# Postmenopausal use of estrogen and occlusion of coronary arteries

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## Abstract:

The degree of coronary artery occlusion was compared between users and nonusers of postmenopausal estrogen among 933 female patients undergoing angiography between the ages 50 and 75 years in the Milwaukee Cardiovascular Data Registry. Users (n = 154) had less occlusion than nonusers (n = 779), and a significant increase in occlusion scores with age was evident for nonusers ($p < 0.001$) but not for users ($p = 0.50$). The age-adjusted odds ratios for use of postmenopausal estrogen among women with moderate and severe levels of occlusion of the coronary arteries were 0.59 (95% confidence interval, 0.48 to 0.73) and 0.37 (95% confidence interval, 0.29 to 0.46), respectively, which indicated a statistically significant, apparent protective effect of postmenopausal estrogen on coronary occlusion. This effect was independent of the type of menopause or other risk factors but not independent of high-density lipoprotein-cholesterol levels. Higher high-density lipoprotein-cholesterol levels among users may indicate a biologic mechanism by which postmenopausal estrogen use lowers the risk of coronary occlusion.

## Article:

Most studies of sufficient size and power have shown a protective effect of replacement estrogen for coronary heart disease (CHD) in postmenopausal women.[1-4] However, simultaneous publication of two papers[5,6] with conflicting results regarding the risks or benefits of postmenopausal estrogen use for cardiovascular disease has engendered an intense debate [7-17] Wilson et al.[5] reported no difference in cardiovascular or total deaths between postmenopausal estrogen users and nonusers in the Framingham Study; Stampfer et al.[6] reported a reduced risk of coronary disease among nurses who had estrogen after menopause. Methodologic differences may have accounted for some of these discrepant findings. For example, the lack of association between postmenopausal estrogen use and coronary heart disease in the Framingham data may have resulted from the inclusion of angina as an indicator of CHD, failure to distinguish current from past use of estrogen, and adjusting CHD risks for high-density lipoprotein (HDL) cholesterol as a confounding variable rather than as a mediator of estrogen effect.[16] More recently, results from the follow-up study of the Lipid Research Clinics Program confirmed an apparent protective effect of postmenopausal estrogen use from death caused by cardiovascular disease.[18] The public health importance of this issue is evident when the high rate of exposure to estrogen by U.S. women is considered, along with the importance of heart disease as a cause of morbidity and mortality.[3,4]

There is reasonably consistent evidence that exogenous estrogen produces lipid profiles that are associated with lower risks of CHD. Estrogen use is associated with higher plasma HDL cholesterol, with lower low-density lipoprotein (LDL) cholesterol and sometimes with higher triglyceride levels.[19-21]

To assess the relationship between postmenopausal estrogen use and the underlying arteriosclerotic process of CHD, we compared the degree of occlusion in coronary arteries between users and nonusers of estrogen. The Milwaukee Cardiovascular Data Registry, which has comprehensive data on more than 14,000 male and female patients who have undergone since 1968, provided the opportunity for this comparison. The hypothesis tested in this study was whether there was a difference in the extent of coronary artery occlusion between patients who took estrogen after menopause and those who did not.

## METHODS

The Registry contained complete information on 933 postmenopausal women, 50 years of age and older. Informed consent was obtained from all patients. These women were referred for diagnostic angiographic examination to two Milwaukee hospitals between 1972 and 1985. The referring diagnoses included unstable angina pectoris or moderate to severe stable angina (69 %) and dyspnea or recurrent chest pain of unknown origin (31%). In addition, 38% of the patients had a previous myocardial infarction (MI). Coronary arteriography was carried out by the technique of either Sones and Shirey[22] or Judkins.[23] The angiograms were evaluated by an experienced cardiologist without knowledge of risk factor data. The extent of coronary artery occlusion was recorded according to the protocol suggested by Rowe et a1.[24] except that the scale was inverted, with occlusion scores ranging from 0 (no occlusion) to 300 (complete occlusion). In this method patients are considered to have three main coronary arteries: right, left anterior descending, and circumflex. If there was an occlusion, an estimate was made of its extent in increments of 25%. For instance, if the left anterior descending artery was considered 75% occluded and the other two vessels were normal, the occlusion score would be 75. If disease was found in a branch of one of the main vessels, the size of the branch was estimated, compared with that of its parent vessel, the degree of occlusion of the branch estimated, and the overall effect of the occlusion approximated. This figure was added to the total score. Because the left main coronary artery supplies both the circumflex and anterior descending arteries, occlusions in this artery were doubled (e.g., a 50% occlusion received a score of 100).

Estrogen use was determined by responses to a checklist of medications, which made up a portion of an extensive questionnaire given to hospitalized patients the day before the angiographic examination. Thus the extent of coronary occlusion in any patient was not known at the time the questionnaire was administered. Patients were asked to indicate which medications on the checklist they were currently taking or had taken within the past 3 months. Therefore postmenopausal estrogen users in this study were women who took this hormone at the time of angiography or within 3 months before angiography. Nonusers were women who had not taken estrogen in the 3 months before angiography. The checklist was developed to assess all current medication usage (not only estrogen), and 3 months was deemed to be the maximum length of reliable and accurate recall. The misclassification of users (as nonusers) because of this time limit reduced the apparent magnitude of differences between these groups and probably underestimated an effect of estrogen on the level of coronary occlusion.

Information on the amount, type, and frequency of alcohol intake was obtained by a self-administered questionnaire, which was based on the method of Khavari and Farber.[25] Alcohol intake was a combination of the amount of beer, wine, and hard liquor consumed and was converted to grams of absolute alcohol per week. Body mass index was computed as weight (kilograms- divided by height squared (centimeters).[26] Exercise was a count of the number of times per month that each person participated in aerobic-type exercises. Lifetime smoking history and current smoker status were measured. A five-point smoking history scale (1 = never-smokers; 5 = long-term heavy smokers) was constructed as reported in a previous publication.[27] Additional questions elicited whether the patient was a current cigarette smoker, former smoker, or never had smoked. The questionnaire responses also provided information on parental history of CHD, personal histories of hypertension, diabetes, angina, or MI, amount of education, number of children, number of pregnancies, and time and type of menopause.

Fasting blood samples, which were collected after an overnight fast, were analyzed for total plasma cholesterol and plasma triglyceride levels by means of automated procedures[28,29] with quality control monitored and certified by the Lipid Standardization Program, Centers for Disease Control, Atlanta, Ga. Plasma HDLs were measured after the heparin-manganese precipitation of the low and very low—density lipoproteins?[30,31] The procedure was standardized with samples of known HDL-cholesterol content supplied by courtesy of Dr. G. R. Cooper, of the Centers for Disease Control, and the laboratory procedures for HDL were also certified. Total cholesterol and triglyceride levels were obtained for the entire study population, but tests to discriminate HDL and LDL cholesterol were instituted in 1978 and therefore were available for a smaller group of patients (n = 247).

**Table I.** Unadjusted comparisons between postmenopausal estrogen users and nonusers on coronary occlusion risk factors and disease histories

| | *Mean ± SD* | |
|---|---|---|
| | *Users (n = 154)* | *Nonusers (n = 779)* |
| Age (yr) | 58.6 (6.1)* | 60.2 (6.3)* |
| Occlusion score | 65.7 (80.2)* | 103.5 (89.2)* |
| Body mass index | 25.3 (4.2)* | 26.6 (5.0)* |
| Exercise index | 59.2 (40.5)† | 52.2 (41.5)† |
| Smoking history index | 2.2 (1.4) | 2.3 (1.4) |
| Weekly alcohol intake (gm) | 69 (102) | 60 (129) |
| Alcohol drinkers (%) | 28.6 | 21.6 |
| Current smokers (%) | 20.9* | 13.4* |
| Ever smokers (%) | 52.3 | 52.3 |
| Parental history of heart disease (%) | 55.2 | 61.6 |
| Personal history of (%) | | |
| Hypertension | 56.2 | 57.3 |
| Diabetes | 10.5 | 11.8 |
| Angina | 72.1 | 68.4 |
| Previous MI | 31.8 | 39.5 |

*$p < 0.01$.
†$p < 0.05$.

Statistical analyses of univariate comparisons between estrogen users and nonusers were done with the unpaired *t* test for continuous variables and the $\chi^2$ test for frequency data.[32] Multivariate analyses used analysis of variance and covariance and stepwise multiple regression methods.[33] The square root transformations of the three variables with nonnormal distributions (smoking history index, alcohol intake, and triglyceride levels) were also used in independent statistical analyses. The transformed variables differed only slightly from the raw data in relation to estrogen use, and only the results of analyses with the raw (untransformed) data are reported. All statistical analyses used the SPSSX statistical package (SPSS, Inc., Chicago, 11).[34]

## RESULTS

The study population of 933 postmenopausal women consisted of 154 (16.5 %) users of estrogen and 779 (83.5%) nonusers (Table I). The ages of the women in the study ranged from 50 to 75 years; the mean age of users (58.6 years) was significantly younger than that of nonusers (60.2 years). Estrogen users also had a significantly lower mean occlusion score than did nonusers.

**Table II.** Multiple regression equation for variables significantly associated with coronary occlusion scores by univariate analysis

| | *Regression coefficients†* | | | |
|---|---|---|---|---|
| *Predictor variables** | *Unstandardized* | *Standardized* | *F statistic* | *Significance level‡* |
| Estrogen user (yes/no) | −34.95 | −0.15 | 19.64 | <0.01 |
| Age at angiography (yr) | 2.13 | 0.15 | 18.68 | <0.01 |
| Exercise index | −0.14 | −0.16 | 3.61 | NS |
| Current smoker (yes/no) | 6.88 | 0.03 | 0.68 | NS |
| Body mass index | 1.63 | 0.01 | 0.15 | NS |
| Variance in occlusion scores explained by these five variables ($R^2$) = 0.052. | | | | |

*Variables are shown in their order of entry into the stepwise equation.
†Regression coefficients are adjusted for all the other variables in the equation.
‡Numbers indicate the probabilities of the relationships between coronary occlusion scores and each predictor variable due to chance. NS = not statistically significant ($p > 0.05$). Probabilities are adjusted for all of the other variables in the equation.

When users of postmenopausal estrogen were compared with nonusers on other suspected risk factors for coronary occlusion, significant differences were also observed for body mass index, exercise index, and percent current smokers (Table I). Estrogen users were more likely to have a lower body mass index, and a higher

exercise index and were more likely to be current smokers. However, no significant differences were observed for smoking history index (which measured lifetime smoking history), weekly alcohol intake, percent Alcohol drinkers, percent ever-smokers, and percent with a parental history of heart disease. There were also no significant differences in the proportions of users and nonusers with histories of parental heart disease or personal histories of hypertension, diabetes, angina, or previous MI. In the latter category the largest percentage difference was for previous MI (31.8% for users and 39.5% for nonusers). The $\chi^2$ for this comparison on the basis of cell frequencies was 3.24 (1 degree of freedom, $p = 0.07$). The higher rate of previous MI among nonusers was independent of their older ages and consistent with either a protective effect of postmenopausal estrogen or a higher rate of cessation of estrogen use by women who experienced an MI. However, even among women with previous MIs users still had significantly lower levels of occlusion than did nonusers (data not shown). Therefore cessation of estrogen use by women with previous MIs and their misclassification as nonusers could not account for the higher levels of coronary occlusion among nonusers.

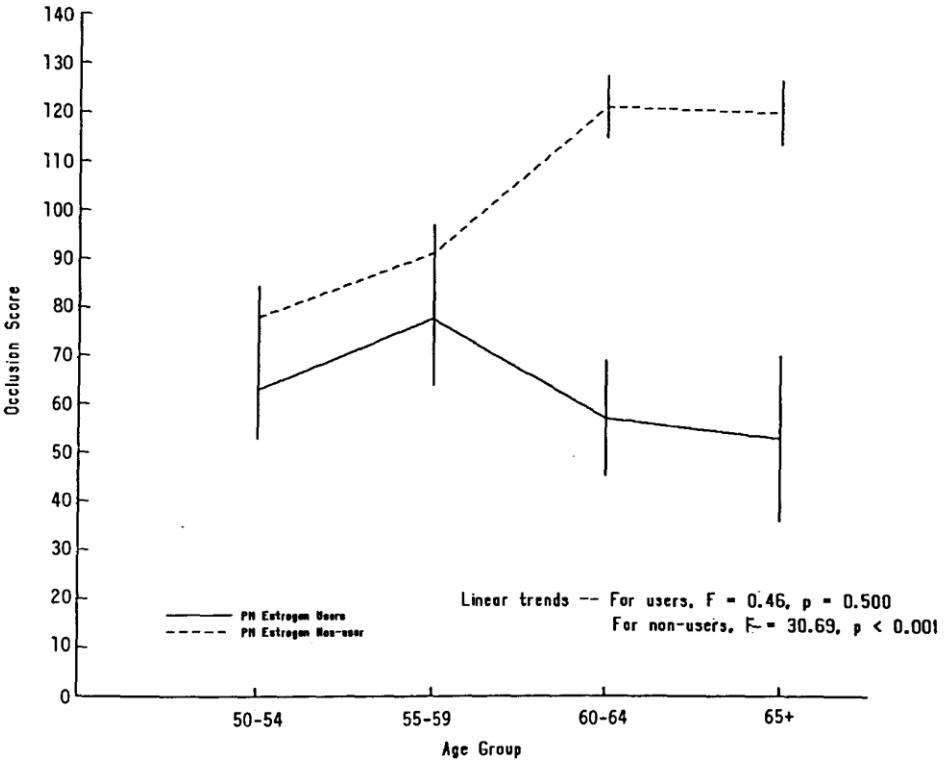


**Fig. 1.** Occlusion scores by age groups for postmenopausal estrogen users and nonusers. The numbers of users and nonusers in each age group are 48/174 (50 to 54 years), 47/224 (55 to 59 years), 35/203 (60 to 64 years), and 24/178 (65+ years).

Additional comparisons revealed no significant differences between users and nonusers in number of pregnancies, number of children, or duration between menopause and angiography (data not shown).

Fig. 1 shows the mean (± SE) occlusion scores by age groups for postmenopausal estrogen users and nonusers. In each age group users had lower occlusion scores than did nonusers, but the divergence Was greatest in the oldest groups (≥60 years). The statistical test for linear trend in occlusion scores with age, which was based on analysis of variance, indicated a highly significant increasing trend for nonusers, but no significant trend among estrogen users.

To assess their combined effects on coronary occlusion, the variables with significant univariate relationships (age, body mass index, exercise index, and current smoker status) were included in a regression model with postmenopausal estrogen use to predict occlusion scores (Table II). Estrogen use was the first variable to enter the stepwise regression equation and was the strongest independent predictor of occlusion scores.

**Table III.** Comparison of plasma lipid values between postmenopausal users and nonusers of estrogen, milligram per deciliter (SD)

| | *Users (n = 152)* | *Nonusers (n = 768)* |
|---|---|---|
| Total cholesterol | 244.4 (48.2) | 246.7 (53.9) |
| Triglycerides | 177.5 (97.5) *(n = 29)* | 172.7 (173.7) *(n = 218)* |
| LDL-cholesterol | 153.7 (45.6) | 159.2 (47.1) |
| HDL-cholesterol | 58.7 (18.1)* | 46.4 (14.4)* |
| Total/HDL-cholesterol | 4.8 (1.9)* | 5.4 (1.9)* |

*$p < 0.001$.

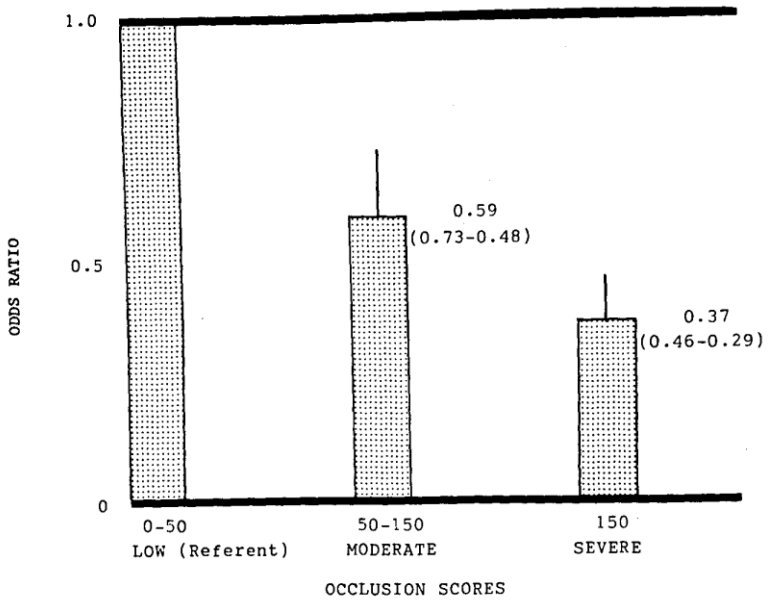


**Fig. 2.** Odds ratios for postmenopausal estrogen use among women with moderate and severe levels of coronary artery occlusion adjusted for age, current smoking status, exercise index, and body mass index. Women with low occlusion scores (0 to 50) were the referent group. *Vertical lines* above the bars represent the 95% confidence limits.

The regression coefficients in the table are adjusted for each of the other independent variables in the equation. The sign of the coefficient for estrogen use is negative, which indicates that it was associated with lower occlusion scores. Other than estrogen use, only age at the time of angiography was a significant predictor of occlusion scores in this model. Current smoking status, body mass index, and exercise were not significant predictors. Together these independent variables explained about 5% of the variance in occlusion scores as indicated by $R^2$.

The apparent protective effect of estrogen for coronary artery disease is also evident in the lower odds ratios of estrogen use among women with moderate and severe levels of coronary occlusion (Fig. 2). Adjusted for age, current smoker status, exercise index, and body mass index, the odds ratio for estrogen use among women with moderate occlusion (i.e., occlusion scores between 51 and 150) is 0.59 (95 % confidence interval, 0.48 to 0.73) and for women with severe occlusion (i.e., scores >150) the odds ratio is 0.37 (95% confidence interval, 0.29 to 0.46), which indicates that the rates of estrogen use among women with moderate and severe occlusion were significantly lower than the rate among women with low occlusion scores.

Once it was determined that postmenopausal estrogen use was associated with lower levels of coronary artery occlusion, independent of other suspected risk factors, we conducted further analyses to investigate the potential role of plasma lipids. The model we tested asked whether plasma lipids could serve as physiologic

intermediaries between exogenous estrogen and coronary occlusion. In this manner, lipids were treated separately as possible explanatory variables rather than as confounding variables.

Comparisons of unadjusted plasma lipid values between postmenopausal users and nonusers of estrogen are given in Table III. Total cholesterol and triglyceride levels were obtained for almost the entire study population, whereas tests to discriminate HDL- and LDL-cholesterol factions were available on patients since 1978. Statistically significant differences in HDL-cholesterol levels and the ratio of total to HDL cholesterol existed between users and nonusers. Other plasma lipid levels were not significantly different between the two groups.

The relationship between plasma lipids and occlusion scores was examined in two separate regression models (Table IV). In model A for the total study sample, plasma total cholesterol was the most important predictor of occlusion scores. In addition age at angiography, postmenopausal estrogen use, and plasma triglyceride levels were each independently significant predictors. The variance in occlusion scores explained by all of the variables in this model was slightly more than 10%.

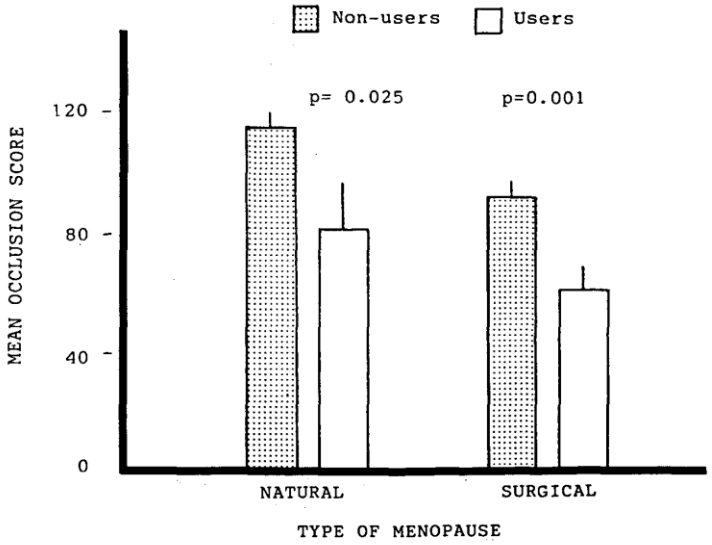


**Fig. 3.** Age-adjusted occlusion scores for users and nonusers of postmenopausal estrogens by type of menopause. *Vertical lines* above the bars represent standard errors.

**Table IV.** Multiple regression equation for plasma lipids, age at angiography, and postmenopausal use of estrogen on coronary occlusion scores

| | *Regression coefficients** | | | |
|---|---|---|---|---|
| *Predictor variables†* | *Unstandardized* | *Standardized* | *F statistic* | *Significance level‡* |
| Model A (n = 920) | | | | |
| Total cholesterol | 0.35 | 0.21 | 37.59 | 0.01 |
| Age at angiography | 2.22 | 0.15 | 22.86 | 0.01 |
| Estrogen user (yes/no) | −34.79 | −0.15 | 21.51 | 0.01 |
| Triglycerides | 0.04 | 0.08 | 5.11 | 0.02 |
| Variance in occlusion scores explained by the four variables in model A ($R^2$) = 0.104 | | | | |
| Model B (n = 247) | | | | |
| HDL-cholesterol | −1.41 | 0.26 | 16.41 | 0.01 |
| LDL-cholesterol | 0.47 | 0.18 | 14.84 | 0.01 |
| Age at angiography | 1.52 | 0.12 | 4.14 | 0.04 |
| Estrogen user (yes/no) | −25.16 | 0.10 | 2.46 | NS |
| Variance in occlusion scores explained by the four variables in model B ($R^2$) = 0.173 | | | | |

*Regression coefficients are adjusted for all of the other variables in the equation.
†Variables are shown in their order of entry into the stepwise equation.
‡Numbers indicate the probabilities of the relationships between coronary occlusion scores and each predictor variable due to chance. NS = not statistically significant ($p > 0.05$). Probabilities are adjusted for all of the other variables in the equation.

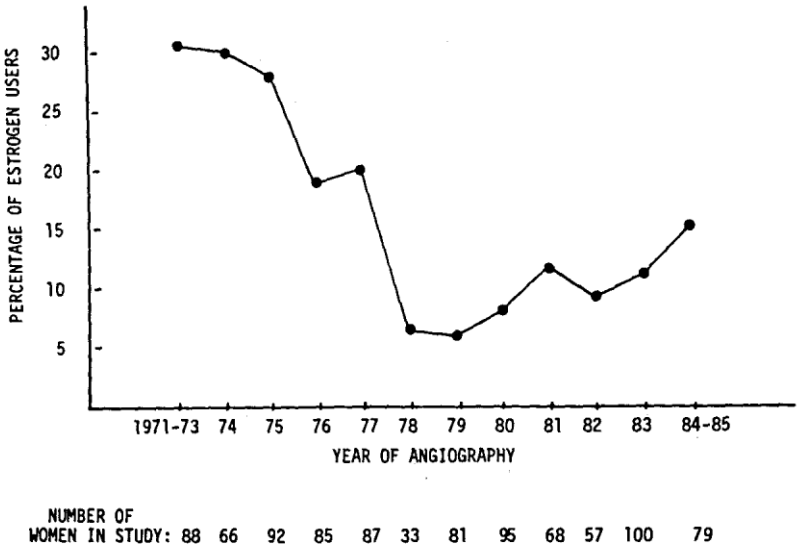


**Fig. 4.** Percent postmenopausal estrogen users in present study by year of angiography.

**Table V.** Multiple regression of CHD risk factors on coronary artery occlusion scores

| | *Regression coefficients* | | |
|---|---|---|---|
| *Entry order* | *Unstandardized* | *Standardized* | *F statistic** |
| Previous MI | 38.77 | 0.23 | 51.83 |
| Cholesterol | 0.31 | 0.19 | 40.83 |
| Smoking Index | 10.59 | 0.18 | 34.81 |
| Age | 2.05 | 0.16 | 27.04 |
| Hypertension | 27.65 | 0.16 | 27.95 |
| Estrogen use | −28.54 | −0.11 | 14.12 |
| Alcohol | −1.52 | −0.05 | 4.60 |
| | | $R^2 = 0.185$ | |

*All seven variables were statistically significant, $p < 0.05$.

In regression model B for the subgroup with plasma HDL- and LDL-cholesterol values, the strongest independent predictor of occlusion scores was HDL cholesterol, with higher HDL-cholesterol values associated with lower occlusion scores. LDL cholesterol and age at angiography were also significant predictors, with higher values of each associated with higher occlusion scores. Estrogen use was not significantly related to occlusion scores in this model and entered the stepwise equation after the three significant variables. The total amount of variance in occlusion scores explained by the variables in this equation was more than 17%, as indicated by the $R^2$. The major finding of this analysis is that inclusion of total cholesterol and triglyceride levels in the regression equation did not alter the significant negative association between estrogen use and coronary occlusion, but that inclusion of HDL cholesterol in the equation substantially reduced that association so that it was no longer statistically significant. This is consistent with the explanation that HDL cholesterol mediates the effect of estrogen on coronary occlusion.

Since data on HDL- and LDL-cholesterol levels were available only for patients who had their angiographies in recent years, we reanalyzed models A and B including a new variable, year of angiography, and also compared triglyceride and total cholesterol values between patients with LDL- and HDL-cholesterol determinations and earlier patients without these determinations. There have been significant changes in the use of postmenopausal estrogen during the 18 years since the beginning of the Registry, but year of angiography was not a significant predictor of occlusion scores and did not modify the significant inverse relationship between postmenopausal estrogen use and occlusion scores (model A) or the fact that postmenopausal estrogen use was not significantly associated with occlusion with HDL cholesterol in the equation (model B).

The distributions of triglyceride and cholesterol values were similar for women with and without LDL- and HDL-cholesterol determinations. Mean age-adjusted triglyceride values were virtually identical for the two groups, but the mean age-adjusted cholesterol value was lower for the group with HDL determinations (234.7 vs 231.8 mg/dl, $p = 0.07$). Nevertheless, the relationship between estrogen use and occlusion scores was similar for women with and without LDL and HDL determinations, and the regression analyses in Tables I and IV (model A) did not differ notably when done separately for each group.

Comparisons of other drug and medication use showed that postmenopausal estrogen users had significantly greater use of antacids, thyroid medication, and tranquilizers/sedatives than had nonusers' and significantly less use of beta-blockers. However, use of these other agents was not related to the degree of coronary occlusion except for the beta blockers: women who used beta blockers had significantly higher occlusion scores than women who did not (data not shown). Separate analysis of betablocker users showed that even among these women estrogen users had significantly lower occlusion scores. Therefore differences in occlusion scores between estrogen users and nonusers could not be attributed to use of these other medications, including beta blockers.

Finally, users of postmenopausal estrogen had lower levels of coronary occlusion than did nonusers, regardless of whether menopause was natural or surgical (Fig. 3). Among women who experienced natural menopause, the mean occlusion score for nonusers was 115 compared with a mean score of 81 for users. Among women who had surgical menopause, the mean occlusion score for nonusers was 92 compared with a mean score of 61 for users. Both of these differences were statistically significant and independent of age. The lower occlusion scores of the women in the surgical menopause groups are probably accounted for by their younger ages.

When postmenopausal estrogen use was combined in a regression model with other risk factors for heart disease, it was an independent, statistically significant predictor of occlusion scores (Table V). Estrogen use entered the stepwise model after history of previous MI, plasma total cholesterol, smoking, age, and hypertension but before alcohol intake and was inversely correlated with occlusion scores. The total variance in occlusion scores explained by these seven risk factors combined was 18.5 %.

## DISCUSSION

Our analysis of female patients undergoing angiography has shown that those who used postmenopausal estrogen had significantly lower levels of coronary artery occlusion. The statistical significance of the association and the progressively lower odds ratios of estrogen use among women with moderate and severe levels of occlusion indicate that this association is not likely to be the result of chance. The protective effect of postmenopausal estrogen against the underlying atherosclerotic process of CHD and evidence of an intermediary effect of plasma HDL cholesterol described by these results help explain the association between postmenopausal estrogen use and lower rates of CHD mortality and symptoms observed by other investigators.[5,7,8,18]

Methodologic issues, including possible biases associated with studies of patients undergoing angiography, have been extensively reviewed by Pearson.[35] Angiographically determined coronary occlusion assesses CHD more directly than symptoms (e.g. anginal pain) or mortality data. The most important disadvantage of using this outcome measure is the selective nature of patients who undergo arteriography. Cases of sudden death from CHD are not represented in these patients, and mild cases of CHD are probably underrepresented. In previous studies of postmenopausal estrogen use and heart disease, differences were not observed in the relationship between estrogen use and fatal vs nonfatal CHD.[4] Whether there is an association between postmenopausal estrogen use and preclinical CHD remains to be seen.

Another potential source of bias is the possibility that women who used postmenopausal estrogen received more medical attention and therefore were referred for angiography on the basis of less severe indicators. This possibility is not supported by the data on other morbidity for women in this study. Users did not have the

higher rates of comorbidity or CHD symptoms, including chest pain and angina, that might be expected if they were given more medical attention than nonusers. In addition, stratified analyses, which compare patients with and without angina or previous MI, showed that the estreogen-occlusion relationship was not dependent on those variables.

The extent to which perceived risks of heart disease influenced postmenopausal estrogen use during the study period is unclear, although the perception of a higher risk of endometrial cancer appears to have been an overriding consideration.[4] The temporal pattern of estrogen use among patients in the study indicates that these women were not atypical compared with other U.S. women. In Fig. 4, the percentages of postmenopausal estrogen users in the present study are depicted by year of angiography. Before 1975, more than 30% used postmenopausal estrogen; after 1975 a sharp drop occurred in the percentage of estrogen users, presumably in response to concern over the reported link between estrogen and endometrial cancer.[36] Since 1980, the percentage of women using estrogen after menopause has gradually increased. This usage pattern is similar to that described for the total U.S. population.[3,37] The overall percentage of estrogen users in this study (16.5%) was lower than the 24% to 35% reported in other study groups.[5,6,18] However, those previous studies obtained information on estrogen use before 1976 when postmenopausal estrogen use was considerably higher than in more recent years. In the study reported here, estrogen use was measured at the time of angiography (between 1972 and 1985), but three fourths of the patients had their angiographic examination during the period of low usage after 1975, which accounted for the lower overall percentage of estrogen users in this study.

Determination of postmenopausal estrogen use in this study was limited to 3 months before angiography. Patients who had used estrogen only before that time were misclassified as "nonusers," which tended to reduce the differences between the user and nonuser groups. Although no estimate of the extent of this misclassification is available, the strengths of the associations between estrogen use and both coronary occlusion and HDL cholesterol are probably underestimated. Therefore it is possible that the effect of postmenopausal estrogen use on the risk of coronary occlusion may be actually greater than that observed. The opposite effect of this misclassification could have occurred if women with more severe heart disease stopped taking estrogen earlier than 3 months before angiography, which would leave fewer patients with severe disease in the user group. Several pieces of evidence suggest that this latter possibility was not a substantial factor in this study. First, although a lower proportion of users had a previous MI, results of parallel analyses for women with and without a previous MI were essentially identical in describing an inverse relationship between estrogen use and the degree of coronary occlusion. Second, although symptoms are not reliable indicators of the degree of coronary occlusion,[38] neither angina, nonanginal chest pain, nor dyspnea was significantly more prevalent in either group.

The manner in which postmenopausal use of estrogen influences the risk of heart disease may involve plasma lipids.[5,15,16,18] The oral estrogen used by the women in this study may result in higher plasma HDL-cholesterol levels through hepatic stimulation. The findings of several other studies are in agreement with this HDL-cholesterol--elevating effect of estrogen.[4,19,20,39,40] However differences between estrogen users and nonusers in total and LDL cholesterol and triglycerides found in some other studies[4,5,19,41-43] were not evident among the postmenopausal estrogen users in the present study. This suggests that a primary effect of postmenopausal estrogen among women in this study may have been to reduce the risk of CHD by increasing plasma HDL-cholesterol levels.

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