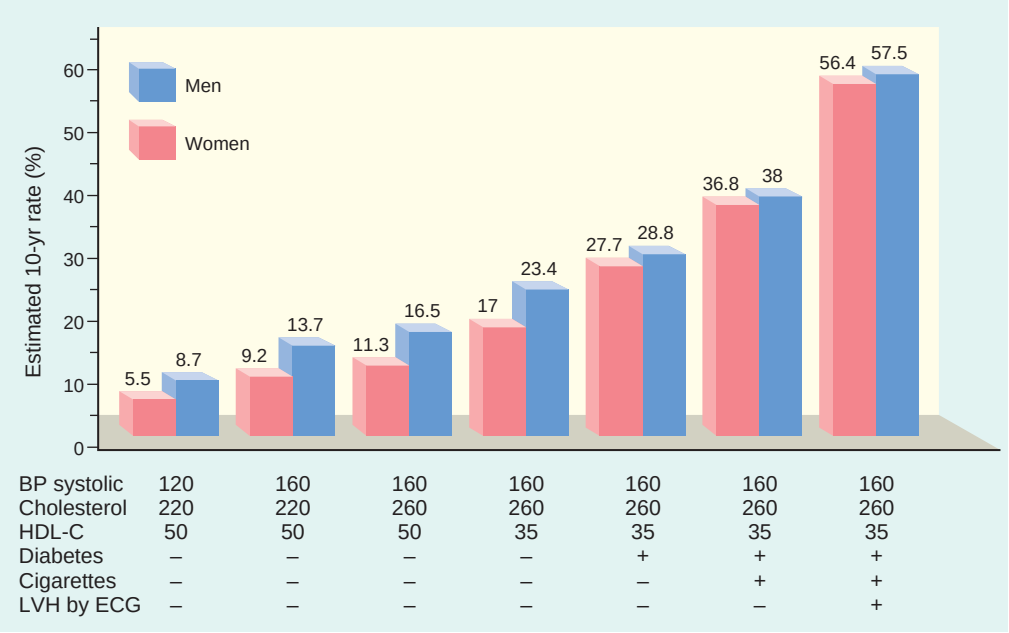

Figure 11-8 Estimated 10-year rate of coronary artery disease in 55-year old men and women as a function of established risk factors (hyperlipidemia, hypertension, smoking, and diabetes). BP, Blood pressure; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy. (From O'Donnell CJ, Kannel WB: Cardiovascular risks of hypertension: Lessons from observational studies. J Hypertension 16 (Suppl. 6):3, 1998.)

dietary intake of cholesterol and saturated fats (present in egg yolks, animal fats, and butter, for example) raises plasma cholesterol levels. Conversely, diets low in cholesterol and/or high in polyunsaturated fats lower plasma cholesterol levels. Omega-3 fatty acids (abundant in fish oils) are beneficial, whereas (trans)-unsaturated fats produced by artificial hydrogenation of polyunsaturated oils (used in baked goods and margarine) adversely affect cholesterol profiles. Exercise and moderate consumption of ethanol raise HDL levels whereas obesity and smoking lower it. *Statins* are a class of drugs that lower circulating cholesterol levels by inhibiting hydroxymethylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis (Chapter 5). In the past two decades, statins have been used widely to lower serum cholesterol levels, arguably one of the most significant success stories of translational research.

- *Hypertension* (see earlier) is another major risk factor for atherosclerosis; both systolic and diastolic levels are important. On its own, hypertension can increase the risk of ischemic heart disease by approximately 60% versus normotensive populations (Fig. 11-8). Chronic hypertension is the most common cause of left ventricular hypertrophy, and hence the latter is also a surrogate marker for cardiovascular risk.
- *Cigarette smoking* is a well-established risk factor in men and likely accounts for the increasing incidence and severity of atherosclerosis in women. Prolonged (years) smoking of one pack of cigarettes or more daily doubles the death rate from ischemic heart disease. Smoking cessation reduces that risk substantially.
- *Diabetes mellitus* induces hypercholesterolemia (Chapter 24) and markedly increases the risk of atherosclerosis. Other factors being equal, the incidence of myocardial infarction is twice as high in patients with diabetes than in those without. There is also an increased risk of stroke and a 100-fold increased risk of atherosclerosis-induced gangrene of the lower extremities.

Additional Risk Factors

As many as 20% of all cardiovascular events occur in the absence of overt risk factors (e.g., hypertension, hyperlipidemia, smoking, or diabetes). Indeed, more than 75% of cardiovascular events in previously healthy women occur with LDL cholesterol levels below 160 mg/dL (levels generally considered to connote low risk). Clearly, other factors also contribute to risk; among those that are proven or suspected are the following:

- *Inflammation*. Inflammation is present during all stages of atherogenesis and is intimately linked with atherosclerotic plaque formation and rupture (see later). With the increasing recognition that inflammation plays a significant causal role in ischemic heart disease, assessment of systemic inflammation has become important in overall risk stratification. While a number of circulating markers of inflammation correlate with ischemic heart disease risk, *C-reactive protein (CRP)* has emerged as one of the simplest to measure and one of the most sensitive.

  CRP is an acute phase reactant synthesized primarily by the liver. Its expression is increased by a number of inflammatory mediators, particularly IL-6, and it augments the innate immune response by binding to bacteria and activating the classical complement cascade. Whether CRP has any causal role in atherosclerosis is controversial. However, it is well established that plasma CRP is a strong, independent marker of risk for myocardial infarction, stroke, peripheral arterial disease,