TABLE 291e-1 MAJOR RISK FACTORS FOR ATHEROSCLEROSIS

High LDL cholesterol
Cigarette smoking
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol[a] (<1.0 mmol/L [<40 mg/dL])
Diabetes mellitus
Family history of premature CHD
Age (men ≥45 years; women ≥55 years)
Lifestyle risk factors
Obesity (BMI ≥30 kg/m^2)
Physical inactivity
Atherogenic diet
Emerging risk factors
Lipoprotein (a)
Prothrombotic factors
Proinflammatory factors
Impaired fasting glucose
Subclinical atherosclerosis

[a]HDL cholesterol ≥1.6 mmol/L (≥60 mg/dL) has been viewed as a "negative" risk factor.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

in cardiovascular event reduction and an acceptable risk-benefit relationship **(Fig. 291e-5)**. Moreover, because almost all statins are now available as generic statins medications, cost has become much less of an impediment to their use.

The clinical use of effective pharmacologic strategies for lowering LDL has reduced cardiovascular events markedly, but a considerable burden of residual risk remains even in patients treated with high-intensity statins. Hence, current studies are evaluating other avenues to address the residual burden of cardiovascular disease that persists despite statin treatment. Inhibitors of genetic studies identified proprotein convertase subtilisin kexin-like 9 (PCSK9) as a regulator of LDL levels associated with cardiovascular outcomes. Interaction of the LDL receptor with PCSK9 hastens the receptor's degradation, and hence yields higher circulating LDL concentrations. Genetic variants that lower PCSK9 activity appear to protect against cardiovascular events. Monoclonal antibodies that neutralize PCSK9 lower LDL levels even in statin-treated patients and are currently under investigation as novel therapeutics to lower cardiovascular risk.

LDL-lowering therapies do not appear to exert their beneficial effect on cardiovascular events by causing a marked "regression" of stenoses. Studies of lipid lowering monitored by angiography or by intravascular imaging modalities have shown at best a modest reduction in coronary artery stenoses over the duration of study, despite abundant evidence of event reduction. These results suggest that the beneficial mechanism of lipid lowering by statins does not require a substantial reduction in the fixed stenoses. Rather, the benefit may derive from "stabilization" of atherosclerotic lesions without substantially decreased stenosis.

TABLE 291e-2 SUMMARY OF THE FOUR STATIN BENEFIT GROUPS DESCRIBED IN THE 2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS

- Clinical ASCVD *"secondary prevention"*
- LDL-C ≥190 mg/dL without secondary cause (e.g., saturated/*trans* fats, drugs, certain diseases)
- Primary prevention *with* diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL
- Primary prevention *without* diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL, estimated ASCVD risk ≥7.5%

Abbreviations: ACC/AHA, American College of Cardiology and American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Source: Adapted from NJ Stone et al: 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. J Am Coll Cardiol 2013, doi: 10.1016/j.jacc.2013.11.002.

Such stabilization of atherosclerotic lesions and the attendant decrease in coronary events may result from the egress of lipids or from favorably influencing aspects of the biology of atherogenesis discussed above. In addition, as sizable lesions may protrude abluminally rather than into the lumen due to complementary enlargement, shrinkage of such plaques may not be apparent on angiograms. The consistent benefit of statins may depend not only on their salutary effects on the lipid profile, but also on direct modulation of plaque biology independent of lipid lowering.

As the prevalence of metabolic syndrome and diabetes increases, many patients present with low concentrations of HDL (HDL cholesterol <1.0 mmol/L [<40 mg/dL]). A baseline measurement of HDL cholesterol indubitably correlates with future cardiovascular risk. Yet, the utility of therapies that raise HDL cholesterol levels in blood as effective interventions to reduce cardiovascular vascular events has come into question. Blood HDL levels vary inversely with those of triglycerides, and the independent role of HDL versus triglycerides as a cardiovascular risk factor remains unsettled. The 2013 guideline does not advocate any specific therapy for raising HDL. Indeed, multiple recent trials failed to show that raising HDL cholesterol levels improves cardiovascular outcomes, and recent genetic studies cast doubt on low HDL as a causal risk factor for atherosclerotic events. Weight loss and physical activity can raise HDL, and these lifestyle measures merit universal adoption **(Table 291e-3)**. Nicotinic acid, particularly in combination with statins, can robustly raise HDL, but clinical trial data do not support the effectiveness of nicotinic acid in cardiovascular risk reduction. Agonists of nuclear receptors provide another potential avenue for raising HDL levels. Yet patients treated with peroxisome proliferator–activated receptors alpha and gamma (PPAR-α and -γ) agonists have not consistently shown improved cardiovascular outcomes, and at least some PPAR agonists have been associated with worsened cardiovascular outcomes. Other agents in clinical development raise HDL levels by inhibiting cholesteryl ester transfer protein (CETP). Two such agents have undergone large-scale clinical evaluation and have not shown efficacy in improving cardiovascular outcomes. Clinical studies currently under way will assess the effectiveness of two other CETP inhibitors that lack some of the adverse off-target actions encountered with the first agent tested.

The mechanism by which elevated LDL levels promote atherogenesis may involve oxidative modification. Yet, rigorous and well-controlled clinical trials have failed to demonstrate that antioxidant vitamin therapy improves coronary heart disease (CHD) outcomes. In regard to nontraditional risk factors including homocysteine and infection, large-scale clinical trials using vitamins to lower homocysteine or using antibiotics have not reduced cardiovascular events. Therefore, the current evidence base does *not* support the use of vitamins or antibiotics to lower cardiovascular risk.

Hypertension **(See also Chap. 298)** A wealth of epidemiologic data support a relationship between hypertension and atherosclerotic risk, and extensive clinical trial evidence has established that pharmacologic treatment of hypertension can reduce the risk of stroke, heart failure, and CHD events.

Diabetes Mellitus, Insulin Resistance, and the Metabolic Syndrome **(See also Chap. 417)** Most patients with diabetes mellitus die of atherosclerosis and its complications. Aging and rampant obesity underlie a current epidemic of type 2 diabetes mellitus. The abnormal lipoprotein profile associated with insulin resistance, known as *diabetic dyslipidemia*, accounts for part of the elevated cardiovascular risk in patients with type 2 diabetes. Although diabetic individuals often have LDL cholesterol levels near the average, the LDL particles tend to be smaller and denser and, therefore, more atherogenic. Other features of diabetic dyslipidemia include low HDL and elevated triglyceride levels. Hypertension also frequently accompanies obesity, insulin resistance, and dyslipidemia. This commonly encountered clinical cluster of risk factors has become known as the *metabolic syndrome* **(Chap. 422)**. Despite legitimate concerns about whether clustered components confer more risk than the individual components, the metabolic syndrome concept may offer clinical utility.