and lowers low-density lipoprotein (LDL), whereas androgens have the opposite effect. Estrogen has direct vasodilatory effects on the vascular endothelium, enhances insulin sensitivity, and has antioxidant and anti-inflammatory properties. There is a striking increase in CHD after both natural and surgical menopause, suggesting that endogenous estrogens are cardioprotective. Women also have longer QT intervals on electrocardiograms, and this increases their susceptibility to certain arrhythmias.

CHD presents differently in women, who are usually 10–15 years older than their male counterparts and are more likely to have comorbidities such as hypertension, congestive heart failure, and diabetes mellitus (DM). In the Framingham study, angina was the most common initial symptom of CHD in women, whereas myocardial infarction (MI) was the most common initial presentation in men. Women more often have atypical symptoms such as nausea, vomiting, indigestion, and upper back pain. Although awareness that heart disease is the leading cause of death in women has nearly doubled over the last 15 years, women remain less aware that its symptoms are often atypical, and they are less likely to contact 9-1-1 when they experience such symptoms.

Women with MI are more likely to present with cardiac arrest or cardiogenic shock, whereas men are more likely to present with ventricular tachycardia. Further, younger women with MI are more likely to die than are men of similar age. However, this mortality gap has decreased substantially in recent years because younger women have experienced greater improvements in survival after MI than men (Fig. 6e-3). The improvement in survival is due largely to a reduction in comorbidities, suggesting a greater attention to modifiable risk factors in women.

Nevertheless, physicians are less likely to suspect heart disease in women with chest pain and less likely to perform diagnostic and therapeutic cardiac procedures in women. Women are less likely to receive therapies such as angioplasty, thrombolytic therapy, coronary artery bypass grafts (CABGs), beta blockers, and aspirin. There are also sex differences in outcomes when women with CHD do receive therapeutic interventions. Women undergoing CABG surgery have more advanced disease, a higher perioperative mortality rate, less relief of angina, and less graft patency; however, 5- and 10-year survival rates are similar. Women undergoing percutaneous transluminal coronary angioplasty have lower rates of initial angiographic and clinical success than men, but they also have a lower rate of restenosis and a better long-term outcome. Women may benefit less and have more frequent serious bleeding complications from thrombolytic therapy compared with men. Factors such as older age, more comorbid conditions, smaller body size, and more severe CHD in women at the time of events or procedures account in part for the observed sex differences.

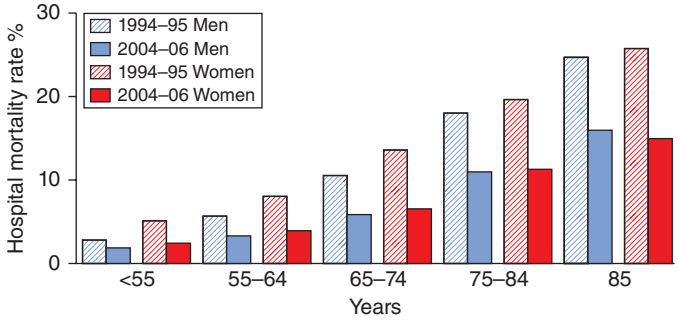

FIGURE 6e-3 Hospital mortality rates in men and women for acute myocardial infarction (MI) in 1994–1995 compared with 2004–2006. Women younger than age 65 years had substantially greater mortality than men of similar age in 1994–1995. Mortality rates declined markedly for both sexes across all age groups in 2004–2006 compared with 1994–1995. However, there was a more striking decrease in mortality in women younger than age 75 years compared with men of similar age. The mortality rate reduction was largest in women less than age 55 years (52.9%) and lowest in men of similar age (33.3%). *(Data adapted from V Vaccarino et al: Arch Intern Med 169:1767, 2009.)*

Elevated cholesterol levels, hypertension, smoking, obesity, low HDL cholesterol levels, DM, and lack of physical activity are important risk factors for CHD in both men and women. Total triglyceride levels are an independent risk factor for CHD in women but not in men. Low HDL cholesterol and DM are more important risk factors for CHD in women than in men. Smoking is an important risk factor for CHD in women—it accelerates atherosclerosis, exerts direct negative effects on cardiac function, and is associated with an earlier age of menopause. Cholesterol-lowering drugs are equally effective in men and women for primary and secondary prevention of CHD. However, because of perceptions that women are at lower risk for CHD, they receive fewer interventions for modifiable risk factors than do men. In contrast to men, randomized trials showed that aspirin was not effective in the primary prevention of CHD in women; it did significantly reduce the risk of ischemic stroke.

The sex differences in CHD prevalence, beneficial biologic effects of estrogen on the cardiovascular system, and reduced risk for CHD in observational studies led to the hypothesis that HT was cardioprotective. However, the WHI, which studied more than 16,000 women on CEE plus MPA or placebo and more than 10,000 women with hysterectomy on CEE alone or placebo, did not demonstrate a benefit of HT for the primary or secondary prevention of CHD. In addition, CEE plus MPA was associated with an increased risk for CHD, particularly in the first year of therapy, whereas CEE alone neither increased nor decreased CHD risk. Both CEE plus MPA and CEE alone were associated with an increased risk for ischemic stroke.

In the WHI, there was a suggestion of a reduction in CHD risk in women who initiated HT closer to menopause. This finding suggests that the time at which HT is initiated is critical for cardioprotection. According to this "timing" hypothesis, HT has differential effects, depending on the stage of atherosclerosis; adverse effects are seen with advanced, unstable lesions. A recent study using data from the Danish Osteoporosis Prevention Study (DOPS), an open-label randomized trial of triphasic oral estradiol compared with no treatment in recently menopausal or perimenopausal women (a cyclic oral synthetic progestin, norethisterone acetate, was added in women who had a uterus), found significantly reduced mortality and CVD after 10 years of HT. However, DOPS was designed to investigate HT for the primary prevention of osteoporotic bone fractures, and CVD outcomes were not prespecified endpoints. Further, there were relatively few CVD events in the study groups.

KEEPS was designed to directly test the "timing" hypothesis. Seven hundred twenty-seven recently menopausal women age 42–58 years (mean 52.7 years) were randomized to oral CEE (lower dose than WHI), transdermal estradiol, or placebo for 4 years; both estrogen arms included oral cyclical micronized progesterone (see above section on AD for dosing details). There were no significant beneficial or deleterious effects on the progression of atherosclerosis by computed tomography assessment of coronary artery calcification in either HT arm. Adverse events including stroke, MI, venous thromboembolism, and breast cancer were not increased in the HT arms compared with the placebo arm. There were improvements in hot flashes, night sweats, mood, sexual function, and bone density in the HT arms. This relatively small study does not suggest that early HT administration, transdermally or orally, reduces atherosclerosis. However, the study suggests that short-term HT may be safely administered for symptom relief in recently menopausal women. **HT is discussed further in Chap. 413.**

DIABETES MELLITUS

(See also Chap. 417) Women are more sensitive to insulin than men are. Despite this, the prevalence of type 2 DM is similar in men and women. There is a sex difference in the relationship between endogenous androgen levels and DM risk. Higher bioavailable testosterone levels are associated with increased risk in women, whereas lower bioavailable testosterone levels are associated with increased risk in men. Polycystic ovary syndrome and gestational DM—common