Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study

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ABSTRACT A cohort of 2270 white women, aged 40-69 years at baseline, were followed for an average of 8.5 years in the Lipid Research Clinics Program Follow-up Study. There were 44 deaths due to cardiovascular disease among the 1677 nonusers of estrogens and six cardiovascular disease deaths among the 593 estrogen users. The age-adjusted relative risk (RR) of cardiovascular disease deaths in users compared with nonusers was 0.34 (95% confidence limits 0.12 to 0.81). After multivariable adjustment for potential confounding factors (age, blood pressure, and smoking), the estimated RR for estrogen use was 0.37 (95% confidence limits 0.16 to 0.88). Analyses were done to explore whether these results could be due to selection bias for estrogen use. However, the prevalence of cardiovascular disease at baseline was slightly higher in estrogen users (12%) than in nonusers (10%); furthermore, the exclusion of all women with prevalent cardiovascular disease at baseline did not alter the apparent protective effect of estrogen use on cardiovascular disease mortality (RR = 0.42, 95% confidence limits 0.13 to 1.10). Additional analyses examining the complex association between estrogen use, lipoprotein levels, and cardiovascular disease mortality suggest that the protective effect of estrogen is substantially mediated through increased high-density lipoprotein levels.

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THE ASSOCIATION between exogenous estrogen use and cardiovascular disease is controversial. Clinical trials of estrogen use in men1-3 and case-control studies of oral contraceptive use in women4-7 are frequently cited as evidence that exogenous estrogen use increases the risk of cardiovascular disease. Recently, the Framingham Study has reported that use of noncontraceptive estrogens increases the risk of cardiovascular disease in postmenopausal women.8

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In contrast to the above-mentioned studies, other reports have suggested that estrogen use protects against the development of cardiovascular disease. Evidence from animal9-11 and autopsy studies12-14 shows that exogenous estrogens may inhibit the development of atherosclerotic coronary lesions. Furthermore, the majority of studies of noncontraceptive estrogen use in women suggest that estrogens either protect against or do not increase the risk of cardiovascular disease.15-25

Given the conflicting evidence on exogenous estrogen use and cardiovascular disease risk, our purpose in this analysis is to examine prospectively the association of estrogen use and subsequent cardiovascular disease mortality in a cohort of women.

Methods

Detailed descriptions of the study population have been published previously26, 27 but are briefly reviewed here. All women included in this study were participants in the Lipid Research Clinics (LRC) Prevalence Study of cardiovascular disease, conducted in 10 North American clinics between 1972 and 1976. One of the primary purposes of the LRC Prevalence Study was to determine the association of lipid and lipoprotein patterns with coronary heart disease and other cardiovascular diseases.

Participants were initially identified in selected target popula-
information on menstrual history questions (n = 25) were excluded. These exclusions resulted in a final sample of 2270 women, 593 of whom reported noncontraceptive estrogen use at baseline and 1677 who reported nonuse.

All-cause and cardiovascular mortality rates were based on number of deaths, age at death, and person-years of observation. The women were followed for an average of 8.5 years, and so those aged 60 to 69 years at visit 2 could contribute person-years and events to the 70 to 79 year category. Cardiovascular death rates were age adjusted by the indirect method using the cardiovascular mortality rates (ICD 390-448) of the 1976 U.S. white female population as the standard. Ninety-five percent confidence limits (CL) on the relative risks were calculated. The Cox proportional hazards model was used to assess the independent effect of estrogen use after adjustment for potentially confounding factors.

Persons with cardiovascular disease at visit 2 were defined to include those who (1) reported a history of myocardial infarction or stroke; (2) reported medication use for angina pectoris, or had a Rose questionnaire diagnosis or angina, or had treadmill angina; (3) reported using antiarrhythmic agents, digitalis, or propranolol; (4) were excluded from the treadmill test because of congestive heart failure, R-on-T type premature ventricular contractions, ventricular tachycardia, parasympathetic focus, atrial flutter, or atrial fibrillation; or (5) had electrocardiographic evidence of diagnostic or equivocal myocardial infarction.

Results

Previous analysis in this cohort showed that after an average follow-up of 5.5 years, women using estrogens at visit 2 had a significantly lower risk of death from all causes combined compared with women not using estrogens (relative risk [RR] = 0.37, 95% CL = 0.17 to 0.79). That analysis was based on a total of nine deaths in estrogen users (3401 person-years of observation) and 63 deaths in nonusers (9386 person-years of observation). The present analysis is based on 53 additional deaths and 6594 additional person-years of follow-up and confirms the findings of the earlier report on total mortality. That is, after an average of 8.5 years of follow-up, estrogen users, compared with nonusers, have a significantly lower risk of death from all causes (RR = 0.54, 95% CL = 0.29 to 0.79).*

Table 1 presents a listing of the death certificate ICD codes (underlying cause of death) for women defined by the Mortality Classification Panel to have died from cardiovascular disease. Fifty-five percent (24/44) of the cardiovascular deaths among the nonusers and 50% (3/6) of deaths among the estrogen users were coded on the death certificate as being due to either ischemic
TABLE 1
Death certificate code for underlying cause of death in women judged to have died from cardiovascular disease by estrogen use at visit 2

<table>
<thead>
<tr>
<th>Death certificate cause of death</th>
<th>ICD code</th>
<th>Nonuser</th>
<th>User</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>410-412</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>425-427</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>430-437</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>440-448</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>250</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Other a</td>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>44</td>
<td>6</td>
</tr>
</tbody>
</table>

*Includes ICD 279 (deficiency of humoral immunity), ICD 395 (rheumatic aortic stenosis), and ICD 492 (emphysema) among the nonusers and ICD 450 (pulmonary embolism) and 519.3 (diseases of the mediastinum) among estrogen users.

The overall prevalence of cardiovascular disease at baseline was 12% in estrogen users (74/593) and 10% in nonusers (162/1677). Four percent of both users (n = 23) and nonusers (n = 60) reported a prior myocardial infarction or stroke. Estrogen users were more likely to take diuretics than nonusers (15% vs 10%). However, there were no other differences between users and nonusers in reported consumption of selected cardiovascular medications.

Cardiovascular mortality rates were recalculated for estrogen users and nonusers after the exclusion of all women with prevalent cardiovascular disease at baseline. After excluding prevalent cases, the mortality rate in users was 12.8/10,000 compared with 30.2/10,000 in nonusers (RR = 0.42, 95% CL = 0.13 to 1.10). Among women with prevalent cardiovascular disease at visit 2, the cardiovascular death rate in users was 13.8/10,000 compared with 66.3/10,000 in nonusers.

The reported prevalence of cardiovascular disease, defined as the occurrence of myocardial infarction, stroke, hypertension, hyperlipidemia, diabetes, or peripheral vascular disease, was examined in all first-degree relatives of estrogen users and nonusers. Fifty-four percent of users and 56% of nonusers reported that their fathers had cardiovascular disease. When histories of cardiovascular disease in mothers, siblings, and children of estrogen users and nonusers were examined, users reported a slightly higher per-

TABLE 2
Age-specific and age-adjusted cardiovascular disease death rates (per 10,000) by estrogen use at visit 2

<table>
<thead>
<tr>
<th>Age at risk</th>
<th>Nonuser (n = 1677)</th>
<th>User (n = 593)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>(95% CL)</td>
</tr>
<tr>
<td>40–49</td>
<td>0.0 (0/3315)</td>
<td>0.0 (0/710)</td>
</tr>
<tr>
<td>50–59</td>
<td>16.2 (9/5549)</td>
<td>4.5 (1/2245)</td>
</tr>
<tr>
<td>60–69</td>
<td>39.1 (16/4907)</td>
<td>11.8 (2/1701)</td>
</tr>
<tr>
<td>70–79</td>
<td>150.8 (19/1260)</td>
<td>61.7 (3/486)</td>
</tr>
<tr>
<td>Crude rate</td>
<td>30.9 (44/14221)</td>
<td>11.7 (6/5142)</td>
</tr>
<tr>
<td>Age-adjusted rate</td>
<td>38.1</td>
<td>13.1</td>
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<tr>
<td>RR</td>
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The Cox proportional hazards model was used to explore the relationship between estrogen use and cardiovascular mortality while controlling for potentially confounding variables. After adjustment for age, systolic blood pressure, and smoking, estrogen use at baseline was negatively and significantly associated with cardiovascular mortality (β = 0.98, p = .02). The addition of total cholesterol to the model did not materially alter the association of estrogen with cardiovascular death (β = 0.82, p = .06).

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percentage of relatives with cardiovascular disease than nonusers (66% vs 62%, 43% vs 40%, and 9% vs 8%, respectively).

In addition, 44% of estrogen users and 40% of non-users were selected into the study because of elevated lipid levels. Among the women randomly selected from target populations, the direct age-adjusted cardiovascular mortality rate (per 10,000) was 13.1 in users and 27.1 in nonusers (RR = 0.48, 95% CL = 0.00 to 1.00). Among women selected because of elevated lipid levels, the direct age-adjusted cardiovascular death rate was 8.2 in estrogen users and 38.7 in nonusers (RR = 0.21, 95% CL = 0.00 to 0.51). In separate Cox model analyses (with age, smoking, and blood pressure as covariates), estrogen use was negatively associated with cardiovascular mortality in women randomly selected to visit 2 and in women selected because of elevated lipid levels.

A history of cigarette smoking was common among those who died from cardiovascular disease. Of the six estrogen users who died from cardiovascular disease, four were current smokers and two were former smokers at visit 2. Among the 44 cardiovascular deaths in nonusers, 18 were in current smokers, 12 occurred in exsmokers, and 14 were in women who had never smoked. When cardiovascular death rates were calculated separately for smokers and nonsmokers, estrogen use was negatively associated with cardiovascular death in all smoking categories. (The cardiovascular mortality rate [per 10,000] in nonsmokers, current smokers, and exsmokers in estrogen users was 0.0, 35.8, and 16.2, respectively; in non-users, the cardiovascular death rate for nonusers was 17.1, for smokers 52.5, and for exsmokers, 46.0).

In many respects, the characteristics of estrogen users and nonusers at baseline were similar (table 3). However, estrogen users had significantly higher high-density lipoprotein (HDL) (67 vs 57 mg/dl) and triglyceride levels (167 vs 142 mg/dl) and significantly lower low-density lipoprotein (LDL) levels (145 vs 156 mg/dl) than did nonusers. Additionally, estrogen users were better educated and thinner than nonusers.

Cardiovascular mortality rates were calculated separately for those with less than a high school education, women who were high school graduates, and women with at least some post–high school education. At each education level, estrogen users had lower cardiovascular death rates (per 10,000) than nonusers (e.g., less than high school, 14.0 vs. 39.6; high school graduate, 16.5 vs 37.0; and greater than high school, 8.9 vs 23.5). Inclusion of education as a covariate in the Cox model (with age, systolic blood pressure, smoking, and total cholesterol) did not alter the magnitude of the negative association between estrogen use and cardiovascular mortality ($\beta = -0.82$, $p = .06$).

The association between estrogen use and cardiovascular death also was examined while controlling in the Cox model for body size. In this model (with age, systolic blood pressure, smoking, total cholesterol, and body mass index as covariates), estrogen use was negatively associated with subsequent cardiovascular death ($\beta = -0.75$, $p = .09$).

Exercise, hysterectomy/oophorectomy status, alcohol use, and LRC clinic were also considered as factors that might be confounding the association between estrogen use and cardiovascular mortality. However, inclusion of any of these factors as covariates in the multivariable model did not alter the negative association between estrogen use and cardiovascular mortality.

Estrogen use is known to modify lipid and lipopro-
tein levels.33-36 Therefore, additional analyses with Cox models were done to assess whether the effects of estrogen use on cardiovascular mortality were mediated through estrogen-induced changes in lipid and lipoprotein levels. An initial multivariable model (table 4) included only age, blood pressure, smoking, and estrogen use as covariates. Estrogen use was negatively (β = −0.98) and significantly (p = .02) associated with subsequent cardiovascular mortality in this model. When total cholesterol was added to the first model, the β-coefficient for estrogen use was −0.82 and p = .06. When HDL and LDL were substituted for total cholesterol in the third model, the coefficient for estrogen use was reduced by over 40% (β = −0.47, p = .29). HDL was inversely and significantly associated with cardiovascular disease mortality in this cohort.

Because of small numbers of cardiovascular deaths in users, more definitive multivariable analysis on the complex association of estrogen use, HDL, LDL, and cardiovascular mortality could not be done. Inclusion of triglycerides or very low-density lipoprotein in the Cox model did not alter the negative association between estrogen use and cardiovascular mortality.

Discussion

In this prospective study, women using noncontraceptive estrogens at baseline had a significantly lower risk of fatal cardiovascular disease during a 8.5 year follow-up period than nonusers. In every age category where cardiovascular deaths occurred, estrogen users had cardiovascular mortality rates lower than those of nonusers. Statistical adjustment (using the Cox model) for major cardiovascular risk factors (age, smoking, and blood pressure) did not alter the significant negative association between estrogen use and subsequent cardiovascular mortality.

SMRs for estrogen users and nonusers were calculated to test the hypothesis that the difference in cardiovascular mortality rates between users and nonusers was caused by excessively high death rates among the nonusers rather than by low rates among the users. The SMR of 67 seen in the nonusers indicates that these women experienced only two-thirds of the cardiovascular death rate of white U.S. women. Such a reduction in mortality is consistent with the “healthy participant effect” seen in observational studies and confirms that the difference in cardiovascular death rates between estrogen users and nonusers is due to the lower rate in the users.

Because estrogens may not have been prescribed or may have been discontinued before baseline in women at an increased risk of cardiovascular disease, additional analyses were done to identify possible selection biases for estrogen use. Overall, there were no significant differences between estrogen users and nonusers in the prevalence of cardiovascular disease at baseline (including prior myocardial infarction or stroke), the frequency of a family history of cardiovascular disease, or (with the exception of diuretics) the use of cardiovascular medications. Given these findings, it seems unlikely that users were selected for estrogen use because they had less cardiovascular disease than nonusers. Nonetheless, the possibility of selection bias for estrogen use cannot be excluded in this or any other observational study.

Estrogen use was negatively associated with subsequent cardiovascular mortality in women randomly selected from target populations, and in those selected because of elevated lipid levels. The more pronounced estrogen effect in women with elevated lipids remains to be explained. However, this observation is compatible with several hypotheses, including (1) estrogen use is more protective against cardiovascular death in hyperlipidemic women than in women with a broader range of lipid levels and (2) given the overlap in the confidence limits of the relative risks in the two groups, lipid levels do not confound the association between estrogen use and cardiovascular risk.

An additional explanation for the greater protective effect of estrogen use in women with high lipid levels may be that the etiology and consequences of hyperlipidemia in estrogen users are different from those in nonusers. Because estrogen use increases triglyceride
and HDL levels, some women with elevated lipid levels may have been selected to visit 2 because of estrogen-induced hypertriglyceridemia or hypercholesterolemia, rather than "true" hyperlipidemia. Given the etiology of their hyperlipidemia, these women may not be at an increased risk of cardiovascular death.

Estrogen users and nonusers were different from each other in several important characteristics, and thus the possibility that these factors may be confounding the association between estrogen use and cardiovascular mortality was also explored. Although estrogen users were both thinner and better educated than nonusers, these variables did not account for the lower risk in users.

Estrogen users were not different than nonusers in their exercise habits, alcohol consumption, or hysterectomy/oophorectomy status, and adjustment for these variables in multivariable models did not alter the negative association between estrogen use and cardiovascular death. Furthermore, inclusion of LRC clinic in the model did not alter the association between estrogen use and cardiovascular mortality. Given these results, it is unlikely that the effects of estrogen on cardiovascular mortality are explained by any of these potential confounders. However, the possibility remains that some factor, as yet unidentified, is associated with both estrogen use and cardiovascular death. Given the magnitude of the difference between the estrogen user and nonuser cardiovascular mortality rates, the identification of such a factor, if it exists, would be of significant public health importance.

Although cigarette smoking was a significant predictor of cardiovascular mortality in this cohort, smoking patterns in estrogen users were not different from those in nonusers. Additionally, cardiovascular mortality rates were lower for estrogen users in every smoking category (current smokers, exsmokers, and nonsmokers), suggesting that the protective effect of estrogen is not modified by cigarette smoking. This finding is contrary to evidence from studies of cardiovascular disease and oral contraceptive use, where smoking acts synergistically with oral contraceptives to increase the risk of a cardiovascular event.

One reason that smoking may not interact with noncontraceptive estrogens is that these agents are different drugs than oral contraceptives. Oral contraceptives contain high doses of synthetic estrogens and nor-progestins, whereas noncontraceptive estrogens are low-dose natural estrogens without additional progestins. Thus it is possible that smoking exerts an interactive effect only when high doses of synthetic estrogens are used, when nor-progestins are used, or when the combination of these specific estrogens and progestins is present.

Estrogen users compared with nonusers had significantly higher mean HDL levels and significantly lower mean LDL levels. Given the strong association between these lipoproteins and cardiovascular mortality, it seemed plausible that the protective effect of estrogen use seen in this study may have been effected through estrogen-induced increases in HDL and decreases in LDL levels in users.

To test this hypothesis, several Cox models were computed, first excluding and then including lipids and lipoproteins as covariates. Estrogen use was negatively and significantly associated with cardiovascular disease mortality after adjustment for age, smoking, and blood pressure. Inclusion of total cholesterol as a covariate in this basic model did not materially alter the β-coefficient for estrogen use. However, substitution of HDL and LDL for total cholesterol in the model resulted in a substantial reduction in the coefficient for estrogen use. Additionally, HDL levels were negatively and significantly associated with subsequent cardiovascular death.

This finding is compatible with two hypotheses. The first is that the protective effect of estrogen use seen here is substantially mediated through estrogen-induced increases in HDL since (1) estrogens increase HDL levels, (2) HDL was negatively and significantly associated with cardiovascular death in this cohort, and (3) estrogen use was not significantly associated with cardiovascular mortality after inclusion of HDL in the model.

However, the coefficient for estrogen use remained negative after the inclusion of the lipoproteins in the multivariable model. Thus a second hypothesis, which cannot be tested with these data, is that estrogen use is protective through mechanisms additional to any effects on HDL. This hypothesis is supported by evidence from a recent animal study, which showed that estrogens retard atherogenesis by interacting directly with the arterial wall and by modifying plasma components other than lipoproteins.37

The results from this prospective study suggest that the occurrence of cardiovascular mortality in estrogen users is one-third of that in nonusers and that much, but not all, of the reduction in risk may be due to estrogen-induced changes in HDL levels. With the sole exception of the Framingham Study, other prospective reports of noncontraceptive estrogen and cardiovascular disease in women also show similar reductions in cardiovascular risk among estrogen users.15–19

The results from the Framingham Study suggest that
noncontraceptive estrogen use increases the risk of all cardiovascular disease. Specifically, it was reported that occurrence of stroke was significantly and positively associated with estrogen use and that the observed adverse effects of estrogen use on cardiovascular disease were compounded by cigarette smoking. In this study, deaths from cerebrovascular disease were included as end points. There was no evidence that estrogen users were at increased risk for death from stroke during the follow-up period, with an RR for cerebrovascular death in estrogen users compared with nonusers of 0.40 (95% CL = 0.01 to 3.07). As noted previously, smoking did not alter the effect of estrogen use and cardiovascular mortality.

There are several limitations to these data. Information on the type and dose of estrogen used and duration of estrogen use is not consistently available. This limits our understanding of the effects of estrogen on cardiovascular risk in that a dose-response association or a duration-of-use effect cannot be assessed.

Also, estrogen use was ascertained at only one point in time, and therefore users and nonusers may have either quit or begun estrogen use during the follow-up interval. The effect of these potential misclassifications as to estrogen use should bias our RR toward one. That is, if estrogen use "truly" reduces the risk of cardiovascular death, then inclusion of past or subsequent users in the nonuser group would tend to reduce the death rate in nonusers, i.e., the true cardiovascular mortality rate in the nonusers would be higher than observed. Classifying women who subsequently stopped using estrogens as users would tend to increase the death rate seen in the user group. Thus the true difference in mortality between estrogen users and nonusers may be even larger than we observed. If estrogen use has no effect on cardiovascular mortality, then misclassification would not affect the results. Finally, if estrogen use truly increases the risk of cardiovascular death, the likelihood of observing a statistically significantly lower cardiovascular risk in users is extremely small.

As in most observational studies, no knowledge was available as to why a woman was or was not prescribed estrogens. The possibility exists that despite the similar cardiovascular disease profile seen in users and nonusers, women who are prescribed these agents are different from nonusers in some as yet undefined but confounding way. It is not possible with these data to ascertain whether any behavioral traits and/or personality factors are associated with both estrogen use and cardiovascular death. However, if such factors exist, they need to be identified.

This study, and nearly all other studies of noncontraceptive estrogen use in women, has evaluated the association between cardiovascular disease and unopposed estrogens rather than estrogen cycled with progestins. This is because baseline data were ascertained from 1972 to 1976, before it was widely known that unopposed estrogen use increased the risk of endometrial cancer. Current medical recommendations call for the addition of a progestin to cyclic estrogen therapy.

Because progestins adversely affect both HDL and LDL levels and because much of the protective effect of estrogen use in this cohort appears to be mediated through increased HDL levels, the results seen in the cohort of women (i.e., lower cardiovascular mortality in estrogen users) may not be applicable to women using estrogen-progestin therapy.

In conclusion, in a cohort of women followed for an average of 8.5 years, those reporting estrogen use at baseline had a significantly lower risk of cardiovascular death than women not using estrogens. It is unlikely that estrogen users at baseline were selected for estrogen use because of cardiovascular health, since the prevalence of cardiovascular disease at baseline was slightly higher in users than in nonusers. Analyses examining the complex association between estrogen use, lipoprotein levels, and cardiovascular mortality suggested that the protective effect of estrogen is substantially mediated through increased HDL levels.

Given the limitations of this and all observational studies, and the potential public health implications, these results indicate a need to consider a clinical trial of noncontraceptive estrogen use in women. However, the relatively low rate of cardiovascular disease events in 40- to 69-year-old women would necessitate a large sample size and a lengthy duration of follow-up. Such an undertaking may not be feasible.

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Appendix


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Natta, M.S.; Patricia Wahl, Ph.D.; and Robert Wallace, M.D.

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