POSTMENOPAUSAL ESTROGEN USE, CIGARETTE SMOKING, AND CARDIOVASCULAR MORBIDITY IN WOMEN OVER 50

The Framingham Study

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Abstract We studied the effect of estrogen use on morbidity from cardiovascular disease in 1234 postmenopausal women, aged 50 to 83 years, participating in the Framingham Heart Study's 12th biennial examination (index examination). The medication history recorded at biennial examinations 8 through 12 was used to classify the degree of estrogen exposure before eight years of observation for cardiovascular morbidity and mortality. Despite a favorable cardiovascular risk profile and control for the major known risk factors for heart disease, women reporting postmenopausal estrogen use at one or more examinations had over a 50 per cent elevated risk of cardiovascular morbidity ($P<0.01$) and more than a twofold risk for cerebrovascular disease ($P<0.01$) after the index examination. Increased rates for myocardial infarction ($P<0.05$) were observed particularly among the estrogen users who smoked cigarettes. Conversely, among nonsmokers estrogen use was associated only with an increased incidence of stroke ($P<0.05$). No benefits from estrogen use were observed in the study group; in particular, mortality from all causes and from cardiovascular disease did not differ for estrogen users and nonusers. (N Engl J Med 1985; 313:1038-43.)

PRESCRIBED estrogen use is very common in our society. In the 1970s it was estimated that more than 30 per cent of postmenopausal women in the United States used prescribed estrogen.[1] Many studies have investigated potential detrimental effects of such medication, directing attention mostly toward heart disease and gynecologic cancer.[2,3] The Framingham Heart Study, with its long-term follow-up and collection of extensive information preceding the administration of postmenopausal estrogen, provided a setting to examine personal attributes before estrogen therapy was initiated. Over a period of eight years, both women who used estrogen and those who did not were followed for disease events, including morbidity and mortality from vascular disease as well as mortality from all causes. This design allowed a critical appraisal of the consequences of postmenopausal estrogen use, and the opportunity to extend a preliminary report from Framingham, which showed an increased risk of coronary heart disease among estrogen users after menopause.[4]

METHODS

Details of the recruitment, biennial examination procedures, and review process for the determination of mortality and cardiovascular sequelae are outlined elsewhere.[4,5] Patients included in this investigation participated in the 12th biennial examination (index examination) between 1970 and 1972 and were followed for eight years. Only postmenopausal women over 50 years of age at the 12th examination were included in the comparisons. The criterion for menopause was cessation of menses more than a year earlier, either as a natural event or after gynecologic surgery.

Follow-up was accomplished by a physician review of clinic notes, hospital and physician records, and death certificates on a biennial basis. In some analyses different end points are grouped. For example, coronary heart disease includes angina pectoris, myocardial infarction, and coronary death or sudden death. Cerebrovascular disease includes the first occurrence of stroke or a transient ischemic attack. Cardiovascular disease includes coronary heart disease, cerebrovascular disease, intermittent claudication, and congestive heart failure. This review process documented cardiovascular disease events, such as angina pectoris, that may not have required hospitalization and included unrecognized myocardial infarctions. The latter were substantiated by the appearance of new Q waves on the electrocardiogram since the last examination. Diagnoses of cerebrovascular disease were confirmed by a review panel, which included a neurologist. For this report, the interval from examination 12 through examination 16 was the follow-up period (eight years). Information about cardiovascular disease events was estimated to be complete for more than 99 per cent of the study group.

Use of postmenopausal estrogen preparations was determined from the time of the 8th through the 12th biennial examination. This study does not include information on estrogen use during the follow-up period (after the index examination). Almost all medications employed were conjugated equine estrogens. Reported use of progestogens was rare (less than 5 per cent for the entire period). Women over 69 were omitted in age-specific analyses (Fig. 2 and 3 only), since too few women in this age group took estrogen preparations, and rates based on these numbers were unstable. Analyses of follow-up data after postmenopausal estrogen therapy classify exposure as positive if the subject ever reported use during examinations 8 through 12. Inquiries during examination 8 included the duration of previous postmenopausal estrogen use; few women reported extensive use before examination 8.

Descriptive variables used in the analyses were taken from the 12th examination, except if certain measurements were made only at the 11th examination. The latter included high-density lipoprotein cholesterol and total plasma cholesterol. Obesity was measured according to the Metropolitan Life Insurance (1959) tables, with the midpoint of the range for men and women of medium frame for a subject's height used as the standard. The body-mass index was determined at the 12th examination and was also used as a measure of obesity in some analyses. It was calculated by dividing the weight in kilograms by the height in meters raised to the second power. Fasting plasma lipoprotein cholesterol values were determined by a modification of the Lipid Research Clinics technique at the 11th examination[6]; earlier concentrations of total serum cholesterol (biennial examinations 1 through 7) were measured in nonfasting serum samples.[7] Weekly alcohol consumption was estimated from reported intake of beer, wine, and hard liquor (a highball or cocktail), using a previously described estimation equation.[8] Cigarette smoking was recorded as positive if the study participant reported that she had smoked cigarettes regularly during the year before the index examination.

Analysis of covariance was employed to test for differences in the mean values of variables between estrogen users and nonusers. Multivariate logistic regression[9] was used to test for statistically significant relations between estrogen use and various morbidity and mortality outcomes. The primary null hypothesis was that mortality from all causes and cardiovascular morbidity did not differ between women who used estrogen and those who did not.

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Table 1. Postmenopausal Estrogen (PME) Use Reported during Any Biennial Examination from Examination 8 through 12, in 1234 Women without Cardiovascular Disease at Examination 12.

PME Use	Age at Examination 12			
	50–59	60–69	70–83	TOTAL
Yes	150	112	40	302
No*	320	361	251	932
Total	470	473	291	1234
% Use	31.9	23.7	13.8	24.4

*Includes women with unknown use.

Results

Postmenopausal estrogen use in the sample studied is summarized in Table 1. The overall rate of use among the 1234 women was 24 per cent (302 of 1234). Proportional use of estrogen declined in older age groups. These estimates represent a summary of use over a 10-year span among postmenopausal women. Figure 1 shows estrogen use among postmenopausal women aged 50 to 83 (in three age groups) at biennial examinations 8 through 12. Age was classified at examination 12 for this figure. Maximal estrogen use was 19.4 per cent in the 50-to-59 group (examination 10), 15 per cent for the 60-to-69 group (examination 10), and 11.0 per cent for the 70-to-83 group (examination 9).

Mean values at the index examination (examination 12) for cigarette smoking, plasma cholesterol and its subfractions, systolic arterial pressure, relative weight according to Metropolitan Life Insurance tables, plasma triglyceride, and alcohol intake are shown in Table 2. Significant age-adjusted differences between the group of estrogen users and the nonuser group were found by analysis of covariance for Metropolitan relative weight, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

Figures 2 and 3 show the associations of estrogen use and nonuse with mortality from all causes and cardiovascular disease, respectively, for women between 50 and 83 years. Figure 2 shows rates of death from all causes for estrogen users and nonusers. No difference between the groups was detected using a logistic-regression model that included age as a covariate. A different result was obtained for cardiovascular death. Age-adjusted incidence rates were significantly higher for women reporting postmenopausal estrogen use (19.6 per 100 per eight years in users vs. 14.5 per 100 per eight years in nonusers, $P<0.01$), and a consistent pattern was evident for each separate age-specific comparison. The difference appeared to be smallest in the oldest age group, in which the fewest women were available for study.

No difference in case fatality rates was found for estrogen users and nonusers. Four of the 14 users with cerebrovascular disease died from vascular disease (cardiovascular or cerebrovascular death), as compared with 12 of 31 nonusers (chi-square, 0.10, 1 degree of freedom; not significant). Similarly, 8 of 37 estrogen users with coronary heart disease died from vascular disease, as compared with 19 of 79 nonusers (chi-square, 2.01, 1 degree of freedom; not significant).

Table 3 shows the results of the multivariate logistic regression of total cardiovascular disease for the following series of variables: systolic blood pressure, ratio of total cholesterol to high-density lipoprotein cholesterol, current cigarette smoking, body-mass index, age, and estrogen use. Statistically significant associations were found for systolic blood pressure, the ratio of total cholesterol to high-density lipoprotein cholesterol, cigarette smoking, age, and estrogen use. Similar results were obtained when the variable "postmenopausal estrogen use ever" was replaced by the number of examinations during which estrogen was used. In addition, separate multiple-logistic-regression analyses were run with the same set of independent variables and the other dependent variables that are shown in Table 4. The values for adjusted relative risk and significance level apply only to the relation of postmenopausal estrogen to the specific outcome (dependent) variable in the analysis. Estrogen use was significantly associated with stroke, particularly atherothrombotic brain infarction; coronary heart disease, including angina pectoris; and total morbidity from cardiovascular disease. No significant associations, either positive or negative, were observed for any of the mortality variables examined.

Cardiovascular risk factors (Metropolitan relative weight, serum cholesterol, and systolic blood pressure) were investigated in examinations preceding the index examination. Throughout the observation period (examination 1 to examination 7, years 1949 through 1962), age-adjusted Metropolitan relative weight and total serum cholesterol were uniformly lower in the women who later reported use of estrogen at examinations 8 through 12. The result for systolic blood pressure appeared to be similar, but after ad-

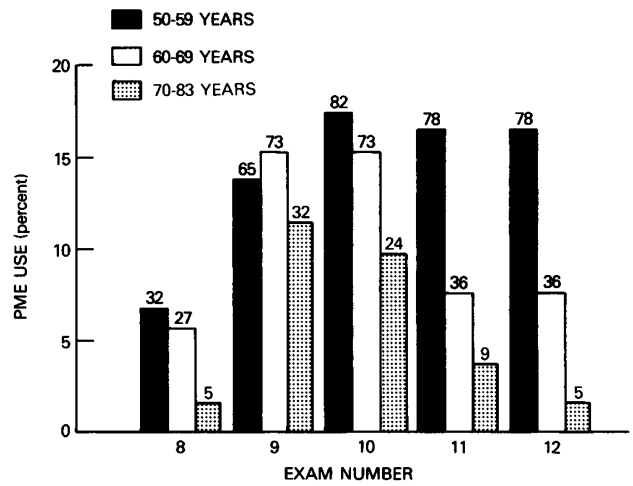

Figure 1. Proportional Use of Postmenopausal Estrogen (PME) at Biennial Examinations 8 through 12 for Women 50 to 59, 60 to 69, and 70 to 83 Years of Age.
The number of PME users is indicated above each bar.

Table 2. Mean Values for Selected Variables at Examination 12.

VARIABLE*	ESTROGEN USERS	ESTROGEN NONUSERS	AGE-ADJUSTED DIFFERENCE
	mean ±S.D.		
Current cigarette smoking	0.268±0.47	0.216±0.44	NS
Systolic blood pressure (mm Hg)	139.4±22.4	142.1±23.4	NS
Metropolitan relative weight	118.8±18.5	122.7±20.8	4.2 (P<0.001)
Alcohol intake (oz/wk)	2.24±2.9	2.09±2.9	NS
Total cholesterol (mg/dl)	238.4±40.3	241.3±41.3	NS
HDL cholesterol (mg/dl)	60.6±17.2	56.9±14.9	3.3 (P<0.05)
LDL cholesterol (mg/dl)	150.8±38.2	156.3±38.3	3.7 (P<0.05)
VLDL cholesterol (mg/dl)	26.9±18.9	28.1±18.9	NS
Total cholesterol:HDL cholesterol	4.28±1.6	4.52±1.4	0.20 (P<0.01)
No. of subjects	302	932	

*HDL denotes high-density lipoprotein, LDL low-density lipoprotein, VLDL very-low-density lipoprotein, and NS not significant. To convert cholesterol values to millimoles per liter, multiply by 0.02586.

justment for age, no significant difference between the two groups was demonstrable.

Reported use of postmenopausal estrogen at each of the biennial examinations 8 through 12 was also evaluated for any interexamination reporting differences. The probability of recurrent use of postmenopausal estrogen was calculated for each age decade and for each possible examination pair. There were no marked aberrations in these interexamination comparisons, providing good evidence that the questions about estrogen use were uniformly administered. Subjects were consistently aware of their medication, and pooling of the individual interexamination data was thought to be justified. The youngest group of women (age 50 to 59 at examination 12) had the highest probability of recurrent use, ranging from 63 per cent (for examinations 10 and 11) to 80 per cent (for examinations 9 and 10), with a pooled probability of 70 per cent.

Because of the possibility of interactions among cigarette smoking, estrogen use, and cardiovascular disease events, a separate multivariate logistic estimation was undertaken for smokers and nonsmokers. As seen in Table 5, there was a marked tendency for adjusted relative risks of coronary heart disease to be higher in women who smoked than in nonsmokers. This association arises especially from a higher risk of myocardial infarction and angina pectoris in the smokers. A slightly different situation was observed for cerebrovascular disease, the relative risk of which did not differ appreciably in smokers and nonsmokers, with a statistically significant association apparent for estrogen use in nonsmokers. Analysis of outcomes such as death and cause of death revealed no striking differences between cigarette smokers and nonsmokers.

Surgical menopause occurred frequently in this sample of women, as shown in Table 6. Since women who have undergone surgical menopause are more likely to have estrogen preparations prescribed, the increased risk of cardiovascular disease associated with estrogen use may result partly from the increased risk after early surgical menopause. To evaluate this possibility, as well as to diminish the chance that the regression-based age-adjustment procedures were inadequate, we estimated age-specific logistic-regression equations (not shown) for models that included surgical menopause as an additional independent (dichotomous) variable. We concluded that surgical menopause had little confounding effect on the relation between estrogen use and morbidity from cardiovascular disease. The small size of the various subgroups precluded statistical tests for each specific menopausal mechanism.

DISCUSSION

Oral estrogen preparations are taken by many postmenopausal women. In the 1970s it was estimated that one third of women over 50 used estrogen.[1] One population-based study in southern California reported estrogen use in 39 per cent of postmenopausal women.[10] In the Framingham sample this proportion was smaller. Only 15 to 20 per cent of women used such preparations at any one time, but 32 per cent of women between 50 and 59 years used the drug between biennial examinations 8 and 12.

Short-term benefits of estrogen therapy in alleviat-

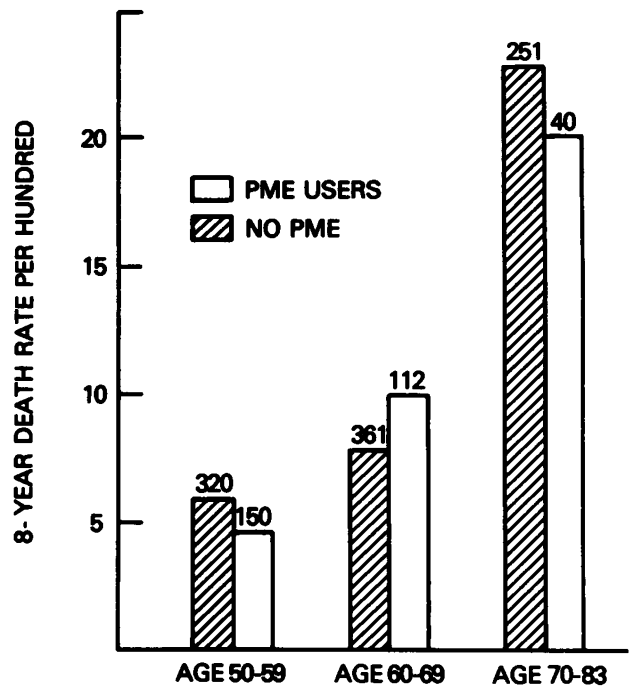

Figure 2. Eight-Year Death Rate for 1234 Women Free of Cardiovascular Disease at the 12th Biennial Examination.
The numbers of postmenopausal estrogen (PME) users and nonusers are shown above the bars.

ing menopausal symptoms are well documented and represent a clinical indication for prescribing estrogen. However, many physicians prescribe estrogen medications for periods longer than the 6 to 12 months often necessary to treat symptoms such as perimenopausal flushing. Nearly two thirds (61.3 per cent) of estrogen users in the Framingham group reported using the medication at two or more of the five examinations covered in this report (examinations 8 through 12). The typical duration of postmenopausal estrogen use has been reported to be about three years.[11]

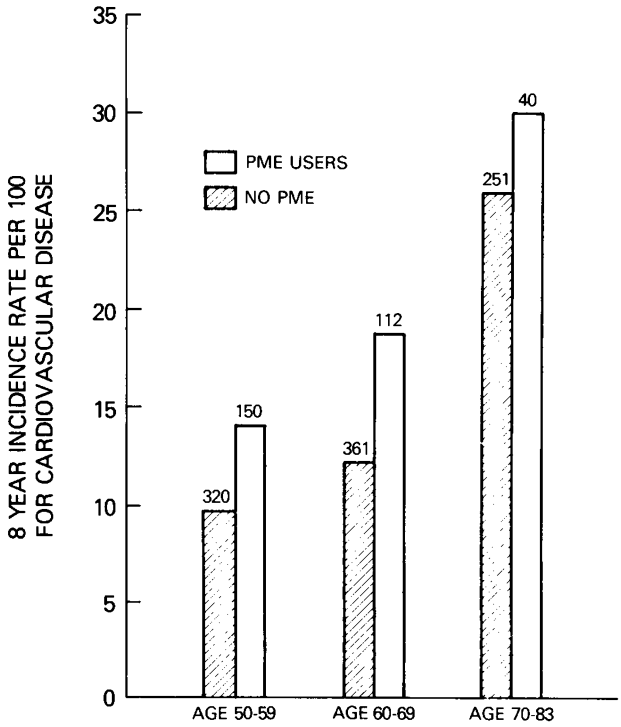

Figure 3. Eight-Year Incidence of Cardiovascular Disease among 1234 Women.

The numbers of postmenopausal estrogen (PME) users and nonusers are shown above the bars.

Postmenopausal estrogen use for more than a few months may elevate the incidence of vascular disease. Determination of the risk associated with postmenopausal estrogen use has been more difficult and is a matter of great interest.[12] Reports of a case–control study in Boston, a study of a retirement community of 15,500 in southern California, and a mail survey of more than 120,000 nurses demonstrated no difference between the numbers of users and nonusers hospitalized for nonfatal myocardial infarction.[3,13,14] However, the Lipid Research Clinics Program has reported that in a study of more than 2000 women followed for an average of six years, the rate of mortality from all causes in estrogen users was approximately half the rate in the nonusers.[2]

Our data provide evidence that postmenopausal estrogens confer no beneficial effect on all-cause mortality or total cardiovascular morbidity (Fig. 2 and 3). When the association of estrogen use and cardiovascular morbidity was examined prospectively, significant detrimental effects were seen for total cardiovascular disease, coronary heart disease, and stroke in particular (Table 4). One difference between our results and those of others may be the more complete ascertainment of vascular events in our study. For example, 18 of the 51 myocardial infarctions (35 per cent) were unrecognized in our study, and the patients were not hospitalized. This finding is concordant with other rates of unrecognized myocardial infarction among all women in the Framingham study.[15]

The benefit of postmenopausal estrogen use reported by the Lipid Research Clinics Program and the description of apparently low-risk coronary profiles in their Rancho Bernardo subpopulation[2,10] stimulated further investigation in the Framingham women. Coronary-disease risk profiles were also advantageous in the women we studied who used postmenopausal estrogen. Average blood lipid levels and obesity measures were more favorable in the group of estrogen users at the index examination. When the available components of the risk profile were studied for women who later used estrogen, the same patterns emerged. In other words, women in our population who used post-

Table 3. Standardized Multivariate Logistic Regression Coefficients, Relative Risks, and Significance Levels for Cases of Cardiovascular Disease.*

Factor	Multivariate Coefficient	Relative Risk	P Value
Systolic pressure	0.292	1.30	<0.01
Total cholesterol:HDL cholesterol	0.244	1.40	<0.01
Cigarette smoking	0.207	1.63	<0.05
Body-mass index	0.122	—	NS
Alcohol intake	−0.057	—	NS
Age	0.450	1.82	<0.001
Postmenopausal estrogen use ever	0.214	1.76	<0.01
No. of cases	194		

*Relative risk for differences: systolic pressure, 20 mm Hg; ratio of total cholesterol to HDL cholesterol, 2 units; cigarette smoking, yes versus no; age, 10 years; and estrogen use ever, yes versus no. HDL denotes high-density lipoprotein, and NS not significant.

Table 4. Relative Risk Associated with Postmenopausal Estrogen (PME) Use, for Various Cardiovascular Diseases.*

Event	No. of Cases	Adjusted Relative Risk for PME Users	P Value
Cerebrovascular disease	45	2.27	<0.01
Atherothrombotic brain infarction	21	2.60	<0.01
Coronary heart disease	116	1.90	<0.01
Myocardial infarction	51	1.87	NS
Angina pectoris	69	2.00	<0.01
Congestive heart failure	43	1.15	NS
Total cardiovascular disease	194	1.76	<0.01
Death from cardiovascular disease	48	1.94	NS
Death from cancer	47	0.70	NS
Death from all causes	130	0.97	NS

*After adjustment for age, systolic blood pressure, body-mass index, ratio of total cholesterol to high-density lipoprotein cholesterol, cigarette smoking, and reported alcohol consumption in the logistic model. NS denotes not significant. Categories are not mutually exclusive. For example, if a subject had both a myocardial infarction and angina pectoris, she was counted only once for total cardiovascular disease.

Table 5. Logistic-Regression Estimate of Relative Risk for Various End Points among Postmenopausal Estrogen Users, According to Smoking Status.*

Event	Smokers (N = 282)			Nonsmokers (N = 952)		
	Adjusted Relative Risk	No. of Cases	P Value	Adjusted Relative Risk	No. of Cases	P Value
Cerebrovascular disease	1.96	10	NS	2.35	35	<0.05
Coronary heart disease	4.17	25	<0.01	1.44	91	NS
Myocardial infarction	3.21	14	<0.05	1.47	37	NS
Angina pectoris	5.23	14	<0.01	1.49	55	NS
Total cardiovascular disease	3.16	44	<0.01	1.26	150	NS

*Adjusted for age, systolic blood pressure, body-mass index, ratio of total cholesterol to high-density lipoprotein cholesterol, and reported alcohol consumption in the logistic model. NS denotes not significant.

menopausal estrogens had favorable profiles well in advance of taking estrogens. Therefore, the seemingly salutary effect of estrogen use on risk factors for coronary disease may partly result from forces that influence the selection of women for estrogen therapy. For this reason, observational studies, such as ours, that attempt to assess the efficacy or consequences of medical therapy are susceptible to misinterpretation.

The potential effect of the duration and dose of medication cannot be examined critically in this report. We chose to gauge exposure during a specific period and then follow the patients. Therefore, use of estrogens in the follow-up period is not included, and duration cannot be accurately assessed. Unfortunately, the actual dose of estrogen was not recorded uniformly during the exposure period, and the potential effect of the dose could not be investigated.

Effects of estrogen preparations on premenopausal women have been studied extensively. Disadvantages include premature vascular disease, especially venous thromboembolism and stroke.[12] Such risks are thought to exist even with the more recently available preparations, which have lower amounts of ethinyl estradiol.[16] Recent reports have emphasized the potential benefit of postmenopausal estrogen use as prophylaxis against osteoporosis,[17] decreased all-cause mortality,[2] and a decrease in ischemic vascular disease.[18]

The women we studied were heterogeneous with respect to the age at which estrogen was prescribed. For example, among the oldest women studied, those over 70 years at examination 12, estrogen had first been prescribed when they were well past the age of 60 years. In contrast, among the youngest women (age 50 to 59 at examination 12), nearly all prescriptions were likely to have been perimenopausal. The relation between age and postmenopausal estrogen use, shown in Table 1, probably reflects the fact that when such therapy was introduced for general use, not all age groups were equally likely to have received it.

Presumably beneficial cardiovascular risk profiles have been described in some groups using postmenopausal estrogen, particularly, higher levels of high-density lipoprotein cholesterol.[10] We had similar results but also found that some changes may antedate estrogen therapy. Another finding of the present study that differs from others is the increase in vascular disease in the group of estrogen users,[13,18-20] in spite of their improved cardiovascular risk profile.

In addition, for certain cardiovascular-disease end points, we found an apparent interaction between cigarette smoking and estrogen use, with large differences between adjusted relative risks of estrogen use for cigarette smokers and nonsmokers. As in premenopausal women using estrogen preparations, smokers had a higher risk of cerebrovascular disease and of total coronary heart disease. Similar results have been reported in women under 46 years of age using noncontraceptive estrogen.[20] Atherothrombotic brain infarction was the most common diagnosis of cerebrovascular disease in this series, in contrast to the greatly increased rates of subarachnoid hemorrhage in oral-contraceptive users, reported by the Royal College of General Practitioners and by Petitti and Wingerd.[21,22] The Framingham results do not agree with the case–control findings of Pfeffer, who reported no increased risk of stroke in estrogen users without hypertension. His study included only a small number of estrogen users who were not hypertensive, and it emphasized older persons with a higher prevalence of hypertension.[19]

The results of our study should be interpreted cautiously. Certain symptoms that lead physicians to prescribe postmenopausal estrogens may be important, and postmenopausal estrogen use may serve only as a reflection of those factors. Since the findings presented in this report appear to contradict those of other studies, we reanalyzed our data using an approach taken by Bush et al.[2] We classified women as estrogen users or nonusers only at biennial examination 11, used the available covariates (including fasting lipoprotein cholesterol levels), and examined relations to death and major cardiovascular morbidity over 10 years, using logistic regression. The results of these analyses suggest that a variable representing a single classification of postmenopausal estrogen use has a different relation to total mortality than the "interval

Table 6. Reported Use of Postmenopausal Estrogen at Examinations 8 through 12, According to Age and Type of Menopause.*

Type of Menopause	Age Group (Yr)		
	50–59	60–69	>70
	no. of women		
Natural	335	323	229
Surgical 1†	54	45	18
Surgical 2‡	78	104	41
Surgical 1 or 2 (%)	28.3	31.6	20.5

*Data are based on 1227 women with a known cause of cessation of menses.

†No ovaries removed or one ovary removed.

‡Two or unknown number of ovaries removed.

use" variable we have employed. Although these results were not statistically significant, the suggestion of an inverse relation between estrogen use reported at examination 11 and total mortality was evident among the younger women in Framingham (age 50 to 59, an age group comparable to that in the Lipid Research Clinics study). When total cardiovascular disease was examined in a similar fashion, there was no relation between estrogen use and cardiovascular disease among the youngest women, but there was a strong positive relation among those over age 60. We interpret these results as suggestive, but far from conclusive, evidence that physicians may not only be selective in prescribing postmenopausal estrogens but may selectively remove certain women from therapy. Determination of postmenopausal estrogen use during a short interval may overstate an assumed salutary effect of such use on mortality, because of a tendency to consider only the "successfully treated" group as estrogen users. Our approach of measuring "interval use" obviates the previously mentioned misclassification of nonusers and should give more valid results.

The prospective design of the Framingham Study (follow-up examinations with ascertainment of stroke as well as events not resulting in hospitalization, such as unrecognized myocardial infarctions) explains some of the differences between this investigation and others. Methodological differences may also be important, as alluded to above, and exposure during an interval may represent postmenopausal estrogen use differently from a simple cross-sectional classification. Our findings suggest that the potential drawbacks to postmenopausal estrogen therapy should be considered carefully before recommending its widespread use.

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