

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-PLA₂ (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-PLA₂ 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-PLA₂ in atherosclerotic plaques, especially complex plaques (253 [EL 4], 254 [EL 4], 255 [EL 4], 256 [EL 4]). Lp-PLA₂ 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-PLA₂ 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-PLA₂ 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-PLA₂ 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 $\mu\text{mol/L}$) 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 B₆ and B₁₂ (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 I 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 erythematosus, 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 119332 female nurses, systemic lupus erythematosus 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 erythematosus (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-PLA₂ (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-PLA₂* (≥ 200 ng/mL) has been independently linked with coronary events (259 [EL 2]). Moreover, *Lp-PLA₂* may act synergistically with CRP, further increasing risk when both are elevated (251 [EL 2], 252 [EL 2]). Measurement of *Lp-PLA₂*, 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 $\mu\text{mol/L}$ are associated with increased CAD risk. Goal levels have been less than 10 $\mu\text{mol/L}$ in the United States and less than 12 $\mu\text{mol/L}$ 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 ^c	46	120	1.6	-4.1 ^b	2.2	-0.9 ^b	
HATS (imaging arm) (340 [EL 1])	Simvastatin + niacin (experimental) vs PBO (control) ^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 ^g	50 ^g	208 ^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	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	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 ultrasound; 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; TG, total cholesterol; TC, triglycerides; QCA, quantitative coronary angiography.

^aLow-density lipoprotein cholesterol levels measured by preparative ultracentrifugation.

^bLesions with stenosis $\geq 50\%$ at baseline.

^cThe 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.

^dDosages varied. Means were 13 mg daily of simvastatin and 2.4 g daily of niacin.

^eNominal change (end of treatment minus baseline).

^fCalculated based on reported figures.

^gAt 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.

^hMedian.

ⁱResults 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 [EL 1], 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 [EL 1], 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, antithrombotic 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*, mg/dL				Reduction, %				Increase, % HDL-C
		Male	Female		LDL-C	TG	HDL-C	LDL-C	TG	PTCA	MI	Cor Death	
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	11001	6801	1.9 y ^{a,k}	108	118	49	NA ^k	NA ^k	NA ^k	54 ^k	47 ^{h,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 ⁿ	+17 ⁿ	NA	19	24	5.4 ^h
Insull et al 2001 (457 [EL 1])	Colesevelam	232	235	24 wks	158 ⁿ	161 ⁿ	49 ⁿ	20 ⁿ	+5-10 ⁿ	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 ⁿ	149 ⁿ	52 ⁿ	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 ⁿ	276 ⁿ	42	22	46 ⁿ	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 [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])

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	37	42	8
CARE (458 [EL 1])	Pravastatin, 40 mg	3583	576	5.0	135	91	39	28	14	27	27	27	24	5
LIPID (287 [EL 1])	Pravastatin, 40 mg	7498	1516	6.1	146 ^b	145 ^b	36 ^b	25	11	19	19	29	24	5
AVERT (459 [EL 4])	Atorvastatin, 80 mg	288	53	1.5	152	172	40 ^c	46	11	^d	^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	NA
GREACE (460 [EL 1])	Atorvastatin, 10-80 mg	624	176	3	180	184	39	46	31	51 ^g	59	47	7	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	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	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 ^{e,e}	8 ^{e,e}	4	22	20	0	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	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	0 ^l	17.9
VA-HIT (85 [EL 1])	Gemfibrozil	2531	NA	5.1	112	160	32	0	31	21 ^m	23	22	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	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	^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 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 [EL 1], 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	<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 ^e	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.

^aEvents: acute myocardial infarction and coronary heart disease death, percentage with events at study end.
^bThe JUPITER trial was halted in March 2008. Median follow-up was 1.9 years; maximal follow-up was 5 years.
^cInclusion criteria included highly sensitive C-reactive protein concentration ≥2.0 mg/L.
^dMedian.
^eCalculated based on 142 and 251 events in rosuvastatin and placebo groups, respectively.
^fNumber 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.
^gAdditional inclusion criteria were either non-ST-elevation acute coronary syndrome or ST-elevation myocardial infarction.
^hCardiovascular 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 90000 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 32752 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

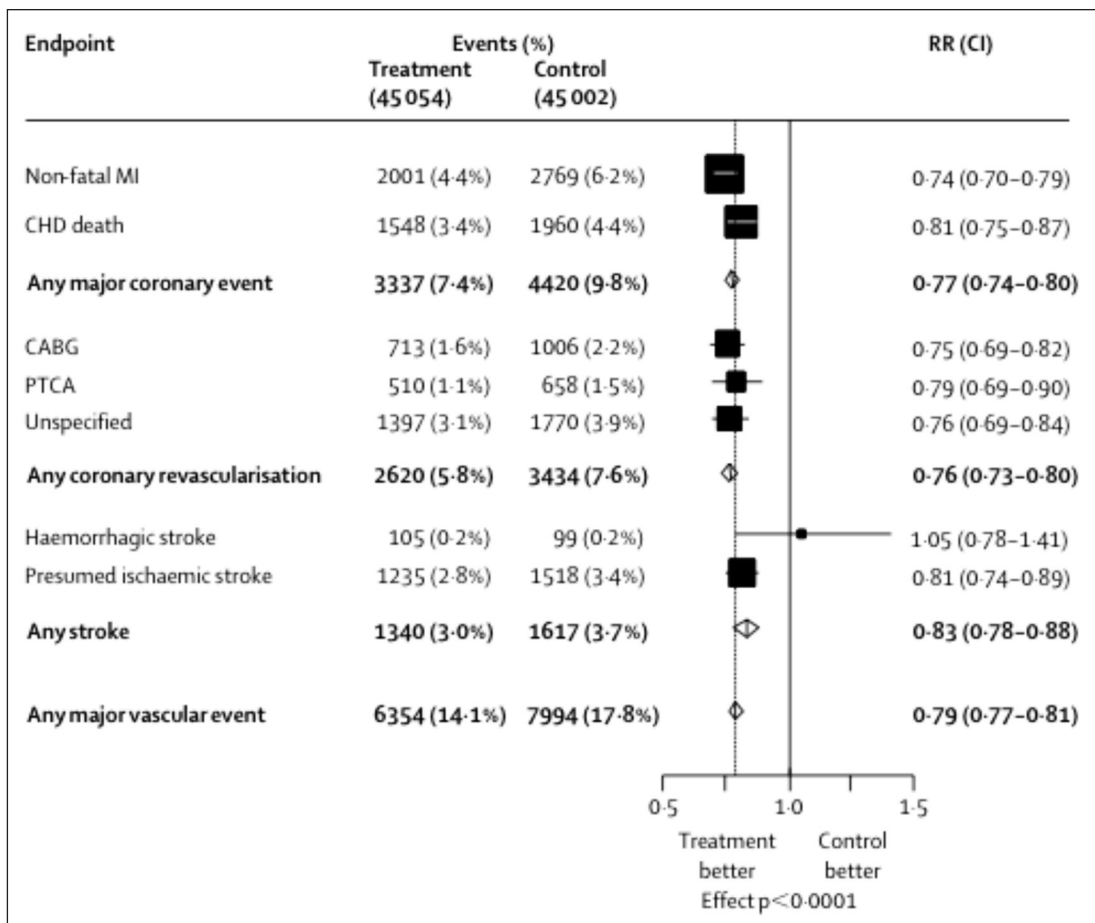


Fig. 2. Meta-analysis of proportional effects on major vascular events per mM/L low-density lipoprotein cholesterol reduction in 90056 participants in 14 randomized trials of statins over a mean period of 5 years (484 [EL 1]) (Cholesterol Treatment Trialists' Collaborators, 2005). Abbreviations: CABG, 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 = 17802), 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 rosuvastatin 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,

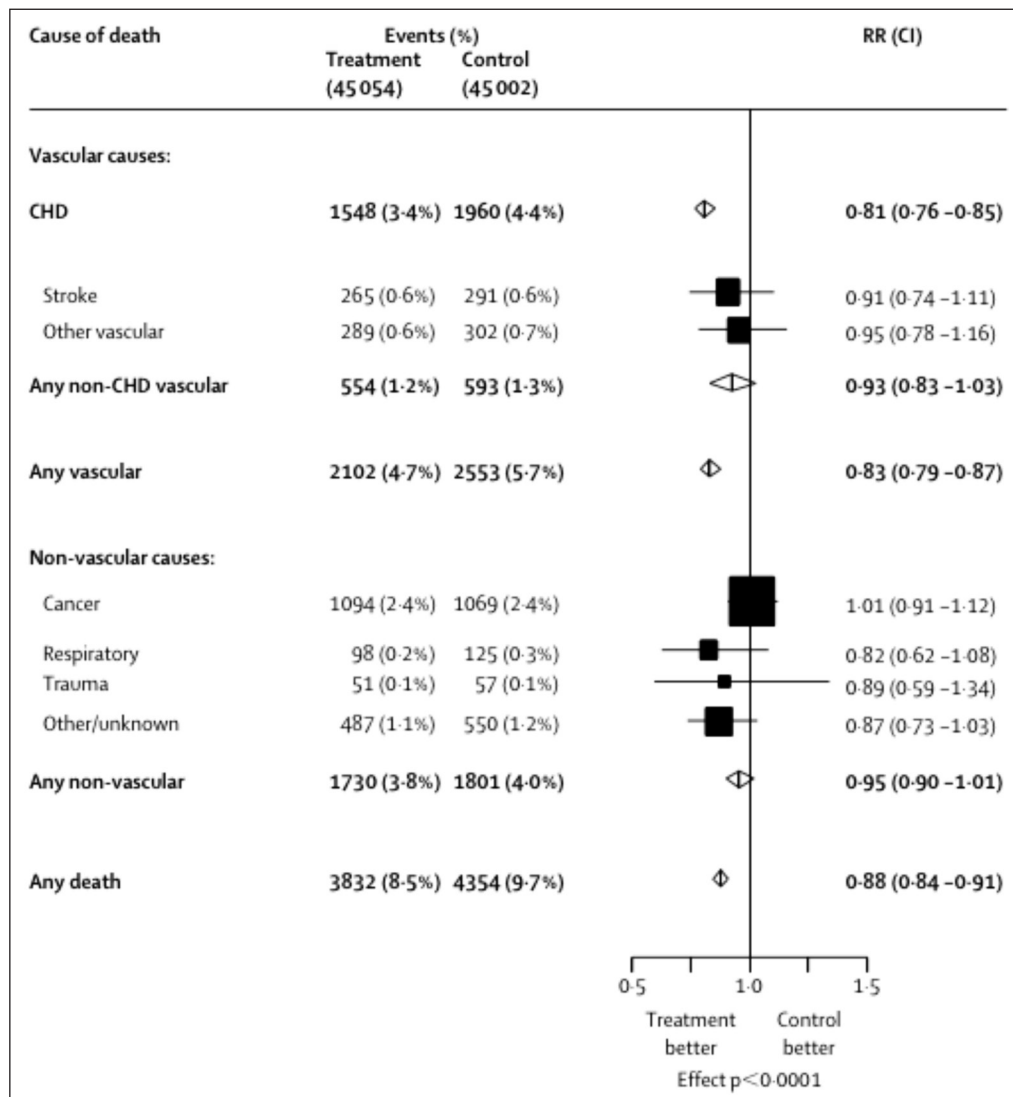


Fig. 3. Meta-analysis of proportional effects on cause-specific mortality per mM/L low-density lipoprotein cholesterol reduction in 90056 participants in 14 randomized trials of statins over a mean period of 5 years (484 [EL 1]) (Cholesterol Treatment Trialists' Collaborators, 2005). Abbreviations: CHD, 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 non-fatal 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 rosuvastatin, 40 mg daily for 24 months, resulted

in a mean percent atheroma volume reduction of -0.98% and a mean change in atheroma volume of -6.1 mm^3 in the most diseased 10-mm³ 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 rosuvastatin 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 74000 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 10000 person-years for statin monotherapy and 5.98 per 10000 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 colesvelam (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 [EL 1]), 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

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

- 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 post-operative 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 colesvelam 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 colesvelam 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 colesvelam 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-naïve 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 hypercholesterolemia. *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, Syväne 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. *Lipid*

- 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. **Bresnake 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 (cholestigel): 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 sulfonyleurea 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 hypercholesterolemia: a 1-year observation. *Eur J Pediatr.* 2003;162:421-425. [EL 3]
573. **McCordle 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, Bresseur 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 hypercholesterolemia 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 hypercholesterolemia. *Arch Dis Child*. 1996;74:157-160. [EL 1]
583. **Liouras 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. *Int 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]