

Cardiovascular Disease in Women

W. LANE DUVALL, M.D.

Abstract

Almost 62 million Americans have one or more types of cardiovascular disease and, of these, more than 32 million are female. This translates into an average of 1 in 5 women, making cardiovascular disease the leading killer of women in the U.S., responsible for more than half a million deaths a year.

While it has been known for some time that differences exist between the sexes regarding coronary heart disease, it has only been in the last 10 years that these disparities in incidence, morbidity, mortality, risk factors, diagnosis, and treatment have been explored. Research has shown a gap in the utilization of medical therapy, diagnostic studies, and revascularization procedures involving women. In addition, women's outcomes after myocardial infarction have been consistently demonstrated to be poorer than those of men. Another important issue that has just started to be addressed is that the predominantly male-focused cardiovascular research has been generalized to women. Only in recent years have women been included in clinical trials or databases in sufficient numbers for sex-based analysis of the data.

The topic of cardiovascular disease in women is diverse and complex. In this article, some of the important issues will be introduced and discussed, to highlight our current understanding of the problem and to emphasize the areas in which further study and progress is needed. These issues include the epidemiology of coronary heart disease, the diagnosis of coronary heart disease, the medical therapy of acute coronary syndromes, coronary revascularization, and hormone replacement therapy.

Key Words: Coronary heart disease, women, coronary artery disease, epidemiology, prevention, risk factors, hormone replacement therapy.

Introduction

OF THE 61.8 MILLION AMERICANS who have one or more types of cardiovascular disease (CVD), 32.1 million are female (1). This translates into an average of 1 in 5 women. CVD is the number one killer of both men and women in the U.S., resulting in 445,871 deaths among men and 512,904 deaths among women in 1999 (2). Of these deaths, coronary heart disease (CHD) was responsible for 267,268 male deaths and 262,391 female deaths (2). In addition to women accounting for the majority of CVD deaths (53.5%), their mortality from coronary heart disease at presentation is approximately twice that of men (3). Despite the fact that 1 in 2.4 of women's deaths are

from CVD and only 1 in 30 are from breast cancer, surveys show that most women are far more afraid of breast cancer than CVD.

While it has been known for some time that differences exist between the sexes regarding CVD, it has only been in the last 10 years that these disparities in incidence, morbidity, mortality, risk factors, diagnosis, and treatment have been explored. During this time there has been a heightened awareness of both sex and gender differences in the delivery of care by the health care community. (Here "sex" refers to biological differences between men and women and "gender" refers to the social and cultural context differences.) The other issue that has just started to be addressed is that the predominantly male-focused cardiovascular research has been generalized to women. Only in recent years have women been included in clinical trials or databases in sufficient numbers for sex-based analysis of the data (4).

The topic of cardiovascular disease in women is complex. This article will attempt to present some of the more important aspects of the topic, to highlight our current understanding as well as to emphasize the areas in which further study and progress is needed.

Fellow in Cardiology, The Zena and Michael Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to W. Lane Duvall, M.D., The Zena and Michael Wiener Cardiovascular Institute, Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; E-mail: william.duvall@mssm.edu

Adapted from a Cardiology Grand Rounds, Controversies in Cardiology presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on April 29, 2002 and updated as of November 2002.

Epidemiology of Coronary Heart Disease in Women

Coronary heart disease remains the leading cause of death among both men and women in the U.S. despite significant advances in the diagnosis and treatment of CHD in the last 30 years. Improvements in therapy for CHD and reduction in the prevalence of CVD risk factors have led to a decline in the CVD death rate in the last three decades. However, this reduction in mortality rates from CVD has not been as pronounced for women as for men, with the recent trend actually toward increasing mortality for women. With the aging of the population, the overall number of CVD deaths has increased recently, and the trend is expected to continue. This trend is especially noticeable among women, who have a longer life expectancy than men.

It is estimated that 12.6 million Americans have CHD, 6.4 million (51%) of them being women, with the lifetime risk of developing CHD after age 40 being 32% for women versus 49% for men (2). The average age of first myocardial infarction (MI) is 70.4 for women and 65.8 for men (2). The prevalence of CVD and CHD in women increases significantly after menopause (2–3 times that of women the same age before menopause) and continues to increase with advancing age. As a rule, the incidence of CHD in women lags behind the incidence in men by approximately 10 years.

Risk Factors

The major traditional risk factors for CHD in women are identical to those for men, and include increasing age, cigarette smoking, hypertension, dyslipidemia, diabetes, family history of premature CHD prior to the age of 65 (55 for men), obesity, and a sedentary lifestyle. Risk factors unique to women include oral contraceptives and menopause. Although the risk factors are similar for both sexes, there are differences in prevalence and magnitude of effect.

Age

The dramatic influence of age on the development of CHD in women was first shown in the Framingham study, which reported a striking 40-fold difference between the oldest age group (75–84 years) and the youngest (35–44 years) (5). The study found a marked sex-associated disparity in the incidence of CHD for the

younger age groups, which diminished progressively during middle age, and disappeared almost entirely among the elderly. In women who undergo natural menopause, the clinical onset of CHD and death are, on average, 10 years later than in men, with MI occurring as much as 20 years later. Menopause plays a large role in the effect of aging on CHD; there was a 10-fold increase in CHD risk after menopause, compared to only a 4.6-fold increase in the same age groups in men. The mechanism of the influence of menopause is still unclear, since it may be related to changes in estrogen levels or other age-associated risk factors.

Family History

A family history of premature CHD in a first-degree relative is an important risk factor for both sexes. Because of the later onset of CHD in women, “premature” is defined as before the age of 55 for men and 65 for women. The Framingham study demonstrated an increased relative risk of 1.6 in women with a positive family history, compared to those without one (6). It is believed that family history contributes to CHD risk both through inherited genetic factors and through shared lifestyle characteristics, such as smoking, dietary habits, and physical activity.

Menopause

The incidence of CHD in women increases markedly in middle age, out of proportion to the increase in men, suggesting that menopause, and presumably the loss of ovarian hormones, is deleterious to the heart. The Nurses’ Health Study found that women who experienced early surgical menopause without hormonal replacement therapy had 2.2 times the risk of CHD compared to age-matched controls (7).

Cigarette Smoking

Approximately 20% of all deaths from CVD are attributable to smoking, which is the leading preventable risk factor among women. There are estimated to be 22.6 million female smokers — about 21.5% of women in the U.S. (2). The Nurses’ Health Study found a clear dose-response relationship between smoking and the risk for CHD (8). In general, studies have shown up to a fourfold increase in risk among heavy smokers and up to a doubling of the risk among light smokers (8, 9). Cigarette

smoking triples the risk of MI in premenopausal women and lowers the age of menopause by 1.5–2 years (10). There appears to be a synergistic effect of smoking and oral contraceptive use; there is a significantly increased risk of CHD with both older contraceptives with high-dose estrogen and newer, low-dose contraceptives (11, 12).

Diabetes

Approximately 10.6 million Americans have been diagnosed with diabetes mellitus; of these, 5.7 million (54%) are women and 4.9 million men (2). Diabetes is a more powerful risk factor for women than for men, essentially negating the protective effect of gender even in premenopausal women, so that all diabetic women have a risk of CHD similar to that of diabetic men (13). In the Framingham study, having diabetes increased a woman's risk of a coronary event 5.4-fold versus only 2.4-fold for men (14). Data from the Nurses' Health Study supports these findings, demonstrating a 3- to 7-fold increase in the risk of CVD events in diabetic women (15). Furthermore, women over the age of 45 are twice as likely to develop diabetes compared to men. Diabetes in women is also associated with less favorable outcomes of MI and revascularization. Diabetic women, compared to non-diabetic women, have a substantially worse short- and long-term prognosis after MI than do men, with a higher risk of death, double the risk of reinfarction, and four times the risk of developing heart failure (16–18).

Dyslipidemia

The AMA found that in the U.S. 53.8 million adult women and 48.2 million adult men had total blood cholesterol levels of 200 mg/dL or higher in 1999 (2). Total cholesterol, LDL, and HDL are well-described risk factors for CHD for both men and women (19). Premenopausal women have lower LDL and higher HDL levels than do men. After menopause, however, LDL levels in women rise progressively, so that by old age, women have higher LDL levels than do men. Although HDL levels decline after menopause, they remain higher in women than in men. A large analysis by the National Heart, Lung, and Blood Institute demonstrated that high total and LDL cholesterol levels were a stronger risk factor in young and middle-aged women than in older women, with

relative risks of 2.44 (total) and 3.27 (LDL) versus 1.12 and 1.13, respectively (20).

Hypertension

Fifty million people in the U.S. have hypertension (systolic blood pressure greater than 140 mm Hg or diastolic blood pressure higher than 90 mm Hg), representing 1 in 4 adult Americans (2). Up to the age of 55, a higher percentage of men than women have high blood pressure. From 55–74 the ratio shifts towards women. After age 75, the number of women with hypertension is consistently higher than that of men (21). Hypertension is 2–3 times more common in women taking oral contraceptives, especially if they are obese or older (22). The Framingham study reported that hypertensive women are 2.2 times more likely to develop CHD than normotensive women; subsequent studies supported this finding and suggested that the risks were similar for men and women (23).

Physical Inactivity and Obesity

A number of large cohort studies have demonstrated a relationship between physical activity and obesity, and cardiovascular risk and death in women. Epidemiologic study has repeatedly shown that women are more sedentary and more likely to be overweight than are men. Men have a higher prevalence of recommended levels of physical activity, with 33–49% of men and 39–57% of women having no leisure-time physical activity (2). If one uses a body mass index (BMI) of 25 or higher as “overweight” and 30 or higher as “obese,” 108.3 million adult Americans can be considered overweight and 44.2 million obese (18.7 million men and 25.6 million women) (2). A recent seven-year follow-up of more than 40,000 postmenopausal women showed a graded, inverse association between physical activity and both all-cause mortality and cardiovascular mortality (24). Follow-up of almost 86,000 women from the Nurses' Health Study evaluated changes in lifestyle in this cohort and attributed a 16% decline in the incidence of CHD to improvement in diet, but an 8% increase in CHD incidence to an increase in BMI (25). Obesity has been demonstrated to be linked to both increased risk of CHD and an increased relative risk of death from CVD of 4.1 compared to the risk level of non-obese women (26–28).

Diagnosis of CHD in Women

While chest pain is the most common presentation of CHD in both sexes, it occurs as the initial presentation of acute MI more frequently in men than in women (29). Atypical and non-chest pain presentations are more common in women, to the extent that it has been suggested that clinical presentation and risk factor analysis are of less value in predicting CHD for women than for men (30). Women are more likely to experience back, jaw, abdominal and neck pain; nausea; shortness of breath; and congestive symptoms. They are less likely to have diaphoresis (29). As a group, women have a higher incidence of silent or unrecognized MI compared to men (31). Women seem to have a greater prevalence of non-cardiac chest pain, and premenopausal women have less angiographically significant coronary artery disease associated with their chest pain than do men. However, at the same time, women are more likely to present with angina than MI as the initial symptom of CHD. Women are also more likely to attribute their symptoms to non-cardiac etiologies, due to their relatively low awareness of their risk of CHD. The diagnosis of CHD in women is more challenging and problematic due to these atypical characteristics of their symptoms, but also due to less certainty in interpreting the results of diagnostic testing.

Exercise Stress Testing

Exercise electrocardiography (ECG) is the most readily available and least costly tool for the diagnosis of CHD, but has been found to be less accurate for women than for men. A meta-analysis of ECG testing of women found a sensitivity of 61% and a specificity of 70% (32) compared to a meta-analysis involving men, which demonstrated a sensitivity of 68% and a specificity of 77% (33). There have been many explanations proposed for this discrepancy in accuracy, including lower prevalence of disease in women, less extensive disease in women, lower heart rate responses to exercise, more frequent repolarization abnormalities on baseline ECGs, and the effect of estrogen on the ST segment (34). Despite the lower accuracy for women, diagnostic scores applied to exercise testing have been tested and validated for them. The Duke Treadmill Score is a weighted index combining ST segment deviation, treadmill time and angina, which provides accurate diag-

nostic and prognostic information for women with suspected CHD (35).

The optimal strategy for diagnosing CHD in women is controversial and the role of exercise ECG uncertain, but any strategy should take into account the pre-test probability of disease in women (36). For women with a low probability of CHD (less than 20%), exercise ECG is usually not recommended because of the possibility of false-positive results and the resultant unnecessary follow-up testing. This population includes young, premenopausal women without risk factors who are at very low risk for CHD. But if an exercise ECG is performed, a negative test has a high negative predictive value and should be trusted, and imaging procedures would not be needed. For women with a high likelihood of CHD (greater than 80%), the most effective strategy may be to proceed directly to catheterization. For the intermediate risk group, there are controversial opinions on how to proceed, because of the sex-specific deficiencies of exercise ECG. The American College of Cardiology/American Heart Association (ACC/AHA) recommends that some form of imaging should be added to the study when there are baseline ECG abnormalities, but as a whole, the negative predictive value for this subset of women is good, with the likelihood of a false negative test actually being lower for women than for men (37).

Nuclear Stress Testing

The use of nuclear tracers such as thallium or technetium for myocardial perfusion imaging adds additional information beyond that of exercise ECG testing alone, because it can identify the presence of coronary artery disease (CAD) and determine its severity. A meta-analysis of thallium imaging for women demonstrated a sensitivity of 78% and a specificity of 64% (32). Results for women may also be less accurate than those for men with this diagnostic modality due to attenuation artifacts and artifacts caused by smaller left ventricular chamber sizes. Soft tissue attenuation from breast tissue most commonly causes defects in the anterior and septal distributions, which may erroneously be reported as infarction or even ischemia if breast tissue shifts during the study. Smaller ventricular chamber size, which is more common in women due to their smaller body surface area (BSA), causes a blurring artifact, reducing the accuracy of the study. The higher energy radioisotope technetium decreases the

problem of breast attenuation and allows for easier gated image acquisition. The improvement in soft tissue attenuation technology made possible by technetium has helped normalize the accuracy between men and women without an overall decline in sensitivity. In a study comparing thallium with technetium in women, investigators found a similar sensitivity but a higher specificity (82%, improved to 92% with ECG gating for technetium compared to 67% for thallium) (38).

Most important, myocardial perfusion imaging is an independent predictor of cardiac events or death. In many studies, after adjustment for other exercise variables, the number of abnormal territories has been the most consistent predictor of mortality. Most studies have shown that increased event rates, based on abnormal imaging and low yearly event rates with normal imaging, are similar for men and women (39, 40).

Stress Echocardiography

Echocardiography can be used in conjunction with exercise testing or pharmacologic stress for the diagnosis of CHD. A meta-analysis of both sexes of exercise stress echocardiography revealed a sensitivity of 85% and specificity of 77% (41), while a second meta-analysis of women showed a sensitivity and specificity of 86% for pharmacologic stress echocardiography (42). A normal stress echocardiogram, either exercise or pharmacologic, portends an excellent prognosis, with cardiac event rates of 1–4% over 3 or more years of follow-up. In other studies, positive echocardiographic result added incremental prognostic value to that provided by the ECG portion of the test, with event rates up to four times higher than for women with negative tests (43–46). Based on reported data, neither nuclear perfusion imaging nor stress echocardiography has proven to be superior; rather, they provide comparable results for the diagnosis of CAD (47). While stress echocardiography may have a slightly higher specificity and be less costly, 5–10% of studies may have poor or incomplete imaging due to technically difficult views. Nuclear imaging, on the other hand, provided extensive data on the prognosis of positive and negative studies, but suffers from the problem of breast attenuation (34).

Medical Therapy of Acute Coronary Syndromes in Women

Nowhere is the discrepancy between the sexes greater than in the morbidity and mortal-

ity resulting from myocardial infarction. MIs are lethal more often for women than for men, regardless of age or comorbidity (48), and both 30-day and one-year crude mortality rates for women after having an MI are nearly double those for men (49, 50). In the 26-year follow-up of the Framingham study, the overall case fatality rate was 32% for women and 27% for men (5). Based on data from the AHA, 25% of men and 38% of women will die within 1 year of having an initial recognized MI (2). Within 6 years of a recognized MI, 18% of men and 35% of women will have another MI, and 22% of men and 46% of women will be disabled with heart failure (2). Even when confounding variables are taken into account, women who have a clear indication for thrombolytic therapy in recent trials have an approximately 15% higher mortality rate than men (49, 50). However, a more recent analysis of a U.S. Medicare population did not show any differences between the sexes in early mortality after MI (51).

Several factors contribute to a worse outcome for women. Upon presentation, women are older, have more comorbidities including diabetes and hypertension, and have more complications such as reinfarction, pulmonary edema, shock, and cardiac rupture (52). Other factors may also play a role, such as delayed presentation to the emergency room, reduced perception of risk of MI by women and health care providers, and atypical, more transient symptoms at presentation (53, 54). Women are also more likely to present with non-ST segment elevation MIs and unstable angina than with ST-elevation MIs. This makes diagnosis more difficult to establish and longer to accomplish (55). Even with all these factors, women with the same symptoms as men are less likely to be admitted to the coronary care unit than are men. These sex-specific differences in MIs are not clearly understood and are sometimes counterintuitive. For example, women have more complications than do men despite having less significant CAD, and women have more CHF than men despite having better left ventricular function (54).

From the data accumulated from clinical trials, it appears that there is no significant difference between men and women with regard to the beneficial effects of the various medical therapies for acute coronary syndromes. Large clinical studies looking at the improvement in morbidity and mortality for those taking aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, thrombolytics and oth-

ers have shown no significant difference between the sexes. However, these therapies may be received less often by women than by men (56). And the data gathered from these clinical trials may actually underestimate morbidity and mortality for women, since all eligible participants receive the planned treatment regardless of age or sex. While women have equivalent infarct artery patency rates after thrombolytics, they are less likely to receive thrombolytics, with only 55% of women, compared to 78% of men, receiving them when indicated, according to the Myocardial Infarction Triage and Intervention Registry (MITI) (57). The discrepancy of women being less likely to receive standard medical therapy also applies to aspirin, beta-blockers, and heparin, with aspirin being used by only 55% of women compared to 70% of men (58). ACE inhibitors seem to be the one exception to this trend, possibly due to a higher incidence of heart failure in women with MI. In general, only 18–25% of subjects in the thrombolytic trials have been women. This is similar to the observed enrollment of approximately 20% in studies of glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparin, which limits the ability to develop sex-specific conclusions.

Coronary Revascularization in Women

Because many of the large trials of CHD treatment have not included women or have included them in very small numbers, the applicability of these studies to women with regard to revascularization strategies remains somewhat speculative. In addition, fewer women than men are referred for invasive testing or interventional strategies, further compromising the ability to evaluate strategies in women.

It was first reported in 1987 that there was a gender bias in referral for cardiac catheterization and, therefore, for considering coronary artery bypass graft (CABG) (59). This lower referral rate for coronary angiography for women has been substantiated in subsequent trials such as Survival and Ventricular Enlargement (SAVE) and TIMI III (60, 61). A report from the National Registry of Myocardial Infarction in 1998 stated that, despite having a higher mortality rate after MI than men, women had lower rates of cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), and CABG (62). Reasons for these lower rates of coronary angiography for women remain unclear. Difficulties in diagnosis due to atypical

presentation in women, poor sensitivity and specificity of diagnostic testing, or even simply poor access to resources may all contribute. Furthermore, the advanced age of women with CHD, misperceptions that CHD rarely affects women or that when women have CHD it is very advanced and they are unlikely to benefit from interventions, may also play a role.

Percutaneous Intervention

All early studies and virtually all registry data on percutaneous interventions have suggested that women do not fare as well as men following coronary angioplasty. Registries, which may provide the best insight into “real life” practices, as opposed to highly structured clinical trials, have consistently shown significantly higher mortality and complication rates for women than for men. In all of these studies, the women were older than the men and had more comorbidities and less body surface area. The higher mortality and complication rates have been blamed on these differences of age, comorbidities, smaller vessel size due to smaller body surface area, and potentially later presentation. A large collection of data from the National Heart, Lung, and Blood Institute’s Coronary Angioplasty Registry from 1985–1986 revealed female sex to be an independent risk factor for death (Risk Ratio [RR] 4.53) (63). Women in this registry were older and had more risk factors, more severe angina, higher initial complications and higher mortality rates than did men, but they did not have more extensive CAD than men. Other registries from Emory University for 1982–1986 (64), from the Mayo Clinic for 1979–1990 (65), and from the Cleveland Clinic for 1980–1985 (66), supported these findings and confirmed female sex to be a risk factor for death, but the latter two studies concluded that the increased mortality rate was related to body surface area and that sex itself was not an independent risk factor.

Randomized trials of coronary interventions have historically included a very small percentage of women, with an average inclusion rate of 20–30% (67). In any event, randomized trials have generally failed to support early registry findings and have not shown any significant difference between men and women with regard to referral or revascularization outcomes. The GUARANTEE study evaluated nearly 3,000 consecutive patients (39% women) admitted for unstable angina in 1996, and did show that cardiac catheterization, PTCA, and CABG were

performed less often on women (56). However, after controlling for relative clinical severity of men and women, the study found that both sexes were appropriately referred to angioplasty at a similar rate. Despite this, fewer women underwent CABG than men. There was, however, no difference between the sexes in the rate of recurrent angina, in-hospital infarction, and death among those undergoing all interventional procedures. The BARI study evaluated more than 1,800 patients (27% women) randomized to PTCA or CABG and found that the women included were older, with more comorbidities, but had similar mortality rates after 5.4 years of follow-up (68). And contrary to previous reports, the investigators actually found that female sex was an independent predictor of improved five-year survival.

Coronary Artery Bypass Graft

Most series of bypass surgery have had a large preponderance of male patients, and as with percutaneous interventions, female sex itself was felt to be an independent risk factor for surgery (69). It is this conception that may have led in part to the bias against referral of women for cardiac catheterization and CABG (70). It is clear, however, that women presenting for bypass surgery have different clinical characteristics than men. Women are consistently older and have more comorbid conditions such as diabetes, hypertension, and peripheral vascular disease; they present with more severe angina and often require surgery on a more urgent basis (71). On the other hand, women tend to have less extensive CAD than do men and have better preservation of left ventricular function (71).

The significance of sex as an independent risk factor for CABG is debatable, and in all likelihood it is the differences in risk factors that contribute most to operative mortality and long-term survival. Explanations for the observation that female sex has been reported to result in higher mortality after CABG include the smaller size of women's coronary arteries, which presents a technical challenge; a referral bias that causes women to present at a more advanced stage of the disease; and an increased number of comorbidities in women (67). The largest registry of CABG results, the Society of Thoracic Surgery database, contains information on more than 300,000 patients (28% women) (72). An analysis of this database found that sex was an independent risk factor

related to operative mortality and that risk factors were almost identical for both sexes, although the relative weight was different depending on the sex. Body size was also clearly related to mortality, with increased mortality with decreasing size. Most reported series demonstrate that women receive fewer arterial grafts than do men; most important, they receive fewer left internal mammary arteries to the left anterior descending artery. While some studies have shown an increased incidence of angina or recurrent MI over time in women after CABG (73), recent studies have shown similar improvement in functional status after surgery (74) and comparable long-term survival in men and women (75).

Hormone Replacement Therapy

Use of hormone replacement therapy (HRT) for menopausal symptoms, osteoporosis, and CHD has been controversial, due to the increased risk of breast and endometrial cancer as well as venous thromboembolism, and possible lack of efficacy resulting from its use. Because of the observed twofold increase in risk of CHD following natural menopause or premature ovarian failure, the beneficial effects of estrogen on the lipid profile, and estrogen's effect on vascular reactivity and endothelial function, ovarian estrogen is felt to be cardioprotective. The argument in favor of estrogen is further bolstered by the observations that men between the ages of 30 and 50 are at higher risk for CVD than are premenopausal, non-diabetic women, and the rate of increase in atherosclerotic lesions in women aged 50–70 is higher than for men. Multiple earlier observational studies have suggested that HRT is associated with a 40–50% reduction in CHD risk, but recent prospective studies have cast doubt on this, suggesting that the findings might instead be related to healthier risk factor profiles for women on HRT (76).

Effects on Lipid Profile

After menopause, as a result of estrogen withdrawal and weight gain, there is a decrease in HDL and an increase in LDL. Oral estrogen replacement therapy increases HDL and decreases LDL. After oral administration, high concentrations of estrogen reach the liver via the portal circulation. This results in increased expression of the LDL receptor and apolipoprotein AI and decreased expression of hepatic li-

pase, leading to a reduction in LDL and an increase in HDL. Estrogen also increases hepatic triglyceride synthesis and can cause hypertriglyceridemia. Transdermal estrogen does not have the same adverse effects on triglycerides, but it also does not increase HDL concentrations (77).

Randomized clinical trials have evaluated the effects of HRT on lipid profiles. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial looked at estrogen alone and estrogen plus either medroxyprogesterone or micronized progesterone (78). All treatments decreased LDL by 14.5–17.7 mg/dL (12–14%) and increased triglycerides by 11.4–13.7 mg/dL (15%). However, the effect on HDL varied: the biggest increase in HDL was 5.6 mg/dL (11%), in the estrogen only group; the smallest increase was 1.2–1.6 mg/dL (3%), in the medroxyprogesterone group. Unopposed estrogen, however, was associated with an increased risk of endometrial hyperplasia and should therefore be limited to women without a uterus. Raloxifene is a selective estrogen modulator — a non-hormonal agent that binds to the estrogen receptor and exhibits agonist or antagonist effects, depending on the target tissue — that has been developed with the hope of lessening some of the side effects of HRT. In a randomized trial, raloxifene decreased LDL by 12%, the same as standard HRT, and had no effect on triglyceride levels, but did not increase HDL levels (79).

Vascular Reactivity and Endothelial Function

There is mounting evidence that estrogen improves vascular reactivity and endothelial function. Vascular reactivity, a blood vessel's ability to dilate in response to a stimulus, is measured as sublingual nitroglycerin-induced brachial artery flow and is felt to facilitate reperfusion to ischemic tissue. Studies have shown that this response to nitroglycerin is lower in men than in women, and that vascular reactivity becomes impaired in postmenopausal women but recovers when they are given HRT (80). The endothelium plays an important role in atherosclerotic disease, since it serves to produce important vasodilating factors, thereby regulating vascular tone; inhibits platelet adhesion; and maintains a balance between thrombosis and fibrinolysis. Early studies have shown that HRT improves endothelial function by increasing nitric oxide production and by mitigat-

ing age-related changes in arterial structure and function (81, 82).

Primary and Secondary Prevention

Because of all the beneficial effects of estrogen on surrogate endpoints and the observed sharp rise in CHD after menopause, HRT appeared to be a straightforward intervention for primary and secondary prevention of CHD and MI in postmenopausal women. Multiple observational studies in the past 10–15 years have supported this conclusion by demonstrating lower rates of CHD events in postmenopausal women who use HRT. Meta-analyses of these epidemiologic findings concluded that HRT reduced the risk of CHD by 35–50% (83, 84). The risk reduction for secondary prevention based on study data appeared to be even higher, at 35–80% (85–88). These observational studies all show lower risks of CHD, reinfarction, cardiac death, and restenosis. However, there have always been reasons to view these observational results of HRT in women cautiously. Consistently, women who took HRT were better educated, had fewer risk factors for CHD, were less likely to be obese or to smoke, and were more likely to follow a low-fat diet and be physically active. Although statistical approaches are used to compensate for such differences, it remains difficult to control for all confounders and impossible to control for unknown confounders. This bias towards a protective effect in users of HRT has been called “prevention bias” (89). “Compliance bias,” which represents another potential bias affecting observational trials of HRT, refers to the reduction in relative risk of CHD found for subjects who were compliant in taking their medications versus those who were not. In fact, it is estimated that only 25–40% of women continue to take postmenopausal hormone therapy for more than one year. This bias has been measured in studies comparing subjects who faithfully took placebo versus those who did not, and in subjects who did and did not regularly take the active drug, and was found to represent a relative risk reduction of 30% (90).

The largest cohort for observational data of HRT in CHD comes from the more than 121,000 women enrolled in the Nurses' Health Study, which started in 1976. The nurse-subjects were between the ages of 30 and 55 at enrollment, and data were collected by biennial questionnaires. There were 3,637 deaths over 18 years, and after correction for confounding

variables, hormone users had a lower risk of death than those who had never used hormones (RR 0.63) (91). However, this benefit decreased with time, to a relative risk of 0.80 after 10 years, which was attributed to the increasing risk of breast cancer. The greatest reduction in risk of death among women taking HRT was found in the group with high CHD risk factors (RR 0.51), and the least reduction was found in those at low risk for CHD (RR 0.89). The Nurses' Health Study had published three earlier analyses of data at different timepoints, also showing an approximately 40% risk reduction of CHD in women taking HRT (92–94). Subsequent publications have tried to determine the effect of HRT on primary and secondary prevention. In the more than 70,000 subjects without CHD, 1,258 major coronary events occurred over 20 years. After taking into account known confounders, the risk for major coronary events was lower among current HRT users, including short-term users, compared with never-users (RR 0.61) (95). In looking at 2,489 women with known CHD, 213 recurrent events or cardiac death were found again, with a lower risk of recurrent events among HRT users (RR 0.65) (96). However, short-term users (< 1 year) had a higher relative risk of events (1.25) compared with never-users, while the relative risk of a second event for long-term users (> 2 years) was only 0.38.

In 1998, when the Heart Estrogen/progestin Replacement Study (HERS) was published, the data from observational studies seemed overwhelming, to the point where it was felt that it was almost unethical to randomize women to placebo in future trials. The HERS trial randomized 2,763 postmenopausal women with CHD and an intact uterus to estrogen and progesterone or placebo and followed them for an average of 4.1 years (97). A majority of subjects had significant CHD and important risk factors, with 42% having had CABG, 45% having had percutaneous coronary intervention (PCI), 62% being current or past smokers, 59% with hypertension, and 23% being diabetic. Despite an improvement in lipid profile, with an 11% decrease in LDL and a 10% increase in HDL, there was no significant difference in death due to MI or CHD between the two groups (Relative Hazard [RH] 0.99). However, there was a significant time trend from the time of randomization. There were more CHD events in the HRT group during the first year than in the placebo group (RH 1.57), but during the last two years this trend reversed, with fewer events in the

HRT group (RH 0.67). Explanations for the time trend of HRT include an early prothrombotic effect of HRT, with the later benefit representing the true effect of HRT. Alternatively, it is possible that all of the high-risk patients died early, leaving a low-risk cohort behind. HERS II consisted of an additional 2.7 years of unblinded follow-up of 2,321 (93%) of the original HERS subjects, in an attempt to explain this time trend (98). HERS II showed that the lower rates of CHD events among women in the HRT group in the final years of HERS did not persist during the additional years of follow-up, with an RH of 1.00 during HERS II and an RH of 0.99 during the entire 6.8 years of HERS and HERS II. In addition, HRT during the 6.8 years of total follow-up significantly increased the risk of venous thromboembolism (RH 2.08) and biliary tract surgery (RH 1.48) (99). As a result of these studies, the AHA recommends that HRT should not be initiated for secondary prevention of CVD and that physicians should consider discontinuation of HRT if a woman develops CHD (100).

The Women's Health Initiative (WHI) enrolled more than 27,000 patients between 1993 and 1998, and is expected to conclude in 2005. These subjects, between the ages of 50 and 79, were for the most part without a history of heart disease; 60% of them were randomized to HRT or placebo, while the other 40%, who had undergone a hysterectomy, were randomized to estrogen-only or placebo. In May 2002, the Data and Safety Monitoring Board discontinued the combination HRT arm of the study, involving 16,608 subjects with an average follow-up of 5.2 years, citing an increased risk of invasive breast cancer in those taking HRT versus placebo (101). At the interim analysis, the test statistic for invasive breast cancer exceeded the stopping boundary, and the overall risks of therapy outweighed the benefits. In particular, there was a statistically significant increased risk of CHD (HR 1.29), stroke (HR 1.41), breast cancer (HR 1.26), and thromboembolic events (HR 2.11). The benefits of HRT included statistically significant reductions in colorectal cancer (HR 0.63) and fractures (HR 0.76). Overall, there was no significant difference in all-cause mortality. Based on this data, the study investigators concluded that the risks of HRT outweigh the benefits and that HRT should not be initiated or continued for the primary prevention of CHD.

Two other important randomized trials of HRT have been published. The estrogen re-

placement study randomly assigned 309 women with angiographically proven coronary disease to estrogen, estrogen plus progesterone, or placebo; the subjects received a repeat angiogram, on average, some 3.2 years later (102). Neither estrogen nor estrogen plus progesterone affected the progression of coronary disease in this population. A secondary analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a randomized and blinded study of nearly 8,000 postmenopausal women, on the effects of raloxifene on bone mineral density, was undertaken to determine the cardiovascular effects of the drug (103). In the overall cohort, after four years there was no significant difference between the treatment groups and placebo with regard to the number of CHD events. However, among the subset of 1,035 women at increased CVD risk, there was a significant risk reduction in cardiovascular events (RR 0.60). Further analysis of events during the first year of therapy did not indicate any increased risk in either the overall cohort or in those at increased CVD risk.

The data from HERS, HERS II, and the WHI did not address all of the issues surrounding HRT and CHD, including the use of unopposed estrogen, alternative HRT regimens, and especially HRT's role in primary prevention. Several randomized studies are currently underway which may shed further light on the HRT issue. The WHI is still following more than 11,000 patients who had undergone a hysterectomy, who were randomized to estrogen-only or placebo; results are expected in 2005. Another similar study, the Women's International Study of Long-Duration Oestrogen after Menopause (WISDOM), is currently recruiting 34,000 women without pre-existing heart disease. In secondary prevention, the Estrogen in the Prevention of Reinfarction Trial (ESPRIT) is currently ongoing. There are also three ongoing angiographic studies of HRT in women with pre-existing heart disease. These studies, which are expected to yield results in the near future, are the Women's Lipid Lowering Heart Atherosclerosis (WELL-HEART), the Women's Angiographic Vitamins and Estrogen (WAVE), and the Estrogen and Graft Atherosclerosis (EAGAR) trials.

Conclusions

Cardiovascular disease is the leading killer of women in the U.S., responsible for more than half a million deaths a year. CVD in women is a diverse and complex topic that in recent years has

been dominated by the issue of HRT and the controversy started by the HERS study. While HRT brings to light issues of procoagulation, thrombosis, and inflammation, it should not overshadow the discrepancies in care, outcome, and research between the sexes. Research has shown a gap in the utilization of medical therapy, diagnostic studies, and revascularization procedures involving women. This gap has not been adequately addressed. Women's outcomes after MI have been consistently demonstrated to be well below those of men. And finally, only about 20% of subjects enrolled in cardiovascular research have been women, severely limiting our ability to resolve these and other important issues.

References

1. National Health and Nutrition Examination Survey III (NHANES III), 1988-94, CDC/NCHS and the American Heart Association.
2. American Heart Association. 2002 Heart and stroke statistical update. Dallas, Texas: American Heart Association, 2001
3. Brister SJ, Turek MA. Introduction to women and ischemic heart disease. *Can J Cardiol* 2001; 17(Suppl D):5D-6D.
4. Harris DJ, Douglas PS. Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *N Engl J Med* 2000; 343:475-480.
5. Lerner DJ, Kannel WB. Patterns of coronary heart disease mortality and morbidity in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1986; 111:383-390.
6. Schildkraut JM, Meyers RH, Cupples LA, et al. Coronary risk associated with age and sex of parental heart disease in the Framingham Study. *Am J Cardiol* 1989; 64:555-559.
7. Colditz GA, Willett WC, Stampfer MJ, et al. Menopause and the risk of coronary heart disease in women. *N Engl J Med* 1987; 316:1105-1110.
8. Willett WC, Green A, Stampfer MJ, et al. Relative and absolute risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987; 317:1303-1309.
9. Bartecchi C, Mackenzie T, Schrier R. The human costs of tobacco use. *N Engl J Med* 1994; 330:907-912.
10. Hansen EF, Andresen LT, von Eyben FE. Cigarette smoking and age at first myocardial infarction and influence of gender and extent of smoking. *Am J Cardiol* 1993; 171:1439-1442.
11. Stradel B. Oral contraceptives and cardiovascular disease. *N Engl J Med* 1981; 305:672-677.
12. Thorgood M, Mann J, Murphy M, Vessey M. Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case control study. *Br J Obstet Gynecol* 1991; 98:1245-1253.
13. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991; 265:627-631.
14. Kannel WB, McGee DL. Diabetes and glucose intolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 1979; 2:120-126.
15. Manson JE, Rimm EB, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 1991; 151:1141-1147.

16. Abbott RD, Donahue RP, Kannel WB, Wilson P. The impact of diabetes on survival following myocardial infarction in men vs women: the Framingham Study. *JAMA* 1988; 260: 3456–3460.
17. Savage MP, Krolewski AS, Kenien GG, et al. Acute myocardial infarction in diabetes mellitus and significance of congestive heart failure as a prognostic factor. *Am J Cardiol* 1988; 62:665–669.
18. Chun BY, Dobson AJ, Heller RF. The impact of diabetes on survival among people with first myocardial infarction. *Diabetes Care* 1997; 20:704–708.
19. Castelli WP, Garrison RJ, Wilson P, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *JAMA* 1986; 256:2835–2838.
20. Manolio TA, Pearson TA, Wenger NK, et al. Cholesterol and heart disease in older persons and women: review of an NHLBI workshop. *Ann Epidemiol* 1992; 2:161–176.
21. Cornoni-Huntley J, LaCroix AZ, Havlik RJ. Race and sex differentials in the impact of hypertension in the United States: the National Health and Nutrition Examination Survey: I — Epidemiologic follow-up study. *Arch Intern Med* 1989; 149:780–788.
22. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Int Med* 1997; 157:2413–2446.
23. Stokes J, Kannel WB, Wolf PA, et al. Blood pressure as a risk factor for cardiovascular disease: the Framingham Study — 30 years of follow-up. *Hypertension* 1989; 13(Suppl I):I13–I18.
24. Kushi LH, Fee RH, Folsom AR, et al. Physical activity and mortality in post-menopausal women. *JAMA* 1997; 277:1287–1292.
25. 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.
26. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; 67:968–977.
27. 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.
28. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med* 1995; 333:677–685.
29. Zucker DR, Griffith JL, Beshansky JR, Selker HP. Presentation of acute myocardial infarction in men and women. *J Gen Intern Med* 1997; 12:79–87.
30. Sullivan AK, Holdright DR, Wright CA, et al. Chest pain in women: clinical, investigative, and prognostic features. *BMJ* 1994; 308:883–886.
31. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction: an update on the Framingham study. *N Eng J Med* 1984; 311:1144–1147.
32. Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol* 1999; 83:660–666.
33. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation* 1989; 80:87–98.
34. Isaac D, Walling A. Clinical evaluation of women with ischemic heart disease: diagnosis and noninvasive testing. *Can J Cardiol* 2001; 17 Suppl D:38D–48D.
35. Alexander KP, Shaw LJ, Shaw LK, et al. Value of exercise treadmill testing in women. *J Am Coll Cardiol* 1998; 32:1657–1664.
36. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Eng J Med* 1996; 334:1311–1315.
37. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997; 30:260–311.
38. Taillefer R, DePuey EG, Udelson JE, et al. Comparative diagnostic accuracy of TI-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol* 1997; 29:69–77.
39. Marwick TH, Shaw LJ, Lauer MS, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Economics of Noninvasive Diagnosis (END) Study Group. *Am J Med* 1999; 106(2):172–178.
40. Travin MI, Duca MD, Kline GM, et al. Relation of gender to physician use of test results and to the prognostic value of stress technetium 99m sestamibi myocardial single-photon emission computed tomography scintigraphy. *Am Heart J* 1997; 134:73–82.
41. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA* 1998; 280:913–920.
42. Tong AT, Douglas PS. Stress echocardiography in women. *Cardiol Clin* 1999; 17:573–582.
43. McCully RB, Roger VL, Mahoney DW, et al. Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: follow-up of 1,325 patients. *J Am Coll Cardiol* 1998; 31:144–149.
44. Heupler S, Mehta R, Lobo A, et al. Prognostic implications of exercise echocardiography in women with known or suspected coronary artery disease. *J Am Coll Cardiol* 1997; 30:414–420.
45. Cortigiani L, Dodi C, Paolini EA, et al. Prognostic value of pharmacological stress echocardiography in women with chest pain and unknown coronary artery disease. *J Am Coll Cardiol* 1998; 32:1975–1981.
46. Chuah SC, Pelliikka PA, Roger VL, et al. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. *Circulation* 1998; 97:1474–1480.
47. O’Keefe JH, Barnhart CS, Bateman TM. Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity. *Am J Cardiol* 1995; 75:25D–34D.
48. Marrugat J, Sala J, Masia R, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. *JAMA* 1998; 280:1405–1409.
49. Weaver WD, White HD, Wilcox RG, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. Gusto-1 Investigators. *JAMA* 1996; 275:777–782.
50. Malacrida R, Genoni M, Maggioni AP, et al. A comparison of the early outcome of acute myocardial infarction in women and men. The Third International Study of Infarct Survival Collaborative Group. *N Eng J Med* 1998; 338:8–14.
51. Gan SC, Beaver SK, Houck PM, et al. Treatment of acute myocardial infarction and 30-day mortality among women and men. *N Eng J Med* 2000; 343:8–15.
52. 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.

53. Clarke KW, Gray D, Keating NA, Hampton JR. Do women with acute myocardial infarction receive the same treatment as men? *BMJ* 1994; 309:563–566.
54. Kudenchuk PJ, Maynard C, Martin JS, et al. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (The Myocardial Infarction Triage and Intervention Registry). *Am J Cardiol* 1996; 78:9–14.
55. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIB Investigators. *N Eng J Med* 1999; 341:226–232.
56. Scirica BM, Moliterno DJ, Every NR, et al. Differences between men and women in the management of unstable angina pectoris (The GUARANTEE Registry). *Am J Cardiol* 1999; 84:1145–1150.
57. 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(5): 972–976.
58. Schwartz LM, Fisher ES, Tosteson NA, et al. Treatment and health outcomes of women and men in a cohort with coronary artery disease. *Arch Intern Med* 1997; 157:1545–1551.
59. Tobin JN, Wassertheil-Smoller S, Wexler JP, et al. Sex bias in considering coronary bypass surgery. *Ann Intern Med* 1987; 107:19–25.
60. Steingart R, Packer M, Hamm P, et al. Sex differences in the management of coronary artery disease: Survival and Ventricular Enlargement investigators. *N Eng J Med* 1991; 325:226–230.
61. Stone PH, Thompson B, Anderson H, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction in the United States and Canada (the TIMI III Registry). *JAMA* 1996; 275:1104–1112.
62. Chandra NC, Ziegelstein RC, Rogers WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. *Arch Intern Med* 1998; 158:981–988.
63. Kelsey S, James M, Holubkov AL, et al. Results of percutaneous transluminal coronary angioplasty in women. 1985–1986 National Heart, Lung, and Blood Institute Coronary Angioplasty Registry. *Circulation* 1993; 87:720–727.
64. Ellis SG, Myler RK, King SB, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. *Circulation* 1988; 77:372–379.
65. Bell MR, Holmes DR, Berger PB, et al. The changing in-hospital mortality of women undergoing percutaneous transluminal angioplasty. *JAMA* 1993; 269:2091–2095.
66. Arnold AM, Mick MJ, Piedmonte MR, Simpfordorfer C. Gender differences for coronary angioplasty. *Am J Cardiol* 1994; 74:18–21.
67. Kells CM, Mickleborough L. Revascularization strategies in women with ischemic heart disease. *Can J Cardiol* 2001; 17(Suppl D):53D–56D.
68. Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). *Circulation* 1998; 98:1279–1285.
69. Hall RJ, Elayda MA, Gray A, et al. Coronary artery bypass: long-term follow-up of 22,284 consecutive patients. *Circulation* 1983; 68(Suppl II):II20–II26.
70. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. *N Eng J Med* 1991; 325:221–225.
71. Mickleborough LL, Takagi Y, Maruyama H, et al. Is sex a factor in determining operative risk for aortocoronary bypass graft surgery? *Circulation* 1995; 92(Suppl II):II80–II84.
72. Edwards FH, Grover FL, Shroyer AL, et al. The Society of Thoracic Surgeons National Cardiac Surgery Database: current risk assessment. *Ann Thorac Surg* 1997; 63:903–908.
73. Brandrup-Wognsen G, Berggren H, Hartford M, et al. Female sex is associated with increased mortality and morbidity early, but not late, after coronary artery bypass grafting. *Eur Heart J* 1996; 17:1426–1431.
74. Stewart RD, Blair JL, Emond CE, et al. Gender and functional outcome after coronary artery bypass. *Surgery* 1999; 126:184–190.
75. Davis KD, Chaitman B, Ryan T, et al. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS registry study. *J Am Coll Cardiol* 1995; 25:1000–1009.
76. Sites CK. Hormone replacement therapy: cardiovascular benefits for aging women. *Coron Artery Dis* 1998; 9:789–793.
77. Walsh BW, Schiff I, Rosner B, et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 1991; 325:1196–1204.
78. 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 Jan 18;273(3):199–208.
79. Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998; 279:1445–1451.
80. Perregaux D, Chaudhuri A, Mohanty P, et al. Effect of gender differences and estrogen replacement therapy on vascular reactivity. *Metabolism* 1999; 48:227–232.
81. Best PJ, Berger PB, Miller VM, Lerman A. The effect of estrogen replacement therapy on plasma nitric oxide and endothelin-1 levels in postmenopausal women. *Ann Intern Med* 1998; 128:285–288.
82. McGrath BP, Liang YL, Teede H, et al. Age-related deterioration in arterial structure and function in postmenopausal women: impact of hormone replacement therapy. *Arterioscler Thromb Vasc Biol* 1998; 18:1149–1156.
83. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991; 20:47–63.
84. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Int Med* 1992; 117:1016–1037.
85. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med* 1991; 151:75–78.
86. O'Brien JE, Peterson ED, Keeler GP, et al. Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions. *J Am Coll Cardiol* 1996; 28:1111–1118.
87. Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. *Am J Cardiol* 1997; 79:847–850.
88. O'Keefe JH, Kim SC, Hall RR, et al. Estrogen replacement therapy after coronary angioplasty in women. *J Am Coll Cardiol* 1997; 29:1–5.
89. Barrett-Connor E. Postmenopausal estrogen and prevention bias. *Ann Intern Med* 1991; 115:455–456.
90. Petitti DB. Coronary heart disease and estrogen replacement therapy: can compliance bias explain the results of observational studies? *Ann Epidemiol* 1994; 4:115–118.

91. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997; 336:1769–1775.
92. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Eng J Med* 1985; 313:1044–1049.
93. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the Nurses' Health Study. *N Eng J Med* 1991; 325:756–762.
94. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Eng J Med* 1996; 335:453–461.
95. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; 133:933–941.
96. Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study. *Ann Intern Med* 2001; 135:1–8.
97. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in women. *JAMA* 1998; 280:605–613.
98. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and estrogen/progestin replacement study follow-up (HERS II). *JAMA* 2002; 288:49–57.
99. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and estrogen/progestin replacement study follow-up (HERS II). *JAMA* 2002; 288:58–66.
100. Mosca L, Collins P, Herrington D, et al. Hormone replacement therapy and cardiovascular disease. A statement for health-care professionals from the American Heart Association. *Circulation* 2001; 104:499–503.
101. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321–333.
102. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Eng J Med* 2000; 343:522–529.
103. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women. Four year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002; 287:847–857.