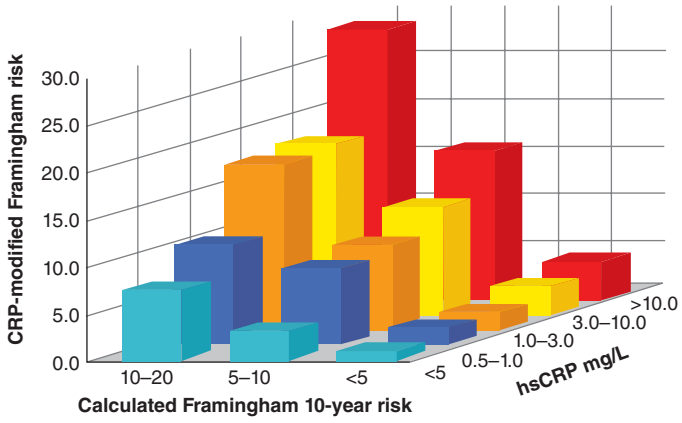

FIGURE 291e-6 C-reactive protein (CRP) level adds to the predictive value of the Framingham score. hsCRP, high-sensitivity measurement of CRP. *(Adapted from PM Ridker et al: Circulation 109:2818, 2004.)*

fibrinogen levels correlate with coronary risk and provide information about coronary risk independent of the lipoprotein profile.

The stability of an arterial thrombus depends on the balance between fibrinolytic factors, such as plasmin, and inhibitors of the fibrinolytic system, such as plasminogen activator inhibitor 1 (PAI-1). Individuals with diabetes mellitus or the metabolic syndrome have elevated levels of PAI-1 in plasma, and this probably contributes to the increased risk of thrombotic events. Lp(a) **(Chap. 421)** may modulate fibrinolysis, and individuals with elevated Lp(a) levels have increased CHD risk.

Aspirin reduces CHD events in several contexts. **Chapter 293** discusses aspirin therapy in stable ischemic heart disease, **Chap. 294** reviews recommendations for aspirin treatment in acute coronary syndromes, and **Chap. 446** describes aspirin's role in preventing recurrent ischemic stroke. In primary prevention, pooled trial data show that low-dose aspirin treatment (81 mg/d to 325 mg on alternate days) can reduce the risk of a first MI in men. Although the Women's Health Study (WHS) showed that aspirin (100 mg on alternate days) reduced strokes by 17%, it did not prevent MI in women. Current AHA guidelines recommend the use of low-dose aspirin (75–160 mg/d) for women with high cardiovascular risk (≥20% 10-year risk), for men with a ≥10% 10-year risk of CHD, and for all aspirin-tolerant patients with established cardiovascular disease who lack contraindications.

Inflammation An accumulation of clinical evidence shows that markers of inflammation correlate with coronary risk. For example, plasma levels of CRP, as measured by a high-sensitivity assay (hsCRP), prospectively predict the risk of MI. CRP levels also correlate with the outcome in patients with acute coronary syndromes. In contrast to several other novel risk factors, CRP adds predictive information to that derived from established risk factors, such as those included in the Framingham score **(Fig. 291e-6)**. Mendelian randomization studies do not support a causal role for CRP in cardiovascular disease. Thus, CRP serves as a validated biomarker of risk, but probably not as a direct contributor to pathogenesis.

Elevations in acute-phase reactants such as fibrinogen and CRP reflect the overall inflammatory burden, not just vascular foci of inflammation. Visceral adipose tissue releases proinflammatory cytokines that drive CRP production and may represent a major extravascular stimulus to the elevation of inflammatory markers in obese and overweight individuals. Indeed, CRP levels rise with body mass index (BMI) or visceral adipose depot as assessed by imaging, and weight reduction lowers CRP levels. Infectious agents might also furnish inflammatory stimuli related to cardiovascular risk.

Statin therapy likely reduces cardiovascular events in part by muting the inflammatory aspects of the pathogenesis of atherosclerosis. For example, in statin trials conducted in both primary (JUPITER) and secondary (PROVE-IT/TIMI-22) prevention populations, prespecified analyses showed that those who achieved lower levels of both LDL and CRP had better clinical outcomes than did those who only reached the lower level of either the inflammatory marker or the atherogenic lipoprotein **(Fig. 291e-7)**. The anti-inflammatory effect of statins appears independent of LDL lowering, because these two variables correlated very poorly in individual subjects in multiple clinical trials.

Lifestyle Modification The prevention of atherosclerosis presents a long-term challenge to all health care professionals and for public health policy. Both individual practitioners and organizations providing health care should strive to help patients optimize their risk factor profiles long before atherosclerotic disease becomes manifest. The current accumulation of cardiovascular risk in youth and in certain minority populations presents a particularly vexing concern from a public health perspective.

The ACC/AHA 2013 Guideline on Lifestyle Management to Reduce Cardiovascular Risk relied on rigorous evidentiary reviews. Few lifestyle interventions have undergone rigorous evaluation in randomized clinical trials. Therefore, these guidelines reflected judicious analysis of carefully selected observational studies and of intervention studies that relied primarily on biomarkers or surrogate endpoints rather than "hard" cardiovascular outcomes. Table 291e-3 summarizes the ACC/AHA lifestyle recommendations.

The care plan for all patients seen by internists should include measures to assess and minimize cardiovascular risk. Physicians must counsel patients about the health risks of tobacco use and provide guidance and resources regarding smoking cessation. Similarly, physicians should advise all patients about prudent dietary and physical activity habits for maintaining ideal body weight. Both National Institutes of Health (NIH) and AHA statements recommend at least 30 min of moderate-intensity physical activity per day. Obesity, particularly the male pattern of centripetal or visceral fat accumulation, can contribute to the elements of the "metabolic syndrome" cluster. Physicians should encourage their patients to take personal responsibility for behavior related to modifiable risk factors for the development of premature atherosclerotic disease. Conscientious counseling and patient education may forestall the need for pharmacologic measures intended to reduce coronary risk.

Issues in Risk Assessment A growing panel of markers of coronary risk presents a perplexing array to the practitioner. Markers measured in peripheral blood include size fractions of LDL particles and concentrations of homocysteine, Lp(a), fibrinogen, CRP, PAI-1, myeloperoxidase, lipoprotein-associated phospholipase A_2, and imaging assessment of subclinical atherosclerosis, among many others. In general, such specialized tests add little to the information available from a careful history and physical examination combined with measurement of a plasma lipoprotein profile and fasting blood glucose. The hsCRP measurement may well prove an exception in view of its robustness in risk

Group	N	Rate
Placebo	7832	1.11
LDL ≥ 70 mg/dL, hsCRP ≥ 2 mg/L	1384	1.11
LDL < 70 mg/dL, hsCRP ≥ 2 mg/L	2921	0.62
LDL ≥ 70 mg/dL, hsCRP < 2 mg/L	726	0.54
LDL < 70 mg/dL, hsCRP < 2 mg/L	2685	0.38

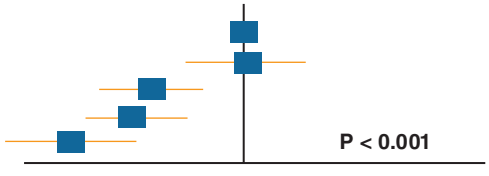

FIGURE 291e-7 Evidence from the JUPITER study that both low-density lipoprotein (LDL)-lowering and anti-inflammatory actions contribute to the benefit of statin therapy in primary prevention. See text for explanation. hsCRP, high-sensitivity measurement of C-reactive protein (CRP). *(Adapted from PM Ridker et al: Lancet 373:1175, 2009.)*