE]) More recent guidelines reflect these changes. While NCEP guidelines continue to be updated (243 [EL 4; NE]), the Expert Panel on Blood Cholesterol Levels in Children and Adolescents report is well over 2 decades old, having been published in 1992 (277 [EL 4; NE]). The American Academy of Pediatrics (AAP) issued a clinical report on lipid screening and cardiovascular health in children to replace its previous position statement regarding cholesterol in children (283 [EL 4; NE]).

The AAP and National Heart, Lung, and Blood Institute (NHLBI) currently recommend universal screening of children for elevated cholesterol between ages 9 and 11 and again after puberty (age 17 to 21) (271 [EL 4; NE]; 271 [EL 4; NE]). Generally, routine screening is not recommended between ages 12 to 16 years unless new knowledge of risk factors is learned (271 [EL 4; NE]). Children aged 2 to 3 years or older who have ASCVD risk factors; moderate- or high-risk medical conditions; or a family history of FH, premature ASCVD, or dyslipidemia should be screened to increase detection of dyslipidemias including FH. (271 [EL 4; NE]; 280 [EL 4; NE]) Children for whom family history is not known should also be screened.

The AACE endorses current AAP, AHA, NHLBI, and NLA recommendations and position statements for targeted and universal dyslipidemia screening in children and adolescents, including recommendations to measure plasma total cholesterol, HDL-C, LDL-C, and TG levels in children with the following: ASCVD risk factors such as obesity (central adiposity and/or elevated BMI), insulin resistance, diabetes, hypertension, cigarette smoking; a moderate-to high-risk medical condition (chronic or end-stage renal disease, postrenal transplant, postorthotopic heart transplant, Kawasaki disease with regressed or current aneurysms, chronic inflammatory disease, HIV, or nephrotic syndrome); or a family history of ASCVD or dyslipidemia (32 [EL 4; NE]; 271 [EL 4; NE]; 277 [EL 4; NE]; 280 [EL 4; NE]; 284 [EL 4; NE]; 285 [EL 4; NE]). Additionally, the AHA indicates that children who have overweight or obesity should be promptly screened for other elements of the insulin resistance syndrome, and that the presence of such factors may alter treatment considerations (286 [EL 4; NE]).

Furthermore, all adolescents older than 16 years should receive dyslipidemia screening (280 [EL 4; NE]; 287 [EL 3; SS]), with more frequent testing of individuals with ASCVD risk factors or a positive family history (10 [EL 4; NE]; 14 [EL 4; NE]; 32 [EL 4; NE]). As there is no available noninvasive method of screening for ASCVD, the NHLBI and AAP suggest that routine screening may consist of a non-fasting non-HDL test. Abnormal results should be followed up with a fasting lipid profile. Targeted screening should consist of a fasting lipid profile (271 [EL 4; NE]). This comprehensive strategy is expected to improve the accuracy of dyslipidemia diagnosis in children and young adults (287 [EL 3; SS]).

Several important points must be considered when interpreting lipid profiles in children and adolescents:

- *Lipid levels fluctuate during childhood and adolescence*. While plasma cholesterol levels normally peak before puberty (age 9-11 years) in boys, they often decline during puberty, along with HDL-C values (288 [EL 4; NE]).
- *Low HDL-C may not have the same implications in children as it does in adults*. More than 50% of children with low HDL-C levels have normal HDL-C

levels as adults (289 [EL 4; NE]; 290 [EL 3; SS]). Furthermore, low HDL-C values do not constitute a hallmark of the insulin resistance syndrome in children; in this population, obesity and hypertriglyceridemia are the best predictors of this condition (290 [EL 4; NE]; 291 [EL 3; CSS]).

- *Lipid levels vary by sex.* Throughout childhood and adolescence, plasma cholesterol levels tend to be higher in girls than in boys (279 [EL 4; NE]).

While LDL-C levels less than 100 mg/dL are generally considered acceptable in children and adolescents, intervention is indicated for those with borderline (100-129 mg/dL) or high (≥130 mg/dL) LDL-C values, as shown in Table 9 (277 [EL 4; NE]; 271 [EL 4; NE]). Furthermore, the AHA has identified abnormal pediatric HDL-C and TG levels as <35 mg/dL and >150 mg/dL, respectively (292 [EL 4; NE]).

4Q2. WHICH SCREENING TESTS ARE RECOMMENDED FOR THE DETECTION OF CARDIOVASCULAR RISK?

The goal of screening is to ascertain an individual's ASCVD risk. The selection of appropriate initial screening tests should be based on individual risk factors and clinical judgment. Basic lipid screening tests are outlined in the following text with brief background information on their utility and accuracy.

4Q2.1. Fasting Lipid Profile

A growing body of evidence suggests that an isolated, nonfasting total cholesterol determination does not sufficiently select and identify individuals at risk for vascular disease. Typically, a fasting lipid profile (total cholesterol, LDL-C, TG, and HDL-C) is recommended for all individuals; however, if this is not clinically practical, increasing evidence indicates that routine use of fasting lipid determinations is not required (10 [EL 4; NE]; 174 [EL 2; PCS]; 293 [EL 3; CSS]). A 9- to 12-hour fast is necessary to avoid the effect of food intake on chylomicron and very-low density lipoprotein (VLDL) TG (10 [EL 4; NE]).

4Q2.2. LDL-C

Historically, LDL-C has been estimated using the Friedewald equation (10 [EL 4; NE]):

$$\text{LDL-C} = \text{total cholesterol} - \text{HDL-C} - (\text{TG}/5)$$

However, this approach is subject to substantial variability in routine use, is valid only for values obtained during the fasting state, becomes increasingly inaccurate when TG levels are greater than 200 mg/dL, and is considered invalid when TG levels are greater than 400 mg/dL (294 [EL 4; NE]; 295 [EL 3; SS]). Therefore, a more precise

method should be used to assess LDL-C in certain high-risk individuals, such as those with fasting TG concentrations greater than 250 mg/dL or those with diabetes or known vascular disease (294 [EL 4; NE]; 296 [EL 2; RCCS]).

Several direct, homogenous LDL-C assays have become available with excellent precision and accuracy over a range of concentrations, as well as a high correlation with the criterion standard beta-quantification assay (294 [EL 4; NE]; 297 [EL 3; SS]). These assays accurately classify individuals with TG concentrations up to 2,000 mg/dL (297 [EL 3; SS]), although they are not recommended for individuals with type III hyperlipidemia (familial dysbetalipoproteinemia) (297 [EL 3; SS]). The benefits and potential drawbacks of direct LDL-C assessment have been discussed in detail by Nauck et al (294 [EL 4; NE]).

4Q2.3. HDL-C

An HDL-C concentration less than 40 mg/dL is an established independent risk factor for ASCVD in both men and women (10 [EL 4; NE]). However, because HDL-C levels tend to be higher in women than in men, an HDL-C concentration less than 50 mg/dL in women is also considered a marginal risk factor (10 [EL 4; NE]; 81 [EL 2; PCS]; 82 [EL 2; MNRCT]; 83 [EL 2; PCS]).

4Q2.4. Non-HDL-C

Many individuals have normal LDL-C concentrations, but elevated TG and low HDL-C (298 [EL 4; NE]). Furthermore, in individuals with TG levels 200 mg/dL or greater, VLDL-C is elevated and ASCVD risk cannot be adequately assessed using LDL-C alone (10 [EL 4; NE]). These deficits have led to an increased awareness of the potential benefits of non-HDL-C screening. Non-HDL-C is the sum of VLDL-C and LDL-C, but is usually calculated as follows:

$$\text{Non-HDL-C} = \text{total cholesterol} - \text{HDL-C} - (\text{TG}/5).$$

Non-HDL-C is highly correlated but not concordant with total apo B and provides a simple way to estimate risk from VLDL-C, LDL-C, intermediate-density lipoprotein cholesterol, and lipoprotein (a) (10 [EL 4; NE]; 31 [EL 4; NE]; 298 [EL 4; NE]). Evidence indicates that compared with LDL-C, non-HDL-C is an equally strong or superior predictor of risk in groups of individuals with moderately elevated TG (200 to 500 mg/dL) (10 [EL 4; NE]), diabetes (299 [EL 4; NE]; 300 [EL 3; SS]; 301 [EL 1; RCT]), the insulin resistance syndrome (10 [EL 4; NE]), and/or established ASCVD (298 [EL 4; NE]; 302 [EL 2; SS]). In these high-risk individuals, non-HDL-C may be an appropriate secondary treatment target (123 [EL 4; NE]). Non-HDL-C may be at goal with persistently elevated apo B levels (303 [EL 4; NE]; 304 [EL 4; NE]). Non-HDL-C targets are 30 mg/dL higher than established LDL-C risk levels (10 [EL 4; NE]).

4Q2.5. TG

A high TG to HDL-C ratio (≥2.4) is a strong indicator of the insulin resistance syndrome (10 [EL 4; NE]; 15 [EL 4; NE]; 77 [EL 3; CSS]). Insulin resistance is more common when a family history of ASCVD or T2DM is present (15 [EL 4; NE]). Evidence indicates that when TG levels exceed 140 mg/dL, there is a substantial increase in the production of small, dense LDL-C (156 [EL 3; CSS]); therefore, the presence of hypertriglyceridemia and low HDL-C in an individual should also prompt clinical suspicion for the presence of the small, dense LDL pattern, as well as elevated postprandial TG (15 [EL 4; NE]). TG, which are present in 5 times the amount of cholesterol, are the more important lipid component of VLDL particles. VLDL-C is only important in that it is calculated in a lipid profile to determine the more important LDL-C.

When fasting TG levels are marginally elevated (140 to 200 mg/dL), 2 additional lipid evaluations may be warranted.

- Direct assessment of the LDL-C pattern B phenotype (small, dense LDL) by ultracentrifugation, nuclear magnetic resonance, or gradient gel electrophoresis may be useful because elevated TG and reduced HDL-C are elements of the dyslipidemic triad (10 [EL 4; NE]). This is particularly relevant because many individuals with the small, dense LDL pattern will have optimal or near-optimal LDL-C levels (<130 mg/dL) (10 [EL 4; NE]).

- Evaluation of postprandial TG levels may be useful because evidence indicates that the small TG-rich lipoproteins produced postprandially are particularly atherogenic and may be indicative of insulin resistance and/or diabetes (173 [EL 4; NE]; 305 [EL 3; CSS]; 306 [EL 4; NE]; 307 [EL 4; NE]; 308 [EL 3; CSS]; 309 [EL 3; CSS] 310 [EL 3; CSS]). Although neither an assessment for postprandial TG levels nor a reference range has been standardized, several studies indicate that nonfasting or random TG exceeding usual fasting cutpoints (≥150 mg/dL) is independently associated with increased ASCVD risk (174 [EL 2; PCS]; 175 [EL 2; PCS]; 311 [EL 4; NE]). Others suggest that lack of standardization of postprandial measurement of TG precludes its current use as a screening test (311 [EL 4; NE]).

Thus, elevated TG in a nonfasting state can no longer be ignored as indicative of no increased ASCVD risk. The treatment of hypertriglyceridemia, however, demands they be measured in a standard fasting state to assess the effect of therapy. Fasting TG measurements represent the lowest 24-hour value because daytime TG levels are postprandial and influenced by dietary fat load and TG clearance efficiency.

4Q2.6. Apolipoproteins

A high plasma apo B level (>130 mg/dL) combined with an LDL-C concentration less than 160 mg/dL, with or without hypertriglyceridemia, identifies hyperapobetalipoproteinemia, which is a cause of premature ASCVD (80 [EL 4; NE]).

Evidence from a series of large studies, including the Apolipoprotein-Related Mortality Risk (AMORIS) and Nurses' studies, suggests that apo B provides a uniquely powerful assessment of total atherogenic particle burden that may be equivalent or superior to LDL-C, non-HDL-C, or other cholesterol ratios in predicting risk. It has also been suggested that apo B is more closely associated with the insulin resistance syndrome than LDL-C or non-HDL-C (31 [EL 4; NE]; 312 [EL 2; PCS]; 313 [EL 2; RCCS]). Additionally, an analysis of the Insulin Resistance Atherosclerosis Study (IRAS) revealed that apo B was more closely associated than non-HDL-C with markers such as central adiposity, insulin resistance, thrombosis, and inflammation (314 [EL 3; SS]). There are clinical circumstances where apo B and non-HDL-C are highly correlated but only moderately concordant because of differences in cholesterol enrichment of LDL-C particles, leaving many high-risk individuals whose non-HDL-C is satisfactory with apo B high enough to warrant more intensive therapy (315 [EL 4; NE]). A 2008 post hoc analysis of combined data from 2 major statin trials (pooled N = 18,018) found that both increased apo B and non-HDL-C demonstrated an equivalent or slightly stronger association with major cardiovascular event risk (HR, 1.19; *P*<.001 for both) than increased LDL-C (HR, 1.15; *P*<.001) (21 [EL 1; MRCT]). Among individuals who achieved the ATP III LDL-C goal of 100 mg/dL or less while on statins, LDL-C ceased to be significantly associated with cardiovascular risk, while apo B and non-HDL-C maintained a significant relationship (21 [EL 1; MRCT]). In addition, the apo B to apo AI ratio was a stronger predictor of risk (HR 1.24, *P*<.001) than either the LDL-C to HDL-C ratio (HR 1.20, *P*<.001) or the total cholesterol to HDL-C ratio (HR 1.21, *P*<.001) (21 [EL 1; MRCT]). Similarly, the INTERHEART study found that the apo B to apo AI ratio was among the most significant risk factors for MI, with an odds ratio of 4.73 (99% CI, 3.93-5.69) for the highest versus lowest decile (18 [EL 2; PCS]).

Based on these findings, when the TG concentration is greater than 150 mg/dL or the HDL-C concentration is less than 40 mg/dL, the apo B or the apo B to apo AI ratio may be particularly useful in assessing residual risk in individuals at risk for ASCVD (even when LDL-C levels are controlled); this includes individuals with established ASCVD, T2DM, or the insulin resistance syndrome who are at high risk for ASCVD.

4Q2.7. Secondary Causes of Dyslipidemia

Secondary causes of dyslipidemia (Table 11) must be excluded with a thorough medical and dietary history, as well as laboratory testing for glucose and thyroid, liver, and renal function levels (10 [EL 4; NE]; 316 [EL 4; NE]; 317 [EL 2; RCCS]). Treating an underlying contributing disease may alleviate the lipid abnormality (10 [EL 4; NE]); however, dyslipidemia in individuals with serious conditions such as diabetes is a sometimes-overlooked indication for aggressive lipid-lowering therapy.

In addition to excluding secondary causes of dyslipidemia, the physician should perform a thorough family history and physical evaluation to identify additional risk factors, including genetic factors, that could cause or contribute to dyslipidemia.

4Q2.8. Additional Tests

Evidence suggests that hsCRP may be helpful in predicting coronary events (318 [EL 1; RCT]). Although studies suggest that hsCRP may be of limited value as a broadly applied screening tool, it may be helpful in stratifying cardiovascular risk in individuals with a standard risk assessment that is borderline (319 [EL 3; SS]) or in those with an LDL-C level less than 130 mg/dL (319 [EL 3; SS]; 320 [EL 1; RCT]). Normal values of hsCRP are classified as being less than 1.0 mg/L, the intermediate range is 1.0 to 3.0 mg/L, and high risk is greater than 3.0 mg/L (319 [EL 3; SS]). However, in the JUPITER trial, a simpler stratification (<2.0 vs. ≥2 mg/L) was strongly suggested (320 [EL 1; RCT]).

Lp-PLA$_2$, similar to hsCRP, may also be helpful in predicting ASCVD risk. As previously discussed, elevated Lp-PLA$_2$ (≥200 ng/mL) has been independently linked with coronary events (223 [EL 2; PCS]). Moreover, Lp-PLA$_2$ may act synergistically with CRP, further increasing risk when both are elevated (217 [EL 2; PCS]; 218 [EL 2; PCS]). Measurement of Lp-PLA$_2$, which appears to be more specific than hsCRP, may be helpful when it is necessary to further stratify an individual's risk for ASCVD, especially in the presence of systemic CRP elevations.

A normal apo A1 level in an individual with low HDL-C suggests the existence of an adequate number of HDL-C particles that contain less cholesterol and is an indication of lower risk (8 [EL 4; NE]). Therefore, an assessment of apo A1 may be useful in certain cases (80 [EL 4; NE]).

Homocysteine has also emerged as a potential independent risk factor for ASCVD. Homocysteine levels greater than 15 μmol/L are associated with increased ASCVD risk. Goal levels have been less than 10 μmol/L in the U.S. and less than 12 μmol/L in Europe. However, lowering homocysteine to these levels has not been shown to reduce ASCVD risk (238 [EL 4; NE]).

CAC and ultrasound measurement of CIMT are noninvasive measures of atherosclerosis that have emerged as adjuncts to standard ASCVD risk factors (321 [EL 3; CSS]; 322 [EL 2; MNRCT]). Noninvasive imaging of carotid arteries is a potential tool for assessing the results of lipid-lowering therapy and has been used in clinical trials of drug efficacy (Table 14) (323 [EL 1; RCT]; 324 [EL 1; RCT]; 325 [EL 1; RCT]; 326 [EL 1; RCT]; 327 [EL 1; RCT]; 328 [EL 1; RCT]; 329 [EL 2; PCS]; 330 [EL 1; RCT]; 331 [EL 1; RCT]; 332 [EL 1; RCT]; 333 [EL 1; RCT]; 334 [EL 1; RCT]). CIMT, along with coronary calcium scoring, is recognized by the AHA as a surrogate marker for coronary artery disease (335 [EL 4; NE]). However, CIMT should not be performed routinely but may be used in certain clinical situations to refine risk stratification and the need for more aggressive preventive strategies (321 [EL 3; CSS]; 322 [EL 2; MNRCT]).

On the other hand, the presence of CAC correlates strongly with coronary atherosclerosis. CAC is an important predictor of ASCVD risk, based on data from MESA, a multicenter, long-term study of subclinical atherosclerosis and its progression and relationship to clinical ASCVD (336 [EL 4; NE]. Multiple analyses of MESA findings show that CAC scores can be a strong marker for ASCVD among individuals with a family history of ASCVD (337 [EL 2; PCS]; 338 [EL 3; SS]), a high risk factor burden (339 [EL 2; PCS]), and even a low lifetime ASCVD risk (340 [EL 2; PCS]). More specifically, a CAC score of 0 (healthy aging) is a strong predictor of low ASCVD risk (341 [EL 2; PCS]). Based on these MESA findings, an algorithm was developed that accurately predicts 10-year ASCVD risk using CAC and traditional risk factors (36 [EL 3; SS]). The MESA algorithm was validated against 2 independent longitudinal cohort studies: Heinz Nixdorf Foundation (HNR) and the Dallas Heart Study (DHS) (36 [EL 3; SS]). The MESA algorithm had an area under the survival receiver-operator characteristic (ROC) curve of 0.81, indicating excellent discrimination between events and nonevents. This compared with a curve of 0.76 without CAC inclusion and provides further evidence of improved prediction with CAC (36 [EL 3; SS]).

Genetic testing to search for mutations in the LDL receptor, apolipoprotein B 100 (ApoB100), or PCSK9 is available to diagnose FH (342 [EL 4; NE]). However, criteria other than genetic testing, such as LDL cholesterol concentrations, physical findings, and family history of early elevated total cholesterol and/or early MI, are most commonly used to diagnose FH (66 [EL 4; NE]; 67 [EL 4; NE]).

Special Considerations: Women
Both the Framingham Heart Study and Lipid Research Clinics Follow-Up Study demonstrated that high total cholesterol, LDL-C, and TG, as well as low HDL-C are ASCVD risk factors in women. Risk assessment tools developed from these and other studies may assist in determining ASCVD risk for women (Table 8).

Elevated fasting and/or postprandial TG may also be independent risk factors in this population (174 [EL 2; PCS]; 343 [EL 4; NE]). In particular, and 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 (344 [EL 3; SS]). Compared with women with high HDL-C, women with low HDL-C have a nearly 3-fold elevated risk of ASCVD (344 [EL 3; SS]).

4Q3. WHAT ARE THE TREATMENT RECOMMENDATIONS IN INDIVIDUALS WITH DYSLIPIDEMIA AND ASCVD RISK?

4Q3.1. Treatment Goals

Treatment goals are outlined in Table 12. In clinical management of dyslipidemia, a reasonable goal is to strive for lipid levels in the normal range; however, more aggressive goals need to be set for higher-risk individuals (28 [EL 4; NE]).

Isolated Low HDL-C

Isolated low HDL-C consists of HDL-C levels less than 40 mg/dL in men and less than 50 mg/dL in women, without accompanying hypertriglyceridemia (10 [EL 4; NE]). Because no research intervention has targeted only HDL-C, it is difficult to determine from clinical trials whether increasing HDL-C levels alone is clinically beneficial (82 [EL 2; MNRCT]; 90 [EL 4; NE]; 345 [EL 1; RCT]). However, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study 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 (345 [EL 1; RCT]; 346 [EL 1; RCT]). These results and other epidemiologic evidence support a cardioprotective role of HDL-C. Therefore, the AACE believes that when secondary causes of low HDL-C have been excluded, intervention is appropriate if HDL-C levels are low and other risk factors are present (including borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD). The goal of intervention should be to raise HDL-C levels by as much as possible, but minimally to greater than 40 mg/dL in both men and women (10 [EL 4; NE]; 86 [EL 2; PCS]; 324 [EL 1; RCT]; 328 [EL 1; RCT]; 331 [EL 1; RCT]).

• *4Q3.1.1. LDL-C*

LDL has been, and remains, the mainstay of efforts to improve lipid profiles in individuals at risk for ASCVD. However, because an isolated focus on LDL-C is not always sufficient to prevent ASCVD in at-risk individuals or to treat existing atherosclerosis, control of HDL-C, non-

HDL-C, and TG is also important (10 [EL 4; NE]). Other important considerations include the individual's age and sex and the presence of T2DM or dysglycemia (impaired fasting glucose and/or impaired glucose tolerance).

• *4Q3.1.2. HDL-C*

HDL-C levels should not be treated alone in individuals with low HDL-C without any accompanying risk factors; clinical trials have not demonstrated a clear clinical benefit to this approach. In those with risk factors, HDL-C levels can be raised as much as possible, but minimally to greater than 40 mg/dL in both men and women (Table 12).

• *4Q3.1.3. Non-HDL-C*

The goal for non-HDL-C is 30 mg/dL above the LDL-C goal (i.e., <100 mg/dL for individuals at highest risk and <130 mg/dL for individuals at medium to high risk) (10 [EL 4; NE]).

• *4Q3.1.4. Apolipoproteins*

Apo B may be elevated in individuals with optimal LDL-C when small, dense LDL particles are present. This generally occurs in individuals with hypertriglyceridemia but may also occur in individuals with TG values of 100 to 149 mg/dL and in some individuals with a genetic basis for small, dense LDL particles who have TG values less than 100 mg/dL (11 [EL 4; NE]; 25 [EL 1; RCT]; 26 [EL 1; RCT]; 27 [EL 1; RCT]; 30 [EL 1; RCT]; 31 [EL 4; NE]). The AACE supports the goals set by the ACC and ADA that optimal apo B levels for individuals at risk of ASCVD, including those with diabetes, are less than 90 mg/dL, while individuals with established ASCVD or diabetes plus 1 or more additional risk factors should have an apo B goal of less than 80 mg/dL (11 [EL 4; NE]; 31 [EL 4; NE]; 347 [EL 4; NE]). Lower apo B targets may be considered in certain clinical situations characterized by persistent ASCVD.

• *4Q3.1.5. TG*

Normal TG levels are less than 150 mg/dL; levels ranging from 150 to 199 mg/dL are classified as borderline high; levels from 200 to 499 mg/dL are high, and levels 500 mg/dL or greater are considered very high (Table 10) (10 [EL 4; NE]).

Although the benefit of targeting TG directly remains uncertain, several studies suggest there may be some advantage to such treatment. Two major studies, the Helsinki Heart Study (HHS) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, found that fibrates were highly effective at lowering TG. Moreover, both studies showed that a reduction in TG was associated with a trend toward fewer ASCVD events and a significant reduction in nonfatal MI (348 [EL 1; RCT]; 349 [EL 1; RCT]). In the 18-year HHS follow-up, TG reduction with fibrates significantly lowered the ASCVD mortality rate (350 [EL 2; PCS]).

Although verifying the independent atherogenicity of TG is difficult, TG-rich remnant lipoproteins (e.g., VLDL and intermediate-density lipoproteins) form the basis for TG targets, since reducing remnant lipoproteins appears to have significant potential to reduce ASCVD risk (10 [EL 4; NE]). Elevated TG can often be effectively treated through lifestyle changes; however, niacin or fibrates in combination with statins may be appropriate options for many individuals with hypertriglyceridemia and associated low HDL-C (326 [EL 1; RCT]; 351 [EL 4; NE]; 352 [EL 1; RCT]; 353 [EL 1; MRCT]; 354 [EL 1; RCT]; 355 [EL 1; RCT]). In addition, omega-3 fatty acid (fish oil) supplementation in dosages ranging from 4 to 12 g daily is very effective in treating hypertriglyceridemia, with studies showing reductions of 30 to 50% (10 [EL 4; NE]; 351 [EL 4; NE]; 356 [EL 2; PCS]; 357 [EL 1; RCT]). For this reason, fish oil supplementation (2 to 4 g/day) is supported for individuals with TG levels exceeding 500 mg/L. However, a recent U.S. Agency for Healthcare Research and Quality (AHRQ) technical review reported moderate-to-high evidence that fish oil intake does not affect major CV adverse events, all-cause death, total CVA, sudden cardiac death, coronary revascularization, atrial fibrillation, or blood pressure (358 [EL 4; NE]). Dietary omega-3 supplements are not FDA approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose.

Borderline Hypertriglyceridemia

When moderate hypertriglyceridemia (150-199 mg/dL) in association with increased serum cholesterol or low HDL-C levels is the primary disorder, physical activity, weight control, smoking cessation, and other lifestyle changes are first-line therapy (10 [EL 4; NE]). The approach to treatment of accompanying elevated LDL-C does not need to be modified. However, if the individual also has decreased HDL-C, the selection of secondary drug therapy may be affected (10 [EL 4; NE]).

Familial Hypertriglyceridemia

Familial hypertriglyceridemia refers to a group of conditions causing borderline-high and high TG levels. Individuals with marginal or elevated TG levels due to familial hypertriglyceridemia have been conventionally considered to be at no increased risk of ASCVD because there is an overproduction of large VLDL particles that are not highly atherogenic. This assumption is largely based on data from a 1976 study (N = 74) that found MI rates among adults with familial combined hyperlipidemia to be significantly increased compared with rates in normolipidemic relatives (17.5% vs. 4.5%), while MI rates among adults with familial hypertriglyceridemia (4.7%) were not (10 [EL 4; NE]; 296 [EL 2; RCCS]; 359 [EL 3; SS]). However, subsequent research cast doubt on this premise. In 2000, Austin et al (360 [EL 2; PCS]) found that 20-year cardiovascular mortality risk was the same

among individuals with familial hypertriglyceridemia and familial combined hyperlipidemia; however, the results for the familial hypertriglyceridemia group were not significant, probably due to a small sample size. A case-control comparison from the NHLBI Family Heart Study published in 2003 found that associated risk was similar and significant for both familial disorders. Individuals with familial hypertriglyceridemia also had a higher prevalence of the insulin resistance syndrome (70.7%) than those with familial combined hyperlipidemia (64.7%) (296 [EL 2; RCCS]). Treatment of familial hypertriglyceridemia should focus on reducing the risk of pancreatitis as a result of an increased TG level (8 [EL 4; NE]; 361 [EL 4; NE]; 362 [EL 3; SCR]; 363 [EL 4; NE]).

Severe Hypertriglyceridemia (Type V)

Most individuals with severe hypertriglyceridemia have type V hyperlipoproteinemia, signifying an increase in both chylomicrons and VLDL-C (364 [EL 4; NE]). The need to lower TG levels in these individuals is urgent to prevent acute pancreatitis and chylomicronemia syndrome (365 [EL 4; NE]).

4Q3.2. Treatment Recommendations

The management of dyslipidemia requires a comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors such as hypertension, diabetes, obesity, and cigarette smoking. Insulin resistance, which is frequently, but not necessarily, associated with obesity and which underlies most cases of T2DM, is strongly associated with dyslipidemia. The first-line approach to primary prevention in individuals with lipid disorders involves the implementation of lifestyle changes including physical activity and medical nutrition therapy. Treatment may also involve pharmacotherapy, as well as education programs to promote further risk reduction through smoking cessation and weight loss. Furthermore, using insulin in individuals with poorly controlled T1DM and T2DM to lower blood glucose will frequently reduce circulating levels of TG.

• 4Q3.2.1. Physical Activity

Regular physical activity helps to increase strength and flexibility, maintain bone density, and improve insulin sensitivity. Physical activity is also associated with reductions in hsCRP levels and improvements in risk factors such as obesity, waist circumference, hypertension, and dyslipidemia (366 [EL 4; NE]). Specific lipid-level improvements associated with regular exercise include reduced VLDL-C, increased HDL-C, and, in some individuals, decreased LDL-C levels (10 [EL 4; NE]).

Numerous published guidelines identify exercise regimens as an essential approach for dyslipidemia control and cardiovascular risk factor reduction. One recom-

mendation that the AACE supports as a reasonable and feasible approach to fitness therapy indicates that exercise programs should 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. Activities may include brisk walking; riding a stationary bike; water aerobics; cleaning/scrubbing; mowing the lawn; and sporting activities such as skiing, basketball, or volleyball with light effort (10 [EL 4; NE]; 128 [EL 4; NE]; 367 [EL 3; SS]; 368 [EL 4; NE]; 369 [EL 1; RCT]; 370 [EL 2; PCS]; 371 [EL 4; NE]; 372 [EL 4; NE]; 373 [EL 2; PCS]; 374 [EL 2; PCS]; 375 [EL 4; NE]; 376 [EL 4; NE]). More recent guidelines indicate that greater benefits are achieved when the duration of exercise is lengthened to 60 to 90 minutes daily, and that 60 or more minutes of daily exercise is recommended for weight loss or weight-loss maintenance (371 [EL 4; NE]). The minimum recommendation remains 30 minutes daily, as overemphasis of the extended recommendations may lead to poor adherence for some individuals. Daily physical activity goals can be met in a single session or multiple sessions throughout the course of a day (10 minutes minimum); for some individuals, breaking activity up throughout the day may help improve adherence to physical activity programs (127 [EL 4; NE]; 371 [EL 4; NE]; 375 [EL 4; NE]; 376 [EL 4; NE]; 377 [EL 1; RCT]; 378 [EL 2; PCS]; 379 [EL 2; CCS]).

Although aerobic exercise is preferred, nonaerobic activities are also beneficial. The IRAS study examined 1,467 individuals and found that improvements in insulin sensitivity correlated with total energy expenditure in total, vigorous, and nonvigorous activity. Vigorous activity was defined as having a metabolic equivalent value of 6 or higher (calculated as the ratio of metabolic rate during activity to resting metabolic rate) and included strenuous home/work activities such as snow shoveling, chopping wood, or heavy construction and intensive sporting activities such as running/jogging, skiing, swimming, racket sports, or vigorous weightlifting. Nonvigorous activities included less strenuous home/work activities such as gardening, nursing, and waiting tables and less strenuous sports such as hunting, bowling, golf, and brisk walking (380 [EL 3; SS]). Additional studies also suggest that weight and resistance training may be beneficial to some individuals with the insulin resistance syndrome, independent of body fat or aerobic fitness (381 [EL 2; NRCT]; 382 [EL 3; CSS]). Therefore, in addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week (375 [EL 4; NE]; 383 [EL 1; MRCT]).

Even though the benefits of exercise are widely accepted, physical activity programs often prove difficult for individuals to maintain (128 [EL 4; NE]). Nonetheless, the AACE underscores the continued application of fitness therapy as a cornerstone of dyslipidemia treatment. Individuals who are nonadherent to fitness therapy should be repeatedly encouraged, and practitioners should apply a variety of strategies as necessary to improve adherence. Strategies may include individually tailored advice, identification of adherence barriers, referral to instructor-led exercise classes, and routine follow-up and consultation (384 [EL 1; RCT]; 385 [EL 1; RCT]; 386 [EL 1; RCT]; 387 [EL 4; NE]).

• 4Q3.2.2. Medical Nutrition Therapy

Research has shown that diet can have a substantial effect on lipid levels and may be an important determinant of ASCVD risk. Therefore, medical nutrition therapy provides an important tool for the management of dyslipidemia.

Dietary Risk Factors: Fats

Dietary fat includes both unsaturated and saturated fatty acids. The substitution of unsaturated fatty acids (including both polyunsaturated and monounsaturated) for saturated fatty acids leads to decreased LDL-C levels; slightly greater LDL-C reductions are observed with poly-unsaturated fatty acids than with monounsaturated fatty acids (10 [EL 4; NE]; 388 [EL 1; MRCT]). While high intake of poly-unsaturated fatty acids may reduce HDL-C and TG levels, the substitution of monounsaturated fatty acids for saturated fatty acids has a minimal effect on HDL-C values and does not raise TG levels (10 [EL 4; NE]; 388 [EL 1; MRCT]; 389 [EL 1; RCT]; 390 [EL 1; MRCT]; 391 [EL 1; RCT]).

Dietary intake of *trans* fatty acids is associated with both increased LDL-C and decreased HDL-C levels (391 [EL 4; NE]). Combined with evidence from epidemiologic cohort studies, these effects indicate that diets high in *trans* fatty acids are associated with an increased risk of ASCVD; evidence indicates that, on a per calorie basis, risk with *trans* fatty acids is higher than with any other macronutrient (391 [EL 4; NE]).

Dietary Changes: Recommendations and Clinical Effects

Nutritional guidelines for the reduction of cardiovascular risk through lipid management recommend diets rich in fruits and vegetables (combined ≥5 servings/day; ≥1 of these servings/day of dark green or orange vegetables), grains (primarily whole grains), legumes, high-fiber cereals, low-fat dairy products, fish, lean meats, and skinless poultry (10 [EL 4; NE]; 393 [EL 1; RCT]; 394 [EL 4; NE]; 395 [EL 1; MRCT]; 396 [EL 1; RCT]; 397 [EL 4; NE]; 398 [EL 2; PCS]; 399 [EL 3; SS]; 400 [EL 1; RCT]). Additional recommendations, such as those provided in the therapeutic lifestyle changes diet, specify limits for the intake of saturated fat (<7% of total calories), *trans* fats (<1% of total calories), and cholesterol (<200 mg/day). Guidelines also indicate that polyunsaturated and monounsaturated fatty acids may comprise up to 10% and 20% of caloric intake, respectively, and that total dietary fat should constitute 25 to 35% of calories consumed (10 [EL 4; NE]).

Further recommendations include a reduction in both salt intake and total calories consumed (10 [EL 4; NE]; 397 [EL 4; NE]; 401 [EL 4; NE]).

Research has shown that lipid value improvements can be further augmented by supplementing with LDL-C-lowering macronutrients including plant stanol esters (~2 g daily) and soluble fiber (10-25 g daily) (10 [EL 4; NE]; 402 [EL 4; NE]; 403 [EL 4; NE]). A number of small studies have compared diets with similar energy and nutrient values, differing only in the amount of soluble fiber intake. In these studies, diets higher in soluble fiber produced total cholesterol reductions of 5 to 19% and LDL-C reductions of 8 to 24% (404 [EL 1; RCT]; 405 [EL 1; RCT]; 406 [EL 1; RCT]; 407 [EL 1; RCT]; 408 [EL 1; RCT]). Foods high in soluble fiber include oat bran, oatmeal, beans, peas, rice bran, barley, citrus fruits, strawberries, and apple pulp (409 [EL 4; NE]). Plant stanol esters are virtually unabsorbable and selectively inhibit dietary and biliary cholesterol absorption in the small intestine (410 [EL 4; NE]). Clinical studies ranging from 4 weeks to 1 year have demonstrated that substitution of conventional home dietary fats with margarine containing plant stanol esters can reduce LDL-C levels by approximately 15 to 20% (411 [EL 2; RCT]; 412 [EL 2; RCT]; 413 [EL 1; RCT]; 414 [EL 4; NE]). Stanols/sterols have been incorporated into a variety of foods, including spreads and dressings, breads and cereals, low-fat milk and yogurt, and, in the U.S., orange juice (410 [EL 4; NE]).

While low-fat diets are generally recommended, it is important to recognize that decreases in dietary fat intake may lead to increased carbohydrate consumption (principally starches and sugars) and subsequent weight gain (10 [EL 4; NE]; 389 [EL 1; RCT]; 390 [EL 1; MRCT]; 415 [EL 1; RCT]; 416 [EL 1; RCT]; 417 [EL 1; RCT]; 418 [EL 1; RCT]). Individuals at risk for the insulin resistance syndrome are advised to avoid excessive carbohydrate intake and consume diets that include relatively more unsaturated fats (10 [EL 4; NE]; 419 [EL 4; NE]). A diet high in carbohydrates (>60% of total energy) will increase TG, while a diet that replaces saturated fatty acids with monounsaturated fatty acids will not (10 [EL 4; NE]).

Because of the demonstrated TG benefits associated with consuming the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, the AHA supports 2 servings of fatty fish per week for the general population. Individuals with ASCVD should consume 1 g of eicosapentaenoic acid and docosahexaenoic acid daily through fatty fish (preferably) or high-quality dietary supplements (420 [EL 4; NE]). Evidence indicates that the consumption of 2 to 4 g daily of fish oil can reduce TG by 25% or more, while producing only slight increases in LDL-C levels (421 [EL 4; NE]; 422 [EL 4; NE]). However, a 2016 AHRQ technical review found moderate- to-high evidence that fish oil intake increases HDL-C levels (358 [EL 4; NE). Emerging evidence also suggests that consumption of fish oil may have additional effects such as reduced atherosclerotic plaque growth, antithrombogenic effects, reduced adverse left ventricular remodeling, reductions in systemic biomarkers of inflammation, and the promotion of endothelial relaxation; however, these findings require further confirmation (358 [EL 4; NE]; 420 [EL 4; NE]; 423 [EL 4; NE]; 424 [EL 4; NE]; 425 [EL 1; RCT]). Clinical trials are in progress and results may modify these conclusions (426 [EL 4; NE]). Some experts warn that over 3 grams of omega-3 fish oil may increase the risk of bleeding, but a 2009 study demonstrated that omega fish oil did not increase bleeding compared to aspirin (427 [EL 2; RCCS]).

Nutrition therapy effectively reduces cholesterol levels. In a trial of individuals with hypercholesterolemia, implementation of the NCEP Step II therapeutic diet led to an 8% decrease in LDL-C values (428 [EL 1; RCT]). In another study, LDL-C levels were reduced by 11% with diets low in saturated fatty acids (comprising 6.1% of caloric intake) (180 [EL 1; RCT]). Hypertriglyceridemia can also be highly responsive to medical nutrition therapy, particularly when carbohydrate intake is limited; a fish oil dosage of approximately 4 g daily has been found to decrease serum TG by 25 to 30% (420 [EL 4; NE]). Dietary fat and carbohydrate restrictions combined with increased physical activity, weight control, and omega-3 supplementation (420 [EL 4; NE]) are considered effective first-line therapies for hypertriglyceridemia (162 [EL 4; NE]; 170 [EL 4; NE]).

Other investigations have revealed potential health benefits of various specialized diets. For example, ASCVD regression was observed in a 1998 study of individuals on the Ornish diet plus lifestyle intervention (incorporating moderate exercise), while the control group (usual care with lifestyle recommendations by primary physician) showed ASCVD progression (429 [EL 1; RCT]). In an analysis comparing the Ornish, Zone, LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition), and Atkins diets, the last was associated with the greatest weight loss and most improvement in HDL-C and TG levels (430 [EL 1; RCT]). In the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study, mortality from ischemic heart disease was lower in vegetarians than in nonvegetarians (431 [EL 3; SS]). In other studies, vegetarian diets were associated with reduced total cholesterol, LDL-C, and systolic blood pressure compared with control or meat-eating diets (432 [EL 1; RCT]; 433 [EL 2; NRCT]).

Duration and Diagnostic Significance of Nutrition Therapy

In primary prevention, nutrition therapy should be applied as the sole therapeutic approach for dyslipidemia management for at least 3 months. Depending on individual progress, nutritional therapy may be extended through 6 months before initiating lipid-lowering drug therapy (8 [EL 4; NE]). For high-risk individuals, it is appropriate to institute nutrition therapy and pharmacotherapy simultaneously.

After lipid levels are controlled, intensified lifestyle changes may be implemented in individuals with the insulin resistance syndrome. Response to medical nutrition therapy is variable and has diagnostic significance; numerous factors may influence individual outcomes, including adherence (434 [EL 4; NE]), baseline diet, sex, genetics (80 [EL 4; NE]), and LDL particle size (435 [EL 1; RCT]; 436 [EL 2; PCS]). Individuals who respond poorly despite good adherence to dietary restrictions are more likely to have genetic dyslipidemia (437 [EL 4; NE]).

Primary Preventive Nutrition in Children

Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children (438 [EL 3; CCS]; 439 [EL 2; PCS]; 440 [EL 1; RCT]). Decades ago, most experts believed that reduced-fat diets could inhibit growth and decrease vitamin and mineral intake and were therefore inappropriate for most children; such diets were generally reserved for high-risk individuals (276 [EL 4; NE]; 441 [EL 4; NE]). Clinical studies have demonstrated that growth and micronutrient intake can, in fact, be maintained with reduced-fat diets, provided that energy needs are met with a variety of alternative, nutritious foods (280 [EL 4; NE]; 281 [EL 2; PCS]; 442 [EL 4; NE]; 443 [EL 2; PCS]; 444 [EL 2; PCS]; 445 [EL 2; PCS]; 446 [EL 2; RCCS]; 447 [EL 1; RCT]; 448 [EL 1; RCT]; 449 [EL 1; RCT]; 450 [EL 1; RCT]; 451 [EL 1; RCT]). Furthermore, the benefits of early "imprinting" of healthy lifestyle habits in children have also been recognized (278 [EL 4; NE]). Measures include caloric intake personalized to reach and maintain healthy weight, total fat intake constituting 30% or less of total calories, protein intake constituting 15 to 20% of total calories, and cholesterol intake of less than 200 mg/day. Clinical studies indicate that young individuals can achieve decreased total cholesterol levels and modest, but significant, LDL-C reductions with low-fat diets (279 [EL 4; NE]; 290 [EL 4; NE]; 447 [EL 1; RCT]; 452 [EL 3; SS]; 453 [EL 4; NE]; 454 [EL 1; RCT]; 455 [EL 3; SS]). The following factors should be considered when prescribing low-fat diets for children and adolescents:

- Total cholesterol and HDL-C levels are positively correlated in individuals 20 years and younger, and low-fat diets that decrease total cholesterol levels have also been associated with HDL-C reductions. A cross-sectional study of 67 children with hypercholesterolemia demonstrated that such HDL-C reductions can be avoided by limiting intake of simple sugars, but not complex carbohydrates (290 [EL 4; NE]; 447 [EL 1; RCT]; 454 [EL 1; RCT]; 456 [EL 3; SS]).
- Increased intake of carbohydrates may increase plasma TG concentrations in children (456 [EL 3; SS]). High carbohydrate intake is not recommended for children with hypertriglyceridemia.
- Fish oil supplements have a profound effect on serum TG levels in children. These supplements have been used effectively in young individuals with end-stage renal insufficiency (457 [EL 2; PCS]).
- Water-soluble fiber can help improve serum cholesterol levels in children. Studies have shown that both children and adults can achieve cholesterol reductions with high-fiber, low-fat diets (458 [EL 4; NE]; 459 [EL 2; PCS]).
- Diets supplemented with plant stanols and sterols can reduce LDL-C in children. Studies indicate that both children and adults can achieve LDL-C reduction between 5 and 10% by eating foods that are supplemented with plant stanols and sterols (e.g., spreads/margarines, orange juice, yogurt drinks, cereal bars, and dietary supplements) (283 [EL 4; NE]; 460 [EL 1; RCT]). The AACE concurs with the AAP and AHA recommendations suggesting that dietary supplementation with plant stanols and sterols may be considered for children with severe hypercholesterolemia or those who are otherwise at high risk (283 [EL 4; NE]; 461 [EL 4; NE]). The main safety concern is that plant stanols and sterols may reduce absorption of fat-soluble vitamins and beta-carotene; therefore, the AHA suggests monitoring fat-soluble vitamin status in children receiving supplementation (283 [EL 4; NE]; 461 [EL 4; NE]).

In general, children and adolescents on low-fat diets may experience decreased absorption of fat-soluble vitamins or minerals (462 [EL 4; NE]) and should be closely supervised to ensure adequate nutrient and energy intake. Furthermore, lipid levels must be carefully monitored to ensure that profile changes are beneficial.

• 4Q3.2.3. Smoking Cessation

Smoking is a modifiable ASCVD risk factor that has been shown to degrade serum lipid profiles in young adults (463 [EL 2; PCS]). Smoking cessation programs for adolescents may involve education, counseling, behavioral therapy, and/or pharmacologic intervention (464 [EL 4; NE]).

• 4Q3.2.4. Pharmacologic Therapy

At the initiation of drug therapy, the physician and individual being treated should collaborate to establish individualized lipid goals, and then treatment should be personalized to achieve those goals. Pharmacotherapy may consist of up to 5 agents depending on risk stratification (i.e., a statin ± cholesterol absorption inhibitor ± fibrate ± niacin ± bile acid sequestrant).

Numerous clinical trials demonstrate that lipid-lowering drug therapy is effective for both the primary and secondary prevention of MI and other cardiovascular outcomes (49 [EL 1; RCT]; 55 [EL 1; RCT]; 56 [EL 2; PCS]; 262 [EL 1; RCT]; 348 [EL 1; RCT]; 465 [EL 1; RCT]; 466 [EL 1; RCT]; 467 [EL 1; RCT]; 68 [EL 1; RCT]; 469 [EL

1; RCT]; 470 [EL 1; MRCT]; 471 [EL 1; MRCT]). Clinical evidence also suggests that lipid-lowering drug therapy can both prevent ASCVD from developing and may stabilize early, occult lesions (347 [EL 4; NE]; 324 [EL 1; RCT]). Lastly, results from several large clinical trials suggest that individuals at high risk may benefit from very aggressive lipid-lowering therapy (10 [EL 4; NE]; 320 [EL 1; RCT]; 473 [EL 1; RCT]).

The Case for Aggressive Therapy

Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no baseline threshold level below which LDL-C lowering ceases to be effective (34 [EL 1; MRCT]; 121 [EL 1; MRCT]; 474 [EL 1; MRCT]). However, uncertainty remains as to whether it is LDL-C reduction or the non-LDL-C benefits derived from statins, or some combination of both, that improve overall risk (474 [EL 1; MRCT]). Nonetheless, reducing lipids to levels below even recommended targets may be beneficial for certain individuals. Consequently, in 2004, the NCEP ATP III updated its guidelines to include an optional LDL-C goal of less than 70 mg/dL for individuals at very high risk (28 [EL 4; NE]). This update further indicated that it is always prudent to initiate therapy at a level sufficient to achieve a 30 to 40% LDL-C reduction (28 [EL 4; NE]). The AHA/ACC 2006 update of its ASCVD secondary prevention guidelines also considers it a "reasonable goal" to reduce LDL-C to less than 70 mg/dL for individuals with established ASCVD (32 [EL 4; NE]). Individuals for whom aggressive therapy may be beneficial are outlined below. Trials relevant to aggressive lipid-lowering therapy are shown in the following tables: Table 15 (drug trials for primary prevention of ASCVD) (27 [EL 1; RCT]; 50 [EL 1; RCT]; 51 [EL 1; RCT]; 320 [EL 1; RCT]; 348 [EL 1; RCT]; 349 [EL 1; RCT]; 369 [EL 1; RCT]; 465 [EL 1; RCT]; 466 [EL 1; RCT]; 469 [EL 1; RCT]; 474 [EL 1; RCT]; 476 [EL 1; RCT]; 476 [EL 4; NE]), Table 16 (drug trials for secondary prevention of ASCVD) (25 [EL 1; RCT]; 35 [EL 1; RCT]; 49 [EL 1; RCT]; 52 [EL 1; RCT]; 54 [EL 1; RCT]; 262 [EL 1; RCT]; 326 [EL 1; RCT]; 346 [EL 1; RCT]; 328 [EL 1; RCT]; 468 [EL 1; RCT]; 477 [EL 1; RCT]; 478 [EL 1; RCT]; 479 [EL 3; CSS]; 480 [EL 1; RCT]; 481 [EL 1; RCT]; 482 [EL 1; RCT]; 483 [EL 1; RCT]; 484 [EL 1; RCT]; 485 [EL 1; RCT]), and Table 17 (statin trials for primary and secondary ASCVD prevention) (25 [EL 1; RCT]; 27 [EL 1; RCT]; 30 [EL 1; RCT]; 35 [EL 1; RCT]; 49 [EL 1; RCT]; 51 [EL 1; RCT]; 52 [EL 1; RCT]; 53 [EL 1; RCT]; 54 [EL 1; RCT]; 55 [EL 1; RCT]; 262 [EL 1; RCT]; 263 [EL 1; RCT]; 320 [EL 1; RCT]; 467 [EL 1; RCT]; 469 [EL 1; RCT]; 472 [EL 1; RCT]; 476 [EL 4; NE]; 482 [EL 1; RCT]; 483 [EL 1; RCT]; 484 [EL 1; RCT]; 486 [EL 4; NE]).

Individuals With Average or Elevated LDL-C

Early trials such as the Scandinavian Simvastatin Survival Study (4S) and Air Force/Texas Coronary Atherosclerosis Prevention (AFCAPS/TexCAPS) study showed that individuals with elevated LDL-C or individuals with marginally increased LDL-C but low HDL-C showed significant reductions in major coronary events over 5 years on statin therapy (49 [EL 1; RCT]; 469 [EL 1; RCT]). The extent of these positive results generated interest in the possible benefits of more aggressive cholesterol lowering. Subsequently, the Heart Protection Study (HPS) secondary prevention trial examined the efficacy of simvastatin for lipid lowering among a large cohort (N = 20,536) of individuals at high risk, including 5,963 with diabetes and approximately 3,500 who entered the study with optimal LDL-C levels (<100 mg/dL). Among those individuals, reducing LDL-C to as low as 65 mg/dL was safe and decreased the relative risk of vascular mortality at a rate similar to that of individuals with higher baseline LDL-C concentrations (about 20%) (25 [EL 1; RCT]). Moreover, a meta-analysis comparing 4 standard-dose vs high-dose statin trials (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction [PROVE-IT–TIMI] 22, A-to-Z, TNT, and End Points Through Aggressive Lipid Lowering [IDEAL]) found a significant 16% decrease in coronary death, MI, or any cardiovascular event among individuals receiving high-dose therapy. High-dose therapy also significantly reduced nonfatal MI, CVA, unstable angina, and revascularization risk (472 [EL 1; MRCT]). The final results of the JUPITER trial provide additional data on aggressive therapy in individuals with moderate-to-low LDL-C levels (<130 mg/dL) combined with elevated inflammation (indicated by hsCRP levels ≥2.0 mg/L). In this trial, individuals receiving rosuvastatin had their LDL-C and hsCRP levels reduced to medians of 55 and 1.8, respectively; these effects were accompanied by significant reductions in cardiovascular events and mortality (320 [EL 1; RCT]; 476 [EL 4; NE]). In addition, several imaging studies have examined the effects of aggressive therapy on atheroma volume and CAC, with varying results.

Extreme Risk

Accumulated evidence suggests a lower limit of LDL-C beyond which no further advantage would be gained. Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, stage 3 or 4 CKD , or HeFH who also have at least 1 additional risk factor are recommended to target a reduced LDL-C treatment goal of <70 mg/dL. However, a group of individuals exists who can be categorized as "Extreme Risk;" these individuals may benefit from an even lower LDL-C treatment goal of <55 mg/dL. Extreme risk indi-

viduals are those with certain risk factors that increase their likelihood of adverse ASCVD outcomes, including:

- progressive ASCVD, including unstable angina, that persists after achieving an LDL-C <70 mg/dL
- established clinical cardiovascular disease in individuals with diabetes, stage 3 or 4 CKD, and/or HeFH, and/or
- a history of premature ASCVD (<55 years of age for males, <65 for females)

Individuals at extreme risk are recommended to receive intensive high-dose statin therapy or statins in combination with ezetimibe or PCSK9 inhibitors to achieve further LDL-C reduction and reach the goal of <55 mg/dL.

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) clarified the benefits of extremely tight lipid control for individuals at very high or extreme risk. This trial investigated the effects of intensified lipid treatment (statins plus ezetimibe) versus statin use alone on a composite cardiovascular outcome (cardiovascular death, MI, hospitalization for unstable angina, coronary revascularization ≥30 days, and CVA) in individuals recently hospitalized for ACS and who had baseline LDL-C levels 50 to 100 mg/dL (individuals receiving lipid-lowering therapy) or 50 to 125 mg/dL (individuals not receiving lipid-lowering therapy). Mean LDL-C at baseline for both groups was 93.8 mg/dL; at 1 year of treatment, mean LDL-C in individuals receiving intensive treatment was 53.2 mg/dL, while individuals receiving statins alone had a mean LDL-C of 69.9 mg/dL (35 [EL 1; RCT]). A 7-year Kaplan-Meier estimate for the primary endpoint showed that 32.7% of individuals in the simvastatin–ezetimibe group experienced an event, compared with 34.7% of individuals who received simvastatin alone; this translated into a 6.4% relative risk reduction (HR: 0.936, 95% CI: 0.89 to 0.99; *P* = .016) and a 2.0% absolute risk reduction.

Individuals with diabetes (diabetes type not specified) comprised 27% of those enrolled in the IMPROVE-IT trial (35 [EL 1; RCT]). Those who received intensified lipid treatment for 1 year experienced a mean LDL-C decrease of 43 mg/dL, compared with a 23 mg/dL decrease in individuals who received statin treatment alone (487 [EL 4; NE]). The Kaplan-Meier estimate of prespecified subgroups showed that the use of intensive treatment resulted in a 14.4% risk reduction for individuals with diabetes (HR: 0.856, 95% CI: 0.779, 0.939) for the cardiovascular endpoint, whereas individuals without diabetes experienced a 2.3% risk reduction (HR: 0.977, 95% CI: 0.915, 1.044; *P* = .023) (35 [EL 1; RCT]; 487 [EL 4; NE]). This represents a 14% decreased risk for cardiovascular events with tight LDL-C control in individuals with diabetes. No other prespecified risk group (current smoker, hypertension, prior percutaneous coronary intervention, prior CVA, or elevated creatinine clearance) showed a significant interaction in subanalyses (35 [EL 1; RCT]; 488[EL 1; RCT]).

Outcomes from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial support extremely tight lipid control for individuals at very high or extreme cardiovascular risk (488 [EL 1; RCT]). This randomized, double-blind, placebo-controlled trial investigated the effects of adding evolocumab to high-intensity statin therapy compared with high-intensity statins alone on a composite cardiovascular outcome that included MI, cardiovascular death, stroke, coronary revascularization, or hospitalization for unstable angina. Median patient follow-up was 2.2 years. Study results included data for over 27,500 individuals (representing 59,865 patient-years) 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).

Patients in the evolocumab group achieved a mean LDL-C of 30 mg/dL, representing a reduction of 59% (95% CI: 58 to 60; *P*<.001) compared with the placebo group (mean LDL-C 69.9 mg/dL). At 26 months, primary composite endpoint events were experienced by 9.8% of individuals in the evolocumab group compared with 11.3% in the placebo group, representing a 15% risk decrease (HR: 0.85, 95% CI: 0.79 to 0.92; *P* <.001). Beyond the second year of the study, this risk reduction increased to 20% (95% CI: 0.73-0.89). A secondary composite endpoint, consisting of cardiovascular death, MI, or stroke, was also significantly decreased in the evolocumab group. This endpoint was experienced by 5.9% of individuals receiving evolocumab compared with 7.4% in the placebo group, for a 20% risk reduction (HR: 0.80, 95% CI: 0.73 to 0.88; *P* <.001). Beyond the second year, this risk reduction increased to 25% (95% CI: 0.66-0.85, *P* <.001). For singular endpoints, evolocumab use significantly reduced the risk of MI (HR: 0.73, 95% CI: 0.65 to 0.82; *P* <.001), stroke (HR: 0.79, 95% CI 0.66 to 0.95, *P* <.01), and coronary revascularization (HR: 0.78, 95% CI: 0.71 to 0.86; *P* <.001). However, cardiovascular death outcomes showed no significant differences at a median follow-up of 26 months.

The additional ASCVD benefit in very high-risk individuals with further lowering of LDL-C to <55 mg/dL utilizing statin therapy in combination with ezetimibe or a PCSK9 inhibitor forms the basis of the AACE recommendation for a new category of risk, extreme risk, with an LDL-C goal of <55 mg/dL.

Additionally, a 2010 Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis (N = 169,138, 26 clinical trials) investigated the benefits of statin therapy for LDL-C reduction in a large population that included individuals with ACS or stable ASCVD; the population also included individuals with diabetes (T1DM [n = 337] and T2DM [n = 5,414]) and/or heart failure. Investigators found that at 1 year of treatment, individuals who received statin

therapy lowered their LDL-C by 41.4 mg/dL more than those who received placebo, and individuals who received intensive statin therapy lowered their LDL-C by 19.7 mg/dL more than those who received standard statin therapy. For all individuals, results showed a 24% reduction in first major vascular events for every 38.7 mg/dL LDL-C reduction. The CTT subanalysis of individuals receiving standard versus intensive statin therapy showed that even individuals with a low baseline LDL-C experienced further benefit if the baseline LDL was lower. For individuals with a baseline LDL-C of <77 mg/dL, every 38.7 mg/dL further reduction in LDL-C corresponded to a ~29% reduction in major vascular events. For individuals with a baseline LDL of <70 mg/dL, a lower LDL-C (38.7 mg/dL) was associated with a 37% decrease in events (121 [EL 1; MRCT]).

A 2014 meta-analysis that included data on individuals with even lower LDL-C levels confirms the CTT results and demonstrated that individuals achieving an LDL-C <50 mg/dL, a non-HDL-C <75 mg/dL, and apo B <50 mg/dL have the lowest ASCVD events (34 [EL 1; MRCT]). The meta-analysis included data for 38,153 individuals from 8 randomized controlled trials evaluating the use of statin therapy for lipid control. Individual participant data were analyzed by the achieved LDL-C at 1 year of follow-up, with cutoff categories of 50, 75, 100, 125, 150, 175, and ≥175 mg/dL. Compared to individuals with an LDL-C ≥175 mg/dL, individuals who achieved an LDL-C level <50 mg/dL experienced decreased risk for major cardiovascular events, with an adjusted HR of 0.44 (95% CI: 0.35, 0.55). Furthermore, the decreased risk for major cardiovascular events experienced by individuals who achieved LDL-C levels <50 mg/dL was statistically significant when compared to individuals who achieved LDL-C levels between 75 and <100 mg/dL, with an adjusted HR of 0.81 (95% CI: 0.70, 0.95) (34 [EL 1; MRCT]).

Because of the ASCVD benefit demonstrated in the IMPROVE-IT randomized controlled trial, with an achieved average LDL-C of 53.2 mg/dL (35 [EL 1; RCT]), an Extreme Risk category of LDL-C <55 mg/dL was established.

Individuals With T2DM

Diabetes increases cardiovascular risk to the extent that it is considered an ASCVD risk equivalent (10 [EL 4; NE]). Individuals with diabetes are considered high risk, very high risk, or extreme risk. Those at high risk (which includes individuals with diabetes and no other risk factors) have an LDL-C target of less than 100 mg/dL. Very high-risk individuals with diabetes have 1 or more additional risk factors and an LDL-C target of less than 70 mg/dL (19 [EL 4; NE]). Extreme risk individuals with diabetes (T1DM and T2DM) will have established clinical cardiovascular disease, stage 3 or 4 CKD, and/or HeFH and have an LDL-C goal of <55 mg/dL (11 [EL 4; NE]; 17 [EL 2; MNRCT]; 25 [EL 1; RCT]; 26 [EL 1; RCT]; 27 [EL 1;

RCT]; 30 [EL 1; RCT]; 31 [EL 4; NE]; 34 [EL 1; MRCT]; 35 [EL 1; RCT]; 121 [EL 1; MRCT]).

Secondary prevention statin studies such as HPS showed significant risk reduction among individuals with diabetes. Based on this, the Collaborative Atorvastatin Diabetes Study (CARDS) was designed to assess the effects of aggressive lipid lowering on the primary prevention of ASCVD in individuals with T2DM. In individuals with average or mildly elevated LDL-C at baseline (mean 117 mg/dL), an LDL-C reduction to a mean of 82 mg/dL was accompanied by a 37% reduction in major cardiovascular events compared with placebo (51 [EL 1; RCT]). CARDS, which originally planned a mean follow-up of 4 years, was terminated 2 years early because of the significant benefit achieved in the statin group (51 [EL 1; RCT]).

Individuals with T1DM or T2DM and the insulin resistance syndrome are at particularly high risk for ASCVD. An analysis of participants in the Third National Health and Nutrition Examination Survey who were 50 years and older found that the presence of insulin resistance syndrome in individuals with diabetes was very high: 86%. Furthermore, the combination of diabetes and the insulin resistance syndrome in these individuals was associated with the highest prevalence of ASCVD (19.2%), while those with neither condition had the lowest prevalence (8.7%) (119 [EL 3; SS]).

Another possibly useful marker of risk in individuals with T2DM is hsCRP. The Health Professionals Follow-up Study examined the predictive value of hsCRP in 750 men with T2DM and no baseline ASCVD. Data from this study showed that increasing hsCRP levels were associated with a progressively greater ASCVD risk, even with adjustment for other risk factors such as BMI, family history of ASCVD, physical activity, and markers of inflammation. The multivariate-adjusted relative risks for MI, coronary revascularization, or CVA by hsCRP values of 1.0, 1.0 to 3.0, and greater than 3.0 were 1.00, 1.50, and 2.09 (P = .028), respectively, over the 5-year follow-up period (489 [EL 2; PCS]). Studies such as these suggest that establishment of the insulin resistance syndrome or elevated hsCRP in individuals with diabetes may aid in identifying increased ASCVD risk and thus candidates for aggressive primary prevention therapy. Individuals with prediabetes, impaired fasting glucose, or impaired glucose tolerance are considered to be at increased risk for ASCVD. Lipid treatment goals should be the same in individuals with prediabetes as in individuals with diabetes (100 [EL 4; NE]). Individuals with T1DM for more than 15 years or with 2 or more risk CV factors should be treated as if they had T2DM (101 [EL 3; CSS]; 102 [EL 2; PCS]; 103 [EL 2; PCS]; 104 [EL 2; PCS]; 105 [EL 2; PCS]; 106 [EL 4; NE]).

Individuals With Small, Dense LDL Pattern B

Various putative mechanisms associate the small, dense LDL pattern B with atherogenicity. Small, dense

LDL pattern B is linked to ASCVD risk, as well as to other risk factors such as T2DM, the insulin resistance syndrome, and PCOS (150 [EL 4; NE]; 151 [EL 2; RCCS]; 152 [EL 3; SS]; 153 [EL 1; RCT]; 157 [EL 3; CSS]; 158 [EL 2; PCS]; 159 [EL 3; CSS]). In fact, in 1997, the Stanford Coronary Risk Intervention Project (SCRIP) - Berkeley investigators reported that multifactorial risk reduction produced significant arteriographic benefit in individuals with LDL-C levels less than 125 mg/dL who had LDL pattern B, but it did not benefit individuals with LDL-C levels less than 125 mg/dL who had LDL pattern A (61 [EL 4; NE]; 490 [EL 4; NE]).

Individuals Undergoing Coronary Artery Bypass Graft (CABG)

Studies show that aggressive LDL-C–lowering statin therapy may benefit individuals who undergo CABG both pre- and postoperatively (491 [EL 4; NE]; 492 [EL 1; RCT]; 493 [EL 3; SS]; 494 [EL 1; RCT]; 495 [EL 2; PCS]; 496 [EL 3; SS]; 497 [EL 1; RCT]; 498 [EL 2; PCS]). However, additional statin-related effects such as improved endothelial function and reduction of inflammatory markers make it unclear whether LDL-C reduction by means other than statin therapy would produce the same benefits (473 [EL 1; MRCT]; 499 [EL 1; RCT]; 500 [EL 4; NE]; 501 [EL 1; RCT]; 502 [EL 1; RCT]; 503 [EL 4; NE]).

In the Post CABG trial, aggressive versus very low-dosage lovastatin therapy (40-80 mg daily vs. 2-2.5 mg daily) resulted in LDL-C levels of 93 to 97 mg/dL compared with levels of 132 to 136 mg/dL, and angiography showed the rate of disease progression decreased by 31% at study end in aggressively treated individuals (492 [EL 1; RCT]). An extended follow-up at 7.5 years found a significant 24% reduction in the composite endpoint (cardiovascular and unknown-cause death, nonfatal MI, CVA, CABG, or angioplasty; P = .001) with aggressive therapy (491 [EL 4; NE]; 492 [EL 1; RCT]; 494 [EL 1; RCT]). Moreover, studies show that individuals taking statins before CABG surgery have reduced postoperative cardiovascular events and death, as well as reductions in inflammatory markers such as interleukin-6 and interleukin-8 (493 [EL 3; SS]; 495 [EL 2; PCS]; 496 [EL 3; SS]; 497 [EL 1; RCT]; 498 [EL 2; PCS]).

Individuals With ACS

Several studies suggest that statin therapy following ACS may provide anti-inflammatory benefits through rapid reductions in hsCRP, which in turn, improve long-term survival (53 [EL 1; RCT]; 501 [EL 1; RCT]; 504 [EL 1; RCT]; 505 [EL 3; RCT]). The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trials, which studied high-dosage atorvastatin versus moderate-dosage pravastatin in individuals with ACS over 2.5 years, found that high-dosage therapy reduced cardiovascular events at a nonstatistically significant rate compared with low-dosage therapy (53 [EL 1; RCT]). Similar results were reported for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, which compared high-dosage atorvastatin with placebo (506 [EL 1; RCT]). Moreover, analyses of the PROVE IT trial data demonstrate that early aggressive statin therapy after ACS can reduce 30-day mortality rates (53 [EL 1; RCT]).

Older Individuals

An analysis of data from the TNT study found that among individuals 65 years or older (N = 3,809), high-dosage statin therapy produced greater reductions (3.2% absolute reduction, 19% relative risk reduction; P = .032) in cardiovascular events and mortality than low-dosage therapy. Adverse event rates in older individuals were slightly greater than in individuals younger than 65 years, but were still low and not significantly higher than with the overall TNT cohort. A small increase in all-cause mortality prompted the investigators to suggest continued caution when treating older individuals with statins (507 [EL 1; RCT]). Nonetheless, subgroup analyses of several statin studies, as well as the CTT meta-analysis, confirm that overall efficacy and adverse events are similar between age groups. This indicates that aggressive statin therapy in selected older individuals may be beneficial (121 [EL 1; MRCT]; 327 [EL 1; RCT]; 329 [EL 2; PCS]; 478 [EL 1; RCT]; 508 [EL 1; RCT]; 509 [EL 1; MRCT]). As noted earlier, the PROSPER trial demonstrated a secondary but not primary prevention ASCVD event benefit for the group older than 70 years treated with pravastatin (26 [EL 1; RCT]). Furthermore, results from the 4S trial, which used simvastatin, 40 mg daily, as its highest dosage, showed that even a submaximal dose produced a reduced event rate at any age. Individuals 60 years and older experienced relative risk reductions for death and major coronary events of 27% (P<.01) and 29% (P<.0001), respectively, compared with placebo (49 [EL 1; RCT]).

Combination Therapy

Certain clinical situations warrant the use of a combination of lipid-lowering agents. Since the adverse effects of 2 or more drugs may be additive, clinical judgment is needed to balance the risks and benefits of combination therapy. Combination therapy should be considered in the following circumstances (23 [EL 4; NE]; 510 [EL 4; NE]; 511 [EL 4; NE]).

Cholesterol Level is Markedly Increased and Monotherapy Does Not Achieve the Therapeutic Goal

Combining a statin with a cholesterol absorption inhibitor, bile acid sequestrants, or PCSK-9 inhibitor should be considered when the desired target cannot be achieved with the statin alone; these agents may be used instead of statins in cases of statin-related adverse events or intolerance.

Statins yield only modest (approximately 6%) LDL-C reductions for each dose doubling above standard dosage (28 [EL 4; NE]). Therefore, in some instances, adding a drug with a complementary mode of action may be more effective than increasing the statin dosage. For example, the combination of simvastatin and ezetimibe is highly effective in lowering LDL-C. The Study of Heart and Renal Protection (SHARP) study, in which simvastatin, 20 mg daily, plus ezetimibe, 10 mg daily, was given, showed that a reduction of LDL-C safely reduced the incidence of major atherosclerotic events in a wide range of individuals with advanced CKD (512 [EL 1; RCT]). The IMPROVE-IT study also demonstrated a significant ASCVD benefit when ezetimibe 10 mg was added to simvastatin treated to an LDL goal of 70 mg/dL in individuals with recent ACS (35 [EL 1; RCT]). The combination of statin and bile acid sequestrant has also been shown to have additive LDL-C lowering effects compared with regular-dosage monotherapy (513 [EL 1; RCT]; 514 [EL 1; RCT]; 515 [EL 1; RCT]; 516 [EL 1; RCT]). Such combinations have been shown to provide LDL-C lowering comparable to or greater than that achieved by high-dosage statin monotherapy (513 [EL 1; RCT]; 514 [EL 1; RCT]; 515 [EL 1; RCT]; 518 [EL 1; RCT]). Examples of potentially appropriate dual therapy include statin + bile acid sequestrant, statin + ezetimibe, and statin + niacin.

Lower Dosages of 2 or More Drugs May Help to Avoid or Minimize Toxicity

Some adverse effects associated with statin drugs are dosage related (e.g., myopathy/rhabdomyolysis), and with some statins, liver dysfunction may increase with increased dosage (519 [EL 4; NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]) and may reverse with lower doses or changing to less than daily dosing (524 [EL 2; RCCS]). Therefore, if statin tolerability is a concern, a combination of drugs at lower dosages may be effective. Moreover, if one combination causes tolerance problems, another combination may safely achieve the desired results (10 [EL 4; NE]). Examples include statin + bile acid sequestrant and statin + ezetimibe.

Mixed Dyslipidemia is Present (High TG, Low HDL-C, High LDL-C)

If high-dosage monotherapy does not achieve lipid goals, a combination regimen may be warranted to lower both cholesterol and TG levels and to raise HDL-C levels (510 [EL 4; NE]; 511 [EL 4; NE]). For example, the statin and niacin combination produces LDL-C reductions comparable to those of statin monotherapy and leads to significantly greater improvements in HDL-C and TG levels (326 [EL 1; RCT]; 352 [EL 1; RCT]; 353 [EL 1; MRCT]).

Niacin increases HDL-C and in higher doses lowers LDL-C; however, no clinical benefit has been demon-strated when niacin is added to aggressive statin regimens (483 [EL 1; RCT]; 525 [EL 4; NE]). Although the ezeti-mibe and fenofibrate combination moderately improves LDL-C, it also substantially improves TG and HDL-C levels (Tables 15 and 16). Examples of combination ther-apy include statin + fibrate, statin + niacin, statin + bile acid sequestrant, ezetimibe + fibrate, and ezetimibe + niacin. The National Institutes of Health Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides (AIM-HIGH) study failed to show a cardiovascular outcome benefit with the addition of niacin in individuals treated with statins and an average LDL-C of 71 mg/dL (525 [EL 4; NE]). The Treatment of HDL to Reduce the Incidence of Vascular Events from the HPS research unit (HPS2-THRIVE) trial found that extended-release niacin in combination with laropiprant added to effective statin-based LDL-C-lowering therapy did not significantly reduce major vascular events but did increase the risk of serious adverse events (484 [EL 1; RCT]).

Choosing Lipid-Lowering Drugs

Currently available lipid-lowering drugs include hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), fibric acid derivatives (fibrates), nicotinic acid (niacin), bile acid sequestrants, cholesterol absorption inhibitors (ezetimibe), PCSK9 inhibitors (alirocumab, evolocumab), a microsomal transfer protein (MTP) inhibi-tor (lomitapide), and an antisense apolipoprotein B oligo-nucleotide (mipomersen). The primary metabolic effects and main drawbacks of these 8 drug classes are summa-rized in Table 13 (410 [EL 4; NE]; 517 [EL 1; RCT]; 519 [EL 4; NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]; 526 [EL 2; PCS]; 527 [EL 1; RCT]; 528 [EL 2; NRCT]; 529 [EL 2; NRCT]; 530 [EL 2; NRCT]; 531 [EL 1; RCT]; 532 [EL 1; RCT]; 533 [EL 1; RCT]; 534 [EL 1; MRCT]; 535 [EL 4; NE]; 536 [EL 1; RCT]; 537 [EL 1; RCT]; 538 [EL 2; PCS]; 539 [EL 1; RCT]; 540 [EL 1; RCT]; 541 [EL 1; RCT]; 542 [EL 1; RCT]; 543 [EL 2; PCS]; 544 [EL 1; RCT]; 545 [EL 1; RCT]; 546 [EL 4; NE]; 547 [EL 1; RCT]; 548 [EL 4; NE]; 549 [EL 4; NE]; 550 [EL 4; NE]; 551 [EL 1; MRCT]; 552 [EL 4; NE]; 553 [EL 1; MRCT]; 554 [EL 4; NE]; 555 [EL 4; NE]; 556 [EL 4; NE]; 557 [EL 4; NE]; 559 [EL 4; NE]; 560 [EL 4; NE]; 561 [EL 4; NE]; 562 [EL 4; NE]; 563 [EL 4: NE]; 564 [EL 4; NE]; 565 [EL 4; NE]). The clinical efficacy of these phar-macologic agents in both primary and secondary preven-tion of coronary events and mortality is outlined Table 15 and Table 16. A summary of available lipid-lowering thera-pies and dosages is presented in Table 18 (519 [EL 4; NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]; 548 [EL 4; NE]; 549 [EL 4; NE]; 552 [EL 4; NE]; 554 [EL 4; NE]; 555 [EL 4; NE]; 556 [EL 4; NE]; 557 [EL 4; NE]; 558 [EL 4; NE]; 559 [EL 4; NE]; 560 [EL 4; NE]; 562 [EL 4; NE]; 563 [EL 4; NE]; 564 [EL 4; NE]; 565 [EL 4; NE]; 566 [EL 4; NE]).

Statins

Statins are the drug of choice for LDL-C reduction. Currently available statins include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Since the publication of the 4S trial in 1994 (49 [EL 1; RCT]; 202 [EL 1; RCT]), numerous large clinical trials have established the efficacy and safety profile of this drug class. Results from the major statin trials are outlined in Table 17.

Statins work by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase, the key rate-limiting enzyme in hepatic cholesterol synthesis. This triggers increased expression of hepatic LDL receptors and increased LDL-C clearance (519 [EL 4; NE]; 521 [EL 4; NE]; 523 [EL 4; NE]; 567 [EL 4; NE]). Clinical trials indicate that statins decrease plasma LDL-C in a dose-dependent fashion by 20 to 55%. Statins also exert modest lowering effects on VLDL-C, intermediate-density lipoprotein cholesterol, and TG (10-30%) and raise HDL-C by 2 to 10% (519 [EL 4; NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]; 550 [EL 4; NE]). Studies also suggest that statin therapy (atorvastatin and rosuvastatin) may improve LDL subfraction profiles, although larger clinical trials may be necessary to confirm the effect of statins on LDL particle size and density (568 [EL 2; PCS]; 569 [EL 1; RCT]; 570 (EL 2; PCS]; 571 [EL 1; RCT]; 572 [EL 2; PCS]; 573 [EL 1; RCT]; 574 [EL 1; RCT]; 575 [EL 1; RCT]). Additionally, results of the HPS suggest that simvastatin may somewhat improve ASCVD risk among individuals who smoke cigarettes, although this benefit does not approach that achieved with smoking cessation (25 [EL 1; RCT]).

A 2010 meta-analysis of 26 randomized clinical trials conducted by the CTT group involving close to 170,000 participants confirmed the benefit of LDL-C lowering with a statin. The CTT found that, over approximately 5 years across all studies evaluated, a 1 mmol/L (~38 mg/dL) reduction in LDL-C resulted in a 21% decrease in major vascular events (nonfatal MI or ASCVD death), a 19% reduction in coronary revascularizations, and a 16% reduction in CVA (Fig. 2). Intensive statin treatment also led to an overall 10% reduction in all-cause mortality compared with that observed in control participants (P<.0001) (Fig. 3) (121 [EL 1; MRCT]).

The CTT 2010 meta-analysis found that further reductions in LDL cholesterol resulted in further reductions in the incidence of heart attack, revascularization, and ischemic CVA; data suggested reducing LDL cholesterol by 2 to 3 mmol/L would reduce the risks by 45 to 50% (121 [EL 1; MRCT]). Compared to standard regimens, more intensive statin therapy regimens showed a highly significant 15% further reduction in major vascular events (121 [EL 1; MRCT]). The analysis found that the size of proportional reduction in major vascular events was directly proportional to the absolute LDL cholesterol reduction achieved,

suggesting a further benefit from more intensive statin therapy, as each reduction by 1.0 mmol/L reduces the risk of occlusive vascular events by about 20%, regardless of baseline cholesterol concentration (121 [EL 1; MRCT]). The authors of the study conclude that the primary goal for individuals at high risk of occlusive vascular events should be to achieve the largest possible LDL cholesterol reduction possible without increasing risk of myopathy, rather than setting an LDL cholesterol target goal (121 [EL 1; MRCT]).

Similar benefits for statin therapy were found in a meta-analysis of CTT participants with T1DM and T2DM, irrespective of whether individuals had a history of vascular disease (576 [EL 1; MRCT]). However, another meta-analysis of data from 32,752 participants without diabetes at baseline from 5 statin trials showed that intensive-dosage statin therapy was associated with a modest increased risk of new-onset diabetes compared with moderate-dosage statin therapy. Importantly, ASCVD events were decreased to a greater extent in the intensively treated group than was the increased risk of diabetes (i.e., 6.5 fewer cases of cardiovascular events per 1,000 patient-years versus 2 additional cases per 1,000 patient-years of diabetes in the intensively treated group) (551 [EL 1; MRCT]).

The JUPITER trial, a randomized, double-blind, placebo-controlled study of statin therapy among individuals with moderate to low LDL-C (<130 mg/dL) but elevated hsCRP (≥2.0 mg/L) (N = 17,802), was halted ahead of schedule. The primary endpoint was first occurrence of a major cardiovascular event (e.g., nonfatal MI, nonfatal CVA, hospitalization for unstable angina, arterial revascularization, or cardiovascular death); the trial's suspension was due to unequivocal evidence of reduced cardiovascular morbidity and mortality in the statin group (320 [EL 1; RCT]; 476 [EL 4; NE]). Median follow-up in this trial was 1.9 years; maximal follow-up was 5 years (320 [EL 1; MRCT]). During the study period, the primary endpoint occurred in 142 and 251 individuals in the rosuvastatin and placebo groups, respectively; this translated to a relative hazard reduction of 44% in the rosuvastatin group (95% CI, 0.46-0.69; *P*<.00001) (320 [EL 1; RCT]). At 12 months, median LDL-C, TG, and hsCRP levels were 50%, 17%, and 37% lower, respectively, in the rosuvastatin group than in the placebo group (320 [EL 1; RCT]). Further analysis of JUPITER study results revealed a 79% ASCVD event reduction in participants who achieved both an LDL-C concentration less than 70 mg/dL and hsCRP concentration less than 1.0 mg/L (472 [EL 1; RCT]).

An analysis of surviving individuals from the West of Scotland Coronary Prevention (WOSCOPS) study indicates that statin therapy may improve long-term outcomes. A follow-up study gathered treatment information at 1, 3, and 5 years after the trial and tracked clinical event data for an additional 10 years. At 5 years after the trial, statin use was only 38.7% in the original pravastatin group and

35.2% in the original placebo group. Compared with what was observed in the original placebo group, the relative reduction of cardiovascular mortality in the original pravastatin group was 34% during the initial trial ($P = .03$), 14% during the post-trial period ($P = .11$), and 19% during the total follow-up period ($P = .01$). Relative risk reduction for a composite endpoint (ASCVD-related death or nonfatal MI) in the original pravastatin group compared with that in the original placebo group was 40% during the trial ($P<.001$), 18% after the trial ($P = .02$), and 27% for the total follow-up period ($P<.001$) (577 [EL 1; RCT]).

The clinically demonstrated lipid-altering effects of various statins in various dosage ranges are shown in Table 19 (578 [EL 1; RCT]; 579 [EL 1; RCT]). These data are from the Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin (CURVES) study (578 [EL 1; RCT]) and the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) study and are generally representative of rates reported in the literature (579 [EL 1; RCT]).

Imaging Studies

Several studies have applied imaging techniques to assess the effect of statin treatment on coronary atherosclerosis regression and progression. Table 14 outlines the key statin imaging trials conducted to date. The Monitored Atherosclerosis Regression Study (MARS) found that in lesions with 50% or greater stenosis at baseline, lovastatin resulted in a significant mean reduction of 4.1% compared with 0.9% with placebo ($P = .005$) (325 [EL 1; RCT]). The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial used intravascular ultrasonography and found that intensive therapy (atorvastatin, 80 mg daily) resulted in a significantly lower progression rate of both atheroma volume and percent atheroma volume compared with moderate therapy (pravastatin, 40 mg daily) (327 [EL 1; RCT]). In the A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) study, a regimen of rosuvastatin, 40 mg daily for 24 months, resulted in a mean percent atheroma volume reduction of –0.98% and a mean change in atheroma volume of –6.1 mm^3 in the most diseased 10-mm^3 subsegment (329 [EL 1; RCT]). The imaging arm of the HDL-Atherosclerosis Treatment Study (HATS) found that the combination of simvastatin and niacin decreased proximal stenosis by 0.4% versus an increase of 3.9% with placebo (326 [EL 1; RCT]). However, in a comparison of high-dosage atorvastatin therapy (80 mg daily) versus moderate-dosage (10 mg daily) over 1 year of treatment, Schmermund et al (330 [EL 1; RCT]) found no difference in CAC progression as measured by electron-beam computed tomography. An unpublished 12-month trial, Carotid Atorvastatin Study in Hyperlipidemic, Postmenopausal Women: a Randomized

Evaluation of Atorvastatin versus Placebo (CASHMERE), studied the effect of atorvastatin on CIMT in postmenopausal women (median age, 57 years) (580 [EL 4; NE]). This study found no significant difference in mean CIMT change from baseline in individuals treated with 40- or 80-mg daily atorvastatin compared with placebo (2.9% and 2.5% change, respectively) (580 [EL 4; NE]), raising the possibility that CIMT may have limitations as a surrogate marker for ASCVD. Data from 2011 directly comparing intensive (maximal dosage) therapy of atorvastatin and rosuvastatin showed that despite the lower LDL-C level and higher HDL-C level achieved with rosuvastatin, a similar degree of regression of atherosclerosis as determined by decreased percent atheroma volume occurred with both agents (581 [EL 1; RCT]).

Metabolism and Adverse Events

Certain differences in the metabolism of various statins may require clinical consideration. Lovastatin, simvastatin, and atorvastatin are partially metabolized by the cytochrome 450 isoenzyme, CYP 3A4. This may result in drug interactions with agents that use the same route of metabolism (i.e., macrolide antibiotics, antifungal agents, and cyclosporine) (520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]). The most common adverse events associated with statin drugs include hepatic, renal, and musculoskeletal complications. A 2006 meta-analysis of 35 randomized controlled trials covering more than 74,000 individuals identified the following rates of adverse events associated with statin use (582 [EL 1; MRCT]):

- myalgia (musculoskeletal pain/symptoms without documented creatine kinase elevations): 15.4%,
- liver toxicity (serum alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal): 1.4%,
- creatine kinase elevations: 0.9%, and
- myopathy/rhabdomyolysis (muscle aches/weakness with creatine kinase levels ≥10 times the upper limit of normal): 0.2%.

In this meta-analysis, rates of myalgia and myopathy/rhabdomyolysis were not statistically different from placebo (582 [EL 1; MRCT]). However, it should be expected that the reported incidence of myalgia in clinical trials is lower than that observed in routine practice; mild symptoms may be underreported, and individuals considered at high risk for statin-related adverse events, including individuals with a history of muscle symptoms or creatine kinase elevations, are generally excluded from trials (582 [EL 1; MRCT]; 583 [EL 2; PCS]; 584 [EL 4; NE]). Observational studies of individuals in usual care settings have identified myalgia rates of 10 to 15% (583 [EL 2; PCS]; 585 [EL 3; SS]). Also, risk may increase with co-administration of other drugs or in individuals with a history of renal insufficiency (52 [EL 1; RCT]; 482 [EL 1; RCT]; 519 [EL 4;

NE]; 520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]; 550 [EL 4; NE]; 579 [EL 1; RCT]; 586 [EL 1; RCT]; 587 [EL 3; SS]; 588 [EL 1; RCT]). Although rhabdomyolysis is rare (reported rates are 0.44 per 10,000 person-years for statin monotherapy and 5.98 per 10,000 person-years for statin/fibrate combination therapy), any reported symptoms require close attention due to the high case fatality rate associated with this condition (582 [EL 1; MRCT]; 589 [EL 1; RCT]).

Physicians should be aware of the potential increased risk of muscle injury with the 80-mg simvastatin dosage compared with the lower dosages of simvastatin. Individuals who have tolerated an 80-mg dosage for more than 1 year may continue therapy, but new regimens should no longer be increased to such dosages. A warning states that simvastatin, 80 mg daily, should not be used with amlodipine or ranolazine (522 [EL 4; NE]).

Additionally, current evidence indicates that a mild elevation in blood glucose levels is associated with intensive statin therapy (551 [EL 1; MRCT]; 590 [EL 2; PCS]). This is not considered to be clinically important in light of the known benefits of statin drugs in reducing ASCVD. Similarly, an increase in new-onset diabetes cases has been observed in individuals treated intensively with statins. However, this occurs to a lesser extent than the associated cardiovascular event reduction (551 [EL 1; MRCT]). An evaluation of new statin users aged 66 years or older found that the odds of new-onset diabetes was ~20% higher for individuals taking atorvastatin or simvastatin (compared with fluvastatin, lovastatin, and pravastatin) (591 [EL 2; PCS]).

Statins are also known to be teratogenic (pregnancy category X) (521 [EL 4; NE]; 522 [EL 4; NE]; 523 [EL 4; NE]). Other lipid-lowering medications such as fibrates (pregnancy category C) or colesevelam (pregnancy category B) may be more appropriate in reproductive-age women (549 [EL 4; NE]; 557 [EL 4; NE]).

Fibrates

Fibrates are effective for treating individuals with severe hypertriglyceridemia and for individuals at risk of ASCVD who have elevated TG and/or low HDL-C levels as their primary lipid abnormality (8 [EL 4; NE]; 361 [EL 4; NE]; 363 [EL 4; NE]; 592 [EL 1; RCT]). Currently available fibrates are gemfibrozil, fenofibrate, and fenofibric acid. Fibrates appear to act by multiple mechanisms, including peroxisome proliferator-activated receptor alpha agonism leading to upregulation of genes encoding lipoprotein lipase and apo AI, downregulation of the gene encoding apo CIII, inhibition of lipoprotein lipase, and reduction of apo B and VLDL-C production (593 [EL 4; NE]).

Clinical trials indicate that fibrates lower TG by 20 to 35% and increase HDL-C by 6 to 18%. Trials such as the VA-HIT study (345 [EL 1; RCT]; 346 [EL 1; RCT]) and HHS (348 [EL 1; RCT]) have additionally demonstrated that fibrate monotherapy decreases cardiovascular events in men with or without ASCVD. Two angiographic trials supported these metabolic findings and revealed an independent effect of fibrate therapy on lesion progression (478 [EL 1; RCT]; 594 [EL 1; RCT]). A secondary outcome, intention-to-treat analysis of VA-HIT found that major coronary events among individuals with insulin resistance were increased in every tertile of HDL-C or TG levels; gemfibrozil reduced events in these individuals at a significant rate of 28%, compared with 20% in non-insulin-resistant individuals (595 [EL 1; RCT]). Notably, in VA-HIT, participants who were current cigarette smokers were the only subgroup to experience no risk reduction from fibrate use, suggesting that the HDL-C-raising effect of fibrates may be blunted in the presence of tobacco use (595 [EL 1; RCT]).

Primary prevention of ischemic cardiovascular events with the use of fibrates was demonstrated only in individuals with both TG levels greater than 200 mg/dL and HDL-C levels less than 40 mg/dL in the FIELD study (secondary endpoints) (349 [EL 1; RCT]). The FIELD study showed that TG reduction over 5 years with fenofibrate was associated with reduced nonfatal ASCVD events and revascularizations (349 [EL 1; RCT]). An independent relationship between fibrate therapy and ASCVD mortality was not identified; however, this may have been because of substantial statin use in the placebo group (349 [EL 1; RCT]). In the nonstatin Bezafibrate Infarction Prevention (BIP) study (480 [EL 1; RCT]; 485 [EL 1; RCT]), a reduction in the primary endpoint of fatal or nonfatal MI or sudden death for individuals with TG values greater than 200 mg/dL was observed. The 18-year follow-up of the HHS found that individuals in the original gemfibrozil group had a 23% lower relative risk of ASCVD mortality than the original placebo group. Among those in the highest baseline tertile for both BMI and TG level, this risk reduction was 71% in the gemfibrozil group, corresponding to a 50% reduction in ASCVD mortality (350 [EL 2; PCS]). The failure to reach the primary endpoint targets of MI and cardiovascular death in the FIELD study (349 [EL 1; RCT]) and in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (596 [EL 1; RCT]) has resulted in an uncertain clinical benefit in treating individuals with fibrates who have lesser TG and HDL-C abnormalities.

In individuals with the small, dense LDL pattern B, fibrate treatment can also significantly reduce small LDL and increase large LDL concentrations without altering the overall LDL-C concentration (597 [EL 2; PCS]). Unlike gemfibrozil, fenofibrate can also reduce total cholesterol and LDL-C in individuals with type IIb hyperlipidemia (592 [EL 1; RCT]).

Adverse Events

Fibrates are associated with increased serum creatinine levels. However, it has been proposed that this is not caused by renal dysfunction, as creatinine clearance and glomerular filtration rates are unchanged with fibrate therapy (538 [EL 2; PCS]; 546 [EL 4; NE]). Therefore, the mechanism of action is unclear, although it has been suggested that the peroxisome proliferator-activated receptor alpha agonist action of the drugs may impair the generation of vasodilatory prostaglandins (546 [EL 4; NE]). Alternately, fibrates may cause increased metabolic production of muscular creatinine. However, an association between increased serum creatinine and increased creatine kinase has not been established (538 [EL 2; PCS]; 546 [EL 4; NE]). Although rare, fibrate use has been associated with myositis, myalgia/myopathy, or rhabdomyolysis; this risk increases with concomitant statin therapy (548 [EL 4; NE]; 549 [EL 4; NE]). Various studies have shown that fenofibrate increases homocysteine levels, while gemfibrozil has no consistent effect (535 [EL 4; NE]; 540 [EL 1; RCT]; 598 [EL 1; RCT]; 599 [EL 2; PCS]). Similarly, fenofibrate has been shown to reduce fibrinogen, while gemfibrozil has shown inconsistent effects on fibrinogen across different studies (478 [EL 1; RCT]; 480 [EL 1; RCT]; 532 [EL 1; RCT]; 533 [EL 1; RCT]; 539 [EL 1; RCT]; 600 [EL 1; RCT]; 601 [EL 1; RCT]; 602 [EL 2; PCS]).

Niacin

Niacin is a potent LDL-C- and TG-lowering drug that also substantially increases HDL-C. Niacin has also been demonstrated to effectively increase LDL subfraction diameter, thereby converting from LDL pattern B to LDL pattern A. Niacin is currently available in 3 formulations: (*1*) immediate-release (crystalline) niacin is available both as an over-the-counter dietary supplement and by prescription; (*2*) long-acting niacin, also called sustained-release or time-release niacin, is only sold over-the-counter as a non-U.S. Food and Drug Administration-approved supplement; and (*3*) extended-release niacin is approved by the U.S. Food and Drug Administration for lipid lowering and is available by prescription (603 [EL 4; NE]). The 3 formulations perform similarly, although a 2003 review by Meyers et al (604 [EL 4; NE]) indicates that certain over-the-counter no-flush niacin preparations may not contain free nicotinic acid, thus compromising their efficacy. The different preparations also have unique adverse effect profiles. The multiple effects of niacin on lipid metabolism include suppression of lipolysis, reduced hepatic synthesis of TG and VLDL-C secretion, increased apo B degradation, and decreased catabolism of HDL-C (603 [EL 4; NE]).

Niacin may produce a more favorable lipid response than fibrates, particularly with regard to HDL-C. Niacin may be preferable for individuals with lipoprotein (a) elevations since niacin decreases lipoprotein (a) levels (605 [EL 1; RCT]; 606 [EL 2; PCS]; 607 [EL 2; PCS]; 608 [EL 2; PCS]), but the possible preventive benefits of this have not been studied. The Arterial Disease Multiple Intervention Trial (ADMIT) and the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT) showed HDL-C increases of 29% and 19 to 24% (dependent on niacin dosage), respectively, versus placebo (352 [EL 1; RCT]; 609 [EL 1; RCT]). In the Coronary Drug Project (CDP) study, a randomized, double-blind, placebo-controlled trial conducted from 1966 to 1974, niacin was associated with a significant 27% reduction in coronary events. Following discontinuation, niacin was associated with reduced coronary heart disease death and MI, as well as reduced all-cause mortality at 6- and 15-year follow-up, respectively (477 [EL 4; NE]; 610 [EL 2; PCS]; 611 [EL 3; CSS]; 612 [EL 1; RCT]).

In combination with statins or cholesterol absorption inhibitors, niacin has been associated with angiographic evidence of reduced progression and some regression of atheromatous plaques (323 [EL 1; RCT]; 324 [EL 1; RCT]; 326 [EL 1; RCT]; 328 [EL 1; RCT]; 613 [EL 1; RCT]). The HATS trial, which evaluated a niacin and statin combination, showed favorable results for individuals with the dyslipidemic triad (614 [EL 1; RCT]). The AIM-HIGH study (483 [EL 1; RCT]), a large, multicenter, phase III trial sponsored by the NHLBI, was intended to confirm these benefits; the trial was suspended in May 2011 because of failure to show additional benefit of niacin added to simvastatin, 40 mg daily, in individuals whose on-statin LDL-C concentration averaged 71 mg/dL. Furthermore, there was an increase in ischemic CVA in the group treated with niacin: 28 strokes (1.6%) reported during the trial among participants taking high-dose, extended-release niacin versus 12 strokes (0.7%) reported in the control group (525 [EL 4; NE]). The HPS2-THRIVE study was a very large international randomized trial of high-dosage, extended-release niacin-laropiprant plus simvastatin; the study found no significant reduction in major vascular events on treatment compared with placebo (13.2% vs. 13.7%; *P* = .29), but a significant increase in fatal or nonfatal serious adverse events (55.6% vs. 52.7%; *P*<.001) (484 [EL 1; RCT]).

Blood glucose elevations have been associated with higher dosages of niacin, particularly in individuals with diabetes. However, results from the ADMIT (609 [EL 1; RCT]), ADVENT (352 [EL 1; RCT]), and HATS (614 [EL 1; RCT]) trials indicate that this effect was transient and manageable, with blood glucose returning to baseline at 14, 16, and 32 weeks, respectively. Data from each of these trials suggested that individuals with diabetes were able to effectively adjust their antidiabetic medications to address blood glucose alterations (326 [EL 1; RCT]; 352 [EL 1; RCT]; 609 [EL 1; RCT]). However, an analysis of the 8,299 HPS2-THRIVE participants who had diabetes showed a 55% proportional increase in serious disturbances to glucose control, most of which resulted in hospital-

ization, among individuals receiving niacin-laropiprant combined with statin therapy (11.1% vs. 7.5% in placebo group, *P*<.001). In addition, among the 17,374 individuals who did not have diabetes at baseline, niacin-laropiprant was associated with a 32% proportional increase in a diabetes diagnosis (5.7% vs. 4.3% in the placebo group, *P*<.001) (484 [EL 1; RCT]).

A re-analysis of data from the CDP study showed that at 1, 2, and 4 years, niacin increased fasting plasma glucose from a baseline of 101 mg/dL to 107, 107, and 108 mg/dL, respectively. Placebo changes from a baseline of 100 mg/dL were 101, 102, and 104 mg/dL, respectively. Similarly, 1-hour plasma glucose levels in the niacin group went from 168 mg/dL at baseline to 179, 179, and 183 mg/dL at 1, 2, and 4 years, respectively. The 1-hour plasma glucose levels in the placebo group went from 169 mg/dL at baseline to 164, 165, and 170 mg/dL at 1, 2, and 4 years, respectively. These blood glucose changes did not provoke any substantial changes to diabetes therapy. In addition, the reduced risks for cardiovascular events and total mortality were consistent across all baseline fasting and 1-hour plasma glucose groups (612 [EL 1; RCT]).

Flushing may occur in most individuals taking niacin, especially at the beginning of therapy; however, this effect often diminishes with continued use. This occurs less frequently with extended-release niacin (research indicates an average of 1.88 events over 4 weeks) than with immediate-release niacin (an average of 8.56 events over 4 weeks) (559 [EL 4; NE]; 603 [EL 4; NE]). In placebo-controlled trials of extended-release niacin, flushing occurs in as many as 88% of individuals; however, discontinuation due to flushing was less than 6% (328 [EL 1; RCT]; 352 [EL 1; RCT]; 559 [EL 4; NE]). Flushing can be ameliorated by pretreating with aspirin or a nonsteroidal anti-inflammatory agent (559 [EL 4; NE]). Flushing and other adverse effects can also be considerably reduced by slowly titrating the dosage upward (559 [EL 4; NE]).

Clinical trials have not demonstrated a cardiovascular benefit with niacin when individuals are well-controlled on statin therapy (483 [EL 1; RCT]; 484 [EL 1; RCT]). It is unclear whether niacin provides a benefit in other patient groups (328 [EL 1; RCT]; 605 [EL 1; RCT]; 607 [EL 2; PCS]; 613 [EL 1; RCT]; 614 [EL 1; RCT]). Therefore, niacin is recommended primarily as an adjunct to reduce TG, and statins remain the initial therapy of choice.

Bile Acid Sequestrants

Until the introduction of statins, bile acid sequestrants were the mainstay treatment for LDL-C reduction. They effectively reduce LDL-C and moderately increase HDL-C. Currently available agents are cholestyramine, colestipol, and colesevelam. Bile acid sequestrants are not absorbed and act by binding to bile acids in the gut, thus depleting the endogenous bile acid pool and indirectly increasing the expression of hepatic LDL receptors. This results in upregulation of 3-hydroxy-3-methylglutaryl-CoA reductase activity and increased hepatic cholesterol synthesis. This limits bile acid sequestrants' efficacy as monotherapy (615 [EL 4; NE]).

At full dosage, bile acid sequestrants reduce LDL-C by 15 to 25% and increase HDL-C by 4 to 8% (613 [EL 1; RCT]; 617 [EL 1; RCT]; 618 [EL 1; RCT]; 619 [EL 1; RCT]; 620 [EL 1; RCT]; 621 [EL 4; NE]). In January 2008, the U.S. Food and Drug Administration approved colesevelam as an adjunct glucose-lowering therapy for adults with T2DM (557 [EL 4; NE]). In one major primary prevention trial, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), cholestyramine reduced major coronary artery disease events by 19% (622 [EL 1; RCT]). Additionally, the Glucose-Lowering Effect of WelChol Study (GLOWS) demonstrated that colesevelam significantly lowered plasma glucose among individuals with T2DM (547 [EL 1; RCT]). In 2008, two 26-week randomized clinical trials evaluated the effectiveness of colesevelam in individuals with T2DM currently treated with sulfonylurea (623 [EL 1; RCT]) or metformin (624 [EL 1; RCT]). In these trials, colesevelam modestly lowered A1C levels (0.54% with metformin, 0.32% with sulfonylurea). Additionally, colesevelam significantly improved a number of lipid parameters, including LDL-C, apo B, and non-HDL-C.

Bile acid sequestrants have been shown to have high discontinuation rates because of adverse events, especially in the gastrointestinal tract (625 [EL 4; NE]; 626 [EL 2; PCS]). However, colesevelam, a newer agent, appears to be better tolerated (620 [EL 1; RCT]; 627 [EL 1; RCT]). Bile acid sequestrants may cause either no change or a modest rise (≤11%) in TG. Caution should therefore be applied when using bile acid sequestrants to treat individuals with elevated TG levels (243 [EL 4; NE]; 556 [EL 4; NE]; 557 [EL 4; NE]; 616 [EL 1; RCT]; 618 [EL 1; RCT]; 619 [EL 1; RCT]; 620 [EL 1; RCT]; 621 [EL 4; NE]).

Cholesterol Absorption Inhibitors

Cholesterol absorption inhibitors primarily reduce LDL-C and may also have beneficial effects on TG, apo B, and HDL-C. Research indicates that these benefits are enhanced in combination therapy with statins. Ezetimibe is the only member of this class currently available; it acts by reducing cholesterol absorption at the brush border of enterocytes via cholesterol transporter interference (35 [EL 1; RCT]; 536 [EL 1; RCT]; 628 [EL 4; NE]). Ezetimibe also promotes biliary excretion of cholesterol by preventing biliary cholesterol from returning to the liver (555 [EL 4; NE]). It also decreases hepatic cholesterol stores and upregulates LDL receptors (555 [EL 4; NE]; 629 [EL 4; NE]). Ezetimibe significantly decreases total cholesterol, LDL-C, apo B-48 and -100, TG, remnant lipoprotein cholesterol levels, and cholesterol and TG levels in VLDL and LDL (630 [EL 2; RCCS]).

Trials demonstrate that ezetimibe reduces LDL-C by 10 to 25%, with significant, favorable changes in TG, apo B, and in some trials, HDL-C (534 [EL 1; MRCT]; 536 [EL 1; RCT]; 553 [EL 1; MRCT]). In combination therapy studies, ezetimibe added to ongoing statin treatment (simvastatin, atorvastatin, lovastatin, pravastatin, or fluvastatin) produced an additional LDL-C reduction of 23 to 30% (537 [EL 1; RCT]; 541 [EL 1; RCT]; 543 [EL 2; PCS]; 544 [EL 1; RCT]), and among individuals not at LDL-C goal, it significantly improved goal attainment (65-81%) compared with statin-only treatment (17-22%) (537 [EL 1; RCT]; 541 [EL 1; RCT]; 543 [EL 2; PCS]; 544 [EL 1; RCT]; 631 [EL 1; RCT]). Two multicenter, randomized, double-blind, placebo-controlled trials found that ezetimibe and simvastatin combination therapy reduced LDL-C levels by 53% (517 [EL 1; RCT]; 518 [EL 1; RCT]). The efficacy of ezetimibe and simvastatin combination has not yet been compared with that of lovastatin, pitavastatin, pravastatin, or fluvastatin monotherapy, but trials have found that this approach produces significantly greater LDL-C reductions than monotherapy with rosuvastatin (52-61% vs. 46-57%) or atorvastatin (47-59% vs. 36-53%) (632 [EL 1; RCT]; 633 [EL 1; RCT]). Ezetimibe is also effective when co-administered with fenofibrate, reducing LDL-C by an additional 20 to 22% (542 [EL 1; RCT]; 545 [EL 1; RCT]).

In 2005, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial studied the effect of the ezetimibe and simvastatin combination in individuals with HeFH using a surrogate endpoint of CIMT (634 [EL 4; NE]). Results indicated no benefit from the addition of ezetimibe to statin therapy (333 [EL 1; RCT]); however, some elements of the trial, including the study population and its baseline characteristics, suggest further study is required before definitive conclusions can be drawn (635 [EL 4; NE]). The population in this study was highly selective since HeFH affects only 2.2% of the population, this is a dyslipidemia type not typical of individuals seen in daily practice and this probably contributed to participants' high mean baseline LDL-C level of 319 mg/dL. Moreover, baseline CIMT was not at a level normally considered diseased (0.68 mm), which may have minimized results; this may have been due to the high percentage (80%) of individuals with a history of statin use (636 [EL 4; NE]).

The SHARP study, published in 2011, showed that a reduction of LDL-C with simvastatin, 20 mg daily, plus ezetimibe, 10 mg daily, safely reduced the incidence of major atherosclerotic events in a wide range of individuals with advanced CKD (512 [EL 1; RCT]). Also of interest are results from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (637 [EL 1; RCT]). This 4-year, randomized, placebo-controlled study enrolled 1,873 men and women with asymptomatic aortic stenosis and found that while the primary endpoint (a composite of cardio-vascular outcomes) was not achieved, ischemic events, a secondary endpoint, were significantly reduced by 20% among individuals taking ezetimibe, 10 mg daily, and simvastatin, 40 mg daily, compared with findings in the placebo group.

Additionally, IMPROVE-IT is the only large randomized clinical trial that evaluated additional LDL-C lowering using ezetimibe in individuals with recent ACS being treated with a statin to LDL-C levels <70 mg/dL. The trial demonstrated a significant reduction in the ASCVD endpoints with an average achieved LDL-C of 53.2 mg/dL in individuals treated with ezetimibe/simvastatin versus simvastatin alone (average LDL-C 69.9 mg/dL) (35 [EL 1; RCT]).

Ezetimibe has minimal adverse effects and a strong safety profile. In several 1-year efficacy/safety studies, ezetimibe in combination with statins or fenofibrate demonstrated no significant difference in adverse event rates compared with either monotherapy (545 [EL 1; RCT]; 586 [EL 1; RCT]; 588 [EL 1; RCT]). Ezetimibe recycling via enterohepatic circulation and its elimination half-life of about 22 hours make it easy to administer in oral form (536 [EL 1; RCT]; 537 [EL 1; RCT]; 586 [EL 1; RCT]; 588 [EL 1; RCT]).

PCSK9 Inhibitors

Two monoclonal antibody inhibitors of PCSK9, a protein that regulates the recycling of LDL receptors, have recently been approved by the FDA (560 [EL 4; NE]; 564 [EL 4; NE]). Alirocumab and evolucumab are subcutaneously injectable LDL-lowering agents capable of further reducing LDL approximately 60% when added to maximum statin therapy (70 [EL 1; RCT]; 638 [EL 1; RCT]). Their strong efficacy in reducing LDL-C and possible synergistic effects with statins, combined with a favorable safety profile and tolerability, give these drugs the potential to revolutionize the treatment of the highest risk individuals, as well as those individuals unable to reach LDL-C goals with maximally tolerated statin dose (639 [EL 4; NE]). Alirocumab and evolucumab are both indicated for individuals with HeFH or as secondary prevention in individuals with clinical ASCVD who require additional LDL-lowering therapy (560 [EL 4; NE]; 564 [EL 4; NE]). Evolocumab is also indicated for treatment of individuals with HoFH (551 EL 4; NE]). This drug class meets a large unmet need for more aggressive lipid-lowering therapy beyond statins in an effort to further reduce residual risk in individuals with clinical ASCVD and diabetes, which up to now has not been possible. The recently published results of the FOURIER trial demonstrate the efficacy of evolucumab in lowering LDL-C and reducing cardiovascular risk in high-risk individuals receiving high intensity statin therapy. In this trial, evolocumab use led to 59% mean reductions in LDL-C and significantly reduced risk for the primary and secondary major cardiovascular event composite outcomes (488

[EL 1; NE]). The ODYSSEY OUTCOMES trial is ongoing to determine the efficacy of the alirocumab for the reduction of the same composite cardiovascular events outcome (640 [EL 4; NE]. Additional PCSK9 inhibitor formulations, including an annual vaccine and oral version, are currently in development (641 [EL 4; NE]).

Imaging Studies

The Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) study compared treatment with the PCSK9 inhibitor evolocumab (420 mg monthly subcutaneous injection) and placebo over 76 weeks in order to evaluate the effect of PCSK9 inhibition on coronary atherosclerosis in statin-treated individuals (334 [EL 1; RCT]). Percent atheroma volume (PAV) change was measured via intravascular ultrasound at baseline and again at 78 weeks in 968 study participants. The results showed that individuals taking evolocumab had PAV decreased by 0.95% (*P*<.001) compared with a PAV increase of 0.05% in the placebo group (between-group difference, –1.0% [95% CI, –1.8% to –0.64%]; *P*<.001). Similarly, total atheroma volume was not significantly changed from baseline in the placebo group (–0.9 mm^3, *P* = .45), but decreased by 5.8 mm^3 in the evolocumab group (*P*<.001). In addition, more evolocumab-treated individuals exhibited PAV regression compared with placebo (64.3% vs. 47.3%, *P*<.001).

Other options

Two new treatment options for individuals with HoFH are lomitapide (MTP inhibitor) and mipomerson (antisense apolipoprotein B oligonucleotide). These new agents, which may be associated with hepatotoxicity, are available with restricted distribution (520 [EL 4; NE]; 562 [EL 4; NE]) and may be useful for individuals with HoFH not responsive to PCSK9 therapy.

Special Considerations: Drug Therapy in Women

In light of the diagnostic challenges that present when trying to identify ASVCD in women, prevention and treatment of dyslipidemia are essential considerations in this population. However, efforts to manage dyslipidemia in women have often been inadequate. While lipid-lowering treatments are used routinely for men, they are frequently underprescribed for women (267 [EL 1; MRCT]). Furthermore, although lowering LDL-C significantly reduces ASVCD risk in women, the unique roles of hormonal change over the lifetime of a woman, HDL-C, and TG must also be addressed.

For women at high risk, the following treatment approach is recommended (37 [EL 4; NE]):

- lipid-lowering pharmacotherapy (preferably with a statin) regardless of LDL-C level;

- niacin or fibrate therapy in the presence of low HDL-C or elevated non-HDL-C; and
- a diet low in saturated fat (<7%), cholesterol (<200 mg/day), and *trans* fat.

For women at intermediate risk, the following treatment approach is recommended (37 [EL 4; NE]):

- lipid-lowering pharmacotherapy (preferably with a statin) in the presence of an LDL-C level greater than 130 mg/dL; and
- niacin or fibrate therapy in the presence of low HDL-C, or elevated non-HDL-C after LDL-C goal is reached.

Supporting Data: Statins

Most early studies of the relationship between dyslipidemia and ASCVD included only middle-aged men (267 [EL 1; MRCT]). Although few clinical trials have evaluated lipid-lowering in women specifically (162 [EL 4; NE]), men and women have been equally represented in most major statin trials (267 [EL 1; MRCT]). In a meta-analysis of 5 randomized, placebo-controlled primary and secondary prevention trials (N = 30,817) to assess the impact of statins on ASCVD development and mortality, statins significantly lowered LDL-C and similarly reduced the risk of major coronary events, coronary mortality, and all-cause mortality in men and women (267 [EL 1; MRCT]). The HPS, a randomized, placebo-controlled trial of simvastatin to reduce LDL-C, reported similar findings in a population of 20,536 men and women with ASCVD, other occlusive arterial disease, or diabetes (25 [EL 1; RCT]). Although sex subgroup analyses were not performed, HPS investigators found no evidence for an LDL-C threshold below which further lowering did not reduce risk (25 [EL 1; RCT]).

The JUPITER study was a primary prevention trial that enrolled a large number of women (N = 6,800) with LDL-C levels less than 130 mg/dL and hsCRP levels 2 mg/L or greater. JUPITER found that women taking rosuvastatin 20 mg daily versus placebo showed a 46% reduction in cardiovascular events, very similar to the reduction in men of 42% (320 [EL 1; RCT]). A reduction in all-cause mortality in women has not yet been demonstrated in a randomized controlled trial.

Supporting Data: Niacin and Fibrates

In numerous studies, both niacin and fibrates have been shown to favorably affect all components that characterize atherogenic dyslipidemia (low HDL-C, elevated TG, and increased numbers of small dense LDL-C particles) (10 [EL 4; NE]). Treatment with these drugs also produces a moderate decrease in ASCVD risk (10 [EL 4; NE]).

Several trials of the lipid-lowering effects of extended release niacin have specifically evaluated cholesterol-lowering efficacy in women. In a meta-analysis of 5 trials (N = 432), extended-release niacin improved HDL-C, LDL-C,

and TG at all dosage levels for both men and women. Mean percentage reductions in LDL-C and TG were greater in women than in men, but with varying statistical significance: –28.7% versus –17.7% for LDL-C (*P* = .006) and –51.0% versus –41.6% for TG (not significant at the highest dosage of 3,000 mg daily) (353 [EL 1; MRCT]).

In a randomized 3-month trial of hormone replacement therapy (HRT) versus a lipid-lowering fibrate (gemfibrozil) in women with overweight and elevated TG (N = 77), both HRT and gemfibrozil lowered LDL-C. The mean percentage changes in HDL-C were +10.4% for the gemfibrozil group and –8.1% for HRT; and the mean percentage change in TG was –49.1% for the gemfibrozil group versus –11.8% for the HRT group (642 [EL 1; RCT]). Additionally, an analysis of 4,271 elderly women (>65 years) in the general population found that, independent of HRT status, those taking a fibrate had a better lipid profile (lower total cholesterol, TG, and non-HDL-C) than those taking a statin or no lipid-lowering agents (643 [EL 3; SS]). Finally, in the FIELD trial (N = 9,795), fenofibrate produced substantial reductions relative to placebo in total cholesterol (–11.4%), LDL-C (–12.0%), and TG (–28.6%) at 4 months in men and women aged 50 to 75 years with T2DM. Fenofibrate also produced increases relative to placebo in HDL-C (+5.1%, *P* = .05) (349 [EL 1; RCT]). Over the 5-year course of the study, fenofibrate reduced the risk of ASCVD events compared with placebo (*P* = .035), primarily in those with TG values greater than 200 mg/dL, and significantly reduced diabetes-related microvascular complications (349 [EL 1; RCT]).

Considerations Specific to Menopausal Women

The hormonal changes of menopause are associated with an increasingly atherogenic lipid profile. This provides both an opportunity and a challenge for the aggressive management of dyslipidemia. The Women's Health Initiative (WHI), a 15-year longitudinal study of morbidity and mortality in more than 160,000 healthy, postmenopausal women (average age 63 years at baseline) (644 [EL 1; RCT] found a lack of cardioprotective effect associated with HRT. The Heart and Estrogen/progestin Replacement Study (HERS) (645 [EL 2; PCS]) and a randomized study conducted in Sweden (642 [EL 1; RCT, open label) showed similar results. Although estrogen replacement did reduce LDL-C and increase HDL-C, it also increased TG and small, dense LDL particles, 2 of the 3 components that characterize atherogenic dyslipidemia (10 [EL 4; NE]). Based on this, WHI findings are consistent with previous trials in which HRT was not shown to protect against ASCVD or CVA. However, subgroup analyses of WHI data did show that younger women (aged 50-59 years) and women with a shorter duration of menopause (<10 years) who received HRT experienced a nonsignificant reduction in ASCVD risk (644 [EL 1; RCT]). Overall, these data support the short-term use of HRT to relieve moderate or severe vaso-

motor symptoms, but they do not support long-term use to prevent ASCVD in postmenopausal women. Furthermore, given the differences in risks and benefits based on age and duration of menopause, each individual should be assessed to determine if and for how long HRT should be used (646 [EL 4; NE]). Based on these data, postmenopausal LDL-C reductions, achieved primarily through the use of statins, remain particularly relevant to this population.

Special Considerations: Therapy in Children

For children and adolescents with elevated lipid levels, intensive lifestyle modification with an emphasis on normalization of body weight and improved dietary intake is recommended as a first-line approach. Lifestyle intervention is considered to be most effective early in life, while behavioral habits are being established. Medical nutrition therapy, physical activity, and smoking cessation (if applicable) form the basis of pediatric dyslipidemia management and are recommended for all individuals with LDL-C levels greater than 100 mg/dL. Few clinical trials have investigated the use of drug therapy for the management of pediatric dyslipidemia, and the potential long-term effects of lipid-lowering medications on growth, development, and biochemical variables are unclear. As such, evidence-based recommendations are limited, and pharmacotherapy must be prescribed based on empiric and indirect evidence (279 [EL 4; NE]), as well as on individual needs. In all cases, selection among this age group for pharmacologic therapy should be performed very carefully in conjunction with expert referral and appropriate consultation. It is recommended that such lifestyle changes in children be implemented for at least 6 to 12 months before considering drug therapy. In a 6-year study, adolescents who maintained a high level of physical activity during the transition into adulthood exhibited higher HDL-C to total cholesterol ratios, lower serum TG and insulin concentrations, and lower body fat percentages than those who were physically inactive (647 [EL 3; SS]).

When evaluating the need for lipid-lowering drug therapy in children and adolescents, both the nature of the pediatric dyslipidemia and the potential impact of delaying treatment until adulthood must be considered. There is general consensus that lipid-lowering medications should be used to achieve LDL-C levels less than 130 mg/dL in children and adolescents with certain types of genetic dyslipidemia, particularly when there is an associated ASCVD risk (e.g., FH or familial combined hyperlipidemia) (462 [EL 4; NE]; 648 [EL 4; NE]). Clinical evidence does indicate that the ability to reverse the major atherogenic effects of childhood dyslipidemia is diminished if treatment is delayed until adulthood (65 [EL 4; NE]; 648 [EL 4; NE]; 649 [EL 3; CSS]; 650 [EL 3; CSS]; 651 [EL 4; NE]). Although genetic dyslipidemia is often difficult to diagnose, persistently increased LDL-C levels coupled with a parental history of dyslipidemia may be a good predictor

of an underlying genetic disorder. While more intensive intervention may be necessary in individuals with high LDL-C values (≥130 mg/dL), pharmacotherapy is generally reserved for those with severe dyslipidemia or genetic lipid disorders (277 [EL 4; NE]). In particular, individuals with an LDL-C concentration of 190 mg/dL or greater, or individuals with an LDL-C concentration greater than 160 mg/dL and either 2 or more ASCVD risk factors or a family history of premature ASCVD (before age 55 years) should be considered candidates for pharmacotherapy. If necessary, smoking cessation should also be implemented (652 [EL 3; CSS]).

As such, drug therapy in children and adolescents older than 10 years of age who satisfy the following criteria, can be considered:

- LDL-C ≥190 mg/dL, or
- LDL-C ≥160 mg/dL and
  - the presence of 2 or more cardiovascular risk factors, even after vigorous intervention (10 [EL 4; NE]; 653 [EL 4; NE]);
  - having overweight or obesity, or having other elements of the insulin resistance syndrome; and/or
  - a family history of premature ASCVD (before age 55 years).

Additionally, the AAP indicates that children with diabetes be considered for pharmacologic intervention if they have an LDL-C concentration of 130 mg/dL or greater (283 [EL 4; NE]).

Statins

A number of statins (atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin) have been approved for the treatment of FH in individuals 10 years or older (520 [EL 4; NE]; 521 [EL 4; NE]; 522 [EL 4; NE]; 550 [EL 4; NE]; 654 [EL 4; NE]), and there is increasing evidence to support the use of these agents in children and adolescents at high risk. Several studies have demonstrated the efficacy of statin treatment in young individuals, including LDL-C reductions of 20 to 40% (655 [EL 4; NE]; 656 [EL 4; NE]; 657 [EL 3; SCR]; 658 [EL 1; RCT]; 659 [EL 1; RCT]; 660 [EL 1; RCT]; 661 [EL 2; PCS]; 662 [EL 1; RCT]; 663 [EL 1; RCT]). For example, a 1-year study of adolescent boys with HeFH showed that lovastatin (10 to 40 mg daily) decreased LDL-C levels by 17 to 27% and had no significant effects on growth, hormonal, or nutritional status (660 [EL 1; RCT]). In another study, pravastatin treatment (20 to 40 mg daily) in children with FH aged 8 to 18 years was associated with a 24% LDL-C reduction and significant carotid atherosclerosis regression; no adverse effects on growth, maturation, hormone levels, or muscle or liver enzymes were observed (663 [EL 1; RCT]). Based on available evidence, the AAP considers statins a safe and effective medication for the treatment of dyslipidemia in young people at high risk (283 [EL 4; NE]).

Bile Acid Sequestrants

Cholestyramine is currently approved for the treatment of hypercholesterolemia in children. The efficacy and safety of colestipol and colesevelam have not yet been established in pediatric populations (556 [EL 4; NE]; 557 [EL 4; NE]). However, colesevelam is approved for children older than 8 years. Because bile acid sequestrants are not absorbed from the gastrointestinal tract, they are not associated with serious adverse effects, such as systemic toxicity. Pediatric studies have demonstrated 15 to 20% LDL-C reductions with bile acid sequestrant therapy, and evidence indicates that these effects may be achieved with relatively low dosages. As such, to maximize tolerability in children, therapy should be initiated at low dosages (<8 g daily of cholestyramine or <10 g daily of colestipol) regardless of body weight. Because bile acid sequestrant treatment may lead to nutrient depletion (e.g., folic acid and cholecalciferol) in children, multivitamin supplementation should be used (279 [EL 4; NE]; 664 [EL 1; RCT]; 665 [EL 1; RCT]). Bile acid sequestrants should not be used in children with hypertriglyceridemia (279 [EL 4; NE]; 666 [EL 2; PCS]).

Other Agents

Fibrates

Fibrates may be useful in children with severely elevated TG levels and an increased risk of pancreatitis (286 [EL 4; NE]). Closely monitored treatment with fibrates may be required when treating the rare child or adolescent with type I or V hyperlipoproteinemia. Further research is needed before fibrates can be routinely recommended in young people.

Ezetimibe

On the basis of studies demonstrating similar pharmacokinetic profiles in adolescents and adults, ezetimibe may be prescribed in individuals 10 to 18 years of age. Until data are available for younger individuals, ezetimibe is not recommended for children younger than 10 years. Thus far, ezetimibe has only been prescribed for children and adolescents with HoFH or sitosterolemia (a rare hereditary lipid disorder characterized by increased absorption and decreased biliary excretion of dietary sterols, resulting in hypercholesterolemia) (667 [EL 1; RCT]). Ezetimibe and statin combination therapy is being investigated for the treatment of children with HeFH (286 [EL 4; NE]).

Niacin

Experience with niacin therapy in children is limited. Niacin must be used cautiously in pediatric populations because of a lack of safety and tolerance data and the potential for adverse effects (668 [EL 3; SS]).

4Q3.3. Follow-Up and Monitoring

Lipid status should be re-assessed 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved. Thereafter, individuals should be tested at 6- to 12-month intervals. The specific interval 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 likely benefit from biannual assessment (10 [EL 4; NE]).

Because most liver abnormalities occur within 3 months of statin or fibric acid initiation, a liver transaminase level should be measured before and 3 months after treatment initiation. This test should be repeated periodically (e.g., semiannually). Individuals taking niacin should have transaminase levels measured at baseline and every 3 months thereafter for the first year, followed by periodic (e.g., semiannual) assessment (10 [EL 4; NE]; 559 [EL 4; NE]).

Transaminase level assessment should be repeated at these intervals whenever lipid therapy is restarted, increased, changed, or combined (10 [EL 4; NE]). Creatine kinase levels should be assessed whenever an individual reports clinically significant myalgias or muscle weakness (10 [EL 4; NE]).

Certain clinical circumstances warrant more frequent lipid status evaluation:

- deterioration of diabetes control,
- the individual starts a new drug known to affect lipid levels,
- the individual's atherothrombotic disease progresses,
- the individual gains considerable weight,
- a recent lipid profile reveals an unexpected adverse change in any lipid parameter,
- the individual develops a new ASCVD risk factor, and/or
- availability of new, convincing clinical trial evidence or guidelines suggests stricter lipid goals.

A full fasting lipid panel, including total cholesterol, LDL-C, HDL-C, and TG should be part of each follow-up assessment. If the physician determines that the individual is not at optimal lipid goals or if the individual's atherothrombotic disease progresses while at optimal guideline goals, advanced lipoprotein testing, including ultracentrifugation, gradient gel electrophoresis, nuclear magnetic resonance testing, apo A and B levels, and/or lipoprotein(a) may be performed to determine characteristic sizes or numbers of certain lipoproteins. However, it should be noted that consistency between methods for LDL particle size measurement has not been established (10 [EL 4; NE]; 80 [EL 4; NE]; 669 [EL 2; PCS]; 670 [EL 3; CSS]; 671 [EL 4; NE]).

Consultation with an endocrinologist or lipid specialist is recommended when:

- abnormal lipid levels persist despite intensive treatment efforts,

- uncontrolled diabetes and dyslipidemia coexist, and/or
- atherothrombotic disease progresses despite favorable lipid levels.

4Q4. IS TREATMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE COST-EFFECTIVE?

Although there are no commonly agreed upon thresholds for cost-effectiveness analyses, interventions have traditionally been considered highly cost-effective when the cost per quality-adjusted life-year (QALY) gained is less than $20,000 to $25,000, moderately high in cost-effectiveness when the cost per QALY is between $25,000 and $50,000, and borderline cost-effective when the cost per QALY is between $50,000 and $100,000. However, more recent expert analyses have suggested that the $50,000 per QALY threshold, in use since the 1990s, could reasonably be increased to $100,000 or $150,000 (672 [EL 4; NE]; 673 [EL 4; NE]). Another commonly used parameter, incremental cost-effectiveness ratios, reflect the ratio of cost savings as compared with life years gained (10 [EL 4; NE]; 674 [EL 4; NE]). The cost-effectiveness studies summarized in this section used effectiveness outcomes related to both cholesterol lowering and/or cardiovascular event reduction; in all cases, the specific efficacy measures applied to each study are indicated.

Nonpharmacologic interventions

Existing evidence indicates that the most cost-effective approach to ASCVD prevention consists of interventions related to diet modification, exercise, weight control, and/or smoking cessation.

Medical Nutrition Therapy and Lifestyle Counseling

A 2007 study used 2 meta-analyses consisting of 1,383 individuals from Europe, Australia, Canada, Japan, and the United States to examine the cost-effectiveness of adding plant stanol esters to the diet (in the form of a food spread) used to prevent coronary heart disease in men and women with total serum cholesterol levels greater than 195 mg/dL. There was a gain in the cost per QALY due to stanol use for all men aged 40 years and older and for women aged 60 years and older (675 [EL 4; NE]).

Another study compared the LDL-C–lowering effects of usual care, consisting of customary cholesterol-lowering advice from a health care provider, to medical nutrition therapy, consisting of a minimum of 2 to 3 registered dietitian visits over a 2- to 3-month period, with an additional 2 to 3 follow-up visits if cholesterol goals have not been met. Medical nutrition therapy was cost-effective, resulting in a 6% decrease in both LDL-C and total cholesterol levels compared with a 2% decrease in LDL-C and a 1% increase in total cholesterol in individuals receiving usual care (676 [EL 1; RCT]). Medical nutrition therapy administered by registered dietitians, with the goal of lowering

cholesterol levels, has also proven cost saving. In a 2001 study examining the effects of medical nutrition therapy/1 year of dietitian intervention on total cholesterol, LDL-C, TG, HDL-C, and BMI, only 50% of eligible individuals required antihyperlipidemic medications. This led to an annual cost savings of $27,449 or $638.35 per individual (677 [EL 3; SS]).

Smoking Cessation

Although smoking cessation is not necessarily a lipid-lowering treatment, the dramatic impact of smoking on ASCVD requires its inclusion in any discussion of ASCVD reduction. Cost-effectiveness studies have demonstrated that smoking cessation programs are a highly economical strategy to improve long-term cardiovascular outcomes (678 [EL 4; NE]; 679 [EL 4; NE]; 680 [EL 4; NE]; 681 [EL 4; NE]).

A 2007 randomized trial of 4,614 adult smokers who used the Oregon Tobacco Quit Line examined the cost-effectiveness of smoking cessation counseling and nicotine replacement therapy in achieving smoking abstinence. Quit rates and incremental cost-effectiveness ratios were calculated for brief (a single 15-minute call), moderate (a 30-minute call plus a follow-up call), and intensive (5 proactive calls) telephone counseling with or without no-cost transdermal nicotine replacement. Interventions that provided multisession counseling sessions and free transdermal nicotine replacement achieved greater quit rates and were highly cost-effective (682 [EL 4; NE]).

A 2007 model used data from the Framingham Heart Study and Framingham Offspring Study to model and compare the cost-effectiveness of smoking cessation, antihypertensive drugs, aspirin, and statins in the primary prevention of cardiovascular disease in 3,742 men aged 45 to 65 years. Outcomes assessed were number of life-years saved and deaths averted over a 10-year period. Smoking cessation therapy was found to be the most cost-effective intervention, with both transdermal nicotine replacement and treatment with bupropion demonstrating cost savings based on cost per life-year saved and incremental cost-effectiveness ratio results (680 [EL 4; NE]).

A 2008 model compared the efficacy and cost-effectiveness of varenicline, a smoking cessation therapy, versus buproprion, a transdermal nicotine replacement, and unaided quitting in preventing morbidity associated with smoking-related disease. A Markov model, the Benefits of Smoking Cessation on Outcomes, was developed to simulate the lifetime direct costs and consequences of a hypothetical cohort of U.S. adult smokers making a single attempt to quit. From a cost-effectiveness standpoint, varenicline dominated all other treatments and prevented the largest number of smoking-related deaths (42 [EL 4; NE]; 681 [EL 4; NE]).

Pharmacologic Therapy

Statins

Overall, statins have proven cost-effective in both secondary and primary prevention of ASCVD events for individuals at moderate to high risk, or low-risk individuals whose LDL-C levels are very high (≥190 mg/dL). In particular, the cost-effectiveness of atorvastatin, pravastatin, and simvastatin has been evaluated in populations that cover both primary and secondary interventions and a wide range of ages and risk factors. Cost-effectiveness data on rosuvastatin has focused on primary prevention in higher risk populations, including individuals with ASCVD or an ASCVD equivalent (10 [EL 4; NE]).

A number of primary and secondary intervention evaluations have found atorvastatin to be cost-effective across a range of cardiovascular endpoints for moderate- to high-risk individuals. In the United States, primary atorvastatin treatment was cost-effective over 25- and 10-year periods among individuals with T2DM. Studies in both Spain and the United Kingdom also found primary intervention with atorvastatin cost-effective in individuals with T2DM. In secondary intervention trials, U.S. analyses found that treatment with high-dosage atorvastatin was moderately cost-effective ($34,000 per QALY) compared with conventional-dosage simvastatin in individuals with stable ASCVD (683 [EL 4; NE]).

A 2008 retrospective database analysis of 10,421 individuals with ASCVD compared the cost effectiveness of branded rosuvastatin and atorvastatin and generic simvastatin, pravastatin, and lovastatin. Effectiveness was measured as percent LDL-C reduction and percentage of individuals achieving NCEP ATP III LDL-C goals; individuals were also stratified by NCEP ASCVD risk. The analysis found that LDL-C reduction with rosuvastatin was significantly greater than with all other statins. The percentage of moderate/high-risk individuals who achieved LDL-C goal was also significantly higher among those taking rosuvastatin compared with the other statin groups. Rosuvastatin was therefore found more cost-effective than branded atorvastatin. Among the generic statins, simvastatin required a 61% discount to achieve equivalent cost-effectiveness to lovastatin, the reference generic (684 [EL 2; RCCS]). Atorvastatin became generically available in November 2011.

In 2015, a Markov simulation model was published to forecast the cost-effectiveness of generic statin use in older individuals (age 75 to 94 years) over a 10-year time frame. The model used inputs from major randomized controlled trials and meta-analyses, including the PROSPER trial and 2010 CTT data. Investigators found that statin use was cost-saving in elderly individuals with LDL-C levels greater than 160 mg/dL, and cost-effective at an incremental cost of $5,300 per disability-adjusted life

year in individuals with LDL-C levels ranging from 130 to 159 mg/dL. This analysis found that statin use was not cost-effective in individuals with diabetes without elevated LDL-C levels (685 [EL 3; SS]).

PCSK9 Inhibitors

Two published simulation model analyses have evaluated the cost-effectiveness of the PCSK9 inhibitors alirocumab (686 [EL 3; SS]) and evolocumab, (686 [EL 3; SS]; 687 [EL 3; SS]) with conflicting results. Kazi et al (686 [EL 3; SS]) assessed the cost-effectiveness of PCSK9 inhibitors versus ezetimibe in those in the U.S. with HeFH or ASCVD. For this study, it was assumed that ezetimibe, PCSK9 inhibitors, and statins all similarly reduced cardiovascular event risk based on achieved LDL-C reductions (mg/dL). The primary outcomes evaluated were a composite of major adverse cardiovascular events (MACE); including cardiovascular death, nonfatal myocardial infarction, or CVA, incremental annual cost per QALY, and total impact on U.S. spending over 5 years. The model was conducted from a health system perspective with a maximum willingness-to-pay threshold of $100,000 per QALY, used a lifetime horizon, and assumed yearly PCSK9 costs of $14,500. Investigators found that adding PCSK9 inhibitors to existing statin therapy versus ezetimibe reduced MACE event rates (313,600 fewer events among individuals with HeFH and 4.3 million in ASCVD), but was not cost-effective versus ezetimibe at the established cost-effectiveness threshold: $503,000 per QALY for HeFH and $414,000 per QALY for ASCVD. The investigators concluded that, to achieve cost-effectiveness, annual PCSK9 drug costs would need to be reduced to $4,536 (686 [EL 3; SS]).

A second study conducted by Gandra et al (687 [EL 3; SS]) evaluated the cost-effectiveness of evolocumab added to standard of care (SOC) treatment versus SOC alone in three groups: individuals with HeFH, individuals with ASCVD without statin intolerance, and individuals with ASCVD with statin intolerance. For this study, the clinical benefit of LDL-C reductions was estimated based on data from the CTT meta-analysis, which found that every 1 mmol/L (38.7 mg/dL) LDL-C reduction resulted in a 21% (statin vs. control therapy) or 28% (less vs. more intensive statin therapy) reduction in major ASCVD event rates. The primary outcomes were ASCVD event rates, cost per life-year gained, and cost per QALY. Specific SOC treatments varied by participant population; high-intensity statin therapy was SOC in individuals with HeFH; medium- to high-intensity statin therapy was SOC in ASCVD individuals without statin intolerance, and no treatment was SOC in statin-intolerant ASCVD individuals. The model was conducted from a payer perspective, used a lifetime horizon, and had a maximum willingness-to-pay threshold of approximately $150,000 per QALY. Annual evolocumab costs were set at $14,139. Investigators found that individuals with HeFH had an incremental cost-effectiveness

ratio of $75,863 per QALY; the equivalent figures for individuals with ASCVD without and with statin intolerance, respectively, were $141,699 and $100,309 per QALY. Based on these results, the investigators concluded that evolocumab represents a cost-effective treatment option for these individual populations (687 [EL 3; SS]).

Based on this evidence, it remains unclear whether PCSK9 inhibitors are cost-effective for use in individuals with HeFH or a history of ASCVD.

Fibrates

Although available research is limited, treatment with fibrates has been found to be cost-effective as both monotherapy and combination therapy for lowering TG and raising HDL-C.

A 2005 analysis compared generic gemfibrozil to fenofibrate in primary prevention of coronary heart disease in a hypothetical cohort of U.S. male and female participants aged 45 to 74 years with low levels of HDL-C, but without pre-existing coronary heart disease or other coronary heart disease risk factors sufficient to indicate drug therapy. The model also calculated cost-effectiveness for lovastatin therapy. Using a cost-effectiveness threshold of $50,000 per QALY, generic gemfibrozil was cost-effective for all individuals. In contrast, fenofibrate was cost-effective for males but not females. In the comparison model, lovastatin monotherapy was more cost-effective than fibrate monotherapy for all groups except men 45 years and older (688 [EL 4; NE]).

An analysis of a 1998 Veteran's Administration study comparing gemfibrozil versus placebo for raising HDL-C and lowering TG levels in men average 64 (±7) years of age with a history of ASCVD, HDL-C levels 40 mg/dL or less, and LDL-C levels 140 mg/dL or less found gemfibrozil to be cost-effective for reducing major cardiovascular events (689 [EL 1; RCT]).

Cholesterol Absorption Inhibitors

Although no long-term U.S. studies exist to evaluate the cost-effectiveness of cholesterol absorption inhibitors, ezetimibe co-administered with statin therapy in individuals unable to meet target LDL-C levels has been identified as a potentially cost-effective strategy to meet LDL-C goals in studies from Canada and the United Kingdom (690 [EL 4; NE], 691 [EL 1; MRCT], 692 [EL 1; RCT]).

A Canadian model compared the cost-effectiveness of adding ezetimibe to atorvastatin therapy versus atorvastatin titration or adding the bile acid sequestrant cholestyramine for lowering LDL-C in individuals classified as being at very high risk for an ASCVD event. Compared with fixed or titrated atorvastatin treatment, ezetimibe co-administration was determined to be the most cost-effective therapy evaluated (690 [EL 4; NE]). A 2008 United Kingdom study used a systematic database review and efficacy data from a series of meta-analyses to evaluate the cost-effectiveness

of ezetimibe in lowering LDL-C and total cholesterol as either combination therapy with statins or as monotherapy in the treatment of primary hypercholesterolemia. Since there were no published clinical endpoint trials with duration greater than 12 weeks, the authors relied on randomized controlled trials with surrogate endpoints. Overall, the obtained results suggested that ezetimibe therapy was potentially cost-effective for individuals with high baseline LDL-C, or for higher risk individuals, such as those with diabetes or HeFH. However, the authors concluded that long-term, clinical endpoint trials would be needed to develop a more precise analysis (691 [EL 1; MRCT]). Most recently, a 2016 UK analysis of SHARP data found that simvastatin plus ezetimibe was moderately cost-effective in individuals with moderate-to-severe kidney disease. However, the authors noted that intensified statin therapy was more cost-effective than ezetimibe (692 [EL 1; RCT]).

Bile Acid Sequestrants

Limited current data are available regarding the cost-effectiveness of bile acid sequestrants; no data have been published since generic availability of these agents. A 1999 U.S. meta-analysis based on trials conducted between 1985 and 1997 found that, for LDL-C lowering, the bile acid sequestrant cholestyramine used in combination therapy with statins was less cost-effective than statin monotherapy. Similarly, a 2006 European analysis of clinical trials published between 1993 and 2003 found cholestyramine monotherapy to be less cost-effective than statin monotherapy for lowering LDL-C levels (693 [EL 2; MNRCT]; 694 [EL 2; MNRCT]).

Niacin

Limited pharmaco-economic data support the cost-effectiveness of niacin in combination with a statin in reaching targeted lipid goals. A 2004 analysis compared lovastatin plus extended-release niacin combination therapy with simvastatin monotherapy for lowering LDL-C and raising HDL-C in 2,430 individuals with LDL-C levels exceeding NCEP-targeted goals. For all groups, lovastatin plus extended-release niacin was found to be more cost-effective than simvastatin (695 [EL 4; NE]).

Table 7
Components of the Insulin Resistance Syndrome
1. Some degree of glucose intolerance
• Impaired fasting glucose
• Impaired glucose tolerance
2. Abnormal uric acid metabolism
• Plasma uric acid concentration
• Renal uric acid clearance
3. Dyslipidemia
• Triglycerides
• HDL-C
• LDL-particle diameter (small, dense LDL-particles)
• Postprandial accumulation of TG-rich lipoproteins
4. Hemodynamic changes
• Sympathetic nervous system activity
• Renal sodium retention
• Blood pressure (~50% of patients with hypertension are insulin resistant)
5. Prothrombotic factors
• Plasminogen activator inhibitor 1
• Fibrinogen
6. Markers of inflammation
• C-reactive protein, white blood cell count, etc.
7. Endothelial dysfunction
• Mononuclear cell adhesion
• Plasma concentration of cellular adhesion molecules
• Plasma concentration of asymmetric dimethylarginine
• Endothelial-dependent vasodilatation
Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; TG = triglycerides

Table 14
Major Imaging Trials

Trial	Agent	Primary endpoint parameter	Patients, n — M	Patients, n — F	F/U, y	Mean baseline lipid values, mg/dL — LDL-C	Mean baseline lipid values, mg/dL — HDL-C	Mean baseline lipid values, mg/dL — TG	Mean achieved lipid values, mg/dL — LDL-C	Mean achieved lipid values, mg/dL — HDL-C	Mean achieved lipid values, mg/dL — TG	Mean experimental % change, primary endpoint — Overall	Mean experimental % change, primary endpoint — Most diseased sub-segment	Mean control % change, primary endpoint — Overall	Mean control % change, primary endpoint — Most diseased sub-segment
STATINS															
MARS	Lovastatin, 80 mg (experimental) vs. PBO (control)	Percent diameter stenosis measured by QCA	247	23	2.2	157a	43	159	86a	46	120	1.6	−4.1b	2.2	−0.9b
HATS (imaging arm)	Simvastatin + niacin (experimental) vs. PBO (control)c,d	Percent diameter stenosis measured by QCA	139	21	3.2	125	31	212	75	40	126	0.4	−5.8b	3.9	0.1b
REVERSAL	Atorvastatin, 80 mg (experimental) vs. pravastatin, 40 mg (control)	Atheroma volume measured by coronary IVUS	362	140	1.5	150	42	197	79 on atorvastatin, 80 mg; 110 on pravastatin, 40 mg	43 on atorvastatin, 80 mg; 45 on pravastatin, 40 mg	148 on atorvastatin, 80 mg; 166 on pravastatin, 40 mg	4.1	−4.2d	5.4	−1.7e
ASTEROID	RRosuvastatin, 40 mg no control group	Atheroma volume measured by coronary IVUS	245	104	2	130	43	152	61	49	121	−0.98	−8.5	NA	NA
Schmermund	Atorvastatin, 80 mg (experimental) vs. atorvastatin, 10 mg (control)	Coronary artery calcification measured by EBCT	149	217	1	155f,g	50f,g	208f,g	87 on atorvastatin, 80 mg; 109 on atorvastatin, 10 mg	53 on atorvastatin, 80 mg; 54 on atorvastatin, 10 mg	137 on atorvastatin, 80 mg; 151 on atorvastatin, 10 mg	27	NA	25	NA
ENHANCE	Simvastatin, 80 mg + ezetimibe, 10 mg (experimental) vs. simvastatin, 80 mg + placebo (control)	Carotid-artery intima-media thickness measured by carotid ultrasound	370	350	2	319 (simvastatin/ezetimibe); 317.8 (simvastatin)	46.7 (simvastatin/ezetimibe); 47.4 (simvastatin)	157 (simvastatin/ezetimibe); 160 (simvastatin)h	141.3 (simvastatin/ezetimibe); 192.7 (simvastatin)	50.9 (simvastatin/ezetimibe); 50.7 (simvastatin)	108 (simvastatin/ezetimibe);120 (simvastatin)h	0.0111i	NA	0.0058i	NA
METEOR	Rosuvastatin, 40 mg (experimental) vs. PBO (control)	Carotid-artery intima-media thickness measured by carotid ultrasound	588	396	2	155 (rosuvastatin); 154 (PBO)	50 (rosuvastatin); 49 (PBO)	126 (rosuvastatin); 134 (PBO)	78	53	98	−0.0014i	NA	0.0131i	NA

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Table 14 *Continued*

Study	Intervention	Description													
Niacin, colestipol and/or combination ARBITER-3	Extended-release niacin added to statin therapy	Mean carotid-artery intima-media change measured by ultrasound following up to 24 months of niacin use	120	10	1 or 2	90.5	39.2	180.4	79.2 (1 year niacin use); 78.4 (2 years niacin use)	48.5 (1 year niacin use); 48.6 (2 years niacin use)	120.5 (both 1 and 2 years niacin use)	−0.027 (12 months); −0.041 (24 months)	NA	NA	NA
CLAS	Niacin + colestipol	Change in Global Coronary Change score based on combined coronary, femoral, and carotid angiograms	162	0	2	171.0	44.6	151.0	97.0	60.8	110	0.3[j]	NA	0.8[i]	NA
FATS	Colestipol 30 g; + niacin 4 g; + Colestipol 30 g + lovastatin 40 mg	Percentage change in disease severity (proximal coronary artery lesion stenosis), measured by arteriography	146	0	2.5	189.9 (niacin + colestipol); 196.1 (lovastatin + colestipol)	39.0 (niacin + colestipol); 35.1 (lovastatin + colestipol)	193.8 (niacin + colestipol); 200.9 (lovastatin + colestipol)	128.9 (niacin + colestipol); 106.9 (lovastatin + colestipol)	54.8 (niacin + colestipol); 40.9 (lovastatin + colestipol)	137.2 (niacin + colestipol); 183.2 (lovastatin + colestipol)	−1.1% (niacin + colestipol); −0.3% (lovastatin + colestipol)	−6.4% (niacin + colestipol); −2.6% (lovastatin + colestipol)	2.0%	1.1%
PCSK9 inhibitors GLAGOV	Evolocumab, 420 mg (experimental) vs. PBO (control)	Nominal change in % atheroma volume, measured by intravascular ultrasound	699	269	6.5	92.6 (evolocumab); 92.4 (PBO)	46.7 (evolocumab); 45.4 (PBO)	117 (evolocumab); 124.5 (PBO)	36.6 (evolocumab)	51.0 (evolocumab)	105.1 (evolocumab)	−0.95	NA	+0.05	NA

Abbreviations: ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; CLAS = Cholesterol Lowering Atherosclerosis Study; EBCT = electron-beam computed tomography; ENHANCE = Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; F = female; F/U = follow-up; FATS = Familial Atherosclerosis Treatment Study; GLAGOV = Global Assessment of Plaque Regression with a PCSK9 Antibody; HATS = HDL-Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; IVUS = intravascular ultrasonography; LDL-C = low-density lipoprotein cholesterol; M = male; MARS = Monitored Atherosclerosis Regression Study; METEOR = Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin; PBO = placebo; QCA = quantitative coronary angiography; REVERSAL = Reversing Atherosclerosis with Aggressive Lipid Lowering; TC = total cholesterol; TG = triglycerides

[a] LDL-C levels measured by preparative ultracentrifugation.
[b] Lesions with stenosis ≥50% at baseline.
[c] The HATS trial also randomly assigned patients to antioxidant vitamins or simvastatin + niacin + antioxidant vitamins. Results provided do not include antioxidant groups; however, results in the vitamin-only group and the drug + vitamin group did not vary significantly from the placebo and drug groups, respectively.
[d] Dosages varied. Means were 13 mg daily of simvastatin and 2.4 g daily of niacin.
[e] Nominal change (end of treatment minus baseline).
[f] Calculated based on reported figures.
[g] At screening. After a 4-week run-in period on atorvastatin, 10 mg daily, for all patients, LDL-C, HDL-C, and TG levels were 107, 52, and 149 mg/dL, respectively.
[h] Median.
[i] Results reported as millimeter change, not percentage change.
[j] Global Change Category: −3 to 0 = no change; 1 = mild worsening; 2-3 = moderate worsening.

Table 15
Summary of Major Randomized Controlled Drug Trials for Primary Prevention of Coronary Artery Disease

Trial	Treatment	Patients, n		F/U y	Baseline value,[a] mg/dL			Reduction, %					Increase, %
		Male	Female		LDL-C	TG	HDL-C	LDL-C	TG	PTCA	MI	Cor Death	HDL-C
Statins													
WOSCOPS	Pravastatin, 40 mg vs. PBO	6,595	0	4.9 y	192	164	44	26	12	37[b]	31	28	5
AFCAPS/TexCAPS	Lovastatin, 20-40 mg vs. PBO	5,608	997	5.2 y	150	158[c]	38	25[d]	15[d]	33[e]	40	f	6.0[d]
ALLHAT-LLT	Pravastatin, 40 mg vs. PBO	5,304	5,051	4.8 y	146	152	48	28	4[g]	NA	9[h,i,j]	i	3.3
ASCOT-LLA	Atorvastatin, 10 mg vs. PBO	8,363	1,942	3.3 y	132	149	50	29	14	NA	36[i]	36[i]	0.0
CARDS	Atorvastatin, 10 mg vs. PBO	1,929	909	4.0 y	117	147[c]	54	40	19	31[e]	33[j]	33[j]	1.0
JUPITER	Rosuvastatin, 20 mg vs. PBO	11,001	6,801	1.9 y[c,k]	108	118	49	NA[k]	NA[k]	NA[k]	54[k]	47[k,l]	NA[k]
Fibrates													
WHO	Clofibrate	3,806	0	5.3 y	188	NA	NA	9 (TC)	NA	NA	19	19	NA
HHS	Gemfibrozil	4,081	0	5.0 y	201	182	47	11	35	NA	34	37	8.5
FIELD	Fenofibrate	6,138	3,657	5.0 y	119	154	43	6	22	21[e]	24	+19	1.2
Bile acid sequestrants													
LRC	Cholestyramine[m]	3,806	NA	7.4 y	205	155	44	15[g]	+17[g]	NA	19	24	5.4[g]

Abbreviations: AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; Cor = coronary; F/U = follow-up; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HDL-C = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; MI = myocardial infarction; NA = not applicable; NC = no change; PBO = placebo; PTCA = percutaneous transluminal coronary angioplasty; TC = total cholesterol; TG = triglycerides; WHO = World Health Organization; WOSCOPS = West of Scotland Coronary Prevention Study; y = year
[a] Mean values, expressed in mg/dL.
[b] Percutaneous transluminal coronary angioplasty or coronary artery bypass graft.
[c] Median.
[d] At 1 year.
[e] All revascularizations.
[f] Too few events to perform survival analysis.
[g] Calculated based on reported figures.
[h] At 6 years.
[i] Endpoint is combined nonfatal MI plus fatal coronary heart disease.
[j] Acute coronary events not including unstable angina.
[k] The JUPITER trial was halted in March 2008 because of unequivocal evidence indicating reductions in cardiovascular morbidity and mortality in patients receiving rosuvastatin compared with placebo. Maximum follow-up period was 5 years.
[l] Myocardial infarction, stroke, or confirmed cardiovascular death.
[m] The bile acid sequestrant colestipol has a mechanism of action and effect similar to that of cholestyramine.
[n] Pooled across multiple dosages of ezetimibe/simvastatin. At highest dosage, reductions in LDL-C and TG were 60.2% and 30.7%, respectively. The increase in HDL-C was 9.8%.

Table 16
Summary of Major Randomized Controlled Drug Trials for Secondary Prevention of Atherosclerotic Cardiovascular Disease

Trial	Treatment	Patients, n Male	Patients, n Female	F/U (y)	Baseline[a] (mg/dL) LDL-C	TG	HDL-C	Reduction (%) LDL-C	TG	PTCA	MI	Cor Death	Increase (%) HDL-C
Statins													
4S	Simvastatin, 20-40 mg	3,617	827	5.4	188	131	46	35	10	37	37	42	8
CARE	Pravastatin, 40 mg	3,583	576	5.0	135	91	39	28	14	27	27	24	5
LIPID	Pravastatin, 40 mg	7,498	1,516	6.1	146[b]	145[b]	36[b]	25	11	19	29	24	5
AVERT	Atorvastatin, 80 mg	288	53	1.5	152	172	40[c]	46	11	[d]	[d]	[d]	8
HPS	Simvastatin, 40 mg	15,454	5,082	5	132	184	41	32[e]	n/a	22[e,f]	37	17[e]	n/a
GREACE	Atorvastatin, 10-80 mg	624	176	3	180	184	39	46	31	51[g]	59	47	7
A to Z	Simvastatin, 40/80 mg vs. PBO/simvastatin, 20 mg	3,396	1,100	2	112	149	39	41[e]	22[e]	7[f]	4	20	12[e]
IDEAL	Atorvastatin, 80 mg vs. simvastatin, 20 mg	7,187	1,701	4.8	121	149	46	23[h]	26[h]	23[f]	17	1	1.3 (simvastatin over atorvastatin)
TNT	Atorvastatin, 80 mg vs. atorvastatin, 10 mg	8,099	1,902	4.9[b]	98	151	47	18[c,e]	8[c,e]	4	22	20	0
Fibrates													
BECAIT	Bezafibrate	92[i]	n/a	5.0	180[b,j]	214[b,j]	34[b,j]	1.9	31.4	k	k	k	9.2
BIP	Bezafibrate	2,825	265	6.2	148	145	35	6.5	20.6	0	12.8[l]	0[l]	17.9
VA-HIT	Gemfibrozil	2,531	n/a	5.1	112	160	32	0	31	21[m]	23	22	6
Niacin													
CDP	Niacin	8,341	0	15	n/a	n/a	n/a	n/a	n/a	n/a	n/a	11[n]	n/a
Combination													
HATS	Simvastatin + niacin	139	121	3.2	125	213	31	42	36	90[o]	90[o]	90[o]	26
ARBITER2	Niacin + background statin	152	15	1	89[e]	163[e]	40[e]	2.3[e]	13[e]	p	p	p	21[e]
IMPROVE-IT	Simvastatin, 40 mg + ezetimibe, 10 mg vs. simvastatin, 40 mg + PBO	13,729	4,415	6	93.8	137.6	42.2	24	q	1.4	1.7	1.8	s
HPS2 THRIVE	Extended-release niacin, 2 g + laropiprant, 40 mg	21,229	4,444	3.6	63	126.7	43.9	13.8	Mean −33 mg/dL change	10[t]	0.3[u]	+0.1[u]	14.3

Table 16 Continued

AIM-HIGH	Simvastatin + niacin, 1,500-2,000 mg vs. simvastatin + PBO[v]	2,910	504	3	74.2	167.5	34.5	13.6[b]	30.8[b]	0.2[w]	+0.7	0.3	25[b]

Abbreviations: AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; ARBITER2 = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2; AVERT = Atorvastatin Versus Revascularization Treatment Study; BECAIT = Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP = Bezafibrate Infarction Prevention Study; CABG = coronary artery bypass graft; CDP = Coronary Drug Project; CARE = Cholesterol and Recurrent Events Trial; Cor = Coronary; F/U = follow-up; GREACE = GREek Atorvastatin and Coronary-Heart-Disease Evaluation; HATS = HDL-Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; HPS = Heart Protection Study; HPS2 THRIVE = Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events; IMPROVE-IT = IMProved Reduction of Outcomes, Vytorin Efficacy International Trial; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; MI = myocardial infarction; n/a = not applicable; PBO = placebo; PTCA = percutaneous transluminal coronary angioplasty; 4S = Scandinavian Simvastatin Survival Study; TC = total cholesterol; TG = triglycerides; TNT = Treating to New Targets; VA-HIT = Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

a Mean values (unless otherwise noted).
b Median.
c Estimated.
d Ischemic events reduced 36% vs. comparator patients, who underwent angioplasty (not statistically significant)
e Calculated based on reported figures.
f All revascularizations.
g PTCA/CABG.
h At 1 year.
i Total number of patients, male and female.
j Bezafibrate group baseline only.
k A 6.4% coronary event rate (re-infarction, CABG, PCTA) in the bezafibrate group compared with a 24.4% event rate in the placebo group.
l A posthoc analysis found that among patients with highest baseline TG (≥200 mg/dL), primary endpoint (nonfatal MI and sudden death) was reduced by 39.5%.
m Carotid endarterectomy reduced 65% .
n Overall mortality reduction, measured after drug discontinuation.
o Reduction compared with PBO in composite endpoint (cardiovascular death, nonfatal MI, or revascularization).
p Clinical cardiovascular events occurred in 3.8% of statin + niacin patients compared with 9.6% of statin + placebo patients.
q –14.04 difference in least squares means at 1 year for simvastatin + ezetimibe vs. simvastatin only, *P*<.001.
r Any revascularization ≥30 days postrandomization.
s 0.67 difference in least squares means at 1 year for simvastatin + ezetimibe vs. simvastatin only, *P*<.001.
t Arterial revascularization (rate ratio, 0.90; 95% confidence interval, 0.82 to 0.99; *P* = .03).
u Absolute difference between event rates.
v PBO included 50 mg niacin to mask the identity of blinded treatment to patients and study personnel.
w Symptom-driven coronary or cerebral revascularizations.

Table 17
Primary and Secondary Statin Atherosclerotic Cardiovascular Disease Prevention Trials

Trial	Agent	Inclusion criteria (mg/dL)			Mean baseline values (mg/dL)	Mean achieved values (mg/dL)	Relative risk reduction	Experimental event rate %[a,g]	Control event rate %	Absolute risk reduction %	NNT
		TG	HDL-C	LDL-C	LDL-C	LDL-C					
Primary prevention											
WOSCOPS 0% Female	Pravastatin, 40 mg vs. PBO	---	---	155-232	192	159	30%	5.5% at 5.0 y	7.9%	2.4%	42
AFCAPS 15% Female	Lovastatin, 20-40 mg vs. PBO	≤400	<45 M <47 F	130-190	150	115	40%	4.0% at 5.2 y	6.8%	1.2%	83
ASCOT-LLA 19% Female	Atorvastatin, 10 mg vs. PBO	<400	---	TC <250	134	90	37%	1.9% at 3.3 y	3.0%	1.1%	91
CARDS 32% Female	Atorvastatin, 10 mg vs. PBO	<600	---	≤160	118	82	35%	3.0% at 4.0 y	4.6%	1.6%	63
JUPITER[b] 38% Female	Rosuvastatin, 20 mg vs. PBO	<500	---	<130[c]	108[d]	55[d]	44%	1.6% at 1.9 y[b,e]	2.8% at 1.9 y[b,e]	---	95[f]
Secondary prevention											
4S 19% Female	Simvastatin, 20-40 mg vs. PBO	≤225	---	TC = 215-315	190	124	35%	8.2% at 5.4 y	11.5%	9.2%	11
CARE 14% Female	Pravastatin, 40 mg vs. PBO	<350	---	115-74	139	98	23%	10.2% at 5.0 y	13.2%	3.0%	33
LIPID 17% Female	Pravastatin, 40 mg vs. PBO	<445	---	TC = 155-271	150	112	23%	12.3% at 6.1 y	15.9%	3.6%	28
HPS 25% Female	Simvastatin, 40 mg vs. PBO	---	---	TC ≥135	129	90	26%	8.7% at 5.0 y	11.8%	3.1%	32
TNT 19% Female	Atorvastatin, 80 mg vs. atorvastatin, 10 mg	≤600	---	<130	98	77 on atorvastatin, 80 mg; 101 on atorvastatin, 10 mg	21% in favor of atorvastatin, 80 mg	6.9% at 4.9 y	8.7%	1.8%	56
PROVE IT – TIMI 22% Female	Atorvastatin, 80 mg vs. pravastatin, 40 mg	---	---	TC ≤240 or TC ≤200 on therapy	106 (median)	62 on atorvastatin, 80 mg; 95 on pravastatin, 40 mg	17% in favor of atorvastatin	8.3% at 2 y	10.0% at 2 y	1.7%	59
A to Z 25% Female	Simvastatin, 40/80 mg vs. PBO/ simvastatin, 20 mg	---	---	TC ≤250[g]	112	66 on simvastatin, 40/80 mg; 81 on PBO/ simvastatin, 20 mg	11% in favor of simvastatin, 40/80 mg	14.4% at 2 y	16.7% at 2 y	---	77[h]

Table 17 *Continued*

IDEAL 19% Female	Atorvastatin, 40-80 mg vs. simvastatin, 20-40 mg	≤600	---	121.5	80 on atorvastatin, 40-80 mg; 100 on simvastatin, 20-40 mg	12% in favor of atorvastatin	9.9% at 4.8 y	11.2% at 4.8 y	1.2%	77
AIM-HIGH 15% female	Simvastatin + niacin, 1,500-2,000 mg vs. simvastatin + PBO[i]	150-400 mg/dL	<40 mg/dL for men; <50 mg/dL for women	74	65	–1%[j]	16.4	16.2	–0.2[j]	–5[j]
IMPROVE-IT 24% female	Simvastatin, 40 mg + ezetimibe, 10 mg vs. simvastatin, 40 mg + PBO	≤350	---	93.8	53.2	5.8%[j]	32.7	34.7	2.0%	50[i]
HPS2-THRIVE 17.3% female	In combination with simvastatin or simvastatin + ezetimibe, extended-release niacin, 2 g + laropiprant, 40 mg vs. PBO	None[k]	None[k]	63	Mean –10 mg/dL change	3.7%[j]	13.2	13.7	0.5%[j]	200[i]

Abbreviations: AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events Trial; HDL-C = high-density lipoprotein cholesterol; HPS = Heart Protection Study; HPS2 THRIVE = Treatment of HDL to Reduce the Incidence of Vascular Events; hsCRP = high-sensitivity C-reactive protein; IDEAL = Incremental Decrease in Endpoints Through Aggressive Lipid lowering; IMPROVE-IT = IMProved Reduction of Outcomes, Vytorin Efficacy International Trial; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease; NNT = number needed to treat to prevent 1 event during study; PBO = placebo; PROVE IT – TIMI = Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction; 4S = Scandinavian Simvastatin Survival Study; TC = total cholesterol; TG = triglycerides; TNT = Treating to New Targets; WOSCOPS = West of Scotland Coronary Prevention Study; y = years

a Events: Acute myocardial infarction and coronary heart disease death, percentage with events at study end.
b The JUPITER trial was halted in March 2008. Median follow-up was 1.9 y; maximal follow-up was 5 y.
c Inclusion criteria included hsCRP protein concentration ≥2.0 mg/L.
d Median.
e Calculated based on 142 and 251 events in rosuvastatin and PBO groups, respectively.
f Number needed to treat for 2 years. Number needed to treat for 4 years is 31; 4-year risks projected over average 5-year treatment periods results in number needed to treat of 25.
g Additional inclusion criteria were either non-ST-elevation acute coronary syndrome or ST-elevation myocardial infarction.
h Cardiovascular death only.
i PBO included 50 mg niacin to mask the identity of blinded treatment to patients and study personnel.
j Calculated based on reported figures.
k Participant's doctor was provided with the total cholesterol result measured during LDL-C-lowering run-in phase. Whether an individual could participate in randomization was then decided by their own doctor.

Table 18 Lipid-Lowering Drug Therapies, Usual Starting Dosages and Dosage Ranges		
Agent	Usual recommended starting daily dosage	Dosage range
Statins		
Lovastatin	20 mg	10-80 mg
Pravastatin	40 mg	10-80 mg
Simvastatin	20-40 mg	5-80 mg[a]
Fluvastatin	40 mg	20-80 mg
Atorvastatin	10-20 mg	10-80 mg
Rosuvastatin	10 mg	5-40 mg
Pitavastatin	2 mg	2-4 mg
Cholesterol absorption inhibitors		
Ezetimibe	10 mg	10 mg
PCSK9 Inhibitors		
Alirocumab	75 mg every 2 weeks	75-150 mg every 2 weeks
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable
Fibrates		
Fenofibrate	48-145 mg	48-145 mg
Gemfibrozil	1,200 mg	1,200 mg
Fenofibric acid	45-135 mg	45-135 mg
Niacin		
Immediate-release	250 mg	250-3,000 mg
Extended-release	500 mg	500-2,000 mg
Bile acid sequestrants		
Cholestyramine	8-16 g	4-24 g
Colestipol	2 g	2-16 g
Colesevelam	3.8 g	3.8-4.5 g
Combination therapies (single pill)		
Ezetimibe/simvastatin	10/20 mg	10/10-10/80 mg
Extended-release niacin/simvastatin	500/20 mg	500/20-1,000/20 mg
MTP inhibitor		
Lomitapide	5 mg, with subsequent titration	5-60 mg
Antisense apolipoprotein B oligonucleotide		
Mipomersen (SubQ injection)	200 mg once weekly	200 mg once weekly
Omega-3 fatty acids		
Omega-3-acid ethyl esters (Lovaza)	4 g per day	4 g per day
Icosapent ethyl (Vascepa®)	4 g per day	4 g per day
Abbreviations: MTP = microsomal transfer protein; PCSK9 = proprotein convertase subtilisin/kexin type 9; SubQ = subcutaneous [a] Simvastatin, 80 mg, not approved for therapy unless individual has been on treatment for more than 1 year without myopathy.		

Table 19
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[a,b] (N = 2,431)

Statin	Dosage range, mg daily	TC	LDL-C	HDL-C	TG
Lovastatin	20-80	↓ 21 to ↓ 36	↓ 29 to ↓ 48	↑ 4.6 to ↑ 8.0	↓ 12 to ↓ 13
Pravastatin	10-40	↓15 to ↓ 22	↓ 20 to ↓30	↑ 3.2 to ↑ 5.6	↑ 8 to ↓ 13
Simvastatin	10-80[d]	↓ 20 to ↓ 33	↓ 28 to ↓ 46	↑ 5.2 to ↑ 6.8	↓ 12 to ↓ 18
Fluvastatin	20-40	↓ 13 to ↓ 19	↓ 17 to ↓ 23	↑ 0.9 to ↑ 3.0	↓ 5 to ↓ 13
Atorvastatin	10-80	↓ 27 to ↓ 39	↓ 37 to ↓ 51	↑ 2.1 to ↑ 5.7[c]	↓ 20 to ↓ 28
Rosuvastatin	10-40	↓ 33 to ↓ 40	↓ 45 to ↓ 55	↑ 7.7 to ↑ 9.6	↓ 20 to ↓ 26

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides
[a] The lipid-lowering effects of the various statins in these studies are representative of those seen in other controlled trials, with one exception. In the CARE (Cholesterol and Recurrent Events), WOSCOPS (West of Scotland Coronary Prevention Study), and LIPID (Long-Term Intervention With Pravastatin in Ischemic Disease) trials, pravastatin had a slightly greater TG-lowering effect.
[b] Figures for lovastatin and fluvastatin are from the 8-week CURVES trial (Comparative Dose Efficacy of Atorvastatin, Simvastatin, Pravastatin, Lovastatin, and Fluvastatin), a comparison of the effects on lipids of lovastatin, fluvastatin, atorvastatin, simvastatin, and pravastatin in men and women with LDL-C levels from 192 to 244 mg/dL (N = 534).
[c] HDL-C increase was with the lowest atorvastatin dosage, and benefit decreased as dosage increased.
[d] Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.
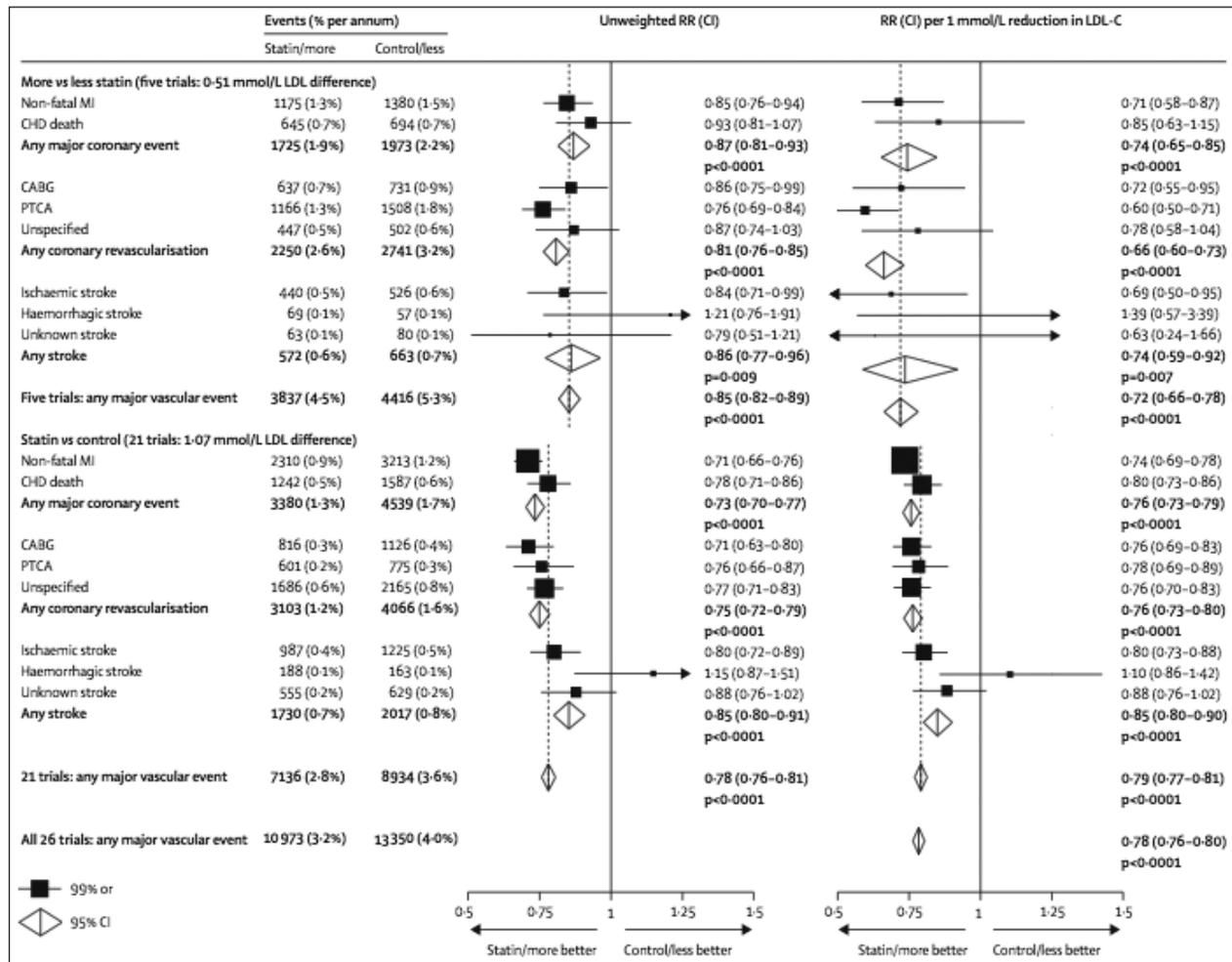

Fig. 2. Meta-analysis of proportional effects on major vascular events per mM/L LDL-C reduction in 169,138 participants in 26 randomized trials of statins over a median period of 5 years (121 [EL 1; MRCT]) (Cholesterol Treatment Trialists' Collaborators, 2010). Left, unweighted RRs are plotted for each comparison of first event rates between randomly allocated treatment groups. Right, RRs are weighted per 1·0 mmol/L LDL cholesterol (LDL-C) difference at 1 year. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds denoting 95% CIs. *CABG* = coronary artery bypass graft; *CHD* = coronary heart disease; *CI* = confidence interval; *LDL-C* = low-density lipoprotein cholesterol; *MI* = myocardial infarction; *PTCA* = percutaneous transluminal coronary angioplasty; *RR* = relative risk. Reprinted from *The Lancet*, Vol 376, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, 1670-1681, Copyright (2010), with permission from Elsevier (121 [EL 1; MRCT]).
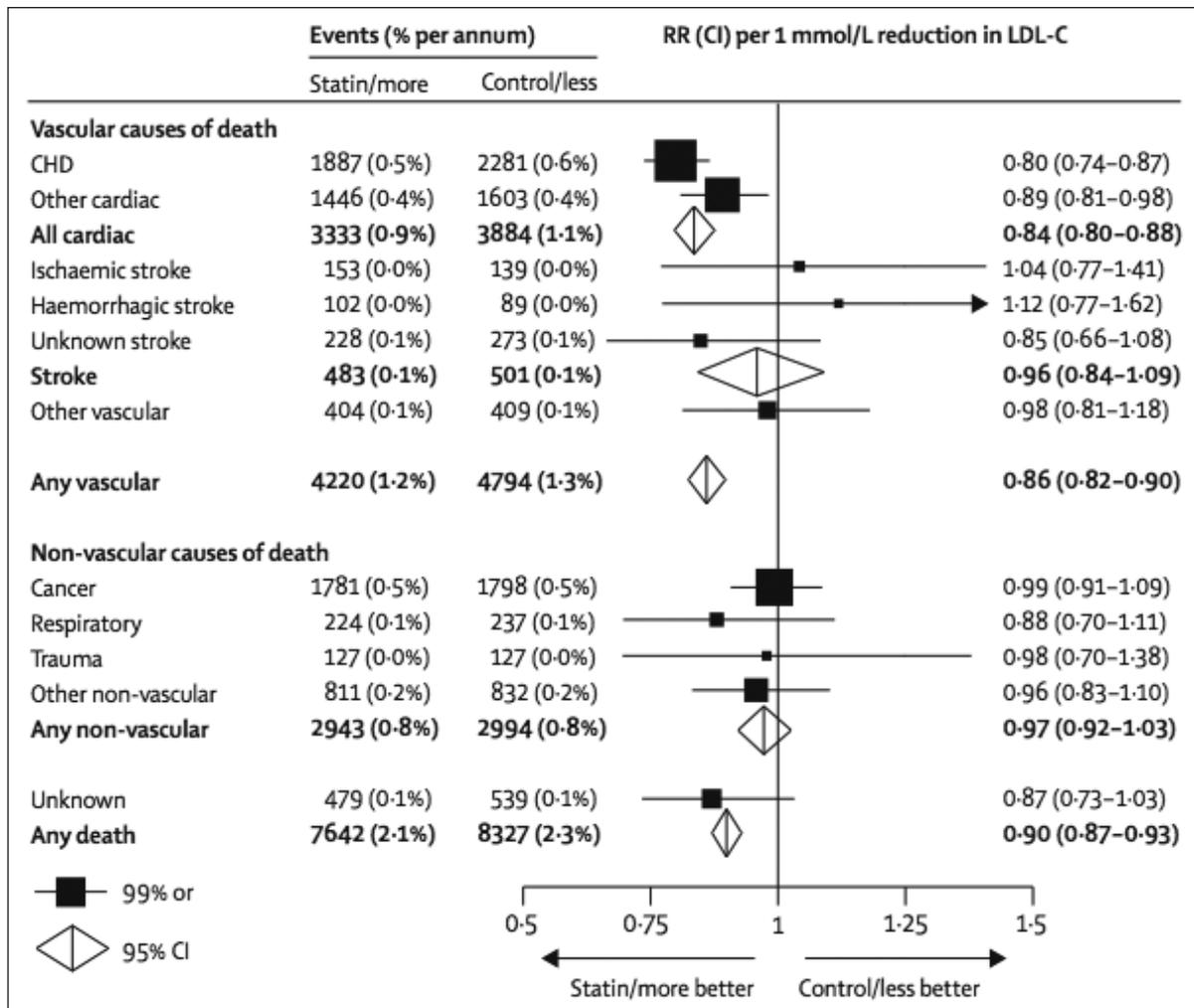
	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL-C	
	Statin/more	Control/less		
Vascular causes of death				
CHD	1887 (0·5%)	2281 (0·6%)		0·80 (0·74–0·87)
Other cardiac	1446 (0·4%)	1603 (0·4%)		0·89 (0·81–0·98)
All cardiac	**3333 (0·9%)**	**3884 (1·1%)**		**0·84 (0·80–0·88)**
Ischaemic stroke	153 (0·0%)	139 (0·0%)		1·04 (0·77–1·41)
Haemorrhagic stroke	102 (0·0%)	89 (0·0%)		1·12 (0·77–1·62)
Unknown stroke	228 (0·1%)	273 (0·1%)		0·85 (0·66–1·08)
Stroke	**483 (0·1%)**	**501 (0·1%)**		**0·96 (0·84–1·09)**
Other vascular	404 (0·1%)	409 (0·1%)		0·98 (0·81–1·18)
Any vascular	**4220 (1·2%)**	**4794 (1·3%)**		**0·86 (0·82–0·90)**
Non-vascular causes of death				
Cancer	1781 (0·5%)	1798 (0·5%)		0·99 (0·91–1·09)
Respiratory	224 (0·1%)	237 (0·1%)		0·88 (0·70–1·11)
Trauma	127 (0·0%)	127 (0·0%)		0·98 (0·70–1·38)
Other non-vascular	811 (0·2%)	832 (0·2%)		0·96 (0·83–1·10)
Any non-vascular	**2943 (0·8%)**	**2994 (0·8%)**		**0·97 (0·92–1·03)**
Unknown	479 (0·1%)	539 (0·1%)		0·87 (0·73–1·03)
Any death	**7642 (2·1%)**	**8327 (2·3%)**		**0·90 (0·87–0·93)**

■— 99% or
◇ 95% CI

0·5 0·75 1 1·25 1·5

Statin/more better Control/less better

Fig. 3. Meta-analysis of proportional effects on cause-specific mortality per mM/L LDL-C cholesterol reduction in 169,138 participants in 26 randomized trials of statins over a median period of 5 years, by baseline prognostic factors (121 [EL 1; MRCT]) (Cholesterol Treatment Trialists' Collaborators, 2010). RRs are plotted for each comparison of first event rates between treatment groups and are weighted per 1·0 mmol/L LDL cholesterol (LDL-C) difference at 1 year. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds showing 95% CIs. *CHD* = coronary heart disease; *CI* = confidence interval; *LDL-C* = low-density lipoprotein cholesterol; *RR* = relative risk. Reprinted from *The Lancet*, Vol 376, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, 1670-1681, Copyright (2010), with permission from Elsevier (121 [EL 1; MRCT]).

DISCLOSURE

Chair

Dr. Paul S. Jellinger reports that he has received speaker honoraria from BI-Lilly, AstraZeneca, Novo Nordisk, Amgen, and Merck.

Task Force Members

Dr. Donald A. Smith reports that he has received research grant support from Sanofi Regeneron and Amgen.

Dr. Yehuda Handelsman reports that he is a consultant for Amarin, Amgen, AstraZeneca, Boehringer Ingelheim (BI), Janssen, Eli Lilly, Eisai, Intarcia, Merck, Novo Nordisk, Sanofi, and Regeneron. He is a speaker for Amarin, Amgen, AstraZeneca, BI-Lilly, Janssen, Novo Nordisk, Sanofi, and Regeneron. Dr. Handelsman has received research grant support from Amgen, AstraZeneca, BI, Esperion, Grifols, Hamni, GSK, Lexicon, Merck, Novo Nordisk, and Sanofi.

Dr. David S. H. Bell reports that he is a consultant and speaker for AstraZeneca, Takeda, Janssen, and Novo Nordisk.

Dr. Zachary T. Bloomgarden reports that he is a consultant for AstraZeneca, Johnson & Johnson, Merck, Intarcia, and Novartis. He is also a speaker for Merck, AstraZeneca, and Johnson & Johnson. He is a shareholder in Allergan, Pfizer, Zimmer Biomet, and Novartis.

Dr. Eliot Brinton reports that he is a consultant for Alexion, Amarin, Aralez, Arisaph, AstraZeneca, Kowa, Merck, Regeneron, Sanofi-Aventis, and PTS Diagnostics. He is also a speaker for Alexion, Amarin, Amgen, Boehringer Ingelheim, Janssen, Kastle, Kowa, Merck, Novo Nordisk, Sanofi-Aventis, Takeda, and Regeneron.

Dr. Michael H. Davidson reports that he is a consultant for Amgen, Regeneron, Sanofi, Merck, and AstraZeneca. He has also received speaker honoraria and has served on the speaker's bureau for Amgen, Regeneron, and Sanofi.

Dr. Sergio Fazio reports that he is a consultant for Amgen, Sanofi, Amarin, Aegerion, and Kowa.

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Dr. Alan J. Garber reports that he is a consultant for Novo Nordisk and Intarcia.

Dr. George Grunberger reports that he has received speaker honoraria from Eli Lilly, BI-Lilly, Novo Nordisk, Sanofi, Janssen, and AstraZeneca. He has received research funding from AstraZeneca, Eli Lilly, Lexicon, and Medtronic.

Dr. Chris Guerin reports that he is a consultant for Janssen and a speaker for Novo Nordisk.

Dr. Jeffrey Mechanick reports that he is a consultant for Abbott Nutrition International.

Dr. Rachel Pessah-Pollack reports that she is a consultant and speaker for Boehringer Ingelheim/Eli Lilly.

Dr. Paul D. Rosenblit reports that he is a consultant for AstraZeneca and a speaker for AstraZeneca (Bristol Myers Squibb), Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, and Takeda. He has also received research grant support from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Ionis, Eli Lilly, Lexicon, Merck, Novo Nordisk, Orexigen, Pfizer, and Sanofi.

Dr. Kathleen Wyne reports that she is a consultant for Novo Nordisk and Abbvie. She has also received speaker honoraria from Roche and Bayer and research grant support from Sanofi and Eli Lilly.

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