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Authors

Newton, Katherine M
LaCroix, Andrea Z
McKnight, Barbara
et al.

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Estrogen Replacement Therapy and Prognosis after First Myocardial Infarction

Katherine M. Newton,[1,2] Andrea Z. LaCroix,[1,2] Barbara McKnight,[3,5] Robert H. Knopp,[4] David S. Siscovick,[2,4] Susan R. Heckbert,[2] and Noel S. Weiss[2,5]

The effects of estrogen replacement therapy on prognosis in women with established coronary disease remain uncertain. The authors conducted a retrospective cohort study of 726 women (mean age, 66.2 years) who survived first myocardial infarction to hospital discharge from 1980 through 1991, while enrolled at Group Health Cooperative of Puget Sound in western Washington State. Estrogen replacement therapy after myocardial infarction (122 women) was ascertained from computerized pharmacy records. Reinfarctions (n = 135) and deaths (n = 183) through 1993 were identified, and relative risks were calculated. The relative risk for reinfarction associated with current estrogen replacement therapy after myocardial infarction, adjusting for age and time since infarction, was 0.64 (95% confidence interval (CI) 0.32–1.30), and that for past estrogen replacement therapy was 0.90 (95% CI 0.62–1.31). The relative risk for all-cause mortality associated with current estrogen replacement therapy was 0.50 (95% CI 0.25–1.00), and that for past estrogen replacement therapy was 0.79 (95% CI 0.56–1.09). While estrogen users were less likely than nonusers to have a history of diabetes or congestive heart failure, adjustment for these and additional prognostic factors altered risk estimates only slightly. Estrogen replacement therapy after first myocardial infarction was not associated with increased risk of reinfarction or mortality. This study provides reassurance regarding the safety of estrogen replacement therapy after myocardial infarction in women. *Am J Epidemiol* 1997;145:269–77.

estrogen replacement therapy; myocardial infarction; prognosis

Observational studies support the hypothesis that postmenopausal estrogen replacement therapy reduces the incidence of myocardial infarction (1, 2). However, established coronary disease is considered by some to be a contraindication to estrogen replacement therapy (3). To date, there is no direct evidence to support or refute such a belief. The purpose of this study was to evaluate the effect of estrogen replacement therapy on reinfarction and survival among women who survived a first myocardial infarction to hospital discharge.

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Abbreviations: CI, confidence interval; GHC, Group Health Cooperative of Puget Sound; ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification.

[1] Center For Health Studies, Group Health Cooperative of Puget Sound, Seattle, WA.
[2] Department of Epidemiology, University of Washington, Seattle, WA.
[3] Department of Biostatistics, University of Washington, Seattle, WA.
[4] Department of Medicine, University of Washington, Seattle, WA.
[5] Fred Hutchinson Cancer Research Center, Seattle, WA.
Reprint requests to Katherine M. Newton, Center For Health Studies, Group Health Cooperative of Puget Sound, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101–1448.

MATERIALS AND METHODS

Cohort identification

This retrospective cohort study was conducted at Group Health Cooperative of Puget Sound (GHC), a health maintenance organization in western Washington State. The study was approved by the institutional review boards at GHC, the University of Washington, and all participating hospitals. We attempted to identify all female enrollees hospitalized for incident acute myocardial infarction between January 1, 1980 and December 31, 1991. Eligibility criteria included 1) enrollment at GHC for at least 12 months at hospitalization; 2) postmenopausal status; 3) age less than 80 years; 4) survival to hospital discharge; 5) no prior cardiac arrest, coronary artery bypass graft surgery, coronary angioplasty, or stroke; 6) absence of contraindications to estrogen use, including thromboembolic events, renal failure, or recent diagnosis of breast or endometrial cancer; and 7) absence of diseases likely to be fatal within 6 months, including cancer of any type and advanced renal failure or pulmonary disease. Menopause was defined as amenorrhea for at least 6 months, menopausal symptoms (e.g., hot flashes) or age greater than 55 years for women with hysterectomy without bilateral oophorectomy, or documented

bilateral oophorectomy. Women aged 80 years and older were excluded due to their low prevalence of estrogen use.

Potential cases were identified by searching four GHC hospitalization databases for *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes indicative of acute myocardial infarction. All hospitalizations with admission or discharge diagnosis codes of acute myocardial infarction, ventricular fibrillation, or cardiac arrest (ICD-9-CM codes 410, 427.4, and 427.5) were selected. In addition, hospitalizations with diagnosis codes for acute ischemic heart disease (ICD-9-CM code 411), subacute ischemic heart disease (ICD-9-CM code 413), and chronic ischemic heart disease (ICD-9-CM code 414) were selected from the two databases that contained only admission diagnosis codes. With this approach, 3,714 women with possible myocardial infarctions were identified. Outpatient and inpatient records were then reviewed for eligibility. Only 105 records (2.8 percent) were not located. Potential cases were classified without knowledge of subsequent estrogen use by one investigator (K. M. N.) as having definite, probable, or no myocardial infarction on the basis of chest pain, cardiac enzymes, and electrocardiographic findings by using the algorithm developed for the Cardiovascular Health Study, based upon the American Heart Association Council on Epidemiology and Prevention criteria (4, 5). Electrocardiographic findings were accepted as read by the hospital cardiologist. When the electrocardiographic interpretation was incomplete, but necessary for coding the myocardial infarction, the electrocardiograms were copied and submitted for review to a GHC cardiologist, who read the electrocardiograms without knowledge of estrogen exposure or outcomes. After outpatient and inpatient record review, 726 women (638 definite myocardial infarctions and 88 probable myocardial infarctions) comprised the study cohort, and 2,883 women were excluded because they failed to meet the eligibility criteria. The reasons for exclusions were: no evidence of myocardial infarction (36.9 percent); intraoperative myocardial infarction, history of myocardial infarction, sudden cardiac arrest, coronary artery bypass surgery, or stroke (12.6 percent); in-hospital death (10.1 percent); premenopausal (10.4 percent); contraindications to hormone replacement therapy (6.6 percent); and failure to meet age, enrollment date, or admission date criteria or the presence of fatal or severe chronic diseases (8.4 percent). Exclusion of women with "probable myocardial infarction" had no effect on the results; thus, the findings are presented for the entire cohort.

Ascertainment and classification of hormone exposure

Postmenopausal hormone use was determined using GHC's computerized pharmacy records (6), which contain information for every prescription filled at GHC pharmacies since 1977. In a recent telephone survey at GHC, 97 percent of women reported filling all of their prescriptions for postmenopausal hormones at GHC pharmacies (6). Three criteria had to be met for classification as a current estrogen user after myocardial infarction: 1) at least two estrogen prescriptions had to be filled; 2) the second prescription had to be filled within 6 months of the runout date of the first prescription; and 3) the second prescription had to be filled on or after the hospital discharge date. Classification of estrogen use changed to current on the date of the second prescription and remained so as long as successive prescriptions were refilled within 6 months of the runout date of the preceding prescription. When a prescription lapsed beyond this interval, coding was changed to past use. Thus, coding of estrogen use was allowed to change during follow-up.

Because of the possibility of long-term benefits from estrogen replacement therapy, women with evidence of estrogen use at any point in time prior to their first myocardial infarction were consistently maintained in a separate category from those with no evidence of estrogen use. Women who were current or past users at the time of their initial myocardial infarction were coded as past users after myocardial infarction until they filled an eligible prescription. Since many women experienced menopause before the pharmacy database was established, a woman was also classified as a past estrogen user if information from the outpatient record indicated prior postmenopausal estrogen use. The pharmacy database and outpatient medical record were also used to ascertain postmenopausal progestin use, which was evaluated in the same manner as estrogen use.

Ascertainment of reinfarctions, deaths, and vital status

Reinfarctions and deaths through December 31, 1993, were determined using information from three sources: 1) outpatient record review; 2) GHC's hospitalization databases; and 3) the GHC death file, constructed annually from Washington State death certificates, the hospitalization databases, and data from the Cancer Surveillance System of western Washington. Possible reinfarction resulting in hospitalization was classified in the same manner as the initial myocardial infarction. In cases in which information from hospitalization was unavailable, we relied on a death cer-

tificate ICD-9-CM code of 410 (acute myocardial infarction) as evidence of fatal myocardial infarction.

If any prescription was filled after December 31, 1993, or if GHC enrollment was active on December 31, 1993, the woman was considered alive at the end of the study. Otherwise, follow-up was censored as of the end of the last quarter of GHC enrollment. Follow-up time was truncated due to disenrollment for only 58 women (8.0 percent).

Ascertainment of prognostic factors

Information on known or suspected prognostic factors was abstracted from information recorded at or prior to the first myocardial infarction in the outpatient and inpatient medical records. The variables collected included age, race (white, nonwhite), marital status (married, single, widowed, divorced), cigarette smoking (never, former, current, and evidence that the women quit smoking after myocardial infarction), body mass index (kg/(m)^2), serum cholesterol (mg/dl), history (yes/no) of physician-diagnosed diabetes, high blood pressure, angina pectoris, hyperlipidemia, congestive heart failure, and peripheral vascular disease prior to first myocardial infarction. The absence of recorded information for physician-diagnosed conditions was treated as a "no"response in the analysis.

Indicators of ventricular function such as the ejection fraction were seldom available in hospital records, particularly for women from the earlier years of the cohort. However, we documented clinical indicators of ventricular dysfunction occurring at the time of myocardial infarction including (yes/no) rales, sinus tachycardia, congestive heart failure, and radiographic evidence of congestive heart failure. Radiographic findings were recorded as reported by the hospital radiologist. The absence of recorded information on indicators of ventricular dysfunction in the inpatient medical record was treated as a "no" response in the analysis. The availability of reliable information on the timing of smoking cessation after first myocardial infarction was inconsistent, and the effects of smoking cessation could not be evaluated.

The chronic disease score (7, 8), a validated measure of comorbidity, was calculated for the year immediately prior to the first myocardial infarction. This score, determined from computerized pharmacy records, is derived from a weighted sum of medication scores reflecting the number and severity of major chronic illnesses during a 1-year period of time.

Statistical analysis

Follow-up time was accrued from the date of hospital discharge for the first myocardial infarction until the date of reinfarction (for the reinfarction analyses only), death, disenrollment from GHC, or December 31, 1993, whichever came first. Follow-up time was divided into never use, past use, and current use time, corresponding to estrogen use status across time. Age-standardized incidence rates for never use, past use, and current use were calculated by the direct method, standardized to the age distribution of person-years for the entire cohort (9). Kaplan-Meier curves were constructed to examine the time course of reinfarction and death. Because the risks for both reinfarction and all-cause mortality associated with age had U-shaped distributions, with highest risk in the youngest and oldest age groups, age was modeled as a categorical, rather than as a continuous, variable.

Cox regression was used to estimate the relative risks associated with past and current estrogen replacement therapy, adjusting for age and other prognostic factors. Estrogen use was modeled as a time-dependent variable, allowing classification of estrogen exposure to vary over follow-up time (10). The numbers of deaths ($n = 6$) and reinfarctions ($n = 3$) in the 45 women who used concurrent progestins after myocardial infarction were too small to evaluate associations between estrogen plus progestin use and reinfarction or mortality separately from women who used only estrogen. Therefore, women taking concurrent progestins were included in the analyses of estrogen exposure.

RESULTS

The 122 women treated with estrogen after myocardial infarction were younger; were more likely to be married; were less likely to have a history of diabetes, hypertension, and congestive heart failure; had a slightly younger age at menopause; and were less likely to have evidence of congestive heart failure during hospitalization compared with never users (table 1). The strongest predictor of estrogen replacement therapy after first myocardial infarction was prior estrogen use. Of the 122 women who used estrogen after myocardial infarction, 67 women were current estrogen users at the time of first myocardial infarction and continued use thereafter, 30 were current or prior users and restarted at some later point after first myocardial infarction, and only 25 had no evidence of prior estrogen use. The forms of estrogen replacement used after myocardial infarction were: conjugated equine estrogen only (40.2 percent), esterified estrogen only (13.1 percent), conjugated equine estrogen and esterified estrogen (44.2 percent), and other estrogens (2.5 percent). Most prescriptions (91.6 percent) were for doses equivalent to 0.625 mg conjugated equine estrogen or less (6, 11).

TABLE 1. Demographic and health characteristics* by timing of estrogen use among postmenopausal women aged less than 80 years who survived first myocardial infarction to hospital discharge, Group Health Cooperative of Puget Sound, 1980–1991

	Estrogen use					
	Never used (n = 404)		Before MI† only (n = 200)		After first MI (n = 122)	
	No.	%	No.	%	No.	%
Age at MI (years)						
35–49	7	1.7	2	1.0	13	10.7
50–59	64	15.8	33	16.5	32	26.2
60–69	149	36.9	82	41.0	60	49.2
70–79	184	45.5	83	41.5	17	13.9
White	363	89.9	187	93.5	116	95.1
Married	202	50.0	110	55.0	83	68.0
Chronic disease score ≥7‡	106	26.2	61	30.5	34	27.9
Age at menopause ≤50 years	234	57.9	138	69.0	88	72.1
Hysterectomy	106	26.2	85	42.5	79	64.8
Oophorectomy	63	15.6	60	30.0	40	32.8
Body mass index >29 kg/m²	93	23.0	43	21.5	21	17.2
Cigarette smoking at MI						
Never/nonsmoker	173	42.8	79	39.5	50	41.0
Former smoker	73	18.1	43	21.5	23	18.9
Current smoker	142	35.1	75	37.5	48	39.3
Quit smoking after MI§	59	14.6	44	22.0	21	17.2
Prior history of:						
Diabetes	91	22.5	45	22.5	13	10.7
High blood pressure	238	58.9	139	69.5	58	47.5
Cholesterol >240 mg/dl	206	51.0	112	56.0	53	43.4
Angina pectoris	132	32.7	61	30.5	39	32.0
Congestive heart failure	39	9.7	23	11.5	3	2.5
Peripheral vascular disease	30	7.4	18	9.0	5	4.1
Physical findings in hospital						
Rales	104	25.7	49	24.5	23	18.9
Congestive heart failure	124	30.7	61	30.5	28	23.0
Sinus tachycardia	114	28.2	58	29.0	32	26.2
X-ray findings in hospital						
Pulmonary congestion	54	13.4	32	16.0	4	3.3
Pulmonary edema	37	9.2	26	13.0	9	7.4
Congestive heart failure	74	18.3	43	21.5	13	10.7
Cardiomegaly	82	20.3	28	14.0	17	13.9

* All characteristics established at or prior to first myocardial infarction.
† MI, myocardial infarction.
‡ Chronic disease score for year prior to first myocardial infarction.
§ Percentage of current smokers at time of first myocardial infarction who subsequently quit smoking.

There were 135 first reinfarctions (101 nonfatal and 34 fatal) during follow-up. Nine women with a nonfatal reinfarction were subsequently hospitalized for what was ultimately a fatal reinfarction; however, only the first reinfarction was used for the analysis of reinfarction risk. There were 183 deaths during follow-up, 99 of which were due to coronary heart disease (coronary heart disease, myocardial infarction, or cardiac arrest). Other causes of death included congestive heart failure and acute pulmonary edema (n = 11), stroke or cerebrovascular disease (n = 14), other cardiovascular disease (n = 7), and cancer (n = 25). Nine women died of lung cancer and two of breast cancer, but there were no deaths from endometrial cancer.

The age-standardized incidence rates of reinfarction and death were highest in women who never used estrogen, lowest during current estrogen use, and intermediate among past users (figure 1). The relative risk for reinfarction associated with current estrogen use, adjusted for age and time since infarction, was 0.64 (95 percent CI 0.32–1.30), and the relative risk for past use of estrogen was 0.90 (95 percent CI 0.62–1.31) compared with never use (table 2). The corresponding relative risk for total mortality associated with current estrogen use was 0.50 (95 percent CI 0.25–1.00), and that associated with past use of estrogen was 0.79 (95 percent CI 0.56–1.09) compared with never use. Adjustment for prognostic factors, including diabetes, peripheral vascular disease, con-

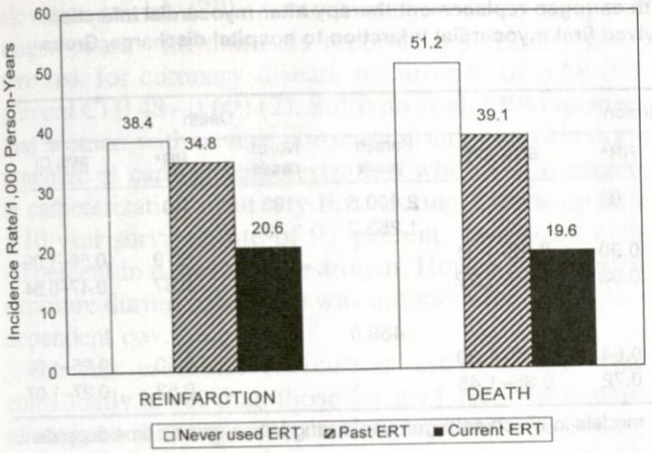

FIGURE 1. Age-standardized rates of reinfarction and death (standardized to age distribution of the cohort) in relation to postmenopausal estrogen replacement therapy (ERT) among postmenopausal women less than age 80 years who survived first myocardial infarction to hospital discharge, Group Health Cooperative of Puget Sound, 1980–1991.

gestive heart failure, rales, sinus tachycardia, radiographic evidence of congestive heart failure in hospital, and the chronic disease score, altered these estimates only slightly (relative risk for reinfarction, current vs. never users = 0.72, 95 percent CI 0.35–1.46; relative risk for death, current vs. never users = 0.53, 95 percent CI 0.27–1.07). Reinfarctions and deaths were distributed throughout the time course of the study. There was no association between calendar year of first myocardial infarction and risk for reinfarction. However, year of first infarction was associated with risk for subsequent death. The relative risk for death, comparing first infarction in 1988–1991 with first infarction in 1980–1983 was 0.53 (95 percent CI 0.34–0.82). However, reference year did not confound the association between estrogen replacement therapy and risk for reinfarction or death. Other prognostic factors that were evaluated but did not confound the association between estrogen replacement and the outcomes of interest included cigarette smoking, race, marital status, history of angina pectoris, high blood pressure, presence of systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg in the last measurement prior to the first myocardial infarction, body mass index, location of myocardial infarction (anterior, other), type of myocardial infarction (transmural, nontransmural), peak creatinine phosphokinase greater than five times normal hospital value, and prescription of beta blockers at hospital discharge. We did not adjust for serum cholesterol because it is thought to lie in the causal pathway whereby estrogen replacement reduces coronary heart disease risk.

The possibility existed that the combination of higher death rates and misclassification of estrogen use in the time immediately after the first infarction biased our results. We therefore repeated the analyses excluding women who had died or had had reinfarction in the first 6 months of follow-up, allowing a woman to be classified as a current estrogen user after only one estrogen prescription was filled. The relative risk for reinfarction associated with current estrogen use, adjusted for age and time since infarction, was 0.62 (95 percent CI 0.30–1.28), and the corresponding relative risk for total mortality associated with current estrogen use was 0.52 (95 percent CI 0.26–1.04) compared with never use. Other subgroup analyses are summarized in table 3. The association between estrogen use after myocardial infarction and reinfarction and death in subgroups of women without major risk factors were similar to those for the entire cohort. The relative risks for reinfarction and death associated with current estrogen use after first myocardial infarction were somewhat lower for the 25 women whose first estrogen use followed first myocardial infarction (relative risk for reinfarction, current vs. never use = 0.48, 95 percent CI 0.11–2.19; relative risk for death, current vs. never use = 0.32, 95 percent CI 0.07–1.49) than those for the 72 women who were current users at the time of first myocardial infarction (relative risk for current vs. never use = 0.68, 95 percent CI 0.33–1.42; relative risk for death, current vs. never use = 0.53, 95 percent CI 0.26–1.10). Because of concerns that concurrent progestin use may reduce the cardioprotective effects of estrogen replacement, we repeated our analysis excluding women who took progestins at any time after their first myocardial infarction, controlling for age and other prognostic factors. In this subgroup, the relative risk for current estrogen use varied little from that for the entire cohort. The relative risk for coronary mortality (number of coronary heart disease deaths = 99) associated with current estrogen use was 0.49 (95 percent CI 0.19–1.24), and the relative risk for coronary mortality associated with past estrogen use was 0.62 (95 percent CI 0.39–1.00).

DISCUSSION

In this population-based retrospective cohort study of 726 women, postmenopausal estrogen replacement therapy after a first myocardial infarction was not associated with an increase in risk of reinfarction or all-cause mortality. Our relative risks of 0.64 for reinfarction and 0.50 for all-cause mortality suggest that current estrogen replacement therapy may be protective against reinfarction and death; however, the low frequency of estrogen use after myocardial infarction resulted in wide confidence intervals surrounding our

TABLE 2. Relative risks for reinfarction and death associated with estrogen replacement therapy after myocardial infarction among postmenopausal women aged less than 80 years who survived first myocardial infarction to hospital discharge, Group Health Cooperative of Puget Sound, 1980–1991

	Reinfarction				Death			
	Person-years	No. of cases	RR*	95% CI†	Person-years	No. of cases	RR*	95% CI
No estrogen use	2,238.3	86	1.0		2,400.5	123	1.0	
Past estrogen use	1,151.1	40			1,253.2	49		
Adjusted for age			0.90	0.62–1.31			0.79	0.56–1.09
Adjusted for age and prognostic factors‡			0.83	0.56–1.22			0.67	0.47–0.94
Current estrogen use	437.7	9			459.0	9		
Adjusted for age			0.64	0.32–1.30			0.50	0.25–1.00
Adjusted for age and prognostic factors‡			0.72	0.35–1.46			0.53	0.27–1.07

* RR, relative risks calculated using proportional hazards regression models in which estrogen use during follow-up was time dependent.
† CI, confidence interval.
‡ The relative risks were adjusted for age (35–49, 50–59, 60–69, and 70–79 years), history of diabetes, high blood pressure, congestive heart failure, and peripheral vascular disease before first myocardial infarction, rales, sinus tachycardia, and radiographic evidence of congestive heart failure in hospital and chronic disease score for the 1-year period prior to first myocardial infarction (0–2, 3–4, 5–6, and ≥7).

TABLE 3. Subgroup analyses for the relative risks* for reinfarction and death associated with estrogen replacement therapy after myocardial infarction among postmenopausal women aged less than 80 years who survived first myocardial infarction to hospital discharge, Group Health Cooperative of Puget Sound, 1980–1991

	Reinfarction			Death	
	No.	RR	95% CI†	RR	95% CI
Age-adjusted estimates	726	0.64	0.32–1.30	0.50	0.25–1.00
Nondiabetics	576	0.67	0.30–1.50	0.60	0.29–1.27
No history of peripheral vascular disease	672	0.61	0.29–1.29	0.55	0.27–1.10
No history of congestive heart failure prior to first MI†	660	0.61	0.29–1.29	0.57	0.29–1.15
No x-ray evidence of congestive heart failure in hospital	534	0.75	0.35–1.60	0.62	0.30–1.32
No sinus tachycardia in hospital	517	0.61	0.26–1.44	0.47	0.20–0.86
No rales in hospital	547	0.64	0.29–1.42	0.57	0.26–1.26
History of one or more of the following: diabetes, peripheral vascular disease, congestive heart failure prior to first myocardial infarction, congestive heart failure in hospital, sinus tachycardia in hospital, or rales in hospital, chronic disease score ≥7	485	0.65	0.28–1.51	0.49	0.21–1.13
None of the above prognostic factors and chronic disease score <7	241	0.75	0.21–2.72	0.62	0.17–2.21
Used after first MI, but not before first MI‡	726	0.48	0.11–2.19	0.32	0.07–1.49
Current use at MI‡	726	0.68	0.33–1.42	0.53	0.26–1.10
Progestin users excluded	681	0.64	0.28–1.49	0.50	0.22–1.14
Coronary heart disease deaths	726			0.49	0.19–1.23

* Relative risks (RR) calculated using Cox regression models in which estrogen use during follow-up was time dependent. All other prognostic factors established prior to or at the time of first myocardial infarction. All models adjusted for age (35–49, 50–59, 60–69, and 70–79 years).
† CI, confidence interval; MI, myocardial infarction.
‡ One model that included all women yielded both estimates. Models included terms for past or current use at the time of the first myocardial infarction and time-dependent terms for estrogen use after the first myocardial infarction. There were 74 women with current estrogen prescriptions at first myocardial infarction who continued estrogen use either immediately or at some time after the first myocardial infarction and 34 women with no history of estrogen use prior to first myocardial infarction who used estrogen at some time after the first myocardial infarction.

risk estimates. Although our observed relative risks are consistent with the evidence relating estrogen replacement to a reduced risk of first coronary heart disease events, our results may have been due to chance.

We know of no other studies of the effect of estrogen replacement on reinfarction or survival after a first myocardial infarction with which direct comparisons of our results are possible. However, of eighteen published cohort studies on the association between estrogen replacement and coronary heart disease risk (12–29), eleven (13, 14, 18–22, 24, 26, 27, 29) reported reductions in risk, with relative risks ranging from 0.30 to 0.69, and only one of the 18 studies reported an

elevation in risk (28). A meta-analysis comparing estrogen users with nonusers reported a summary relative risk for coronary disease occurrence of 0.58 (95 percent CI 0.48–0.69) (2). Sullivan et al. (30) reported that women with severe coronary artery stenosis documented at cardiac catheterization who used estrogen at catheterization or at any time during follow-up had a 10-year survival rate of 97 percent, compared with 60 percent in nonusers of estrogen. However, estrogen exposure during follow-up was not modeled as a time-dependent covariate.

Our risk estimates for current estrogen use were consistently lower than those for past use. The benefit of exogenous estrogen on the development of coronary heart disease is thought to occur in part through its favorable effects on serum lipids and in part through direct effects on coronary artery walls and blood flow (14, 31, 32). In addition, estrogen appears to prevent the increase in fibrinogen associated with menopause (33, 34). The women in our study had evidence of serious atherosclerosis by virtue of their documented myocardial infarction. In this population, the effects of estrogen on lipids may be relatively less important than its acute effects on coronary artery endothelium and vascular smooth muscle that promote vasodilation (31), counter the tendency toward vasospasm in atherosclerotic coronary arteries (31), and increase blood flow (32). These effects would quickly diminish upon the cessation of estrogen replacement, a mechanism consistent with benefit primarily from current use.

Sixty-one percent of women who took estrogen after myocardial infarction had current prescriptions at the time of myocardial infarction. Nevertheless, our risk estimates suggest that even though estrogen use failed to protect these current estrogen users from experiencing a first myocardial infarction, they may have a reduced risk of subsequent reinfarction and death associated with estrogen use after myocardial infarction compared with nonuse.

The study setting had many strengths. Estrogen users and nonusers had similar access to care, although estrogen users might have utilized this care more fully. The ability to access complete outpatient and inpatient medical records allowed systematic ascertainment of the history of illnesses such as diabetes, hypertension, and congestive heart failure. Approximately 9 percent of women in this study were less than age 56 years. We were able to ascertain menopausal status for all women who were otherwise eligible for the study. Despite the long time period of the study, less than 10 percent of subjects had follow-up truncated due to withdrawal from GHC. The use of computerized pharmacy records avoided recall or reporting biases and allowed us to define periods of use with precision rarely possible in observational studies and avoided the problems associated with self-report of drug use. However, the use of pharmacy records can result in some imprecision when trying to define current use of a medicine. It is impossible to define precisely when use stops because a lag period is required to determine that the prescription has not been refilled.

The study also had several potential limitations. Women entered the study over a 12-year interval, during which the acute and long-term management of coronary disease and myocardial infarction underwent extensive changes and increasing numbers of women were prescribed estrogen replacement therapy. However, we found no evidence that reference year confounded the associations between estrogen replacement therapy and reinfarction or survival. We were unable to identify the small proportion of women who did not fill estrogen prescriptions at a GHC pharmacy, and thus, three or four women who were taking hormone replacement therapy may have been included with the past or never users. Their inclusion among never users would bias the relative risk toward the null. Our case definition included only women who survived first myocardial infarction. If estrogen replacement therapy is proven to be of benefit to women with coronary artery disease, other groups of interest might include women with angina pectoris, those with coronary artery disease diagnosed at cardiac catheterization, and those who have undergone revascularization procedures.

Our classification of estrogen use after myocardial infarction was conservative. Women were classified as past or never users until they filled two estrogen prescriptions within a specified time interval. We chose this approach to avoid classifying as current users women who filled a single prescription but never took it or took it for only a very short period of time. Although we do not know that women actually took all tablets obtained, our insistence on evidence that prescriptions were being refilled increased the likelihood that we were measuring drug use. We also classified use as current until a prescription had lapsed for 6 months. Our classification approach would bias the results toward minimizing the effects of estrogen if the benefits of estrogen use accrue immediately or if any reduced risk of reinfarction and/or death wanes quickly upon cessation of therapy. Past estrogen use was defined less precisely than current use. We relied on outpatient records for ascertainment of estrogen use prior to 1977, and it is possible that some prior estrogen use was not documented in these records. This misclassification would also likely bias our results toward minimizing the effects of estrogen.

Approximately a third of the women taking estrogen after myocardial infarction were also taking progestins. Despite concern that progestins diminish estrogen's protective effects (34), Psaty et al. (35) found no difference in the reduction in risk of a first myocardial infarction when women on estrogen alone or women on estrogen plus progestin were compared with women who did not use hormones. In animal models (31), estrogen alone or with progestins conferred the same 50 percent reduction in experimental atherosclerosis. Subanalyses of our data showed little difference in the risk estimates for reinfarction and death when women who took progestins were excluded.

It has been reported that women who use estrogen are healthier (36) and more likely to report healthy lifestyle behaviors and preventive health care (37) than are women not taking estrogen. Individuals who comply with medications in randomized trials, whether taking the real drug or a placebo, have better survival than those who do not (38, 39). Compared with never users, women in our study who used estrogen after myocardial infarction were younger, less likely to be diabetic, and less likely to have several indices of congestive heart failure both before and during hospitalization. However, in subgroup analyses, the association between estrogen and risk of reinfarction and death remained when women with histories of diabetes, congestive heart failure or peripheral vascular disease, or congestive heart failure in hospital were excluded. Body mass index, history of hypertension, and the proportion smoking were similar in the three estrogen groups, and a higher proportion of estrogen users than never users had a history of hyperlipidemia prior to first myocardial infarction. We also accounted for health status before the first myocardial infarction by controlling for the chronic disease score (7). Although confounding from unknown sources remains a possibility, our data permitted extensive consideration of effects that might have occurred as a result of health differences in the three groups.

Uncertainty remains concerning the safety of postmenopausal estrogen replacement in women with established coronary artery disease. A postal survey in England revealed that 11 percent of consultant gynecologists and 20 percent of general practitioners viewed a history of ischemic heart disease as an absolute contraindication to estrogen replacement therapy, and another 45 percent in each group viewed ischemic heart disease as a relative contraindication to estrogen replacement therapy (3). This was found despite the fact that 86 percent of consulting gynecologists and 74 percent of general practitioners considered that estrogen replacement therapy decreases the risk of subsequent ischemic heart disease (3). A similar survey in Finland found that 24 percent of nonspecialist physicians believed estrogen-progestin therapy increased the risk of cardiovascular disease (40). Although the reasons for these beliefs are unclear, they may reflect concerns stemming from the association of early, high-dose oral contraceptives with an increase in risk of myocardial infarction in women over age 35 years and the results of the Coronary Drug Project, which showed a dramatic increase in risk of myocardial infarction and thromboembolic events in men given high-dose estrogen (41). Whether US physicians share these attitudes is unknown. Our findings provide some measure of reassurance concerning the safety of low-dose estrogen replacement therapy for women with coronary disease. Randomized trials of estrogen replacement in women with established coronary disease that will provide more complete assurance that biases and confounding have been adequately controlled are underway but are several years from completion (42).

In conclusion, our findings provide evidence for the safety of estrogen replacement therapy after myocardial infarction in women. Estrogen replacement therapy after first myocardial infarction was not associated with an increase in risk of reinfarction or all-cause mortality in postmenopausal women. Furthermore, consistent with the evidence relating estrogen replacement to a reduced risk of first coronary heart disease events, our relative risks for reinfarction and all-cause mortality suggest that estrogen replacement therapy may be protective against reinfarction and death. However, the low frequency of estrogen use after myocardial infarction resulted in wide confidence intervals surrounding our risk estimates, and our results may have been due to chance.

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