Postmenopausal Estrogen Supplementation: A Cardiologist's Perspective

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September 2, 1993

Introduction

Five hundred years ago, women died in their thirties, still in the midst of their reproductive years. At the turn of the century, women were living to an average age of 48 (1). Current census figures predict that women today are expected to live to an average age of 73.5 (black women) to 79.2 years (white women) (2). Given that the current median age of natural menopause occurs at age 50 years, women will survive their ovaries by a period of some 25-30 years and spend nearly one third of their lives after cessation of reproductive function (3). This growing population of postmenopausal women compels the medical community to recognize the implications of menopause for both health and disease as well as the risks and benefits of hormonal replacement therapy . Today, the goal of maximizing the quality of the last third of each's women's life is at the forefront in both the lay and scientific press (4). The goal of this grand rounds is to discuss the relationship between menopause and coronary heart disease (CHD) risk and evaluate the risks and benefits of hormonal replacement therapy from a cardiologist's perspective.

The Physiology of Menopause

Hormonal Changes: As a women ages, ovarian function begins to fail. The number of follicles in the ovaries decreases and less estrogen is synthesized (Figure 1). A deficiency in follicular inhibin and estrogen leads to decreased negative feedback on the anterior pituitary gland which results in an increase in levels of follicle-stimulating hormone and luteinizing hormone (1). Estradiol, produced by the ovary, is the predominant estrogen in premenopausal women. The predominant estrogen in postmenopausal women is estrone, a less active form of estrogen, which is synthesized in the periphery, primarily in adipose tissue, from the conversion of androstenedione by the enzyme aromatase (Figure 2) (3).

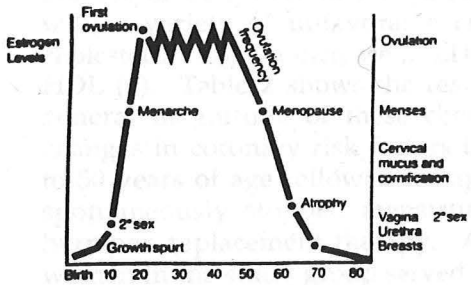

Fig. 1. Relative biologic levels of estrogen (ref. 1).

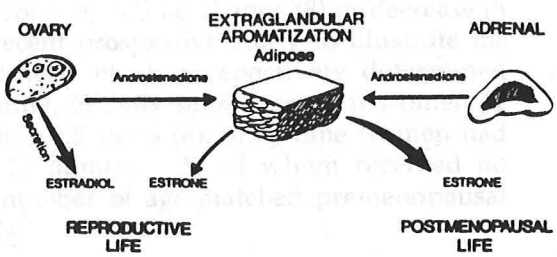

Fig. 2. Sources of estrogen during reproductive and postmenopausal life (ref. 3).

General Symptoms: A number of symptoms preceding and subsequent to the menopause are attributable to estrogen deficiency. Table 1 lists target organs and potential symptoms or problems that can arise in perimenopausal and postmenopausal women (1).

Table 1. Potential Problems of the Untreated Menopause

Target Organ	Possible Symptom or Problem
Vulva	Atrophy, dystrophy, pruritus
Vagina	Dyspareunia, vaginitis
Bladder and urethra	Incontinence, urethritis
Uterus and pelvic floor	Prolapse
Skin and membranes	Atrophy, pruritus, dry mouth
Vocal cords	Voice changes
Skeleton	Osteoporosis, fractures
Neuroendocrine system	Hot flashes, irritability
Cardiovascular system	Atherosclerosis, angina, CHD

From: Utian. Am J Obstet Gynecol 161(6Pt2):1828-31, 1989.

Urogenital atrophy manifests as a loss of soft tissue elasticity and a decrease in muscle tone and secretions resulting in the kinds of symptoms noted here. After menopause, bone turnover increases overall but resorption increases more than formation, leading to a negative calcium balance and bone loss (5). Hot flashes, which occur in 75% to 85% of climacteric women, may also be accompanied by sleep disturbances and increased fatigue and irritability (1). Before we discuss the effects, if any, of menopause on the cardiovascular system, a review of the effects of menopause on coronary risk factors is in order.

Cardiac Risk Factors: No changes have been reported in blood pressure, blood glucose or body weight after menopause (6,7). Menopause is, however, associated with a variety of unfavorable changes in the lipid profile: an increase in total cholesterol (7,8), an increase in LDL cholesterol (8,9) and no change (8) or decrease in HDL (6). Table 2 shows the results of a recent prospective study to illustrate the general magnitude of these changes. Matthews et al. prospectively determined changes in coronary risk factors in 541 healthy, initially premenopausal women 42 to 50 years of age followed for approximately 2.5 years (8). Sixty-nine women had spontaneously stopped menstruating for 12 months, 37 of whom received no hormone replacement therapy. An equal number of age-matched premenopausal women in the study group served as controls.

Table 2. Effect of Menopause on Cholesterol, LDL and HDL

	Baseline		% Change at Follow-Up	
Characteristic	Menopausal Women	Premenopausal Controls	Menopausal Women	Premenopausal Controls
Total cholesterol*	193.0(3.9)	180.6(3.9)	+9.7(3.1)	+6.6(2.3)
LDL*#	114.5(3.9)	108.3(3.9)	+12.0(3.9)	+5.4(1.9)
HDL*#	60.3(1.9)	56.8(1.6	-3.5(1.1)	0.0

*mg/dl; # The changes in LDL and HDL among menopausal women compared to their premenopausal controls are significant after adjustment for age, body-mass index and cigarette use. Adapted from: Matthews et al. New Engl J Med 321:641-6, 1989.

Methodologic Considerations in Assessing Menopause and the Risk of CHD

Advancing Age: Do these unfavorable changes in the lipid profile with menopause translate into increased risk for CHD? The effect of menopause on the cardiovascular system is difficult to assess because of the relations among coronary disease, menopause and coronary risk factors that influence the occurrence of menopause such as advancing age and tobacco use (10). In Figure 3, the United States death rate from CHD in 1988 (acute and chronic MI, ischemic heart disease and angina) in men and women is shown stratified according to age (11).

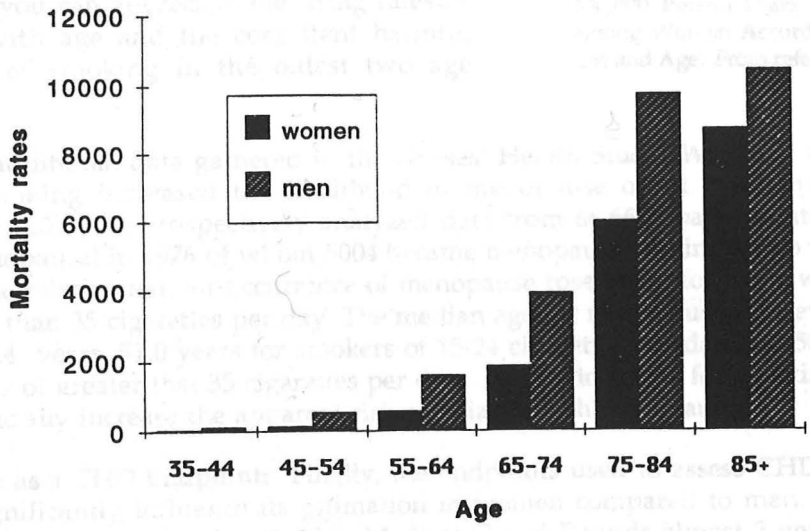

Figure 3. The United States Death Rate from CHD in Men and Women Stratified According to Age. From: U.S. Vital Statistics, 1988.

The rate of coronary mortality rises very sharply with age among both men and women. Even a few years difference in age can have a big impact on the mortality rate. A difference of 5 years, between 42 and 47, corresponds to a 125% increase in the rate of CHD mortality in women (11). Although natural menopause occurs over an age range, in general, postmenopausal women will be older than premenopausal women. Hence, a close control of age is essential to avoid mixing the potential effects of menopause with the effects of age alone. Inadequate control for age would tend to artificially increase the risk associated with menopause.

Tobacco Use: Cigarette smoking is a major coronary risk factor for women. Willett et al. examined the incidence of coronary heart disease in relation to cigarette smoking in a cohort of 119,404 female nurses participating in the Nurses' Health Study who were 30 to 55 years of age in 1976 and were free of diagnosed coronary disease (12). This data was gathered from questionnaires sent to the participants every two years for a total of six years of follow-up. Figure 4 shows the rates of total coronary heart disease (fatal coronary heart disease and non-fatal myocardial infarction) per 100,000 person-years on the vertical scale among women according to cigarette use and age on the horizontal scales. Again, you can appreciate the rising rates of CHD with age and the consistent harmful effects of smoking in the oldest two age groups.

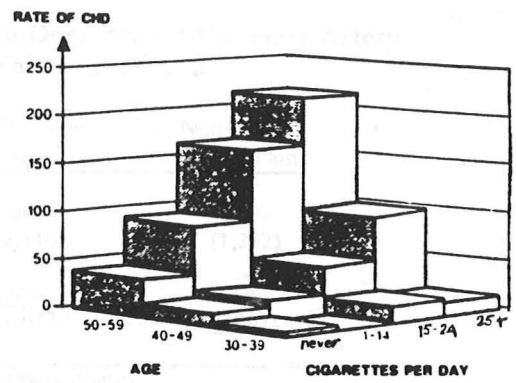

Figure 4. Rates of Total CHD per 100,000 Person-Years (Vertical Scale) among Women According to Cigarette Use and Age. From reference 12.

Using additional data gathered in the Nurses' Health Study, Willett et al. reported that smoking increased the likelihood of menopause onset in a dose response manner (13). He prospectively analyzed data from 66,663 participants who were premenopausal in 1976 of whom 5004 became menopausal during a two year follow-up. The relative risk for occurrence of menopause rose to 2.0 for those who smoked greater than 35 cigarettes per day. The median age for menopause for never-smokers was 52.4 years, 51.0 years for smokers of 15-24 cigarettes per day and 50.4 years for smokers of greater that 35 cigarettes per day. Failure to adjust for smoking will tend to artificially increase the apparent risk associated with menopause.

Angina as a CHD Endpoint: Finally, the endpoints used to assess CHD prevalence can significantly influence its estimation in women compared to men. Dr. Margo Denke illustrated this nicely in her Medical Grand Rounds almost 2 years ago (14). The purest endpoint of CHD is death due to coronary disease documented by autopsy or medical records. This endpoint can be enriched by adding additional

endpoints such as myocardial infarction, positive invasive and non-invasive testing and symptoms such as angina pectoris. Compared with men, angina in women is not as sensitive or specific a predictor of CHD. In the Coronary Artery Surgery Study (CASS), 8157 male and female patients underwent cardiac catheterization for the evaluation of chest pain (15). The chest pain was classified into three categories: definite angina, probable angina and non-specific chest pain. Table 3 shows the percentage of men and women with documented coronary artery stenoses of greater that 70% diameter according to chest pain type.

Table 3. Percentage of Men and Women with Documented Coronary Artery Stenoses According to Chest Pain Type, CASS

	Definite Angina	Probable Angina	Non-Specific Chest Pain
Men	93% (1,919)*	66% (2,146)	14% (1,282)
Women	72% (401)	36% (1012)	6% (1397)

* number of subjects is listed in parentheses
From Chaitman et al. Circulation 64(2):360-367, 1981

In each category, the number of women who have documented CAD is much lower that the number of men. This reduced specificity of angina to predict the prevalence of CAD in women is attributed to the lower prevalence rate of CAD in women overall.

Natural Menopause and the Risk of CHD

Population Statistics: With these caveats in mind, I will review data which evaluate the relationship between natural menopause and coronary heart disease prevalence. As shown previously, Figure 3 shows the mortality rate of coronary heart disease for men and women grouped according to age. Conclusions you might draw from this figure include: (1) the death rate climbs quickly after age 55 in women; therefore, menopause is associated with an increased risk of CHD or (2) the difference in mortality rates between men and women is greatest prior to menopause and then becomes progressively smaller after menopause; therefore, menopause is associated with an increased risk of CHD. Again because of the effect of age on CHD mortality in both men and women, you cannot attribute the increase in the rate of death in women to menopause alone. A very instructive way to look at these data is to plot the age-adjusted death rate on a log scale versus age on a linear scale (Gompertz

plot). A linear distance between two points on a logarithmic scale represents the ratio between the respective numbers (log a/b = log a - log b) (16). The rate may have a steady increase over time due to age, but if menopause has an effect, the rate of increase should accelerate in the fifth or sixth decade for women.

Figure 5 shows the rate of increase in coronary mortality for men and women in 1988. There is no abrupt increase in the rate of increase at menopause and the smaller difference in mortality rates in older men and women is due to a slowing of the rate of increase in men (10). Because the age of menopause varies over many years, a moderate effect of menopause could easily be lost in population statistics. Studies of individuals with known menopausal status provide more appropriate data to evaluate the relationship between menopause and the risk of coronary disease. We will examine the relationship in both case-control studies and prospective cohort studies.

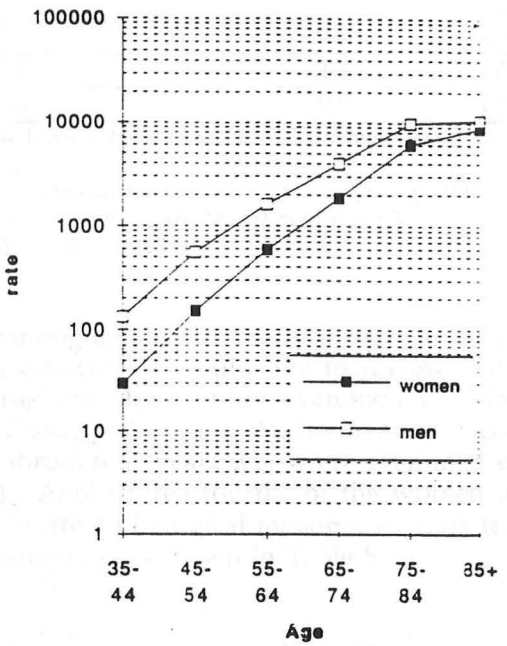

Figure 5. Gompertz plot of mortality rate of CHD in Men and Women According to age. From U.S. Vital Statistics, 1988.

Case-Control Studies: Several case-control studies had been performed which examine the relationship between natural menopause and the risk of myocardial infarction and report relative risks of 1.3 (95% confiedence limits (CL) 0.7 and 2.1) (17), 1.2 (% CL 0.4 and 3.2) (18) and 2.4 (95% CL 1.2 and 4.7) (19); however, adjustments for the effects of age and tobacco use were not made.

This is not the case, however, in a case-control study of menopause and nonfatal myocardial infarction conducted by Rosenberg et al. who identified 279 women who had been hospitalized for myocardial infarction (cases) and 5580 age-matched control subjects from 121,964 female nurses who completed the Nurses' Health Study baseline questionnaire (20). Their results for women with a natural menopause are listed in Table 4.

Table 4. Relation of Risk of MI to Age at Natural Menopause
The Nurses' Health Study

Age (years)	<35	35-39	40-44	≥45
Case Subjects	1	3	7	14
Control Subjects	7	49	149	488
RR* Estimate	3.4	1.5	1.1	0.7
Adjusted#RR estimate	2.8	1.1	0.9	0.5

*RR = Relative risk: The 156 premenopausal case subjects and the 3721 premenopausal control subjects constitute the reference group.
Adjusted by multiple logistic regression analysis for hormone use, obesity, cigarette use, hypertension, diabetes, hypercholesterolemia, angina, parental MI before age 50.
From: Rosenberg et.al. Am J Obstet Gynecol 139:47-51, 1981.

Prospective Cohort Studies: The Framingham Heart Study is frequently cited in discussions of menopause and heart disease. I would like to review it in some detail. Initiated in 1948, the Framingham Heart Study examined the effects of natural and surgical menopause on CHD by observing the occurrence of coronary disease among 2873 women aged 29 through 62 years who were examined every 2 years over a period of 24 years (21). About three fourths of the women became menopausal naturally and about one fourth had surgical menopause. Data for CHD in women who underwent natural menopause is shown in Table 5.

Table 5. CHD Cases in Women with Natural Menopause
Framingham Study: 24-Year Follow-Up

Age/Menopausal Status	Person-Years	No. CHD Cases
40 to 44 years old		
Premenopausal	4518	1
Postmenopausal	280	0
45 to 49 years old		
Premenopausal	3266	4 (1)*
Postmenopausal	1752	6 (2)
50 to 54 years old		
Premenopausal	600	1
Postmenopausal	5704	25 (11)

* Parenthetical entries are numbers of CHD cases presenting other than angina pectoris. From: Gordon et al. Ann Int Med 89:157-161, 1978.

Despite the long follow-up, there were few cases of major coronary disease (myocardial infarction, coronary insufficiency and coronary death) in women with natural menopause and even fewer such cases in premenopausal women. For women ages 45 to 54 years, the authors report an age-adjusted relative risk of 2.7 including angina as an endpoint. Excluding angina, the relative risk was 2.0 (95% CL 0.6 and 6.3, p = 0.26), without statistical significance. Moreover, these results do not adjust for tobacco use.

The Lipid Research Clinics (LRC) Prevalence Study of CVD was conducted in 10 North American Clinics between 1972 and 1976 and included participants two thirds of whom were selected randomly and one third of whom were selected because they had hyperlipidemia (22). The information ascertained for all participants at baseline (called visit 2) is listed in Table 6.

Table 6. Lipid Research Clinics Prevalence Study of CVD Baseline Data

Age
Tobacco Use
Education Level
Medication Use
Alcohol Consumption
Estrogen Use
Exercise Habits
Blood Pressure
Body Mass Index
Total Cholesterol
HDL, LDL
Triglycerides
Resting and Exercise EKG

From: reference 22.

Participants who were 30 years of age and older and who participated in visit 2 were enrolled in the on-going prospective mortality study called the LRC Follow-up Study. In one analysis, published in the proceedings of an N.I.H. workshop, which evaluated the effect of menopause on CVD, data from 2270 white women ages 40-69 at visit 2 with an average follow-up of 8.5 years were included (22). CVD death included deaths from ischemic heart disease, cardiomyopathies, cerebrovascular disease, arteriosclerosis and diabetes mellitus.

Table 7 shows the CVD mortality by menopausal status in women aged 50 to 59 years. They limited this analysis to this age group because no women over the age of 60 years were premenopausal and because no CVD deaths occurred among women under 50 years of age. The authors note that these findings must be interpreted with caution because the rates are based on very small numbers and the confidence limits are extremely wide. Furthermore, there was no control for other

coronary risk factors, such as smoking for example, in this analysis.

Table 7. CVD Mortality Rates by Menopausal Status in Women Aged 50 to 59 Years, LRC Follow-Up Study

Menopausal Status	CVD Deaths	Person-Years of Follow-Up	Relative Risk*
Premenopausal	2	2,749	1.0
Natural Menopause	4	2,635	2.16 (0.30 - 23)
Oophorectomy	4	1,210	4.52 (0.65 - 50)

* Compared with premenopausal women, confidence intervals in parentheses.
From: Bush et al. in Coronary Heart Disease in Women, Eaker et al. (eds), Haymarket Doyma, NY, pp106-112.

The largest prospective study of natural menopause and heart disease was from the Nurses' Health Study in which 116,258 female nurses aged 35-55 years who were free of coronary disease at baseline in 1976 were followed for 6 years with biennial questionnaires for the occurrence of nonfatal myocardial infarction and fatal coronary heart disease (23). At baseline, there were 14,732 women with natural menopause and additional women became postmenopausal with each follow-up period. The risk of heart disease among women reporting a natural menopause compared with premenopausal women is summarized in Table 8.

Table 8. Natural Menopause and Rate Ratios for CHD Risk, The Nurses' Health Study

Analysis Adjustment	Rate Ratio for CHD
age (five-year)	1.7 (1.1 and 2.8)*
age (one-year)	1.2 (0.9 and 1.9)
cigarette use	1.0 (0.8 and 1.8)
estrogen use	1.2 (0.8 and 1.8)

* 95% confidence limits are noted in parentheses
CHD = fatal and non-fatal myocardial infarction
From Colditz et al. N Engl J Med 316:1105-10, 1987.

After adjustment for age in five-year categories, the age-adjusted rate ratio was 1.7 (95% CL 1.1 and 2.8). Since age and natural menopause are highly correlated, the analysis was repeated for one-year intervals with a reduction in the rate ratio to 1.2 (95% CL 0.8 and 1.9). Further adjustment for cigarette smoking reduced the risk to 1.0 (95% CL 0.8 and 1.3). Because estrogen use may influence the risk of CHD, the

age and smoking-adjusted ratio was adjusted for estrogen use. Women who had never used estrogen had a nonsignificant, slightly increased risk at 1.2 (95% CL 0.8 and 1.8).

Surgical Menopause and the Risk of CHD

Case-Control Studies: While the data supporting the notion that natural menopause increases CHD risk are lacking, there is evidence for an increased risk of CHD in women who have undergone a surgical menopause. This kind of data is particularly appealing because surgical menopausal is not as closely correlated with advancing age and is not associated with other coronary risk factors.

Most, but not all studies, show an elevated risk with surgical menopause. Data published from the LRC Follow-up Study, shown previously in Table 7, lists an elevated risk of 4.52 for women age 50 to 59 years with a surgical menopause. However, in a multivariate analysis controlling for age, smoking, blood pressure, cholesterol and estrogen use, oophorectomy was not a significant predictor of subsequent CVD death (22). Data which support an elevated risk associated with surgical menopause are found in both case-control and prospective cohort studies of which two examples are shown below.

In the well designed case-control study of Nurses' Health Study participants described previously (20), Rosenberg et al. also examined the risk of myocardial infarction in women having a surgical menopause. Their results are shown in Table 9. There is higher adjusted risk in women who had bilateral oophorectomy at a younger age.

Table 9. Relation of Risk of MI to Age at Surgical Menopause
The Nurses' Health Study

Age (years)	<35	35-39	40-44	≥45
Case Subjects	19	9	10	10
Control Subjects	63	82	116	136
RR* Estimate	7.2	2.6	2.1	1.8
Adjusted# RR estimate	7.7	2.9	1.9	1.3

*RR = Relative risk: The 156 premenopausal case subjects and the 3721 premenopausal control subjects constitute the reference group.
Adjusted by multiple logistic regression analysis for hormone use, obesity, tobacco use, hypertension, diabetes, hypercholesterolemia, angina, parental MI before age 50.
From: Rosenberg et.al. Am J Obstet Gynecol 139:47-51, 1981.

Prospective Studies: While data from the Framingham Heart Study is much less convincing, it merits review because it is so frequently cited. Women aged 45 to 54 years with a surgical menopause were found to have the same elevated risk as women with natural menopause, 2.7 to 1 (21). As you can see in Table 10, if angina is excluded, the number of CVD cases in this age range is small with 1 case in the premenopausal group and 10 cases in the postmenopausal group.

Table 10. CHD Cases in Women with Surgical Menopause (Framingham Study: 24-Year Follow-Up)

Age/Menopausal Status	Person-Years	No. CHD Cases
40 to 44 years old		
Premenopausal	4518	1
Postmenopausal	1374	5 (1)*
45 to 49 years old		
Premenopausal	3266	4 (1)
Postmenopausal	2336	7 (3)
50 to 54 years old		
Premenopausal	600	1
Postmenopausal	3138	14 (7)

* Parenthetical entries are numbers of CHD cases presenting other than angina pectoris. From: Gordon et al. Ann Int Med 89:157-161, 1978

In the prospective Nurses' Health Study investigation described earlier, the effects of bilateral oophorectomy on CVD mortality were also assessed (23). In 1976, 31.4% of the participants without CHD indicted that their menses had ceased: 14,732 had a natural menopause and 8502 had a hysterectomy with bilateral oophorectomy. For simplicity, those with unilateral oophorectomy or hysterectomy only will be excluded from this analysis. Data from these groups are shown in Table 11.

Table 11. Risk of CHD in Women with Surgical Menopause The Nurses' Health Study

Group	Person-Years	CHD Cases	Relative Risk*
Premenopausal	436,003	88	1.0
Surgical Menopause			
- estrogen	9,630	14	2.2 (1.2 and 4.2)
+ estrogen	42,299	27	0.9 (0.6 and 1.6)

*Adjusted for both age and smoking; 95% confidence limits are noted in parentheses.
From: Colditz et al. N Engl J Med 316:1105-10, 1987.

In summary then, during menopause. there are changes in the lipid profile which could favor the development of CHD. Furthermore, there is convincing evidence to indicate that the risk of CHD increases with surgical menopause. Given that ovarian function begins to decline long before menopause and continues to decline long after menopause, perhaps it is not surprising that the moment of natural menopause is not associated with an abrupt increase in CHD risk. However, given the change in the lipid profile and the increased risk of CHD with advancing age, it may signal a period of increasing risk. Could estrogen supplementation reduce this increased risk of CHD?

Effect of Estrogen on CHD Risk in Men

Exogenous Estrogen: Serious study of the relationship between estrogen therapy and CHD in men began in the 1960s when a Veterans Administration Cooperative Study was inaugurated to evaluate the efficacy of several modes of treatment for prostate cancer (25). The treatment arms are listed in Table 12.

Table 12. Treatment Groups and Prostate Cancer Stage
VA Co-Operative Urological Research Group

Treatment	Stage
Prostatectomy plus placebo	I, II
Prostatectomy plus estrogen*	I, II
Placebo only	III, IV
Estrogen* only	III, IV
Orchiectomy plus placebo	III, IV
Orchiectomy plus estrogen*	III, IV

* 5 mg diesthlystilbestrol
From: VACURG, Surg Gyn Obstet, 124:10111-1018, 1967.

Estrogens reduced the mortality from prostate cancer but increased deaths from other causes. There were 1.7 times more deaths from CHD and stroke in those treated with estrogen compared to those who were not. There was no difference in the rates of death from pulmonary embolus.

Men also received estrogen in the Coronary Drug Project Study which was designed to test the efficacy and safety of several drugs in the long term therapy of CHD in 8,341 men aged 30 to 64 with proved previous myocardial infarction (26). The pharmacologic agents used are listed in Table 13. Patients were followed for 5 years. The primary endpoint was death. Other endpoints which were being monitored included: incidence and mortality of MI, congestive heart failure and stroke and incidence rates of angina pectoris.

Table 13. Treatment Arms in the Coronary Drug Project

Estrogen, 2.5 mg/day
Estrogen, 5.0 mg/day
Clofibrate, 1.8 gm/day
Dextrothyroxine, 6.0 mg/day
Niacin, 3.0 gm/day
Placebo

From: CDP. JAMA 214(7):1303-1313, 1970.

After an average of 18 months of follow-up, in the high dose estrogen group, there were an excess number of events of non-fatal MI (6.% versus 3.2% in the placebo group), and pulmonary embolism or thrombophlebitis (5.0% versus 1.7 % in the placebo group). This treatment arm was abandoned. After an average of 56 months of follow-up, researchers concluded that the low dose estrogen regimen had no therapeutic efficacy and possible adverse effects and it was subsequently discontinued as well. The possible adverse effects were trends toward a higher incidence of pulmonary embolism and thrombophlebitis and mortality from all cancers and lung cancer (27).

Endogenous Estrogen: Following these results, there were a flurry of reports showing elevated endogenous estrogen levels in men with acute myocardial infarction and chronic angina pectoris. However, when adjustments were made for the risk factor of smoking (which increases estrogen levels in healthy men), endogenous estrogen levels were not found to be associated with CHD mortality in men (28,29).

Effect of Supplemental Estrogen on CHD Risk in Post-Menopausal Women

While it appears that estrogen supplementation has no role in the treatment of CHD in men, it may have an important role in the treatment of postmenopausal women. For an exhaustive discussion of the methods and results of a large number of studies which address the relationship between CVD morbidity and mortality and estrogen use in postmenopausal women, I recommend two recent comprehensive reviews by Stampfer and Colditz (30) and Barrett-Conner and Bush (31). I would like to summarize and highlight their work.

Case-Control Studies: Table 14 summarizes the results of both hospital-based and community -based case-control studies. The case-control design has some important limitations: the possibility of recall bias and the problem of proper selection of controls especially in the hospital-based studies. For example, the study described in reference 35 was designed before it was widely appreciated that estrogens reduce the likelihood of certain fractures. Twenty-seven percent of the control subjects had a discharge diagnosis of trauma (mainly fractures). These controls are less likely to

be estrogen users than comparably age women in the population and this might magnify a positive correlation between CHD and estrogen use.

The only study which showed a significant result was by Jick et al. (32) who studied 17 women younger than 46 years who were discharged from a hospital with a diagnosis of acute MI. Estrogen use was present in 53% of the cases and 12% of the controls. The estrogen users had a risk of MI 7.5 times the non-users. However, all but one of the cases (94%) smoked whereas only 47% of the controls did; the risk estimate was not adjusted for this confounding variable. The remaining studies listed in this table did not show any significant reduction in CHD risk with postmenopausal estrogen use.

Table 14. Summary of Case-Control Studies of Current Estrogen Use in Women: Fatal and Nonfatal CHD Risk

Author	Base	Size (Cases/Controls)	Endpoint	Adjusted Risk
Jick (32)	H*	17/34	NF MI	7.50 (2.4-24)‡
Rosenberg (33)	H	336/6730	NF† MI	0.97 (0.48-1.95)
LaVecchia (34)	H	116/160	NF MI	1.85 (0.68-5.01)
Rosenberg (35)	H	105/303	NF MI	1.0 (0.6-1.7)
Szklo (36)	H	36/39	NF MI	0.61 (0.20-1.88)
Talbott (37)	C*	64/64	SD†	0.34 (0.09-1.30)
Beard (38)	C	86/150	MI, SD	0.55 (0.24-1.30)
Thompson (39)	C	603/1206	MI, Stroke	1.09 (0.65-1.82)
Bain (40)	C	120/2438	NF MI	0.07 (0.4-1.1)

* H=hospital-based, C=community-based; †NF=Nonfatal, SD=Sudden Death;
‡ confidence limits in parentheses.

Angiographic Studies: Table 15 summarizes findings from three studies in which the degree of coronary disease and the use of postmenopausal estrogens were ascertained among women undergoing coronary angiography. In all cases, the adjusted risk shows a significant reduction in the risk of angiographically significant coronary artery disease in estrogen users.

Table 15. Summary of Studies of Coronary Artery Occlusion Among Women With and Without Postmenopausal Estrogen who had Coronary Angiography

Author	No. Pts	% ERT Use	Adjusted Risk
Sullivan (41)	2,188	4.4% Current	0.44 (0.29-0.67)* 70% stenosis vs 0%
Gruchow (42)	933	17% Current	0.59(0.48-0.73)‡ mod vs low 0.37 (0.29-0.46) high vs low
McFarland (43)	283	41% Ever	0.5 (0.3-0.8)# 70% occlusion vs 0%

* Adjusted for age, cigarette use, diabetes, cholesterol and hypertension.
‡ Adjusted for age, cigarette use, exercise index and body mass index.
# Adjusted for age only.

Prospective Studies: This section will describe prospective studies which followed women with and without estrogen exposure thus including internal controls (as opposed to comparing the estrogen-using cohort to general population statistics). Table 16 summarizes the results of these prospective studies with internal controls whihc evaluated the risk of CHD in women who were "current" or "ever" users of postmenopausal estrogen. Relative risk values are calculated adjusted for age and adjusted for cardiac risk factors evaluated in the specific study. Findings in the first four studies (44,45,46,47) do not show a significant reduction or increase in CHD risk in estrogen users compared with non-users. With the exception of one study (53), the remaining studies show a protective effect of estrogen use in terms of CHD risk. I would like to comment specifically on three studies.

Only one study (double-blind clinical trial) listed in Table 16 evaluated the effect of estrogen with progestin on CHD risk (47). Nachtigall et al. randomly assigned 84 pairs of postmenopausal women who were residents of a long-term chronic care hospital to one of two treatment groups: the treatment participant receiving either estrogen alone or estrogen with medroxyprogesterone for 7 days a month with the control participant receiving placebo. After 10 years of follow-up, the relative risk for fatal and nonfatal MI for hormone users was 0.3 (95% CL 0.1-2.8). With only 1 MI in the hormone users and 3 MIs in the control patients, and these confidence limits, it is difficult to draw any conclusions from this study.

Table 16. Prospective Studies with Internal Controls Evaluating the Risk of CHD with Postmenopausal Estrogen Use

Author (ref) Estrogen Use‡	Study Size	Follow-up (years)	Study Endpoint	Adj. Risk (CL) by Age/RF*
Lafferty (44) current	124	8.6, mean	All MI	Age: 0.17(0.03-1.06)† RF: not available
Petitti (45) ever	6,093	10-13, range	CVD Death	Age: 0.9 (0.2-3.3) RF: 0.6 (0.3-1.1)
Avila (46) current	24,900	5, mean	All MI	Age: 0.7(0.4-1.3) RF: 0.7 (0.4-1.4)
Nachtigall (47) current	168	10, mean	All MI	Age:0.33 (0.04-2.82)† RF: not available
Hammond (48) current	619	>5, mean	CHD, CHF Stroke	Age:0.33 (0.19-0.56)† RF: not available
Henderson (49) ever	8,807	4.6, mean	Fatal MI	Age: 0.59(0.42-0.82) RF: 0.59(0.42-0.82)
Stampfer (50) current	32,317	3.3, mean	All MI	Age: 0.30 (0.20-0.60) RF: 0.30 (0.14-0.64)
Stampfer (51) current	48,470	7.0, mean	All MI	Age:0.51 (0.40-.80) RF: 0.56 (0.40-0.80)
Bush (52) current	2,270	8.5, mean	CVD death	Age: 0.34 (0.16-0.88) RF: 0.37(0.16-0.88)
Wilson (53) ever	1,234	8.0, mean	Total CVD	RF: 1.75 ($p<.01$)

‡ Estrogen use is classified as "ever" or "current."
†relative risk calculated in reference 30 from data given in the original text.
*CL=confidence limits, relative risk is age adjusted or multiple risk factor (RF) adjusted.

Two additional studies that merit review are widely cited and somewhat controversial. They were published in the same issue of the New England Journal of Medicine in 1985 and reported contradictory findings (50, 53). In contrast to all other cohort studies, Wilson et al. (53) from the Framingham Heart Study reported an increase in risk for cardiovascular disease associated with estrogen use. During an 8 year period, between biennial examinations 8 and 12, a participant was classified as an estrogen user if estrogen was included on the medication form. Follow-up, which continued for 8 years, began at the end of that 8 year interval (after biennial examination 12) for 1,234 women who were postmenopausal and 50 years of age or older. Of those, 302 (24%) were on estrogens. After adjustment for age, hypertension, obesity, total cholesterol, HDL, smoking and alcohol consumption, the relative risk for all cardiovascular disease among ever users of estrogen was 1.76 compared with never users. However, when the risk is calculated for MI only, it is no longer statistically significant (1.87).

In a reanalysis of this data, Eaker and Castelli reported that these results were sensitive to the choice of baseline examination (54). The second analysis was limited to CHD without angina, and considered two time periods (examination 11 and 12) instead of one as the baseline for assessing estrogen use for the subsequent 10 year follow-up. There was a nonsignificant protective effect among women ages 50 to 59 with a relative risk of 0.4 (95% CL 0.1-2.3) and a nonsignificant adverse effect in women ages 60-69 with a relative risk of 1.8 ((%% CL 0.5-5.9).

Stampfer et al. reported results from the Nurses' Health Study (50). Of the 121,964 women who completed the questionnaire in 1976, 32,317 were postmenopausal by 1978. They were followed for an average of 3.3 years for a total follow-up for 105,786 person-years. Overall, the age-adjusted relative risk for total coronary disease among women who had ever used postmenopausal hormones, as compared with women who never had, was 0.5 (95% CL 0.3-0.8), The protective effect was largely confined to current users in whom the relative risk for total coronary disease was 0.30 (95% CL 0.14-0.64). There was little change with adjustment for other risk factors.

These data were updated in 1991 when Stampfer et al. reported on the ten-year follow-up from the Nurses' Health Study (54). The relative risk for mortality from cardiovascular disease for current and former users of estrogen as compared with those who never used it was 0.72 (95% CL 0.55-0.95). With this longer follow-up, the protective effect persisted for current users in whom the relative risk for total coronary disease was 0.56 (95% CL 0.40-0.80).

Potential Mechanisms of the Estrogen Effect on CHD Risk

In summary, there is convincing evidence from both angiographic studies (Table 15) and prospective studies (particularly the Nurses' Health Study (53,54) and The Lipid Research Clinics Follow-up Study (52)) which suggests reduction in CHD risk with estrogen use in postmenopausal women. The precise mechanisms of this effect are not entirely clear. Estrogens have numerous actions on several biological systems

that could influence the risk of CHD. The most promising explanation of a large part of the beneficial effect of estrogen on CHD risk is through changes in the lipid profile.

Effects on the Lipid Profile: Nabulsi et al. have recently published a study which illustrates the effects of hormonal replacement therapy (estrogen alone or estrogen with progestin) on the lipid profile in postmenopausal women (55). Using data from the Atherosclerosis Risk in Communities study in this cross-sectional analysis, they included 4958 postmenopausal women, both black and white, who were free of cardiovascular disease at the baseline visit. They were assigned to one of four groups: current users of estrogen alone (17%), current users of estrogen with progestin (4%), nonusers who had formerly used hormones (16%)and nonusers who had never used them (63%). The adjusted mean values for physiologic variables, according to use of replacement hormones, are listed in Table 17.

Table 17. Adjusted Mean Values for Physiologic Variables, According to Use of Replacement Hormones

Variable	Current Users*		Nonusers*		P Value	
	Estrogen	Estrogen–Progestin	Former Use	No Use	Estrogen vs. Estrogen–Progestin	Users vs. Nonusers
Total triglycerides (mg/dl)†	141	131	123	120	0.102	<0.001
Cholesterol (mg/dl)‡						
LDL	125	127	141	141	0.595	<0.001
HDL	67	66	58	58	0.295	<0.001
HDL_3	46	45	42	41	0.264	<0.001
HDL_2	21	21	17	16	0.640	<0.001
Apolipoproteins (mg/dl)						
A-I	159	156	141	140	0.180	<0.001
B	91	92	95	95	0.608	0.015
Lipoprotein(a) (μg/ml)	101	101	114	116	0.975	0.006
Fibrinogen (g/liter)	2.98	2.98	3.10	3.15	0.976	<0.001
Factor VII (%)	136	127	126	125	<0.001	<0.001
Factor VIII (%)	134	132	133	136	0.624	0.453
Von Willebrand factor (%)	119	118	119	121	0.693	0.464
Antithrombin III (%)	110	113	114	115	0.170	0.002
Protein C (μg/ml)	3.47	3.30	3.29	3.27	0.001	<0.001

*Values were adjusted for age, race, level of education, body-mass index, sports index, smoking, drinking, diabetes, antihypertensive-medication use, and study region.

From: Nabulsi et al. N Engl J Med 328(15):1069-1074, 1993.

As described previously (56), users of estrogens alone had higher levels of HDL and HDL_2 cholesterol and lower levels of LDL cholesterol than nonusers. It is believed that estrogen suppresses hepatic lipase activity thus increasing levels of HDL cholesterol (57) while it increases the rate of LDL clearance from the plasma thus lowering LDL cholesterol (56).

Lobo has suggested that the addition of a progestin the hormone regimen may oppose many of the beneficial effects of estrogen by lowering the level of HDL_2 (58,59). This is not born out in this study which showed that users of estrogen with progestin and users of estrogen alone had similar levels of HDL, HDL_2, HDL_3, cholesterol, LDL cholesterol, apolipoproteins A-I and B and lipoprotein (a). This similarity may be due to the fact that the majority of the users of estrogen and progestin were taking medroxyprogesterone acetate, a progestin with low levels of androgenic activity, which when compared with progestins with higher androgenic activity may have slight effects if any on lipoproteins levels (60). Finally, Barrett-Conner et al. also reported no difference in levels of HDL and LDL cholesterol in users of estrogen alone and those users of estrogen with medroxyprogesterone acetate (61).

The authors estimated the potential effects of these physiologic findings, if causal, on the risk of CHD. In a clinical trial in men, a reduction of 1 mg/dl in the LDL cholesterol level decreased the risk of CHD by 1% (62). In observational studies of men, an increase in 1 mg/dl in the HDL cholesterol level decreased the risk by 2% (63). In observational studies that included women, a decrease in the fibrinogen level of 0.01g/L decreased the risk by 0.5% (64). If these associations are independent, additive and causal, then the observation in hormone users of a 16 mg/dl reduction in LDL, a 9 mg/dl elevation in HDL and a 0.16 g/L reduction in fibrinogen should represent a 42% (16 X 1 + 9 X 2 + 16 X 0.5) reduction in CHD risk in users compared to nonusers.

Other mechanisms: Other mechanisms for an estrogen effect have been reviewed elsewhere and may include: changes in prostacyclin levels: direct action on the vessel walls through estrogen receptors or estrogen mediated modulation of vasomotion in atherosclerotic coronary arteries (65).

Risk/Benefit Ratio of Estrogen Supplementation

The data suggest that postmenopausal estrogen therapy reduces the risk of CHD. Furthermore, both estrogen alone and estrogen with progestin favorably effect the lipid profile. These benefits however, must be interpreted within the context of the risks and benefits of hormonal replacement therapy (HRT) to the women as a whole. While there is an extensive literature describing the multi-system risks and benefits of HRT, I have written this section quoting directly from the recommendations in a comprehensive review published in Annals of Internal Medicine in 1992 entitled "Hormone Therapy to Prevent Disease and Prolong Life in Postmenopausal Women (66)" which is accompanied by the American College of

Physicians "Guidelines for Counseling Postmenopausal Women about Preventive Hormone Therapy. (67) In this review, the authors used standard meta-analytic statistics to pool estimates from studies to determine summary relative risks for endometrial cancer, breast cancer, coronary heart disease, osteoporosis and stroke in women receiving estrogen therapy and estrogen plus progestin therapy.

Endometrial Cancer. "The evidence that unopposed estrogen therapy increases the risk for endometrial cancer is extensive, strong and consistent (66)." The addition of a progestin to the estrogen regimen prevents the increase in endometrial cancer risk associated with estrogen therapy.

Breast Cancer: "The data concerning the effect of estrogen therapy on risk for breast cancer is not consistent. Although there appears no increased risk for breast cancer among short-term users of estrogen, the risk for breast cancer may increase slightly among long-term users (66)."

Coronary Heart Disease: "There is extensive and consistent observational data that estrogen use reduces the risk for CHD. Compared with women who do not take hormones, risk for CHD is probably reduced among women taking estrogen plus progestin, but the data are inadequate to determine the magnitude of the benefit (66)."

Osteoporotic Hip Fracture: "Limited but consistent observational evidence shows that estrogen therapy reduces the risk for hip fracture by about 25%. Estrogen plus progestin therapy is probably at least as effective as unopposed estrogen in preventing hip fracture (66)."

Stroke: "There is no convincing evidence that estrogen therapy increases or decreases the risk of stroke. There is no information on the effect of estrogen plus progestin on stroke risk in women (66)."

In summary then, there is evidence that estrogen therapy decreases the risk for coronary heart disease and for hip fracture, but long-term estrogen therapy increases the risk of endometrial cancer and may be associated with a small increase in the risk of breast cancer. The increase in endometrial cancer risk can be avoided by adding a progestin to the estrogen regimen for women who have a uterus, but the effects of combination hormones on the risk for other diseases has not been adequately studied. Table 18 describes the hormone regimens and Table 19 describes the management strategy for hormone therapy in postmenopausal women recommended by the American College of Physicians (67).

Table 18. Hormone Regimens

Unopposed Estrogen

- The dose of estrogen should be 0.625 mg of oral conjugated estrogen or the equivalent once per day.
- Estrogen should be taken every day without interruption.
- The oral route is preferred.

Estrogen and Progestin

- Two regimens are common in clinical use:

  1. Estrogen plus cyclic progestin (such as medroxyprogesterone acetate (MPA)), 5 to 10 mg orally per day or the equivalent for 10 to 14 days per month.

  2. Estrogen plus continuous progestin (such as MPA), 2.5 mg orally per day or the equivalent.

Duration of Treatment

- Guidelines were developed using the example of a 50 year old women but treatment in older women may also be beneficial.
- Maximum benefits of therapy for reducing CHD and fracture risk are more likely to be achieved with long-term therapy (10-20 years).
- Because the risk for endometrial and breast cancers probably increases with duration of hormone use, duration of therapy should be minimized in women treated only for menopausal symptoms.

Table 19. Management Strategy for Hormone Therapy in Postmenopausal Women

- Assessment of hysterectomy status and risk for CHD, breast cancer and osteoporotic fractures.
- Estimation of the benefits and risk of hormone therapy based on risk group.
- Patient information and education.
- Management decision based on estimated effect of hormone therapy on life expectancy, lifetime probability of developing disease, side effects, uterine bleeding and the need for endometrial monitoring.
- Surveillance for Endometrial Cancer.

  1. In women taking unopposed estrogen: pelvic examination with endometrial examination to rule out hyperplasia or cancer at the onset of treatment, for yearly screening and for any episode of vaginal bleeding unless normal evaluation in previous 6 months.

  2. In women taking estrogen plus progestin: pelvic examination without endometrial evaluation at the onset of treatment, no routine screening while on treatment, for bleeding episode that occur other than at time of expected withdrawal bleeding.
- Surveillance for Breast Cancer. Annual clinical breast examination and mammogram for all postmenopausal women regardless of HRT.

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