Appendix I: Evidence on HRT and Coronary Heart Disease

I

Coronary heart disease (CHD) is the leading cause of death among U.S. women, surpassing the rates from cancer and other diseases (13). Any change in the risk of CHD due to hormone replacement therapy (HRT) would profoundly alter the risk-benefit equation of HRT.

Prior to menopause, women have a lower incidence of CHD than men. The Framingham study showed that men had three times the incidence of heart disease of age-matched premenopausal women (50). Women within the first few years after natural menopause have no substantial increased risk of heart disease over premenopausal women (21). However, by age 70, the incidence of CHD is approximately the same in women and men. Moreover, after surgical or premature menopause women develop a substantially increased risk of CHD at an earlier age than women who undergo natural menopause at a later age (89).

HOW ESTROGEN MAY AFFECT CHD

One mechanism for a possible beneficial effect of estrogen against CHD is the ability of estrogen to favorably alter lipoprotein levels. Estrogen use has been shown to increase the level of high density lipoprotein cholesterol (HDL) (8,16,23,53,57, 75,101). Studies have demonstrated that serum concentrations of HDL are inversely related to the development of CHD (57,75). Estrogens also lower the serum concentration of low density lipoprotein cholesterol (LDL), and LDL levels are directly related to the development of coronary heart disease (8,15,16,23,46,53,57,86,).

The Lipid Research Clinics Follow-up study showed that women using conjugated equine estrogens at the usual doses indicated for postmenopausal women had HDL levels 16.8 percent higher than women not taking estrogens (15). Estrogen users also had LDL levels approximately 7 percent lower than those of nonusers. Coronary heart disease deaths were reduced by 65 percent in estrogen users compared with nonusers. The investigators concluded that this benefit was substantially mediated by the increase in HDL levels.

Recent research has demonstrated that elevations of HDL and decreases in LDL may also occur with percutaneous and subdermal estrogen administration (46,105). However, there is evidence that transdermal estrogens do not produce the same degree of favorable alterations of lipoprotein cholesterol levels as oral estrogens (10, 20,1 15). Oral estrogen has a much greater lipid effect (increasing HDL, decreasing LDL) than a comparable transdermal dosage, perhaps because of higher concentrations of estrogen in the portal circulation of the liver with oral therapy.

The cardioprotective effect of hormone replacement therapy may also be mediated through lowering lipoprotein(a), an independent risk factor for heart disease in postmenopausal women (69,95,100).

There is evidence that estrogen protects the heart by reversing other changes in metabolism that occur at menopause (106). Estrogen has been found to reverse the unfavorable effects of menopause on glucose and insulin metabolism (69,74). Central obesity is linked to heart disease risk, and estrogen may reverse the changes in body fat distribution that results from loss of estrogen production at menopause (106).

Estrogen may also exert its heart protective effects by favorably altering the balance between coagulation and fibrinolysis (18,82,97), by inhibiting platelet function (5), or by relaxing arterial walls (58,124).[1] Estrogen increases production of prostacyclin, a prostoglandin in the arterial wall (82) that reduces platelet aggregation (70) and causes dilatation of the blood vessels (124). In coronary artery occlusion, the release of thromboxane may induce the aggregation of platelets and reduce blood flow. Prostacyclin counteracts the effect of thromboxane by reducing platelet aggregation and increasing blood flow, and in this way may reduce the risk of coronary artery occlusion.

Estrogen may also protect the heart by favorably altering cardiovascular hemodynamics. Receptors for estrogen have been found on arterial walls (52,68), and estrogen may directly relax the arteries throughout the body (22,25,58). By reducing the resistance to blood flow through the arteries, the work load on the heart is reduced (22). By reducing the workload of the heart, its oxygen needs are reduced. Thus, there is less likelihood that the oxygen requirements of the heart will exceed the oxygen that is available from blood flowing through partially occluded coronary arteries (87).

Rosano demonstrated in a clinical trial the immediate effect that estrogens have on heart disease (87). The investigators studied the acute effect of sublingual estradiol on exercise tolerance and angina in 11 women with coronary artery disease. The women did two exercise treadmill tests (EKG) on two separate days. Forty minutes before each test, they took sublingual estradiol or placebo, in random order. Six patients developed exertional angina and EKG changes after administration of sublingual estradiol, whereas all 11 developed angina and EKG changes on placebo. The authors posited that this immediate beneficial effect of estrogens maybe due to a direct coronary artery relaxant effect of estrogen, dilation of peripheral arteries and arterioles, or to a combination of these mechanisms.

EVIDENCE ON ERT AND CHD

All but four of the more than 30 studies that have evaluated the effect of estrogen replacement therapy (ERT) on coronary heart disease (CHD) **have** shown a reduced risk in estrogen users. The following is a discussion of the evidence on the relationship between ERT and cardiovascular disease risk. Coronary evidence falls into five categories based on methods and data sources:

- hospital-based case-control studies,
- population-based case-control studies,
- prospective cohort studies,
- cross-sectional studies, and
- randomized clinical trials.

Each is discussed in turn.

Hospital-Based Case-Control Studies

The earliest studies examining the risk of coronary heart disease in noncontraceptive estrogen users used as "cases" individuals hospitalized for myocardial infarction (heart attack) over a specified time period. "Controls" were a comparison group of patients with other diagnoses from the

[1] For recent reviews of the potentially important nonlipoprotein-mediated mechanisms of reduction in coronary heart disease risk, see K.F. Ganger, B.A. Reid, D. Crook, et al., 1993; M. Riedel, W. Raffenbeul, and P. Lichtlen, 1993; J.C. Stevenson, D. Crook, I.F. Godsland, et al., 1994; M.J. Tikkanen, 1993.

same hospitals as the cases. The researchers then determined which women in each group had or had not had ERT in the past through interviews with the women, medical records, and other sources.

Five hospital-based case-control studies have examined ERT among patients hospitalized for myocardial infarction. (See table I-1.) Of these, one showed an increased risk of coronary heart disease among estrogen users (48), two showed virtually no change in risk (88,91), and two showed a decreased risk of CHD that was not statistically significant.[2]

A well recognized problem with case-control studies is that the ascertainment of exposure to the agent in question (e.g., estrogen) often depends on the recall of the study participants. Because cases may differ from controls in the accuracy of recall of exposure, a biased estimate of risk can occur.

A second problem particular to hospital-based case-control studies is that a control group composed of hospitalized patients is not likely to be representative of the general population from which the cases were drawn with regard to exposure to estrogen. In the context of ERT, the results of hospital-based case-control studies are difficult to interpret because many diseases are related in some way to estrogen use. For example, some members of the control group may have been hospitalized because of fracture, and women with fracture are less likely to have used estrogen.

Even selecting controls from patients with diseases unrelated to estrogen use is problematical, because some physicians may be less willing to prescribe ERT to patients who are already burdened with other medications (103). The net effect of this last bias would be to underestimate the impact of estrogen on heart disease risks.

The first case-control study that did not detect a lower risk of CHD in estrogen users was of hospitalized patients aged 40 to 75 enrolled in the Boston Collaborative Drug Surveillance Program. The relative risk of nonfatal myocardial infarction (MI) in estrogen users was 0.47, but the relative risk was not significantly different from one after statistical adjustment for differences in heart disease risk factors between the two groups (88). Also, heart disease risk is thought to be more markedly reduced among those who are currently using estrogen ("current users") compared with those that have used estrogens in the past (14), and only eight of the 336 cases in the study (2 percent) were "current users" of estrogens.

The second study finding no decreased risk was of women aged 30 to 49 years old admitted to hospital coronary care units (91). The adjusted relative risk was near one both in patients who had ever used estrogen ("ever users") and in "current users." The results of this study may not be generalizable to all postmenopausal women because it was conducted among women under 50 years of age. Because of their young age, these women had infrequent use of ERT and were at minimal risk of coronary heart disease. Moreover, a substantial proportion of controls in this study were fracture patients (13,103).

Jick and colleagues reported the highest relative risk of coronary heart disease in estrogen users among all studies (48). They reported a relative risk of first nonfatal MI of 7.5 (95 percent confidence intervals 2.4 to 24) among estrogen users under 46 years of age and a relative risk of 4.2 (95 percent confidence intervals 1.0-18.8) among postmenopausal estrogen users. This study had a small number of cases and a large loss of study participants over time. Sixteen of the 17 cases (94

2 The change in risk of disease in these studies is expressed either as a relative risk or as an odds ratio (42,94). The odds ratio is obtained from the exposure ratio in the cases divided by the exposure ratio in the controls. To determine the odds ratio in a hospital-based case-control study of myocardial infarction and estrogen use, one would calculate the ratio of estrogen users to nonusers among myocardial infarction patients (cases) and divide that by the ratio of estrogen users to nonusers in the comparison patients hospitalized with other diagnoses (controls). Results of a case-control study can also be expressed as a relative risk, which is the rate with which the disease occurs in exposed people divided by the rate of the disease's occurrence in unexposed people. If these two rates of occurrence are very small and if no distortions have occurred in the four groups that make up the case-control study, the odds ratio will be approximately equal to the risk ratio.

TABLE I-1: Postmenopausal Estrogen Use and Coronary Heart Disease Hospital-Based Case-Control Studies (page 1 of 3)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Rosenberg (1976)	Cases were two sets of patients hospitalized for myocardial infarction in the Boston Collaborative Drug Study. First set of cases was from 21 hospitals in the United States, Great Britain, Canada, Germany, New Zealand, Italy, and Israel, admitted since 1969, Second set was from general medical and surgical wards of 24 Boston hospitals in 1972. Study subjects were ages 40 to 75 years; average age 54 years. Controls were patients from same hospital admitted for neoplasm, gallbladder disease, and breast or reproductive organ disease. Data were obtained from interviews and hospital records. Current use was defined as use during the month prior to hospitalization.	Cases (set 1: 163; set 2: 173) (2.4% conjugated estrogen users); controls (set 1: 2,536; set 2: 4,194)	Nonfatal MI	Current users: age-adjusted relative risk 0.71 (0.34-1 .46) risk-factor adjusted* relative risk 0.97 (0.49-1 .95) *adjusted for age, history of MI, angina, diabetes, hypertension, and smoking
Jick (1 978a)	Cases were women ages 39 to 45 years of age discharged within the first 6 months of 1975 with a diagnosis of AMI. Cases were identified from a national hospital discharge database. Controls were drawn from the national hospital discharge database, were about the same age as cases, were hospitalized for acute illnesses (other than MI) or elective surgery, and were discharged about the same time as cases. Both cases and controls had no other illnesses that predisposed to MI or contraindications to estrogen use. Cases and controls had a natural menopause, hysterectomies, or tubal ligation, or their husband had a vasectomy. Current estrogen use was defined as use of noncontraceptive estrogens within 3 months of admission.	17 cases (53% estrogen users); 34 controls (12% estrogen users)	First nonfatal MI	Current estrogen use: 7.5 (90% confidence interval 2.4 to 24) adjusted for type of sterilization Ninety-four percent of cases, but only 47% of the controls, were cigarette smokers.

TABLE I-1: Postmenopausal Estrogen Use and Coronary Heart Disease Hospital-Based Case-Control Studies (page 2 of 3)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Jick (1 978)	Cases were women ages 35 to 45 discharged during the first 6 months of 1975 with a diagnosis of AMI. Cases and controls were identified from a national hospital discharge database. Controls were women about the same age as cases, who were hospitalized for acute illnesses (other than MI) or surgery, and discharged about the same time as cases. Results are reported for cases and controls who had no serious chronic illnesses (other than MI in cases) or contraindications to estrogen use. Current use was defined as use of noncontraceptive estrogens within three months of admission.	19 cases (53% estrogen users), 39 controls (10% estrogen users)	First nonfatal MI	Current estrogen use 9.3 (lower 95% confidence interval 3.1) adjusted for menopausal status
Rosenberg (1980)	Cases were women ages 30 to 49 years of age selected from interviews between July 1976 and April 1979 with a discharge diagnosis of first MI. Hospitals were located in Greater Boston, Long Island, New York, and the coastal area of northern New York City and the Delaware Valley. Controls were selected from the same hospitals as cases but did not have a discharge diagnosis of MI. Information was gathered by nurse interviewers. Current use was defined as use within the month preceding admission,	99 cases post menopausal (18% current users) (24% past users); 463 controls	First MI	Current users: age-adjusted relative risk 1.39 (0.71 -2,74)
Szklo (1 984)	Cases were white female patients 35 to 64 years of age admitted to 5 general hospitals in Maryland with a first MI between 1971-1972. Two controls were matched to each case. Controls were females from the same hospitals as cases, with no history of MI or abnormal Q waves on EKG, and matched by age and date of admission. Data were obtained from interviews and review of medical records,	39 cases (28% ever users), 81 controls	First MI	Ever users age-adjusted OR 0,8 (NS) risk-factor adjusted* OR 0,61 (0.20-1 .88) risk-factor adjusted* OR for surgical menopause only 0.37 (0.04-3,23) *adjusted for history of cardiovascular disease, smoking, educational level, and type of menopause

TABLE I-1: Postmenopausal Estrogen Use and Coronary Heart Disease Hospital-Based Case-Control Studies (page 3 of 3)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[ab]
La Vecchia (1987)	Cases were women less than 55 years of age admitted between January 1983 and December 1984 to the coronary care units of 30 hospitals in Northern Italy. Controls were matched to cases for index hospital and 5-year age group. Controls were admitted for acute conditions except cardiovascular, cancer, endocrine, gynecological, or primary diagnosis potentially related to cigarette smoking or hormone use. Data were gathered by trained interviewers.	168 cases, 100 pre-menopausal (5% current users) (3% past users); 251 controls	First MI	Current users: age-adjusted relative risk 1.85 (0.68-5.01) risk-factor adjusted* relative risk 2.95 (0.80-10.80) Past users: age-adjusted relative risk 1,01 (0.31-3.27) risk-factor adjusted* relative risk 0.77 (0.1 6-3.60) 'adjusted for multiple heart disease risk factors "No relation was evident with duration of use."

[a]Numbers in parentheses are 95 percent confidence intervals.
b Risk estimates are in terms of relative risk, unless otherwise specified,

KEY: AM I = acute myocardial infarction; EKG = electrocardiogram; ERT = estrogen replacement therapy; MI = myocardial infarction; NS = not statistically significant; OR = odds ratio.

SOURCE: Office of Technology Assessment, 1995.

percent) were smokers, which confounds interpretation of results. Also, the subjects were under 50 years of age, so the findings may not be generalizable to the overall population of postmenopausal women (14).

Population-Based Case-Control Studies

Among the seven population-based case-control studies of myocardial infarction and ERT, all but one demonstrated a trend toward decreased relative risk of myocardial infarction in estrogen users, although the results were statistically significant in only one of the studies that showed a trend toward decreased relative risk (92). (See table I-2.)

Population-based case-control studies differ from hospital-based case-control studies in that the cases and controls come from the community or a sample of the general population. Controls selected from the community rather than a hospital are likely to be more representative of the general population from which the cases were drawn than hospital-based case-control studies.

In one of the largest population-based case-control studies of myocardial infarction and estrogen use, Pfeffer and colleagues found among current users of estrogens an adjusted relative risk of 0.7 (0.3-1.4) for fatal and nonfatalMI(81). Estrogen use in this study was ascertained by review of pharmacy records. In a reanalysis of Pfeffer's data, Ross found that estrogen use among cases was underestimated, because one-third of the women who had estrogen usage noted on their medical records did not have records of estrogen prescriptions in the pharmacy records (92). The mean duration of use was less than three months, which would also bias the findings toward an underestimate because such a short duration is unlikely to be sufficient for a plausible biological effect (103).

Unlike the other case control studies in this group which used myocardial infarction as an endpoint, Thompson and colleagues used a combined endpoint of stroke and myocardial infarction (111). In that study, each of 603 women with stroke or myocardial infarction identified in 83 physicians' practices were matched with two controls from the same physician's practice and of the same age. Estrogen use was ascertained from medical records and patient interviews. Thompson showed a "weak" association between estrogen use and stroke and myocardial infarction, with a relative risk of 1.36 in estrogen users (95 percent confidence intervals 1.01 to 1.81). An association between estrogen use and decreased risk of coronary heart disease may have been obscured by combining the myocardial infarction endpoint with the endpoint of stroke.

Cohort Studies

The published results of 15 cohort studies all showed a reduced risk of coronary heart disease in estrogen users, although the results of one cohort study, the Framingham study, are equivocal.

Most cohort studies followed women with and without estrogen exposure, and thus had a control group internal to the study. In three studies, however, mortality in a cohort of estrogen users was compared with national mortality rates. These cohort studies without internal controls showed the lowest apparent relative risk of cardiovascular disease with estrogen use. (See table I-3.) But women who take estrogens are on average of higher socioeconomic status and more educated and therefore are probably healthier than the general population (19,103). Consequently, cohort studies without internal controls may overestimate the effect of estrogen exposure on cardiovascular disease.

The findings of cohort studies with internal controls, including the Framingham study, are summarized in table I-4. One of the largest cohort studies of cardiovascular disease risk among postmenopausal estrogen users is the Lipid Research Clinics Follow-up study, initiated by the National Heart, Lung, and Blood Institute in 1971 (12,15). Almost 2,300 women have been followed in this study. A 1987 report noted a statistically significant reduction in incidence of CHD or stroke death among current estrogen users (average length of use 8.5 years) compared with nonusers. The relative risk of cardiovascular death in estrogen users was 0.34. Adjustment for other potential

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 1 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Talbott (1 977)	Cases were white female residents of Allegheny County, Pennsylvania who had no prior recorded history of heart disease and who were ages 25 to 64 years old (mean age 55.6) when they died suddenly of atherosclerotic heart disease outside of the hospital between September 1973 and April 1975. Cases were identified from county coroner records and death certificates. Cases were matched to controls who were females living on the same block and who were within 10 years of patient's age. Information about cases was gathered from interviews of subjects' family and physicians. Information about controls was gathered from interviews of subjects.	64 cases (unknown number postmenopausal) (5% current users); 64 controls	Sudden death	Current users:[b] age-adjusted relative risk 0.34 (0.09-1 .30)
Pfeffer (1 978)	Cases and controls were women ages 50 to 98 years who were residents of a Southern California retirement community between 1964 and 1974. Cases had their first MI while in residence. Controls were drawn from a file containing all women in residence during the study interval. There were no black members of the population. Data was obtained from review of medical clinic and pharmacy records,	171 cases (30% ever users) (8.7% current users); 171 controls	First MI	Ever users: risk-factor adjusted* relative risk 0.86 (0.54-1 .37) current users: risk-factor adjusted* relative risk 0.68 (0.32-1 .42) *adjusted for age, hypertension, and diabetes
ROSS (1981)	Cases were women less than 80 years old living in a retirement community near Los Angeles who died of coronary heart disease between 1971 and 1975 inclusive. For each case a living and deceased female control were selected, matched for race, age, date of entry into the community, and, for deceased control, date of death. The deceased control was used to remove bias for extra medical attention the cases may have had toward the end of their lives Data was gathered from medical clinic records	133 cases (percent ever users not provided), 133 living controls; 133 deceased controls	Fatal coronary heart disease	Ever users. age-adjusted relative risk living controls: 0.43 (0.24-0.75) dead controls 0.57 (0.33-0.99) risk- factor adjusted* relative risk living controls. unchanged dead controls. unchanged *adjusted for multiple heart disease risk factors

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 2 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Bain (1981)	Cases were postmenopausal female nurses ages 30 to 55 in 1976 who reported hospitalization for MI. Twenty female nurses hospitalized in the same year with no history of MI were matched as controls to each case on the basis of year of birth and menopausal status at hospitalization. Information was gathered by questionnaire.	120 cases (53% ever users) (27% current users), 2,400 controls	First MI	Ever users. age-adjusted relative risk 0.9 (0.6-1.2) risk-factor adjusted* relative risk 0.8 (0.6-1 .3) current users. age-adjusted relative risk 0.7 (0,5- 1,1) risk-factor adjusted* relative risk 0.7 (0.4-1.1) age-adjusted relative risk in women with natural menopause 1,3 (0.5-3.4) age-adjusted relative risk in women with hysterectomy 1.0 (0,5-2,2) age-adjusted relative risk in women with hysterectomy and bilateral oophorectomy 0.4 (0.2-0.8) *adjusted for multiple heart disease risk factors
Adam (1981)	Cases were women ages 50 to 59 who died of MI in England and Wales during November 1978 identified from death certificates. Two controls matched by age to cases were randomly selected from the practice list of the general practitioner responsible for the care of the patient during life. Information was gathered from hospital records, postmortem reports, and questionnaires completed by the subject's general practitioner.	76 cases (12% ever users) (3% current users); 152 controls	Fatal MI	Ever users: unadjusted relative risk[b] 0.65 (0.29-1 .45) current users: unadjusted relative risk[b] 0.97 (0.41 -2.28)
Croft (1989)	A nested case-control was carried out on cohort data collected during the Royal College of General Practitioners' oral contraceptive study. Subjects were recruited by U.K. general practitioners, and were followed between May 1968 and July 1969. The cases were all women who had had their first AMI while under observation in the study. Controls were chosen from randomly selected general practice registers, matched for age to cases. Medical records were examined.	158 cases (9 estrogen users), 474 controls (32 estrogen users)	First MI	Ever users. unadjusted relative risk 0.8 (no c.i. provided) adjusted relative risk* 0.8 (0.3 to 1.8) *adjusted for social class, smoking, use of oral contraceptives, history of pre-eclampsia, hypertension, and hysterectomy

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 3 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Beard (1989)	Cases were female residents of Rochester, Minnesota between 1960 and 1982 whose first manifestations of heart disease were sudden death or MI occurring between the ages of 40 and 59. Two controls matched by age to each case were selected from women seen at the Mayo Clinic. Information was obtained from review of medical records.	86 cases (27% ever users); 150 controls	MI or sudden death	Ever users: risk-factor adjusted* odds ratio 0.55 (0.24-1 .30) *adjusted for age, year, menopausal status, smoking, hypertension, and diabetes
Thompson (1989)	Cases were white women ages 45 to 69 who developed MI or stroke between 1981 to 1986 and whose general practitioners reported to Northwick Park Hospital, England. Controls were white female clinic patients matched for age and general practitioner. Information gathered from review of medical records and interviews.	603 cases (94% past users); 1,206 controls	MI and stroke	Ever users of estrogen alone, age-adjusted relative risk 1.12 (0.79-1 ,57) risk-factor adjusted* relative risk 1,09 (0,65-1 ,82) past users of estrogen alone: age-adjusted relative risk 0,86 (0.43-1 ,74) risk-factor adjusted* relative risk 1,16 (0.43-3.12) ever users of progestin alone. age-adjusted relative risk 1.90 (1,1 1 -3,25) risk-factor adjusted* relative risk 1.02 (0.45-2.32) ever users of combined estrogen -progestin: age-adjusted relative risk 0,86 (0,43-1 .74) risk-factor adjusted* relative risk 1.16 (0.43-3,12) *adjusted for marital status, smoking, history of hypertension venous thrombosis, stroke, MI, diabetes, and family history of MI

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 4 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Rosenberg (1993)	Cases were women, ages 45 to 69 (median age 60 years), who were residents of Massachusetts from 1986 until 1990. Controls were women, matched by metropolitan precinct and 5-year age group, with no prior history of MI, Ninety-eight percent of cases and 97 percent of controls were white. Data were gathered from interviews of physicians and patients,	858 cases (21% used unopposed estrogens, 3% used estrogen and progestins); 858 controls (21 % used unopposed estrogens, 3.5% used estrogens and progestins)	First MI	Ever users. risk-factor adjusted* relative risk 0.9 (0.7-1 .2) recent users: risk-factor adjusted* relative risk 0.8 (0.4-1 .3) past users: risk-factor adjusted* relative risk 0.9 (0.7-1 .3) unopposed estrogen users: risk-factor adjusted relative risk 1.3 (0.4-4.9) estrogen and progestin users: risk-factor adjusted relative risk 1.2 (0.6-2.4) progestin only users: risk-factor adjusted relative risk 1.3 (0.4-4.9)

*adjusted for multiple heart disease risk factors The estimated relative risk decreased with increased duration of unopposed estrogen use to 06 (O 4-1 1) (test for trend p= 0.08), The association of decreased risk with duration of use was stronger with recent use (test for trend p< O 05) than for past use (test for trend P=O. 86)

TABLE I-2: Postmenopausal Estrogen Use and Coronary Heart Disease—Community/Population-Based Case Control Studies (Page 5 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Mann (1994)	Cases and controls were women ages 45 to 64 years who were included in the general practice files of the VAMP database of the British National Health Service beginning in June 1987 to May 1993. Cases comprised all incidents of both fatal and non-fatal cases of MI where there were records of HRT prescriptions within 6 months of the date of the MI. Controls were females in the same age group with no prior history of MI. Four controls were matched to each case. Data was gathered from computerized medical records.	1,521 cases (7.7% ever users); 6,084 controls (9.2% ever users)	MI	Ever users. age-adjusted odds ratio 0.82 (0.67-1 .01) risk-factor adjusted* odds ratio 0.83 (0.66-1 .03) age-adjusted odds ratio for estrogen-progestin 0.68 (0.47-0.97) age-adjusted odds ratio for unopposed estrogen 0.93 (0.47-1 .86) *adjusted for history of smoking, diabetes, hypertension, hysterectomy, and hyperlipidemia

[a]95 percent confidence intervals are reported after risk estimates.
b Figure obtained from reanalysis of data in original paper, included in meta-analysis by M.J. Stampfer, and G. A. Colditz,"Estrogen Replacement Therapy and Coronary Heart Disease A Quantitative Assessment of the Epidemiological Evidence," Preventive Medicine 20:47-63, 1991
KEY' AM I = acute myocardial infarction; c.i. = confidence interval; HRT = hormonal replacement therapy; MI = myocardial Infarction.

SOURCE: Office of Technology Assessment, 1995

TABLE I–3: Postmenopausal Estrogen Use and Coronary Heart Disease Cohort Studies Without Internal Controls (Page 1 of 2)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Byrd (1977)	Cohort included women mean age 44 years, who received hysterectomies from one Nashville, TN, gynecologist from the late 1940s to 1977. All cohort members received postmenopausal ERT (typically 1.5 mg CEE per day), and were followed for at least 5 years (average duration of followup was 14,3 years). The women were followed up by personal contacts, office visits, and questionnaires. Expected rates of fatal heart disease were obtained from the report of the Division of Vital Statistics, Tennessee Department of Public Health.	1,016 women (all estrogen users); 13 cases of fatal CHD	Fatal CHD	Ever users: unadjusted relative risk[c] 0,37 (p<o.oo5)
MacMahon (1978)	Followup of study by Hoover, et al. (1976) originally assembled for the evaluation of cancer risk, to include mortality from all causes. The medical records of all white women seen in one private practice in Louisville, KY, from 1939 to 1972, were reviewed, Average age of women in the cohort at baseline was 49 years. Mean duration of followup was 12 years, Rates of fatal CHD in the cohort were compared to the age-specific death rates in the general population.	1,891 women (all estrogen users); 33 cases of fatal CHD	Fatal CHD	Current users: age-adjusted relative risk 0.30 (0.21 -0,42)
Hunt (1990)	Cohort included women receiving HRT recruited between 1977 and 1982 from 21 menopause clinics around Britain. Subjects were followed through 1988 and median duration of followup was 8.0 years. Sixty-three percent of cohort was 45 to 54 years of age upon entry into cohort. Mortality rates in the cohort were compared to the expected rates in the female population of England and Wales. Information about deaths was obtained through death registries, and diagnosis was confirmed by review of medical records.	4,544 women (2,726 postmenopausal) (all HRT users) (43% estrogen-progestin users); 36 cases of fatal IHD	Fatal IHD	Ever users: age-adjusted relative risk 0.41 (0.20-0.61)

TABLE I–3: Postmenopausal Estrogen Use and Coronary Heart Disease Cohort Studies Without Internal Controls (Page 2 of 2)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a,b]
Falkeborn (1992)	Cohort comprised 23,174 women aged 35 and older (median age 54 at study entry) from the Uppsala Health Care Region of Sweden, who had been treated with estrogen/progestin. Subjects were identified from pharmacy records as having been prescribed non-contraceptive estrogens from 1977 to 1983, Subjects were followed for an average of 5.8 years. Cases of MI within cohort were identified through a regional hospital inpatient registry. A subcohort of 735 women were surveyed in 1980 and 1984 by mailed questionnaire to further characterize the cohort with respect to lifetime hormone exposure and the presence of other risk factors. The incidence of first MI in the cohort was compared with that in the general population.	23,174 women (all HRT users, 21% current users), 227 cases of first MI	First MI	Ever users. age-adjusted relative risk estradiol/ conjugated estrogens 0.74 (0.61 -0.88) other estrogens only 0.90 (0.74-1 .08) estrogen/progestin combination 0.50 (0.28-0.80) overall age-adjusted relative risk 0,81 (0.71 -0.92) "The relative risk tended to decrease with increased duration of followup, " from a relative risk of 0,96 (0,44-1 .83) during the first year to a relative risk of 0.76 (0.55-1 .02) during the last (6 years later).

KEY: CHD = coronary heart disease, IHD = ischemic heart disease, MI = myocardial infarction

[a] Estimates are of relative risk unless otherwise specified
b 95% confidence intervals are provided in parentheses.

C Figures obtained from reanalysis of data in text. Reanalysis of data was presented in M J Stampfer, and G A Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease A Quantitative Assessment of the Epidemiological Evidence," Preventive Medicine 2047-63, 1991

SOURCE Off Ice of Technology Assessment, 1995

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls
(Page 1 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Hammond (1979)	Study subjects were identified through Duke University Medical Center's (Durham, NC) inpatient medical record retrieval system and outpatient office records. All cohort subjects received diagnoses related to hypoestrogenism between 1940 and 1964, who returned for followup for five or more years after diagnosis, and had most recently been seen at Duke after January 1, 1974. Patients referred to Duke were excluded from the sample. Mean age of subjects was 46.3 years at baseline.	610 women (49% estrogen users); 58 cases	CHD	Ever users: unadjusted odds ratio[b] 0.33 (0.1 9-0.56)
Lafferty (1985)	The cohort was recruited from 173 private practice patients of the author for a prospective study between 1966-1981, Candidates had been followed for not less than 3 years and had periodic physical exams and laboratory studies. The mean duration of followup was 1.6 years. The mean age of subjects was 53,7 years (range 45 to 60 years) at baseline.	124 women (49% estrogen users); 7 cases	MI	Ever users: unadjusted odds ratio[b] 0.17 (0.03-1 .06)
Wilson (1985)	Patients considered for inclusion were members of the Framingham (Massachusetts) Heart Study cohort who participated in the 12th biennial exam (index) between 1970 and 1972 and who were postmenopausal and over 50 years of age at that exam. The cohort was followed for 8 years.	1,234 women (14Y0 past users of estrogen, 1O% current users); 194 cases of CVD, 48 cases of CVD death, and 51 cases of MI	All CVD	Ever users: relative risk for all CVD 1,76 (p< O.01) adjusted for age and HDL level; relative risk for CVD death 1.94(p<0.05) adjusted for age and HDL level; relative risk for MI 1.87(p<0.05) adjusted for age and HDL level

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls (Page 2 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Eaker (1987)	The author reanalyzed the data from the cohort of the Framingham (Massachusetts) Heart Study, described above (Wilson, 1985).The subjects included women in the Framingham Study cohort who were 50-59 years of age or 60-69 years of age upon exam 1 in 1950, exam 6 in 1960, or exam 11 in 1970. The cohort was divided on the basis of the subject's age at exam. Duration of followup was 10 years.	1,297 women (14% past users, 10% current users) 695 women ages 50 to 59; 35 cases 602 women ages 60 to 69; 51 cases	CHD except angina	50-59 years of age: relative risk 0.26 (0.06-1 .22) adjusted for age and HDL level relative risk 0.4 (p< O.05)adjusted for multiple risk-factors including HDL level 50-69 years of age: relative risk 1.68 (0.71 -4.00) adjusted for age and HDL level relative risk 2.2 (p< O.05) adjusted for multiple risk-factors, including HDL level
Bush (1987a)	The cohort consisted of 2,270 white women, ages 40 to 69 at baseline, who were followed for an average of 8.5 years. All women included in the study were participants in the Lipid Research Clinic (LRC) Prevalence Study of CVD, that was conducted in 10 North American clinics between 1972 and 1976. Study was restricted to whites due to the small number of minorities in the LRC study.	2,270 women (26% ever estrogen users); 50 cases	Fatal CVD	Ever users: age-adjusted relative risk 0.34 (0.12-0.81) risk-factor adjusted relative risk 0,37 (0.16-0.88)
Pettiti (1987)	The cohort included women aged 18 to 54 during December 1968 through February 1972 who participated in the Walnut Creek Contraceptive Drug Study who never used any type of estrogens or used estrogens for reasons other than contraception. Duration of followup was 10 to 13 years.	6,093 women (44% ever users); 40 cases of AM I	Fatal CVD or fatal MI	Ever users: age-adjusted relative risk 0.9 (0.2-3.3) for fatal CVD risk-factor adjusted relative risk 0.61 (0.3-1 .1) for fatal CVD age-adjusted relative risk 0.3 (0.1 -1 .3) for fatal MI
Criqui (1988)	Study subjects were followed between 1972 to 1986 when they participated in a community survey of homogeneous, white, upper-middle class residents of a planned, small Southern California retirement community (Rancho Bernardo). Women were 50 to 79 years of age at baseline. Average duration of followup was 12 years.	1,868 women (39% ever users), 87 cases	Fatal CHD	Ever users: age-adjusted relative risk 0.75 (0.45-1 24) risk-factor adjusted relative risk 0.99 (0.59-1 .67)

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls (Page 3 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints
Avila (1 990)	The study cohort comprised all female members of the Group Health Cooperative of Puget Sound who were ages 50 to 64 years upon entry to cohort between 1978 to 1984. Cases were selected from women who were hospitalized and later discharged with a first occurrence of MI. Average duration of followup was 5 years.	24,900 women (14% current users), 120 cases	MI	Current users, age-adjusted relative risk 0.07 (0.4-1 .3) risk-factor adjusted relative risk 0,7 (0.4-1 .4)
Henderson (1991)	The cohort comprised female residents of Leisure World Retirement Community, Laguna Hills, California, who responded to a health questionnaire. The cohort was followed for 7.5 years using death certificate records of the local health department. Female residents were almost uniformly white, moderately affluent, and well educated with a median age of 73 years.	8,853 women (41% past users, 17.3% current users), 203 cases	Fatal AM I or fatal IHD	Current users: age-adjusted relative risk 0.601 (p< O.001) for fatal AMI age-adjusted relative risk of 0.79 (NS) for IHD Duration (for a fatal AM I): <3 years: 0.64 (p<0.05) 4-14 years: 0.60 (p<0.05) >15 years: 0.52 (p<O.O1) There was a significant trend toward decreased risk with increased duration of use for both IHD and AMI. Recency (years since last use) for fatal AMI. >15 years, 0,73 (NS) 2-14 years. 0.47 (p<O.01) O-1 year. 0.51 (p< O.05) There was a significant trend toward decreased risk of both AMI and IHD with increased recency of use,

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls (Page 4 of 5)

Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Stampfer (1 991)	The cohort includes participants in the Nurses Health Study. The study cohort began in 1976 when 121,700 female married registered nurses in 11 large states completed questionnaires about their medical histories and postmenopausal hormone use. Followup questionnaires were mailed at two year intervals thereafter. The study population includes participants ages 30 to 55 at baseline who had no preexisting cancers or CVD history that could be associated with hormone use. Mean duration of followup was 7 years.	48,470 female registered nurses (21.8% current estrogen users; 25.2% past users), 405 cases	Nonfatal MI and fatal CHD	Current users. age-adjusted relative risk 0.51 (0.37-0.70) risk-factor adjusted relative risk 0.56 (0.40-0.80) Past users: age adjusted relative risk 0,91 (0.73-1 .14) risk-factor adjusted relative risk 0.83 (0.65-1 .05) Ever users: risk-factor adjusted relative risk 0.72 (0.55-0.95) There were no significant trends with regard to duration of use or recency of use (time since last use).
wolf (1 991)	This cohort consists of a natural sample of women from the National Health and Nutrition Examination (NHANES) followup study who were at least 55 years of age and menopausal at baseline survey between 1971 and 1975. The study was restricted to white female participants. Followup occurred from 1982 to 1984, and again in 1986 and 1987. Followup intervals ranged from 11,4 -16.3 years (mean 14.1 years) for survivors and 2 months to 16,3 years (mean 8.6 years) for the descendants. Women were categorized as either ever users or never users of HRT on the basis of their response to the 1982-1984 followup questionnaire. HRT type was almost exclusively conjugated equine estrogens (Premarin). Mean age at baseline exam was 65.7 years.	1,944 women (21 % ever users); 347 cases	Fatal CVD	Ever users: risk-factor adjusted relative risk 0.66 (0.48-0.90)

TABLE I–4: Postmenopausal Estrogen Use and Coronary Heart Disease—Cohort Studies with Internal Controls °
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Author	Description of study	Number of study subjects	Measured endpoint	Relationship of hormonal replacement therapy to heart disease endpoints[a]
Manolio (1 993)	Cardiovascular Health Study participants were recruited from a random sample of Health Care Financing Administration Medicare eligibility lists in 4 U.S. communities: Forsyth Co., NC; Sacramento, CA, Washington Co., MD; and Allegheny Co., PA. The participants were females from 65 to 100 years of age with a mean age of 72.4 years.	Cases, 461 12% current users 39% ever users cohort size, 2,955 39% post menopausal	Definite CHD	Ever versus never users[a] age adjusted relative risk P = 0.4

KEY: AMI = acute myocardial infarction, CHD = coronary heart disease, CVD = cardiovascular disease, ERT = estrogen replacement therapy, HDL = high-density lipoprotein cholesterol, IHD = ischemic heart disease, MI = myocardial infarction

[a] Ninety-five percent confidence intervals are provided in parentheses, unless otherwise specified
b Estimates of crude odds ratio derived from reanalysis of data in the text or from meta-analysis by Stampfer and Colditz in M J, Stampfer and G.A Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease' A Quantitative Assessment of the Epidemiological Evidence, " *Preventive Medicine 20:47-63, 1991*

SOURCE: Office of Technology Assessment, 1995.

confounding factors (age, blood pressure, and smoking) did not substantially change the finding of a reduction in risk of cardiovascular death among current estrogen users.

On the basis of multivariate analysis of the results of this study, the investigators concluded that the beneficial effect of estrogens on cardiovascular disease risk was substantially mediated through HDL levels. When the multivariate analysis included HDL, the benefit of cardiovascular disease mortality among estrogen users compared with nonusers was reduced and no longer statistically significant, a finding consistent with the hypothesis that the protective effect of estrogens is substantially mediated through increased HDL levels. Preliminary data from the 15-year follow up of patients in the study demonstrated a 65-percent reduction in cardiovascular disease and an approximately 50-percent reduction in all-cause mortality (28). Even after adjusting for age, HDL, and LDL, estrogen users continued to have a risk of 60 percent that of nonusers.

A nationwide study of nurses also found postmenopausal estrogens to have a protective effect on major coronary disease (102). The Nurses' Health Study was established in 1976 with 121,700 female nurses ages 30 to 55 years old. By 1986,48,470 of these women were postmenopausal. Participants who reported ever using estrogens in the past had a statistically significant relative risk for nonfatal and fatal coronary heart disease of 0.51 after an average of 7 years' follow-up. Adjustments for a variety of cardiac risk factors including high cholesterol, family history of heart disease, hypertension, diabetes, obesity, and smoking did not substantially change these relative risk estimates.

In an ongoing prospective study in a retirement community near Los Angeles (Leisure World), Henderson and colleagues found that women who used ERT had a relative risk of fatal acute MI of 0.60 compared with nonusers (39). This study was begun in 1981 to investigate the risks and benefits of menopausal ERT. A questionnaire was mailed to all 20,000 residents of this retirement community in 1981, and the two-thirds who completed and returned the questionnaire became members of the study cohort. About 9,000 of these were women (77). After 7.5 years of followup, current users had an age-adjusted relative risk of fatal ischemic heart disease of 0.46 compared with nonusers. Adjustment for several CHD risk factors did not substantially change the results. Henderson also found that the overall mortality rate in those who had ever used estrogen was 20 percent lower than lifetime nonusers (95 percent confidence intervals 0.7 to 0.87) and the overall mortality in current users of estrogen with more than 15 years of estrogen use was 36 percent below that in nonusers (95 percent confidence intervals 0.51 to 0.82) (39).

A cohort of 6,093 women ages 18 to 54 from the Kaiser Permanence Medical Program was followed for an average of 10 to 13 years (80). The mortality rate from heart disease and stroke was slightly lower among estrogen users, with a relative risk of 0.9 (95 percent confidence intervals 0.2 to 3.3). After adjustment for a variety of cardiovascular risk factors, including age, hypertension, obesity, and smoking, the apparent benefit was more marked, with a relative risk of 0.6 but the reduction in risk remained statistically insignificant (95 percent confidence intervals 0.3 to 1.1).

In contrast to the other cohort studies, the Framingham Heart Study[3] reported a 50 percent increased risk for all circulatory disorders in postmenopausal estrogen users (120). An increased incidence of MI was observed among estrogen users, particularly those who smoked cigarettes.

One criticism of the Framingham study's conclusions with respect to postmenopausal ERT and

3 The Framingham Heart Study, named for the Boston suburb where residents have participated since 1948, began with 5,209 healthy men and women ages 30 to 62. In 1971, the ongoing study was expanded to include the offspring of the original participants. The effects on diet, medication, and life-style on health have been assessed every two years (biennial examinations).

cardiovascular disease is that a reduction in cardiovascular disease risk in estrogen users may have been obscured by including in the estrogen user group women whose use was remote; in the Framingham study, anyone who had used estrogen at some time in the eight years before the twelfth biennial examination was counted as an estrogen user (119).

Another criticism of the Framingham study is that the investigators adjusted the results for HDL levels. Because estrogen's beneficial effects are thought to be substantially mediated through its effect on HDL level (15), the analysis may have underestimated the cardiovascular benefits of postmenopausal ERT.

The Framingham study has also been criticized for the use of subjective measures of cardiovascular disease (29). In the Framingham study, the relative risk of cardiovascular disease was estimated using a number of endpoints including angina pectoris (chest pain due to inadequate oxygenation of the heart), coronary heart disease, intermittent claudication (symptom associated with atherosclerosis and other occlusive arterial diseases characterized by leg pain with walking and relieved by rest), transient ischemic attack (occlusive vascular disease symptom characterized by brief periods of cerebral dysfunction, with no persistent necrologic deficit), myocardial infarction, congestive heart failure, coronary heart disease death, and sudden death. Chest pain can be due to a wide variety of causes, some of which can be mistakenly attributed to the presence of coronary heart disease. In a reanalysis of the Framingham data, excluding the nonspecific endpoint of angina pectoris, Eaker demonstrated a statistically nonsignificant reduction in risk of coronary heart disease among younger estrogen users (relative risk 0.4,95 percent confidence interval 0.1 to 2.3) and a statistically nonsignificant increase in risk of coronary heart disease among older estrogen users (relative risk 1.8, 95 percent confidence interval 0.5 to 6.9).

Although prospective cohort studies have important advantages over case-control studies in avoiding bias from the subject recall of exposure and the difficulties in selection of controls, a problem with some cohort studies is that estrogen use was often ascertained only at the initiation of the observation period and not reascertained at a later point in the study (103). By failing to update estrogen use status, current and former users may be misclassified, and an underestimate of the effect of estrogen may result, particularly because the benefits of estrogen use are most pronounced among current or recent users.

Cross-Sectional Studies

Recently, a number of cross-sectional surveys of estrogen use in women who have had coronary angiography (heart catheterization) have been reported; these studies have found reduced incidence of CHD in estrogen users (table I-5). Angiographically demonstrated coronary artery obstruction is thought to be a more specific endpoint for the presence of CHD than signs and symptoms such as angina pectoris or MI. Coronary angiography involves the injection of x-ray opaque dye into each artery of the heart (78). X-ray images of the heart (cineangiograms) are recorded, and these images are then reviewed by the cardiologist for evidence of obstructions of the coronary arteries.

Cross-sectional studies are a subcategory of case-control studies where the presence of disease and the exposure to the agent are ascertained simultaneously (94). In the studies listed in table I-5, the presence of angiographically demonstrated coronary artery obstruction and the patient's history of estrogen exposure were simultaneously ascertained. These studies have found reduced disease in women who had taken estrogen. For example, Gruchow et al. reports on a series of 933 women ages 50 to 75 years who underwent coronary angiography (36). Estrogen users were one-half as likely as nonusers to have moderate or severe occlusion of the coronary arteries. In nonusers, the likelihood of occlusion increased with age, whereas in users, no age trend was evident.

Hong et al. reported on a series of 90 consecutive women 55 years old or older undergoing diagnostic coronary angiography (41). Only 22

percent of estrogen users had significant obstruction of a major coronary artery (defined as 25 percent or more luminal diameter narrowing), whereas 68 percent of nonusers had significant obstruction.

Randomized Clinical Trials

In the only prospective randomized double-blind clinical trial of estrogen use and heart disease, Nachtigall and colleagues reported on the 10-year followup of eighty-four pairs of chronically ill women in a long-term-care hospital matched for age and diagnosis, who were randomly assigned to take estrogen opposed with progestin (PERT) or placebo (73). PERT users had a lower relative risk of myocardial infarction than nonusers, but there were only four myocardial infarctions in the study and the difference in risk was not statistically significant. In a study this small, however, one would expect only very large differences in relative risk of disease to be capable of producing statistically significant results.

Some investigators have argued that much of the reported heart disease benefit of HRT may be due to "healthy user" bias—the selection of relatively healthy women with a lower risk of heart disease for HRT. These investigators argue that estrogen users are generally of higher social class than nonusers (8), and social class is inversely associated with both heart disease and cancer (51,65). They also argue that the lower heart disease incidence in ERT users maybe because doctors were reluctant to prescribe estrogens to women with coronary risk factors 10 years ago, because, at that time, estrogen was contraindicated in these women because earlier studies had found increased risk of thrombosis and heart attack in young women taking oral contraceptives and in older men treated with estrogen.

One investigator showed that cohort studies that found a reduction of heart disease incidence in ERT users also showed a reduction in risk of total cancer incidence in ERT users, even though ERT would not be expected to have a beneficial effect on total cancer incidence (83).

Estrogen replacement therapy, however, has been found to prolong survival even in women who are not "healthy" women who already have significant coronary artery disease. Recent studies have compared the later survival of estrogen users versus nonusers with previously documented coronary artery lesions demonstrated by arteriography. Sullivan et al. recently found all-cause mortality over a 10-year period to be lower in women with coronary artery disease who used ERT than in those who never used estrogen (1 07). They reported a retrospective analysis of postmenopausal estrogen use, coronary artery obstruction (stenosis), and survival in 2,268 women 55 years or older who underwent coronary arteriography in the past. They compared overall survival in estrogen users and nonusers who initially had various degrees of coronary artery obstruction as demonstrated by arteriography. Over 10 years of followup, there was no difference in survival between estrogen users and nonusers with no initial evidence of coronary artery obstruction on arteriography. But in those with initially mild to moderate coronary artery occlusion (less than 70 percent stenosis), 10-year survival was 85 percent in never users versus 95.6 percent in ever users of estrogen. And in those who initially had severe occlusion (70 percent or greater stenosis), survival was 60 percent among those who never used estrogen and 97 percent among those who had ever used estrogen. One implication of these findings is that ERT may have beneficial effects on the heart even when started in older women with preexisting coronary heart disease.

Barrett-Connor found that, even within a group of women from the same socioeconomic class, women taking estrogen were different from nonusers with regard to health promotion and disease prevention measures (6). In order to minimize the bias introduced by differences in socioeconomic status between estrogen users and nonusers, Barrett-Connor evaluated the estrogen use patterns of 1,057 postmenopausal women from the same socioeconomically upper-middle-class community in California (6). The women were categorized as

never users, past users, and current users. After an average followup period of 4.4 years, 95 percent of these women completed a mailed health survey questionnaire that asked about lifestyle and health care factors related to good health. In general, women who never used estrogen were least likely to have implemented healthy behavior changes, and were least likely to have had screening evaluations. Seventy percent of the group of current estrogen users had had a mammogram in the last 12 months, whereas 45 percent of the never users had had one ($p < 0.001$).

Other investigators have also argued that users of ERT are relatively compliant, and that "compliance bias" may account for some of the apparent benefit of ERT on heart disease (79). To examine the magnitude of "compliance bias," analyses of data from two randomized clinical trials of drug treatments for heart disease have examined total mortality in persons who complied with the taking of placebo (24,43). In these analyses, subjects who complied with the taking of a placebo had significantly lower overall mortality. The benefit of compliance with placebo was not reduced by adjustment for a large number of variables, both medical and sociodemographic, that might affect mortality.

The issue of selection bias will not be completely resolved until completion of randomized controlled clinical trials of HRT and heart disease. A number of randomized controlled clinical trials have been performed that have examined the effect of HRT on lipids and lipoproteins. In women, levels of high density lipoprotein (HDL) and triglycerides, and to a lesser extent, low density lipoproteins (LDL) predict cardiovascular death in women (9). These studies have demonstrated that ERT, and to a lesser extent, PERT, have induced favorable changes in lipids and lipoproteins, consistent with a reduced risk of heart disease in HRT users.

A controlled clinical trial that uses the endpoint of coronary heart disease symptoms or mortality would be expensive because of the large number of study participants and the long duration of followup that would be required (71). Therefore, many trials have been conducted that measure estrogen's effect on various intermediate endpoints for coronary heart disease, such as blood lipid and lipoprotein levels. The first long-term large-scale controlled clinical trial of HRT using coronary heart disease endpoints was begun in fall 1993 as part of the Women's Health Initiative. This 15-year, $625 million study, sponsored by the National Institutes of Health, will examine the effect of HRT, as well as low fat diets, calcium supplements, and vitamin D supplements on the incidence of heart disease, osteoporosis, and other diseases. The study includes a clinical trial involving 57,000 women ages 50 to 79, and an observational study involving 100,000 women from 45 medical centers across the United States.

Randomized controlled clinical trials examining the effect of estrogen on heart disease risk factors have shown evidence of heart disease benefits in users of estrogen. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial involved 875 women, 45 to 64 years old at study entry, who were randomly assigned to either estrogen, one of three estrogen/progestin combinations, or placebo (122). During this three-year multicenter trial, the women were monitored for changes in a number of heart disease risk factors, including blood pressure LDL, HDL, and hemostatic factors. At the end of the three year trial period, women taking estrogen alone had significant increases in HDL, decreases in LDL, and decreased fibrinogen levels changes consistent with a decreased risk of heart disease in estrogen users.

EVIDENCE ON PERT AND CHD

The primary indication for adding progestins to the HRT regime is to reduce the risk of estrogen-induced irregular bleeding, endometrial hyperplasia (abnormal overgrowth of the inner lining of the uterus, or endometrium), and endometrial cancer (118). (See appendix G for more discussion.) But an important unresolved issue is whether the benefits of PERT in protecting the endometrium are outweighed by the effect of progestins on the risk of coronary artery disease. Studies of the relationship of HRT to coronary artery disease have been largely limited to ERT. The effect of proges-

tin supplementation has not been extensively evaluated because the routine addition of progestins to prevent estrogen-induced endometrial carcinoma has been recommended only recently (66).

Progestins are suspected to have an adverse impact on cardiovascular disease risk because progestins have opposite effects on lipid and lipoprotein metabolism from estrogens (84). Progestins decrease HDL levels (40,76,99). Different types of progestins, however, vary in their impact on lipids and lipoproteins, with the more androgenic progestins, particularly those derived from the male hormone testosterone, having a greater adverse impact. For example, Hirvonen et al. found that the progestins levonorgestrel and norethindrone in large doses (up to 10 mg) substantially reduced HDL, and the less androgenic progestin medroxyprogesterone acetate (10 mg) also reduced HDL levels, but not to as great an extent (40). Ottosson found that medroxyprogesterone acetate lowered HDL-2 cholesterol level, negating the increase observed with oral estrogens (76). Some evidence suggests that progestins may also adversely affect vessel-wall physiology (62).

There is some evidence that lower doses of the less androgenic progestins are sufficient to induce endometrial transformation and not substantially attenuate estrogen's beneficial effect on lipoproteins (2,34,45,49, 100,113,116,1 17,123) and other metabolic changes associated with heart disease risk (69,97). Progestin's effect on lipoproteins appears to be dose dependent, and lower doses of progestins may not substantially reduce estrogen's beneficial effect on HDL (45).

Nabulsi and colleagues found in a cross-sectional analysis of postmenopausal women that the addition of progestins did not attenuate estrogen's beneficial effects on heart disease risk factors; users of estrogen with progestin actually had a better profile of heart disease risk factors than users of estrogen alone (72). The investigators examined heart disease risk factors among 4,958 postmenopausal women, ages 45 to 64, from four regions of the United States, who were participating in the Atherosclerosis Risk in Communities study. They examined the associations of HRT with blood pressure, concentrations of plasma lipids and hemostatic factors, and fasting serum concentrations of glucose and insulin. Approximately 63 percent of the women had never used HRT, 16 percent had formerly used HRT, and 21 percent currently used HRT. Among current users of HRT, 83 percent were using estrogen alone (primarily conjugated equine estrogens (CEE)), and 17 percent were using PERT (primarily CEE with low dose medroxyprogesterone acetate).

The investigators found that, after adjusting for differences in other heart disease risk factors, current users of estrogen had significantly increased levels of HDL and decreased levels of LDL than did nonusers (72). They also found no significant difference in levels of HDL and LDL between users of ERT and users of PERT. Users of ERT had significantly higher plasma triglyceride levels than users of PERT. As elevated triglyceride levels are thought to increase heart disease risk, users of estrogen alone had a somewhat poorer plasma lipid profile than users of estrogen with progestin, but both groups of current users had better lipid profiles than nonusers. Finally, current HRT users had significantly lower levels of lipoprotein(a) than nonusers, with users of PERT having significantly lower levels of lipoprotein(a) than users of estrogen alone. Lipoprotein(a) concentrations may be inversely related to heart disease risk (98). Other changes were observed in the two groups of current users that would be predicted to lower the risk of coronary artery disease: a decline in fibrinogen levels (a serum protein involved in coagulation) and a decrease in glucose and insulin levels. Users of ERT had higher levels of coagulation factor VII and protein C than users of PERT and nonusers. This would suggest that PERT would have a better hemostatic profile than ERT.

These findings confirm three other population-based studies in which HDL levels in women who received ERT were similar to those in women who received PERT (8,32,1 14).

Recently, Falkeborn et al. reported the results of a study of first MI among a cohort of 23,174 postmenopausal estrogen/progestin users compared with postmenopausal women in the community (31). They found an age-adjusted relative

risk of first MI among current users of CEE (or estradiol) with progestin of 0.74 (0.61 to 0.81).

Results from the PEPI trial have also shown evidence of heart disease benefits in users of PERT, although the benefits are not as great as those in users of ERT (122). At the end of the three year trial period, women taking estrogen plus a synthetic progestin (medroxy progesterone) had a 2 milligram per deciliter (mg/dL) increase in HDL, whereas users of estrogen alone or estrogen plus a natural progestin (micronized progesterone, available in Europe) had about a 6 milligram per deciliter (mg/dL) increase in HDL, and the women assigned to the placebo group experienced no increase in HDL. Both the ERT group and the PERT group had significantly lower LDL than the placebo group. Both treatment groups experienced improvements in hemostatic factors and no change in blood pressure compared with the placebo group.

CONCLUSIONS

The conclusion of authors of several recent reviews of the evidence is that ERT reduces the risk of coronary heart disease (30,38,59). Both Stampfer and Bush, in recent meta-analyses of the data, concluded that the evidence strongly suggests that women taking estrogen therapy are at a risk for coronary heart disease about half that of nonusers (13,102). Several authors have found that the consistency of findings is stronger in the better designed and analyzed studies (13,56,59,84,93, 102).

Several studies demonstrated that women who currently use estrogen (current users) had a lower risk of coronary heart disease than women who had used them in the past (past users) (4,39, 64,81,88,90,91,102,111). Few data are available about whether dose, length of use, and type of estrogen affect risk. One study that examined the effect of estrogen duration on CHD risk failed to detect any effect of duration (102). However, Henderson et al. showed that women with a history of use showed a decrease in relative risk of fatal acute MI and fatal ischemic heart disease with increased duration of use (39). Rosenberg et al., in a case-control study, also found a significant trend toward decreased risk of first MI with increased duration of use of HRT, but only among current users (90).

Studies that examined dose failed to demonstrate a decreased risk of coronary heart disease with greater doses (39,102). But Ross found a nonsignificant trend toward decreased risk with higher doses of conjugated equine estrogens (92). Studies have not examined whether there are differences in efficacy with different estrogen preparations. Further study is needed on whether dose, length of use, and type of estrogen used affect risk.

There is evidence that HRT's heart disease benefits will continue into women's later years. Epidemiologic studies have demonstrated HRT's heart disease benefits in elderly women (15,39, 88,107,108).

OTA's review of the evidence concurs with those of other reviewers: there is both a theoretical rationale and empirical evidence to support a reduced risk of heart disease in women who use estrogens.

OTA chose a relative risk of 0.5 as the base case estimate of heart disease risk in current users of estrogen. In formulating this estimate, OTA placed greater emphasis on cohort studies than case-control studies, because cohort studies are less prone to bias. In general, cohort studies have demonstrated a greater heart protective effect of ERT than case control studies. Among cohort studies, 10 of 17 estimated relative risks of heart disease of 0.5 or below, and 13 of 17 were consistent with the hypothesis that ERT reduces heart disease risk in current users by half (confidence intervals included **0.5).**[4] The major disadvantage of cohort studies without internal controls is that the "control" group may not be comparable to the clinic

4 0TA relied on the results of the **Framingham** cohort published by Eaker (29), because the results of the major paper on heart disease in the Framingham cohort did not report the crude or age-adjusted cardiovascular disease rates.

TABLE I–5: Cross–Sectional Surveys of Coronary Artery Occlusion Among Women With and Without Postmenopausal Estrogen Who had Coronary Angiography

Study	Patient's age	Number of patients	Type of estrogen use	Percentage of estrogen users	Age-adjusted relative risk[a]	Risk–factor adjusted relative risk[a]
Sullivan, et al. (1988)	Mean age 62.8	2,188	Current use	4.4%	0.44 (0.29-0.67) for 70+ percent occlusion vs. no steriosls	0.58 (0.35-0.97)
Gruchow, et al. (1988)	Age range 50 to 75	933	Current use	15,5	0.59 (0.48-0.73) moderate vs. low occlusion score[b] 0.37 (0.29-0.46) severe vs. low occlusion score	
McFarland, et al. (1989)	Age range 35 to 59	283	Ever use	41	0.5 (0.3-0.8) for 70+ percent occlusion vs. no stenosis	**0.50**[c]
Hong (1992)	Mean age 62.3	**90**	Current use	**20**	OR for coronary artery disease = 0.13 ($p < 0.001$) in estrogen users vs. nonusers.	

KEY OR = odds ratio

[a] **95** percent confidence intervals are given in parentheses

b Value not provided.

[c] Confidence interval not provided.

Adapted from: M.J. Stampfer, and G.A. Colditz, "Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiological Evidence," *Preventive Medicine 20:47-63,* 1991.

population. Among cohort studies with internal controls, seven of 12 reported reductions in heart disease risk greater than 0.5 in ERT users.

OTA's base case estimate of heart disease risk in ERT users is also consistent with all of the angiographic studies, which show 50-to 60-percent reductions in the amount of coronary artery stenosis in ERT users (table I-5). These studies of angiographically defined coronary artery disease should provide more precise estimates of heart disease risk than studies using clinical endpoints of heart attack or ischemic heart disease symptoms. This is because many postmenopausal women with significant coronary artery occlusions have no symptoms, and these women will be misclassified as having no heart disease. This misclassification diminishes the ability of an epidemiologic study of ERT users and nonusers to detect differences in risk of heart disease between the groups.

OTA's base case estimate of heart disease risk in ERT users is consistent with that of the meta-analyses by Barrett-Connor and Bush (7) (approximately 50-percent reduction in risk of heart disease in ERT users), Bush (13) (a reduction in risk of 40- to 50-percent), and Mack (60) (an estimated 50-percent reduction in risk). This is also consistent with the meta-analysis by Stampfer et al. of cohort studies with internal controls and cross-sectional angiographic studies (102). Stampfer et al. obtained a somewhat higher estimate of heart disease in ERT users when the results of cohort studies without internal controls and case control studies were also factored in to the estimate (102). OTA's estimate of relative risk of heart disease in ERT users was less than the meta-analysis of Grady et al., who calculated a relative risk of heart disease in ERT users of 0.65 (35).

Because of the uncertainty about the magnitude of the heart protective effect of ERT, OTA tested the sensitivity of the model to a wide range of estimates of heart disease risk in ERT users. Although most cohort studies have demonstrated a reduced risk of heart disease in ERT users, the range of estimates of the relative risk varies widely, to as low as 0.17. In addition, cohort studies of current ERT users have, on average, estimated a lower risk of heart disease than studies of ever users or past users of ERT. To encompass the range of estimates from these studies in our sensitivity analysis, OTA chose a relative risk of 0.2 as a best case estimate of heart disease risk in ERT users, and a relative risk of 0.8 as a worst case estimate.

OTA assumed as a base case that users of PERT would have no heart disease benefit, and as a best case, that estrogen/progestin users would have a 20-percent lower risk of heart disease than nonusers (relative risk 0.8). Randomized clinical trials examining estrogen with progestin's effect on lipids and lipoproteins suggest that the heart disease benefits of estrogen would be reduced when progestins are added, although this reduction maybe minimized by using the lowest effective dose of the least androgenic progestins.

OTA's estimates of the relative risk of heart disease in PERT users are consistent with recent epidemiologic studies. Because the addition of a progestin to ERT has become standard medical practice only relatively recently, there are few epidemiologic studies with sufficient numbers of estrogen/progestin users to estimate its impact on heart disease risk.

The evidence is weak to support a protective effect extending beyond the period of use. In the absence of such evidence, a reasonably conservative assumption is that ERT (when not combined with progestins) reduces heart disease rates by one-half, but only during the therapy period. Once HRT ceases, heart disease rates can be assumed to return quickly to the rates in the general population of women of the same age.

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