AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS' GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROSIS

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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. We encourage medical professionals 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 patient circumstances.

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Abbreviations
AACE = American Association of Clinical Endocrinologists; **ATP** = Adult Treatment Panel; **apo** = apolipoprotein; **BEL** = best evidence level; **CAD** = coronary artery disease; **CPG** = clinical practice guidelines; **CRP** = C-reactive protein; **CVD** = cardiovascular disease; **EL** = evidence level; **HDL-C** = high-density lipoprotein cholesterol; **HRT** = hormone replacement therapy; **IMT** = intimal media thickness; **LDL-C** = low-density lipoprotein cholesterol; **Lp-PLA$_2$** = lipoprotein-associated phospholipase A_2; **MI** = myocardial infarction; **NCEP** = National Cholesterol Education Program; **QALY** = quality-adjusted life-year; **VLDL-C** = very low-density lipoprotein cholesterol

1. INTRODUCTION

Each year, an estimated 785 000 Americans will have a new coronary artery disease (CAD) event, and approximately 470 000 will have a recurrent attack. CAD caused approximately 1 of every 6 deaths in the United States in 2007. Although rates of stroke are declining, mortality data from 2007 indicate that stroke accounted for 1 of every 18 deaths in the United States. An estimated 33 600 000 adults 20 years or older have total serum cholesterol levels of 240 mg/dL or greater, for a prevalence of 15% of the American population **(1 [EL 3])**. Dyslipidemia is a primary, major risk factor for CAD and may even be a prerequisite for CAD, 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 stroke **(2 [EL 4])**. Increasing evidence also points to insulin resistance—which results in increased levels of plasma triglycerides 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 3])**, stroke, and CAD **(4 [EL 3])**.

Analysis of 30-year national trends in serum lipid levels shows improvements in total cholesterol and LDL-C levels, which 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 US adults have LDL-C concentrations above 100 mg/dL. Furthermore, the doubling in the prevalence of persons who are obese and the high percentage of patients with elevated triglyceride levels (33%) (and the correlation between obesity and elevated triglycerides) point to the need for continued vigilance on the part of physicians to reduce the risks of cardiovascular disease **(5 [EL3])**.

These clinical practice guidelines (CPGs) are for the diagnosis and treatment of dyslipidemia and prevention of atherosclerosis. 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])** and complements the Diabetes Mellitus Comprehensive Care Plan CPG **(7 [EL 4])**. The landmark National Cholesterol Education Program (NCEP) guidelines **(8 [EL 4])** serve as the backbone of these lipid recommendations.

These guidelines are unique in that they support the use of apolipoprotein (apo) B or LDL particle number measurements to refine our efforts to achieve effective LDL-C lowering, provide screening recommendations for persons of different ages, and identify special issues for pediatric patients. They also touch on the unique challenges associated with atherosclerosis and heart disease in women. They continue to emphasize the importance of LDL-C lowering and support the measurement of inflammatory markers to stratify risk in certain situations. Finally, an evaluation of the cost-effectiveness of lipid-lowering therapy is presented.

This document is organized into discrete clinical questions, with responses in the Executive Summary and the full guidelines that provide the evidence base supporting these recommendations. The objectives of this CPG are to:

- Present an overview of the screening recommendations, assessment of risk, and treatment recommendations for various lipid disorders.
- Give special consideration for patients with diabetes, women, and pediatric patients who have dyslipidemia.
- Provide cost-effectiveness data to support treatment.

After this prefatory summary, a more in-depth scientific analysis of these issues is presented.

2. METHODS

This CPG was developed in accordance with the AACE Protocol for Standardized Production of Clinical Practice Guidelines—2010 Update **(9 [EL 4])**. Reference citations in the text of this document include the reference number, numerical descriptor (EL 1-4), and semantic descriptor (Table 1) **(9 [EL 4])**.

Recommendations are assigned evidence level (EL) ratings on the basis of the quality of supporting evidence (Table 2) **(9 [EL 4])** all of which have also been rated for strength (Table 3) **(9 [EL 4])**. The format of this CPG is based on specific and relevant clinical questions. 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.

Clinical experts submitted contributions to specific clinical questions, which were subsequently reviewed, discussed, and integrated into the final document. Their valuable input provides the basis for the recommendations herein. Clinical questions are labeled "**Q**." Recommendations are labeled "**R**," and are based on importance and evidence (Grades A, B, and C) or expert opinion when there is a lack of conclusive clinical evidence (Grade D). The best evidence level (BEL), which corresponds to the best conclusive evidence found in the full guidelines to follow, accompanies the recommendation grade in this Executive Summary; definitions of ELs are provided in Figure 1 and Table 1 **(9 [EL 4])**. There are

Table 1
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating[a]

Numerical descriptor (evidence level)[b]	Semantic descriptor
1	Meta-analysis of randomized controlled trials
1	Randomized controlled trials
2	Meta-analysis of nonrandomized prospective or case-controlled trials
2	Nonrandomized controlled trial
2	Prospective cohort study
2	Retrospective case-control study
3	Cross-sectional study
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database)
3	Consecutive case series
3	Single case reports
4	No evidence (theory, opinion, consensus, review, or preclinical study)

[a] Adapted from: *Endocr Pract*. 2010;16:270-283 (9 [EL 4]).
[b] 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; and 4 = no evidence.

Table 2
2010 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*. 2010;16:270-283 (9 [EL 4]).

4 intuitive levels of evidence: 1 = strong, 2 = intermediate, 3 = weak, and 4 = no evidence (Table 3) **(9 [EL 4])**. 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])**. Details regarding each recommendation may be found in the corresponding section of the full guidelines. Thus, the process leading to a final recommendation and grade is not rigid, but rather it incorporates a complex expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making and to enhance patient care. Where appropriate, multiple recommendations are provided, so that the reader has management options. This document represents only a guideline. Individual patient circumstances and presentations differ, and the ultimate clinical management is based on what is in the best interest of the individual patient, involving patient input and reasonable clinical judgment by the treating clinicians.

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

Table 3
2010 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*. 2010;16:270-283 (9 [EL 4]).

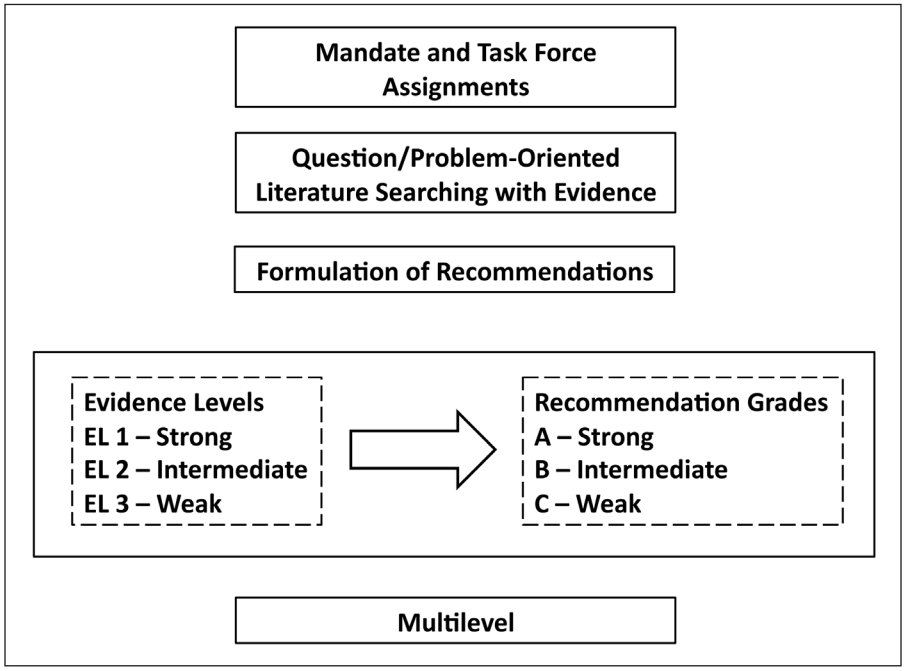

Fig. 1. 2010 American Association of Clinical Endocrinologists Clinical Practice Guideline Methodology. Current American Association of Clinical Endocrinologists Clinical Practice Guidelines have a problem-oriented focus that results in a shortened production timeline, middle-range literature searching, 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.

Table 4
2010 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*. 2010;16:270-283 (9 [EL 4]).

3. EXECUTIVE SUMMARY

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

3Q1.1. Global Risk Assessment

- **R1.** Identify risk factors (Table 5) **(10 [EL 4], 11 [EL 4], 12 [EL 4], 13 [EL 4], 14 [EL 2], 15 [EL 4], 16 [EL 2], 17 [EL 4], 18 [EL 2], 19 [EL 2], 20 [EL 4], 21 [EL 3]) and categorize degrees of risk** (Table 6) **(20 [EL 4], 22 [EL 4], 23 [EL 4])**, which enables the physician to personalize therapy for dyslipidemia according to each patient's risk level and thereby maximize treatment effectiveness **(Grade A; BEL 1)**.

  Major risk factors include advancing age, high serum total cholesterol levels, high non–HDL-C levels, high LDL-C levels, established CAD, family history of CAD, presence of hypertension or diabetes mellitus, and cigarette smoking. Additional risk factors (obesity, family history, elevated apo B, increased LDL particle number, small dense LDL, fasting/postprandial hypertriglyceridemia, polycystic ovary syndrome in women, dyslipidemic triad) should be considered, as should nontraditional risk factors (eg, inflammatory markers, highly sensitive C-reactive protein [CRP], lipoprotein-associated phospholipase A_2 [Lp-PLA_2], lipoprotein [a], hyperhomocysteinemia, hyperuricemia).
- **R2.** Determine the 10-year risk (high, intermediate, low) of a coronary event using the Framingham Risk Assessment Tool or Reynolds Risk Score (www.reynoldsriskscore.org), (the latter includes highly sensitive CRP and family history of premature CAD) **(Grade A; BEL 4)**.
- **R3.** Because of the diagnostic difficulties and differences in clinical presentation, AACE recommends that special attention be given to assessing women for CAD risk. Determine the 10-year risk (high, intermediate, low) of a coronary event using Reynolds Risk Score (www.reynoldsriskscore.org) or the Framingham Risk Assessment Tool **(Grade A; BEL 4)**. The Framingham Risk Score provides 10-year probability of women experiencing a coronary event in the presence of

Table 5
Major Coronary Artery Disease Risk Factors (10 [EL 4], 11 [EL 4], 12 [EL 4], 13 [EL 4], 14 [EL 2], 15 [EL 4], 16 [EL 2], 17 [EL 4], 18 [EL 2], 19 [EL 2], 20 [EL 4], 21 [EL 3])

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age[a,d]	Obesity, abdominal obesity[c,d]	Elevated lipoprotein (a)
High total serum cholesterol level[a,b,d]	Family history of hyperlipidemia[d]	Elevated clotting factors
High non–HDL-C[d]	Small, dense LDL-C[d]	Inflammation markers (hsCRP; Lp-PLA_2)
High LDL-C[a,d]	⇧ Apo B[d]	Hyperhomocysteinemia
Low HDL-C[a,d,e]	⇧ LDL particle number	Apo E4 isoform
Diabetes mellitus[a,b,c,d]	Fasting/postprandial hypertriglyceridemia[d]	Elevated uric acid
Hypertension[a,b,c,d]	PCOS[d]	
Cigarette smoking[a,b,c,d]	Dyslipidemic triad[f]	
Family history of CAD[a,d,g]		

Abbreviations: apo, apolipoprotein; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase A_2; 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).

[e] Elevated high-density lipoprotein cholesterol is a negative risk factor.

[f] Hypertriglyceridemia; low high-density lipoprotein cholesterol; and small, dense low-density lipoprotein cholesterol.

[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.

specific clinical diagnoses or scenarios (Table 7) **(24 [EL 3], 25 [EL 4])**, but unlike the Reynolds Risk Score, it appears to underestimate CAD risk in women with 2 risk factors.

- **R4.** AACE recommends early diagnosis and management of pediatric dyslipidemia to reduce the levels of LDL-C that may eventually increase risk of cardiovascular events in adulthood **(Grade A; BEL 1)**. Classification of LDL-C levels as acceptable, borderline, or high is outlined in Table 8 **(26 [EL 4])**.
- **R5.** Categorize lipid-related risks as optimal/near-optimal, borderline, and high risk (Table 9) **(10 [EL 4])**. An HDL-C concentration greater than 60 mg/dL is an independent negative risk factor in both sexes, and when the HDL-C concentration is greater than 60 mg/dL, 1 risk factor can be subtracted from a patient's overall risk profile **(Grade A; BEL 1)**.
- **R6.** AACE recommends classifying elevated triglycerides (Table 10**) (10 [EL 4])** to aid in treatment decisions **(Grade A; BEL 1)**.

3Q1.2. Screening

- **R7.** AACE recommends more frequent assessments for all patients with a family history of premature CAD (definite myocardial infarction [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) **(Grade C; BEL 4)**. AACE suggest considering more frequent testing for individuals with CAD risk factors **(Grade C; BEL 4)**.

Adults With Diabetes

- **R8.** Annually screen all adult patients with diabetes mellitus for dyslipidemia **(Grade B; BEL 2)**.

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

- **R9.** Evaluate all adults 20 years of age for dyslipidemia every 5 years as part of a global risk assessment **(Grade A; BEL 3)**.

Table 6
Coronary Artery Disease Risk Categories and Low-Density Lipoprotein Treatment Goals
(20 [EL 4], 22 [EL 4], 23 [EL 4])

Risk category	Risk factors[a]/10-year risk[b]	LDL-C treatment goal
Very high risk	Established or recent hospitalization for coronary, carotid, and peripheral vascular disease or diabetes plus 1 or more additional risk factor(s)	<70 mg/dL
High risk	≥2 risk factors and 10-year risk >20% or CHD risk equivalents[c], including diabetes with no other risk factors	<100 mg/dL
Moderately high risk	≥2 risk factors and 10-year risk 10%-20%	<130 mg/dL
Moderate risk	≥2 risk factors and 10-year risk <10%	<130 mg/dL
Low risk	≤1 risk factor	<160 mg/dL

Abbreviations: CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.
[a] Major independent risk factors are high low-density lipoprotein cholesterol, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low high-density lipoprotein cholesterol (<40 mg/dL), family history of coronary artery disease (n male first-degree relative younger than 55 years; in female first-degree relative younger than 65 years), and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high high-density lipoprotein cholesterol (≥60 mg/dL) (10 [EL 4], 11 [EL 4]).
[b] Framingham risk scoring is applied to determine 10-year risk (10 [EL 4]).
[c] Coronary artery disease risk equivalents include diabetes and clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease).

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

- **R10.** In the absence of CAD risk factors, screen middle-aged persons for dyslipidemia at least every 1 to 2 years. AACE recommends more frequent lipid testing when multiple *global CAD risk factors* are present **(Grade C; BEL 3)**. The frequency of testing should be based on individual clinical circumstances and the clinician's best judgment **(Grade C; BEL 4)**.

Older Adults (Older Than 65 Years)

R11. Annually screen older adults with 0 to 1 CAD risk factor for dyslipidemia **(Grade C; BEL 1)**. In addition, older patients should undergo lipid assessment if they have multiple CAD global risk factors (ie, risk factors other than age) **(Grade C; BEL 4)**.

- **R12.** AACE believes that screening recommendations apply based on age and risk, not based on sex; therefore, women should be screened in the same way as men **(Grade A; BEL 1)**.

Children and Adolescents

- **R13.** *S*creen children older than 2 years every 3 to 5 years if they have CAD risk factors or a family history of premature CAD or dyslipidemia, are overweight or obese, have other elements of the insulin resistance syndrome, or have no available family history **(Grade A; BEL 4)**.
- **R14.** Screen adolescents older than 16 years every 5 years or more frequently if they have CAD risk factors, are overweight or obese, have other elements of the insulin resistance syndrome, or have a family history of premature CAD **(Grade A; BEL 3)**.

AACE joins the American Heart Association and the US Preventive Services Task Force in recommending further research to determine the effect of pediatric dyslipidemia screening and treatment on adult outcomes **(27 [EL 4], 28 [EL 4])**.

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

3Q2.1. Fasting Lipid Profile

- **R15.** Use a fasting lipid profile to ensure the most precise lipid assessment. This should include total cholesterol, LDL-C, triglycerides, and HDL-C **(Grade C; BEL 4)**.

Table 7
Framingham Risk Score–Based 10-Year Probability of Women Experiencing a Coronary Event in the Presence of Specific Clinical Diagnoses or Scenarios
(24 [EL 3], 25 [EL 4])

Risk group	Framingham Global Risk (10-year absolute CAD risk)	Clinical examples
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 ▪ Metabolic syndrome ▪ 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, metabolic syndrome, or 1 or no risk factors
Optimal	<10%	▪ Optimal levels of risk factors and heart-healthy lifestyle

[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%.

3Q2.2. Low-Density Lipoprotein Cholesterol

Calculated

- **R16.** AACE does not recommend estimating LDL-C values in certain clinical circumstances. LDL-C is frequently and inexpensively estimated using the Friedewald equation: **(Grade A, BEL 1) (10 [EL 4])**:

$$\text{LDL-C} = (\text{total cholesterol} - \text{HDL-C}) - \frac{\text{triglycerides}}{5}$$

However, this method is valid only for values obtained during the fasting state. It becomes increasingly inaccurate when triglyceride levels are greater than 200 mg/dL, and the equation is no longer valid when triglyceride levels are greater than 400 mg/dL.

Direct Measurement

- **R17.** AACE recommends direct measurement of LDL-C in certain high-risk patients, such as those with fasting triglyceride levels greater than 250 mg/dL or those with diabetes mellitus or known vascular disease **(Grade C; BEL 3)**.

3Q2.3. High-Density Lipoprotein Cholesterol

- **R18.** AACE recommends measurement of HDL-C as a screening test for dyslipidemia. Low HDL-C can act synergistically with other lipid risk factors to increase CAD risk. An HDL-C concentration greater than 60 mg/dL is an independent *negative* risk factor in both sexes.

Table 8
Classification of Low-Density Lipoprotein Cholesterol Levels in Children and Adolescents (26 [EL 4])

Category	Low-density lipoprotein cholesterol, mg/dL
Acceptable	<110
Borderline	110-129
High	≥130

Table 9
Optimal/Near-Optimal, Borderline, and High-Risk Serum Lipid Concentrations
(10 [EL 4])

Lipid	Optimal/near-optimal serum concentration	Borderline serum concentration	High-risk/very high-risk serum concentration
TC, mg/dL	<200	200-239	≥240
HDL-C, mg/dL	≥60 (negative risk factor)	40-59 (men) 50-59 (women)	<40 men <50 women[b]
LDL-C, mg/dL	<100 optimal (100-129 near-optimal)	130-159	160-189 high ≥190 very high
TG[a], mg/dL	<150	150-199	200-499 high ≥500 very high
Apo B, mg/dL	<90 (patients at risk of CAD, including those with diabetes) <80 (patients with established CAD or diabetes plus ≥1 additional risk factor)		

Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
[a] Both borderline and high-risk values may signify familial combined dyslipidemia or dyslipidemia of diabetes; values >1000 indicate high risk for pancreatitis.
[b] Moderate reductions of high-density lipoprotein cholesterol in women may indicate insulin resistance syndrome.

3Q2.4. Non–High-Density Lipoprotein Cholesterol

- **R19.** Calculate non–HDL-C (total cholesterol minus HDL-C) in patients with moderately elevated triglycerides (200 to 500 mg/dL), diabetes mellitus, and/or established CAD **(Grade C; BEL 2)**.
- **R20.** If insulin resistance is suspected, AACE recommends evaluating non–HDL-C to gain useful information regarding the patient's total atherogenic lipoprotein burden. In addition, in any circumstance when triglycerides are 200 mg/dL or greater but less than 500 mg/dL, a non–HDL-C calculation will provide better risk assessment than LDL-C alone **(Grade C; BEL 4)**. Non–HDL-C targets are 30 mg/dL higher than established LDL-C risk levels **(Grade C; BEL 4)**.

3Q2.5. Triglycerides

- **R21.** Increasing clinical evidence suggests that elevated triglycerides may be an independent risk factor for CAD; therefore, AACE recommends screening of triglycerides as a component of lipid screening. Triglycerides levels that are even moderately elevated (>150 mg/dL) may identify individuals at risk for the insulin resistance syndrome. Triglyceride levels 200 mg/dL or greater may indicate a substantial increase in CAD risk **(10 [EL 4])**.

3Q2.6. Apolipoproteins

- **R22.** AACE recommends that optimal apo B levels for patients at risk of CAD, including those with diabetes, are less than 90 mg/dL, while patients with established CAD or diabetes who have 1 or more additional risk factor(s) should have an apo B goal of less than 80 mg/dL **(Grade D; BEL 4)**. When the triglyceride level is greater than 150 mg/dL or the HDL-C level is less than 40 mg/dL, AACE believes that the apo B or the apo B to apo AI ratio may be particularly useful in assessing residual risk in patients at risk for CAD *(even when LDL-C levels are controlled)*; this includes patients with established CAD, type 2 diabetes, or the insulin resistance syndrome who are at high risk for CAD. AACE therefore recommends apo B testing in such patients **(Grade B; BEL 2)**.
- **R23.** AACE recommends apo B measurements to assess the success of LDL-C–lowering therapy. Apo B reflects LDL particle number, which may be elevated in patients at or below LDL-C goal. While LDL-C and LDL particle *size* (eg, small, dense LDL) are associated with atherogenicity, LDL particle *number* as reflected by apo B is a more potent measure of cardiovascular disease (CVD) risk than either of these 2 measures **(Grade B; BEL 2)**.
- **R24.** AACE believes that assessment of apo AI may be useful in certain cases **(Grade B; BEL 2)**. A normal apo AI level in a patient with low HDL-C suggests the existence of an adequate number of HDL-C particles that contain less cholesterol and may be an indication of less risk. The INTERHEART study found that the apo B to apo AI ratio was among the most significant risk factors for MI **(14 [EL 2])**.

3Q2.7. Secondary Causes of Dyslipidemia

- **R25.** Rule out secondary causes of dyslipidemia. Numerous conditions may variably affect total cholesterol and LDL-C or triglycerides and very low-density lipoprotein cholesterol (VLDL-C) (Table 11) **(10 [EL 4], 29 [EL 4])**.

3Q2.8. Additional Tests

- **R26.** Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP and Lp-PLA_2 provide useful additional information in these instances and appear to be synergistic in predicting risk of CVD and stroke **(Grade B; BEL 1)**.
- **R27.** Use highly sensitive CRP to stratify CVD risk in patients with a standard risk assessment that is borderline, or in those with an LDL-C concentration less than 130 mg/dL **(Grade 2; BEL B)**.
- **R28.** Measure Lp-PLA_2, which in some studies has demonstrated more specificity than highly sensitive CRP, when it is necessary to further stratify a patient's CVD risk, especially in the presence of systemic highly sensitive CRP elevations **(Grade 2; BEL B)**.

Table 10
Classification of Elevated Triglyceride Levels
(10 [EL 4])

Triglyceride category	Triglyceride concentration, mg/dL	Goal
Normal	<150	<150 mg/dL
Borderline-high	150-199	
High	200-499	
Very high	≥500	

- **R29.** AACE does not recommend routine measurement of homocysteine, uric acid, plasminogen activator inhibitor 1, or other inflammatory markers because the benefit of doing so is unclear **(Grade 4; BEL D)**. Although recent data from the third National Health and Nutrition Examination Survey **(30 [EL 3])** and MESA (Multi-Ethnic Study of Atherosclerosis) **(31 [EL 3])** have shown that the addition of homocysteine is useful in CVD risk stratification, especially when used in conjunction with the Framingham Risk Score, to identify patients at high CVD risk who might otherwise be classified as intermediate risk, several studies have demonstrated no benefit from intervention **(32 [EL 4], 33 [EL 1], 34 [EL 1], 35 [EL 2], 36 [EL 1])**.
- **R30.** Noninvasive measures of atherosclerosis such as carotid intima media thickness (IMT) and coronary artery calcification should not be performed routinely, but may be used in certain clinical situations as adjuncts to standard CVD risk factors in an attempt to refine risk stratification and the need for more aggressive preventive strategies. Although coronary calcium correlates strongly with coronary atherosclerosis, there is a lack of definite evidence that this risk factor independently predicts coronary events **(Grade 4; BEL D)**.

3Q3. WHAT ARE THE TREATMENT RECOMMENDATIONS IN PATIENTS WITH DYSLIPIDEMIA AND CAD RISK?

3Q3.1. Treatment Goals

Table 12 summarizes the AACE recommended treatment goals for major lipid parameters in patients *at risk for*

Table 11
Common Secondary Causes of Dyslipidemia
(10 [EL 4])

Affected lipids	Conditions
↑ Total cholesterol and low-density lipoprotein cholesterol	• 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]
↑ Total triglycerides and very low-density lipoprotein cholesterol	• Chronic renal failure • Type 2 diabetes mellitus[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]

Abbreviation: HIV, human immunodeficiency virus.
[a] Progestational agents, especially those with androgenic activity, can increase low-density lipoprotein cholesterol and decrease high-density lipoprotein cholesterol.
[b] Protease inhibitors can induce peripheral lipodystrophy, increased visceral fat, insulin resistance, and diabetes. Protease inhibitor-induced dyslipidemia may include elevated low-density lipoprotein cholesterol and/or the atherogenic dyslipidemia pattern of high triglycerides, small, dense, low-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol. However, newer generation protease inhibitors may have improved lipid profiles.
[c] Diabetic dyslipidemia is often similar to atherogenic dyslipidemia: high triglycerides, small, dense low-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol (10 [EL 4], 29 [EL 4]).
[d] Transdermally administered estrogens are not associated with increased triglyceride levels.

CAD **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL 1], 41 [EL 4])**. However, lipid goals for all patients should be personalized by levels of risk **(20 [EL 4], 22 [EL 4], 23 [EL 4])**.

3Q3.1.1. Low-Density Lipoprotein Cholesterol

- **R31.** In adults of both sexes, AACE recommends a target LDL-C concentration less than 100 mg/dL and less than 70 mg/dL in *all* patients at very high risk **(Grade A; BEL 4)**. For patients with diabetes mellitus, AACE recommends an LDL-C goal of less than 100 mg/dL, and in those with 1 or more additional risk factor(s) (eg, existing CVD), the recommended LDL-C goal is less than 70 mg/dL **(Grade A; BEL 1)** (Table 12) **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])**.
- **R32.** AACE concurs with the American Academy of Pediatrics that acceptable, borderline, and high LDL-C levels for children and adolescents are less than 110 mg/dL, 110 to 129 mg/dL, and 130 mg/dL or greater, respectively (Table 8) **(26 [EL 4])**.

3Q3.1.2. High-Density Lipoprotein Cholesterol

- **R33.** AACE recommends raising HDL-C levels as much as possible, but *minimally* to greater than 40 mg/dL in both men and women **(Grade C; BEL 4)** (Table 12) **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])**. Table 13 **(10 [EL 4])** summarizes the basic treatment approach to isolated low HDL-C.
- **R34.** Exclude secondary causes (eg, cigarette smoking, certain drugs, genetic factors) of isolated low HDL-C. AACE then recommends pharmacologic intervention if HDL-C levels are low and other risk factors are present (including borderline elevated LDL-C levels, a family history of premature CAD, or a personal history of CAD) **(Grade A; BEL 1)** (Table 11) **(10 [EL 4])**. AACE does not recommend increasing HDL-C levels alone (ie, low HDL-C without any accompanying risk factors) because it is difficult to determine from clinical trials whether increasing HDL-C levels alone is clinically beneficial.

3Q3.1.3. Non–High-Density Lipoprotein Cholesterol

- **R35.** AACE recommends a non–HDL-C goal (total cholesterol minus HDL-C) that is 30 mg/dL higher than the patient-specific LDL-C goal **(Grade A, BEL 1)** (Table 12) **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL 1], 41 [EL 4])**.
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3Q3.1.4. Apolipoproteins

- **R36.** AACE recommends that an optimal apo B level for patients at risk of CAD, including those with diabetes, is less than 90 mg/dL, while patients with established CAD or diabetes plus 1 or more additional risk factor(s) should have an apo B goal less than 80 mg/dL **(Grade D, BEL 4)** (Table 12) **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL 1], 41 [EL 4])**.

Table 12
Lipid Goals for Patients at Risk for Coronary Artery Disease
(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])

Lipid Parameter	Goal	EL
TC, mg/dL	<200	EL 1
LDL-C, mg/dL	<100; <70 (*all* very high risk patients)	EL 1
HDL-C, mg/dL	As high as possible, but at least >40 in both men and in women	EL 1
Non–HDL-C, mg/dL	30 above LDL-C goal	EL 1
TG, mg/dL	<150	EL 1
Apo B, mg/dL	<90 (patients at risk of CAD, including those with diabetes) <80 (patients with established CAD or diabetes plus ≥1 additional risk factor)	EL 4

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

3Q3.1.5 Triglycerides

- **R37.** Triglyceride levels less than 150 mg/dL in both men and women are recommended **(Grade A; BEL 4)** (Table 12) **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL 1], 41 [EL 4]**). There is increased atherogenicity of LDL particles at increasing triglyceride levels, which correlate with risk.

3Q3.2. Treatment Recommendations

- **R38.** AACE recommends a comprehensive strategy to control lipid levels and to address associated metabolic abnormalities and modifiable risk factors such as hypertension, diabetes, obesity, and cigarette smoking. The first-line approach to primary prevention in patients with lipid disorders involves the implementation of lifestyle changes, including physical activity and medical nutrition therapy. Treatment may also involve pharmacotherapy, as well as patient education programs, to promote further risk reduction through smoking cessation and weight loss.

3Q3.2.1. Physical Activity

- **R39.** AACE recommends a reasonable and feasible approach to fitness therapy, ie, 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. Suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities **(Grade A; BEL 2)**. Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum). For some patients, breaking activity up throughout the day may help improve adherence to physical activity programs **(Grade B; BEL 4)**. In addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week **(Grade B; BEL 2)**.

3Q3.2.2. Medical Nutrition Therapy

- **R40.** For adults, AACE recommends a reduced-calorie diet consisting of fruits and vegetables (≥5 servings/day) **(Grade A; BEL 2)**, grains (≥6 servings/day, one-third of those as whole grains), fish, and lean meats **(Grade B; BEL 2)**. 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)**.
- **R41.** AACE recommends primary preventive nutrition in all healthy children older than 2 years **(Grade A; BEL 4)**.

3Q3.2.3. Smoking Cessation

- **R42.** Every effort should be made to support patients in their efforts to cease smoking **(Grade A; BEL 3)**. Cigarette smoking is a powerful risk factor, especially for MI, peripheral vascular disease, and stroke. Smoking accelerates coronary plaque development and may lead to plaque rupture and is particularly dangerous in persons with advanced coronary atherosclerosis. 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 triglycerides. However, smoking cessation significantly increases HDL-C, with improvement observed in as few as 30 days.

Table 13
Recommended Basic Approach to Treatment for Patients With Isolated Low High-Density Lipoprotein Cholesterol[a]
(10 [EL 4])

Weight loss, physical activity, smoking cessation	Drug therapy	Minimal Goal[c]
HDL-C <40 mg/dL	HDL-C <40 mg/dL with strong risk factors[b]	HDL-C >40 mg/dL

Abbreviation: HDL-C, high-density lipoprotein cholesterol.
[a] Isolated low HDL-C is present when HDL-C is decreased without accompanying hypertriglyceridemia.
[b] Coronary artery disease or coronary artery disease risk equivalents, 10-year risk >20%.
[c] Minimal goal; high-density lipoprotein cholesterol should be raised as high as possible.

3Q3.2.4. Pharmacologic Therapy

- **R43.** AACE recommends aggressive lipid-modifying therapy to lower LDL-C to less than 100 mg/dL in patients with average or elevated LDL-C. This has been shown to reduce vascular mortality in patients at high risk **(Grade A; BEL 1)** and to decrease coronary death, MI, or any cardiovascular events in patients on aggressive statin therapy **(Grade A; BEL 1).** Table 14 summarizes the primary lipid-lowering drug classes **(42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4]), 49 [EL 1]), 50 [EL 4], 51 [EL 4], 52 [EL 4], 53 [EL 3], 54 [EL 4], 55 [EL 4], 56 [EL 3], 57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 66 [EL 1], 67 [EL 1], 68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2], 77 [EL 1], 78 [EL 3]**), and Table 15 summarizes initial dosage recommendations **(43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 50 [EL 4], 51 [EL 4], 52 [EL 4], 55 [EL 4], 57 [EL 4], 79 [EL 4], 80 [EL 4], 81 [EL 4], 82 [EL 4]**).
- **R44.** AACE recommends an LDL-C goal less than 70 mg/dL as an appropriate goal for *all* patients with established CAD. Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no threshold below which LDL-C lowering ceases to be effective **(Grade A; BEL 1)**. Reducing lipids to levels even below recommended targets may be beneficial for certain patients (eg, those with metabolic syndrome). Consequently, in 2004, the NCEP Adult Treatment Program (ATP) III updated its guidelines to include an "optional" LDL-C goal less than 70 mg/dL for patients at very high risk. *The 2004 NCEP ATP III update further indicated that it is always prudent to initiate therapy at a level sufficient to achieve a 30% to 40% LDL-C reduction* **(23 [EL 4])**. The American Heart Association/American College of Cardiology 2006 update of its CVD secondary prevention guidelines also considers reduction of LDL-C to less than 70 mg/dL for patients with established CAD a "reasonable goal."

Patients for whom AACE recommends aggressive therapy:

- Patients undergoing coronary artery bypass graft **(Grade A; BEL 1)**.
- Patients with acute coronary syndrome **(Grade A; BEL 1)**.
- Certain healthy and functional older patients at high risk who may be appropriate candidates for aggressive therapy **(Grade A; BEL 1)**.

Statins

- **R45.** AACE recommends statins as the drug of choice for LDL-C reduction on the basis of findings from morbidity and mortality outcome trials **(Grade A; BEL 1)**. Agents currently available are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin; see Table 14 (**42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4], 49 [EL 1], 50 [EL 4], 51 [EL 4], 52 [EL 4], 53 [EL 3], 54 [EL 4], 55 [EL 4], 56 [EL 3], 57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 66 [EL 1], 67 [EL 1], 68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2], 77 [EL 1], 78 [EL 3]**) and Table 15 (**43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 50 [EL 4], 51 [EL 4], 52 [EL 4], 55 [EL 4], 57 [EL 4], 79 [EL 4], 80 [EL 4], 81 [EL 4], 82 [EL 4]**).

Fibrates

- **R46.** AACE recommends fibrates for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL) **(Grade A; BEL 1)**. Adjunct use of 2 to 4 g of omega 3 fish oil can be used, if necessary, to achieve satisfactory triglyceride lowering.

For *primary prevention* of ischemic cardiovascular events, fibrate therapy can reduce the occurrence of MI and cardiovascular death in those with both triglyceride concentrations greater than 200 mg/dL and HDL-C concentrations less than 40 mg/dL **(83 [EL 3], 84 [EL 2])**.

For *secondary prevention*, fibrate monotherapy was shown to reduce events in those with HDL-C concentrations less than 40 mg/dL in the VA-HIT trial (Veterans Affairs HDL Intervention Trial) **(85 [EL 1])** and in those with triglyceride concentrations of 200 mg/dL or greater in the Bezafibrate Infarction Prevention trial **(86 [EL 1])**. The FIELD trial demonstrated a more certain preventive effect in patients with both triglyceride levels greater than 200 mg/dL and HDL-C levels less than 40 mg/dL **(83 [EL 3])**.

In those on a statin with an LDL-C concentration less than 100 mg/dL, prespecified subgroup analyses in the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) demonstrate that fibrate therapy reduces further cardiovascular ischemic events only in those with both lipid abnormalities (triglycerides ≥200 mg/dL, HDL-C ≤35 mg/dL) **(87 [EL 1])**. The failure to reach primary endpoint targets of MI and cardiovascular death in the FIELD and ACCORD trials has resulted in an uncertain clinical benefit in treating patients with lesser triglyceride and HDL-C abnormalities with fibrates. Available agents are

Table 14
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 Effect on HDL-C is less pronounced (↑ 2%-10%) ↓ TG 6%-30% (42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4])	Monitoring of liver function required Myalgias and muscle weakness in some patients Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, cyclosporine, warfarin, and protease inhibitors (42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4]) Myopathy/rhabdomyolysis in rare cases; increased risk with coadministration of some drugs (see product labeling) (42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4]) Simvastatin dosages of 80 mg are no longer recommended Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine (44 [EL 4]) Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups (44 [EL 4]). Slight increase in new-onset diabetes in patients treated intensively with statins, which occurs to a lesser extent than the associated cardiovascular event reduction (49 [EL 1])
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 (50 [EL 4], 51 [EL 4], 52 [EL 4]) 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 (rare); interaction less likely with fenofibrate or fenofibric acid (52 [EL 4]) Myopathy/rhabdomyolysis when used with statin (rare); interaction less likely with fenofibrate or fenofibric acid (52 [EL 4]) Fibrates associated with increased serum creatinine levels, which may not be caused by renal dysfunction (53 [EL 3], 54 [EL 4])

Table 14 *(Continued)*
Primary Lipid-Lowering Drug Classes

Drug class	Metabolic effect[a]	Main considerations[b]
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 particle size and thus decreasing particle number	Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatoxicity (rare but may be severe), nausea, peptic ulcer 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 at the intestinal level Colesevelam ↓ glucose and hemoglobin A_{1c} (~0.5%) (55 [EL 4], 56 [EL 3])	May ↑ serum TG Frequent non–life-threatening GI events, which can reduce patient adherence Many potential drug interactions, less so with colesevelam (see product labeling) May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K
Cholesterol absorption inhibitors (ezetimibe)	Primarily ↓ LDL-C 10%-18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver (57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1]) ↓ Apo B 11%-16% (57 [EL 4], 59 [EL 1]) In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34%-61% (57 [EL 4], 60 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1]) In combination with fenofibrate, ↓ LDL-C 20%-22% and ↓ apo B 25%-26% without reducing ↑ HDL-C (57 [EL 4], 66 [EL 1], 67 [EL 1])	Myopathy/rhabdomyolysis (rare) (57 [EL 4]) Myopathy/rhabdomyolysis (rare) (57 [EL 4]) When coadministered with statins or fenofibrate, risks associated with those drugs remain (eg, myopathy/rhabdomyolysis, cholelithiasis) (57 [EL 4])

Abbreviations: apo, apolipoprotein; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, hydroxymethylglutaryl-coenzyme A; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol; TC, total 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 (68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2]).

[d] Results vary. Gemfibrozil has been shown to have no effect on or increase homocysteine (77 [EL 1], 78 [EL 3]).

gemfibrozil, fenofibrate, and fenofibric acid; see Table 14 (**42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4], 49 [EL 1], 50 [EL 4], 51 [EL 4], 52 [EL 4], 53 [EL 3], 54 [EL 4], 55 [EL 4], 56 [EL 3], 57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 66 [EL 1], 67 [EL 1], 68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2], 77 [EL 1], 78 [EL 3]**) and Table 15 (**43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 50 [EL 4], 51 [EL 4], 52 [EL 4], 55 [EL 4], 57 [EL 4], 79 [EL 4], 80 [EL 4], 81 [EL 4], 82 [EL 4]**).

Niacin

- **R47.** AACE recommends niacin for reducing triglycerides, increasing HDL-C, and reducing LDL-C **(Grade B; BEL 2)**. Adjunct use

Table 15
Lipid-Lowering Drug Therapies, Usual Starting Dosages and Dosage Ranges
(43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 50 [EL 4], 51 [EL 4], 52 [EL 4], 55 [EL 4], 57 [EL 4], 79 [EL 4], 80 [EL 4], 81 [EL 4], 82 [EL 4])

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
Fibrates		
Fenofibrate	48-145 mg	48-145 mg
Gemfibrozil	1200 mg	1200 mg
Fenofibric acid	45-135 mg	45-135 mg
Niacin		
Immediate-release	250 mg	250-3000 mg
Extended-release	500 mg	50 mg 0-2000 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
Cholesterol absorption inhibitors		
Ezetimibe	10 mg	10 mg
Combination therapies (single-pill)		
Ezetimibe/simvastatin	10/20 mg	10/10 to 10/80 mg
Extended-release niacin/simvastatin	500/20 mg	500/20 to 1000/20 mg

[a] Simvastatin, 80 mg, not approved for therapy unless patient has been on treatment for more than 1 year without myopathy.

of 2 to 4 g of omega-3 fish oil can be used, if necessary, to achieve satisfactory triglyceride lowering. In contrast to the existing secondary cardiovascular preventive evidence from the Coronary Drug Project **(88 [EL 2])**, HATS (HDL-Atherosclerosis Treatment Study) **(89 [EL 1])**, and ARBITER 6–HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis) **(90 [EL 1])** trials, cessation of the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) **(91 [EL 1])** makes it uncertain whether niacin benefits all simvastatin-treated patients with very well-controlled LDL-C. Niacin is currently available in 3 formulations: intermediate, long-acting, and extended-release; see Table 14 (**42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4], 49 [EL 1], 50 [EL 4], 51 [EL 4], 52 [EL 4], 53 [EL 3], 54 [EL 4], 55 [EL 4], 56 [EL 3], 57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 66 [EL 1], 67 [EL 1], 68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2], 77 [EL 1], 78 [EL 3]**) and Table 15 (**43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 50 [EL 4], 51 [EL 4], 52 [EL 4], 55 [EL 4], 57 [EL 4], 79 [EL 4], 80 [EL 4], 81 [EL 4], 82 [EL 4]**).

Bile Acid Sequestrants

- **R48.** AACE recommends bile acid sequestrants for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase triglycerides **(Grade B; BEL 1)**. Bile acid sequestrants have a glucose-lowering effect; colesevelam is now also approved for treatment of type 2 diabetes. Available agents in this drug class are cholestyramine, colestipol, and colesevelam; see Table 14 (**42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4], 49 [EL 1], 50 [EL 4], 51 [EL 4], 52 [EL 4], 53 [EL 3], 54 [EL 4], 55 [EL 4], 56 [EL 3], 57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 66 [EL 1], 67 [EL 1], 68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2], 77 [EL 1], 78 [EL 3]**) and Table 15 (**43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 50 [EL 4], 51 [EL 4], 52 [EL 4], 55 [EL 4], 57 [EL 4], 79 [EL 4], 80 [EL 4], 81 [EL 4], 82 [EL 4]**).

Cholesterol Absorption Inhibitors

- **R49**. Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. AACE recommends combination therapy with statins because current research indicates that this enhances these benefits and further improves the beneficial effects of statins on triglycerides and HDL-C **(Grade A; BEL 1)**. It is uncertain whether cholesterol absorption inhibitor therapy has a direct benefit on reducing cardiovascular events **(Grade B; BEL 1)**. Ezetimibe is currently the only member of this drug class; see Table 14 (**42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4], 49 [EL 1], 50 [EL 4], 51 [EL 4], 52 [EL 4], 53 [EL 3], 54 [EL 4], 55 [EL 4], 56 [EL 3], 57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 66 [EL 1], 67 [EL 1], 68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2], 77 [EL 1], 78 [EL 3]**) and Table 15 (**43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 50 [EL 4], 51 [EL 4], 52 [EL 4], 55 [EL 4], 57 [EL 4], 79 [EL 4], 80 [EL 4], 81 [EL 4], 82 [EL 4]**).

Combination Therapy

- **R50.** Certain clinical situations warrant the use of a combination of lipid-lowering agents. Because the adverse effects of 2 or more drugs may be additive, clinical judgment is needed to balance the risks and benefits of combination therapy.

AACE recommends that combination therapy be considered in the following circumstances:

- When the cholesterol level is markedly increased and monotherapy does not achieve the therapeutic goal **(Grade A; BEL 1)**.
    - The recent SHARP trial (Study of Heart and Renal Protection) demonstrated a reduction of LDL-C via treatment with simvastatin, 20 mg daily, plus ezetimibe, 10 mg daily, which safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease **(92 [EL 1])**.
- When mixed dyslipidemia is present **(Grade C; BEL 3)**.
- Niacin or fibrates in combination with statins may be appropriate options for many patients with hypertriglyceridemia and associated low HDL-C **(Grade B; BEL 2)**.

- *It is uncertain whether, or in whom, niacin use in patients with very well-controlled LDL-C levels on statin therapy adds additional benefit, based on the results of the recently terminated AIM-HIGH study* **(Grade A; BEL 1) (91 [EL 1])**. HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events), a large international trial of high-dosage, extended-release niacin plus simvastatin (results expected in 2013), should help clarify the role of simvastatin in combination with niacin **(93 [EL 4])**.

- To reduce the risk of dosage-related adverse effects **(Grade D; BEL 4)**.

Special Considerations: Women

- **R51.** AACE recommends that women should be identified for CAD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient **(Grade A; BEL 1)**. In light of the diagnostic challenges that present when trying to identify CAD 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 **(94 [EL 1])**. Furthermore, although lowering LDL-C significantly reduces CAD risk in women, the unique roles of hormonal change on cardiovascular risk, HDL-C, and triglycerides must also be addressed.
- **R52.** AACE does *not* recommend hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women **(Grade A; BEL 1)**.

Special Considerations: Pediatric Patients

- **R53.** AACE recommends pharmacotherapy for children and adolescents older than 8 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria **(Grade B; BEL 3)**:
  - 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, *or*
    - A family history of premature CAD (before 55 years of age) *or,*
    - Overweight, obese, or other elements of the insulin resistance syndrome.

Colesevelam has been approved for patients older than 8 years. Atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older. Cholestyramine may also be used in children.

3Q3.3. Follow-up and Monitoring

- **R54.** AACE recommends reassessing patients' lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved. Thereafter, AACE recommends that patients be tested at 6- to 12-month intervals. The specific interval should depend on patient adherence to therapy and lipid profile consistency. If adherence is a concern or the lipid profile is unstable, the patient will probably benefit from biannual assessment **(Grade C; BEL 4)**.
- **R55.** AACE recommends more frequent lipid status evaluation in the following *clinical* circumstances:
  - Deterioration of diabetes control.
  - The use of a new drug known to affect lipid levels.
  - Progression of atherothrombotic disease.
  - Considerable weight gain.
  - An unexpected adverse change in any lipid parameter.
  - Development of a new CAD risk factor.
  - Convincing new clinical trial evidence or guidelines that suggest stricter lipid goals.
- **R56.** AACE recommends that a liver transaminase level be measured before and 3 months after statin or fibric acid treatment initiation, because most liver abnormalities occur within 3 months of treatment initiation. AACE recommends that this test be repeated periodically (eg, semiannually) **(Grade A; BEL 3)**.
- **R57.** AACE recommends that patients taking niacin have transaminase levels measured at baseline and every 3 months thereafter for the first year, followed by periodic (eg, semiannual) assessment **(Grade A; BEL 3)**. AACE recommends that transaminase level assessment be repeated at these intervals whenever lipid-altering therapy is restarted, increased, changed, or combined **(Grade A; BEL 3)**.
- **R58.** AACE recommends assessment of creatine kinase levels whenever a patient reports clinically significant myalgias or muscle weakness **(Grade A; BEL 3)**.

3Q4. IS TREATMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROSIS COST-EFFECTIVE?

- **R59.** Nonpharmacologic interventions such as dietary management and smoking cessation are the most cost-effective options available for CAD prevention **(Grade A; BEL 3)**.
- **R60.** When nonpharmacologic interventions fail, pharmacologic intervention is a recommended cost-effective option for primary and secondary intervention in persons at moderate to high risk **(Grade A; BEL 3)**.
- **R61.** Among otherwise healthy persons 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 B; BEL 3)**.
- **R62**. Statins have proven cost-effective in both secondary and primary prevention of CVD events in patients at moderate to high risk, or in patients at low risk whose LDL-C levels are very high **(Grade A; BEL 1)**.
- **R63.** Treatment with fibrates has been found cost-effective as both monotherapy and combination therapy for lowering triglycerides and raising HDL-C **(Grade B; BEL 2)**, but not in reducing cardiovascular events except in patients with triglyceride concentrations greater than 200 mg/dL and HDL-C concentrations less than 40 mg/dL **(Grade A; BEL 1)**.
- **R64.** Ezetimibe coadministered with statin therapy in patients unable to meet target LDL-C levels has been identified as a cost-effective strategy to achieve LDL-C goals in studies from Canada and the United Kingdom **(Grade B; BEL 2)**.
- **R65.** Available pharmacoeconomic data, derived before generic availability of bile acid sequestrants, do not support the cost-effectiveness of bile acid sequestrants compared with statin therapy **(Grade C; BEL 3)**.
- **R66.** Limited pharmacoeconomic data support the cost-effectiveness of niacin in combination with a statin in reaching targeted lipid goals **(Grade C; BEL 3)**.

4. SOURCE DOCUMENT: EVIDENCE BASE

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

4Q1.1. Global Risk Assessment

The third report of the NCEP ATP categorizes CAD risk based on a system of risk factor counting and 10-year risk according to Framingham risk scoring **(10 [EL 4])**. In addition, the American Diabetes Association/ American College of Cardiology 2008 Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk establishes risk categorization for patients with diabetes **(20 [EL 4])**. An overview of accepted CAD risk categories and factors is outlined in Table 5 **(20 [EL 4], 22 [EL 4], 23 [EL 4])** and Table 6 **(10 [EL 4], 11 [EL 4], 12 [EL 4], 13 [EL 4], 14 [EL 2], 15 [EL 4], 16 [EL 2], 17 [EL 4], 18 [EL 2], 19 [EL 2], 20 [EL 4], 21 [EL 3]**). The remainder of this section will review these major CAD risk factors, as well as important nontraditional risk factors.

Risk Factors for CAD

The risk of CAD and CAD-related mortality is substantially greater in the presence of multiple risk factors. Since epidemiologic evidence indicates that CAD risk factors frequently cluster, it should be expected that many patients have multiple risk factors **(95 [EL 4], 96 [EL 3])**. The Framingham Heart Study and the MRFIT trial (Multiple Risk Factor Intervention Trial) showed that approximately 85% of excess risk for premature CAD is due to 1 or more major risk factor **(13 [EL 4], 18 [EL 2])**. More recently, the INTERHEART trial, which gathered data on 29 972 patients in 52 countries, identified 9 CAD 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 **(14 [EL 2]).** Recent guidelines and position statements such as the American College of Endocrinology Position Statements on polycystic ovary syndrome and the insulin resistance syndrome (available at http://www.aace.com) also identify other risk factors as having significant associations with CAD **(11 [EL 4], 12 [EL 4])**. Based on available evidence, Table 5 outlines the most important current major, additional, and nontraditional CAD risk factors **(10 [EL 4], 11 [EL 4], 12 [EL 4], 13 [EL 4], 14 [EL 2], 15 [EL 4], 16 [EL 2], 17 [EL 4], 18 [EL 2], 19 [EL 2], 20 [EL 4], 21 [EL 3])**.

Advancing Age

Men 45 years and older and women 55 years and older have an increased risk of CAD; CAD occurs most commonly in persons 65 years and older **(10 [EL 4])**.

High LDL-C and Total Cholesterol

The association between high serum cholesterol levels, especially high LDL-C, and CAD is causal and independent of other risk factors **(97 [EL 3], 98 [EL 2], 99 [EL 4], 100 [EL 4])**. The CARE trial (Cholesterol and Recurrent Events) determined that LDL-C–attributable risk is not linear and increases sharply within higher ranges **(101 [EL 2])**. The MRFIT study found a strong and progressive relationship between elevated total cholesterol levels and death of CAD **(16 [EL 2])**.

Since multiple studies have demonstrated that lowering LDL-C results in decreased CAD risk **(37 [EL 1], 38 [EL 1], 39 [EL 1], 102 [EL 1], 103 [EL 2], 104 [EL 1], 105 [EL 1], 106 [EL 1], 107 [EL 1])**, the focus of risk prediction and reduction has shifted toward LDL-C management in CAD and primary prevention in persons with multiple risk factors **(10 [EL 4])**.

Low HDL-C

Low HDL-C is associated with hypertriglyceridemia, type 2 diabetes, being overweight or obese, physical inactivity, cigarette smoking, very high carbohydrate intake, certain drugs (β-adrenergic blockers, anabolic steroids, progestational agents), and genetic factors **(10 [EL 4])**. Low HDL-C can act synergistically with other lipid risk factors to increase CAD risk. For example, the ratio of total cholesterol or LDL-C to HDL-C may be a clinically valuable and potentially sensitive marker of CAD risk **(108 [EL 2], 109 [EL 2], 110 [EL 4])**. A recent reanalysis of data from the TNT trial (Treating to New Targets) found that both ratios of total cholesterol to HDL-C and LDL-C to HDL-C were highly predictive of major cardiovascular event risk **(111 [EL 2])**, while a clinical study of 258 normotensive, overweight, nondiabetic persons determined that a triglyceride to HDL-C ratio 2.4 or higher was predictive of the presence of insulin resistance **(112 [EL 3])**. In addition, low HDL-C was a significant predictor of cardiovascular risk in all treatment groups, including patients with the lowest (<70 mg/dL) LDL-C levels **(111 [EL 2])**.

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 triglyceride levels. Carriers of this trait do not show signs of atherosclerosis typically associated with this lipid profile **(113 [EL 3], 114 [EL 3])**. In fact, a normal apo AI level in a patient 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 **(115 [EL 4])**.

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 a patient's overall risk profile **(10 [EL 4])**. An analysis of 4 large epidemiologic studies suggests that each 1 mg/dL increase in HDL-C is associated with a decrease in CAD risk of 2% in men and 3% in women **(116 [EL 2])**. The cardioprotective effect of HDL-C may be because of its role in reverse cholesterol transport and other mechanisms such as the ability of HDL-C to prevent LDL oxidation **(117 [EL 4], 118 [EL 4])**.

Research shows a strong predictive link between HDL-C levels and longevity; healthy older persons tend to have higher HDL-C levels than younger persons, regardless of the younger persons' CAD status **(119 [EL 4], 120 [EL 3], 121 [EL 3], 122 [EL 2])**. These results apply to the general population, however, and a high HDL-C concentration may not confer cardioprotection for every individual patient **(123 [EL 4])**.

Type 2 Diabetes Mellitus

Approximately 65% of diabetes-related mortality is due to heart disease and stroke. In comparison with patients who do not have diabetes, patients with type 2 diabetes have a significantly increased risk of CAD. For example, patients with diabetes plus a previous MI have been shown to have a 2.5-fold greater risk of subsequent CAD events than patients with CVD but no diabetes **(124 [EL 4], 125 [EL 4])**. Epidemiologic data from Finland similarly suggest that persons with diabetes and no history of MI have cardiovascular risk (fatal or nonfatal MI or stroke and overall cardiovascular mortality) equivalent to those without diabetes and a history of MI. This same study found that patients with diabetes and previous MI were at the highest risk, with a 7-year fatal or nonfatal MI incidence of 45% **(126 [EL 3])**. Moreover, among patients in the TNT study, only established cerebrovascular disease was more predictive of cerebrovascular events than was diabetes **(106 [EL 1])**.

In addition to hyperglycemia, individuals with type 2 diabetes commonly have other risk factors including hypertension; low HDL-C; hypertriglyceridemia; small, dense LDL-C; a procoagulant state; and a proinflammatory milieu **(15 [EL 4], 124 [EL 4], 127 [EL 4], 128 [EL 4], 129 [EL 3], 130 [EL 2], 131 [EL 4])**. Based on this level of risk, the NCEP ATP III and the American Diabetes Association/American College of Cardiology Consensus Statement consider patients with type 2 diabetes to manifest a CAD equivalent (a 10-year risk of CAD events that is equal to that of patients with established CAD) and therefore to be high-risk patients **(10 [EL 4], 20 [EL 4])**. Furthermore, the American Diabetes Association/American College of Cardiology categorizes patients with diabetes and 1 or more additional risk factor (eg, existing CVD) as "very high risk" **(20 [EL 4])**.

Patients with prediabetes (impaired fasting glucose and/or impaired glucose tolerance), especially those with the metabolic syndrome, are considered to be at increased risk for CAD. Lipid treatment goals for these patients should be the same as those for patients with diabetes **(132 [EL 4])**.

Type 1 Diabetes Mellitus

Most patients with diabetes mellitus have type 2 diabetes, and thus most existing data relate to those patients. However, type 1 diabetes is also associated with increased CAD risk. Persons with type 1 diabetes often do not have

insulin resistance or its features, such as a low HDL-C level or high triglycerides **(133 [EL 2])**. In fact, their HDL-C levels are typically higher than those of the general population **(134 [EL 4], 135 [EL 4])**. Nonetheless, patients with type 1 diabetes tend to develop atherosclerosis earlier than otherwise healthy individuals; have accelerated progression of coronary events, strokes, and peripheral arterial disease; and have higher associated mortality **(136 [EL 3], 137 [EL 4], 138 [EL 3], 139 [EL 3], 140 [EL 3], 141 [EL 4], 142 [EL 3], 143 [EL 3])**. The Pittsburgh Epidemiology of Diabetes Complications Study and the EURODIAB study found a similarly high prevalence of CAD among patients with type 1 diabetes in both the United States (7.3% in men, 7.5% in women) and in Europe (8.8% in men, 8.6% in women) **(144 [EL 3])**. Several studies of individuals with type 1 diabetes have suggested other factors that may increase risk for ischemic CVD:

- Proteinuria **(145 [EL 3])**
- In individuals with late-onset type 1 diabetes (older than 30 years) but no nephropathy, risk is increased with:
  - Previous history of MI *or*
  - Marked elevations in hemoglobin A_{1c} (>10.4%) *or*
  - Duration of disease greater than 16 years **(146 [EL 2])**
- Insulin resistance or the metabolic syndrome **(147 [EL 3])**
- Highly sensitive CRP concentration greater than 3.0 mg/L (2.9 with CAD, 1.7 without CAD) **(148 [EL 3])**

Given the risks associated with type 1 diabetes and CAD, dyslipidemia in this population must not be overlooked, and should be treated aggressively. Recommended optimal lipid levels for these patients are outlined in Table 12 **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])**.

For a more comprehensive review of the treatment of diabetes, see the *AACE Medical Guidelines for the Management of Diabetes Mellitus* and the *AACE Medical Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan* at www.aace.com.

Hypertension

Hypertension increases CAD risk independently of other risk factors, and this risk increases as blood pressure increases **(17 [EL 4])**. Available evidence stongly suggests that insulin resistance predisposes patients to hypertension **(23 [EL 4])**, and epidemiologic studies show a very high correlation between hypertension and dyslipidemia **(10 [EL 4])**.

Even mild elevations in blood pressure can increase risk. In persons aged 40 to 70 years with a blood pressure starting at 115/75 mm Hg, CAD risk doubles with each increase of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure **(17 [EL 4])**. Blood pressure–lowering therapy has been associated with significant decreases in the incidence of MI (20% to 25%), stroke (35% to 40%), and heart failure (>50%) **(17 [EL 4])**; however, hypertension may remain a CAD risk factor even when normalized with treatment **(149 [EL 4], 150 [EL 2], 151 [EL 2], 152 [EL 3])**.

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 patients **(17 [EL 4], 23 [EL 4], 153 [EL 2], 154 [EL 3])**.

Cigarette Smoking

Cigarette smoking is a powerful risk factor, especially for MI, peripheral artery disease, and stroke. Smoking accelerates coronary plaque development and may lead to plaque rupture and is particularly dangerous in patients with advanced coronary atherosclerosis **(13 [EL 4])**. The risk of CAD mortality for persons 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 **(155 [EL 4])**. One possible explanation for the CAD 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 triglycerides **(156 [EL 3], 157 [EL 2], 158 [EL 3], 159 [EL 3], 160 [EL 3], 161 [EL 3])**. However, smoking cessation significantly increases HDL-C, with improvement observable in as few as 30 days **(162 [EL 2])**.

Family History of CAD

A parental history of heart disease or MI has been established as an independent risk factor for CAD **(163 [EL 2], 164 [EL 2], 165 [EL 3])**. It has been estimated that 77% of patients with CAD and 54% of their first- and second-degree relatives express genetically linked dyslipidemia. Moreover, CAD risk is approximately 50% in siblings of patients with premature CAD **(166 [EL 4])**. In addition, recent studies of asymptomatic individuals indicate that a positive family history of CAD increases the risk of subclinical atherosclerosis (coronary artery calcification and carotid IMT) compared with risk of patients without a positive family history **(167 [EL 2], 168 [EL 2], 169 [EL 3])**.

Although it is an important risk factor, familial history is often overlooked during evaluations of individual cardiovascular risk. A family history of CAD, however, is both highly predictive and typically easy to access by direct inquiry.

Obesity and Overweight

Approximately two-thirds of the adults in the United States are overweight (body mass index 25 to 29.9 kg/m^2) or obese (body mass index ≥30 kg/m^2) **(170 [EL 4], 171 [EL 3])**. It is well documented that persons who are overweight have a high prevalence of risk factors such as hypertension, type 2 diabetes, and dyslipidemia **(172 [EL 3], 173 [EL 3])**. In particular, excess visceral or intra-abdominal fat increases and independently predicts CAD risk **(14 [EL 2], 170 [EL 4], 174 [EL 2], 175 [EL 2])**. Elevated intra-abdominal fat is highly and independently correlated with insulin resistance **(176 [EL 3], 177 [EL 3])** and is also associated with prothrombotic/proinflammatory states; increased triglycerides; total cholesterol; LDL-C; small, dense LDL-C; and apo B and decreased HDL-C **(10 [EL 4], 176 [EL 3], 177 [EL 3])**.

Intra-abdominal obesity is one of the most reliable markers of the insulin resistance syndrome **(176 [EL 3])**. Existing US 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])**. 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 **(178 [EL 4])**.

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 **(179 [EL 3], 180 [EL 4], 181 [EL 4], 182 [EL 4], 183 [EL 4], 184 [EL 4])**. Several studies point to increased CAD risk associated with small, dense LDL-C **(185 [EL 3], 186 [EL 2], 187 [EL 2])**. In addition, evidence from the Framingham Offspring Cohort indicates that primary consideration should be given to measuring and adjusting risk based on *LDL particle numbers* (LDL 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 CAD risk **(21 [EL 3])**. MESA (Multi-Ethnic Study of Atherosclerosis) and the Cardiovascular Health Study both demonstrated that although LDL-C and LDL particle size are associated with atherogenicity, *LDL particle number is a more potent measure of CVD risk than either of these 2 measures* **(188 [EL 2], 189 [EL 3])**.

Small, Dense LDL

Small, dense LDL-C is found in 50% of men with CAD and is also referred to as LDL pattern B **(166 [EL 4])**. This pattern is often observed in persons with elevated triglycerides and low HDL-C, a combination known as the *dyslipidemic triad* (see below), as well as in patients with type 2 diabetes, the insulin resistance syndrome, and/or chronic anovulation or polycystic ovarian syndrome **(181 [EL 4], 190 [EL 4], 191 [EL 4], 192 [EL 3], 193 [EL 2]).** Elevated non–HDL-C (that is, total serum cholesterol minus HDL-C) and apo B levels are also clinical markers for the presence of small, dense LDL **(115 [EL 4])**. Approximately 25% of patients with small, dense LDL particles inherit this abnormality and do not have hypertriglyceridemia. Measurement of apo B will identify these patients **(190 [EL 4])**. Elevated non–HDL-C (that is, total serum cholesterol minus HDL-C) and apo B levels are also clinical markers for the presence of small, dense LDL **(115 [EL 4])**. Approximately 25% of patients with small, dense LDL particles inherit this abnormality and do not have hypertriglyceridemia.

Fasting and/or Postprandial Hypertriglyceridemia

Triglyceride levels are an important component of risk evaluation in both men and women **(10 [EL 4])**. 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 triglyceride levels may be an independent risk factor **(10 [EL 4], 97 [EL 3], 98 [EL 2], 157 [EL 2], 194 [EL 2], 195 [EL 2], 196 [EL 3], 197 [EL 2], 198 [EL 2], 199 [EL 2], 200 [EL 4], 201 [EL 2], 202 [EL 4])**. Triglycerides that are even moderately elevated (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome **(12 [EL 4])**. Triglyceride levels 200 mg/dL or higher may indicate a substantial increase in CAD risk **(10 [EL 4])**. Although hypertriglyceridemia can be an independent genetic disorder, it is widely accepted as a marker of insulin resistance **(12 [EL 4], 203 [EL 4])**. Hypertriglyceridemia is also commonly associated with a procoagulant state and hypertension **(204 [EL 4])**.

As triglyceride levels increase with age, the importance of hypertriglyceridemia as a CAD risk factor also appears to increase **(199 [EL 2], 200 [EL 4], 202 [EL 4])**. Furthermore, research suggests that like low HDL-C, high serum triglyceride levels may act synergistically with other lipid abnormalities to increase CAD risk. For example, the PROCAM study (Prospective Cardiovascular Münster) demonstrated that hypertriglyceridemia increased the incidence of definite CAD by approximately 2.5-fold in men and women with LDL-C levels greater than 155 mg/dL **(97 [EL 3])**. Serum triglyceride 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 **(97 [EL 3], 98 [EL 2], 205 [EL 2], 206 [EL 4], 207 [EL 4])**.

Because hypertriglyceridemia is interrelated with so many other lipid and nonlipid risk factors, the benefit of lowering triglycerides directly remains uncertain **(12 [EL 4])**. Furthermore, several recent studies indicate that postprandial, or nonfasting, triglycerides may be an equally or more potent CAD risk factor than fasting triglycerides. 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 triglycerides were independently associated with MI and ischemic heart disease **(208 [EL 2], 209 [EL 2])**. In the Women's Health Study, the association between both fasting and nonfasting triglycerides and cardiovascular events was significant in univariate analysis ($P<.001$ for trend across tertiles). The relationship of fasting triglycerides lost statistical significance after adjustment for total cholesterol and HDL-C and weakened further with adjustment for markers of insulin resistance (diabetes mellitus, body mass index, and CRP). However, the association for nonfasting triglyceride levels remained significant with adjustment ($P = .006$ for trend) **(208 [EL 2])**. In addition, elevated postprandial triglycerides were the only variable independently associated with cardiovascular events among women with normal (≥50 mg/dL) HDL-C levels **(213 [EL 2])**.

Proposed explanations for the association between postprandial triglycerides and CAD risk include increased postprandial production of triglyceride-rich lipoprotein remnants, which are highly atherogenic, and an abnormal response to an oral fat load, which indicates insulin resistance **(208 [EL 2], 209 [EL 2], 210 [EL 3], 211 [EL 4], 212 [EL 4], 213 [EL 3], 214 [EL 4], 215 [EL 4], 216 [EL 2])**. Recent data **(217 [EL 1])** suggest that in patients with normal glucose tolerance, postprandial triglyceride levels are useful in assessing cardiovascular risk, but provide no extra prognostic value in those with dysglycemia.

Polycystic Ovary Syndrome

Polycystic ovary syndrome 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 polycystic ovary syndrome also fulfill the criteria for the insulin resistance syndrome **(11 [EL 4], 218 [EL 3])**. Studies indicate that patients with polycystic ovary syndrome have greater than average levels of coronary artery calcification and carotid IMT **(11 [EL 4], 219 [EL 3], 220 [EL 2])**, as well as significantly higher rates of CAD and CAD risk factors such as type 2 diabetes and hypertension **(11 [EL 4], 219 [EL 3], 221 [EL 3], 222 [EL 3], 223 [EL 3])**.

The Dyslipidemic Triad

Patients 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 CAD **(166 [EL 4], 185 [EL 3], 190 [EL 4])**. This type of dyslipidemia is one of the components of the high-risk insulin resistance syndrome (Table 16) **(12 [EL 4])**, and is also common among persons with type 2 diabetes **(10 [EL 4])**. 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])**. Its presence alongside elevated LDL-C significantly enhances risk, and each condition should be addressed.

Other Risk Factors

Data are emerging on several additional nonlipid risk factors, including their levels of associated risk and their role in the CAD process. A brief summary follows.

Increased Lipoprotein (a)

Production of lipoprotein (a), an LDL variant, is largely genetically determined and its pathogenic mechanism remains unclear; however, elevated plasma concentrations are independently associated with CAD risk **(224 [EL 4], 225 [EL 4])**. Data on the level of risk associated with lipoprotein (a) are inconsistent **(226 [EL 2], 227 [EL 2], 228 [EL 2], 229 [EL 2], 230 [EL 3], 231 [EL 1], 232 [EL 2], 233 [EL 2])**; however, a recent 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 **(234 [EL 3])**.

Risk associated with elevated lipoprotein (a) appears to vary by ethnic group; for example, data from the CARDIA study (Coronary Artery Risk Development in Young Adults) 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) **(235 [EL 3])**. However, lipoprotein (a) elevation appeared to confer a stronger risk for white participants than for African American participants **(235 [EL 3])**. 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 **(225 [EL 4], 226 [EL 2])**. Some evidence suggests that statin-induced LDL-C reduction may attenuate the risk associated with lipoprotein (a) **(236 [EL 1])**. Testing for lipoprotein (a) is therefore not generally recommended, although it may provide useful information to ascribe risk in white patients

with CAD or in those with an unexplained family history of early CAD.

Factors Related to Blood Clotting

Available data suggest that *plasminogen activator inhibitor 1* is related to intra-abdominal obesity, insulin resistance, and, in patients with diabetes, hyperinsulinemia and hyperproinsulinemia. Consequently, elevated plasminogen activator inhibitor 1 may be a risk factor for CAD **(237 [EL 4], 238 [EL 4], 239 [EL 2], 240 [EL 4])**. Assays for plasminogen activator inhibitor 1 are not standardized, however. For these reasons, plasminogen activator inhibitor 1 screening is not generally recommended.

Fibrinogen is a clotting factor that, at elevated levels, may lead to a prothrombotic state **(241 [EL 3])**. An increased fibrinogen level is a strong, established marker of CAD risk in men and women **(242 [EL 4], 243 [EL 4], 244 [EL 4], 245 [EL 4])**. 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 CAD may affect fibrinogen levels **(242 [EL 4], 244 [EL 4], 245 [EL 4])** and no standard measurement assay exists **(243 [EL 4], 244 [EL 4])**. Nonetheless, prospective studies consistently show that adding fibrinogen to lipid evaluations significantly improves CAD risk prediction **(246 [EL 4])**. Fibrinogen may also be a marker of inflammation (see following text) **(241 [EL 3])**. Nonetheless, prospective studies consistently show that adding fibrinogen to lipid evaluations significantly improves CAD risk prediction **(246 [EL 4])**. Fibrinogen may also be a marker of inflammation (see following text) **(241 [EL 3])**.

Markers of Inflammation

CRP is a sensitive marker of systemic inflammation that can indicate CVD risk **(247 [EL 2], 248 [EL 2])**. Concentration of highly sensitive CRP less than 1.0 mg/L is considered normal, 1.0 to 3.0 mg/L is intermediate, and greater than 3.0 mg/L is high risk **(249 [EL 4])**. Highly sensitive CRP measurements have been shown to add to

Table 16
Components of the Insulin Resistance Syndrome
(12 [EL 4])

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
• ⇩ High-density lipoprotein cholesterol
• Low-density lipoprotein particle diameter (small, dense low-density lipoprotein particles)
• Postprandial accumulation of triglyceride-rich lipoproteins
4. Hemodynamic changes
• Sympathetic nervous system activity
• Renal sodium retention
• ⇧ Blood pressure
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

the predictive value of standard lipid tests in determining risk for future CVD events **(248 [EL 2], 250 [EL 2])**. Even after adjustment for standard CVD risk factors, elevated highly sensitive CRP levels have a progressive association with increased MI and stroke among men aged 40 to 84 years **(247 [EL 2])**. Elevated highly sensitive CRP levels (≥1.9 mg/L) also correspond to increased CVD risk in healthy, postmenopausal women with LDL-C levels less than 130 mg/dL **(248 [EL 2])**. Furthermore, significantly elevated highly sensitive CRP in combination with significantly elevated Lp-PLA_2 (eg, both in the highest tertile) constitutes very high risk in individuals with low or moderately elevated LDL-C **(251 [EL 2], 252 [EL 2])**. The significance of highly sensitive CRP lowering by statins in the JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) is discussed in "Choosing Lipid-Lowering Drugs" under "Statins."

Lp-PLA_2 is a blood enzyme that hydrolyzes oxidized phospholipids, causing atherogenic vascular inflammation **(252 [EL 2])**. 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 **(253 [EL 4], 254 [EL 4], 255 [EL 4], 256 [EL 4])**. Lp-PLA_2 has been identified as a strong and independent predictor of CVD events and stroke in patients with and without manifest CAD **(257 [EL 3], 258 [EL 2], 259 [EL 2])**, as well as in patients with low LDL-C **(252 [EL 2])**. Current best evidence 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 **(252 [EL 2], 259 [EL 2])**. Lp-PLA_2 appears to act synergistically with CRP (described above) such that when both are elevated, risk is substantial **(251 [EL 2], 252 [EL 2])**. However, while CRP is a marker of general inflammation, Lp-PLA_2 appears to specifically indicate vascular inflammation and is not influenced by obesity **(247 [EL 2], 254 [EL 4], 255 [EL 4])**.

Hyperhomocysteinemia

Homocysteine, a precursor of methionine, is highly reactive, and elevated levels may damage vessel walls and induce intimal fibrosis **(260 [EL 4], 261 [EL 4])**. Prospective clinical studies of patients with CAD or CAD risk factors have consistently demonstrated increased levels of serum homocysteine (>15 μmol/L) alongside cardiovascular events and mortality **(260 [EL 4], 262 [EL 4], 263 [EL 2])**. However, the link between homocysteine levels and cardiovascular event risk is much stronger after disease onset **(246 [EL 4], 260 [EL 4], 262 [EL 4], 264 [EL 2], 265 [EL 3], 266 [EL 2], 267 [EL 2], 268 [EL 2], 269 [EL 2])**. Evaluation of homocysteine levels in patients with established CAD (including ischemia) may help explain the CAD etiology **(260 [EL 4])**. Recent data from the National Health and Nutrition Examination Survey III and MESA have shown that the addition of homocysteine is a powerful tool when used in conjunction with Framingham Risk Score to identify patients with CVD 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 B_6 and B_{12} **(270 [EL 4])**. Although treatment with these supplements lowers plasma homocysteine levels, research to date does not indicate that such therapy reduces CAD risk **(32 [EL 4], 33 [EL 1], 34 [EL 1], 35 [EL 2], 36 [EL 1])**. Homocysteine measurement, therefore, is not recommended as part of routine screening.

Elevated Uric Acid

Increased serum uric acid levels are linked to the insulin resistance syndrome, obesity, dyslipidemia, and hypertension **(271 [EL 3])**. 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 CVD 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 **(271 [EL 3])**.

CAD Risk and the Insulin Resistance Syndrome

Persons who have insulin resistance are at increased risk for developing a cluster of abnormalities known as the insulin resistance syndrome **(12 [EL 4])**. Although this is sometimes referred to as the metabolic syndrome or dysmetabolic syndrome, 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 **(12 [EL 4])**. The components of the insulin resistance syndrome, outlined in Table 16 **(12 [EL 4])**, include important risk factors for CAD. Thus, individuals with the insulin resistance syndrome are at increased risk for developing CAD. Likewise, patients who do not have diabetes, but who have a diagnosis of CAD have a greater prevalence of the insulin resistance syndrome than those without CAD **(12 [EL 4])**. Persons 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 **(12 [EL 4])**.

Elevated blood glucose is a late and possibly terminal manifestation of insulin resistance. Before the development of hyperglycemia, diagnosis of the insulin resistance syndrome may be difficult, with no simple, single clinically measurable test available **(12 [EL 4])**. However, the components of the insulin resistance syndrome are frequently identifiable. Patients 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 **(12 [EL 4])**.

Chronic Kidney Disease

Growing evidence suggests that patients with chronic kidney disease, who represent a growing population, have increased risk for CAD. It appears that the increased risk of CAD does not occur only in patients 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 chronic kidney disease as a CAD equivalent **(6 [EL 4])**.

Chronic Inflammatory Conditions

Patients with chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematous, and ankylosing spondylitis, appear to have an increased risk of CAD. In the Nurses' Health Study, for example, patients who had had rheumatoid arthritis for more than 10 years appear to have an increased risk for CAD when compared with patients without rheumatoid arthritis (relative risk, 3.1; confidence interval, 1.64-5.87) **(272 [EL 2])**. 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 CAD was 2.25 (95% confidence interval, 1.77-4.27) when after adjustment for other traditional risk factors, the hazard ratio remained greater than 2 for the group of women with systemic lupus erythematous **(273 [EL 2])**. Increased prevalence of CAD has been also reported in patients with ankylosing spondylitis **(274 [EL 3])**.

Human Immunodeficiency Virus

Patients with human immunodeficiency virus appear to have increased risk of CAD. It is not well established whether the increased risk for CAD is secondary to traditional risk factors or to nontraditional risk factors, such as changes in body composition (lipoatrophy/lipodystrophy) or inflammation, effect of the antiretroviral medications, or direct effects of the human immunodeficiency virus to the vasculature **(275 [EL 4])**.

4Q1.2. Screening

AACE advocates screening for dyslipidemia in all adults up to age 75 years regardless of CAD risk status, and in adults older than age 75 years who have multiple CAD risk factors.

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

Young Adults (≥20 Years of Age) (10 [EL 4])

A number of studies have shown that atherosclerosis can be present early in life, well before symptoms occur **(276 [EL 3], 277 [EL 3], 278 [EL 3])**. Although CAD risk in young adults is low, AACE recommends that adults older than 20 years be evaluated for dyslipidemia every 5 years as part of a global risk assessment **(10 [EL 4])**. More frequent assessments are warranted for young persons with a family history of premature CAD (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])**. Consideration of more frequent testing should also be given to individuals with CAD risk factors **(10 [EL 4], 11 [EL 4], 12 [EL 4], 13 [EL 4], 14 [EL 2], 15 [EL 4], 16 [EL 2], 17 [EL 4], 18 [EL 2], 19 [EL 2], 20 [EL 4], 21 [EL 3])**. All young adults with diabetes should be screened annually **(15 [EL 4])**.

Middle-Aged Adults (Men ≥45 Years of Age; Women ≥55 Years of Age) (10 [EL 4], 24 [EL 3])

Intervention trials involving middle-aged men and women have shown that treatment of dyslipidemia in patients at high risk (eg, those with established CAD, diabetes, or hypertension) is beneficial **(37 [EL 1], 39 [EL 1], 102 [EL 1], 105 [EL 1], 279 [EL 1])**. However, the benefits of primary prevention using lipid-lowering treatment in patients at low risk are not as well established **(279 [EL 1])**.

This information must be considered in the context of existing risk in the US 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 triglycerides **(5 [EL 3])**. The recent MESA study, which had a multicenter cohort of patients aged 45 to 84 years with no CVD at baseline (n = 6814), found a 29.3% prevalence of dyslipidemia **(280 [EL 3])**. Moreover, several community-based, population screening studies of middle-aged patients described as "typically health-conscious" found dyslipidemia prevalence ranging from 21% to 49% **(281 [EL 3], 282 [EL 3], 283 [EL 3])**. Given these high prevalence rates, AACE recommends that even when no CAD risk factors are present, middle-aged persons should be screened for dyslipidemia at least every 1 to 2 years. More frequent lipid testing is recommended when multiple CAD risk factors are present **(10 [EL 4], 12 [EL 4], 15 [EL 4])**. The frequency of testing should be based on individual clinical circumstances and the clinician's best judgment. All patients with diabetes should be screened at least annually **(15 [EL 4])**.

Older Adults (≥65 Years of Age) (10 [EL 4], 284 [EL 4])

Although the association between high LDL-C and CAD weakens with age **(10 [EL 4])**, increased serum cholesterol in older patients (men ≥65 years, women ≥75 years) is associated with a greater absolute number of acute coronary events compared with middle-aged or younger populations **(285 [EL 4], 286 [EL 4])**. In patients older than 70 years, the 5804-patient PROSPER trial (Prospective Study of Pravastatin in the Elderly at Risk) demonstrated a secondary, but not primary, prevention CAD event benefit for the group treated with pravastatin **(38 [EL 1])**.

Because many older patients may benefit from lipid-lowering therapy, those with 0 to 1 CAD risk factor should be screened for dyslipidemia annually **(10 [EL 4], 37 [EL 1], 38 [EL 1], 107 [EL 1], 287 [EL 1])**. In addition, older patients should undergo lipid assessment if they have multiple CAD risk factors (ie, risk factors other than age) **(10 [EL 4])**. Consideration should also be given to the fact that treatment to lower lipid levels and attenuate atherosclerosis may potentially decrease stroke and transient ischemic attack incidence in this population **(37 [EL 1], 38 [EL 1], 102 [EL 1], 106 [EL 1], 287 [EL 1], 288 [EL 1])**.

Women

CVD is the leading cause of mortality in women in the United States, killing more than 460 000 women each year **(286 [EL 4])**. Minority women, in particular African-American women, have higher death rates than white women because of both CAD and stroke **(286 [EL 4])**. Diagnosis of CAD in women can be particularly problematic. Approximately 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 appropriate therapy, and increased mortality **(289 [EL 4], 290 [EL 4])**. In addition, traditional diagnostic methods, such as imaging, electrocardiography, and exercise testing, may be less accurate in women whose anatomy, hormonal milieu, age at CAD onset, and age-related comorbidities are unique **(291 [EL 4])**.

Children and Adolescents

A growing body of evidence indicates that atherosclerosis begins early in life **(278 [EL 3], 292 [EL 3], 293 [EL 4], 294 [EL 4])**. Furthermore, studies show that the presence and severity of atherosclerotic lesions in children and young adults are related to serum lipid levels **(293 [EL 4], 295 [EL 2], 296 [EL 2], 297 [EL 3], 298 [EL 3])**. Although there is increasing consensus that early intervention is warranted, even in very young patients **(26 [EL 4], 299 [EL 3], 300 [EL 4], 301 [EL 4], 302 [EL 2], 303 [EL 4], 304 [EL 4])**, the most effective diagnostic and treatment approaches for pediatric dyslipidemia are far from clear. While NCEP guidelines continue to be updated **(32 [EL 4])**, the Expert Panel on Blood Cholesterol Levels in Children and Adolescents report is well over a decade old, having been published in 1992. In 2008, the American Academy of Pediatrics issued a clinical report on lipid screening and cardiovascular health in children to replace its previous position statement regarding cholesterol in children **(305 [EL 4])**. This section reviews current evidence relating to dyslipidemia screening and management in pediatric populations and provides recommendations based on this evidence.

Children older than 2 years who have CAD risk factors or a family history of CAD or dyslipidemia, and children for whom family history is not known, should be screened for dyslipidemia; these patients should be rescreened every 3 to 5 years. In all adolescents older than 16 years, screening should be repeated every 5 years, or more frequently for patients with CAD risk factors or a family history of CAD.

AACE endorses current American Academy of Pediatrics, American Heart Association, and NCEP guidelines for targeted dyslipidemia screening in children and adolescents, including recommendations to measure plasma total cholesterol, HDL-C, LDL-C, and triglyceride levels in children with CAD risk factors such as obesity (central adiposity and/or elevated body mass index), insulin resistance, diabetes, hypertension, cigarette smoking, or a family history of CAD or dyslipidemia **(22 [EL 4], 26 [EL 4], 300 [EL 4], 306 [EL 4], 307 [EL 4])**. In addition to these risk factors, the American Academy of Pediatrics recommends screening pediatric patients for whom family history is not known. The American Academy of Pediatrics and the American Heart Association also state that children who are overweight or obese should be considered to be in a separate risk category and screened regardless of the presence of other risk factors or family history **(27 [EL 4], 305 [EL 4])**. Additionally, the American Heart Association indicates that children who are overweight or obese should be promptly screened for other elements of the insulin resistance syndrome, and that the presence of such factors may alter treatment considerations **(27 [EL 4])**. Initial screening should take place between the ages of 2 and 10 years; if lipid levels are within acceptable ranges, children should be rescreened every 3 to 5 years **(305 [EL 4])**.

Furthermore, AACE recommends dyslipidemia screening in *all adolescents older than 16 years* **(300 [EL 4], 308 [EL 3])**, with more frequent testing of patients with CAD risk factors or a positive family history **(6 [EL 4])**. As there is no available noninvasive method of screening for CAD, the American Academy of Pediatrics recommends a fasting lipid profile for children **(305 [EL 4])**. This comprehensive strategy is expected to improve the accuracy of dyslipidemia diagnosis in children and young adults **(308 [EL 3])**.

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 8-11 years) in white boys, they often decline profoundly during puberty, along with HDL-C values **(309 [EL 4]).**

- *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 **(310 [EL 4], 311 [EL 3])**. 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 **(310 [EL 4], 312 [EL 3])**.
- *Lipid levels vary by sex*. Throughout childhood and adolescence, plasma cholesterol levels tend to be higher in girls than in boys **(303 [EL 4])**.

While LDL-C levels less than 110 mg/dL are generally considered acceptable in pediatric patients, NCEP guidelines indicate that intervention is indicated for those with borderline (110-129 mg/dL) or high (≥130 mg/dL) LDL-C values, as shown in Table 8 **(26 [EL 4])**. Further, the American Heart Association has identified abnormal pediatric HDL-C and triglyceride levels as less than 35 mg/dL and greater than 150 mg/dL, respectively **(313 [EL 4])**.

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

The goal of screening is to ascertain a patient's individual CAD risk. The selection of appropriate initial screening tests should be based on patient risk factors and clinical judgment. Basic lipid screening tests are outlined in the following text alongside brief background 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 patients at risk for vascular disease. Therefore, although a nonfasting assessment has been useful in the past as a minimal screen, to ensure the most precise lipid profile assessment, a *fasting lipoprotein profile* (total cholesterol, LDL-C, triglycerides, and HDL-C) is now recommended for all patients **(10 [EL 4])**. A 9- to 12-hour fast is necessary to avoid the effect of food intake on chylomicron and VLDL triglycerides **(10 [EL 4])**.

4Q2.2. Low-Density Lipoprotein Cholesterol

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

$$\text{LDL-C} = (\text{total cholesterol} - \text{HDL-C}) - \frac{\text{triglycerides}}{5}$$

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 triglyceride levels are greater than 200 mg/dL, and is considered inaccurate when triglyceride levels are greater than 400 mg/dL **(314 [EL 3], 315 [EL 4])**. Therefore, a more precise method should be used to assess LDL-C in certain high-risk patients, such as those with fasting triglyceride concentrations greater than 250 mg/dL or those with diabetes or known vascular disease **(315 [EL 4], 316 [EL 3])**.

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 β-quantification assay **(315 [EL 4], 317 [EL 4])**. These assays accurately classify patients with triglyceride concentrations up to 2000 mg/dL **(317 [EL 4])**, although they are not recommended for patients with type III hyperlipidemia (familial dysbetalipoproteinemia) **(317 [EL 4])**. The benefits and potential drawbacks of direct LDL-C assessment have been discussed in detail by Nauck and colleagues **(315 [EL 4])**. These assays accurately classify patients with triglyceride concentrations up to 2000 mg/dL **(317 [EL 4])**, although they are not recommended for patients with type III hyperlipidemia (familial dysbetalipoproteinemia) **(317 [EL 4])**. The benefits and potential drawbacks of direct LDL-C assessment have been discussed in detail by Nauck and colleagues **(315 [EL 4])**.

4Q2.3. High-Density Lipoprotein Cholesterol

An HDL-C concentration less than 40 mg/dL is an established independent risk factor for CAD in both men and women **(10 [EL 4])**. 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])**. The evidence of low HDL-C as a positive risk factor for CVD and the evidence for high HDL-C as a negative risk CVD risk factor are described above in "Global Risk Assessment: Risk Factors for CAD."

4Q2.4. Non–High-Density Lipoprotein Cholesterol

Many patients have normal LDL-C concentrations, but elevated triglycerides and low HDL-C **(318 [EL 4])**. Furthermore, in patients with triglyceride levels 200 mg/dL or greater, VLDL-C is elevated and CAD risk cannot be adequately assessed using LDL-C alone **(10 [EL 4])**. 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:

$$\text{total cholesterol} - \text{HDL-C} = \text{non–HDL-C}$$

Non–HDL-C is highly correlated, but is 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], 41 [EL 4], 318 [EL 4])**. Current evidence indicates that, compared with LDL-C, non–HDL-C is an equally strong or superior predictor of risk in groups of patients with moderately elevated triglycerides (200 to 500 mg/dL) **(10 [EL 4])**, diabetes **(319 [EL 4], 320 [EL 2], 321 [EL 2])**, insulin resistance syndrome **(10 [EL 4])**, and/or established CAD **(318 [EL 4], 322 [EL 2])**. In these high-risk patients, non–HDL-C may be an appropriate secondary treatment target **(149 [EL 4])**. Non–HDL-C may be at goal with persistently elevated apo B levels **(323 [EL 4], 324 [EL 4])**. Non–HDL-C targets are 30 mg/dL higher than established LDL-C risk levels **(10 [EL 4])**.

4Q2.5. Triglycerides

A high triglyceride to HDL-C ratio (≥2.4) is a strong indicator of the insulin resistance syndrome **(10 [EL 4], 12 [EL 4], 112 [EL 3])**. Insulin resistance is more common when a family history of CAD or type 2 diabetes is present **(12 [EL 4])**. Evidence indicates that when triglyceride levels exceed 140 mg/dL, there is a substantial increase in the production of small, dense LDL-C **(190 [EL 4])**; therefore, the presence of hypertriglyceridemia and low HDL-C in a patient should also prompt clinical suspicion for the presence of the small, dense LDL pattern, as well as elevated postprandial triglycerides **(12 [EL 4])**. Triglycerides, 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 calculate the more important LDL-C.

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

- Direct assessment of the LDL-C pattern B phenotype (small, dense LDL) by ultracentrifugation, nuclear magnetic resonance, or gradient gel electrophoresis because elevated triglycerides and reduced HDL-C are elements of the *dyslipidemic triad* **(10 [EL 4])**. This is particularly relevant because many patients with the small, dense LDL pattern will have optimal or near-optimal LDL-C levels (<130 mg/dL) **(10 [EL 4])**.
- Evaluation of postprandial triglyceride levels may be useful because evidence indicates that the small triglyceride-rich lipoproteins produced postprandially are particularly atherogenic and may be indicative of insulin resistance and/or diabetes **(206 [EL 4], 325 [EL 3], 326 [EL 4], 327 [EL 4], 328 [EL 3], 329 [EL 3], 330 [EL 3])**. Although neither an assessment for postprandial triglyceride levels nor a reference range has been standardized, several recent studies indicate that nonfasting triglycerides exceeding usual fasting cutpoints (≥150 mg/dL) are independently associated with increased CAD risk **(208 [EL 2], 209 [EL 2], 331 [EL 4])**. Others suggest that lack of standardization of postprandial measurement of triglycerides precludes its current use as a screening test **(331 [EL 4])**.

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

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 CAD **(115 [EL 4])**.

Emerging evidence from a series of large studies, including the AMORIS (Apolipoprotein-Related Mortality Risk) 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 **(41 [EL 4], 332 [EL 2], 333 [EL 2])**. Additionally, an analysis of the IRAS study (Insulin Resistance Atherosclerosis Study) found that apo B was more closely associated than non–HDL-C with markers such as central adiposity, insulin resistance, thrombosis, and inflammation **(334 [EL 3])**. 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 patients whose non–HDL-C is satisfactory with apo B high enough to warrant more intensive therapy **(335 [EL 4])**. A 2008 post hoc analysis of combined data from 2 major statin trials (pooled n = 18018) found that both increased apo B and non–HDL-C demonstrated an equivalent or slightly stronger association with major cardiovascular event risk (hazard ratio, 1.19; $P<.001$ for both) than increased LDL-C (hazard ratio, 1.15; $P<.001$) **(19 [EL 2])**. Among patients 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 **(19 [EL 2])**. In addition, the apo B to apo AI ratio was a stronger predictor of risk (hazard ratio 1.24; $P<.001$) than either the LDL-C to HDL-C ratio (hazard ratio 1.20, $P<.001$) or the total cholesterol to HDL-C ratio (hazard ratio 1.21; $P<.001$) **(19**

[EL 2]). 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% confidence interval, 3.93-5.69) for the highest vs lowest decile **(14 [EL 2]**).

Based on these findings, when the triglyceride 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 patients at risk for CAD *(even when LDL-C levels are controlled)*; this includes patients with established CAD, type 2 diabetes, or the insulin resistance syndrome who are at high risk for CAD. AACE therefore recommends apo B testing in such patients **(19 [EL 2], 20 [EL 4]**).

4Q2.7. Secondary Causes of Dyslipidemia

Secondary causes of dyslipidemia (Table 11) **(10 [EL 4])** must be excluded with a thorough medical and dietary history, as well as laboratory testing for glucose and thyroid, liver, and renal function **(10 [EL 4])**. Treating an underlying contributing disease may alleviate the lipid abnormality **(10 [EL 4]**); however, dyslipidemia in patients 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. The following are examples of clinical situations where a more detailed lipid evaluation or other studies may be useful.

4Q2.8. Additional Tests

Additional tests may be warranted in certain situations; these are described in the following text. For greater detail on the described risk factors described, see Risk Factors for CAD under Global Risk Factors Assessment for Atherosclerosis.

Evidence suggests that *highly sensitive CRP* may be helpful in predicting coronary events **(336 [EL 1]**). Although studies suggest that highly sensitive CRP may be of limited value as a broadly applied screening tool, it may be helpful in stratifying cardiovascular risk in patients with a standard risk assessment that is borderline **(337 [EL 3])** or in those with an LDL-C level less than 130 mg/dL. Although studies suggest that highly sensitive CRP may be of limited value as a broadly applied screening tool, it may be helpful in stratifying cardiovascular risk in patients with a standard risk assessment that is borderline **(337 [EL 3])** or in those with an LDL-C level less than 130 mg/dL **(337 [EL 3], 338 [EL 1]**). Normal values of highly sensitive CRP are classified as being less than 1.0 mg/L, intermediate range is 1.0 to 3.0 mg/L, and high risk is greater than 3.0 mg/L **(337 [EL 3]**). However, in the most recent JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), a simpler stratification (<2.0 vs ≥2 mg/L) was strongly suggested **(338 [EL 1])**.

Lp-PLA$_2$ (see section 4Q1.1. Risk Factors for CAD, Other Risk Factors), like highly sensitive CRP, may also be helpful in predicting CAD risk. As discussed earlier, elevated Lp-PLA$_2$ (≥200 ng/mL) has been independently linked with coronary events **(259 [EL 2]**). Moreover, Lp-PLA$_2$ may act synergistically with CRP, further increasing risk when both are elevated **(251 [EL 2], 252 [EL 2]**). Measurement of Lp-PLA$_2$, which appears to be more specific than highly sensitive CRP, may be helpful when it is necessary to further stratify a patient's risk for CVD, especially in the presence of systemic CRP elevations.

A normal *apo AI* level in a patient with low HDL-C suggests the existence of an adequate number of HDL-C particles that contain less cholesterol and is an indication of less risk (8). Therefore, an assessment of apo AI may be useful in certain cases **(115 [EL 4]**).

Homocysteine has also emerged as a potential independent risk factor for CAD. Homocysteine levels greater than 15 μmol/L are associated with increased CAD risk. Goal levels have been less than 10 μmol/L in the United States and less than 12 μmol/L in Europe. As discussed in the following text, lowering homocysteine to these levels, however, has not been shown to reduce CAD risk **(270 [EL 4]**).

Coronary artery calcification and ultrasound measurement of carotid IMT are noninvasive measures of atherosclerosis that have emerged as adjuncts to standard CVD risk factors in an attempt to refine risk stratification and the need for more aggressive preventive strategies. 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 (see statin imaging studies; Table 17 **[339 (EL 1), 340 (EL 1), 341 (EL 1), 342 (EL 1), 343 (EL 1), 344 (EL 3), 345 (EL 1)]**). Carotid IMT, along with coronary calcium scoring, is recognized by the American Heart Association as a surrogate marker for coronary artery disease **(346 [EL 4]**). The presence of coronary calcium correlates strongly with coronary atherosclerosis. Coronary artery calcium scoring by computed tomography may prove useful in certain clinical situations to further assess intermediate risk suggested by Framingham or other risk assessment tools or to consider the need for more aggressive lipid lowering therapy. However, since there is lack of definite evidence that this emerging risk factor independently predicts coronary events, it remains unclear as to the general clinical utility of coronary artery scoring **(347 [EL 4]**). A recent commentary by Stein et al reviewed the comparison of carotid IMT to coronary calcium scoring, with favorable

Table 17
Major Statin Imaging Trials

Trial	Agent	Primary endpoint parameter	Patients, No.		F/U, y	Mean baseline lipid values, mg/dL			Mean achieved lipid values, mg/dL			Mean experimental % change		Mean control % change	
			M	F		LDL-C	HDL-C	TG	LDL-C	HDL-C	TG	Overall	Most diseased sub-segment	Overall	Most diseased sub-segment
MARS (339 [EL 1])	Lovastatin, 80 mg, (experimental) vs PBO (control)	Percent diameter stenosis measured by QCA	247	23	2.2	157[a]	43	159	86[a]	46	120	1.6	–4.1[b]	2.2	–0.9[b]
HATS (imaging arm) (340 [EL 1])	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	–5.8[b]	3.9	0.1[b]
REVERSAL (341 [EL 1])	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	–4.2[d]	5.4	–1.7[e]
ASTEROID (342 [EL 1])	Rosuvastatin, 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 (343 [EL 1])	Atorvastatin, 80 mg, (experimental) vs atorvastatin, 10 mg (control)	Coronary artery calcification measured by EBCT	149	217	1	155[f,g]	50[f,g]	208[f,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 (344 [EL 3])	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]	0.0111[i]	NA	0.0058[i]	NA
METEOR (345 [EL 1])	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	–0.0014[i]	NA	0.0131[i]	NA

Abbreviations: ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; EBCT, electron-beam computed tomography; ENHANCE, Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; F, female; F/U, follow-up; 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; REVERSAL, Reversing Atherosclerosis with Aggressive Lipid Lowering; TC, total cholesterol; TG, triglycerides; QCA, quantitative coronary angiography.

[a] Low-density lipoprotein cholesterol levels measured by preparative ultracentrifugation.

[b] Lesions with stenosis ≥50% at baseline.

[c] The HATS trial (HDL-Atherosclerosis Treatment Study) 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, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were 107 mg/dL, 52 mg/dL, and 149 mg/dL, respectively.

[h] Median.

[i] Results reported as millimeter change, not percentage change.

findings for carotid IMT, especially in the healthy young and middle-aged populations, as well as in women and African American persons in whom coronary calcification has more limited utility **(323 [EL 4])**. Findings of the MESA study indicate further that increased carotid IMT predicts CVD events in individuals without coronary calcification **(345 [EL 1])**.

Special Considerations: Women

Both the Framingham Heart Study and the Lipid Research Clinics Follow-Up Study have demonstrated that high total cholesterol, LDL-C, and triglycerides and low HDL-C are CAD risk factors in women. Elevated fasting and/or postprandial triglycerides may also be independent risk factors in this population **(208 [EL 2], 349 [EL 4])**. In particular, and in stark contrast to findings in men, very low HDL-C (<40 mg/dL) is an independent risk factor for CAD development and mortality in women, even in the presence of total cholesterol concentrations less than 200 mg/dL or normal LDL-C and/or triglyceride levels **(350 [EL 2])**, Compared with women with high HDL-C, women with low HDL-C have a nearly 3-fold elevated risk of CAD **(350 [EL 2])**. In particular, and in stark contrast to findings in men, very low HDL-C (<40 mg/dL) is an independent risk factor for CAD development and mortality in women, even in the presence of total cholesterol concentrations less than 200 mg/dL or normal LDL-C and/or triglyceride levels **(350 [EL 2]**). Compared with women with high HDL-C, women with low HDL-C have a nearly 3-fold elevated risk of CAD **(350 [EL 2])**.

4Q3. WHAT ARE THE TREATMENT RECOMMENDATIONS IN PATIENTS WITH DYSLIPIDEMIA AND CAD RISK?

4Q3.1. Treatment Goals

Treatment goals are outlined in Table 12 **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])**. In clinical management of dyslipidemia, a reasonable goal is to strive for lipid levels in the range of normal; however, more aggressive goals can be set for higher-risk patients **(23 [EL 4])**. Optimal, borderline, and abnormal serum lipid concentrations are outlined in Table 9 **(10 [EL 4])**.

Isolated Low HDL-C

As shown in Table 13 **(10 [EL 4])**, 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])**. Because no researched intervention has targeted only HDL-C, it is difficult to determine from clinical trials whether increasing HDL-C levels alone is clinically beneficial **(116 [EL 2], 123 [EL 4], 351 [EL 1])**. The VA-HIT study, however, showed that increasing HDL-C and lowering triglycerides in patients with CAD whose primary lipid abnormality was low HDL-C significantly reduced the rate of coronary events **(351 [EL 1])**. These results and other epidemiologic evidence support a cardioprotective role of HDL-C. Therefore, 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 CAD, or a personal history of CAD). 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 in women **(10 [EL 4], 122 [EL 4], 340 [EL 1], 352 [EL 3], 353 [EL 3])**.

4Q3.1.1. Low-Density Lipoprotein Cholesterol

LDL has been, and remains, the mainstay of efforts to improve lipid profiles in patients at risk for CVD. However, because an isolated focus on LDL-C is not always sufficient to prevent CAD in at-risk patients or to treat existing atherosclerosis, control of HDL-C, non–HDL-C, and triglycerides is also important **(10 [EL 4])**. Other important considerations include patient age and sex and the presence of type 2 diabetes or dysglycemia (impaired fasting glucose and/or impaired glucose tolerance).

4Q3.1.2. High-Density Lipoprotein Cholesterol

AACE does not recommend increasing HDL-C levels alone (ie, low HDL-C without any accompanying risk factors) because it is difficult to determine from clinical trials whether increasing HDL-C levels alone is clinically beneficial. In those with risk factors, AACE recommends raising HDL-C levels as much as possible, but *minimally* to greater than 40 mg/dL in both men and women **(Grade C; BEL 4)** (Table 12) **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])**.

4Q3.1.3. Non–High-Density Lipoprotein Cholesterol

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

4Q3.1.4. Apolipoproteins

Apo B may be elevated in patients with optimal LDL-C when small, dense LDL particles are present. This generally occurs in patients with hypertriglyceridemia, but may also occur in patients with triglyceride values of 100 to 149 mg/dL and in some patients with a genetic basis for small, dense LDL particles who have triglyceride values less than 100 mg/dL **(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL 1], 41 [EL 4])**. AACE recommends the goals set by the American College of Cardiology and the American Diabetes Association that optimal apo B levels for patients at risk of CAD, including those with diabetes, are less than 90 mg/dL, while patients with established CAD or diabetes plus 1 or more additional risk factor should have an apo B

goal of less than 80 mg/dL **(20 [EL 4], 41 [EL 4], 354 [EL 4])**. Lower apo B targets may be considered in certain clinical situations characterized by persistent CAD.

4Q3.1.5. Triglycerides

Normal triglyceride 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])**.

Although the benefit of targeting triglycerides directly remains uncertain, several studies suggest there may be some advantage to such treatment. Two major studies, the HHS (Helsinki Heart Study) and the FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes), found that fibrates were highly effective at lowering triglycerides. Moreover, both studies showed that a reduction in triglycerides was associated with a trend toward fewer CVD events and a significant reduction in nonfatal MI **(88 [EL 3], 355 [EL 1])**. In the 18-year HHS follow-up, triglyceride reduction with fibrates significantly lowered the CAD mortality rate **(84 [EL 2])**.

Although verifying the independent atherogenicity of triglycerides is difficult, triglyceride-rich remnant lipoproteins (ie, VLDL and intermediate-density lipoproteins) form the basis for triglyceride targets, since reducing remnant lipoproteins appears to have significant potential to reduce CAD risk **(10 [EL 4])**. Elevated triglycerides can often be effectively treated through lifestyle changes; however, niacin, fibrates, and combination therapy with statins may be appropriate options for many patients **(356 [EL 4], 357 [EL 1], 358 [EL 1])**. 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], 356 [EL 4], 359 [EL 1], 360 [EL 3])**.

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 (see section 4Q3.2.1. Physical Activity and section 4Q3.2.2. Medical Nutrition Therapy) **(10 [EL 4])**. The approach to treatment of accompanying elevated LDL-C does not need to be modified. However, if the patient also has decreased HDL-C, the selection of secondary drug therapy may be affected **(10 [EL 4])**.

Familial Hypertriglyceridemia

Familial hypertriglyceridemia refers to a group of conditions causing borderline-high and high triglyceride levels. Patients with marginal or elevated triglyceride levels due to familial hypertriglyceridemia have been conventionally considered to be at no increased risk of CAD because there is an overproduction of large VLDL particles that are not highly atherogenic. This assumption is based largely 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], 316 [EL 3], 361 [EL 3])**. However, subsequent research has cast doubt on this premise. In 2000, Austin and colleagues found that 20-year cardiovascular mortality risk was the same among persons with familial hypertriglyceridemia and with familial combined hyperlipidemia; however, the results for the familial hypertriglyceridemia group were not significant, probably due to a small sample size **(362 [EL 2])**. More recently, a case-control comparison from the National Heart, Lung, and Blood Institute Family Heart Study found that associated risk was similar and significant for both familial disorders. Patients with familial hypertriglyceridemia also had a higher prevalence of the insulin resistance syndrome (70.7%) than those with familial combined hyperlipidemia (64.7%) **(316 [EL 3])**. Treatment of familial hypertriglyceridemia should focus on reducing the risk of pancreatitis as a result of an increased triglyceride level **(8 [EL 4], 363 [EL 4], 364 [EL 3], 365 [EL 3])**.

Severe Hypertriglyceridemia (Type V)

Most patients with severe hypertriglyceridemia have type V hyperlipoproteinemia, signifying an increase in both chylomicrons and VLDL-C **(366 [EL 4])**. The need to lower triglyceride levels in these patients is urgent to prevent acute pancreatitis and the chylomicronemia syndrome **(367 [EL 4])**.

4Q3.2. Treatment Recommendations

The management of dyslipidemia requires a comprehensive strategy to control lipid levels and to 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 type 2 diabetes, is strongly associated with dyslipidemia. The first-line approach to primary prevention in patients with lipid disorders involves the implementation of lifestyle changes, including physical activity and medical nutrition therapy. Treatment may also involve pharmacotherapy, as well as patient education programs to promote further risk reduction through smoking cessation and weight loss. Furthermore, using insulin in patients with poorly controlled type 1 and type 2 diabetes to lower blood glucose will frequently reduce circulating levels of triglycerides.

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 highly sensitive CRP levels and improvements in risk factors such as obesity, waist circumference, hypertension, and dyslipidemia **(368 [EL 4])**. Specific lipid level improvements associated with regular exercise include reduced VLDL-C, increased HDL-C, and, in some persons, decreased LDL-C levels **(10 [EL 4])**.

Numerous published guidelines identify exercise regimens as an essential approach for dyslipidemia control and cardiovascular risk factor reduction. One current recommendation, which 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], 155 [EL 4], 369 [EL 4], 370 [EL 4], 371 [EL 2], 372 [EL 4], 373 [EL 2], 374 [EL 2], 375 [EL 4], 376 [EL 1], 377 [EL 2], 378 [EL 4])**. 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 **(369 [EL 4])**. AACE's minimum recommendation remains 30 minutes daily, as over-emphasis of the extended recommendations may lead to poor adherence for some patients. Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum); for some patients, breaking activity up throughout the day may help improve adherence to physical activity programs **(155 [EL 4], 369 [EL 4], 370 [EL 4], 375 [EL 4])**.

Although aerobic exercise is preferred, nonaerobic activities are also beneficial. The IRAS study (Insulin Resistance Atherosclerosis Study) examined 1467 patients 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 **(379 [EL 3])**. Recent studies also suggest that weight and resistance training may be beneficial to some patients with the insulin resistance syndrome, independent of body fat or aerobic fitness **(380 [EL 2], 381 [EL 3])**. Therefore, in addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week **(375 [EL 4])**.

Even though the benefits of exercise are widely accepted, physical activity programs often prove difficult for patients to maintain **(155 [EL 4])**. Nonetheless, AACE underscores the continued application of fitness therapy as a cornerstone of dyslipidemia treatment. Patients 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 patient-tailored advice, identification of adherence barriers, referral to instructor-led exercise classes, and routine patient follow-up and consultation **(382 [EL 1], 383 [EL 1], 384 [EL 4], 385 [EL 2])**.

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 CAD 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 polyunsaturated fatty acids than with monounsaturated fatty acids **(10 [EL 4], 386 [EL 2])**. While high intake of polyunsaturated fatty acids may reduce HDL-C and triglyceride levels, the substitution of monounsaturated fatty acids for saturated fatty acids has a minimal effect on HDL-C values and does not raise triglyceride levels **(10 [EL 4], 386 [EL 2], 387 [EL 1], 388 [EL 1], 389 [EL 1])**.

Dietary intake of *trans* fatty acids is associated with both increased LDL-C and decreased HDL-C levels **(390 [EL 3])**. Combined with evidence from epidemiologic cohort studies, these effects indicate that diets high in *trans* fatty acids are associated with an increased risk of CAD; current evidence indicates that, on a per calorie basis, risk with *trans* fatty acids is higher than with any other macronutrient **(390 [EL 3])**.

Dietary Changes: Recommendations and Clinical Effects

Current nutritional guidelines for the reduction of cardiovascular risk through lipid management recommend diets rich in fruits (≥2 servings/day), vegetables (≥3 servings/day, ≥1 of these servings/day of dark green or orange vegetables), grains (≥6 servings/day, one-third of those as whole grains), legumes, high-fiber cereals, low-fat dairy products, fish, lean meats, and skinless poultry **(10 [EL**

4], 391 [EL 4], 392 [EL 4]). 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])**. Further recommendations include a reduction in both salt intake and total calories consumed **(10 [EL 4], 391 [EL 4], 393 [EL 4])**. Further recommendations include a reduction in both salt intake and total calories consumed.

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], 394 [EL 4], 395 [EL 4])**. 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% **(396 [EL 3], 397 [EL 3], 398 [EL 3], 399 [EL 3], 400 [EL 3])**. Foods high in soluble fiber include oat bran, oatmeal, beans, peas, rice bran, barley, citrus fruits, strawberries, and apple pulp **(401 [EL 4])**. Plant stanol esters are virtually unabsorbable and selectively inhibit dietary and biliary cholesterol absorption in the small intestine **(42 [EL 4])**. 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% **(402 [EL 1], 403 [EL 2], 404 [EL 2], 405 [EL 4])**. 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 United States, orange juice **(42 [EL 4])**.

While low-fat diets are generally recommended, it is important to recognize that decreases in dietary fat intake may lead to increased carbohydrate consumption and subsequent weight gain **(10 [EL 4], 387 [EL 1], 388 [EL 1], 406 [EL 1], 407 [EL 1], 408 [EL 2], 409 [EL 2])**. Patients at risk for the insulin resistance syndrome are advised to avoid excessive carbohydrate intake and to consume diets that include relatively more unsaturated fats **(10 [EL 4], 410 [EL 4])**. A diet high in carbohydrates (>60% of total energy) will increase triglycerides, while a diet that replaces saturated fatty acids with monounsaturated fatty acids will not **(10 [EL 4])**.

Because of the demonstrated lipid benefits (eg, decreased triglyceride levels, antiarrhythmic, and modest hypotensive effects) associated with consuming the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, the American Heart Association recommends 2 servings of fatty fish per week for the general population. Patients with CAD should consume 1 g of eicosapentaenoic acid and docosahexaenoic acid daily through fatty fish (preferably) or high-quality dietary supplements **(411 [EL 4])**. Evidence indicates that the consumption of 2 to 4 g daily of fish oil can reduce triglycerides by 25% or more, while producing only slight increases in LDL-C levels and having no significant effect on HDL-C values **(412 [EL 4], 413 [EL 4])**. Emerging evidence also suggests that consumption of fish oil may have additional effects such as reduced atherosclerotic plaque growth, antithrombogenic effects, and the promotion of endothelial relaxation; however, these findings require further confirmation **(411 [EL 4], 414 [EL 4], 415 [EL 2])**.

Nutrition therapy effectively reduces cholesterol levels. In a trial of patients with hypercholesterolemia, implementation of the NCEP Step II therapeutic diet led to an 8% decrease in LDL-C values **(416 [EL 1])**. In another study, LDL-C levels were reduced by 11% with diets low in saturated fatty acids (comprising 6.1% of caloric intake) **(216 [EL 2])**. 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 triglycerides by 25% to 30% **(411 [EL 4])**. Dietary fat and carbohydrate restrictions, combined with increased physical activity, weight control, and omega-3 supplementation **(411 [EL 4])**, are considered effective first-line therapy for hypertriglyceridemia **(200 [EL 4], 204 [EL 4])**.

Other investigations have revealed potential health benefits of various specialized diets. For example, CAD regression was observed in a 1998 study of patients on the Ornish diet plus lifestyle intervention (eg, moderate exercise), while the control group (usual care—lifestyle adjustment based on advice of regular physician) showed CAD progression **(417 [EL 3])**. In an analysis comparing the Ornish, Zone, Lifestyle, Exercise, Attitudes, Relationships, and Nutrition (LEARN) and Atkins diets, the latter was associated with the greatest weight loss and most improvement in HDL-C and triglyceride levels **(418 [EL 1])**. In the EPIC-Oxford study (European Prospective Investigation into Cancer and Nutrition-Oxford), mortality from ischemic heart disease was observed to be lower in vegetarians than in nonvegetarians **(419 [EL 2])**. In other studies, vegetarian diets were associated with reduced total cholesterol, LDL-C, and systolic blood pressure when compared with control or meat-eating diets **(420 [EL 3], 421 [EL 3])**.

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 patient progress, nutritional therapy may be extended through 6 months before initiating lipid-lowering drug therapy **(8 [EL 4])**. For high-risk patients, it is appropriate to institute nutrition therapy and pharmacotherapy simultaneously.

After lipid levels are controlled, intensified lifestyle changes may be implemented in patients with the insulin resistance syndrome.

Patient response to medical nutrition therapy has diagnostic significance. Individual response to nutrition therapy is variable, and numerous factors may influence patient outcomes, including adherence **(422 [EL 4])**, baseline diet, sex, genetics **(115 [EL 4])**, and LDL particle size **(423 [EL 1], 424 [EL 2])**. Patients who respond poorly despite good adherence to dietary restrictions are more likely to have genetic dyslipidemia **(425 [EL 4])**.

Primary Preventive Nutrition in Children

A decade ago, most experts believed that reduced-fat diets could inhibit growth and decrease vitamin and mineral intake and were therefore inappropriate for most pediatric patients; such diets were generally reserved for high-risk individuals **(301 [EL 4], 426 [EL 4])**. 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 **(300 [EL 4], 302 [EL 2], 427 [EL 1], 428 [EL 1], 429 [EL 2], 430 [EL 2], 431 [EL 3], 432 [EL 2], 433 [EL 2], 434 [EL 2], 435 [EL 1], 436 [EL 2])**. Furthermore, the benefits of early "imprinting" of healthy lifestyle habits in children have also been recognized **(304 [EL 4])**. 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 pediatric patients can achieve decreased total cholesterol levels and modest, but significant, LDL-C reductions with low-fat diets **(303 [EL 4], 310 [EL 4], 427 [EL 1], 437 [EL 4], 438 [EL 3], 439 [EL 1], 440 [EL 2])**. 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 patients 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 **(310 [EL 4], 427 [EL 1], 439 [EL 1], 441 [EL 3])**.
- *Increased intake of carbohydrates may increase plasma triglyceride concentrations in children* **(441 [EL 3])**. High carbohydrate intake is not recommended for children with hypertriglyceridemia.
- *Fish oil supplements have a profound effect on serum triglyceride levels in children*. These supplements have been used effectively in pediatric patients with end-stage renal insufficiency **(442 [EL 2])**.
- *Increased intake of carbohydrates may increase plasma triglyceride concentrations in children* **(441 [EL 3])**. High carbohydrate intake is not recommended for children with hypertriglyceridemia.
- *Fish oil supplements have a profound effect on serum triglyceride levels in children*. These supplements have been used effectively in pediatric patients with end-stage renal insufficiency **(442 [EL 2])**.
- *Water-soluble fiber can help to improve serum cholesterol levels in children*. Studies have shown that both children and adults can achieve cholesterol reductions with high-fiber, low-fat diets **(443 [EL 4], 444 [EL 3])**.
- *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 (such as spreads/margarines, orange juice, yogurt drinks, cereal bars, and dietary supplements) **(305 [EL 4], 445 [EL 2])**. AACE agrees with the American Academy of Pediatrics and the American Heart Association 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 **(305 [EL 4], 446 [EL 4])**. The main safety concern is that plant stanols and sterols may reduce absorption of fat-soluble vitamins and betacarotene; therefore, the American Heart Association recommends monitoring fat-soluble vitamin status in children receiving supplementation **(305 [EL 4], 446 [EL 4])**.

Children and adolescents on low-fat diets may experience decreased absorption of fat-soluble vitamins or minerals **(447 [EL 4])** 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 CAD risk factor that has been shown to degrade serum lipid profiles in young adults **(448 [EL 3])**. Smoking cessation programs for adolescents may

involve patient education, counseling, behavioral therapy, and/or pharmacologic intervention **(449 [EL 4])**.

4Q3.2.4. Pharmacologic Therapy

At the initiation of drug therapy, the physician and patient should collaborate to establish the patient's lipid goal and then treatment should be personalized to achieve that goal. Pharmacotherapy may consist of 1, 2, or, in cases of severe dyslipidemia, 3 or even 4 agents (that is, a statin ± cholesterol absorption inhibitor ± fibrate ± niacin).

Numerous clinical trials demonstrate that lipid-lowering drug therapy is effective for both the primary and secondary prevention of MI and other cardiovascular outcomes **(10 [EL 4])**. Clinical evidence also suggests that lipid-lowering drug therapy can both prevent CAD from developing and may stabilize early, occult lesions **(354 [EL 4], 450 [EL 4], 450 [EL 2])**. Last, results from several recent, large clinical trials suggest that patients at high risk may benefit from very aggressive lipid-lowering therapy **(10 [EL 4], 338 [EL 1], 451 [EL 2])**.

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. 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 **(452 [EL 1])**. Nonetheless, reducing lipids to levels even below recommended targets may be beneficial for certain patients. Consequently, in 2004, the NCEP ATP III updated its guidelines to include an optional LDL-C goal of less than 70 mg/dL for patients at very high risk **(23 [EL 4])**. *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* **(23 [EL 4])**. The American Heart Association/American College of Cardiology 2006 update of its CVD secondary prevention guidelines also considers it a "reasonable goal" to reduce LDL-C to less than 70 mg/dL for patients with established CAD **(22 [EL 4])**. Patients for whom aggressive therapy may be beneficial are outlined below, and trials relevant to aggressive lipid-lowering therapy are shown in Table 18 **(39 [EL 1], 59 [EL 1], 62 [EL 1], 66 [EL 1], 83 [EL 3], 103 [EL 2], 105 [EL 1], 338 [EL 1], 355 [EL 1], 376 [EL 1], 453 [EL 1], 454 [EL 4], 455 [EL 1], 456 [EL 1], 457 [EL 1]**), Table 19 (**37 [EL 1], 85 [EL 1], 86 [EL 1], 102 [EL 1], 106 [EL 1], 107 [EL 1], 287 [EL 1], 340 [EL 1], 353 [EL 3], 458 [EL 1], 459 [EL 4], 460 [EL 1], 461 [EL 1], 462 [EL 2]**), and Table 20 (**39 [EL 1], 40 [EL 1], 93 [EL 4], 102 [EL 1], 105 [EL 1], 106 [EL 1], 107 [EL 1], 287 [EL 1], 288 [EL 1], 451 [EL 2], 453 [EL 1], 454 [EL 4], 461 [EL 1], 463 [EL 1]**).

Patients With Average or Elevated LDL-C

Early trials such as the 4S study (Scandinavian Simvastatin Survival Study) and the AFCAPS/TexCAPS study (Air Force/Texas Coronary Atherosclerosis Prevention Study) showed that patients with elevated LDL-C or patients with marginally increased LDL-C but low HDL-C showed significant reductions in major coronary events over 5 years on statin therapy **(102 [EL 1], 453 [EL 1])**. The extent of these positive results generated interest in the possible benefits of more aggressive cholesterol lowering. More recently, the HPS secondary prevention trial (Heart Protection Study) examined the efficacy of simvastatin for lipid lowering among a large cohort (n = 20 536) of patients at high risk, including approximately 3500 who entered the study with optimal LDL-C levels (<100 mg/dL). Among those patients, 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 patients with higher baseline LDL-C concentrations (about 20%) **(37 [EL 1])**. Moreover, a recent meta-analysis comparing 4 standard-dosage vs high-dosage statin trials (PROVE-IT–TIMI 22 [Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22], A-to-Z, TNT [Treating to New Targets], and IDEAL [End Points Through Aggressive Lipid Lowering]) found a significant 16% decrease in coronary death, MI, or any cardiovascular event among patients receiving high-dosage therapy. High-dosage therapy also significantly reduced nonfatal MI, stroke, unstable angina, and revascularization risk **(452 [EL 1])**. The final results of the JUPITER trial (see the section on Statins) provide additional data on aggressive therapy in patients with moderate-to-low LDL-C levels (<130 mg/dL) combined with elevated inflammation (indicated by highly sensitive CRP levels ≥2.0 mg/L). In this trial, patients receiving rosuvastatin had their LDL-C and highly sensitive CRP levels reduced to medians of 55 and 1.8, respectively; these effects were accompanied by significant reductions in cardiovascular events and mortality **(338 [EL 1], 454 [EL 4])**. In addition, several imaging studies have examined the effects of aggressive therapy on atheroma volume and coronary artery calcification, with varying results (see Statins: Imaging Studies).

Patients With Diabetes

Diabetes increases cardiovascular risk to the extent that it is considered a CAD risk equivalent **(10 [EL 4])**. According to the NCEP ATP III and the 2008 American Diabetes Association/American College of Cardiology Consensus Statement, patients with diabetes alone should be considered high risk, with an accompanying LDL-C target of less than 100 mg/dL, while patients with diabetes and 1 or more additional risk factor (eg, existing CVD) are considered to be at very high/highest risk and should have an LDL-C target of less than 70 mg/dL **(20 [EL 4])**.

Table 18
Summary of Major Randomized Controlled Drug Trials for Primary Prevention of Coronary Artery Disease
(39 [EL 1], 59 [EL 1], 61 [EL 1], 66 [EL 1], 83 [EL 3], 103 [EL 2], 105 [EL 1], 338 [EL 1], 355 [EL 1], 376 [EL 1], 453 [EL 1], 454 [EL 4], 455 [EL 1], 456 [EL 1], 457 [EL 1])

Trial	Treatment	Patients, No.		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 (376 [EL 1])	Pravastatin, 40 mg, vs PBO	6595	0	4.9 y	192	164	44	26	12	37[b]	31	28	5
AFCAPS/TexCAPS (453 [EL 1])	Lovastatin, 20-40 mg, vs PBO	5608	997	5.2 y	150	158[c]	38	25[d]	15[d]	33[e]	40	[f]	6.0[d]
ALLHAT-LLT (103 [EL 2])	Pravastatin, 40 mg, vs PBO	5304	5051	4.8 y	146	152	48	28	4[g]	NA	9[h,i]	[i]	3.3
ASCOT-LLA (39 [EL 1])	Atorvastatin, 10 mg, vs PBO	8363	1942	3.3 y	132	149	50	29	14	NA	36[i]	36[i]	0.0
CARDS (105 [EL 1])	Atorvastatin, 10 mg, vs PBO	1929	909	4.0 y	117	147[c]	54	40	19	31[e]	33[j]	33[j]	1.0
JUPITER (338 [EL 1], 454 [EL 4])	Rosuvastatin, 20 mg, vs PBO	11 001	6801	1.9 y[c,k]	108	118	49	NA[k]	NA[k]	NA[k]	54[k]	47[k,l]	NA[k]
Fibrates													
WHO (455 [EL 1])	Clofibrate	3806	0	5.3 y	188	NA	NA	9 (TC)	NA	NA	19	19	NA
HHS (355 [EL 1])	Gemfibrozil	4081	0	5.0 y	201	182	47	11	35	NA	34	37	8.5
FIELD (83 [EL 3])	Fenofibrate	6138	3657	5.0 y	119	154	43	6	22	21[e]	24	+19	1.2
Bile acid sequestrants													
LRC (456 [EL 1])	Cholestyramine[m]	3806	NA	7.4 y	205	155	44	15[g]	+17[g]	NA	19	24	5.4[g]
Insull et al 2001 (457 [EL 1])	Colesevelam	232	235	24 wks	158[g]	161[g]	49[g]	20[c]	+5-10[c]	NA	NA	NA	3-4
Cholesterol absorption inhibitors													
Ezetimibe Study Group 1 (59 [EL 1])	Ezetimibe	434	458	12 wks	168	175	52	17	6	NA	NA	NA	1.3
Combination													
Ezetimibe Study Group 2 (62 [EL 1])	Ezetimibe + simvastatin (single tablet)	736	792	12 wks	178[g]	149[c,g]	52[g]	53[n]	24.3[n]	NA	NA	NA	7.2[n]
McKenney et al 2006 (66 [EL 1])	Fenofibrate + ezetimibe	331	245	48 wks	162[g]	276[g]	42	22	46[c]	NA	NA	NA	20.9

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; CABG, coronary artery bypass graft; CARDS, Collaborative Atorvastatin Diabetes Study; Cor, coronary; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; F/U, follow-up; 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, Lipid Research Clinics Coronary Primary Prevention Trial; MI, myocardial infarction; NA, not applicable; PBO, placebo; PTCA, percutaneous transluminal coronary angioplasty; TC, total cholesterol; TG, triglycerides; WHO, World Health Organization; WOSCOPS, West of Scotland Coronary Prevention Study.

[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 myocardial infarction 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 low-density lipoprotein cholesterol and triglycerides were 60.2% and 30.7%, respectively. The increase in high-density lipoprotein cholesterol was 9.8%.

Table 19
Summary of Major Randomized Controlled Drug Trials for Secondary Prevention of Coronary Artery Disease
(37 [EL 1], 85 [EL1], 86 [EL 1], 102 [EL 1], 106 [EL 1], 107 [EL 1], 287 [EL 1], 340 [EL 1], 353 [EL 3], 458 [EL 1], 459 [EL 4], 460 [EL 1], 461 [EL 1], 462 [EL 2])

Trial	Treatment	Patients, No.		F/U, y	Baseline[a], mg/dL			Reduction, %					Increase, %
		Male	Female		LDL-C	TG	HDL-C	LDL-C	TG	PTCA	MI	Cor Death	HDL-C
Statins													
4S (102 [EL 1])	Simvastatin, 20-40 mg	3617	827	5.4	188	131	46	35	10	37	37	42	8
CARE (458 [EL 1])	Pravastatin, 40 mg	3583	576	5.0	135	91	39	28	14	27	27	24	5
LIPID (287 [EL 1])	Pravastatin, 40 mg	7498	1516	6.1	146[b]	145[b]	36[b]	25	11	19	29	24	5
AVERT (459 [EL 4])	Atorvastatin, 80 mg	288	53	1.5	152	172	40[c]	46	11	[d]	[d]	[d]	8
HPS (37 [EL 1])	Simvastatin, 40 mg	15 454	5082	5	132	184	41	32[e]	NA	22[e,f]	37	17[e]	NA
GREACE (460 [EL 1])	Atorvastatin, 10-80 mg	624	176	3	180	184	39	46	31	51[g]	59	47	7
A to Z (461 [EL 1])	Simvastatin, 40/80 mg vs PBO/simvastatin, 20 mg	3396	1100	2	112	149	39	41[e]	22[e]	7[f]	4	20	12[e]
IDEAL (107 [EL 1])	Atorvastatin, 80 mg vs simvastatin, 20 mg	7187	1701	4.8	121	149	46	23[h]	26[h]	23[f]	17	1	1.3 (simvastatin over atorvastatin)
TNT (106 [EL 1])	Atorvastatin, 80 mg, vs atorvastatin, 10 mg	8099	1902	4.9[b]	98	151	47	18[c,e]	8[c,e]	4	22	20	0
Fibrates													
BECAIT (462 [EL 2])	Bezafibrate	92[i]	NA	5.0	180[b,j]	214[b,j]	34[b,j]	1.9	31.4	[k]	[k]	[k]	9.2
BIP (86 [EL 1])	Bezafibrate	2825	265	6.2	148	145	35	6.5	20.6	0	12.8[l]	0[l]	17.9
VA-HIT (85 [EL 1])	Gemfibrozil	2531	NA	5.1	112	160	32	0	31	21[m]	23	22	6
Combination													
HATS (340 [EL 1])	Simvastatin + Niacin	139	121	3.2	125	213	31	42	36	90[n]	90[n]	90[n]	26
ARBITER2 (353 [EL 3])	Niacin + background statin	152	15	1	89[e]	163[e]	40[e]	2.3[e]	13[e]	[o]	[o]	[o]	21[e]

Abbreviations: 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; 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; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; MI, myocardial infarction; NA, not applicable; NC, no change; PTCA, percutaneous transluminal coronary angioplasty; 4S, Scandinavian Simvastatin Survival Study; Stockholm, Stockholm Ischaemic Heart Disease Secondary Prevention 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 significant).
[e] Calculated based on reported figures.
[f] All revascularizations.
[g] Percutaneous transluminal coronary angioplasty/coronary artery bypass graft.
[h] At 1 year.
[i] Total number of patients, male and female.
[j] Bezafibrate group baseline only.
[k] 6.4% coronary event rate (reinfarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty) in the bezafibrate group compared with a 24.4% event rate in the placebo group.
[l] A post hoc analysis found that among patients with highest baseline triglycerides (≥200 mg/dL), primary endpoint (nonfatal myocardial infarction and sudden death) was reduced by 39.5%.
[m] Carotid endarterectomy reduced 65%.
[n] Reduction compared with placebo in composite endpoint (cardiovascular death, nonfatal myocardial infarction, or revascularization).
[o] Clinical cardiovascular events occurred in 3.8% of statin + niacin patients compared with 9.6% of statin + placebo patients.

Table 20
Primary and Secondary Statin Cardiovascular Disease Prevention Trials
(37 [EL 1], 39 [EL 1], 40 [EL1], 93 [EL 4], 102 [EL 1], 104 [EL 1], 105 [EL 1], 106 [EL 1], 107 [EL 1], 287 [EL 1], 288 [EL 1], 451 [EL 2], 453 [EL 1], 454 [EL 4], 461 [EL 1], 463 [EL 1])

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 (463 [EL 1]) 0% female	Pravastatin, 40 mg, vs PBO	…	…	155-232	192	159	30%	5.5% at 5.0 years	7.9%	2.4%	42
AFCAPS (453 [EL 1]) 15% female	Lovastatin, 20-40 mg, vs PBO	≤400	<45 M <47 F	130-190	150	115	40%	4.0% at 5.2 years	6.8%	1.2%	83
ASCOT-LLA (39 [EL 1]) 19% female	Atorvastatin, 10 mg, vs PBO	<400	…	TC = <250	134	90	37%	1.9% at 3.3 years	3.0%	1.1%	91
CARDS (105 [EL 1]) 32% female	Atorvastatin, 10 mg, vs PBO	<600	…	≤160	118	82	35%	3.0% at 4.0 years	4.6%	1.6%	63
JUPITER[b] (338 [EL 1], 454 [EL 4]) 38% female	Rosuvastatin, 20 mg, vs PBO	<500	…	<130[c]	108[d]	55[d]	44%	1.6% at 1.9 years[b,e]	2.8% at 1.9 years[b,e]	…	95[f]
Secondary prevention											
4S (102 [EL 1]) 19% female	Simvastatin, 20-40 mg, vs PBO	≤225	…	TC = 215-315	190	124	35%	8.2% at 5.4 years	11.5%	9.2%	11
CARE (288 [EL 1]) 14% female	Pravastatin, 40 mg, vs PBO	<350	…	115-74	139	98	23%	10.2% at 5.0 years	13.2%	3.0%	33
LIPID (287 [EL 1]) 17% female	Pravastatin, 40 mg, vs PBO	<445	…	TC = 155-271	150	112	23%	12.3% at 6.1 years	15.9%	3.6%	28
HPS (37 [EL 1]) 25% female	Simvastatin, 40 mg, vs PBO	…	…	TC ≥135	129	90	26%	8.7% at 5.0 years	11.8%	3.1%	32
TNT (106 [EL 1]) 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 years	8.7%	1.8%	56
PROVE IT – TIMI 22 (104 [EL 1]) 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 years	10.0% at 2 years	1.7%	59
A to Z (461 [EL 1]) 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 years	16.7% at 2 years	…	77[h]
IDEAL (107 [EL 1]) 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 years	11.2% at 4.8 years	1.2%	77

Abbreviations: 4S, Scandinavian Simvastatin Survival Study; AFCAPS, Airforce 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; IDEAL, Incremental Decrease in Endpoints Through Aggressive Lipid lowering; 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; TC, total cholesterol; TG, triglycerides; TNT, Treating to New Targets; WOSCOPS; West of Scotland Coronary Prevention Study.

[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 years; maximal follow-up was 5 years.

[c] Inclusion criteria included highly sensitive C-reactive protein concentration ≥2.0 mg/L.

[d] Median.

[e] Calculated based on 142 and 251 events in rosuvastatin and placebo groups, respectively.

[f] Number needed to treat for 2 years. NNT 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.

Secondary prevention statin studies such as HPS (Heart Protection Study) showed significant risk reduction among patients with diabetes. Based on this, the CARDS study (Collaborative Atorvastatin Diabetes Study) was designed to assess the effects of aggressive lipid lowering on the primary prevention of CAD in patients with type 2 diabetes. In patients 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 **(105 [EL 1])**. 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 **(105 [EL 1])**.

Patients with diabetes and the insulin resistance syndrome are at particularly high risk for CAD. An analysis of participants in the Third National Health and Nutrition Examination Survey who were 50 years and older found that the presence of the insulin resistance syndrome in persons with diabetes was very high: 86%. Furthermore, the combination of diabetes and the insulin resistance syndrome in these persons was associated with the highest prevalence of CAD (19.2%), while those with neither condition had the lowest prevalence (8.7%) **(147 [EL 3])**.

Highly sensitive CRP may be another useful marker of risk in patients with diabetes. The Health Professionals Follow-up Study examined the predictive value of highly sensitive CRP in 750 men with type 2 diabetes and no baseline CAD. Data from this study showed that increasing highly sensitive CRP levels were associated with a progressively greater CAD risk, even with adjustment for other risk factors such as body mass index, family history of CAD, physical activity, and markers of inflammation **(464 [EL 2])**. The multivariate adjusted relative risks for MI, coronary revascularization, or stroke by highly sensitive CRP values of 1.0, 1.0-3.0, and greater than 3.0 were 1.00, 1.50, and 2.09 (P = .028), respectively, over the 5-year follow-up period **(464 [EL 2])**. Studies such as these suggest that the establishment of the insulin resistance syndrome or elevated highly sensitive CRP in patients with diabetes may aid in identifying increased CAD risk, and thus candidates for aggressive primary prevention therapy. Patients with prediabetes, impaired fasting glucose, or impaired glucose tolerance are considered to be at increased risk for CAD. Lipid treatment goals should be the same in patient prediabetes as in patients with diabetes **(132 [EL 4])**.

Patients 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 CAD risk, as well as to other risk factors such as type 2 diabetes, the insulin resistance syndrome, and polycystic ovary syndrome **(181 [EL 4], 185 [EL 3], 186 [EL 2], 187 [EL 2], 191 [EL 4], 192 [EL 3], 193 [EL 2])**. In fact, in 1997, SCRIP-Berkeley investigators reported that multifactorial risk reduction produced significant arteriographic benefit in patients with LDL-C levels less than 125 mg/dL who had LDL pattern B, but did not benefit patients with LDL-C levels less than 125 mg/dL who had LDL pattern A **(166 [EL 4], 465 [EL 4])**.

Patients Undergoing Coronary Artery Bypass Graft

Studies show that aggressive LDL-C–lowering statin therapy may benefit patients who undergo coronary artery bypass grafting, both preoperatively and postoperatively **(466 [EL 2], 467 [EL 1], 468 [EL 4], 469 [EL 2], 470 [EL 3], 471 [EL 3], 472 [EL 3], 473 [EL 4])**. 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 **(452 [EL 1], 474 [EL 1], 475 [EL 2], 476 [EL 4], 477 [EL 1], 478 [EL 4], 479 [EL 4])**.

In the Post CABG clinical trial (Post Coronary Artery Bypass Graft), aggressive vs 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 patients **(467 [EL 1])**. An extended follow-up at 7.5 years found a significant 24% reduction in the composite endpoint (cardiovascular and unknown-cause death, nonfatal MI, stroke, coronary artery bypass graft, or angioplasty; P = .001) with aggressive therapy **(466 [EL 2], 467 [EL 1], 468 [EL 4])**. Moreover, recent studies show that patients taking statins before coronary artery bypass graft surgery have reduced postoperative cardiovascular events and death, as well as reductions in inflammatory markers such as interleukin-6 and interleukin-8 **(469 [EL 2], 470 [EL 3], 471 [EL 3], 472 [EL 3], 473 [EL 4])**.

Patients With Acute Coronary Syndrome

Several recent studies suggest that statin therapy following acute coronary syndrome may provide anti-inflammatory benefits through rapid reductions in highly sensitive CRP, which in turn improve long-term survival **(104 [EL 1], 477 [EL 1], 480 [EL 1], 481 [EL 3])**. The PROVE IT trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy), which studied high-dosage atorvastatin vs moderate-dosage pravastatin in patients with acute coronary syndrome over 2.5 years, found that high-dosage therapy reduced cardiovascular events at a nonstatistically significant rate compared with low-dosage therapy **(104 [EL 1])**. The MIRACL study (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study, which compared high-dosage atorvastatin with placebo, had similar results **(482 [EL 1])**. Moreover, analyses of the PROVE IT trial data demonstrate that early aggressive statin therapy after acute coronary syndrome can reduce 30-day mortality rates **(104 [EL 1])**.

Older Patients

A recent analysis of data from the TNT study (Treating to New Targets) found that among patients 65 years or older (n = 3809), 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 patients were slightly greater than in patients younger than 65 years, but were still low and not significant compared with the overall TNT cohort. A small increase in all-cause mortality prompted the investigators to suggest continued caution when treating older patients with statins **(483 [EL 1])**. Nonetheless, subgroup analyses of several statin studies, as well as the CTT meta-analysis (Cholesterol Treatment Trialists'), confirm that overall efficacy and adverse events are similar between age groups. *This indicates that aggressive statin therapy in selected older patients may be beneficial* **(284 [EL 4], 341 [EL 1], 342 [EL 1], 462 [EL 1], 484 [EL 1])**. As noted earlier, the PROSPER trial (Prospective Study of Pravastatin in the Elderly at Risk) demonstrated a secondary but not primary prevention CAD event benefit for the group older than 70 years treated with pravastatin **(38 [EL 1])**. Furthermore, results from the 4S trial (Scandinavian Simvastatin Study), which used simvastatin, 40 mg daily, as its highest dosage, showed that even a submaximal dose produced a reduced event rate at any age. Patients 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 **(102 [EL 1])**.

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:

Cholesterol Level is Markedly Increased and Monotherapy Does Not Achieve the Therapeutic Goal **(485 [EL 4], 486 [EL 4], 487 [EL 4])**

Statins yield only modest (approximately 6%) incremental LDL-C reductions for each dose doubling above standard dosage **(23 [EL 4])**. 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 (see Cholesterol Absorption Inhibitors). The recent SHARP study (Study of Heart and Renal Protection) 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 patients with advanced chronic kidney disease. The combination of statin and bile acid sequestrant has also been shown to have additive LDL-C lowering compared with regular-dosage monotherapy **(488 [EL 1], 489 [EL 1], 490 [EL 2], 491 [EL 3])**. Such combinations have been shown to provide LDL-C lowering comparable to or greater than that achieved by high-dosage statin monotherapy **(62 [EL 1], 489 [EL 1], 490 [EL 2], 492 [EL 1])**. 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 **(485 [EL 4], 487 [EL 4])**

Some adverse effects associated with statin drugs are dosage-related (eg, myopathy/rhabdomyolysis), and with some statins, liver dysfunction may increase with increased dosage **(43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4])**. 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])**. Examples include statin + bile acid sequestrant and statin + ezetimibe.

Mixed Dyslipidemia is Present (High Triglycerides, 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 triglyceride levels and to raise HDL-C levels **(486 [EL 4], 487 [EL 4])**. 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 triglyceride levels **(340 [EL 1])**. Although the ezetimibe and fenofibrate combination moderately improves LDL-C, it substantially improves triglyceride and HDL-C levels; see Table 18 **(39 [EL 1], 59 [EL 1], 62 [EL 1], 66 [EL 1], 83 [EL 3], 103 [EL 2], 105 [EL 1], 338 [EL 1], 355 [EL 1], 376 [EL 1], 453 [EL 1], 454 [EL 4], 455 [EL 1], 456 [EL 1], 457 [EL 1])** and Table 19 **(37 [EL 1], 85 [EL 1], 86 [EL 1], 102 [EL 1], 106 [EL 1], 107 [EL 1], 287 [EL 1], 340 [EL 1], 353 [EL 3], 458 [EL 1], 459 [EL 4], 460 [EL 1], 461 [EL 1], 462 [EL 2])**.

Examples include statin + fibrate; statin + niacin; statin + bile acid sequestrant; ezetimibe + fibrate; or ezetimibe + niacin. The National Institutes of Health AIM-HIGH study (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides) failed to show a cardiovascular outcome benefit with the addition of niacin in patients treated with statins and an average LDL-C of 71 mg/dL **(493 [EL 1])**. The HPS2-THRIVE trial (Treatment of HDL to Reduce the Incidence of Vascular Events from the HPS research unit) is an ongoing large international trial of high-dosage, extended-release niacin (results expected

in 2013) that should help clarify the role of simvastatin in combination with niacin **(93 [EL 4])**.

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, and cholesterol absorption inhibitors (ezetimibe). The primary metabolic effects and main drawbacks of these 5 drug classes are summarized in Table 14 **(42 [EL 4], 43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4]) (49 [EL 1]) (50 [EL 4], 51 [EL 4], 52 [EL 4], 53 [EL 3], 54 [EL 4], 55 [EL 4], 56 [EL 3], 57 [EL 4], 58 [EL 1], 59 [EL 1], 60 [EL 1], 61 [EL 1], 62 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 57 [EL 4], 66 [EL 1], 67 [EL 1], 68 [EL 2], 69 [EL 1], 70 [EL 2], 71 [EL 1], 72 [EL 2], 73 [EL 2], 74 [EL 2], 75 [EL 1], 76 [EL 2], 77 [EL 1], 78 [EL 3])**. The clinical efficacy of these pharmacologic agents in both primary and secondary prevention of coronary events and mortality is outlined in Table 18 **(39 [EL 1], 59 [EL 1], 62 [EL 1], 66 [EL 1], 83 [EL 3], 103 [EL 2], 105 [EL 1], 338 [EL 1], 355 [EL 1], 376 [EL 1], 453 [EL 1], 454 [EL 4], 455 [EL 1], 456 [EL 1], 457 [EL 1])**, and Table 19 **(37 [EL 1], 85 [EL 1], 86 [EL 1], 102 [EL 1], 106 [EL 1], 107 [EL 1], 287 [EL 1], 340 [EL 1], 353 [EL 3], 458 [EL 1], 459 [EL 4], 460 [EL 1], 461 [EL 1], 462 [EL 2])**. A summary of available lipid-lowering therapies and dosages is presented in Table 21 **(494 [EL 1], 495 [EL 1])**.

Statins

Statins are the drug of choice for LDL-C reduction; agents currently available are atorvastatin, fluvastatin lovastatin, pravastatin, rosuvastatin, and simvastatin. Since the publication of the 4S trial (Scandinavian Simvastatin Survival Study) in 1994, 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 20.

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 **(45 [EL 4], 46 [EL 4], 47 [EL 4], 496 [EL 4])**. 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 triglycerides (10% to 30%) and raise HDL-C by 2% to 10% **(43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4])**. Recent, preliminary studies also suggest that statin therapy (particularly atorvastatin) may improve LDL subfraction profiles, although

Table 21
Comparison of Statin Effects on Lipids After 6 Weeks of Treatment in Men and Women With Low-Density Lipoprotein Cholesterol ≥160 mg/dL and ≤250 mg/dL[a,b]
(n = 2431) (494 [EL 1], 495 [EL 1])

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) (292 [EL 1]) trials, pravastatin had a slightly greater triglyceride-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 low-density lipoprotein cholesterol levels from 192 to 244 mg/dL (n = 534).

[c] High-density lipoprotein cholesterol increase was with the lowest atorvastatin dosage, and benefit decreased as dosage increased.

[d] Not to be used at dosages of 80 mg unless patient has been on treatment for more than 12 months.

larger clinical trials are necessary to confirm the effect of statins on LDL particle size and density **(497 [EL 3], 498 [EL 2], 499 [EL 3], 500 [EL 2], 509 [EL 3], 502 [EL 3], 503 [EL 2], 504 [EL 1])**. Additionally, results of the HPS study (Heart Protection Study) suggest that simvastatin may somewhat improve CAD risk among persons who smoke cigarettes, although this benefit does not approach that achieved with smoking cessation **(37 [EL 1])**.

A meta-analysis of 14 randomized clinical trials conducted by the Cholesterol Treatment Trialists' (CTT) group involving more than 90 000 participants confirmed the benefit of LDL-C lowering with a statin. The CTT found that, over approximately 5 years, a 1 mmol/L (~38 mg/dL) reduction in LDL-C resulted in a 23% decrease in major coronary events (MI or CAD death), a 24% reduction in coronary revascularizations, and a 17% reduction in fatal or nonfatal stroke (Fig. 2) **(484 [EL 1])**. Treatment also led to a 12% reduction in all-cause mortality compared with that observed in control participants (P<.0001 for all) (Fig. 3) **(484 [EL 1])**.

Benefits of statin therapy were found to be similar in a CTT analysis of patients with diabetes, irrespective of whether there was a history of vascular disease. However, a recent 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, CVD events were decreased to a greater extent in the intensively treated group than was the increased risk of diabetes (ie, 6.5 fewer

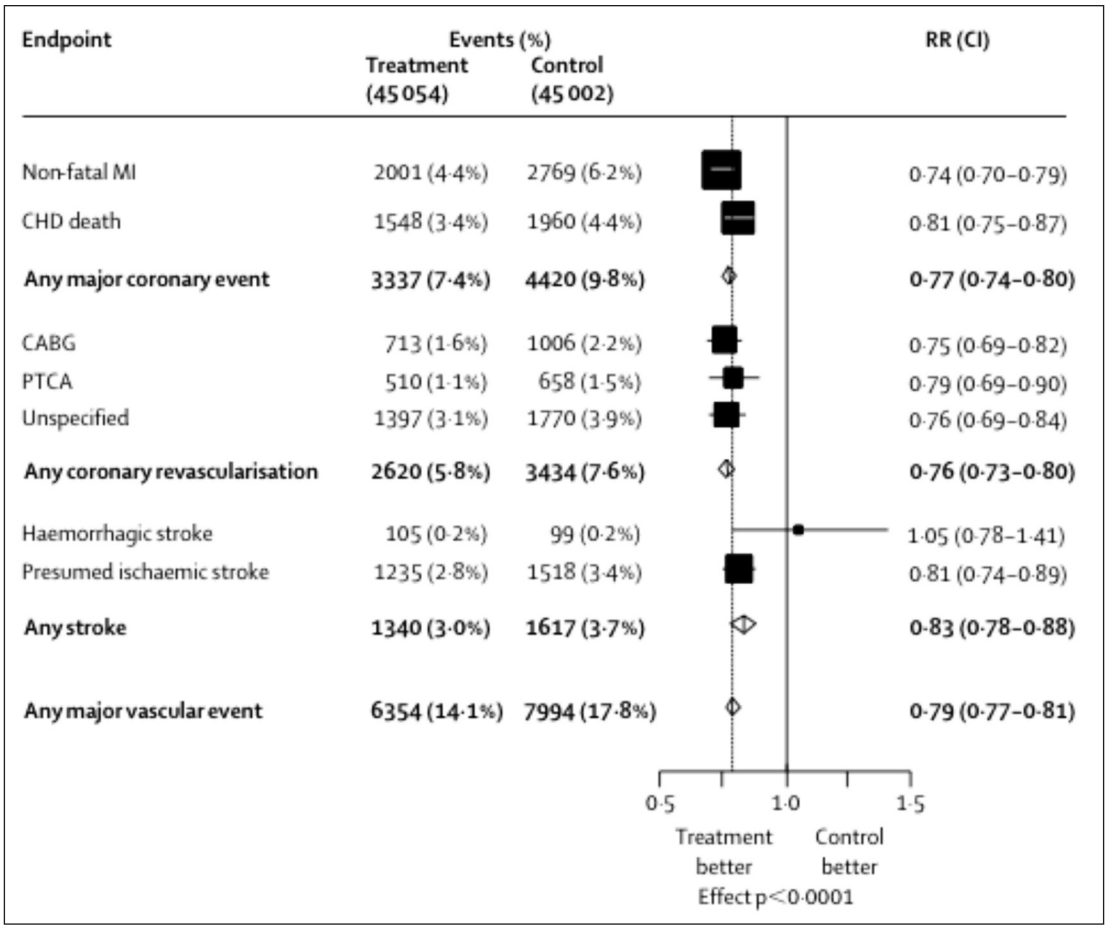

Fig. 2. Meta-analysis of proportional effects on major vascular events per mM/L low-density lipoprotein cholesterol reduction in 90 056 participants in 14 randomized trials of statins over a mean period of 5 years **(484 [EL 1])** (Cholesterol Treatment Trialists' Collaborators, 2005). Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; RR, relative risk. Reprinted from *The Lancet*, Vol 366, Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, 1267-1278, Copyright (2005), with permission from Elsevier.

cases of cardiovascular events per 1000 patient years vs 2 additional cases per 1000 patient years of diabetes in the intensively treated group) **(49 [EL 1])**.

Recently, the JUPITER trial (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin), a randomized, double-blind, placebo-controlled study of statin therapy among patients with moderate to low LDL-C (<130 mg/dL) but elevated highly sensitive CRP (≥2.0 mg/L) (n = 17 802), was halted ahead of schedule. The primary endpoint was first occurrence of a major cardiovascular event (eg, nonfatal MI, nonfatal stroke, 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 **(338 [EL 1], 454 [EL 4])**. Median follow-up in this trial was 1.9 years; maximal follow-up was 5 years **(338 [EL 1])**. During the study period, the primary endpoint occurred in 142 and 251 patients in the rosuvastain and placebo groups, respectively; this translated to a relative hazard reduction of 44% in the rosuvastatin group (95% confidence interval, 0.46-0.69; *P*<.00001) **(338 [EL 1])**. At 12 months, median LDL-C, triglycerides, and highly sensitive CRP levels were 50%, 17%, and 37% lower, respectively,

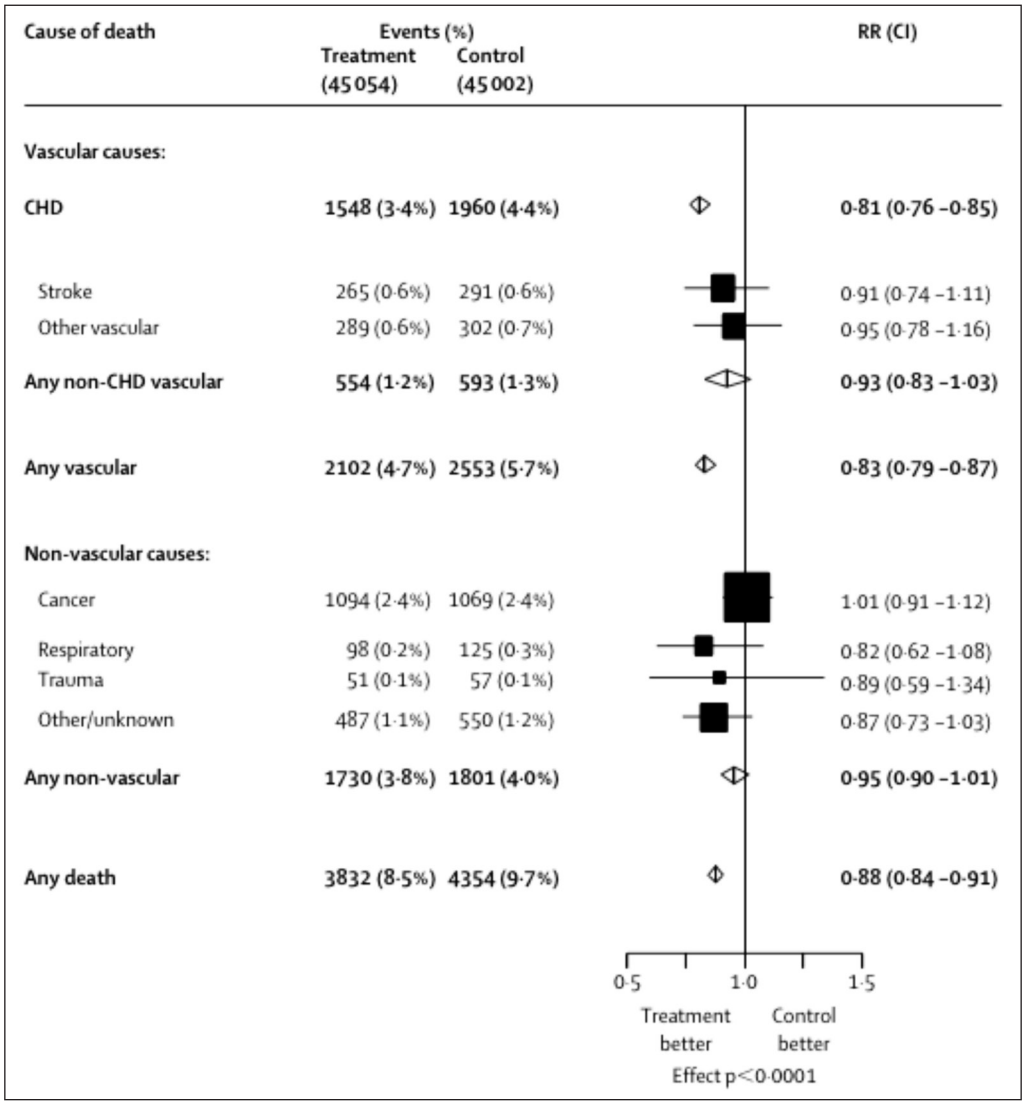

Fig. 3. Meta-analysis of proportional effects on cause-specific mortality per mM/L low-density lipoprotein cholesterol reduction in 90 056 participants in 14 randomized trials of statins over a mean period of 5 years **(484 [EL 1])** (Cholesterol Treatment Trialists' Collaborators, 2005). Abbreviations: CHD, coronary heart disease; CI, confidence interval; RR, relative risk. Reprinted from *The Lancet*, Vol 366, Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, 1267-1278, Copyright (2005), with permission from Elsevier.

in the rosuvastatin group than in the placebo group **(338 [EL 1])**. Further analysis of JUPITER study results has revealed a 79% CVD event reduction in participants who achieved both an LDL-C concentration less than 70 mg/dL and highly sensitive CRP concentration less than 1.0 mg/L **(451 [EL 2])**.

An analysis of surviving patients from the WOSCOPS study (West of Scotland Coronary Prevention 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 posttrial period ($P = .11$), and 19% during the total follow-up period ($P = .01$). Relative risk reduction for a composite endpoint (CAD-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 ($P<.001$) **(505 [EL 2])**.

The clinically demonstrated lipid-altering effects of various statins in various dosage ranges are shown in Table 21 **(494 [EL 1], 495 [EL 1])**. These data are from the CURVES study (Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin) **(495 [EL 1])** and the STELLAR study (Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin) and are generally representative of rates reported in the literature **(494 [EL 1])**.

Statins: Imaging Studies

Several studies have applied imaging techniques to assess the effect of statin treatment on coronary atherosclerosis regression and progression. Table 17 **(339 [EL 1], 340 [EL 1], 341 [EL 1], 342 [EL 1], 343 [EL 1], 344 [EL 3], 345 [EL 1])** outlines the key statin imaging trials conducted to date. The MARS study (Monitored Atherosclerosis Regression Study) 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 ($P = .005$) **(339 [EL 1])**. More recently, the REVERSAL trial (Reversal of Atherosclerosis with Aggressive Lipid Lowering) 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) **(341 [EL 1])**. In the ASTEROID study (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden), a regimen of rosuvustatin, 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 **(342 [EL 1])**. The imaging arm of the HATS study (HDL-Atherosclerosis Treatment Study) found that the combination of simvastatin and niacin decreased proximal stenosis by 0.4% vs an increase of 3.9% with placebo **(340 [EL 1])**. However, in a comparison of high-dosage atorvastatin therapy (80 mg daily) vs moderate-dosage (10 mg daily) over 1 year of treatment, Schmermund and colleagues found no difference in coronary artery calcification progression as measured by electron-beam computed tomography **(343 [EL 1])**. An unpublished 12-month trial, CASHMERE (Carotid Atorvastatin Study in Hyperlipidemic, Postmenopausal Women: a Randomized Evaluation of Atorvastatin versus Placebo), studied the effect of atorvastatin on carotid IMT in postmenopausal women (median age, 57 years). This study found no significant difference in mean carotid IMT change from baseline in patients treated with 40-mg daily atorvastatin or 80-mg daily atorvastatin compared with placebo (2.9% and 2.5% change, respectively) **(506 [EL 4])**, raising the possibility that carotid IMT may have limitations as a surrogate marker for CAD. Very recent data directly comparing intensive (maximal dosage) therapy of atorvastatin and rosuvustatin showed that despite the lower LDL-C level and the 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 **(507 [EL 2])**.

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 (ie, macrolide antibiotics, antifungal agents, and cyclosporine) **(43 [EL 4], 44 [EL 4], 47 [EL 4], 43 [EL 4], 44 [EL 4], 47 [EL 4])**. The most common adverse events associated with statin drugs include hepatic, renal, and musculoskeletal complications. A recent meta-analysis of 35 randomized controlled trials covering more than 74 000 patients identified the following rates of adverse events associated with statin use:

- Myalgia (musculoskeletal pain/symptoms without documented creatine kinase elevations): 15.4% **(508 [EL 3])**
- Liver toxicity (serum alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal): 1.4% **(508 [EL 3])**
- Creatine kinase elevations: 0.9% **(508 [EL 3])**
- Myopathy/rhabdomyolysis (muscle aches/weakness with creatine kinase levels ≥10 times the upper limit of normal): 0.2% **(508 [EL 3])**

In this meta-analysis, rates of myalgia and myopathy/rhabdomyolysis were not statistically different from placebo **(508 [EL 3])**. 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 go underreported, and patients 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 **(508 [EL 3], 509 [EL 4], 510 [EL 3])**. Recent observational studies of patients in usual care settings have identified myalgia rates of 10% to 15% **(510 [EL 3], 511 [EL 3])**. Also, risk may increase with coadministration of other drugs or in patients with a history of renal insufficiency **(43 [EL 4], 44 [EL 4], 45 [EL 4], 46 [EL 4], 47 [EL 4], 48 [EL 4], 107 [EL 1], 461 [EL 1], 494 [EL 1], 512 [EL 1], 513 [EL 1], 514 [EL 3])**. 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 **(508 [EL 3], 515 [EL 3])**.

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. Patients who have tolerated an 80-mg dosage for more than 1 year may continue therapy, but patients' regimens should no longer be increased to such dosages. A recent warning states that simvastatin, 80 mg daily, should not be used with amlodipine or ranolazine **(44 [EL 4])**.

Statins are known to be teratogenic (pregnancy category X); however other medications such as fibrates (pregnancy category C) or colesevelam (pregnancy category B) may be more appropriate.

Fibrates

Fibrates are effective for treating patients with severe hypertriglyceridemia and for patients at risk of CAD who have elevated triglycerides and/or low HDL-C levels as their primary lipid abnormality **(8 [EL 4], 363 [EL 4], 364 [EL 3], 516 [EL 1])**. Currently available fibrates are gemfibrozil, fenofibrate, and fenofibric acid. Fibrates appear to act by multiple mechanisms, including peroxisome proliferator–activated receptor α agonism leading to up-regulation of genes encoding lipoprotein lipase and apo AI, down-regulation of the gene encoding apo CIII, inhibition of lipoprotein lipase, and reduction of apo B and VLDL-C production **(517 [EL 4])**.

Clinical trials indicate that fibrates lower triglycerides by 20% to 35% and increase HDL-C by 6% to 18%. Trials such as the VA-HIT study (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial) **(351 [EL 1])** and the Helsinki Heart Study **(355 [EL 1])** have additionally demonstrated that fibrate monotherapy decreases cardiovascular events in men with or without CAD. Two angiographic trials supported these metabolic findings and revealed an independent effect of fibrate therapy on lesion progression **(462 [EL 2], 518 [EL 1])**. A secondary outcome, intention-to-treat analysis of VA-HIT found that major coronary events among patients with insulin resistance were increased in every tertile of HDL-C or triglyceride levels; gemfibrozil reduced events in these patients at a significant rate of 28%, compared with 20% in non–insulin-resistant patients **(519 [EL 1])**. 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 **(519 [EL 1])**.

Primary prevention of ischemic cardiovascular events with the use of fibrates was demonstrated only in patients with both triglyceride levels greater than 200 mg/dL and HDL-C levels less than 40 mg/dL in the FIELD study (Secondary Endpoints from the Fenofibrate Intervention and Event Lowering in Diabetes) **(83 [EL 3])**. The FIELD study showed that triglyceride reduction over 5 years with fenofibrate was associated with reduced nonfatal CVD events and revascularizations **(83 [EL 3])**. An independent relationship between fibrate therapy and CVD mortality was not identified; however, this may have been because of substantial statin use in the placebo group **(83 [EL 3])**. In the nonstatin BIP study (Bezafibrate Infarction Prevention Trial) **(86 [EL 1])**, a reduction in the primary endpoint of fatal or nonfatal MI or sudden death for patients with triglyceride values greater than 200 mg/dL was observed. The 18-year follow-up of the Helsinki Heart Study found that patients in the original gemfibrozil group had a 23% lower relative risk of CAD mortality than the original placebo group. Among those in the highest baseline tertile for both body mass index and triglyceride level, this risk reduction was 71% in the gemfibrozil group, corresponding to a 50% reduction in CAD mortality **(84 [EL 2])**. The failure to reach the primary endpoint targets of MI and cardiovascular death in the FIELD study **(83 [EL 3])** and in the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) **(87 [EL 1])** has resulted in an uncertain clinical benefit in treating patients with fibrates who have lesser triglyceride and HDL-C abnormalities.

In patients 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 **(348 [EL 1])**. Unlike gemfibrozil, fenofibrate can also reduce total cholesterol and LDL-C in patients with type IIb hyperlipidemia **(516 [EL 1])**.

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 **(53 [EL 3], 54 [EL 4])**. Therefore, the mechanism of action is unclear, although it has been suggested that the peroxisome proliferator–activated receptor α agonist action of the drugs may impair the generation of vasodilatory prostaglandins **(54 [EL 4])**. 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 **(53 [EL 3], 54 [EL 4])**. Although rare, fibrate use has been associated with myositis, myalgia/myopathy, or rhabdomyolysis; this risk increases with concomitant statin therapy **(50 [EL 4], 51 [EL 4])**. Various studies have shown that fenofibrate increases homocysteine levels, while gemfibrozil has no consistent effect **(77 [EL 1], 78 [EL 3], 520 [EL 1], 521 [EL 3])**. Similarly, fenofibrate has been shown to reduce fibrinogen, while gemfibrozil has shown inconsistent effects on fibrinogen across different studies **(68 [EL 2], 69 [EL 1], 70 [EL 2], 86 [EL 1], 462 [EL 2], 522 [EL 2], 523 [EL 3], 524 [EL 3])**.

Niacin

Niacin is a potent LDL-C– and triglyceride-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: (a) immediate-release (crystalline) niacin is available both as an over-the-counter dietary supplement and by prescription; (b) long-acting niacin, also called sustained-release or time-release niacin, is only sold over-the-counter as a non–US Food and Drug Administration–approved supplement; and (c) extended-release niacin is approved by the US Food and Drug Administration for lipid lowering and is available by prescription **(525 [EL 4])**. The 3 formulations perform similarly, although a recent review by Meyers et al indicates that certain over-the counter no-flush niacin preparations may not contain free nicotinic acid, thus compromising their efficacy **(526 [EL 4])**. The discrete preparations also have unique adverse effect profiles (described in the following text). The multiple effects of niacin on lipid metabolism include suppression of lipolysis, reduced hepatic synthesis of triglycerides and VLDL-C secretion, increased apo B degradation, and decreased catabolism of HDL-C **(525 [EL 4])**.

Niacin may produce a more favorable lipid response than fibrates, particularly with regard to HDL-C. Because it decreases lipoprotein (a), niacin may be preferable for patients with lipoprotein (a) elevations **(527 [EL 1], 528 [EL 2], 529 [EL 3], 530 [EL 3])**, but the possible preventive benefits of this have not been studied. The ADMIT study (Arterial Disease Multiple Intervention Trial) and the ADVENT study (Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial) showed HDL-C increases of 29% and 19% to 24%, respectively, vs placebo **(531 [EL 1], 532 [EL 1])**. In the CDP study (Coronary Drug Project), 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 **(88 [EL 2], 533 [EL 1], 534 [EL 3], 535 [EL 1])**.

In combination with statins or cholesterol absorption inhibitors, niacin has been associated with angiographic evidence of reduced progression and some regression of atheromatous plaques **(340 [EL 1], 353 [EL 3], 450 [EL 2], 536 [EL 1], 537 [EL 3])**. The HATS trial (HDL-Atherosclerosis Treatment Study), which evaluated a niacin and statin combination, showed favorable results for patients with the dyslipidemic triad **(89 [EL 1])**. The AIM-HIGH study (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides) study **(91 [EL1])**, a large, multicenter, phase III trial sponsored by the National Heart, Lung, and Blood Institute, 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 patients whose on-statin LDL-C concentration averaged 71 mg/dL. Furthermore, there was an increase in ischemic strokes in the group treated with niacin: 28 strokes (1.6%) reported during the trial among participants taking high-dose, extended-release niacin vs 12 strokes (0.7%) reported in the control group **(493 [EL 1])**. The HPS2-THRIVE study (Treatment of HDL to Reduce the Incidence of Vascular Events) is an ongoing, very large international trial of high-dosage, extended-release niacin plus simvastatin (results expected in 2013) that should help clarify the role of simvastatin in combination with niacin **(93 [EL 4])**.

Blood glucose elevations have been associated with higher dosages of niacin, particularly in patients with diabetes. However, results from the ADMIT **(531 [EL 1])**, **ADVENT (532 [EL 1])**, and HATS **(89 [EL 1])** 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 patients with diabetes were able to effectively adjust their antidiabetic medications to address blood glucose alterations **(340 [EL 1], 531 [EL 1], 532 [EL 1])**. A recent reanalysis 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 mg/dL, 107 mg/dL, and 108 mg/dL, respectively. Placebo changes from a baseline of 100 mg/dL were 101 mg/dL, 102 mg/dL, and 104 mg/dL, respectively. Similarly, 1-hour plasma glucose levels in the niacin group went from 168 mg/dL at baseline to 179 mg/dL, 179 mg/dL, 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 mg/dL, 165 mg/dL, and 170 mg/dL at 1, 2, and 4 years, respectively **(533 [EL 1])**. These blood glucose changes did not provoke any substantial changes to diabetes therapy. In addition, the reduced risk for cardiovascular events and total mortality was consistent across all baseline fasting and 1-hour plasma glucose groups **(533 [EL 1])**.

Flushing may occur in most patients 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) **(80 [EL 4], 525 [EL 4])**. In placebo-controlled trials of extended-release niacin, flushing occurs in as many as 88% of patients; however, discontinuation due to flushing was less than 6% **(80 [EL 4], 353 [EL 3], 532 [EL 1])**. Flushing can be ameliorated by pretreating with aspirin or a nonsteroidal anti-inflammatory agent **(80 [EL 4])**. Flushing and other adverse effects can also be considerably reduced by slowly titrating the dosage upward **(80 [EL 4])**.

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 **(538 [EL 4])**.

At full dosage, bile acid sequestrants reduce LDL-C by 15% to 25% and increase HDL-C by 4% to 8% **(539 [EL 2], 540 [EL 1], 541 [EL 3], 542 [EL 4], 543 [EL 2], 544 [EL 1])**. In one major primary prevention trial, the LRC-CPPT study (Lipid Research Clinics Coronary Primary Prevention Trial), cholestyramine reduced major coronary artery disease events by 19% **(545 [EL 1])**. Additionally, the recent GLOWS study (Glucose-Lowering Effect of WelChol Study) demonstrated that colesevelam significantly lowered plasma glucose among patients with type 2 diabetes **(56 [EL 3])**; a series of larger phase III clinical trials have been conducted to confirm this outcome, although results have not yet been published **(546 [EL 4], 547 [EL 4], 548 [EL 4], 549 [EL 4])**. In January 2008, the US Food and Drug Administration approved colesevelam as an adjunct glucose-lowering therapy for adults with type 2 diabetes **(55 [EL 4])**.

Bile acid sequestrants have been shown to have high discontinuation rates because of adverse events, especially in the gastrointestinal tract **(550 [EL 3], 551 [EL 2])**. However, colesevelam, a newer agent, appears to be better tolerated **(457 [EL 1], 540 [EL 1])**. Bile acid sequestrants may cause either no change or a modest rise (≤11%) in triglycerides. Caution should therefore be applied when treating patients with elevated triglyceride levels **(32 [EL 4], 55 [EL 4], 79 [EL 4], 540 [EL 1], 541 [EL 3], 542 [EL 4], 543 [EL 2], 544 [EL 1])**.

Cholesterol Absorption Inhibitors

Cholesterol absorption inhibitors primarily reduce LDL-C and may also have beneficial effects on triglycerides, apo B, and HDL-C. Current 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 **(59 [EL 1], 552 [EL 4])**.

Trials demonstrate that ezetimibe reduces LDL-C by 10% to 25%, with significant, favorable changes in triglycerides, apo B, and, in some trials, HDL-C **(58 [EL 1], 59 [EL 1], 61 [EL 1])**. 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% **(60 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1])** and among patients not at LDL-C goal, significantly improved goal attainment (65-81%) compared with statin-only treatment (17%-22%) **(60 [EL 1], 63 [EL 3], 64 [EL 1], 65 [EL 1], 553 [EL 1])**. Two multicenter, randomized, double-blind, placebo-controlled trials found that ezetimibe and simvastatin combination therapy reduced LDL-C levels by 53% **(62 [EL 1], 492 [EL 1])**. The efficacy of ezetimibe and simvastatin combination has not yet been compared with that of lovastatin, 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%) **(554 [EL 1], 555 [EL 1])**. Ezetimibe is also effective when coadministered with fenofibrate, reducing LDL-C by an additional 20% to 22% **(66 [EL 1], 67 [EL 1])**.

Recently, the ENHANCE trial (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) studied the effect of the ezetimibe and simvastatin combination in patients with heterozygous familial hypercholesterolemia using a surrogate endpoint of carotid artery IMT **(556 [EL 4])**. Results indicated no benefit from the addition of ezetimibe to statin therapy **(344 [EL 3])**; 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 **(557 [EL 4])**. The population in this study was highly select; since heterozygous familial

hypercholesterolemia affects only 2.2% of the population, this is a dyslipidemia type not typical of patients seen in daily practice and this probably contributed to participants' high mean baseline LDL-C level of 319 mg/dL. Moreover, baseline IMT 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 patients with a history of statin use. Most important, however, is the fact that ENHANCE was not a clinical endpoint trial. An ongoing CVD outcome trial comparing ezetimibe/simvastatin with simvastatin, IMPROVE-IT (Improved Reduction of Outcomes and Vytorin Efficacy International Trial), is expected to conclude in June 2013 **(558 [EL 4])** and should provide a comprehensive analysis of the ezetimibe and simvastatin combination **(558 [EL 4])**. The SHARP study (Study of Heart and Renal Protection) has just been published and 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 patients with advanced chronic kidney disease. Also of interest are recent, preliminary results from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis). This 4-year, randomized, placebo-controlled study, which enrolled 1873 men and women with asymptomatic aortic stenosis found that while the primary endpoint (a composite of cardiovascular outcomes) was not achieved, ischemic events, a secondary endpoint, were significantly reduced by 20% among patients taking ezetimibe, 10 mg daily, and simvastatin, 40 mg daily, compared with findings in the placebo group.

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 **(66 [EL 1], 512 [EL 1], 513 [EL 1])**. Ezetimibe's recycling via enterohepatic circulation and its elimination half-life of about 22 hours make it easy to administer in oral form **(59 [EL 1], 60 [EL 1], 512 [EL 1], 513 [EL 1])**.

Special Considerations: Drug Therapy in Women

In light of the diagnostic challenges that present when trying to identify CAD 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 **(94 [EL 1])**. Furthermore, although lowering LDL-C significantly reduces CAD risk in women, the unique roles of hormonal change over the lifetime of a woman, HDL-C, and triglycerides must also be addressed.

For all women at *high risk*, the following treatment approach is recommended **(25 [EL 4])**:

- 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.
- A diet low in saturated fat (<7%), cholesterol (<200 mg/day), and trans fat

For all women at *intermediate risk*, the following treatment approach is recommended **(25 [EL 4])**:

- 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 CAD included only middle-aged men **(94 [EL 1])**. Although few clinical trials have evaluated lipid-lowering in women specifically **(200 [EL 4])**, men and women have been equally represented in most major statin trials **(94 [EL 1])**. In a meta-analysis of 5 randomized, placebo-controlled primary and secondary prevention trials (n = 30 817) to assess the impact of statins on CAD 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 **(94 [EL 1])**. The HPS study (Heart Protection Study), a randomized, placebo-controlled trial of simvastatin to reduce LDL-C, reported similar findings in a population of 20 536 men and women with CAD, other occlusive arterial disease, or diabetes **(37 [EL 1])**. 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 **(37 [EL 1])**.

The JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) was a primary prevention trial that enrolled a large number of women (n = 6800) with LDL-C levels less than 130 mg/dL and highly sensitive CRP levels 2 mg/L or greater. JUPITER found that women taking rosuvastatin, 20 mg daily, vs placebo showed a 46% reduction in cardiovascular events, very similar to the reduction in men of 42% **(338 [EL 1])**. 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 triglycerides; and increased numbers of small, dense LDL-C particles) **(10 [EL 4])**. Treatment with these drugs

also produces a moderate decrease in CAD risk **(10 [EL 4])**.

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 triglycerides at all dosage levels for both men and women. Mean percentage reductions in LDL-C and triglycerides were greater in women than in men (for example, –28.7% vs –17.7% for LDL-C, $P = .006$, and –51.0% vs –41.6% for triglycerides, not significant, at the highest dosage of 3000 mg daily) **(559 [EL 1])**.

In a randomized 3-month trial of hormone replacement therapy (HRT) vs a lipid-lowering fibrate (gemfibrozil) in overweight women with elevated triglycerides (n = 77), both HRT and gemfibrozil lowered LDL-C. Mean percentage change in HDL-C was +10.4% for the gemfibrozil group vs –8.1% for HRT; and mean percentage change in triglycerides was –49.1% for the gemfibrozil group vs –11.8% for the HRT group **(560 [EL 3])**. Additionally, a recent analysis of 4271 elderly women (older than 65 years) in the general population found that, independent of HRT status, those taking a fibrate had a better lipid profile (lower total cholesterol, triglycerides, and non–HDL-C) than those taking a statin or no lipid-lowering agents **(561 [EL 3])**. Finally, in the FIELD trial (Fenofibrate Intervention and Event Lowering in Diabetes) trial (n = 9795), fenofibrate produced significant reductions relative to placebo ($P = .05$) in total cholesterol (–11.4%), LDL-C (–12.0%), and triglycerides (–28.6%) at 4 months in men and women aged 50 to 75 years with type 2 diabetes mellitus. Fenofibrate also produced increases relative to placebo in HDL-C (+5.1%, $P = .05$) **(83 [EL 3])**. Over the 5-year course of the study, fenofibrate reduced the risk of CVD events compared with placebo ($P = .035$), primarily in those with triglyceride values greater than 200 mg/dL, and significantly reduced diabetes-related microvascular complications **(83 [EL 3])**.

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 WHI (Women's Health Initiative), a 15-year longitudinal study of morbidity and mortality in more than 160 000 healthy, postmenopausal women (average age 63 years at baseline) **(562 [EL 4])**, found a lack of cardioprotective effect associated with HRT. Although estrogen replacement did reduce LDL-C and increase HDL-C, it also increased triglycerides and small, dense LDL particles, 2 of the 3 components that characterize atherogenic dyslipidemia **(10 [EL 4])**. Based on this, WHI findings are consistent with previous trials in which HRT was not shown to protect against CAD or stroke. 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 CAD risk **(562 [EL 4])**. Overall, these data support the short-term use of HRT to relieve moderate or severe vasomotor symptoms, but not long-term use to prevent CAD in postmenopausal women. Furthermore, given the differences in risks and benefits based on age and duration of menopause, physicians should assess each patient individually to determine if, and for how long, HRT should be used **(563 [EL 4])**. 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. Because 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 cornerstone of pediatric dyslipidemia management and are recommended for all patients with LDL-C levels greater than 110 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 **(303 [EL 4])**, as well as on patient needs. In all cases, AACE recommends that selection among this age group for pharmacologic therapy 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 triglyceride and insulin concentrations, and lower body fat percentages than those who were physically inactive **(564 [EL 2])**.

When evaluating the need for lipid-lowering drug therapy in pediatric patients, 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 CAD risk (eg, familial hypercholesterolemia and familial combined hyperlipidemia) **(447 [EL 4], 565 [EL 4])**. Clinical evidence does indicate that the ability to reverse the major atherogenic effects of childhood dyslipidemia is diminished if

treatment is delayed until adulthood **(565 [EL 4], 566 [EL 4], 567 [EL 3], 568 [EL 3], 569 [EL 4]**). 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 patients with high LDL-C values (≥130 mg/dL), pharmacotherapy is generally reserved for those with severe dyslipidemia or genetic lipid disorders **(26 [EL 4]**). In particular, patients with an LDL-C concentration of 190 mg/dL or greater, or patients with an LDL-C concentration greater than 160 mg/dL and either 2 or more CAD risk factors or a family history of premature CAD (before age 55 years) should be considered candidates for pharmacotherapy. If necessary, smoking cessation should also be implemented **(570 [EL 3]**).

As such, AACE recommends considering drug therapy in children and adolescents older than 8 years who satisfy the following criteria:

- 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])**
    - Being overweight, being obese, or having other elements of the insulin resistance syndrome, *or*
    - A family history of premature CAD (before age 55 years)

Additionally, the American Academy of Pediatrics recommends that pediatric patients with diabetes be considered for pharmacologic intervention if they have an LDL-C concentration of 130 mg/dL or greater **(305 [EL 4]**).

Statins

A number of statins (atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin) have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older **(43 [EL 4], 44 [EL 4], 47 [EL 4], 48 [EL 4], 571 [EL 4]**), and there is increasing evidence to support the use of these agents in children and adolescents at high risk. Recent studies have demonstrated the efficacy of statin treatment in pediatric patients, including LDL-C reductions of 20% to 40% **(572 [EL 3], 573 [EL 1], 574 [EL 1], 575 [EL 4], 576 [EL 4], 577 [EL 3], 578 [EL 1], 579 [EL 1], 580 [EL 1]**). For example, a 1-year study of adolescent boys with heterozygous familial hypercholesterolemia 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 **(580 [EL 1]**). In another investigation, pravastatin treatment (20 to 40 mg daily) in children with familial hypercholesterolemia 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 **(574 [EL 1]**). Based on available evidence, the American Academy of Pediatrics considers statins a safe and effective medication for the treatment of dyslipidemia in pediatric patients at high risk **(305 [EL 4]**).

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 **(55 [EL 4], 79 [EL 4]**). 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 recent evidence indicates that these effects may be achieved with relatively low dosages. As such, to maximize tolerability in pediatric patients, therapy should be initiated at low dosages (<8 g daily of cholestyramine

Table 22
Initial Bile Acid Sequestrant Dosage Schedule for the Treatment of Familial Hypercholesterolemia in Children and Adolescents

No. of daily doses	Total cholesterol, mg/dL	Low-density lipoprotein cholesterol, mg/dL
1	<245	<195
2	245-300	195-235
3	301-345	236-280
4	>345	>280

or <10 g daily of colestipol) regardless of body weight. Table 22 outlines a recommended initial dosage schedule for bile acid sequestrant therapy in children with familial hypercholesterolemia.

Because bile acid sequestrant treatment may lead to nutrient depletion (eg, folic acid and cholecalciferol) in children, multivitamin supplementation should be used **(303 [EL 4], 581 [EL 1], 582 [EL 1])**. Bile acid sequestrants should not be used in children with hypertriglyceridemia **(303 [EL 4], 583 [EL 2])**.

Other Agents

Fibrates

Fibrates may be useful in children with severely elevated triglyceride levels and an increased risk of pancreatitis **(27 [EL 4])**. 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 pediatric patients.

Ezetimibe

On the basis of studies demonstrating similar pharmacokinetic profiles in adolescents and adults, ezetimibe may be prescribed in patients 10 to 18 years of age. Until data are available for younger patients, ezetimibe is not recommended for children younger than 10 years. Thus far, ezetimibe has only been prescribed for children and adolescents with homozygous familial hypercholesterolemia or sitosterolemia (a rare hereditary lipid disorder characterized by increased absorption and decreased biliary excretion of dietary sterols, resulting in hypercholesterolemia) **(584 [EL 2])**. Ezetimibe and statin combination therapy is currently being investigated for the treatment of children with heterozygous familial hypercholesterolemia **(27 [EL 4])**.

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 **(585 [EL 3])**.

4Q3.3. Follow-Up and Monitoring

Patients' lipid status should be reassessed 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved. Thereafter, patients should be tested at 6- to 12-month intervals. The specific interval should depend on patient adherence to therapy and lipid profile consistency. If adherence is a concern or the lipid profile is unstable, the patient will likely benefit from biannual assessment **(10 [EL 4])**.

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 (eg, semiannually). Patients taking niacin should have transaminase levels measured at baseline and every 3 months thereafter for the first year, followed by periodic (eg, semiannual) assessment **(10 [EL 4], 80 [EL 4])**.

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

Certain clinical circumstances warrant more frequent lipid status evaluation:

- Deterioration of diabetes control.
- The patient starts a new drug known to affect lipid levels.
- The patient's atherothrombotic disease progresses.
- The patient gains considerable weight.
- A recent lipid profile reveals an unexpected adverse change in any lipid parameter.
- The patient develops a new CAD risk factor.
- 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 triglycerides should be part of each follow-up assessment. If the physician determines that the patient is not at optimal lipid goals or if the patient'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], 115 [EL 4], 586 [EL 2], 587 [EL 4], 588 [EL 3])**.

Consultation with an endocrinologist or lipid specialist is recommended when:

- Abnormal lipid levels persist despite intensive treatment efforts
- Uncontrolled diabetes and dyslipidemia coexist
- Atherothrombotic disease progresses despite favorable lipid levels

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

Although there are no commonly agreed upon thresholds for cost-effectiveness analyses, interventions are

typically 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, borderline cost-effective when the cost per QALY is between $50 000 and $100 000, and generally not cost-effective as the cost per QALY further increases. Another commonly used parameter, incremental cost-effectiveness ratios, reflect the ratio of cost savings as compared with life years gained **(10 [EL 4], 589 [EL 4])**. 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 CAD 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 1383 patients 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 gained due to stanol use for all men aged 40 years and older and for women aged 60 years and older **(590 [EL 3])**.

Another study compared the LDL-C–lowering effects of usual patient 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 patients receiving usual care **(591 [EL 4])**. 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, triglycerides, HDL-C, and body mass index, only 50% of eligible patients required antihyperlipidemic medications. This led to an annual cost savings of $27 449 or $638.35 per patient **(592 [EL 3])**.

Smoking Cessation

Although smoking cessation is not necessarily a lipid-lowering treatment, the dramatic impact of smoking on CAD requires its inclusion in any discussion of CAD reduction. Cost-effectiveness studies have demonstrated that smoking cessation programs are a highly economical strategy to improve long-term cardiovascular outcomes **(593 [EL 4], 594 [EL 4], 595 [EL 3], 596 [EL 4])**.

A 2007 randomized trial of 4614 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 **(597 [EL 4])**.

A 2007 model used data from the Framingham Heart Study and the 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 3742 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 **(594 [EL 4])**.

A 2008 model compared the efficacy and cost-effectiveness of varenicline, a recently approved smoking cessation therapy, vs buproprion, 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 US adult smokers making a 1-time attempt to quit. From a cost-effectiveness standpoint, varenicline dominated all other treatments and prevented the largest number of smoking-related deaths **(595 [EL 3])**.

Pharmacologic Therapy

Statins

Overall, statins have proven cost-effective in both secondary and primary prevention of CVD events for individuals at moderate to high risk, or low-risk individuals whose LDL-C levels are very high. In particular, the cost-effectiveness of atorvastatin, pravastatin, and simvastatin has been evaluated in populations that cover both primary and secondary intervention 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 CAD or a CAD equivalent **(10 [EL 4])**.

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 patients. In the United States, primary atorvastatin treatment was cost-effective over 25- and 10-year periods among patients with type 2 diabetes; studies in both Spain and the United Kingdom also found primary intervention with atorvastatin cost-effective in patients with type 2 diabetes. In secondary intervention trials, US analyses found that treatment with high-dosage atorvastatin was moderately cost-effective ($34 000 per QALY) compared with conventional-dosage simvastatin in patients with stable CAD **(598 [EL 4])**.

A 2008 retrospective database analysis of 10 421 patients with CHD 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 patients achieving NCEP ATP III LDL-C goals; patients were also stratified by NCEP CAD risk. The analysis found that LDL-C reduction with rosuvastatin was significantly greater than with all other statins. The percentage of moderate/high-risk patients 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. Atorvastatin became generically available in November 2011.

Fibrates

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

A 2005 analysis compared generic gemfibrozil to fenofibrate in primary prevention of coronary heart disease in a hypothetical cohort of US male and female participants aged 45 to 74 years with low levels of HDL-C, but without preexisting 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 for females. In the comparison model, lovastatin monotherapy was more cost-effective than fibrate monotherapy for all groups except men 45 years and older **(599 [EL 4])**.

An analysis of a 1998 Veteran's Administration study comparing gemfibrozil vs placebo for raising HDL-C and lowering triglyceride levels in men 74 years of age with a history of CAD, 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 **(600 [EL 3])**.

Cholesterol Absorption Inhibitors

Although no long-term US studies exist to evaluate the cost-effectiveness of cholesterol absorption inhibitors, ezetimibe coadministered with statin therapy in patients unable to meet target LDL-C levels has been identified as a cost-effective strategy to meet LDL-C goals in studies from Canada and the United Kingdom.

A Canadian model compared the cost-effectiveness of adding ezetimibe to atorvastatin therapy vs atorvastatin titration or adding the bile acid sequestrant cholestyramine for lowering LDL-C in patients classified as being at very high risk for a CAD event. Compared with fixed or titrated atorvastatin treatment, ezetimibe coadministration was determined to be the most cost-effective therapy evaluated **(601 [EL 3])**. 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 patients with high baseline LDL-C, or for higher risk patients, such as those with diabetes or heterozygous familial hypercholesterolemia. However, the authors concluded that long-term, clinical endpoint trials would be needed to develop a more precise analysis **(602 [EL 3])**.

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 US 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 **(603 [EL 4], 604 [EL 3])**.

Niacin

Limited pharmacoeconomic data support the cost-effectiveness of niacin in combination with a statin in reaching targeted lipid goals.

A 2007 European study estimated the cost-effectiveness of adding extended-release niacin to statin treatment to raise HDL-C in patients with established CAD and low HDL-C. Overall, niacin plus statin treatment proved cost-effective, producing a 7.1% risk reduction for all CAD events. For high-risk groups who had diabetes and/or smoked cigarettes, cost-effectiveness was greater **(605 [EL 3])**. A 2004 analysis compared lovastatin plus extended-release niacin combination therapy with simvastatin monotherapy for lowering LDL-C and raising HDL-C in 2430 patients with LDL-C levels exceeding NCEP-targeted goals. For all patient groups, lovastatin plus extended-release niacin was found to be more cost-effective than simvastatin **(606 [EL 4])**.

ACKNOWLEDGMENT

We acknowledge the medical writing assistance of Caitlin Rothermel and Kate Mann, PharmD, and the evidence-ranking support of Zeina Habib, MD.

DISCLOSURE

Chair

Dr. Paul S. Jellinger reports that he has received speaker honoraria from Amylin Pharmaceuticals, Inc, Eli Lilly and Company, Merck & Co, Inc, and NovoNordisk A/S and has served on advisory boards for NovoNordisk A/S, Merck & Co, Inc, Boehringer Ingelheim, and Amylin Pharmaceuticals, Inc.

Task Force Members

Dr. Donald A. Smith reports that he has received advisory board honoraria from Abbott Laboratories.

Dr. Adi E. Mehta reports that he has served on the speakers' bureaus for Merck & Co, Inc, and Pfizer.

Dr. Om Ganda reports that he has received advisory board honoraria from Abbott Laboratories and speaker honoraria from Abbott Laboratories, AstraZeneca, Kowa Pharmaceuticals America, Inc, and GlaxoSmithKline plc.

Dr. Yehuda Handelsman reports that he has received research grant support from Boehringer Ingelheim, Daiichi Sankyo, Inc, GlaxoSmithKline plc, NovoNordisk A/S, Takeda Pharmaceutical Company Limited, sanofi-aventis U.S., XOMA, Tolerx, Inc; consultant fees from Daiichi Sankyo, Inc, Gilead, Genentech, Inc, GlaxoSmithKline plc, Merck & Co, Inc, XOMA, and Tolerx, Inc; and speakers' bureau honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Inc, GlaxoSmithKline, plc, Merck & Co, Inc, and Novo Nordisk A/S.

Dr. Helena W. Rodbard reports that she has received speakers' bureau honoraria from Merck & Co, Inc, Bristol-Myers Squibb, AstraZeneca, Amylin Pharmaceuticals, Inc, and Eli Lilly and Company; advisory committee honoraria from AstraZeneca; consulting fees from Biodel; and clinical research grant support from NovoNordisk A/S and sanofi-aventis U.S., LLC. She also reports that her spouse has received consulting fees from Kraft, LifeScan, Inc, sanofi-aventis U.S., LLC, and Amylin Pharmaceuticals, Inc, and speaker honoraria from Abbott Laboratories.

Dr. Mark D. Shepherd reports that he does not have any multiplicity of interest to disclose.

Dr. John A. Seibel reports that he has received speaker honoraria from Abbott Laboratories, Auxilium Pharmaceuticals, Inc, and Bristol-Myers Squibb.

Reviewers

Dr. Robert Kreisberg reports that he does not have any multiplicity of interest to disclose.

Dr. Ronald Goldberg reports that he has received research grant support from Abbott Laboratories, GlaxoSmithKline plc, and Roche Diagnostics.

REFERENCES

*Note: Reference sources are followed by an evidence level [EL] rating of 1, 2, 3, or 4. The strongest evidence levels (**EL 1** and **EL 2**) appear in red for easier recognition.*

1. **Roger VL, Go AS, Lloyd-Jones DM,** et al; American Heart Association Statistics Committee and Stroke Statistics Committee. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. (Errata in: *Circulation*. 2011;123:e240 and *Circulation*. 2011;124:e426). 2011;123:e18-e209. [EL 3]
2. **Nicholls S, Lundman P**. The emerging role of lipoproteins in atherogenesis: beyond LDL cholesterol. *Semin Vasc Med*. 2004;4:187-195. [EL 4]
3. **Wild SH, Byrne CD, Tzoulaki I, et al**. Metabolic syndrome, haemostatic and inflammatory markers, cerebrovascular and peripheral arterial disease: The Edinburgh Artery Study. *Atherosclerosis*. 2009;203:604-609. [EL 3]
4. **Rodriguez-Colon SM, Mo J, Duan Y, et al**. Metabolic syndrome clusters and the risk of incident stroke: the atherosclerosis risk in communities (ARIC) study. *Stroke*. 2009;40:200-205. [EL 3]
5. **Cohen JD, Cziraky MJ, Cai Q, et al**. 30-year trends in serum lipids among United States adults: results from the National Health and Nutrition Examination Surveys II, III, and 1999-2006. (Erratum in: *Am J Cardiol*. 2010;106:1826). *Am J Cardiol*. 2010;106:969-975. [EL 3]
6. **Jellinger PS, Dickey RA, et al**; AACE Lipid Guidelines Committee; The American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis. (Erratum in: *Endocr Pract*. 2008;14:802-903). *Endocr Pract*. 2000;6:162-213. [EL 4]
7. **Handelsman Y, Mechanick JI, Blonde L, et al; AACE Task Force for Developing Diabetes Comprehensive Care Plan.** American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract*. 2011;17(Suppl 2):1-53. [EL 4]

8. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA*. 1993;269:3015-3023. [EL 4]
9. **Mechanick JI, Camacho PM, Cobin RH, et al**. American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Practice Guidelines--2010 update. *Endocr Pract*. 2010;16:270-283. [EL 4]
10. **National Institutes of Health; National Heart Lung, and Blood Institute; 2002 National Cholesterol Education Program**. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III): Final Report. NIH Publication No. 02-5215. September 2002. [EL 4]
11. **American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Writing Committee**. American Association of Clinical Endocrinologists Position Statement on Metabolic and Cardiovascular Consequences of Polycystic Ovary Syndrome. *Endocr Pract*. 2005;11:126-134. [EL 4]
12. **Einhorn D, Reaven GM, Cobin RH, et al**. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9:237-252. [EL 4]
13. **Grundy SM, Balady GJ, Criqui MH, et al**. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. *Circulation*. 1998;97:1876-1887. [EL 4]
14. **Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators**. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-952. **[EL 2]**
15. **American Diabetes Association**. Standards of medical care in diabetes--2009. *Diabetes Care*. 2009;32(Suppl 1):S13-S61. [EL 4]
16. **Neaton JD, Blackburn H, Jacobs D, et al**. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:1490-1500. **[EL 2]**
17. **US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program**. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 04-5230. August 2004. [EL 4]
18. **Stamler J, Wentworth D, Neaton JD**. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256:2823-2828. **[EL 2]**
19. **Kastelein JJ, van der Steeg WA, Holme I, et al; TNT Study Group; IDEAL Study Group**. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*. 2008;117:3002-3009. **[EL 2]**
20. **Brunzell JD, Davidson M, Furberg CD, et al; American Diabetes Association; American College of Cardiology Foundation**. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. 2008;31:811-822. [EL 4]
21. **Cromwell WC, Otvos JD, Keyes MJ, et al**. LDL Particle number and risk of future cardiovascular disease in the Framingham offspring study - implications for LDL management. *J Clin Lipidol*. 2007;1:583-592. [EL 3]
22. **Smith SC Jr, Allen J, Blair SN, et al; AHA/ACC; National Heart, Lung, and Blood Institute**. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. (Erratum in: *Circulation*. 2006;113:e847.) *Circulation*. 2006;113:2363-2372. [EL 4]
23. **Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association**. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239. [EL 4]
24. **Lloyd-Jones DM, Wilson PW, Larson MG, et al**. Framingham and risk score prediction of lifetime risk for coronary heart disease. *Am J Cardiol*. 2004;94:20-24. [EL 3]
25. **Mosca L, Appel LJ, Benjamin EJ, et al; American Heart Association.** Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*. 2004;109:672-693. [EL 4]
26. American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89:525-584. [EL 4]
27. **McCrindle BW, Urbina EM, Dennison BA, et al; American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee; American Heart Association Council of Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular Nursing**. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation*. 2007;115:1948-1967. [EL 4]
28. **US Preventive Services Task Force**. Screening for lipid disorders in children: US Preventive Services Task Force recommendation statement. *Pediatrics*. 2007;120:e215-e219. [EL 4]
29. **Rodbard HW, Blonde L, Braithwaite SS, et al; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force.** American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus (Erratum in *Endocr Pract*. 2008;14:802-803). *Endocr Pract*. 13(Suppl 1):1-68. [EL 4]
30. **Park CS, Ihm SH, Yoo KD, et al**. Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levels and leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA. *Am J Cardiol*. 2010;105:1284-1288. [EL 3]

31. **Veeranna V, Zalawadiya SK, Niraj A, et al**. Homocysteine and reclassification of cardiovascular disease risk. *J Am Coll Cardiol*. 2011;58:1025-1033. [EL 3]
32. **US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute**. Pediatric cardiovascular risk reduction initiative: background. Available at: http://www.nhlbi.nih.gov/guidelines/cvd_ped/background.htm. Accessed on September 25, 2008. [EL 4]
33. **Bonaa KH, Njolstad I, Ueland PM, et al**; **NORVIT Trial Investigators** Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med*. 2006;354:1578-1588. **[EL 1]**
34. **Lonn E, Yusuf S, Arnold MJ, et al; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators**. Homocysteine lowering with folic acid and B vitamins in vascular disease. (Erratum in: *N Eng J Med*. 2006;355:746). *N Engl J Med*. 2006;354:1567-1577. **[EL 1]**
35. **Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E; Heart Outcomes Prevention Evaluation 2 (HOPE-2) Investigators**. Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial. *Ann Intern Med*. 2007;146:761-767. **[EL 2]**
36. **Toole JF, Malinow MR, Chambless LE, et al**. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA*. 2004;291:565-575. **[EL 1]**
37. **Heart Protection Study Collaborative Group**. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22. **[EL 1]**
38. **Shepherd J, Blauw GJ, Murphy MB, et al; PROspective Study of Pravastatin in the Elderly at Risk**. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623-1630. **[EL 1]**
39. **Sever PS, Dahlof B, Poulter NR, et al; ASCOT investigators**. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-1158. **[EL 1]**
40. **Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E**. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. *J Am Coll Cardiol*. 2005;45:1644-1648. **[EL 1]**
41. **Barter PJ, Ballantyne CM, Carmena R, et al**. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259:247-258. [EL 4]
42. **International Food Information Council Foundation**. Functional Foods Fact Sheet: Plant Stanols and Sterols. Available at: http://www.foodinsight.org/Resources/Detail.aspx?topic=Functional_Foods_Fact_Sheet_Plant_Stanols_and_Sterols. Accessed for verification February 1, 2012. [EL 4]
43. Mevacor [prescribing information]. Whitehouse Station, NJ: Merck &Co; 2010. Available at: http://www.merck.com/product/usa/pi_circulars/m/mevacor/mevacor_pi.pdf. Accessed on August 4, 2011. [EL 4]
44. Zocor (simvastatin) [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; 2011. [EL 4]
45. Lescol (fluvastatin sodium) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; 2011. [EL 4]
46. Crestor (rosuvastatin calcium) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2011. [EL 4]
47. Lipitor (atorvastatin calcium) [prescribing information]. New York, NY: Pfizer; 2009. Available at: http://www.pfizer.com/files/products/uspi_lipitor.pdf. Accessed on August 4, 2011. [EL 4]
48. **American Diabetes Association**. Data from the 2011 National Diabetes Fact Sheet (released January 26, 2011). Available at: http://www.diabetes.org/diabetes-basics/diabetes-statistics/. Accessed for verification February 1, 2012. [EL 4]
49. **Preiss D, Seshasai SR, Welsh P, et al.** Risk of Incident Diabetes with Intensive-Dose Compared with Moderate-Dose Statin Therapy: A Meta-Analysis. *JAMA*. 2011;305:2556-2564. **[EL 1]**
50. Lopid (gemfibrozil) [prescribing information]. New York, NY: Parke-Davis (Pfizer); 2008. [EL 4]
51. Tricor (fenofibrate) [prescribing information]. North Chicago, IL: Abbott Laboratories; 2010. [EL 4]
52. Trilipix (fenofibric acid) [prescribing information]. North Chicago, IL: Abbott Laboratories; 2008. Available at: http://www.rxabbott.com/pdf/Trilipix_pi.pdf. Accessed March 20, 2009. [EL 4]
53. **Hottelart C, El Esper N, Rose F, Achard JM, Fournier A**. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. *Nephron*. 2002;92:536-541. [EL 3]
54. **Davidson MH, Armani A, McKenney JM, Jacobson TA**. Safety considerations with fibrate therapy. *Am J Cardiol*. 2007;99:3C-18C. [EL 4]
55. WelChol (colesevelam hydrochloride) [prescribing information]. Parsippany, NJ: Daiichi Sanko, Inc; 2011. [EL 4]
56. **Zieve FJ, Kalin MF, Schwartz SL, Jones MR, Bailey WL**. Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. *Clin Ther*. 2007;29:74-83. [EL 3]
57. Zetia (ezetimibe) [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; 2011. [EL 4]
58. **Bays HE, Moore PB, Drehobl MA, et al; Ezetimibe Study Group.** Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. (Erratum in: *Clin Ther*. 2001;23:1601). *Clin Ther*. 2001;23:1209-1230. **[EL 1]**
59. **Dujovne CA, Ettinger MP, McNeer JF, et al; Ezetimibe Study Group**. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. (Erratum in: *Am J Cardiol*. 2003;91:1399). *Am J Cardiol*. 2002;90:1092-1097. **[EL 1]**
60. **Gagne C, Bays HE, Weiss SR, et al; Ezetimibe Study Group**. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol*. 2002;90:1084-1091. **[EL 1]**
61. **Knopp RH, Dujovne CA, Le Beaut A, Lipka LJ, Suresh R, Veltri EP; Ezetimbe Study Group**. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two

controlled phase III clinical studies. *Int J Clin Pract*. 2003; 57:363-368. **[EL 1]**

62. **Bays HE, Ose L, Fraser N, et al; Ezetimibe Study Group**. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. *Clin Ther*. 2004;26:1758-1773. **[EL 1]**
63. **Bissonnette S, Habib R, Sampalis F, Boukas S, Sampalis JS; Ezetrol Add-On Investigators**. Efficacy and tolerability of ezetimibe 10 mg/day coadministered with statins in patients with primary hypercholesterolemia who do not achieve target LDL-C while on statin monotherapy: A Canadian, multicentre, prospective study--the Ezetrol Add-On Study. (Erratum in: *Can J Cardiol*. 2007;23:159). *Can J Cardiol*. 2006;22:1035-1044. [EL 3]
64. **Brohet C, Banai S, Alings AM, Massaad R, Davies MJ, Allen C**. LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. *Curr Med Res Opin*. 2005;21:571-578. **[EL 1]**
65. **Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM.** Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. *Diab Vasc Dis Res*. 2006;3:93-102. **[EL 1]**
66. **McKenney JM, Farnier M, Lo KW, et al**. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol*. 2006;47:1584-1587. **[EL 1]**
67. **Farnier M, Freeman MW, Macdonell G, et al; Ezetimibe Study Group.** Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J*. 2005;26:897-905. **[EL 1]**
68. **Aguilar-Salinas CA, Fanghanel-Salmón G, Meza E, et al**. Ciprofibrate versus gemfibrozil in the treatment of mixed hyperlipidemias: an open-label, multicenter study. *Metabolism*. 2001;50:729-733. **[EL 2]**
69. **Guyton JR, Blazing MA, Hagar J, et al**. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. *Arch Intern Med*. 2000;160:1177-1184. **[EL 1]**
70. **Insua A, Massari F, Rodríguez Moncalvo JJ, Rubén Zanchetta J, Insua AM.** Fenofibrate of gemfibrozil for treatment of types IIa and IIb primary hyperlipoproteinemia: a randomized, double-blind, crossover study. *Endocr Pract*. 2002;8:96-101. **[EL 2]**
72. **Durrington PN, Mackness MI, Bhatnagar D, et al**. Effects of two different fibric acid derivatives on lipoproteins, cholesteryl ester transfer, fibrinogen, plasminogen activator inhibitor and paraoxonase activity in type IIb hyperlipoproteinaemia. *Atherosclerosis*. 1998;138:217-225. **[EL 1]**
72. **Kockx M, de Maat MP, Knipscheer HC, et al.** Effects of gemfibrozil and ciprofibrate on plasma levels of tissue-type plasminogen activator, plasminogen activator inhibitor-1 and fibrinogen in hyperlipidaemic patients. *Thromb Haemost*. 1997;78:1167-1172. **[EL 2]**
73. **Bröijersén A, Hamsten A, Silveira A, et al.** Gemfibrozil reduces thrombin generation in patients with combined hyperlipidaemia, without influencing plasma fibrinogen, fibrin gel structure or coagulation factor VII. *Thromb Haemost*. 1996;76:171-176. **[EL 2]**
74. **Athyros VG, Papageorgiou AA, Avramidis MJ, Kontopoulos AG**. Long-term effect of gemfibrozil on coronary heart disease risk profile of patients with primary combined hyperlipidaemia. *Coron Artery Dis*. 1995;6:251-256. **[EL 2]**
75. **Avellone G, Di Garbo V, Cordova R, et al.** Improvement of fibrinolysis and plasma lipoprotein levels induced by gemfibrozil in hypertriglyceridemia. *Blood Coagul Fibrinolysis*. 1995;6:543-548. **[EL 1]**
76. **Bröijersen A, Eriksson M, Wiman B, Angelin B, Hjemdahl P**. Gemfibrozil treatment of combined hyperlipoproteinemia. No improvement of fibrinolysis despite marked reduction of plasma triglyceride levels. *Arterioscler Thromb Vasc Biol*. 1996;16:511-516. **[EL 2]**
77. **Syvänne M, Whittall RA, Turpeinen U, et al**. Serum homocysteine concentrations, gemfibrozil treatment, and progression of coronary atherosclerosis. *Atherosclerosis*. 2004;172:267-272. **[EL 1]**
78. **Westphal S, Dierkes J, Luley C**. Effects of fenofibrate and gemfibrozil on plasma homocysteine. *Lancet*. 2001; 358:39-40. [EL 3]
79. Colestid (colestipol hydrochloride) [prescribing information]. New York, NY: Pfizer; 2006. [EL 4]
80. Niaspan (niacin extended-release) [prescribing information]. Cranbury, NJ: Kos Pharmaceuticals, Inc; 2007. [EL 4]
81. Pravachol (pravastatin sodium) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2011. Available at: <http://packageinserts.bms.com/pi/pi_pravachol.pdf%3E. Accessed on August 4, 2011. [EL 4]
82. Livalo (pitavastatin) [prescribing information]. Montgomery, AL: Kowa Pharmaceuticals America, Inc; 2011. [EL 4]
83. **Keech A, Simes RJ, Barter P, et al; FIELD study investigators**. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. (Erratum in: *Lancet*. 2006;368:1415 and *Lancet*. 2006;368:1420). *Lancet*. 2005;366:1849-1861. [EL 3]
84. **Tenkanen L, Mänttäri M, Kovanen PT, Virkkunen H, Manninen V**. Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med*. 2006;166:743-748. **[EL 2]**
85. **Robins SJ, Collins D, Wittes JT, et al**. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA*. 2001;285:1585-1591. **[EL 1]**
86. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation*. 2000;102:21-27. **[EL 1]**
87. **Ginsberg HN, Elam MB, Lovato LC, et al**. Effects of combination lipid therapy in type 2 diabetes mellitus. (Erratum in: *N Engl J Med*. 2010;362:1748). *N Engl J Med*. 2010;362:1563-1574. **[EL 1]**
88. **Canner PL, Berge KG, Wenger NK, et al**. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245-1255. **[EL 2]**
89. **Vittone F, Chait A, Morse JS, Fish B, Brown BG, Zhao XQ**. Niacin plus Simvastatin Reduces Coronary Stenosis Progression Among Patients with Metabolic Syndrome Despite a Modest Increase in Insulin Resistance: A Subgroup Analysis of the HDL-Atherosclerosis Treatment Study (HATS). *J Clin Lipidol*. 2007;1:203-210. **[EL 1]**

90. **Villines TC, Stanek EJ, Devine PJ, et al**. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration. *J Am Coll Cardiol*. 2010;55:2721-2726. **[EL 1]**
91. **AIM-HIGH Investigators**. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. *Am Heart J*. 2011;161:538-543. **[EL 1]**
92. **Baigent C, Landray MJ, Reith C, et al; SHARP Investigators**. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181-2192. **[EL 1]**
93. **University of Oxford, Merck**. A randomized trial of the long-term clinical effects of raising HDL cholesterol with extended release niacin/laropiprant (HPS2-THRIVE). Clinical trial identifier NCT00461630. Accessed August 31, 2007 at http://www.clinicaltrials.gov. [EL 4]
94. **LaRosa JC, He J, Vupputuri S**. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340-2346. **[EL 1]**
95. **Smith SC Jr**. Multiple risk factors for cardiovascular disease and diabetes mellitus. *Am J Med*. 2007;120(3 Suppl 1):S3-S11. [EL 4]
96. **Qureshi AI, Suri MF, Kirmani JF, Divani AA.** The relative impact of inadequate primary and secondary prevention on cardiovascular mortality in the United States. *Stroke*. 2004;35:2346-2350. [EL 3]
97. **Assmann G, Cullen P, Schulte H**. The Munster Heart Study (PROCAM). Results of follow-up at 8 years. *Eur Heart J*. 1998;19(Suppl A):A2-A11. [EL 3]
98. **Assmann G, Schulte H, Cullen P**. New and classical risk factors--the Münster heart study (PROCAM). *Eur J Med Res*. 1997;2:237-242. **[EL 2]**
99. **Betteridge DJ**. Lipid management: past, present, and future. *Br J Clin Pract Suppl*. 1996;77A:1-10. [EL 4]
100. **Van Horn L, Kavey RE.** Diet and cardiovascular disease prevention: what works? *Ann Behav Med*. 1997;19:197-212. [EL 4]
101. **Pfeffer MA, Sacks FM, Moye LA, et al**. Influence of baseline lipids on effectiveness of pravastatin in the CARE Trial. Cholesterol And Recurrent Events. *J Am Coll Cardiol*. 1999;33:125-130. **[EL 2]**
102. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389. **[EL 1]**
103. **ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial**. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;288:2998-3007. **[EL 2]**
104. **Ray KK, Cannon CP, McCabe CH, et al; PROVE IT-TIMI 22 Investigators**. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2005;46:1405-1410. **[EL 1]**
105. **Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS investigators**. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696. **[EL 1]**
106. **Waters DD, LaRosa JC, Barter P, et al**. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. *J Am Coll Cardiol* 2006;48:1793-1799. **[EL 1]**
107. **Pedersen TR, Faergeman O, Kastelein JJ, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group**. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. (Erratum in: *JAMA*. 2005;28:3092). *JAMA*. 2005;294:2437-2445. **[EL 1]**
108. **Natarajan S, Glick H, Criqui M, Horowitz D, Lipsitz SR, Kinosian B**. Cholesterol measures to identify and treat individuals at risk for coronary heart disease. *Am J Prev Med*. 2003;25:50-57. **[EL 2]**
109. **Kinosian B, Glick H, Garland G**. Cholesterol and coronary heart disease: predicting risks by levels and ratios. *Ann Intern Med*. 1994;121:641-647. **[EL 2]**
110. **Castelli WP, Anderson K, Wilson PW, Levy D**. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol*. 1992;2:23-28. [EL 4]
111. **Barter P, Gotto AM, LaRosa JC, et al; Treating to New Targets Investigators**. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357:1301-1310. **[EL 2]**
112. **McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G**. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med*. 2003;139:802-809. [EL 3]
113. **Gualandri V, Franceschini G, Sirtori CR, et al**. AIMilano apoprotein identification of the complete kindred and evidence of a dominant genetic transmission. *Am J Hum Genet*. 1985;37:1083-1097. [EL 3]
114. **Sirtori CR, Calabresi L, Franceschini G, et al**. Cardiovascular status of carriers of the apolipoprotein A-I(Milano) mutant: the Limone sul Garda study. *Circulation*. 2001;103:1949-1954. [EL 3]
115. **Rubenfire M, Coletti AT, Mosca L**. Treatment strategies for management of serum lipids: lessons learned from lipid metabolism, recent clinical trials, and experience with the HMG CoA reductase inhibitors. *Prog Cardiovasc Dis*. 1998;41:95-116. [EL 4]
116. **Gordon DJ, Probstfield JL, Garrison RJ, et al**. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 1989;79:8-15. **[EL 2]**
117. **Harper CR, Jacobson TA**. New perspectives on the management of low levels of high-density lipoprotein cholesterol. *Arch Intern Med*. 1999;159:1049-1057. [EL 4]
118. **Mackness MI, Arrol S, Abbott C, Durrington PN**. Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. *Atherosclerosis*. 1993;104:129-135. [EL 4]
119. **Barter P**. HDL: a recipe for longevity. *Atheroscler Suppl*. 2004;5:25-31. [EL 4]

120. **Nikkilä M, Pitkäjärvi T, Koivula T, Heikkinen J**. Elevated high-density-lipoprotein cholesterol and normal triglycerides as markers of longevity. *Klin Wochenschr*. 1991;69:780-785. [EL 3]
121. **Nikkilä M, Heikkinen J**. High-density lipoprotein cholesterol and longevity. *Age Ageing*. 1990;19:119-124. [EL 3]
122. **Schaefer EJ, Moussa PB, Wilson PW, McGee D, Dallal G, Castelli WP**. Plasma lipoproteins in healthy octogenarians: lack of reduced high density lipoprotein cholesterol levels: results from the Framingham Heart Study. *Metabolism*. 1989;38:293-296. **[EL 2]**
123. **Gotto AM Jr**. Prognostic and therapeutic significance of low levels of high-density lipoprotein cholesterol: current perspectives. *Arch Intern Med*. 1999;159:1038-1040. [EL 4]
124. **Haffner SM**. Management of dyslipidemia in adults with diabetes. *Diabetes Care*. 1998; 21:160-178. [EL 4]
125. **National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases**. Diabetes in America, 2nd Edition. NIH Publication No. 95-1468. 1995. [EL 4]
126. **Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M**. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234. [EL 3]
127. **Sowers JR, Epstein M, Frohlich ED**. Diabetes, hypertension, and cardiovascular disease: an update. (Erratum in: *Hypertension*. 2001;37:1350). *Hypertension*. 2001;37:1053-1059. [EL 4]
128. **Boden G, Rao AK**. Effects of hyperglycemia and hyperinsulinemia on the tissue factor pathway of blood coagulation. *Curr Diab Rep*. 2007;7:223-227. [EL 4]
129. **Targher G, Bertolini L, Zoppini G, Zenari L, Falezza G**. Increased plasma markers of inflammation and endothelial dysfunction and their association with microvascular complications in Type 1 diabetic patients without clinically manifest macroangiopathy. *Diabet Med*. 2005;22:999-1004. [EL 3]
130. **Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH**. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes*. 2002;51:1157-1165. **[EL 2]**
131. **Frohlich J, Steiner G**. Dyslipidaemia and coagulation defects of insulin resistance. *Int J Clin Pract Suppl*. 2000;14-22. [EL 4]
132. **Garber AJ, Handelsman Y, Einhorn D, et al**. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract*. 2008;14:933-946. [EL 4]
133. **Orchard TJ, Olson JC, Erbey JR, et al**. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care*. 2003;26:1374-1379. **[EL 2]**
134. **Nikkilä EA, Hormila P**. Serum lipids and lipoproteins in insulin-treated diabetes. Demonstration of increased high density lipoprotein concentrations. *Diabetes*. 1978;27:1078-1086. [EL 4]
135. **Taskinen MR**. Quantitative and qualitative lipoprotein abnormalities in diabetes mellitus. *Diabetes*. 1992;41 (Suppl 2):12-17. [EL 4]
136. **Valsania P, Zarich SW, Kowalchuk GJ, Kosinski E, Warram JH, Krolewski AS**. Severity of coronary artery disease in young patients with insulin-dependent diabetes mellitus. *Am Heart J*. 1991;122:695-700. [EL 3]
137. **Libby P, Nathan DM, Abraham K, et al**; National Heart, Lung, and Blood Institute; National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. *Circulation*. 2005;111:3489-3493. [EL 4]
138. **Dabelea D, Kinney G, Snell-Bergeon JK, et al; Coronary Artery Calcification in Type 1 Diabetes Study**. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. (Erratum in: *Diabetes*. 2004;53:2177). *Diabetes*. 2003;52:2833-2839. [EL 3]
139. **Miettinen H, Lehto S, Salomaa V, et al**. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care*. 1998;21:69-75. [EL 3]
140. **Chun BY, Dobson AJ, Heller RF**. The impact of diabetes on survival among patients with first myocardial infarction. *Diabetes Care*. 1997;20:704-708. [EL 3]
141. **Ferguson JJ**. NHLI BARI clinical alert on diabetics treated with angioplasty. *Circulation*. 1995;92:3371. [EL 4]
142. **Rozenman Y, Sapoznikov D, Mosseri M, et al.** Long-term angiographic follow-up of coronary balloon angioplasty in patients with diabetes mellitus: a clue to the explanation of the results of the BARI study. Balloon Angioplasty Revascularization Investigation. *J Am Coll Cardiol*. 1997;30:1420-1425. [EL 3]
143. **Savage MP, Krolewski AS, Kenien GG, Lebeis MP, Christlieb AR, Lewis SM**. Acute myocardial infarction in diabetes mellitus and significance of congestive heart failure as a prognostic factor. *Am J Cardiol*. 1988;62:665-669. [EL 3]
144. **Orchard TJ, Stevens LK, Forrest KY, Fuller JH**. Cardiovascular disease in insulin dependent diabetes mellitus: similar rates but different risk factors in the US compared with Europe. *Int J Epidemiol*. 1998;27:976-983. [EL 3]
145. **Borch-Johnsen K, Kreiner S**. Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *Br Med J (Clin Res Ed)*. 1987;294:1651-1654. [EL 3]
146. **Lehto S, Rönnemaa T, Pyörälä K, Laakso M**. Poor glycemic control predicts coronary heart disease events in patients with type 1 diabetes without nephropathy. *Arterioscler Thromb Vasc Biol*. 1999;19:1014-1019. **[EL 2]**
147. **Alexander CM, Landsman PB, Teutsch SM, Haffner SM; Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP).** NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52:1210-1214. [EL 3]

148. **Mackness B, Hine D, McElduff P, Mackness M**. High C-reactive protein and low paraoxonase1 in diabetes as risk factors for coronary heart disease. *Atherosclerosis*. 2006;186:396-401. [EL 3]
149. **National Cholesterol Education Program**. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation*. 1994;89:1333-1445. [EL 4]
150. **Almgren T, Persson B, Wilhelmsen L, Rosengren A, Andersson OK**. Stroke and coronary heart disease in treated hypertension -- a prospective cohort study over three decades. *J Intern Med*. 2005;257:496-502. **[EL 2]**
151. **Andersson OK, Almgren T, Persson B, Samuelsson O, Hedner T, Wilhelmsen L**. Survival in treated hypertension: follow up study after two decades. *BMJ*. 1998;317:167-171. **[EL 2]**
152. **Nanchahal K, Ashton WD, Wood DA**. Association between blood pressure, the treatment of hypertension, and cardiovascular risk factors in women. *J Hypertens*. 2000;18:833-841. [EL 3]
153. **Boggia J, Li Y, Thijs L, et al; International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators**. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet*. 2007;370:1219-1229. **[EL 2]**
154. **Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB**. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-1847. [EL 3]
155. **US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, The President's Council on Physical Fitness and Sports**. Physical activity and health: a Report of the Surgeon General. Executive Summary. Atlanta, GA, 1996:1-14 [EL 4]
156. **Axelsen M, Eliasson B, Joheim E, Lenner RA, Taskinen MR, Smith U**. Lipid intolerance in smokers. *J Intern Med*. 1995;237:449-455. [EL 3]
157. **Cullen P, Schulte H, Assmann G**. Smoking, lipoproteins and coronary heart disease risk. Data from the Munster Heart Study (PROCAM). *Eur Heart J*. 1998;19:1632-1641. **[EL 2]**
158. **Freeman DJ, Griffin BA, Murray E, et al**. Smoking and plasma lipoproteins in man: effects on low density lipoprotein cholesterol levels and high density lipoprotein subfraction distribution. *Eur J Clin Invest*. 1993;23:630-640. [EL 3]
159. **Mero N, Van Tol A, Scheek LM, Van Gent T, Labeur C, Rosseneu M, Taskinen MR**. Decreased postprandial high density lipoprotein cholesterol and apolipoproteins A-I and E in normolipidemic smoking men: relations with lipid transfer proteins and LCAT activities. *J Lipid Res*. 1998;39:1493-1502. [EL 3]
160. **Razay G, Heaton KW**. Smoking habits and lipoproteins in British women. *QJM*. 1995;88:503-508. [EL 3]
161. **Schuitemaker GE, Dinant GJ, van der Pol GA, van Wersch JW**. Relationship between smoking habits and low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides in a hypercholesterolemic adult cohort, in relation to gender and age. *Clin Exp Med*. 2002;2:83-88. [EL 3]
162. **Maeda K, Noguchi Y, Fukui T**. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. *Prev Med*. 2003;37:283-290. **[EL 2]**
163. **Barrett-Connor E, Khaw K**. Family history of heart attack as an independent predictor of death due to cardiovascular disease. *Circulation*. 1984;69:1065-1069. **[EL 2]**
164. **Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring JE**. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation*. 2001;104:393-398. **[EL 2]**
165. **Shea S, Ottman R, Gabrieli C, Stein Z, Nichols A**. Family history as an independent risk factor for coronary artery disease. *J Am Coll Cardiol*. 1984;4:793-801. [EL 3]
166. **Superko HR**. Did grandma give you heart disease? The new battle against coronary artery disease. *Am J Cardiol*. 1998;82:34Q-46Q. [EL 4]
167. **Fornage M, Lopez DS, Roseman JM, Siscovick DS, Wong ND, Boerwinkle E**. Parental history of stroke and myocardial infarction predicts coronary artery calcification: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Eur J Cardiovasc Prev Rehabil*. 2004;11:421-426. **[EL 2]**
168. **Juonala M, Viikari JS, Räsänen L, Helenius H, Pietikäinen M, Raitakari OT**. Young adults with family history of coronary heart disease have increased arterial vulnerability to metabolic risk factors: the Cardiovascular Risk in Young Finns Study. *Arterioscler Thromb Vasc Biol*. 2006;26:1376-1382. **[EL 2]**
169. **Nasir K, Michos ED, Rumberger JA, et al**. Coronary artery calcification and family history of premature coronary heart disease: sibling history is more strongly associated than parental history. *Circulation*. 2004;110:2150-2156. [EL 3]
170. **NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US)**. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD: National Heart, Lung, and Blood Institute, 1998. [EL 4]
171. **Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM**. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006;295:1549-1555. [EL 3]
172. **Lamon-Fava S, Wilson PW, Schaefer EJ**. Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham Offspring Study. *Arterioscler Thromb Vasc Biol*. 1996;16:1509-1515. [EL 3]
173. **Thomas F, Bean K, Pannier B, Oppert JM, Guize L, Benetos A**. Cardiovascular mortality in overweight subjects: the key role of associated risk factors. *Hypertension*. 2005;46:654-659. [EL 3]
174. **Onat A, Sari I, Hergenc G, Yazici M, Uyarel H, Can G, Sansoy V**. Predictors of abdominal obesity and high susceptibility of cardiometabolic risk to its increments among Turkish women: a prospective population-based study. *Metabolism*. 2007;56:348-356. **[EL 2]**
175. **Onat A, Uyarel H, Hergenc G, Karabulut A, Albayrak S, Can G**. Determinants and definition of abdominal obesity as related to risk of diabetes, metabolic syndrome and coronary disease in Turkish men: a prospective cohort study. *Atherosclerosis*. 2007;191:182-190. **[EL 2]**
176. **Carr DB, Utzschneider KM, Hull RL, et al**. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes*. 2004;53:2087-2094. [EL 3]

177. **Nieves DJ, Cnop M, Retzlaff B, et al**. The atherogenic lipoprotein profile associated with obesity and insulin resistance is largely attributable to intra-abdominal fat. *Diabetes*. 2003;52:172-179. [EL 3]
178. **International Diabetes Federation**. IDF Consensus Worldwide Definition of the Metabolic Syndrome. Brussels, Belgium: IDF Communications, 2006: 1-24. Available at: http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf.1-24 [EL 4]
179. **Chait A, Brazg RL, Tribble DL, Krauss RM**. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med*. 1993;94:350-356. [EL 3]
180. **de Graaf J, Hak-Lemmers HL, Hectors MP, Demacker PN, Hendriks JC, Stalenhoef AF**. Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. *Arterioscler Thromb*. 1991;11:298-306. [EL 4]
181. **Krauss RM.** Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care*. 2004;27:1496-1504. [EL 4]
182. **Tribble DL, Holl LG, Wood PD, Krauss RM**. Variations in oxidative susceptibility among six low density lipoprotein subfractions of differing density and particle size. *Atherosclerosis*. 1992;93:189-199. [EL 4]
183. **Krauss RM**. Triglycerides and atherogenic lipoproteins: rationale for lipid management. *Am J Med*. 1998;105:58S-62S. [EL 4]
184. **Ballantyne CM**. Low-density lipoproteins and risk for coronary artery disease. *Am J Cardiol*. 1998;82:3Q-12Q. [EL 4]
185. **Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM**. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA*. 1988;260:1917-1921. [EL 3]
186. **Williams PT, Superko HR, Haskell WL, et al**. Smallest LDL particles are most strongly related to coronary disease progression in men. *Arterioscler Thromb Vasc Biol*. 2003;23:314-321. **[EL 2]**
187. **Gardner CD, Fortmann SP, Krauss RM**. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA*. 1996;276:875-881. **[EL 2]**
188. **Kuller L, Arnold A, Tracy R, et al**. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. *Arterioscler Thromb Vasc Biol*. 2002;22:1175-1180. **[EL 2]**
189. **Mora S, Szklo M, Otvos JD, et al**. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211-217. [EL 3]
190. **Austin MA, King MC, Vranizan KM, Krauss RM**. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation*. 1990;82:495-506. **[EL 2]**
191. **Garvey WT, Kwon S, Zheng D, et al.** Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003;52:453-462. [EL 4]
192. **Goff DC Jr, D'Agostino RB Jr, Haffner SM, Otvos JD**. Insulin resistance and adiposity influence lipoprotein size and subclass concentrations. Results from the Insulin Resistance Atherosclerosis Study. *Metabolism*. 2005;54:264-270. [EL 3]
193. **Pirwany IR, Fleming R, Greer IA, Packard CJ, Sattar N**. Lipids and lipoprotein subfractions in women with PCOS: relationship to metabolic and endocrine parameters. *Clin Endocrinol (Oxf)*. 2001;54:447-453. **[EL 2]**
194. **Assmann G, Schulte H, Funke H, von Eckardstein A**. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. *Eur Heart J*. 1998;19(Suppl M):M8-M14. **[EL 2]**
195. **Austin MA, Hokanson JE, Edwards KL**. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81:7B-12B. **[EL 2]**
196. **Aznaouridis K, Vlachopoulos C, Dima I, Ioakeimidis N, Stefanadis C**. Triglyceride level is associated with wave reflections and arterial stiffness in apparently healthy middle-aged men. *Heart*. 2007;93:613-614. [EL 3]
197. **Sarwar N, Danesh J, Eiriksdottir G, et al**. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115:450-458. **[EL 2]**
198. **Onat A, Sari I, Yazici M, Can G, Hergenc G, Avci GS**. Plasma triglycerides, an independent predictor of cardiovascular disease in men: a prospective study based on a population with prevalent metabolic syndrome. *Int J Cardiol*. 2006;108:89-95. **[EL 2]**
199. **Stampfer MJ, Krauss RM, Ma J, et al**. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA*. 1996;276:882-888. **[EL 2]**
200. **LaRosa JC**. Triglycerides and coronary risk in women and the elderly. *Arch Intern Med*. 1997;157:961-968. [EL 4]
201. **Jeppesen J, Hein HO, Suadicani P, Gyntelberg F**. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. (Erratum in: *Circulation*. 1998;97:1995). *Circulation*. 1998;97:1029-1036. **[EL 2]**
202. **Castelli WP**. The triglyceride issue: a view from Framingham. *Am Heart J*. 1986;112:432-437. [EL 4]
203. **Grundy SM**. Consensus statement: Role of therapy with "statins" in patients with hypertriglyceridemia. *Am J Cardiol*. 1998;81:1B-6B. [EL 4]
204. **Grundy SM.** Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol*. 1999;83:25F-29F. [EL 4]
205. **Assmann G, Schulte H**. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Prospective Cardiovascular Münster study. *Am J Cardiol*. 1992;70:733-737. **[EL 2]**
206. **Gotto AM Jr**. Triglyceride as a risk factor for coronary artery disease. *Am J Cardiol*. 1998;82:22Q-25Q. [EL 4]
207. **Kannel WB, Castelli WP, Gordon T**. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. *Ann Intern Med*. 1979;90:85-91. [EL 4]
208. **Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM**. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309-316. **[EL 2]**
209. **Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A**. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299-308. **[EL 2]**
210. **Chen YD, Swami S, Skowronski R, Coulston A, Reaven GM**. Differences in postprandial lipemia between patients with normal glucose tolerance and noninsulin-dependent

diabetes mellitus. *J Clin Endocrinol Metab*. 1993;76:172-177. [EL 3]

211. **Daugherty A, Lange LG, Sobel BE, Schonfeld G**. Aortic accumulation and plasma clearance of beta-VLDL and HDL: effects of diet-induced hypercholesterolemia in rabbits. *J Lipid Res*. 1985;26:955-963. [EL 4]
212. **Kolovou GD, Anagnostopoulou KK, Daskalopoulou SS, Mikhailidis DP, Cokkinos DV**. Clinical relevance of postprandial lipaemia. *Curr Med Chem*. 2005;12:1931-1945. [EL 4]
213. **Malmstrom R, Packard CJ, Caslake M, et al**. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. *Diabetologia*. 1997;40:454-462. [EL 3]
214. **Proctor SD, Mamo JC**. Retention of fluorescent-labelled chylomicron remnants within the intima of the arterial wall--evidence that plaque cholesterol may be derived from post-prandial lipoproteins. *Eur J Clin Invest*. 1998;28:497-503. [EL 4]
215. **Rapp JH, Lespine A, Hamilton RL, et al**. Triglyceride-rich lipoproteins isolated by selected-affinity anti-apolipoprotein B immunosorption from human atherosclerotic plaque. *Arterioscler Thromb*. 1994;14:1767-1774 [EL 4]
216. **Ginsberg HN, Kris-Etherton P, Dennis B, et al**. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the DELTA Study, protocol 1. *Arterioscler Thromb Vasc Biol*. 1998;18:441-449. **[EL 2]**
217. **Laufs U, Barter P**. HCS: Prospective evaluation of postprandial triglycerides and cardiovascular events in patients with coronary artery disease. Abstract presented at the European Society of Cardiology Congress; August 28, 2011; Paris, France [Session number 706003-706004]. **[EL 1]**
218. **Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L**. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. *Metabolism*. 2003;52:908-915. [EL 3]
219. **Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF 2nd, Fitzpatrick LA**. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2003;88:2562-2568. [EL 3]
220. **Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS**. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2004;89:5454-5461. **[EL 2]**
221. **Cibula D, Cífková R, Fanta M, Poledne R, Zivny J, Skibová J**. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. *Hum Reprod*. 2000;15:785-789. [EL 3]
222. **Dahlgren E, Janson PO, Johansson S, Lapidus L, Odén A**. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet Gynecol Scand*. 1992;71:599-604. [EL 3]
223. **Dahlgren E, Johansson S, Lindstedt G, et al**. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. *Fertil Steril*. 1992;57:505-513. [EL 3]
224. **Scanu AM**. Lipoprotein(a). A genetic risk factor for premature coronary heart disease. *JAMA*. 1992;267:3326-3329. [EL 4]
225. **Marcovina SM, Koschinsky ML**. Lipoprotein(a) as a risk factor for coronary artery disease. *Am J Cardiol*. 1998;82:57U-66U; discussion 86U. [EL 4]
226. **Danesh J, Collins R, Peto R**. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation*. 2000;102:1082-1085. **[EL 2]**
227. **Luc G, Bard JM, Arveiler D, et al; PRIME Study Group**. Lipoprotein (a) as a predictor of coronary heart disease: the PRIME Study. *Atherosclerosis*. 2002;163:377-384. **[EL 2]**
228. **Ridker PM, Hennekens CH, Stampfer MJ**. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA*. 1993;270:2195-2199. **[EL 2]**
229. **Ridker PM, Stampfer MJ, Hennekens CH**. Plasma concentration of lipoprotein(a) and the risk of future stroke. *JAMA*. 1995;273:1269-1273. **[EL 2]**
230. **Schaefer EJ, Lamon-Fava S, Jenner JL, et al**. Lipoprotein(a) levels and risk of coronary heart disease in men. The lipid Research Clinics Coronary Primary Prevention Trial. *JAMA*. 1994;271:999-1003. [EL 3]
231. **van Wissen S, Smilde TJ, Trip MD, de Boo T, Kastelein JJ, Stalenhoef AF**. Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia. *Heart*. 2003;89:893-896. **[EL 1]**
232. **Gaw A, Murray HM, Brown EA; PROSPER Study Group.** Plasma lipoprotein(a) [Lp(a)] concentrations and cardiovascular events in the elderly: evidence from the prospective study of pravastatin in the elderly at risk (PROSPER). *Atherosclerosis*. 2005;180:381-388. **[EL 2]**
233. **Sharrett AR, Ballantyne CM, Coady SA, et al; Atherosclerosis Risk in Communities Study Group**. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2001;104:1108-1113. **[EL 2]**
234. **Suk Danik J, Rifai N, Buring JE, Ridker PM**. Lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. *JAMA*. 2006;296:1363-1370. [EL 3]
235. **Marcovina SM, Albers JJ, Jacobs DR Jr, et al**. Lipoprotein[a] concentrations and apolipoprotein[a] phenotypes in Caucasians and African Americans. The CARDIA study. *Arterioscler Thromb*. 1993;13:1037-1045. [EL 3]
236. **Berg K, Dahlén G, Christophersen B, Cook T, Kjekshus J, Pedersen T**. Lp(a) lipoprotein level predicts survival and major coronary events in the Scandinavian Simvastatin Survival Study. *Clin Genet*. 1997;52:254-261. **[EL 1]**
237. **Mertens I, Van Gaal LF**. Visceral fat as a determinant of fibrinolysis and hemostasis. *Semin Vasc Med*. 2005;5:48-55. [EL 4]
238. **Skurk T, Hauner H**. Obesity and impaired fibrinolysis: role of adipose production of plasminogen activator inhibitor-1. *Int J Obes Relat Metab Disord*. 2004;28:1357-1364. [EL 4]
239. **Smith A, Patterson C, Yarnell J, Rumley A, Ben-Shlomo Y, Lowe G**. Which hemostatic markers add to the predictive value of conventional risk factors for coronary heart disease and ischemic stroke? The Caerphilly Study. *Circulation*. 2005;112:3080-3087. **[EL 2]**

240. **Trost S, Pratley R, Sobel B**. Impaired fibrinolysis and risk for cardiovascular disease in the metabolic syndrome and type 2 diabetes. *Curr Diab Rep*. 2006;6:47-54. [EL 4]
241. **Stec JJ, Silbershatz H, Tofler GH, et al**. Association of fibrinogen with cardiovascular risk factors and cardiovascular disease in the Framingham Offspring Population. *Circulation*. 2000;102:1634-1638. [EL 3]
242. **Folsom AR**. Fibrinogen and cardiovascular risk markers. *Blood Coagul Fibrinolysis*. 1999;10(Suppl 1):S13-16. [EL 4]
243. **Lowe G, Rumley A**. Clinical benefit of fibrinogen evaluation. *Blood Coagul Fibrinolysis*. 1999;10(Suppl 1):S87-89. [EL 4]
244. **Mehta P, Mehta JL**. Should fibrinogen be measured routinely in patients with unstable coronary heart disease? *Blood Coagul Fibrinolysis*. 1999;10(Suppl 1):S29-33. [EL 4]
245. **Montalescot G, Collet JP, Choussat R, Thomas D**. Fibrinogen as a risk factor for coronary heart disease. *Eur Heart J*. 1998;19(Suppl H):H11-17. [EL 4]
246. **Ridker PM**. Evaluating novel cardiovascular risk factors: can we better predict heart attacks? *Ann Intern Med*. 1999;130:933-937. [EL 4]
247. **Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH**. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973-979. **[EL 2]**
248. **Ridker PM, Hennekens CH, Buring JE, Rifai N**. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342:836-843. **[EL 2]**
249. **Ridker PM**. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation*. 2001;103:1813-1818. [EL 4]
250. **Ridker PM, Glynn RJ, Hennekens CH** C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation*. 1998;97:2007-2011. **[EL 2]**
251. **Koenig W, Khuseyinova N, Löwel H, Trischler G, Meisinger C**. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. *Circulation*. 2004;110:1903-1908. **[EL 2]**
252. **Ballantyne CM, Hoogeveen RC, Bang H, et al**. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2004;109:837-842. **[EL 2]**
253. **Caslake MJ, Packard CJ**. Lipoprotein-associated phospholipase A2 (platelet-activating factor acetylhydrolase) and cardiovascular disease. *Curr Opin Lipidol*. 2003;14:347-352. [EL 4]
254. **Häkkinen T, Luoma JS, Hiltunen MO, et al**. Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase, is expressed by macrophages in human and rabbit atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 1999;19:2909-2917. [EL 4]
255. **Laine P, Kaartinen M, Penttilä A, Panula P, Paavonen T, Kovanen PT**. Association between myocardial infarction and the mast cells in the adventitia of the infarct-related coronary artery. *Circulation*. 1999;99:361-369. [EL 4]
256. **MacPhee CH, Moores KE, Boyd HF, et al**. Lipoprotein-associated phospholipase A2, platelet-activating factor acetylhydrolase, generates two bioactive products during the oxidation of low-density lipoprotein: use of a novel inhibitor. *Biochem J*. 1999;338:479-487. [EL 4]
257. **Corsetti JP, Rainwater DL, Moss AJ, Zareba W, Sparks CE**. High lipoprotein-associated phospholipase A2 is a risk factor for recurrent coronary events in postinfarction patients. *Clin Chem*. 2006;52:1331-1338. [EL 3]
258. **Koenig W, Twardella D, Brenner H, Rothenbacher D**. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. *Arterioscler Thromb Vasc Biol*. 2006;26:1586-1593. **[EL 2]**
259. **Packard CJ, O'Reilly DS, Caslake MJ, et al**. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 2000;343:1148-1155. **[EL 2]**
260. **Andreotti F, Burzotta F, Mazza A, Manzoli A, Robinson K, Maseri A**. Homocysteine and arterial occlusive disease: a concise review. *Cardiologia*. 1999;44:341-345. [EL 4]
261. **Tyagi SC**. Homocyst(e)ine and heart disease: pathophysiology of extracellular matrix. *Clin Exp Hypertens*. 1999;21:181-198. [EL 4]
262. **Cattaneo M.** Hyperhomocysteinemia, atherosclerosis and thrombosis. *Thromb Haemost*. 1999;81:165-176. [EL 4]
263. **Nygård O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE**. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med*. 1997;337:230-236. **[EL 2]**
264. **Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M**. Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis*. 1989;78:145-150. **[EL 2]**
265. **Slunga L, Johnson O, Dahlén GH, Eriksson S**. Lipoprotein(a) and acute-phase proteins in acute myocardial infarction. *Scand J Clin Lab Invest*. 1992;52:95-101. [EL 3]
266. **Egerton W, Silberberg J, Crooks R, Ray C, Xie L, Dudman N**. Serial measures of plasma homocyst(e)ine after acute myocardial infarction. *Am J Cardiol*. 1996;77:759-761. **[EL 2]**
267. **Lindgren A, Brattström L, Norrving B, Hultberg B, Andersson A, Johansson BB**. Plasma homocysteine in the acute and convalescent phases after stroke. *Stroke*. 1995;26:795-800. **[EL 2]**
268. **Evans RW, Shaten BJ, Hempel JD, Cutler JA, Kuller LH**. Homocyst(e)ine and risk of cardiovascular disease in the Multiple Risk Factor Intervention Trial. *Arterioscler Thromb Vasc Biol*. 1997;17:1947-1953. **[EL 2]**
269. **Folsom AR, Nieto FJ, McGovern PG, et al**. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 1998;98:204-210. **[EL 2]**
270. **Stanger O, Herrmann W, Pietrzik K, et al**. Clinical use and rational management of homocysteine, folic acid, and B vitamins in cardiovascular and thrombotic diseases. *Z Kardiol*. 2004;93:439-453. [EL 4]
271. **Fang J, Alderman MH**. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA*. 2000;283:2404-2410. [EL 3]

272. **Solomon DH, Karlson EW, Rimm EB, et al**. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*. 2003;107:1303-1307. **[EL 2]**
273. **Hak AE, Karlson EW, Feskanich D, Stampfer MJ, Costenbader KH**. Systemic lupus erythematosus and the risk of cardiovascular disease: results from the nurses' health study. *Arthritis Rheum*. 2009;61:1396-1402. **[EL 2]**
274. **Papadakis JA, Sidiropoulos PI, Karvounaris SA, et al.** High prevalence of metabolic syndrome and cardiovascular risk factors in men with ankylosing spondylitis on anti-TNFalpha treatment: correlation with disease activity. *Clin Exp Rheumatol*. 2009;27:292-298. [EL 3]
275. **Grinspoon SK, Grunfeld C, Kotler DP, et al**. State of the science conference: Initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary. (Erratum in: *Circulation*. 2008;118:e109). *Circulation*. 2008;118:198-210. [EL 4]
276. **Oren A, Vos LE, Uiterwaal CS, Grobbee DE, Bots ML**. Cardiovascular risk factors and increased carotid intima-media thickness in healthy young adults: the Atherosclerosis Risk in Young Adults (ARYA) Study. *Arch Intern Med*. 2003;163:1787-1792. [EL 3]
277. **Paul TK, Srinivasan SR, Wei C, et al**. Cardiovascular risk profile of asymptomatic healthy young adults with increased femoral artery intima-media thickness: The Bogalusa Heart Study. *Am J Med Sci*. 2005;330:105-110. [EL 3]
278. **Tuzcu EM, Kapadia SR, Tutar E, et al**. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. *Circulation*. 2001;103:2705-2710. [EL 3]
279. **Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK**. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166:2307-2313. **[EL 1]**
280. **Goff DC Jr, Bertoni AG, Kramer H, et al**. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. *Circulation*. 2006;113:647-656. [EL 3]
281. **Harris RE, Backlund JY, Haley NJ, Wynder EL**. Population screening for plasma cholesterol: community-based results from Atlanta. *South Med J*. 1989;82:1370-1376. [EL 3]
282. **Harris RE, Haley NJ, Muscat JE, Wynder EL**. Population screening for plasma cholesterol: community-based results from Miami. *J Fla Med Assoc*. 1989.76:853-860. [EL 3]
283. **Wynder EL, Harris RE, Haley NJ**. Population screening for plasma cholesterol: community-based results from Connecticut. *Am Heart J*. 1989;117:649-656. [EL 3]
284. **Olsson AG, Schwartz GG, Szarek M, Luo D, Jamieson MJ**. Effects of high-dose atorvastatin in patients > or =65 years of age with acute coronary syndrome (from the myocardial ischemia reduction with aggressive cholesterol lowering [MIRACL] study). *Am J Cardiol*. 2007;99:632-635. [EL 4]
285. **Hoyert DL, Heron MP, Murphy SL, Kung HC.** Deaths: final data for 2003. *Natl Vital Stat Rep*. 2006;54:1-120. [EL 4]
286. **Thom T, Haase N, Rosamond W, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee**. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. (Erratum in: *Circulation*. 2006;113:e696 and *Circulation*. 2006;114:e630). *Circulation*. 2006;113:e85-151. [EL 4]
287. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339:1349-1357. **[EL 1]**
288. **Plehn JF, Davis BR, Sacks FM, et al**. Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. The Care Investigators. *Circulation*. 1999;99:216-223. **[EL 1]**
289. **Bugiardini R**. Women, 'non-specific' chest pain, and normal or near-normal coronary angiograms are not synonymous with favourable outcome. *Eur Heart J*. 2006;27:1387-1389. [EL 4]
290. **Bugiardini R, Bairey Merz CN.** Angina with "normal" coronary arteries: a changing philosophy. *JAMA*. 2005;293:477-484. [EL 4]
291. **Nasir K, Redberg RF, Budoff MJ, Hui E, Post WS, Blumenthal RS**. Utility of stress testing and coronary calcification measurement for detection of coronary artery disease in women. *Arch Intern Med*. 2004;164:1610-1620. [EL 4]
292. **Joseph A, Ackerman D, Talley JD, Johnstone J, Kupersmith J**. Manifestations of coronary atherosclerosis in young trauma victims--an autopsy study. *J Am Coll Cardiol*. 1993;22:459-467. [EL 3]
293. **McGill HC Jr, McMahan CA**. Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Am J Cardiol*. 1998;82:30T-36T. [EL 4]
294. **Davies H**. Atherogenesis and the coronary arteries of childhood. *Int J Cardiol*. 1990;28:283-291. [EL 4]
295. **Li S, Chen W, Srinivasan SR, et al.** Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. 2003;290:2271-2276. **[EL 2]**
296. **Klag MJ, Ford DE, Mead LA, et al**. Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med*. 1993;328:313-318. [EL 2]
297. **Newman WP 3rd, Freedman DS, Voors AW, et al**. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. *N Engl J Med*. 1986;314:138-144. [EL 3]
298. **Tracy RE, Newman WP 3rd, Wattigney WA, Berenson GS**. Risk factors and atherosclerosis in youth autopsy findings of the Bogalusa Heart Study. *Am J Med Sci*. 1995;310 (Suppl 1):S37-41. [EL 3]
299. **Strong JP, Malcom GT, McMahan CA, et al**. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA*. 1999;281:727-735. [EL 3]
300. **Jacobson MS.** Heart healthy diets for all children: no longer controversial. *J Pediatr*. 1998;133:1-2. [EL 4]
301. **Jacobson MS, Lillienfeld DE**. The pediatrician's role in atherosclerosis prevention. *J Pediatr.* 1988;112:836-841. [EL 4]
302. **Jacobson MS, Tomopoulos S, Williams CL, Arden MR, Deckelbaum RJ, Starc TJ.** Normal growth in high-risk hyperlipidemic children and adolescents with dietary intervention. *Prev Med*. 1998;27:775-780. **[EL 2]**
303. **Tonstad S.** A rational approach to treating hypercholesterolaemia in children. Weighing the risks and benefits. *Drug Saf*. 1997;16:330-341. [EL 4]

304. **Deckelbaum RJ.** Preventive nutrition in childhood: a rationale. *Public Health Rev*. 1996;24:105-111. [EL 4]
305. **Daniels SR, Greer FR; Committee on Nutrition**. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008;122:198-208. [EL 4]
306. **Akerblom HK, Chandra RK, Franklin FA, et al**. Conclusions, guidelines and recommendations from the IUNS/WHO Workshop: nutrition in the pediatric age group and later cardiovascular disease. *J Am Coll Nutr.* 1992;11(Suppl):1S-2S. [EL 4]
307. **American Academy of Pediatrics. Committee on Nutrition**. American Academy of Pediatrics. Committee on Nutrition. Cholesterol in childhood. *Pediatrics*. 1998; 101:141-147. [EL 4]
308. **Rifai N, Neufeld E, Ahlstrom P, Rimm E, D'Angelo L, Hicks JM**. Failure of current guidelines for cholesterol screening in urban African-American adolescents. *Pediatrics*. 1996;98:383-388. [EL 3]
309. **Kwiterovich PO Jr**. Biochemical, clinical, epidemiologic, genetic, and pathologic data in the pediatric age group relevant to the cholesterol hypothesis. *Pediatrics*. 1986;78:349-362. [EL 4]
310. **Kasim-Karakas SE.** Dietary fat controversy: is it also applicable to children? *Am J Clin Nutr*. 1998;67:1106-1107. [EL 4]
311. **Webber LS, Srinivasan SR, Wattigney WA, Berenson GS**. Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. *Am J Epidemiol*. 1991;133:884-899. [EL 3]
312. **Arslanian S, Suprasongsin C.** Insulin sensitivity, lipids, and body composition in childhood: is "syndrome X" present? *J Clin Endocrinol Metab*. 1996;81:1058-1062. [EL 3]
313. **Kavey RE, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K; American Heart Association**. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation*. 2003;107:1562-1566. [EL 4]
314. **Lindsey CC, Graham MR, Johnston TP, Kiroff CG, Freshley A**. A clinical comparison of calculated versus direct measurement of low-density lipoprotein cholesterol level. *Pharmacotherapy*. 2004;24:167-172. [EL 3]
315. **Nauck M, Warnick GR, Rifai N.** Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation. *Clin Chem*. 2002;48:236-254. [EL 4]
316. **Hopkins PN, Heiss G, Ellison RC, et al**. Coronary artery disease risk in familial combined hyperlipidemia and familial hypertriglyceridemia: a case-control comparison from the National Heart, Lung, and Blood Institute Family Heart Study. *Circulation*. 2003;108:519-523. [EL 3]
317. **Esteban-Salán M, Guimón-Bardesi A, de La Viuda-Unzueta JM, Azcarate-Ania MN, Pascual-Usandizaga P, Amoroto-Del-Río E**. Analytical and clinical evaluation of two homogeneous assays for LDL-cholesterol in hyperlipidemic patients. *Clin Chem*. 2000;46:1121-1131. [EL 4]
318. **Xydakis AM, Ballantyne CM**. Role of non-high-density lipoprotein cholesterol in prevention of cardiovascular disease: updated evidence from clinical trials. *Curr Opin Cardiol*. 2003;18:503-509. [EL 4]
319. **Hsia SH**. Non-HDL cholesterol: into the spotlight. *Diabetes Care*. 2003;26:240-242. [EL 4]
320. **Jialal I, Miguelino E, Griffen SC, Devaraj S**. Concomitant reduction of low-density lipoprotein-cholesterol and biomarkers of inflammation with low-dose simvastatin therapy in patients with type 1 diabetes. *J Clin Endocrinol Metab*. 2007;92:3136-3140. **[EL 2]**
321. **Lu W, Resnick HE, Jablonski KA, et al**. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. *Diabetes Care*. 2003;26:16-23. **[EL 2]**
322. **Bittner V, Hardison R, Kelsey SF, Weiner BH, Jacobs AK, Sopko G; Bypass Angioplasty Revascularization Investigation.** Non-high-density lipoprotein cholesterol levels predict five-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation*. 2002;106:2537-2542. **[EL 2]**
323. **Stein JH, Johnson HM**. Carotid intima-media thickness, plaques, and cardiovascular disease risk: implications for preventive cardiology guidelines. *J Am Coll Cardiol*. 2010;55:1608-1610. [EL 4]
324. **Sniderman AD**. Apolipoprotein B versus non-high-density lipoprotein cholesterol: and the winner is. *Circulation*. 2005;112:3366-3367. [EL 4]
325. **Karamanos BG, Thanopoulou AC, Roussi-Penesi DP**. Maximal post-prandial triglyceride increase reflects postprandial hypertriglyceridaemia and is associated with the insulin resistance syndrome. *Diabet Med*. 2001;18:32-39. [EL 3]
326. **Ooi TC, Ooi DS.** The atherogenic significance of an elevated plasma triglyceride level. *Crit Rev Clin Lab Sci*. 1998;35:489-516. [EL 4]
327. **Lefèbvre PJ, Scheen AJ**. The postprandial state and risk of cardiovascular disease. *Diabet Med*. 1998;15(Suppl 4):S63-68. [EL 4]
328. **Boquist S, Ruotolo G, Tang R, et al**. Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men. *Circulation*. 1999;100:723-728. [EL 3]
329. **Karpe F, Hellénius ML, Hamsten A**. Differences in postprandial concentrations of very-low-density lipoprotein and chylomicron remnants between normotriglyceridemic and hypertriglyceridemic men with and without coronary heart disease. *Metabolism*. 1999;48:301-307. [EL 3]
330. **Patsch JR, Miesenböck G, Hopferwieser T, et al**. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. *Arterioscler Thromb*. 1992;12:1336-1345. [EL 3]
331. **Cohn JS.** Postprandial lipemia and remnant lipoproteins. Clin Lab Med 2006;26:773-786. [EL 4]
332. **Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E**. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001;358:2026-2033. **[EL 2]**
333. **Shai I, Rimm EB, Hankinson SE, et al**. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. *Circulation*. 2004;110:2824-2830. **[EL 2]**
334. **Sattar N, Williams K, Sniderman AD, D'Agostino R Jr, Haffner SM**. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with other cardiovascular risk factors in patients with the metabolic syndrome in the Insulin Resistance Atherosclerosis Study. *Circulation*. 2004;110:2687-2693. [EL 3]
335. **Sniderman A, Williams K, Cobbaert C.** ApoB versus non-HDL-C: what to do when they disagree. *Curr Atheroscler Rep*. 2009;11:358-363. [EL 4]
336. **Ridker PM, Rifai N, Clearfield M, et al; Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators**. Measurement of C-reactive protein for

the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med*. 2001;344:1959-1965. **[EL 1]**

337. **Miller M, Zhan M, Havas S**. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors: the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2005;165: 2063-2068. [EL 3]
338. **Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group**. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-2207. **[EL 1]**
339. **Blankenhorn DH, Azen SP, Kramsch DM, et al; MARS Research Group**. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med*. 1993;119:969-976. **[EL 1]**
340. **Brown BG, Zhao XQ, Chait A, et al.** Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345: 1583-1592. **[EL 1]**
341. **Nissen SE, Tuzcu EM, Schoenhagen P, et al; REVERSAL Investigators**. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291: 1071-1080. **[EL 1]**
342. **Nissen SE, Nicholls SJ, Sipahi I, et al; ASTERIOD Investigators**. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295:1556-1565. **[EL 1]**
343. **Schmermund A, Achenbach S, Budde T, et al.** Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. *Circulation*. 2006;113:427-437. **[EL 1]**
344. **Kastelein JJ, Akdim F, Stroes ES, et al; ENHANCE Investigators.** Simvastatin with or without ezetimibe in familial hypercholesterolemia. (Erratum in: *N Engl J Med*. 2008;358:1977). *N Engl J Med*. 2008;358:1431-1443. [EL 3]
345. **Crouse JR 3rd, Raichlen JS, Riley WA, et al; METEOR Study Group**. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA*. 2007;297:1344-1353. **[EL 1]**
346. **Wexler L, Brundage B, Crouse J, et al**. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. *Circulation*. 1996;94:1175-1192. [EL 4]
347. **Smith SC Jr, Greenland P, Grundy SM**. AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: executive summary. American Heart Association. *Circulation*. 2000;101:111-116. [EL 4]
348. **Folsom AR, Kronmal RA, Detrano RC, et al.** Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med*. 2008;168:1333-1339. **[EL 1]**
349. **Castelli WP.** Cholesterol and lipids in the risk of coronary artery disease--the Framingham Heart Study. *Can J Cardiol*. 1988;4(Suppl A):5A-10A. [EL 4]
350. **Bass KM, Newschaffer CJ, Klag MJ, Bush TL**. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med*. 1993;153:2209-2216. **[EL 2]**
351. **Rubins HB, Robins SJ, Collins D, et al.** Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410-418. **[EL 1]**
352. **Taylor AJ, Lee HJ, Sullenberger LE**. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin*. 2006;22:2243-2250. [EL 3]
353. **Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA**. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. (Errata in: *Circulation*. 2005;111:e446 and *Circulation*. 2004;110:3615). *Circulation*. 2004;110:3512-3517. [EL 3]
354. **Genest J Jr, Cohn JS**. Clustering of cardiovascular risk factors: targeting high-risk individuals. *Am J Cardiol*. 1995;76:8A-20A. [EL 4]
355. **Frick MH, Elo O, Haapa K, et al**. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237-1245. **[EL 1]**
356. **Kris-Etherton PM, Taylor DS, Zhao G.** Is there an optimal diet for the hypertriglyceridemic patient? *J Cardiovasc Risk*. 2000;7:333-337. [EL 4]
357. **Look AHEAD Research Group; Pi-Sunyer X, Blackburn G, Brancati FL, et al**. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care*. 2007;30:1374-1383. **[EL 1]**
358. **Ratner R, Goldberg R, Haffner S, et al; Diabetes Prevention Program Research Group**. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care*. 2005;28:888-894. **[EL 1]**
359. **Davidson MH, Stein EA, Bays HE, et al; COMBination of prescription Omega-3 with Simvastatin (COMBOS) Investigators.** Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007; 29:1354-1367. **[EL 1]**
360. **Harris WS, Rothrock DW, Fanning A, et al**. Fish oils in hypertriglyceridemia: a dose-response study. *Am J Clin Nutr*. 1990;51:399-406. [EL 3]
361. **Brunzell JD, Schrott HG, Motulsky AG, Bierman EL**. Myocardial infarction in the familial forms of hypertriglyceridemia. *Metabolism*. 1976;25:313-320. [EL 3]
362. **Austin MA, McKnight B, Edwards KL, et al**. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. *Circulation*. 2000;101:2777-2782. **[EL 2]**
363. **Rader DJ, Haffner SM**. Role of fibrates in the management of hypertriglyceridemia. *Am J Cardiol*. 1999;83:30F-35F. [EL 4]
364. **Hulley SB, Rosenman RH, Bawol RD, Brand RJ.** Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. *N Engl J Med*. 1980;302:1383-1389. [EL 3]
365. **Santamarina-Fojo S, Brewer HB Jr**. The familial hyperchylomicronemia syndrome. New insights into underlying genetic defects. *JAMA*. 1991;265:904-908. [EL 3]

366. **Online Mendelian Inheritance in Man, OMIM**. Hyperlipoproteinemia, Type V [OMIM #144650]. Baltimore, MD: Johns Hopkins University Press; 2000. Available at: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=144650. [EL 4]
367. **Yuan G, Al-Shali KZ, Hegele RA**. Hypertriglyceridemia: its etiology, effects and treatment. *CMAJ*. 2007;176:1113-1120. [EL 4]
368. **Plaisance EP, Grandjean PW**. Physical activity and high-sensitivity C-reactive protein. *Sports Med*. 2006;36:443-458. [EL 4]
369. **Krauss RM, Eckel RH, Howard B, et al.** AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*. 2000;102:2284-2299. [EL 4]
370. **Centers for Disease Control and Prevention**. Physical activity for everyone. CDC Web site. Available at: http://www.cdc.gov/nccdphp/dnpa/physical/everyone/recommendations/index.htm. Accessed on July 21, 2008. [EL 4]
371. **Gregg EW, Cauley JA, Stone K, et al. Study of Osteoporotic Fractures Research Group**. Relationship of changes in physical activity and mortality among older women. *JAMA*. 2003;289:2379-2386. **[EL 2]**
372. **Kesaniemi YK, Danforth E Jr, Jensen MD, Kopelman PG, Lefèbvre P, Reeder BA**. Dose-response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc*. 2001;33:S351-S358. [EL 4]
373. **Manson JE, Greenland P, LaCroix AZ, et al**. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med*. 2002;347:716-725. **[EL 2]**
374. **Manson JE, Hu FB, Rich-Edwards JW, et al.** A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *N Engl J Med*. 1999;341:650-658. **[EL 2]**
375. **Haskell WL, Lee IM, Pate RR, et al; American College of Sports Medicine; American Heart Association.** Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081-1093. [EL 4]
376. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation*. 1998;97:1440-1445. **[EL 1]**
377. **Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB**. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med*. 1993;328:538-545. **[EL 2]**
378. **Pate RR, Pratt M, Blair SN, et al**. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273:402-407. [EL 4]
379. **Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, et al.** Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA*. 1998;279:669-674. [EL 3]
380. **Levinger I, Goodman C, Hare DL, Jerums G, Selig S**. The effect of resistance training on functional capacity and quality of life in individuals with high and low numbers of metabolic risk factors. *Diabetes Care*. 2007;30:2205-2210. **[EL 2]**
381. **Wijndaele K, Duvigneaud N, Matton L, et al**. Muscular strength, aerobic fitness, and metabolic syndrome risk in Flemish adults. *Med Sci Sports Exerc*. 2007;39:233-240. [EL 3]
382. **Hughes AR, Mutrie N, Macintyre PD.** Effect of an exercise consultation on maintenance of physical activity after completion of phase III exercise-based cardiac rehabilitation. *Eur J Cardiovasc Prev Rehabil*. 2007;14:114-121. **[EL 1]**
383. **Isaacs AJ, Critchley JA, Tai SS, et al**. Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only. *Health Technol Assess;* 2007;11:1-165, iii-iv; **[EL 1]**
384. **Kirk A, De Feo P**. Strategies to enhance compliance to physical activity for patients with insulin resistance. *Appl Physiol Nutr Metab*. 2007;32:549-556. [EL 4]
385. **Kirk A, Mutrie N, MacIntyre P, Fisher M**. Increasing physical activity in people with type 2 diabetes. *Diabetes Care*. 2003;26:1186-1192. **[EL 2]**
386. **Mensink RP, Katan MB**. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler Thromb*. 1992;12:911-919. **[EL 2]**
387. **Garg A**. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr*. 1998;67:577S-582S. **[EL 1]**
388. **Garg A, Grundy SM, Unger RH**. Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. *Diabetes*. 1992;41:1278-1285. **[EL 1]**
389. **Kris-Etherton PM, Pearson TA, Wan Y, et al.** High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. *Am J Clin Nutr*. 1999;70:1009-1015. **[EL 1]**
390. **Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC**. Trans fatty acids and cardiovascular disease. *N Engl J Med*. 2006;354:1601-1613. [EL 3]
391. **American Diabetes Association**. Nutrition recommendations and principles for people with diabetes mellitus. *Diabetes Care*. 2000;23(Suppl 1):S43-S46. [EL 4]
392. **Krauss RM, Deckelbaum RJ, Ernst N, et al.** Dietary guidelines for healthy American adults. A statement for health professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1996;94:1795-1800. [EL 4]
393. **Havel RJ, Rapaport E**. Management of primary hyperlipidemia. (Erratum in: *N Engl J Med*. 1995;333:467). *N Engl J Med*. 1995; 332:1491-1498. [EL 4]
394. **American Heart Association**. Fats and Oil: AHA Recommendations. Available at: http://www.heart.org/HEARTORG/GettingHealthy/FatsAndOils/Fats101/Fats-and-Oils-AHA-Recommendation_UCM_316375_Article.jsp#.TymAIphZDe4. Accessed for verification February 1, 2012.
395. **Van Horn L.** Fiber, lipids, and coronary heart disease. A statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1997;95:2701-2704. [EL 4]
396. **Anderson JW, Gilinsky NH, Deakins DA, et al**. Lipid responses of hypercholesterolemic men to oat-bran and wheat-bran intake. *Am J Clin Nutr*. 1991;54:678-683. [EL 3]
397. **Anderson JW, Gustafson NJ, Spencer DB, Tietyen J, Bryant CA**. Serum lipid response of hypercholesterolemic men to single and divided doses of canned beans. *Am J Clin Nutr*. 1990;51:1013-1019. [EL 3]
398. **Anderson JW, Spencer DB, Hamilton CC, et al**. Oat-bran cereal lowers serum total and LDL cholesterol in

hypercholesterolemic men. *Am J Clin Nutr*. 1990;52:495-499. [EL 3]
399. **Anderson JW, Story L, Sieling B, Chen WJ, Petro MS, Story J**. Hypocholesterolemic effects of oat-bran or bean intake for hypercholesterolemic men. *Am J Clin Nutr*. 1984;40:1146-1155. [EL 3]
400. **Kirby RW, Anderson JW, Sieling B, et al**. Oat-bran intake selectively lowers serum low-density lipoprotein cholesterol concentrations of hypercholesterolemic men. *Am J Clin Nutr*. 1981;34:824-829. [EL 3]
401. **American Heart Association**. Whole Grains and Fiber. Available at: http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HealthyDietGoals/Whole-Grains-and-Fiber_UCM_303249_Article.jsp#.Tyl_65hZDe4. Accessed for verification February 1, 2012.
402. **Hallikainen MA, Uusitupa MI**. Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects. *Am J Clin Nutr*. 1999;69:403-410. **[EL 1]**
403. **Gylling H, Miettinen TA**. Cholesterol reduction by different plant stanol mixtures and with variable fat intake. *Metabolism*. 1999;48:575-580. **[EL 2]**
404. **Gylling H, Puska P, Vartiainen E, Miettinen TA**. Serum sterols during stanol ester feeding in a mildly hypercholesterolemic population. *J Lipid Res*. 1999;40:593-600. **[EL 2]**
405. **Miettinen TA, Gylling H**. Regulation of cholesterol metabolism by dietary plant sterols. *Curr Opin Lipidol*. 1999;10:9-14. [EL 4]
406. **Chen YD, Coulston AM, Zhou MY, Hollenbeck CB, Reaven GM.** Why do low-fat high-carbohydrate diets accentuate postprandial lipemia in patients with NIDDM? *Diabetes Care*. 1995;18:10-16. **[EL 1]**
407. **Knopp RH, Walden CE, Retzlaff BM, et al.** Long-term cholesterol-lowering effects of 4 fat-restricted diets in hypercholesterolemic and combined hyperlipidemic men. The Dietary Alternatives Study. *JAMA*. 1997;278:1509-1515. **[EL 1]**
408. **Grundy SM**. Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. *N Engl J Med*. 1986;314:745-748. **[EL 2]**
409. **Mensink RP, Katan MB**. Effect of monounsaturated fatty acids versus complex carbohydrates on high-density lipoproteins in healthy men and women. *Lancet*. 1987;1:122-125. **[EL 2]**
410. **Katan MB, Grundy SM, Willett WC**. Should a low-fat, high-carbohydrate diet be recommended for everyone? Beyond low-fat diets. *N Engl J Med*. 1997;337:563-566; discussion 566-567. [EL 4]
411. **American Heart Association**. Fish and Omega-3 Fatty Acids. Available at: http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HealthyDietGoals/Fish-and-Omega-3-Fatty-Acids_UCM_303248_Article.jsp#.Tyl_uphZDe4. Accessed for verification February 1, 2012.
412. **Harris WS.** n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997;65:1645S-1654S. [EL 4]
413. **Harris WS**. Nonpharmacologic treatment of hypertriglyceridemia: focus on fish oils. *Clin Cardiol*. 1999;22:II40-43. [EL 4]
414. **Mozaffarian D**. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. *Am J Clin Nutr*. 2008;87:1991S-1996S. [EL 4]
415. **Mozaffarian D, Rimm EB**. Fish intake, contaminants, and human health: evaluating the risks and the benefits. (Erratum in: *JAMA*. 2007;297:590). *JAMA*. 2006;296:1885-1899. **[EL 2]**
416. **Walden CE, Retzlaff BM, Buck BL, McCann BS, Knopp RH**. Lipoprotein lipid response to the National Cholesterol Education Program step II diet by hypercholesterolemic and combined hyperlipidemic women and men. *Arterioscler Thromb Vasc Biol*. 1997;17:375-382. **[EL 1]**
417. **Ornish D, Scherwitz LW, Billings JH, et al**. Intensive lifestyle changes for reversal of coronary heart disease. (Erratum in: *JAMA*. 1999;281:1380). *JAMA*. 1998;280:2001-2007. [EL 3]
418. **Gardner CD, Kiazand A, Alhassan S, et al**. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. (Erratum in: *JAMA*. 2007;298:178). *JAMA*. 2007;297:969-977. **[EL 1]**
419. **Key TJ, Appleby PN, Davey GK, Allen NE, Spencer EA, Travis RC**. Mortality in British vegetarians: review and preliminary results from EPIC-Oxford. *Am J Clin Nutr*. 2003;78(Suppl 3):533S-538S. **[EL 2]**
420. **Sacks FM, Castelli WP, Donner A, Kass EH**. Plasma lipids and lipoproteins in vegetarians and controls. *N Engl J Med*. 1975;292:1148-1151. [EL 3]
421. **Sacks FM, Donner A, Castelli WP, et al**. Effect of ingestion of meat on plasma cholesterol of vegetarians. *JAMA*. 1981;246:640-644. [EL 3]
422. **Schaefer EJ**. New recommendations for the diagnosis and treatment of plasma lipid abnormalities. *Nutr Rev*. 1993;51:246-253. [EL 4]
423. **Dreon DM, Fernstrom HA, Miller B, Krauss RM**. Low-density lipoprotein subclass patterns and lipoprotein response to a reduced-fat diet in men. *FASEB J*. 1994;8:121-126. **[EL 1]**
424. **Dreon DM, Fernstrom HA, Williams PT, Krauss RM**. LDL subclass patterns and lipoprotein response to a low-fat, high-carbohydrate diet in women. *Arterioscler Thromb Vasc Biol*. 1997;17:707-714. **[EL 2]**
425. **Borgia MC, Medici F**. Perspectives in the treatment of dyslipidemias in the prevention of coronary heart disease. *Angiology*. 1998;49:339-348. [EL 4]
426. **Newman TB, Browner WS, Hulley SB**. The case against childhood cholesterol screening. *JAMA*. 1990;264:3039-3043. [EL 4]
427. **Lapinleimu H, Viikari J, Jokinen E, et al.** Prospective randomised trial in 1062 infants of diet low in saturated fat and cholesterol. *Lancet*. 1995;345:471-476. **[EL 1]**
428. **Tershakovec AM, Jawad AF, Stallings VA, et al.** Growth of hypercholesterolemic children completing physician-initiated low-fat dietary intervention. *J Pediatr*. 1998;133:28-34. **[EL 1]**
429. **Copperman N, Schebendach J, Arden MR, Jacobson MS**. Nutrient quality of fat- and cholesterol-modified diets of children with hyperlipidemia. *Arch Pediatr Adolesc Med*. 1995;149:333-336. **[EL 2]**
430. **Obarzanek E, Hunsberger SA, Van Horn L, et al**. Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC). *Pediatrics*. 1997;100:51-59. **[EL 2]**
431. **O'Connell JM, Dibley MJ, Sierra J, Wallace B, Marks JS, Yip R**. Growth of vegetarian children: The Farm Study. *Pediatrics*. 1989;84:475-481. [EL 3]
432. **Shea S, Basch CE, Stein AD, Contento IR, Irigoyen M, Zybert P**. Is there a relationship between dietary fat and stature or growth in children three to five years of age? *Pediatrics*. 1993;92:579-586. **[EL 2]**
433. **Boulton TJ, Magarey AM.** Effects of differences in dietary fat on growth, energy and nutrient intake from

infancy to eight years of age. *Acta Paediatr*. 1995;84:146-150. **[EL 2]**

434. **Niinikoski H, Viikari J, Rönnemaa T, et al.** Regulation of growth of 7- to 36-month-old children by energy and fat intake in the prospective, randomized STRIP baby trial. *Pediatrics*. 1997;100:810-816. **[EL 2]**
435. **Niinikoski H, Viikari J, Rönnemaa T, et al**. Prospective randomized trial of low-saturated-fat, low-cholesterol diet during the first 3 years of life. The STRIP baby project. *Circulation*. 1996;94:1386-1393. **[EL 1]**
436. **Budow L, Beseler L, Arden M, et al**. The effect of dietary therapy on growth in hyperlipidemic children and adolescents: a prospective clinical trial [Abstract]. *Pediatr Res*. 1989;25:22A. **[EL 2]**
437. **Kwiterovich PO Jr**. Dyslipoproteinemia and other risk factors for atherosclerosis in children and adolescents. *Atherosclerosis*. 1994;108(Suppl):S55-S71. [EL 4]
438. **Mietus-Snyder M, Baker AL, Neufeld EJ, et al**. Effects of nutritional counseling on lipoprotein levels in a pediatric lipid clinic. *Am J Dis Child*. 1993;147:378-381. [EL 3]
439. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). The Writing Group for the DISC Collaborative Research Group. *JAMA*. 1995;273:1429-1435. **[EL 1]**
440. **Hennermann JB, Herwig J, März W, Asskali F, Böhles HJ**. Lipid and lipoprotein profiles in children with familial hypercholesterolaemia: effects of therapy. *Eur J Pediatr*. 1998;157:912-918. **[EL 2]**
441. **Starc TJ, Shea S, Cohn LC, Mosca L, Gersony WM, Deckelbaum RJ**. Greater dietary intake of simple carbohydrate is associated with lower concentrations of high-density-lipoprotein cholesterol in hypercholesterolemic children. *Am J Clin Nutr.* 1998;67:1147-1154. [EL 3]
442. **Goren A, Stankiewicz H, Goldstein R, Drukker A.** Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. *Pediatrics*. 1991; 88:265-268. **[EL 2]**
443. **Gidding SS, Dennison BA, Birch LL, et al; American Heart Association; American Academy of Petiatrics**. 2005 Dietary recommendations for children and adolescents: a guide for practitioners: consensus statement from the American Heart Association. (Errata in: *Circulation*. 2005;112:2375 and *Circulation*. 2006;113:e857). *Circulation*. 2005;112:2061-2075. [EL 4]
444. **Roberts CK, Chen AK, Barnard RJ**. Effect of a short-term diet and exercise intervention in youth on atherosclerotic risk factors. *Atherosclerosis*. 2007;191:98-106. [EL 3]
445. **Tammi A, Rönnemaa T, Miettinen TA, et al**. Effects of gender, apolipoprotein E phenotype and cholesterol-lowering by plant stanol esters in children: the STRIP study. Special Turku Coronary Risk Factor Intervention Project. *Acta Paediatr*. 2002;91:1155-1162. **[EL 2]**
446. **Lichtenstein AH, Deckelbaum RJ**. AHA Science Advisory. Stanol/sterol ester-containing foods and blood cholesterol levels. A statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation*. 2001;103:1177-1179. [EL 4]
447. **Porkka KV, Raitakari OT**. Serum lipoproteins in children and young adults: determinants and treatment strategies. *Curr Opin Lipidol*. 1996;7:183-187. [EL 4]
448. **Raitakari OT, Leino M, Räkkönen K, et al**. Clustering of risk habits in young adults. The Cardiovascular Risk in Young Finns Study. *Am J Epidemiol*. 1995;142:36-44. [EL 3]
449. **Fiore M, Bailey W, Cohen S, et al**. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service, 2008. Available at: http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf. Accessed for verification February 1, 2012. [EL 4]
450. **Brown G, Albers JJ, Fisher LD, et al**. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1289-1298. **[EL 2]**
451. **Ridker PM, Danielson E, Fonseca FA, et al**; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet*. 2009;373:1175-1182. **[EL 2]**
452. **Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E**. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48:438-445. **[EL 1]**
453. **Downs JR, Clearfield M, Weis S, et al**. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615-1622. **[EL 1]**
454. **Ridker PM, Fonseca FA, Genest J, et al; JUPITER Trial Study Group**. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol*. 2007;100:1659-1664. [EL 4]
455. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. *Br Heart J*. 1978;40:1069-1118. **[EL 1]**
456. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251:351-364. **[EL 1]**
457. **Insull W Jr, Toth P, Mullican W, et al**. Effectiveness of colesevelam hydrochloride in decreasing LDL cholesterol in patients with primary hypercholesterolemia: a 24-week randomized controlled trial. *Mayo Clin Proc*. 2001;76:971-982. **[EL 1]**
458. **Sacks FM, Pfeffer MA, Moye LA, et al.** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001-1009. **[EL 1]**
459. **McCormick LS, Black DM, Waters D, Brown WV, Pitt B.** Rationale, design, and baseline characteristics of a trial comparing aggressive lipid lowering with Atorvastatin Versus Revascularization Treatments (AVERT). *Am J Cardiol*. 1997;80:1130-1133. [EL 4]
460. **Athyros VG, Papageorgiou AA, Mercouris BR, et al.** Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin*. 2002;18:220-228. **[EL 1]**
461. **de Lemos JA, Blazing MA, Wiviott SD, et al; A to Z Investigators**. Early intensive vs a delayed conservative simvastatin strategy in patients with acute

coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292:1307-1316. **[EL 1]**

462. **Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, de Faire U.** Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet*. 1996.347:849-853. **[EL 2]**
463. **Shepherd J, Cobbe SM, Ford I, et al**. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301-1307. **[EL 1]**
464. **Schulze MB, Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB**. C-reactive protein and incident cardiovascular events among men with diabetes. *Diabetes Care*. 2004;27:889-894. **[EL 2]**
465. **Superko H, Krauss R**. Arteriographic benefit of multifactorial risk reduction in patients with LDL-C <125 mg/dL is seen in LDL pattern B but not pattern A. Presented at the 4th International Symposium on Multiple Risk Factors in Cardiovascular Disease; April 1997; Washington, DC.
466. **Knatterud GL, Rosenberg Y, Campeau L, et al**. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. Post CABG Investigators. *Circulation*. 2000;102:157-165. **[EL 2]**
467. **Campeau L, Hunninghake DB, Knatterud GL, et al**. Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors. NHLBI post coronary artery bypass graft clinical trial. Post CABG Trial Investigators. *Circulation*. 1999;99:3241-3247. **[EL 1]**
468. **White CW**. Benefit of aggressive lipid-lowering therapy: insights from the post coronary artery bypass graft study and other trials. *Am J Med*. 1998;105:63S-68S. [EL 4]
469. **Chello M, Patti G, Candura D, et al.** Effects of atorvastatin on systemic inflammatory response after coronary bypass surgery. *Crit Care Med*. 2006;34:660-667. **[EL 2]**
470. **Dotani MI, Elnicki DM, Jain AC, Gibson CM**. Effect of preoperative statin therapy and cardiac outcomes after coronary artery bypass grafting. *Am J Cardiol*. 2000;86:1128-1130 [A1126]. [EL 3]
471. **Marín F, Pascual DA, Roldán V, et al**. Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. *Am J Cardiol*. 2006;97:55-60. [EL 3]
472. **Pan W, Pintar T, Anton J, Lee VV, Vaughn WK, Collard CD**. Statins are associated with a reduced incidence of perioperative mortality after coronary artery bypass graft surgery. *Circulation*. 2004;110:II45-49. [EL 3]
473. **Brull DJ, Sanders J, Rumley A, Lowe GD, Humphries SE, Montgomery HE**. Statin therapy and the acute inflammatory response after coronary artery bypass grafting. *Am J Cardiol*. 2001;88:431-433. [EL 4]
474. **Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators.** Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001;286:64-70. **[EL 1]**
475. **Economides PA, Caselli A, Tiani E, Khaodhiar L, Horton ES, Veves A**. The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes. *J Clin Endocrinol Metab*. 2004;89:740-747. **[EL 2]**
476. **Hayward RA, Hofer TP, Vijan S**. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. *Ann Intern Med*. 2006;145:520-530. [EL 4]
477. **Kinlay S, Schwartz GG, Olsson AG, et al; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study Investigators**. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation*. 2003;108:1560-1566. **[EL 1]**
478. **Liao JK, Laufs U**. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol*. 2005;45:89-118. [EL 4]
479. **McFarlane SI, Muniyappa R, Francisco R, Sowers JR**. Clinical review 145: Pleiotropic effects of statins: lipid reduction and beyond. *J Clin Endocrinol Metab*. 2002;87:1451-1458. [EL 4]
480. **Macin SM, Perna ER, Farías EF, et al**. Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study. *Am Heart J*. 2005;149:451-457. **[EL 1]**
481. **Morrow DA, de Lemos JA, Sabatine MS, et al**. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation*. 2006;114:281-288. [EL 3]
482. **Schwartz GG, Olsson AG, Ezekowitz MD, et al; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators**. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711-1718. **[EL 1]**
483. **Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK; Treating to New Targets Study Steering Committee and Investigators.** Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. *Ann Intern Med*. 2007;147:1-9. [EL 1]
484. **Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. (Errata in: *Lancet*. 2008;371:2084 and *Lancet*. 2005;366:1358). *Lancet*. 2005;366:1267-1278. **[EL 1]**
485. **Stone NJ**. Lipid management: current diet and drug treatment options. *Am J Med*. 1996;101:4A40S-48S; discussion 48S-49S. [EL 4]
486. **Tikkanen MJ**. Statins: within-group comparisons, statin escape and combination therapy. *Curr Opin Lipidol*. 1996;7:385-388. [EL 4]
487. **Davignon J**. Advances in drug treatment of dyslipidemia: focus on atorvastatin. *Can J Cardiol*. 1998;14 (Suppl B): 28B-38B. [EL 4]
488. **Ballantyne CM, Miller E, Chitra R**. Efficacy and safety of rosuvastatin alone and in combination with cholestyramine in patients with severe hypercholesterolemia: a randomized, open-label, multicenter trial. *Clin Ther*. 2004;26:1855-1864. **[EL 1]**
489. **Davidson MH, Toth P, Weiss S, et al**. Low-dose combination therapy with colesevelam hydrochloride and lovastatin effectively decreases low-density lipoprotein cholesterol in patients with primary hypercholesterolemia. *Clin Cardiol*. 2001;24:467-474. **[EL 1]**

490. **Hunninghake D, Insull W, Jr., Toth P, Davidson D, Donovan JM, Burke SK**. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis*. 2001;158:407-416. **[EL 2]**
491. **Knapp HH, Schrott H, Ma P, et al**. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. *Am J Med*. 2001;110:352-360. [EL 3]
492. **Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB; Ezetimibe Study Group**. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2004;79:620-629. **[EL 1]**
493. **NHLBI Communications Office**. NIH stops clinical trial on combination cholesterol treatment [Press release]. May 26, 2011. **[EL 1]**
494. **Jones PH, Davidson MH, Stein EA, et al; STELLAR Study Group**. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003; 92:152-160. **[EL 1]**
495. **Jones P, Kafonek S, Laurora I, Hunninghake D**. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). (Erratum in: *Am J Cardiol*. 1998;82:128). *Am J Cardiol*. 1998;81:582-587. **[EL 1]**
496. **Lennernäs H, Fager G.** Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences. *Clin Pharmacokinet*. 1997; 32:403-425. [EL 4]
497. **Baldassarre S, Scruel O, Deckelbaum RJ, Dupont IE, Ducobu J, Carpentier YA**. Beneficial effects of atorvastatin on sd LDL and LDL phenotype B in statin-naive patients and patients previously treated with simvastatin or pravastatin. *Int J Cardiol*. 2005;104:338-345. [EL 3]
498. **Bevilacqua M, Righini V, Barrella M, Vago T, Chebat E, Dominguez LJ**. Effects of fluvastatin slow-release (XL 80 mg) versus simvastatin (20 mg) on the lipid triad in patients with type 2 diabetes. *Adv Ther*. 2005;22:527-542. **[EL 2]**
499. **Guerin M, Egger P, Soudant C, et al**. Dose-dependent action of atorvastatin in type IIB hyperlipidemia: preferential and progressive reduction of atherogenic apoB-containing lipoprotein subclasses (VLDL-2, IDL, small dense LDL) and stimulation of cellular cholesterol efflux. *Atherosclerosis*. 2002;163:287-296. [EL 3]
500. **Miller M, Dobs A, Yuan Z, Battisti WP, Palmisano J**. The effect of simvastatin on triglyceride-rich lipoproteins in patients with type 2 diabetic dyslipidemia: a SILHOUETTE trial sub-study. *Curr Med Res Opin*. 2006; 22:343-350. **[EL 2]**
501. **Pontrelli L, Parris W, Adeli K, Cheung RC**. Atorvastatin treatment beneficially alters the lipoprotein profile and increases low-density lipoprotein particle diameter in patients with combined dyslipidemia and impaired fasting glucose/type 2 diabetes. *Metabolism*. 2002;51:334-342. [EL 3]
502. **Sakabe K, Fukuda N, Wakayama K, Nada T, Shinohara H, Tamura Y.** Effects of atorvastatin therapy on the low-density lipoprotein subfraction, remnant-like particles cholesterol, and oxidized low-density lipoprotein within 2 weeks in hypercholesterolemic patients. *Circ J*. 2003;67:866-870. [EL 3]
503. **Sirtori CR, Calabresi L, Pisciotta L, et al**. Effect of statins on LDL particle size in patients with familial combined hyperlipidemia: a comparison between atorvastatin and pravastatin. *Nutr Metab Cardiovasc Dis*. 2005;15:47-55. **[EL 2]**
504. **van Tits LJ, Smilde TJ, van Wissen S, de Graaf J, Kastelein JJ, Stalenhoef AF**. Effects of atorvastatin and simvastatin on low-density lipoprotein subfraction profile, low-density lipoprotein oxidizability, and antibodies to oxidized low-density lipoprotein in relation to carotid intima media thickness in familial hypercholesterolemia. *J Investig Med*. 2004;52:177-184. **[EL 1]**
505. **Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM; West of Scotland Coronary Prevention Study Group**. Long-term follow-up of the West of Scotland Coronary Prevention Study. N *Engl J Med*. 2007;357:1477-1486. **[EL 2]**
506. **Pfizer, Inc.** CASHMERE Protocol A2581051 29 October 2007 Final Report. Available at: http://bmartinmd.com/Cashmere_Study_Pfizer.pdf. Accessed for verification February 1, 2012. **[EL 1]**
507. **Nicholls SJ, Ballantyne CM, Barter PJ, et al.** Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med*. 2011;365:2078-2087. **[EL 2]**
508. **Kashani A, Phillips CO, Foody JM, et al.** Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation*. 2006;114:2788-2797. [EL 3]
509. **Harper CR, Jacobson TA**. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr Opin Lipidol*. 2007;18:401-408. [EL 4]
510. **Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B**. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19:403-414. [EL 3]
511. **Scott RS, Lintott CJ, Wilson MJ**. Simvastatin and side effects. *N Z Med J*. 1991;104:493-495. [EL 3]
512. **Ballantyne CM, Lipka LJ, Sager PT, et al**. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. *Int J Clin Pract*. 2004;58:653-658. **[EL 1]**
513. **Masana L, Mata P, Gagné C, et al; Ezetimibe Study Group**. Long-term safety and, tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. *Clin Ther*. 2005;27:174-184. **[EL 1]**
514. **Shepherd J, Hunninghake DB, Stein EA, et al.** Safety of rosuvastatin. *Am J Cardiol*. 2004;94:882-888. [EL 3]
515. **Graham DJ, Staffa JA, Shatin D, et al.** Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA*. 2004;292:2585-2590. [EL 3]
516. **Jen SL, Chen JW, Lee WL, Wang SP**. Efficacy and safety of fenofibrate or gemfibrozil on serum lipid profiles in Chinese patients with type IIb hyperlipidemia: a single-blind, randomized, and cross-over study. *Zhonghua Yi Xue Za Zhi (Taipei)*. 1997;59:217-224. **[EL 1]**
517. **Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC**. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*. 1998;98:2088-2093 [EL 4]
518. **Frick MH, Syvänne M, Nieminen MS, et al**. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Lopid

Coronary Angiography Trial (LOCAT) Study Group. *Circulation*. 1997;96:2137-2143. **[EL 1]**

519. **Robins SJ, Rubins HB, Faas FH, et al; Veterans Affairs HDL Intervention Trial (VA-HIT).** Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care*. 2003;26:1513-1517. **[EL 1]**
520. **Giral P, Bruckert E, Jacob N, Chapman MJ, Foglietti MJ, Turpin G**. Homocysteine and lipid lowering agents. A comparison between atorvastatin and fenofibrate in patients with mixed hyperlipidemia. *Atherosclerosis*. 2001;154:421-427. **[EL 1]**
521. **Mayer O Jr, Simon J, Holubec L, Pikner R, Trefil L**. Folate co-administration improves the effectiveness of fenofibrate to decrease the lipoprotein oxidation and endothelial dysfunction surrogates. *Physiol Res*. 2006;55:475-481. [EL 3]
522. **Koh KK, Han SH, Quon MJ, Yeal Ahn J, Shin EK**. Beneficial effects of fenofibrate to improve endothelial dysfunction and raise adiponectin levels in patients with primary hypertriglyceridemia. *Diabetes Care*. 2005;28:1419-1424. **[EL 2]**
523. **Saklamaz A, Comlekci A, Temiz A, et al.** The beneficial effects of lipid-lowering drugs beyond lipid-lowering effects: a comparative study with pravastatin, atorvastatin, and fenofibrate in patients with type IIa and type IIb hyperlipidemia. *Metabolism*. 2005;54:677-681. [EL 3]
524. **Wu TJ, Ou HY, Chou CW, Hsiao SH, Lin CY, Kao PC.** Decrease in inflammatory cardiovascular risk markers in hyperlipidemic diabetic patients treated with fenofibrate. *Ann Clin Lab Sci*. 2007;37:158-166. [EL 3]
525. **McKenney J**. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med*. 2004; 164:697-705. [EL 4]
526. **Meyers CD, Carr MC, Park S, Brunzell JD**. Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. *Ann Intern Med*. 2003;139:996-1002. [EL 4]
527. **Guyton JR, Goldberg AC, Kreisberg RA, Sprecher DL, Superko HR, O'Connor CM.** Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia. *Am J Cardiol*. 1998;82:737-743. **[EL 1]**
528. **Morgan JM, Capuzzi DM, Guyton JR, et al.** Treatment Effect of Niaspan, a Controlled-release Niacin, in Patients With Hypercholesterolemia: A Placebo-controlled Trial. *J Cardiovasc Pharmacol Ther*. 1996;1:195-202. **[EL 2]**
529. **Pan J, Lin M, Kesala RL, Van J, Charles MA**. Niacin treatment of the atherogenic lipid profile and Lp(a) in diabetes. *Diabetes Obes Metab*. 2002;4:255-261. [EL 3]
530. **Pan J, Van JT, Chan E, Kesala RL, Lin M, Charles MA**. Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein(a) in diabetes. *Metabolism*. 2002;51:1120-1127. [EL 3]
531. **Elam MB, Hunninghake DB, Davis KB, et al.** Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. *JAMA*. 2000;284:1263-1270. **[EL 1]**
532. **Grundy SM, Vega GL, McGovern ME, et al; Diabetes Multicenter Research Group**. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med*. 2002;162:1568-1576. **[EL 1]**
533. **Canner PL, Furberg CD, Terrin ML, McGovern ME**. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). *Am J Cardiol*. 2005;95:254-257. **[EL 1]**
534. **Blankenhorn DH, Johnson RL, Nessim SA, Azen SP, Sanmarco ME, Selzer RH**. The Cholesterol Lowering Atherosclerosis Study (CLAS): design, methods, and baseline results. *Control Clin Trials*. 1987;8:356-387. [EL 3]
535. **Brown BG, Hillger L, Zhao XQ, Poulin D, Albers JJ**. Types of change in coronary stenosis severity and their relative importance in overall progression and regression of coronary disease. Observations from the FATS Trial. Familial Atherosclerosis Treatment Study. *Ann N Y Acad Sci*. 1995;748:407-417; discussion 417-408. **[EL 1]**
536. **Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L**. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. (Erratum in: *JAMA*. 1988;259:2698). *JAMA*. 1987;257:3233-3240. **[EL 1]**
537. **Cashin-Hemphill L, Mack WJ, Pogoda JM, Sanmarco ME, Azen SP, Blankenhorn DH**. Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. *JAMA*. 1990;264:3013-3017. [EL 3]
538. **Shepherd J**. Mechanism of action of bile acid sequestrants and other lipid-lowering drugs. **Cardiology**. 1989;76(Suppl 1):65-71; discussion 71-64. [EL 4]
539. **Brensike JF, Levy RI, Kelsey SF, et al**. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. *Circulation*. 1984;69:313-324. **[EL 2]**
540. **Davidson MH, Dillon MA, Gordon B, et al**. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med*. 1999;159:1893-1900. **[EL 1]**
541. **Hunninghake DB, Probstfield JL, Crow LO, Isaacson SO**. Effect of colestipol and clofibrate on plasma lipid and lipoproteins in type IIa hyperlipoproteinemia. *Metabolism*. 1981;30:605-609. [EL 3]
542. **Insull W Jr.** Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J*. 2006;99:257-273. [EL 4]
543. **Lyons D, Webster J, Fowler G, Petrie JC.** Colestipol at varying dosage intervals in the treatment of moderate hypercholesterolaemia. *Br J Clin Pharmacol*. 1994;37:59-62. **[EL 2]**
544. **Superko HR, Greenland P, Manchester RA, et al**. Effectiveness of low-dose colestipol therapy in patients with moderate hypercholesterolemia. *Am J Cardiol*. 1992;70:135-140. **[EL 1]**
545. **Probstfield JL, Rifkind BM**. The Lipid Research Clinics Coronary Primary Prevention Trial: design, results, and implications. *Eur J Clin Pharmacol*. 1991;40(Suppl 1): S69-75. **[EL 1]**
546. **Bays HE, Cohen DE**. Rationale and design of a prospective clinical trial program to evaluate the glucose-lowering effects of colesevelam HCl in patients with type 2 diabetes mellitus. *Curr Med Res Opin*. 2007;23:1673-1684. [EL 4]
547. **Daiichi Sankyo, Inc**. WelChol and insulin in treating patients with type 2 diabetes (WEL-302). Clinical trial identifier NCT00151749. Accessed March 13, 2008 at http://www.clinicaltrials.gov. [EL 4]

548. **Daiichi Sankyo, Inc**. WelChol and sulfonylurea in treating patients with type 2 diabetes (WEL-303). Clinical trial identifier NCT00147758. Accessed March 13, 2008 at http://www.clinicaltrials.gov. [EL 4]
549. **Daiichi Sankyo, Inc**. WelChol with metformin in treating patients with type 2 diabetes (WEL-301). Clinical trial identifier NCT00147719. Accessed March 13, 2008 at http://www.clinicaltrials.gov. [EL 4]
550. **Andrade SE, Walker AM, Gottlieb LK, et al.** Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med*. 1995;332:1125-1131. [EL 3]
551. **Avorn J, Monette J, Lacour A, et al**. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA*. 1998;279:1458-1462. **[EL 2]**
552. **Altmann SW, Davis HR Jr, Zhu LJ, et al**. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science*. 2004;303:1201-1204. [EL 4]
553. **Cruz-Fernández JM, Bedarida GV, Adgey J, Allen C, Johnson-Levonas AO, Massaad R**. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. *Int J Clin Pract*. 2005;59:619-627. **[EL 1]**
554. **Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J**. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. (Erratum in: *Am Heart J*. 2005;149:882). *Am Heart J*. 2005;149:464-473. **[EL 1]**
555. **Catapano AL, Davidson MH, Ballantyne CM, et al.** Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. *Curr Med Res Opin*. 2006;22:2041-2053. **[EL 1]**
556. **Kastelein JJ, Sager PT, de Groot E, Veltri E**. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. *Am Heart J*. 2005;149:234-239. [EL 4]
557. **Jellinger P**. Looking beyond the ezetimibe controversy. *Internal Medicine News*. 2008;41:9. [EL 4]
558. **Schering-Plough, Merck**. Study to establish the clinical benefit/safety of Vytorin (ezetimibe/simvastatin tablet) vs simvastatin in subjects with acute coronary syndrome (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial - IMPROVE IT). Clinical trial identifier NCT00202878. Accessed November 15, 2007 at http://www.clinicaltrials.gov. [EL 4]
559. **Goldberg AC.** A meta-analysis of randomized controlled studies on the effects of extended-release niacin in women. *Am J Cardiol*. 2004;94:121-124. **[EL 1]**
560. **Nerbrand C, Nyberg P, Nordström L, Samsioe G.** Effects of a lipid lowering fibrate and hormone replacement therapy on serum lipids and lipoproteins in overweight postmenopausal women with elevated triglycerides. *Maturitas*. 2002;42:55-62. [EL 3]
561. **Dupuy AM, Carrière I, Scali J, et al.** Lipid levels and cardiovascular risk in elderly women: a general population study of the effects of hormonal treatment and lipid-lowering agents. *Climacteric*. 2008;11:74-83. [EL 3]
562. **Lukes A.** Evolving issues in the clinical and managed care settings on the management of menopause following the women's health initiative. *J Manag Care Pharm*. 2008;14:7-13. [EL 4]
563. **Utian WH, Archer DF, Bachmann GA, et al; North American Menopause Society**. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause*. 2008;15:584-602. [EL 4]
564. **Raitakari OT, Porkka KV, Taimela S, Telama R, Räsänen L, Viikari JS**. Effects of persistent physical activity and inactivity on coronary risk factors in children and young adults. The Cardiovascular Risk in Young Finns Study. *Am J Epidemiol*. 1994;140:195-205. **[EL 2]**
565. **Rifkind BM, Schucker B, Gordon DJ**. When should patients with heterozygous familial hypercholesterolemia be treated? *JAMA*. 1999;281:180-181. [EL 4]
566. **Goldstein J, Hobbs H, Brown M**. Familial hypercholesterolemia. In: Scriver C, Beaudet A, Sly W, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 7th ed. New York: McGraw-Hill, 1995: 1981-2030. [EL 4]
567. **Tonstad S, Joakimsen O, Stensland-Bugge E, et al**. Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects. *Arterioscler Thromb Vasc Biol*. 1996;16:984-991. [EL 3]
568. **Sorensen KE, Celermajer DS, Georgakopoulos D, Hatcher G, Betteridge DJ, Deanfield JE**. Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein(a) level. *J Clin Invest*. 1994;93:50-55. [EL 3]
569. **Hegele RA**. Small genetic effects in complex diseases: a review of regulatory sequence variants in dyslipoproteinemia and atherosclerosis. *Clin Biochem*. 1997;30:183-188. [EL 4]
570. **Assouline L, Levy E, Feoli-Fonseca JC, Godbout C, Lambert M.** Familial hypercholesterolemia: molecular, biochemical, and clinical characterization of a French-Canadian pediatric population. *Pediatrics*. 1995;96:239-246. [EL 3]
571. **Gotto AM Jr**. Targeting high-risk young patients for statin therapy. *JAMA*. 2004;292:377-378. [EL 4]
572. **Dirisamer A, Hachemian N, Bucek RA, Wolf F, Reiter M, Widhalm K**. The effect of low-dose simvastatin in children with familial hypercholesterolaemia: a 1-year observation. *Eur J Pediatr.* 2003;162:421-425. [EL 3]
573. **McCrindle BW, Ose L, Marais AD**. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr*. 2003;143:74-80 **[EL 1]**
574. **Wiegman A, Hutten BA, de Groot E, et al**. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 2004;292:331-337. **[EL 1]**
575. **Ducobu J, Brasseur D, Chaudron JM, et al**. Simvastatin use in children. *Lancet*. 1992;339:1488. [EL 4]
576. **Sinzinger H, Schmid P, Pirich C, et al.** Treatment of hypercholesterolaemia in children. *Lancet*. 1992;340:548-549. [EL 4]
577. **Sinzinger H, Mayr F, Schmid P, Granegger S, O'Grady J, Peskar BA**. Sleep disturbance and appetite loss after lovastatin. *Lancet*. 1994;343:973. [EL 3]
578. **Knipscheer HC, Boelen CC, Kastelein JJ, et al.** Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res*. 1996;39:867-871. **[EL 1]**
579. **Lambert M, Lupien PJ, Gagné C, et al**. Treatment of familial hypercholesterolemia in children and adolescents:

effect of lovastatin. Canadian Lovastatin in Children Study Group. *Pediatrics*. 1996;97:619-628. **[EL 1]**

580. **Stein EA, Illingworth DR, Kwiterovich PO Jr, et al.** Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 1999;281:137-144. **[EL 1]**
581. **Tonstad S, Knudtzon J, Sivertsen M, Refsum H, Ose L**. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr*. 1996;129:42-49. **[EL 1]**
582. **Tonstad S, Sivertsen M, Aksnes L, Ose L**. Low dose colestipol in adolescents with familial hypercholesterolaemia. *Arch Dis Child*. 1996;74:157-160. **[EL 1]**
583. **Liacouras CA, Coates PM, Gallagher PR, Cortner JA**. Use of cholestyramine in the treatment of children with familial combined hyperlipidemia. *J Pediatr.* 1993; 122:477-482. **[EL 2]**
584. **Salen G, von Bergmann K, Lütjohann D, et al**. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation*. 2004;109:966-971. **[EL 2]**
585. **Colletti RB, Neufeld EJ, Roff NK, McAuliffe TL, Baker AL, Newburger JW**. Niacin treatment of hypercholesterolemia in children. *Pediatrics*. 1993;92:78-82. [EL 3]
586. **Blake GJ, Otvos JD, Rifai N, Ridker PM**. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation*. 2002; 106:1930-1937. **[EL 2]**
587. **Ensign W, Hill N, Heward CB.** Disparate LDL phenotypic classification among 4 different methods assessing LDL particle characteristics. *Clin Chem*. 2006;52:1722-1727. [EL 4]
588. **Witte DR, Taskinen MR, Perttunen-Nio H, Van Tol A, Livingstone S, Colhoun HM**. Study of agreement between LDL size as measured by nuclear magnetic resonance and gradient gel electrophoresis. *J Lipid Res*. 2004;45:1069-1076. [EL 3]
589. **Detsky AS, Naglie IG**. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med*. 1990;113:147-154. [EL 4]
590. **Martikainen JA, Ottelin AM, Kiviniemi V, Gylling H**. Plant stanol esters are potentially cost-effective in the prevention of coronary heart disease in men: Bayesian modelling approach. *Eur J Cardiovasc Prev Rehabil*. 2007;14:265-272. [EL 3]
591. **Delahanty LM, Sonnenberg LM, Hayden D, Nathan DM**. Clinical and cost outcomes of medical nutrition therapy for hypercholesterolemia: a controlled trial. *J Am Diet Assoc*. 2001;101:1012-1023. [EL 4]
592. **Sikand G, Kashyap ML, Wong ND, Hsu JC**. Dietitian intervention improves lipid values and saves medication costs in men with combined hyperlipidemia and a history of niacin noncompliance. *J Am Diet Assoc*. 2000;100:218-224. [EL 3]
593. **Elixhauser A**. The costs of smoking and the cost effectiveness of smoking-cessation programs. *J Public Health Policy*. 1990;11:218-237. [EL 4]
594. **Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L**. Primary prevention of cardiovascular disease: cost-effectiveness comparison. I*nt J Technol Assess Health Care*. 2007;23:71-79. [EL 4]
595. **Howard P, Knight C, Boler A, Baker C**. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO Simulation model: application to a population of US adult smokers. *Pharmacoeconomics*. 2008;26:497-511. [EL 3]
596. **Probstfield JL**. How cost-effective are new preventive strategies for cardiovascular disease? *Am J Cardiol*. 2003; 91:22G-27G. [EL 4]
597. **Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K**. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. *Tob Control*. 2007;16(Suppl 1):i53-59. [EL 4]
598. **Plosker GL, Lyseng-Williamson KA.** Atorvastatin: a pharmacoeconomic review of its use in the primary and secondary prevention of cardiovascular events. *Pharmacoeconomics*. 2007;25:1031-1053. [EL 4]
599. **Hay JW, Sterling KL**. Cost effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. *Pharmacoeconomics*. 2005;23:133-141. [EL 4]
600. **Nyman JA, Martinson MS, Nelson D, et al; VA-HIT Study Group.** Cost-effectiveness of gemfibrozil for coronary heart disease patients with low levels of high-density lipoprotein cholesterol: the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial. *Arch Intern Med*. 2002;162:177-182. [EL 3]
601. **Kohli M, Attard C, Lam A, et al**. Cost effectiveness of adding ezetimibe to atorvastatin therapy in patients not at cholesterol treatment goal in Canada. *Pharmacoeconomics*. 2006;24:815-830. [EL 3]
602. **Ara R, Tumur I, Pandor A, et al**. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol Assess*. 2008;12:iii, xi-xiii, 1-212. [EL 3]
603. **Hilleman DE, Phillips JO, Mohiuddin SM, Ryschon KL, Pedersen CA.** A population-based treat-to-target pharmacoeconomic analysis of HMG-CoA reductase inhibitors in hypercholesterolemia. *Clin Ther.* 1999;21:536-562. [EL 4]
604. **Plans-Rubio P.** Cost-effectiveness analysis of cholesterol-lowering therapies in Spain. *Am J Cardiovasc Drugs*. 2006;6:177-188. [EL 3]
605. **Roze S, Ferrières J, Bruckert E, et al.** Cost-effectiveness of raising HDL cholesterol by adding prolonged-release nicotinic acid to statin therapy in the secondary prevention setting: a French perspective. *Int J Clin Pract*. 2007;61:1805-1811. [EL 3]
606. **Armstrong EP, Zachry WM 3rd, Malone DC.** Cost-effectiveness analysis of simvastatin and lovastatin/extended- release niacin to achieve LDL and HDL goal using NHANES data. *J Manag Care Pharm*. 2004;10:251-258. [EL 4]