REVIEW

HANI JNEID, MD
Department of Internal Medicine, Cleveland Clinic

HOLLY L. THACKER, MD
Head, Section of Women's Health, Departments of General Internal Medicine and Obstetrics and Gynecology, Cleveland Clinic; Director of Women's Health Track GIM Fellowship, Clinical Associate Professor of Medicine, Penn State University

Coronary artery disease in women: Different, often undertreated

ABSTRACT

Cardiovascular disease is responsible for more deaths in women each year than all other causes combined. Women have different cardiac presentations than men and are more likely to be underdiagnosed and undertreated for coronary artery disease. This article addresses gender-specific issues in prevention, diagnosis, and treatment of coronary artery disease.

KEY POINTS

Premenopausal women have a lower incidence of cardiovascular events than men, presumably because estrogen has cardioprotective effects.

Diabetes eliminates the protective advantage of female gender in premenopausal women.

Hormone replacement therapy is an important therapeutic option for postmenopausal women with risk factors for coronary artery disease, although it is not specifically indicated for secondary prevention.

Lipid markers have different predictive values in men and women. However, statin agents are first-line therapy to reduce cardiovascular events in both genders.

A healthy lifestyle plays a significant role in reducing the incidence of coronary heart disease in women.

DISCLOSURE: This paper discusses treatment information that is "off-label," ie, not approved by the Food and Drug Administration for the indication under discussion.

IN CORONARY ARTERY DISEASE, gender matters. Although coronary artery disease is a major public health problem in both sexes, it does not receive the attention and concern in women that it receives in men.

Risk factors carry different predictive values in women than in men, necessitating a gender-specific approach to primary and secondary prevention. Furthermore, documented differences exist in the manifestations in men and women, making it more likely that coronary artery disease will be overlooked or discounted. Of particular concern: women with coronary artery disease are more likely than men to receive suboptimal and less-aggressive care.

Complicating any discussion of coronary risk and treatment in women is the issue of hormone replacement therapy: although hormone replacement has effects on serum lipid levels that should reduce risk, prospective studies in women with established coronary artery disease have failed to show a benefit.

CORONARY DISEASE: THE SINGLE LARGEST KILLER OF WOMEN

Contrary to popular perception, coronary artery disease is the primary cause of death in women, responsible for more deaths in women each year than all other causes combined: more than a quarter million. Although coronary artery disease mortality has been on the decline in the United States (recent data from the Nurses' Health Study[1] showed a 31% decrease in coronary artery disease incidence in women from the 2-year period 1980–1982 to the 2-year period 1992–1994), the rates of decline have been slower in women than in men.[2] More importantly, women with coro-

TABLE 1

Major risk factors for coronary artery disease in women

- Cigarette smoking
- Diabetes mellitus
- Dyslipidemia
- Hypertension (including systolic hypertension)
- Obesity
- Sedentary lifestyle

nary artery disease have a higher mortality rate than do men with coronary artery disease.[3]

Yet women and even many of their physicians underestimate the risk of coronary artery disease. Although many women think they are at higher risk of death from breast cancer, in fact, the risk of a 50-year-old Caucasian woman dying of coronary artery disease is 10 times greater than the mortality risk from hip fracture and breast cancer combined.[4] And for African-American and Hispanic women the risk is even higher.

Diabetes increases risk more for women than for men

A source of the confusion is that women are generally older than men at the onset of coronary artery disease. The Framingham study showed that women have a lower incidence of coronary artery disease than men do up until age 75.[5] Presumably this is because endogenous estrogen in premenopausal women is cardioprotective. Supporting this assumption are observational data from prematurely menopausal women and women who underwent bilateral oophorectomy without hormone replacement therapy, who have a higher risk for coronary artery disease than premenopausal women of the same age.[6,7]

SOME RISK FACTORS ARE DIFFERENT FOR WOMEN

The major risk factors for coronary artery disease in women were defined in a statement from the American Heart Association and the American College of Cardiology (TABLE 1).[8] Although most of these risk factors are similar in men and women, some gender differences have been documented, especially in dyslipidemia and diabetes. The statement asserts that coronary artery disease is largely preventable.

Hypertension: More common in women

Hypertension is more common in American women than in American men, because the prevalence of hypertension increases with age, and women live longer. Renovascular hypertension due to fibromuscular dysplasia is more common in women than in men, although other causes of secondary hypertension occur equally in both genders.[9]

As in men, left ventricular hypertrophy, a consequence of hypertension, carries an increased risk of cardiac events in women. It is important to use gender-specific echocardiographic criteria for left ventricular mass, because even after controlling for body size, left ventricular mass is lower in women.

Today's oral contraceptive pills, which contain low doses of synthetic estrogen and progestin, carry minimal risk of increasing blood pressure, but nevertheless can sometimes cause hypertension by activating the renin-angiotensin system.

Diabetes triples the risk

Diabetes mellitus is a more powerful risk factor for women than for men. In one study,[10] mortality rates from coronary artery disease were three to seven times higher in diabetic women than nondiabetic women, compared with two to four times higher in diabetic men than in nondiabetic men. The Framingham Study[11] found that diabetes doubled the age-adjusted risk for cardiovascular disease in men and tripled it in women.

Diabetes eliminates the protective effect of female gender: premenopausal women with diabetes have approximately the same risk as diabetic men of the same age. The mechanism may be by impairing estrogen binding.[12]

Diabetes also decreases the beneficial effects of hormone replacement therapy on serum lipid levels. In nondiabetic women, hormone replacement therapy causes high-density lipoprotein (HDL) levels to rise. One cross-sectional study[13] showed that hormone replacement therapy appeared to reduce low-density lipoprotein (LDL) levels by a similar amount in diabetic and nondiabetic women, but it increased HDL levels less in diabetic

women and it increased triglyceride levels more.

After a myocardial infarction, diabetic women have a higher mortality rate compared with nondiabetic persons.[14] Diabetes is an independent risk factor for poor outcome after percutaneous transluminal angioplasty in both genders.[15]

Lipids: Low HDL is a stronger predictor of risk

Gender differences exist when predicting coronary artery disease risk on the basis of lipid profiles.

Low HDL levels are a stronger predictor of risk in women than in men.[16,17]

High LDL levels do not constitute as strong a risk factor for coronary artery disease as low HDL levels in women who do not yet have evidence of coronary disease.[18,19]

On the other hand, LDL reduction has comparable benefits for men and women with known coronary artery disease. The Scandinavian Simvastatin Survival Study (4S),[20] a randomized placebo-controlled study in men and women with established coronary artery disease, showed that taking the lipid-lowering drug simvastatin reduced the risk of major coronary events by about 35% regardless of gender.

Elevated triglyceride levels appear to be an independent predictor of coronary artery disease in older women.[18]

Lipoprotein (a). It is uncertain whether lipoprotein (a) [Lp(a)] is an independent risk factor for coronary artery disease in women. Despite conflicting results of a prospective study of men, there is a suggestion of a stronger association between Lp(a) and coronary artery disease risk in younger women.[21,22] Statins and other widely used lipid-lowering drugs do not reduce Lp(a), but estrogen and niacin do.

Guidelines the same. The National Cholesterol Education Program (NCEP) guidelines for therapy for men and women are based on LDL levels and do not include triglyceride or HDL levels except as modifying factors.[23] New NCEP guidelines are expected soon.

Statin drugs may have other benefits. A recent case-control study from the United States found that women older than 60 years who took statins were less likely to suffer nonpathological fractures.[24] This finding is supported by another contemporary population-based, case-control analysis from the United Kingdom,[25,26] which revealed a 45% lower fracture risk in women over 50 years old who used statins compared with those who did not use lipid-lowering agents. Although these two studies did not prove that statins improve bone mass or reduce fracture risk, this is an area of research to follow closely.

IS HORMONE REPLACEMENT BENEFICIAL? WHAT STUDIES SHOW

As primary cardiovascular prevention (ie, in apparently healthy women), hormone replacement therapy may have additive effects when combined with conventional lipid-lowering drugs, or even supplant them for some women who have other indications for hormone replacement. However, hormone replacement therapy is not currently recommended for secondary prevention, ie, to prevent coronary events in women with known coronary artery disease.

As primary prevention, hormone replacement should lower risk

Menopause, whether natural, surgical, or premature, may constitute a risk factor for heart disease in women. Various observational studies indicated that postmenopausal women who take hormone replacement therapy have a 40% to 50% lower risk of coronary artery disease compared with those not taking hormone replacement therapy.[27]

A major question remains whether hormone users have healthier lifestyles and whether the characteristics of hormone users, rather than the hormone replacement per se, account for the large reduction in cardiovascular disease seen in the observational studies.

Nevertheless, a recent prospective observational study of postmenopausal hormone therapy[28] showed a significantly decreased risk of 40% for major coronary events in women without previous heart disease. The study controlled for lifestyle factors, including body mass index, diabetes, and tobacco use. Women who took the ultra-low doses (0.3 mg) of oral conjugated equine estrogen

Low HDL is a stronger risk factor in women than in men

TABLE 2

Benefits of hormone replacement therapy in cardiovascular disease risk reduction

Increases high-density lipoprotein
Decreases low-density lipoprotein
Decreases fibrinogen levels
Decreases fasting insulin levels
Decreases lipoprotein (a) levels

enjoyed a cardiovascular risk reduction similar to that seen with the standard daily dose of 0.625 mg.

Mixed effect on lipids. If hormone replacement therapy does decrease the risk of coronary artery disease, it may do so through its effect on lipid levels.

In the Postmenopausal Estrogen/Progestin Intervention Trial (PEPI),[29] published in 1995, oral conjugated equine estrogen therapy significantly reduced LDL levels and increased HDL levels (TABLE 2). Adding progestin attenuated but did not eliminate the increase in HDL, and had no effect on LDL reduction.

Hormone replacement lowers LDL and raises HDL, but raises triglycerides

On the other hand, estrogen raised triglyceride levels by as much as 15%, especially in those with elevated triglyceride levels at baseline, by increasing the production of very-low density lipoprotein (VLDL). Progestin did not counteract this effect.

Elevated baseline levels of triglycerides mandate careful monitoring of lipid levels following institution of hormone therapy. A switch to the transdermal patch may be necessary since the patch has no impact on triglyceride levels.[30]

Although the National Cholesterol Education Program Guidelines do not consider estrogen a first-line lipid-lowering therapy, many clinicians believe that it should be considered as such in postmenopausal women with hypercholesterolemia and low HDL. This is particularly important if there are other indications for estrogen treatment, such as menopausal symptoms or osteoporosis prevention.

As secondary prevention, hormone replacement has uncertain benefit

The long-term effects of hormone replacement therapy on established heart disease are still uncertain.

The Heart and Estrogen/Progestin Replacement Study (HERS),[31,32] a randomized, double-blind placebo-controlled trial, addressed the role of hormone replacement therapy in secondary prevention of coronary artery disease events. A total of 2,763 postmenopausal women with preexisting coronary artery disease were randomized to receive combined hormone replacement therapy (conjugated equine estrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg daily) or placebo. After a mean of 4.1 years follow-up, there was no difference in the primary combined end point of nonfatal myocardial infarction or coronary artery disease death.

The lack of benefit from hormone replacement therapy was attributed to several factors. Follow-up may have been too short for the presumed antiatherogenic effects of hormone replacement to become manifest. In the "statin era" during which this study took place, the event rates were lower than anticipated in the placebo group, giving the study less statistical power than anticipated.

Of interest, during the first year of the study the incidence of coronary artery disease events was *higher* in the group receiving hormone replacement than in the placebo group. This increase may have been due to chance—or it may have a physiologic basis. A possible explanation is that hormone replacement has early prothrombotic effects in some susceptible women, which are later outweighed by benefits in atherosclerosis.[31,32]

Another possible explanation: A retrospective subgroup analysis from the HERS trial suggested that variations in Lp(a) levels may explain the early risk for coronary artery disease events in the trial, and that women with heart disease and low Lp(a) values were harmed by hormone replacement.

The PEPI trial[29] found that hormone replacement therapy lowered fibrinogen levels with little effect on insulin levels and blood pressure, which are desirable effects and argue against the thrombotic hypothesis. However, a look-back analysis of the PEPI trial[33] showed a

large sustained increase in the concentration of C-reactive protein (up to 85%) in postmenopausal women taking hormone replacement therapy. These data suggest that hormone replacement therapy may adversely affect women with established coronary artery disease through increased inflammation mediators, possibly related to plaque destabilization, or thrombosis (TABLE 3).

The Estrogen Replacement and Atherosclerosis Trial (ERA) showed no benefit of postmenopausal hormone replacement therapy (conjugated equine estrogen alone or in combination with medroxyprogesterone) on the angiographic progression of coronary artery disease in women with established coronary artery disease after an average of 3 years of follow-up.[34] Importantly, no early harm with hormone replacement therapy was found.

Who should receive hormone replacement therapy?

While waiting for the 7-year follow-up data from the HERS trial, one should not extrapolate these negative secondary prevention findings to healthy women free of known coronary artery disease. The Women's Health Initiative is examining the effect of hormone replacement therapy in primary prevention, and results should be available by 2006.

The decision to start hormone replacement therapy should be individualized and based on:

- Presence or absence of risk factors for coronary artery disease
- Risk of osteoporosis
- Risk of breast, endometrial, or colon cancer
- Quality-of-life concerns.

HEALTHY LIFESTYLE DECREASES RISK BUT FEW WOMEN FOLLOW IT

Data from the Nurses' Health Study[35] indicates that a healthy lifestyle could reduce the risk of coronary artery disease dramatically—by as much as four fifths. Unfortunately, very few women adhere to such a healthy lifestyle.

The investigators identified a group of women who had a "low-risk lifestyle." Specifically, these women:

TABLE 3

Risks of hormonal replacement therapy with respect to cardiovascular disease

Increases triglyceride levels with oral estrogens in some susceptible women

Increases ultrasensitive C-reactive protein levels

Increases relative risk of thromboembolic events, particularly in the early months of use (absolute risk is low)

- Did not smoke
- Had a body mass index less than 25
- Engaged in 30 minutes of moderate to vigorous exercise daily
- Consumed, on the average, at least 5 g of alcohol per day (equivalent to about a half a glass of wine)
- Adhered to a healthy diet.

During 14 years of follow-up, this low-risk group had an 83% lower incidence of coronary events compared with the other women in the cohort. The investigators estimated that 82% of the coronary events in the study cohort could be attributed to lack of adherence to this low-risk pattern. Unfortunately, only 3% of the study cohort were in the lowest-risk group.

Obesity: Even being merely overweight doubles the risk

The prevalence of obesity has increased among men, women, and children in the United States in the past decade. One third of adult women are classified as obese, ie, having a body mass index over 30. In the Nurses' Health Study,[36] involving more than 120,000 middle-aged women, the risk of coronary artery disease was nearly twice as high in mildly to moderately overweight women (body mass index 25 to 28.9) as in very lean women (body mass index 21).

Even after accounting for the influence of other known risk factors, obesity is still an independent risk factor for coronary artery disease mortality in women and therefore should be aggressively treated.[37] The pattern of obesity may be important, with the abdominal android-type (upper, apple-shaped) obesity conferring a greater risk than the gynecoid-

Some suggest that hormone replacement harms women with established coronary disease

type (pear-shaped). This association is found to be independent of the degree of obesity.

Physical activity: It's never too late to start

Physical activity reduces the incidence of coronary artery disease and all causes of mortality in women, presumably through its beneficial effect on body weight and HDL levels.[38,39] Prospective data from a large cohort of women in the Nurses' Health Study showed that brisk walking (3 hours/week) and vigorous exercise (1.5 hours/week) reduced the incidence of coronary events by 30% to 40%.[40] Even in middle adulthood or later, a change from a sedentary lifestyle to an active lifestyle confers a lower coronary risk in women.

Alcohol consumption: A mixed benefit

Light-to-moderate alcohol drinking has been associated with a decreased risk of cardiovascular death.

On the other hand, women are much more sensitive to the effects of alcohol than are men, and heavier drinking by women is associated with increased mortality from other causes, especially cirrhosis and possibly breast cancer. Alcohol contributes to hypertension, obesity, and the problem of alcoholism in women.

Women are less likely than men to stop smoking

Current guidelines from the American Heart Association and the American College of Cardiology[41] recommend limiting alcohol to 1 drink or less per day for women (4 ounces wine, 12 ounces beer, or 1.5 ounces of 80-proof liquor).

Smoking: On the rise in young women

Although the prevalence of smoking has been declining in both men and women, it has been declining more slowly in women than in men. Of concern, smoking is strikingly on the rise in young women.

A woman who smokes has a two to four times higher risk of coronary artery disease than a nonsmoking one. The risk appears to be present even with minimal exposure (so-called "low-yield" cigarettes), and the relation follows a dose-response curve.[12] Fortunately, most of the increased cardiovascular disease risk induced by tobacco begins to decline within months of cessation and completely dissipates within 2 to 3 years, unlike lung cancer risk.

There is striking synergism between smoking and use of oral contraceptives in increasing coronary artery disease risk, especially in women over age 35. The duration of smoking does not affect this risk among current users, and the risk rapidly returns to baseline after stopping the oral contraceptive. Possibly a short-term mechanism such as accelerated risk of atherothrombosis accounts for the increased coronary artery disease risk. Therefore, smoking cessation is a very gratifying clinical intervention. Nevertheless, women are less likely than men to quit, owing to concerns of secondary weight gain. Tobacco reduces the age of menopausal onset by 1 to 2 years.

CORONARY PRESENTATION IS DIFFERENT IN WOMEN

Women have a very different coronary presentation than men. According to the Framingham Heart Study,[42,43] angina is the most frequent initial coronary presentation in women, while men tend to present initially with myocardial infarction. Women with coronary artery disease tend to be older and have more comorbid illnesses, which add more diagnostic confusion. Women are also more likely than men to experience pain at rest, during sleep, and with mental stress; neck and shoulder pain; abdominal pain; and nausea and vomiting. In addition, women are more prone to noncardiac chest pain in general.[44,45] Therefore, chest pain is a poorer predictor of coronary artery disease in women compared to men. But in women older than 65 years, exertional chest pain is as likely to be ischemic as it is in men.

Mechanisms may differ. Women may have different mechanisms of coronary artery disease, with more prevalence of vasospastic angina (syndrome X) and microvascular angina, which have more favorable prognoses. However, women also have a higher incidence of nontransmural myocardial infarctions and clinically silent myocardial infarctions.

Exercise stress electrocardiography has lower sensitivity and specificity in women than in men presenting with chest pain.[8] This can be attributed to the lower prevalence of

coronary artery disease in younger women, lower prevalence of multivessel disease, and higher repolarization abnormalities in women. However, using the abnormal heart recovery score,[46] stress electrocardiography was found to have equal prognostic value among middle-aged men and women in predicting mortality over a 5-year follow-up. (The heart rate recovery score is the difference between the heart rates at peak exercise and 1 minute into recovery. A value of 12 or less has been shown to predict mortality in both genders. A value of 8 or less has been shown to predict all-cause death as well.) Abnormal heart recovery was an independent predictor of mortality in women, and was predictive of death in screening and in symptomatic patients, conferring risk-stratification power even over the Duke treadmill score.

WOMEN RECEIVE LESS AGGRESSIVE CARE

Cross-sectional studies showed that women are less likely than men to be prescribed aspirin and beta-blockers after an MI.

In primary prevention, the Nurses' Health Study[47] found that women older than 50 years who took six or more aspirin tablets per week had fewer coronary artery disease events than women who did not (the trend had borderline statistical significance), but aspirin had no benefit in younger women or those taking higher doses. Therefore, we believe that one should consider aspirin therapy for women older than 50 years who are at increased cardiovascular risk.

Women with myocardial infarction are also less likely to receive thrombolytics (even after controlling for eligibility), and receive them later.[48] They are also less likely to be scheduled for stress testing or referred for coronary angiography after initial exercise treadmill testing.[49] They face a longer hospital delay in the treatment of acute myocardial infarction and have greater prevalences of tachycardia and heart block and a higher Killip class. They also have higher rates of in-hospital complications from myocardial infarction, including strokes, bleeding, shock, and cardiac rupture.[50,51]

A recent retrospective analysis from the Cooperative Cardiovascular Project[8] confirms that women receive less aggressive treatment than men do during the early management of myocardial infarction: they are less likely to undergo diagnostic catheterization, receive aspirin early on, or receive thrombolysis. However, this did not translate into a mortality difference at 30 days after the infarction.

During angioplasty, men and women have comparable rates of technical success, but women have higher mortality and complication rates from angioplasty, probably because they are older and smaller and have smaller arteries and more concomitant diseases.[52,53] They are more likely to have urgent or emergent coronary artery bypass grafting and have higher mortality and morbidity rates perioperatively. This higher perioperative mortality rate is attributed to a greater number of comorbid conditions at the time of referral, which suggests that women are not being evaluated aggressively enough.[54]

In women, the most common coronary presentation is angina

REFERENCES

1. **Hu FB, Stampfer MJ, Manson JE, et al.** Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. N Engl J Med 2000; 343:530–537.
2. **Centers for Disease Control and Prevention.** Trends in ischemic heart disease mortality—United States, 1980–1988. MMWR 1992; 41:548–556.
3. **Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailey KR, Gersh BJ.** Gender differences in use of stress testing and coronary heart disease mortality: a population-based study in Olmsted County, Minnesota. J Am Coll Cardiol 1998; 32:345–352.
4. **Cummings SR, Black DM, Rubin SM.** Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med 1989; 149:2445–2448.
5. **Kannel WB, Hjortland MC, McNamara PM, Gordon T.** Menopause and risk of cardiovascular disease: the Framingham study. Ann Intern Med 1976; 85:447–452.
6. **Rosenberg L, Hennekens CH, Rosner B, Belanger C, Rothman KJ, Speizer FE.** Early menopause and the risk of myocardial infarction. Am J Obstet Gynecol 1981; 139:47–51.
7. **Centerwall BS.** Premenopausal hysterectomy and cardiovascular disease. Am J Obstet Gynecol 1981; 139:58–61.
8. **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.
9. **Komaroff A, Robb-Nicholson C, Woo B.** Women's health. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, editors. Harrison's principles of internal medicine. 14th ed. New York: McGraw-Hill; 1998:21–24.
10. **Mosca L, Grundy SM, Judelson D, et al.** AHA/ACC scientific statement: consensus panel statement. Guide to preventive cardiology for women. American Heart Association/American College of Cardiology. J Am Coll Cardiol 1999; 33:1751–1755.
11. **Kannel WB, McGee DL.** Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979; 59:8–13.
12. **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.

13. **Robinson JC, Folsom AR, Nabulsi AA, Watson R, Brancati FL, Cai J.** Can postmenopausal hormone replacement improve plasma lipids in women with diabetes? The Atherosclerosis Risk in Communities Study Investigators. Diabetes Care 1996; 19:480–485.
14. **Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG, on behalf of the GISSI-2 Investigators.** Influence of diabetes on mortality in acute myocardial infarction: Data from the GISSI-2 study. J Am Coll Cardiol 1993; 22:1788–1794.
15. **The BARI Investigators.** Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. J Am Coll Cardiol 2000; 35:1122–1129.
16. **Miller VT.** Lipids, lipoproteins, women and cardiovascular disease. Atherosclerosis 1994; 108 (suppl):S73–82.
17. **Braunwald E.** Heart disease: a textbook of cardiovascular medicine. 5th ed. Philadelphia: W.B. Saunders Co; 1997:1704–1714.
18. **Bass KM, Newschaffer CJ, Klag MJ, Bush TL.** Plasma lipoprotein levels as predictors of cardiovascular death in women. Arch Intern Med 1993; 153:2209–2216.
19. **Walsh JM, Grady D.** Treatment of hyperlipidemia in women. JAMA 1995; 274:1152–1158.
20. **Scandinavian Simvastatin Survival Study Group.** Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383–1389.
21. **Orth-Gomer K, Mittleman MA, Schenck-Gustafsson K, et al.** Lipoprotein(a) as a determinant of coronary heart disease in young women. Circulation 1997; 95:329–334.
22. **Sunayama S, Daida H, Mokuno H, et al.** Lack of increased coronary atherosclerotic risk due to elevated lipoprotein(a) in women > or = 55 years of age. Circulation 1996; 94:1263–1268.
23. **National Cholesterol Education Program.** 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.
24. **Chan KA, Andrade SE, Boles M, et al.** Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. Lancet 2000; 355:2185–2188.
25. **Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H.** HMG-CoA reductase inhibitors and the risk of fractures. JAMA 2000; 283:3205–3210.
26. **Cummings SR, Bauer DC.** Do statins prevent both cardiovascular disease and fracture? JAMA 2000; 283:3255–3257.
27. **Stampfer MJ, Colditz GA.** Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991; 20:47–63.
28. **Goldstein F, Manson J, Golditz GA, et al.** A prospective observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000; 133:933–941.
29. **The Writing Group for the PEPI Trial.** Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1995; 273:199–208.
30. **Bhathena RK, Anklesaria BS, Ganatra AM.** The treatment of hypertriglyceridaemia in menopausal women with transdermal oestradiol therapy. Br J Obstet Gynaecol 1999; 106:980–982.
31. **Hulley S, Grady D, Bush T, et al.** Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280:605–613.
32. **Herrington DM.** The HERS trial results: paradigms lost? Heart and Estrogen/progestin Replacement Study. Ann Intern Med 1999; 131:463–466.
33. **Cushman M, Legault C, Barrett-Connor E, et al.** Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. Circulation 1999; 100:717–722.
34. **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.
35. **Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC.** Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000; 343:16–22.
36. **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.
37. **Jousilahti P, Tuomilehto J, Vartiainen E, Pekkanen J, Puska P.** Body weight, cardiovascular risk factors, and coronary mortality. 15-year follow-up of middle-aged men and women in eastern Finland. Circulation 1996; 93:1372–1379.
38. **Blair SN, Kohl HWD, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW.** Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989; 262:2395–2401.
39. **Owens JF, Matthews KA, Wing RR, Kuller LH.** Can physical activity mitigate the effects of aging in middle-aged women? Circulation 1992; 85:1265–1270.
40. **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.
41. **Mosca L, Grundy SM, Judelson D, et al.** Guide to preventive cardiology for women. AHA/ACC Scientific Statement Consensus Panel statement. Circulation 1999; 99:2480–2484.
42. **Murabito JM.** Women and cardiovascular disease: contributions from the Framingham Heart Study. J Am Med Womens Assoc 1995; 50:35–39.
43. **Kannel WB, Vokonas PS.** Demographics of the prevalence, incidence, and management of coronary heart disease in the elderly and in women. Ann Epidemiol 1992; 2:5–14.
44. **Birdwell BG, Herbers JE, Kroenke K.** Evaluating chest pain. The patient's presentation style alters the physician's diagnostic approach. Arch Intern Med 1993; 153:1991–1995.
45. **Goldberg RJ, O'Donnell C, Yarzebski J, Bigelow C, Savageau J, Gore JM.** Sex differences in symptom presentation associated with acute myocardial infarction: a population-based perspective. Am Heart J 1998; 136:189–195.
46. **Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS.** Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000; 284:1392–1398.
47. **Manson JE, Stampfer MJ, Colditz GA, et al.** A prospective study of aspirin use and primary prevention of cardiovascular disease in women. JAMA 1991; 266:521–527.
48. **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.
49. **Lauer MS, Pashkow FJ, Snader CE, Harvey SA, Thomas JD, Marwick TH.** Sex and diagnostic evaluation of possible coronary artery disease after exercise treadmill testing at one academic teaching center. Am Heart J 1997; 134(5 Pt 1):807–813.
50. **Tofler GH, Stone PH, Muller JE, et al.** Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. J Am Coll Cardiol 1987; 9:473–482.
51. **Greenland P, Reicher-Reiss H, Goldbourt U, Behar S.** In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. Circulation 1991; 83:484–491.
52. **Kelsey SF, James M, Holubkov AL, Holubkov R, Cowley MJ, Detre KM.** Results of percutaneous transluminal coronary angioplasty in women. 1985–1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry. Circulation 1993; 87:720–727.
53. **Weintraub WS, Wenger NK, Kosinski AS, et al.** Percutaneous transluminal coronary angioplasty in women compared with men. J Am Coll Cardiol 1994; 24:81–90.
54. **Williams MR, Choudhri AF, Morales DLS, Helman DN, Ox MC.** Gender differences in patients undergoing coronary artery bypass surgery, from a mandatory statewide database. J Gend Specif Med 2000; 3:41–48.

ADDRESS: *Holly L. Thacker, MD, FACP, Department of General Internal Medicine and Obstetrics and Gynecology, A91, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail thackeh@ccf.org.*