

# Cardiovascular Disease and Dyslipidemia in Women

Francine K. Welty, MD, PhD

Cardiovascular disease, primarily coronary heart disease (CHD), outnumbers the next 16 causes of death in women combined. However, the long-held belief that heart disease in women has a more benign prognosis than in men has resulted in less aggressive diagnosis and management patterns. Appreciation of the differences between men and women in CHD risk factors and presentation can assist in treatment decisions. Although estrogen replacement offers substantial beneficial effects on lipid levels in postmenopausal women, the first 2 randomized trials of estrogen alone and estrogen plus progestin, the Heart and Estrogen/Progestin Replacement Study and Estrogen Replacement and Atherosclerosis Study, observed no benefit in reducing risk of CHD death and nonfatal myocardial infarction and angiographic progression of CHD, respectively, in women with CHD. Available data show that lipid-lowering therapy reduces women's CHD risk and mortality but also indicate that a considerable proportion of women remains untreated or undertreated. Randomized trials of statins for primary and secondary prevention of coronary heart disease suggest that these agents are at least as effective for lowering coronary disease risk in women as in men. Therefore, statin drugs should be the drug of first choice for women with established CHD. Hypercholesterolemic postmenopausal women who require estrogen for menopausal symptoms may derive further reductions in low-density lipoprotein cholesterol and reductions in triglyceride levels with the addition of a statin drug. *Arch Intern Med.* 2001;161:514-522

Cardiovascular disease (CVD), particularly coronary heart disease (CHD), is the leading cause of death among women aged 60 years and older.<sup>1-4</sup> Cardiovascular disease deaths, primarily from CHD, outnumber the next 16 causes of death in women combined, including all cancers.<sup>5</sup> Indeed, women are 4 to 8 times more likely to die of CVD than of any other disease.<sup>6</sup> African American women have an even poorer prognosis: for ages 35 to 74 years, the age-adjusted CHD mortality rate is 69% higher than that of white women.<sup>5</sup>

Approximately 520 000 women die of CVD each year.<sup>5</sup> Since 1980, death from CVD has declined dramatically in men, whereas it has increased in women. Since 1984, annual CVD mortality in women has

exceeded that of men by about 50 000 a year.<sup>5</sup>

## PRESENTATION OF CVD IN WOMEN

Despite this abundant evidence to the contrary, the perception persists that CVD mainly affects men and is not a serious concern for women. This misconception arose in part from sex differences in age at onset. In general, CHD begins about a decade later in women than in men. The incidence of CHD in women is significantly lower before menopause, a protection that has been attributed to the effects of estrogen.<sup>3,7</sup> Women develop angina about 10 years later and a first myocardial infarction (MI) about 20 years later than men do.<sup>1,2,8</sup>

An additional reason for this misconception is that chest pain is less likely to be associated with substantial epicardial

From the Cardiovascular Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass. Dr Welty is a consultant to Pfizer Inc and Merck & Co, Inc.

coronary artery disease in women. As a result, sex differences in outcome after a diagnosis of angina have been reported. In Framingham, although more women (47%) than men (29%) had angina as their presenting symptom, it led to more serious disease in only 19% of the women vs 44% of the men.<sup>9</sup> Men had 43% of the MIs vs 29% for women. In a 10-year follow-up of all Rochester, Minn, residents diagnosed as having angina between 1960 and 1979, women with angina had a lower risk of MI and a relative risk (RR) of 0.45 of dying compared with men.<sup>10</sup> In neither study was the diagnosis of angina confirmed by objective measures.

Studies of patients presenting with acute chest pain have reported lower rates of MI in women than in men. In the Myocardial Infarction Triage and Intervention Registry (MITI) study, only 19% of women vs 26% of men admitted to coronary care units for suspected MI developed MI.<sup>11</sup> In another study, although equal numbers of men and women presented to emergency departments complaining of chest pain, 19% of men compared with only 10% of women were found to have MI.<sup>12</sup>

A possible explanation for these sex differences is that chest pain syndromes in women are more likely than those in men to be accompanied by angiographically normal coronary arteries. Overall, 50% of women examined for chest pain in the Coronary Artery Surgery Study (CASS) had minimal or no coronary arterial narrowing compared with only 17% of men.<sup>13</sup> Reflecting this pattern, data from more than 80 000 hospital discharges in 2 states indicate that women have higher rates of hospital admission for ischemic symptoms without evidence of CHD; men who present with chest pain are more likely to have severe coronary artery stenoses.<sup>14</sup> These and similar findings led most physicians to conclude that most women with chest pain did not have CHD or that their CHD prognosis was benign. Consequently, women's participation in primary and secondary prevention trials has been limited until recently.<sup>15</sup>

Compounding diagnostic problems, exercise treadmill testing has less specificity in women than in

men and, therefore, has less utility as a diagnostic tool in women.<sup>16-21</sup> The addition of thallium to exercise treadmill testing improves sensitivity and specificity in women; however, in a study of 390 consecutive patients referred for exercise treadmill testing with thallium, of patients with a positive test, 40% of men but only 4% of women were referred for catheterization.<sup>22</sup> Of women with abnormal results of stress tests, 28% were considered by their physicians to have a noncardiac cause for their chest pain compared with 13% of men.<sup>22</sup> Among patients with an ejection fraction less than 0.40 after MI enrolled in the Survival and Ventricular Enlargement (SAVE) study, men were twice as likely as women to have undergone a cardiac procedure before the index infarction, even though women reported greater functional disability from angina before the MI.<sup>23</sup> Although coronary angiography and percutaneous transluminal coronary angioplasty (PTCA) may be used less often in high-risk women than in high-risk men, of those who do undergo coronary angiography, referral rates for PTCA and coronary artery bypass grafting (CABG) are equivalent to those for men.<sup>11,23</sup> These findings suggest that, once an angiographic diagnosis of CHD is made in women, referral rates for PTCA and CABG are similar.

Difficulties in diagnosing CHD in women on the basis of chest pain and noninvasive testing may contribute to lower referral rates for catheterization and revascularization. Newer noninvasive diagnostic modalities, such as electron beam computed tomography, which can identify the presence or absence of coronary artery disease, may assist in the diagnosis of coronary artery disease in women. Unequivocal identification of coronary artery disease would allow for early aggressive risk factor modification and medical management, including dietary changes, exercise, and lipid-lowering therapy to prevent progression of disease.

Early diagnosis in women is important, since two thirds of sudden deaths occur in women with no CHD history.<sup>1</sup> In addition, women have a

poorer prognosis and more severe outcome after MI, PTCA, and CABG compared with men.<sup>1</sup> Women are more likely than men to die after a first MI, and, for survivors, there is a higher risk of another infarction and death.<sup>1</sup> In the Framingham Heart Study, 44% of women who had an MI died within 1 year, compared with 27% of men.<sup>3</sup> Some of the sex differences in outcome may be related to the greater age of women at which they develop CHD. Because age is a nonmodifiable risk factor, it is important to recognize risk factors for CHD in women early and aggressively reduce them to prevent CHD.

## CHD RISK FACTORS IN WOMEN

### Menopause and Dyslipidemia

Natural menopause confers a 3-fold increase in CHD risk.<sup>3</sup> In the Nurses' Health Study cohort, women undergoing bilateral oophorectomy had up to an 8-fold increase in risk of CHD.<sup>24</sup> After age 50 years, cholesterol levels plateau in men; however, levels of low-density lipoprotein (LDL) cholesterol increase an average of 0.05 mmol/L (2 mg/dL) per year between ages 40 and 60 years in women.<sup>25</sup> At least part of this increase results from declining levels of estrogen, which result in down-regulation of the LDL receptor on the liver.<sup>7,26,27</sup> A high LDL cholesterol level is a strong predictor of CHD risk in women younger than 65 years and a somewhat weaker predictor in women aged 65 years and older.<sup>28</sup> Increases in levels of total cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglycerides have also been observed after menopause.<sup>26,27</sup>

In the cross-sectional National Health and Nutrition Examination Surveys (NHANES), high-density lipoprotein (HDL) cholesterol levels were lower in men than in women and did not change with age.<sup>25</sup> However, in 2 smaller longitudinal studies, levels of HDL cholesterol decreased in postmenopausal women.<sup>27,29</sup> A low HDL cholesterol level is a stronger predictor of CHD mortality in women than in men and particularly so in women 65 years of age and older.<sup>2,28,30</sup> Stevenson et al<sup>27</sup> reported that the

HDL<sub>2</sub> cholesterol subfraction, which is considered to be more cardioprotective than HDL<sub>1</sub> or HDL<sub>3</sub>, showed a marked drop after the onset of menopause. The risk of coronary events increases with each increment in the ratio of total to HDL cholesterol. In the Framingham Heart Study, the 8-year risk of heart disease was 7% for women with a total/HDL cholesterol ratio less than 5, 12% for those with ratios of 5 to 7, and 20% for those with ratios greater than 7.<sup>3</sup> In a study of 2500 women aged 71 years and older, those with HDL cholesterol levels less than 0.9 mmol/L (35 mg/dL) had a RR of CHD mortality twice that of women with HDL cholesterol levels of 1.6 mmol/L (60 mg/dL) or more.<sup>30,31</sup>

Elevated triglyceride concentrations are a particularly significant risk factor in women, especially when the HDL cholesterol level falls below 1.03 mmol/L (40 mg/dL).<sup>32,33</sup> Average or high HDL cholesterol levels appear to attenuate the triglyceride-associated CHD risk. An increase in small, dense LDL particles also characterizes the postmenopausal atherogenic shift<sup>34</sup>; these particles are associated with a 3-fold increase in MI risk.<sup>35</sup>

### Smoking

The leading preventable cause of CHD in women is cigarette smoking.<sup>4</sup> More than 50% of MIs in middle-aged women can be attributed to tobacco use.<sup>2</sup> The risk in heavy smokers ( $\geq 20$  cigarettes per day) is 2 to 4 times higher than in nonsmokers, and even light smokers (1-4 cigarettes per day) have double the risk of nonsmokers.<sup>4,36</sup> Stopping smoking decreases the CHD risk within months. Although the prevalence of smoking in recent years has dropped in both men and women, women's rate of smoking cessation is still lower than that of men. Almost one fourth of women still smoke cigarettes; the greatest increase in the prevalence of smoking is in women aged 65 years and older.<sup>1</sup>

### Hypertension

Elevated systolic and diastolic blood pressure confers an increased risk of CHD in both men and women. Women with hypertension have a

4-fold risk of heart disease compared with normotensive women, whereas hypertension in men is associated with a 3-fold increase.<sup>2,37</sup> Isolated systolic hypertension in older women, which has a 30% prevalence in women older than 65 years, is of particular concern.<sup>2</sup>

The prevalence of hypertension increases with age, and, because of their survival advantage, women with hypertension outnumber men with hypertension in the older age groups.<sup>38</sup> Its estimated prevalence (identified as a blood pressure  $\geq 140/90$  mm Hg or use of antihypertensive medication) in women older than 45 years is 60% for white women and 79% for African American women.<sup>2</sup>

### Diabetes Mellitus

Diabetes is a greater predictor of CHD for women than for men.<sup>4,39</sup> Diabetes also reduces women's life-expectancy advantage.<sup>4,40</sup> Women with diabetes have a CHD-related mortality rate 3 to 7 times higher than that of nondiabetic women, whereas men's CHD mortality rate is 2 to 4 times higher than that of nondiabetic men.<sup>41</sup> The reasons for this sex difference are not clear but may be related to differences in lipid levels. A low HDL cholesterol level of 1.3 mmol/L (50 mg/dL) or less and a VLDL cholesterol level of 0.5 mmol/L (20 mg/dL) or more confer a higher CHD risk in diabetic women than in men with diabetes.<sup>39</sup>

### Obesity and Physical Inactivity

Obesity has been increasing in both men and women in the United States in the past few decades. Obesity and a sedentary lifestyle are interrelated.<sup>2,42</sup> About 25% of women report that they have no regular, sustained physical activity.<sup>42</sup> An increase in body mass index has been associated with an increase in the RR of nonfatal MI and fatal CHD.<sup>42</sup> Abdominal obesity may be a particularly important CHD risk factor in women; the waist-hip circumference appears to be a more important predictor of risk than the body mass index.<sup>43</sup>

Although few studies of exercise and CHD risk have included

women, available data suggest that active women have a lower risk than their sedentary counterparts.<sup>2</sup> Even brisk walking and other moderate-intensity activities will substantially reduce CHD risk.<sup>44</sup> Exercise and dietary modifications resulting in weight loss have beneficial effects on triglyceride levels even in persons with diabetes,<sup>45</sup> and HDL cholesterol levels have shown a dose-response relationship in female runners.

In summary, risk factors for CHD are similar in men and women,<sup>2,3,46</sup> although sex differences in LDL cholesterol and HDL cholesterol exist, and women with diabetes have a worse outcome than men with diabetes. Some, such as hypertension, dyslipidemia, and glucose intolerance, are metabolically linked and tend to cluster.<sup>3</sup> Multiple factors have synergistic effects on CHD risk, so that the presence of several risk factors is more than simply additive. Similarly, modification of a single risk factor can have beneficial effects on others. For example, weight loss may lower blood pressure and triglyceride levels and improve glucose tolerance.<sup>46</sup> Early recognition and modification of these risk factors could potentially decrease the rates of CHD in women.

### POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY

A meta-analysis of more than 30 observational studies showed a 56% reduction in risk of a major coronary event or fatal CVD in healthy current estrogen users compared with women who have never used estrogen replacement.<sup>47</sup> Problems with observational studies include the fact that healthier women, who already may have the lowest risk of developing heart disease, may be more likely to be prescribed and to take hormone replacement. These women may modify other risk factors and be in closer contact with the medical system; thus, the lower risk in women taking estrogen in these observational studies may be due to confounding factors.

Postmenopausal estrogen replacement therapy would be predicted to offer cardioprotection via a number of potential mechanisms. These include lowering levels of

LDL cholesterol, lipoprotein(a), plasminogen activator inhibitor 1, and fibrinogen; raising levels of HDL cholesterol; improving endothelium-dependent vasodilation; inhibiting proliferation and migration of smooth muscle cells; decreasing inflammatory cell activation; and acting as an antioxidant.<sup>2,7,48-53</sup> The Lipid Research Clinics Program Follow-up Study suggested that estrogen's cardioprotective effect is largely mediated through an increased HDL cholesterol level.<sup>54</sup>

Despite these potential cardioprotective mechanisms, in the first large randomized trial of hormone replacement therapy (HRT) in women with CHD, the Heart and Estrogen/Progestin Replacement Study (HERS), women randomized to estrogen and progestin (HRT group) had no significant differences in the combined incidence of CHD death and nonfatal MI (RR, 0.99; 95% confidence interval [CI], 0.80-1.22) or on CHD mortality (RR, 1.24; 95% CI, 0.87-1.75) compared with women receiving placebo at 5-year follow-up (**Table 1**).<sup>55</sup> This lack of effect occurred even though women receiving HRT had a mean reduction in LDL cholesterol level of 11% and mean increase in HDL cholesterol level of 10%. Initial adverse effects on coagulation and proischemic effects were postulated to account for a significant increase in risk for primary coronary events in year 1, and beneficial effects on lipid changes were thought to account for reduced risk in years 4 and 5.

A potential reason for the early adverse outcome in hormone-treated women is an increase in C-reactive protein level, a marker of inflammation. C-reactive protein level has been shown to be an independent predictor of risk of CHD in the Women's Health Study.<sup>56</sup> C-reactive protein levels are higher in women treated with estrogen and combined HRT than in women taking placebo.<sup>57</sup> Other possible lipid-related adverse effects of estrogen include increases in the liver's production of triglycerides and VLDL particles.<sup>1</sup> Elevated triglyceride levels increase the risk of CHD in women, as noted above. Whether the increase in triglyceride levels in hormone-treated women in HERS was associated with lack of effect is unknown.

**Table 1. Deaths and Adverse Events in the Heart and Estrogen/Progestin Replacement Study\***

	Hormone (n = 1380)	Placebo (n = 1383)	RR (95% CI)	P
<b>Deaths</b>				
CHD death	71	58	1.24 (0.87-1.75)	.23
Nonfatal MI	116	129	0.91 (0.71-1.17)	.46
Resuscitated cardiac arrest	19	13	1.48 (0.73-3.00)	.28
Stroke/TIA	108	96	1.13 (0.85-1.48)	.40
Cancer death	19	24	0.80 (0.44-1.46)	.47
Non-CHD, noncancer death	37	36	1.04 (0.66-1.64)	.87
Unadjudicated death	4	5		
Total deaths	131	123	1.08 (0.84-1.38)	.56
<b>Adverse events</b>				
Deep vein thrombosis	25	8	3.18 (1.43-7.04)	.004
Pulmonary embolism	11	4	2.79 (0.89-8.75)	.08
Any thromboembolic event	34	12	2.89 (1.50-5.58)	.002
Gallbladder disease	84	62	1.38 (1.00-1.92)	.05

\*Hormone indicates estrogen plus progestin; RR, relative risk; CI, confidence interval; CHD, coronary heart disease; MI, myocardial infarction; and TIA, transient ischemic attack. Adapted with permission from Hulley et al.<sup>55</sup>

Hormone replacement therapy was associated with adverse events in HERS (summarized in Table 1). Venous thromboembolic events were 3 times as frequent in the hormone-treated women (6.3/1000 woman-years) as in the placebo group (2.2/1000 woman-years).<sup>55</sup> Hormone-treated women also had a significant increase in risk of gallbladder disease. Estrogen replacement has other adverse effects. Postmenopausal women with an intact uterus who take long-term unopposed estrogen have a 3- to 8-fold increase in lifetime risk of developing endometrial cancer.<sup>7,58-61</sup> In general, the potential risk of endometrial hyperplasia and endometrial cancer from unopposed estrogen restricts its use to women whose uterus has been surgically removed.<sup>7</sup> Women with a uterus must take estrogen with a progestin to prevent endometrial hyperplasia.

A second, large, randomized trial of HRT in women with CHD, the Estrogen Replacement and Atherosclerosis (ERA) Study, also observed no benefit of HRT with the use of quantitative coronary angiography.<sup>62</sup> Women with previous MI or PTCA and a mean age of 65.8 years were randomized to receive conjugated estrogens, conjugated estrogens plus medroxyprogesterone acetate, or placebo. After 3 years of follow-up, the mean change in lumen diameter was not significantly different in those receiving HRT compared with placebo

(**Table 2**). Although there was no significant difference in clinical events among the 3 groups, estrogen-only users had higher rates of deep vein thrombosis and pulmonary emboli compared with users of estrogen plus progestin or placebo.

On the basis of the HERS and ERA results, there appears to be no benefit in initiating either an estrogen-only or an estrogen plus progestin regimen for secondary prevention of CHD in women. In fact, it may be harmful during the first year of use. The HERS authors suggested that women who have taken estrogen plus progestin therapy for longer than 1 year are presumably beyond the time frame for increased risk of prothrombotic events and should be able to safely continue it. Although the ERA results suggest that there may be no benefit in continuing HRT for prevention of angiographic progression of atherosclerosis,<sup>55</sup> women may wish to continue HRT for menopausal symptoms or prevention of osteoporosis. The Women's Health Initiative trial is hoped to better define the risks and benefits of HRT for postmenopausal women without CHD.<sup>63</sup>

## DYSLIPIDEMIA THERAPY

### A Gender Gap in Treatment of Dyslipidemia

The US National Cholesterol Education Program (NCEP) guidelines

**Table 2. Estrogen Replacement and Atherosclerosis Study\***

	E (n = 100)	E + P (n = 104)	Placebo (n = 105)	P†
Mean minimum diameter, mm	1.86	1.84	1.87	.81
Mean change, %	-0.09	-0.12	-0.09	.97
Total CHD events, No. (%)	4 (4)	2 (2)	3 (3)	.65
Nonfatal MI, No. (%)	6 (6)	6 (6)	7 (7)	>.99
DVT/PE, No. (%)	5 (5)	2 (2)	1 (1)	.16

\*E indicates estrogen; E + P, estrogen plus progestin; CHD, coronary heart disease; MI, myocardial infarction; DVT, deep vein thrombosis; and PE, pulmonary embolus. Adapted from data published in Herrington et al.<sup>62</sup>

†Estrogen vs placebo.

recommend an LDL cholesterol goal of less than 2.59 mmol/L (100 mg/dL) for men and women with documented CHD.<sup>64</sup> Clinical evidence has shown that aggressive treatment effectively lowers elevated LDL cholesterol levels. Although a study of 825 patients hospitalized for CHD at major US and Canadian medical centers between 1993 and 1996 indicated a trend toward increasing use of lipid-lowering therapy, significantly more men than women received this therapy during each year of the study.<sup>65</sup> The multicenter HERS study of postmenopausal women with CHD found that less than half (47%) were taking lipid-lowering medication, and LDL cholesterol levels in 91% of the study sample exceeded NCEP goals.<sup>66</sup> Only one third of women with LDL cholesterol levels greater than 4.14 mmol/L (160 mg/dL) were receiving a lipid-lowering agent.

#### Efficacy of Cholesterol-Lowering Therapy in Women

Data on cholesterol-lowering therapy in women are limited because most studies have included only men or a small number of women. Studies including women are summarized below.

**Primary Prevention.** Only 2 primary prevention trials have included a large number of women without CVD. In the first, 1184 women were randomized to receive colestipol or placebo. At an average follow-up of 2 years, treatment with colestipol lowered cholesterol level an average of 10% but had no effect on CHD mortality (RR, 0.93; 95% CI, 0.38-2.26).<sup>67</sup> This study may have lacked power to examine CHD mortality.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a primary prevention trial enrolling men and women with average total and LDL cholesterol levels and below-average HDL cholesterol levels (mean, 1.03 mmol/L [40 mg/dL] for women). At the end of 1 year, treatment with lovastatin reduced LDL cholesterol level by 25%, total cholesterol level by 18%, and triglyceride levels by 15%, and increased HDL cholesterol level by 6% compared with baseline.<sup>68</sup> After an average 5.2 years of follow-up, the risk of a first acute major coronary event (fatal or nonfatal MI, unstable angina, or sudden cardiac death) was reduced by 37% in the total group randomized to lovastatin compared with those taking placebo ( $P < .001$ ). The reduction in RR was greater for women (46%) than men (37%), but the difference was not significant because of a small number of events among women (7 in the lovastatin group vs 13 in the placebo group). The trial had insufficient power to examine CHD mortality or total mortality.

**Secondary Prevention.** In the Scandinavian Simvastatin Survival Study (4S), 3617 men and 827 women with angina or previous MI and mean LDL cholesterol level of 4.86 mmol/L (188 mg/dL) (total cholesterol level ranging from 5.48 to 7.99 mmol/L [212 to 309 mg/dL]) were randomized to receive simvastatin, 20 mg/d (titrated to 40 mg/d if necessary to lower total cholesterol level to <5.17 mmol/L [<200 mg/dL]) vs placebo.<sup>69</sup> At median follow-up of 5.4 years, simvastatin lowered LDL cholesterol levels by 37.4% in women and significantly reduced the risk of

the combined end point (all-cause mortality, CHD death, nonfatal MI, or resuscitated cardiac arrest) by 34% in both women and men. The need for CABG or PTCA was reduced by 49% in women (95% CI, 0.30-0.86). Both CHD and total mortality were significantly reduced in men; however, there was no significant reduction in CHD mortality and no benefit on total mortality in women (RR, 1.16; 95% CI, 0.68-1.99), a finding related to the lower total and CHD mortality of 6% and 4%, respectively, in women in the placebo group compared with 13% and 8%, respectively, in men. One potential reason for the lack of mortality differences is that women were more likely than men to be enrolled for only angina (37% vs 17%). Since chest pain in women is less likely to be associated with marked epicardial stenoses than in men, a majority of women with only angina in the Scandinavian Simvastatin Survival Study may not have had coronary artery disease as a cause of their chest pain. These sex differences must be considered when results of clinical trials that enrolled patients on the basis of a history of angina rather than MI or diagnostically confirmed CHD are interpreted.

In the Cholesterol and Recurrent Events (CARE) trial, 3583 men and 576 postmenopausal women with a history of MI and mean LDL cholesterol level of 3.59 mmol/L (139 mg/dL) were randomized to receive pravastatin sodium, 40 mg, or placebo.<sup>70</sup> At 5-year follow-up, the reduction in risk of CHD death or nonfatal MI was about twice as great in women randomized to receive pravastatin as in men (43% vs 21%). Although CHD mortality was significantly reduced in men but not in women, women had a greater reduction in nonfatal MI (51%) compared with men (15%). The need for PTCA or CABG was decreased by 48% and 39%, respectively, in women compared with 17% and 24% in men. Women experienced a 56% reduction in stroke ( $P = .07$ ). There was no reduction in total mortality for the total study population.

The Long-term Intervention With Pravastatin in Ischemic Disease (LIPID) trial, conducted in Aus-

tralia and New Zealand, randomized 7498 men and 1516 women with previous MI or unstable angina to receive pravastatin sodium, 40 mg/d, or placebo.<sup>71</sup> At an average follow-up of 6.2 years, pravastatin was associated with a 26% reduction in CHD death or nonfatal MI in men (95% CI, 17%-35%) but a nonsignificant 11% reduction in women. For the total study population, total mortality was reduced by 22%; CHD death, 24%; MI, 29%; CHD death or nonfatal MI, 24%; stroke, 19% ( $P=.048$ ); and revascularization, 20%. Mortality data for women were not reported.

A quantitative coronary angiographic trial also supports a benefit of statin drugs in women. Women with diffuse coronary atherosclerosis, various coronary risk factors, and total cholesterol levels between 5.69 and 7.76 mmol/L (220 and 300 mg/dL) enrolled in the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) were examined with repeated coronary arteriography 2 years after randomization to either lovastatin or placebo.<sup>72</sup> Lovastatin lowered LDL cholesterol level by 32% and total cholesterol level by 24%. Women taking lovastatin had less progression of coronary atherosclerosis and fewer new lesions than women receiving placebo.

The multicenter Women's Atorvastatin Trial on Cholesterol (WATCH) assessed the effectiveness of atorvastatin calcium in achieving NCEP target levels of LDL cholesterol in premenopausal and postmenopausal women with and without CVD and with dyslipidemia.<sup>73</sup> In this 16-week trial, atorvastatin treatment enabled 87% of women with 2 or more CHD risk factors and 80% of women with documented CHD to reach their LDL cholesterol goals. The trial showed that lowering LDL cholesterol level to the NCEP goal of 2.59 mmol/L (100 mg/dL) or less is feasible for the majority of women with dyslipidemia and CVD.

In summary, statins in primary and secondary prevention trials have demonstrated substantial effects in women: up to a 46% reduction in risk of major coronary events, together with significant beneficial effects on lipoproteins.<sup>68-72</sup> These randomized trials suggest that statins are at least

**Table 3. Effects of Pravastatin Compared With HRT on Lipid Levels\***

	Non-HDL-C	LDL-C	HDL-C	TG
CEE	-13.0†	-13.5†	+22.5†	+4.2
Pravastatin sodium	-23.7†	-25.4†	+3.7	-12.1†
CEE + pravastatin	-25.2†	-28.7†	+21.2†	-0.9

\*Shown as percentage change compared with baseline. HRT indicates hormone replacement therapy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; and CEE, conjugated equine estrogen. Adapted with permission from Davidson et al.<sup>74</sup>  
† $P<.05$  compared with baseline.

**Table 4. Effect of Atorvastatin and Estradiol on Lipid Levels\***

	TC	LDL-C	HDL-C	TG	VLDL-C
Placebo	+1	0	+2	+9	+12
Atorvastatin calcium	-31†	-43†	+4†	-7†	-14†
Estradiol	-3	-9	+11	+7	-4
Atorvastatin + estradiol	-30†	-46†	+16†	-5†	-18†

\*Shown as percentage change compared with baseline. TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; and VLDL-C, very-low-density lipoprotein cholesterol. Adapted from Heinonen et al.<sup>75</sup>  
† $P<.05$ , atorvastatin vs estradiol and estradiol vs atorvastatin + estradiol.

as effective for lowering cholesterol levels and reducing cardiovascular events in women as in men with CHD; thus, statins should be first-line therapy in postmenopausal women with CHD. In addition, it is reasonable to recommend statins as first-line therapy for postmenopausal women with elevated LDL cholesterol levels; however, it is also important to consider use of niacin for women who have low HDL cholesterol levels in addition to elevated LDL cholesterol levels.

#### Combination Therapy

Estrogen is very beneficial in alleviating hot flashes and vaginal dryness and atrophy; therefore, symptomatic menopausal women may require it for these symptoms. For hypercholesterolemic postmenopausal women, it is important to know the effects of HRT alone and in combination with various statins on lipid levels. Four recent trials in postmenopausal women have compared the effectiveness of HRT, a statin, or both.<sup>74-77</sup> In a 4-arm trial, 76 women with hypercholesterolemia were randomized to receive treatment with 0.625 mg of conjugated equine estrogen alone; pravastatin sodium, 20 mg, alone; both combined; or placebo. Non-HDL cholesterol and LDL cholesterol levels were

significantly reduced in all active-treatment arms, least so by estrogen monotherapy (**Table 3**).<sup>74</sup> Both estrogen-treated groups saw a marked rise in HDL cholesterol levels (22.5% and 21.2%), compared with only a 3.7% increase in the group treated with pravastatin alone (Table 3). In sum, combination treatment more favorably affected the lipid profile than either estrogen or pravastatin alone.<sup>74</sup>

A parallel design was used to compare atorvastatin calcium, 10 mg; estradiol, 1 mg; atorvastatin plus estradiol; or placebo in 83 postmenopausal women in a 12-week trial. Lipid changes in the atorvastatin and atorvastatin plus estradiol groups were of similar magnitude and significantly greater than in the estradiol group (**Table 4**). Atorvastatin reduced total cholesterol level by 31%, LDL cholesterol level by 43%, and triglyceride levels by 7% and increased HDL cholesterol level by 4%. Combination therapy increased HDL cholesterol level by 16%.<sup>75</sup> Therefore, the advantage of combination therapy is a greater increase in HDL cholesterol level. Since low levels of HDL cholesterol level may be a strong risk factor for CHD in women, it is important to increase HDL levels as much as possible.

The effects of estrogen and statin therapies on vascular function were

studied in 28 hypercholesterolemic postmenopausal women with a mean age of 57 years.<sup>76</sup> The combination of conjugated equine estrogen, 0.625 mg, and simvastatin, 10 mg, lowered LDL cholesterol level more than did either alone (2.92 mmol/L [113 mg/dL] for combination vs 3.72 mmol/L [144 mg/dL] for estrogen alone and 3.13 mmol/L [121 mg/dL] for simvastatin alone) and also lowered the ratio of LDL/HDL cholesterol to a greater degree. Estrogen alone or in combination with statin therapy reduced levels of lipoprotein(a) and plasminogen activator inhibitor 1, a marker of fibrinolytic activity. Similarly, estrogen alone or in combination therapy significantly reduced levels of markers of inflammation: E-selectin, intercellular adhesion molecule, and vascular cell adhesion molecule. C-reactive protein, an inflammatory marker increased by estrogen, was not examined. Only estrogen significantly improved flow-mediated dilation of the brachial artery, and only statins significantly reduced triglyceride levels. Although both treatments were beneficial, only the inclusion of estrogen improved fibrinolysis and inflammation considered to be important in atherogenesis. This study suggests that estrogen may provide additional vasculoprotective benefit to hypercholesterolemic postmenopausal women already receiving statin therapy; however, further research will be necessary to determine the net effect of estrogen on all markers of inflammation, including C-reactive protein.

In a randomized, crossover, placebo-controlled 8-week study of 16 postmenopausal women with hypercholesterolemia and CHD, simvastatin alone (20 mg) and simvastatin with 0.625 mg of estrogen and 2.5 mg of medroxyprogesterone acetate (HRT) were similarly effective in significantly lowering total cholesterol level (35% and 33%, respectively) and LDL cholesterol level (45% and 46%, respectively) compared with placebo and significantly more effective than HRT alone, which lowered LDL cholesterol level by 20%.<sup>77</sup> Simvastatin reduced triglyceride levels by 33% in contrast to HRT plus simvastatin, which lowered triglyceride levels by 13.9%, and HRT, which had

no effect. The HDL cholesterol levels were not significantly altered by any treatment.

It is important that HRT will not lower LDL cholesterol levels to goal (<2.59 mmol/L [ $<100$  mg/dL]) in women with established CVD unless the baseline LDL cholesterol level is 3.10 to 3.18 mmol/L (120-123 mg/dL), assuming the average reduction of 14.5% to 17.5% observed with estrogen and/or progestin over 3 years in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.<sup>78</sup> Thus, women with CVD who require estrogen for menopausal symptoms will almost always also require a statin or other lipid-lowering drug to reach LDL cholesterol goal.

#### CURRENT AND FUTURE RESEARCH PROSPECTS

Since difficulties in diagnosing CHD in women on the basis of chest pain and noninvasive testing may contribute to lower referral rates for catheterization and revascularization, it is important to improve symptom evaluation and diagnosis of ischemic heart disease in women. The Women's Ischemia Syndrome Evaluation (WISE), sponsored by the National Heart, Lung, and Blood Institute, will address this issue and is hoped to add to the limited information about the pathophysiology of ischemia without substantial epicardial coronary artery stenoses, a syndrome more common in women than men, as noted earlier.<sup>79</sup>

The Women's Health Initiative Study Group is conducting a long-term, comprehensive clinical investigation of strategies to prevent and control the most common causes of morbidity and mortality among postmenopausal women.<sup>63</sup> These include cancer, CVD, and osteoporotic fractures. A clinical trial will evaluate 3 interventions: a low-fat diet, HRT, and calcium and vitamin D supplementation. An observational study is a separate component of the overall investigation planned for completion in 2007.

A prospective, randomized, double-blind study, the Beyond Endorsed Lipid Levels Evaluation Study (BELLES), which is currently recruiting postmenopausal women,

will compare the effects of 12 months' treatment with atorvastatin or pravastatin on regression of coronary atherosclerosis. Efficacy will be determined by the percentage change from baseline in total plaque volume as measured by electron beam computed tomography.

#### CONCLUSIONS

Despite the abundant evidence that CVD is virtually epidemic in older women, the belief that women have innate protection from coronary events still prevails. In the face of considerable morbidity and mortality rates, prevention and treatment strategies are still less aggressive for women than for men. The control of CHD risk factors in women will require recognition of the differences as well as the similarities between men and women in manifestation of risk factors.

The rate of CHD can be reduced by aggressively lowering LDL cholesterol to levels recommended by the NCEP guidelines, which recommend an LDL cholesterol goal of 2.59 mmol/L (100 mg/dL) or less for men and women with documented CHD. For those without CHD, NCEP guidelines recommend an LDL cholesterol goal of less than 3.36 mmol/L (130 mg/dL) for those with 2 or more risk factors for CHD and less than 4.14 mmol/L (160 mg/dL) for those with 1 or no risk factors for CHD. Diet and exercise should be tried first. Although few primary and secondary prevention trials have included women until recently, available data suggest that women can substantially benefit from lipid-lowering drug therapies if diet and exercise fail to lower LDL cholesterol level to goal. Statins have proved particularly effective in lowering women's CHD risks and mortality. Estrogen and HRTs to reduce CHD risk have been popular among postmenopausal women, but in view of the recent HERS and ERA findings, results of future trials will be required to define the true benefit in reducing cardiovascular risk before it can be safely prescribed in this clinical context. On the basis of the HERS and ERA results, statin drugs should be the drug of first choice for women with established

CHD. Hypercholesterolemic postmenopausal women who require estrogen for menopausal symptoms may derive further lipid-lowering benefits with the addition of a statin drug.

Finally, the population of older women can be expected to increase in the coming decades. A major public health problem will doubtless ensue if clinical issues fail to be addressed now.

Accepted for publication September 18, 2000.

Corresponding author and reprints: Francine K. Welty, MD, PhD, 1 Autumn St, Fifth Floor, Boston, MA 02215 (e-mail: fwelty@caregroup.harvard.edu).

## REFERENCES

- Eaker ED, Chesebro JH, Sacks FM, Wenger NK, Whisnant JP, Winston M. Cardiovascular disease in women. *Circulation*. 1993;88:1999-2009.
- Mosca L, Manson JE, Sutherland SE, Langer RD, Manolio T, Barrett-Connor E. Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1997;96:2468-2482.
- Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease advantage. *Arch Intern Med*. 1995;155:57-61.
- Rich-Edwards JW, Manson JE, Hennekens CH, Buring JE. The primary prevention of coronary heart disease in women. *N Engl J Med*. 1995;332:1758-1766.
- American Heart Association. 1999 *Heart and Stroke Statistical Update*. Dallas, Tex: American Heart Association; 1998:1-29.
- Anderson RN, Kochanek KD, Murphy SL. Report of final mortality statistics, 1995. *Mon Vital Stat Rep*. 1997;45(suppl 2):1-80.
- Welty FK. Who should receive hormone replacement therapy? *J Thromb Thrombolysis*. 1996;3:13-21.
- Murabito JM. Women and cardiovascular disease: contributions from the Framingham Heart Study. *J Am Med Womens Assoc*. 1995;50:35-55.
- Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986;111:383-390.
- Orencia A, Bailey K, Yawn BP, Kottke T. Effect of gender on long-term outcome of angina pectoris and myocardial infarction/sudden unexpected death. *JAMA*. 1993;269:2392-2397.
- Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction: results from the Myocardial Infarction Triage and Intervention Registry. *Arch Intern Med*. 1992;152:972-976.
- Cunningham MA, Lee TH, Cook EF, et al. The effect of gender on the probability of myocardial infarction among emergency department patients with acute chest pain: a report from the multicenter chest pain study group. *J Gen Intern Med*. 1989;4:392-398.
- Chaitman BR, Bourassa MG, Davis K, et al. An-  
giographic prevalence of high-risk coronary artery disease in patient subsets (CASS). *Circulation*. 1982;64:360-367.
- Ayanian JZ, Epstein AM. Differences in the use of procedures between men and women hospitalized for coronary heart disease. *N Engl J Med*. 1991;325:221-225.
- Association of Professors of Gynecology and Obstetrics (APGO). *Managing Hyperlipidemia in Women*. Washington, DC: APGO; 1999. APGO Educational Series on Women's Health Issues.
- Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing: correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). *N Engl J Med*. 1979;301:230-235.
- Barolsky SM, Gilbert CA, Faruqui A, et al. Differences in electrocardiographic response to exercise of women and men: a non-Bayesian factor. *Circulation*. 1979;60:1021-1027.
- Guiteras VP, Chaitman BR, Waters DD, et al. Diagnostic accuracy of exercise ECG lead systems in clinical subsets of women. *Circulation*. 1982;65:1465-1474.
- Detry JM, Kapita MB, Cosyns J, et al. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. *Circulation*. 1977;56:756-761.
- Hung J, Chaitman BR, Lam J, et al. Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy, exercise electrocardiography and exercise thallium perfusion scintigraphy. *J Am Coll Cardiol*. 1984;4:8-17.
- Melin JA, Piret LJ, Vanbutsele RJM, et al. Diagnostic value of exercise electrocardiography and thallium myocardial scintigraphy in patients without previous myocardial infarction: a Bayesian approach. *Circulation*. 1981;63:1019-1024.
- Tobin JN, Wassertheil-Smoller S, Wexler JP, et al. Sex bias in considering coronary bypass surgery. *Ann Intern Med*. 1987;107:19-25.
- Steingart RM, Packer M, Hamm P, et al, for the Survival and Ventricular Enlargement Investigators. Sex differences in the management of coronary artery disease. *N Engl J Med*. 1991;325:226-230.
- Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. *N Engl J Med*. 1987;316:1105-1110.
- Johnson CL, Rifkind BM, Sempos CT, et al. Declining serum total cholesterol levels among US adults: the National Health and Nutrition Examination Surveys. *JAMA*. 1993;269:3002-3008.
- Campos H, McNamara JR, Wilson PWF, Ordozva JM, Schaefer EJ. Differences in low density lipoprotein subfractions and apolipoproteins in premenopausal and postmenopausal women. *J Clin Endocrinol Metab*. 1988;67:30-35.
- Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis*. 1993;98:83-90.
- Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and women: review of an NHLBI workshop. *Ann Epidemiol*. 1992;2:161-176.
- Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. *N Engl J Med*. 1989;321:641-646.
- Walsh JM, Grady D. Treatment of hyperlipidemia in women. *JAMA*. 1995;274:1152-1158.
- Corti M-C, Guralnik JM, Salive ME, et al. HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA*. 1995;274:539-544.
- LaRosa JC. Triglycerides and coronary risk in women and the elderly. *Arch Intern Med*. 1997;157:961-968.
- Castelli WP. The triglyceride issue: a view from Framingham. *Am Heart J*. 1986;112:432-437.
- Campos H, Blijlevens E, McNamara JR, et al. LDL particle size distribution: results from the Framingham offspring study. *Arterioscler Thromb*. 1992;12:1410-1419.
- Austin MA, Breslow C, Hennekens CH, Buring JE, Willett WS, Krauss RM. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA*. 1988;260:1917-1921.
- Willett WC, Green A, Stampfer MJ, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med*. 1987;317:1303-1309.
- Kitler ME. Differences in men and women in coronary artery disease, systemic hypertension and their treatment. *Am J Cardiol*. 1992;70:1077-1080.
- Anastos K, Charney P, Charon RA, et al, for the Women's Caucus, Working Group on Women's Health of the Society of General Internal Medicine. Hypertension in women: what is really known? *Ann Intern Med*. 1991;115:287-293.
- Goldschmid MG, Barrett-Connor E, Edelstein SL, Wingard DL, Cohn BA, Herman WH. Dyslipidemia and ischemic heart disease mortality among men and women with diabetes. *Circulation*. 1994;89:991-997.
- Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1987;30:123-131.
- Krowlewski AS, Warram JF, Valsanie P, et al. Evolving natural history of coronary artery disease in diabetes mellitus. *Am J Med*. 1991;90(suppl):52S-56S.
- Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med*. 1990;322:882-889.
- Folsom AR, Kaye SA, Sellers TA, et al. Body fat distribution and 5-year risk of death in older women. *JAMA*. 1993;269:483-487.
- Manson JE, Hu FB, Rich-Edwards JW, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *N Engl J Med*. 1999;341:650-658.
- American Diabetes Association. Detection and management of lipid disorders in diabetes. *Diabetes Care*. 1996;19(suppl):S96-S102.
- Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. *N Engl J Med*. 1993;329:247-256.
- Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med*. 1991;20:47-63.
- McCrohan R, Adams MR, McCredie RJ, et al. Hormone replacement therapy is associated with improved arterial physiology in healthy postmenopausal women. *Clin Endocrinol*. 1996;45:435-441.
- Greiner DZ, Bradley E, Andrews TC. Effects of withdrawal of chronic estrogen therapy on brachial artery vasoreactivity in women with coronary artery disease. *Am J Cardiol*. 1999;83:247-249.
- Reis SE, Gloth ST, Blumenthal RS, et al. Ethinyl estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. *Circulation*. 1994;89:52-60.
- Lieberman EH, Gerhard MD, Uehata A, et al. Es-

- trogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med.* 1994;121:936-941.
52. Gilligan DM, Quyyumi AA, Cannon RO. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. *Circulation.* 1994;89:2545-2551.
  53. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO. Effects of estrogen replacement therapy on peripheral vasomotor function in postmenopausal women. *Am J Cardiol.* 1995;75:264-268.
  54. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation.* 1987;75:1102-1109.
  55. Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605-613.
  56. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation.* 1998;98:731-733.
  57. Cushman M, Meilahn EN, Psaty BM, et al. Hormone replacement therapy, inflammation, and hemostasis in elderly women. *Arterioscler Thromb Vasc Biol.* 1999;19:893-899.
  58. Folsom AR, Mink PJ, Sellers TA, Hong CP, Zheng W, Potter JD. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. *Am J Public Health.* 1995;85:1128-1132.
  59. Paganini-Hill A, Ross R, Henderson B. Endometrial cancer and patterns of use of oestrogen replacement therapy: a cohort study. *Br J Cancer.* 1989;59:445-447.
  60. Buring JE, Bain CJ, Ehrmann RL. Conjugated estrogen use and risk of endometrial cancer. *Am J Epidemiol.* 1986;124:434-441.
  61. Shapiro S, Kelly J, Rosenberg L, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. *N Engl J Med.* 1985;313:969-972.
  62. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med.* 2000;343:522-529.
  63. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19:61-109.
  64. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA.* 1993;269:3015-3023.
  65. Miller M, Byington RP, Hunninghake D, Furberg CD, Pitt B, for the PREVENT Investigators. Lipid lowering therapy in CAD patients at academic medical centers: undertreatment and evidence of a gender gap [abstract]. *J Am Coll Cardiol.* 1998;31(suppl):A186.
  66. Schrott HG, Bittner V, Vittinghoff E, Herrington DM, Hulley S, for the HERS Research Group. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: the Heart and Estrogen/Progestin Replacement Study (HERS). *JAMA.* 1997;277:1281-1286.
  67. Dorr AE, Gunderson K, Schneider JC, et al. Colestipol hydrochloride in hypercholesterolemic patients: effect on serum cholesterol and mortality. *J Chron Dis.* 1978;31:5-14.
  68. Downs JR, Clearfield M, Weis S, et al, for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA.* 1998;279:1615-1622.
  69. Miettinen TA, Pyorala K, Olsson AG, et al, for the Scandinavian Simvastatin Survival Study Group. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris. *Circulation.* 1997;96:4211-4218.
  70. Lewis SJ, Sacks FM, Mitchell JS, et al, for the CARE investigators. Effect of pravastatin on cardiovascular events in women after myocardial infarction: the Cholesterol and Recurrent Events (CARE) trial. *J Am Coll Cardiol.* 1998;32:140-146.
  71. LIPID Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:1349-1357.
  72. Waters D, Higginson L, Gladstone P, et al, for the CCAIT Study Group. Effects of cholesterol lowering on the progression of coronary atherosclerosis in women: a Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) substudy. *Circulation.* 1995;92:2404-2410.
  73. McPherson R, Genest J Jr, Angus C, Murray P. The Women's Atorvastatin Trial on Cholesterol (WATCH): frequency of achieving NCEP-II target LDL-C levels in women with and without established CVD. Abstract presented at: 71st European Atherosclerosis Society Congress and Satellite Symposia; May 28, 1999; Athens, Greece.
  74. Davidson MH, Testolin LM, Maki KC, von Duvillard S, Drennan KB. A comparison of estrogen replacement, pravastatin, and combined treatment for the management of hypercholesterolemia in postmenopausal women. *Arch Intern Med.* 1997;157:1186-1192.
  75. Heinonen T, Schrott H, Broyles F, et al. The effects of atorvastatin in postmenopausal women. In: *Abstracts of the 66th Congress of the European Society of Atherosclerosis, Florence, Italy, July 13-17, 1996.* Houston, Tex: Giovanni Lorenzini Medical Foundation; 1996:56.
  76. Koh KK, Cardillo C, Bui MN, et al. Vascular effects of estrogen and cholesterol-lowering therapies in hypercholesterolemic postmenopausal women. *Circulation.* 1999;99:354-360.
  77. Sbarouni E, Kyriakides ZS, Kremastinos DTH. The effect of hormone replacement therapy alone and in combination with simvastatin on plasma lipids of hypercholesterolemic postmenopausal women with coronary artery disease. *J Am Coll Cardiol.* 1998;32:1244-1250.
  78. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA.* 1995;273:199-208.
  79. Merz CNB, Kelsey SF, Pepine CJ, et al, for the WISE Study Group. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. *J Am Coll Cardiol.* 1999;33:1453-1461.