POSTMENOPAUSAL ESTROGEN AND PROGESTIN USE AND THE RISK OF CARDIOVASCULAR DISEASE

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ABSTRACT

Background   Estrogen therapy in postmenopausal women has been associated with a decreased risk of heart disease. There is little information, however, about the effect of combined estrogen and progestin therapy on the risk of cardiovascular disease.

Methods   We examined the relation between cardiovascular disease and postmenopausal hormone therapy during up to 16 years of follow-up in 59,337 women from the Nurses' Health Study, who were 30 to 55 years of age at base line. Information on hormone use was ascertained with biennial questionnaires. From 1976 to 1992, we documented 770 cases of myocardial infarction or death from coronary disease in this group and 572 strokes. Proportional-hazards models were used to calculate relative risks and 95 percent confidence intervals, adjusted for confounding variables.

Results   We observed a marked decrease in the risk of major coronary heart disease among women who took estrogen with progestin, as compared with the risk among women who did not use hormones (multivariate adjusted relative risk, 0.39; 95 percent confidence interval, 0.19 to 0.78) or estrogen alone (relative risk, 0.60; 95 percent confidence interval, 0.43 to 0.83). However, there was no significant association between stroke and use of combined hormones (multivariate adjusted relative risk, 1.09; 95 percent confidence interval, 0.66 to 1.80) or estrogen alone (relative risk, 1.27; 95 percent confidence interval, 0.95 to 1.69).

Conclusions   The addition of progestin does not appear to attenuate the cardioprotective effects of postmenopausal estrogen therapy. (N Engl J Med 1996;335:453-61.)

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MORE than 30 epidemiologic studies have found that postmenopausal women who use estrogen are at lower risk for coronary disease than those who do not use estrogen[1]; however, most data are for estrogen alone.[2] Progestins added to estrogen reduce or eliminate the excess risk of endometrial cancer due to the unopposed effect of estrogen.[3] The use of progestins combined with estrogen is now common, but information about the risk of cardiovascular disease associated with combined therapy is sparse.

Experimental data suggest that the addition of progestin may diminish the apparent cardioprotective effect of hormone therapy. Progestins alone tend to raise low-density lipoprotein (LDL) cholesterol levels and lower high-density lipoprotein (HDL) cholesterol levels.[4] In the Postmenopausal Estrogen/Progestin Interventions trial,[5] all hormone regimens lowered LDL cholesterol levels, but medroxyprogesterone acetate significantly attenuated the estrogen-induced increase in HDL cholesterol levels. Moreover, progestins tend to oppose estrogen's beneficial effects on arterial dilatation and blood flow.[6]

In an earlier report, we examined the relation between postmenopausal hormone therapy and cardiovascular disease on the basis of 10 years of follow-up data from the Nurses' Health Study,[2] but at the time of that analysis, few women were taking progestin with estrogen. We now report on the relation be-

tween combined hormone therapy and cardiovascular disease. Our analysis is based on 16 years of follow-up data in 59,337 postmenopausal women participating in the Nurses' Health Study.

METHODS

The Nurses' Health Study began in 1976, when 121,700 female nurses, 30 to 55 years of age, completed a mailed questionnaire about their use of postmenopausal hormones and their medical history, including cardiovascular disease and associated risk factors. We updated the information with biennial follow-up questionnaires. Starting in 1980, we included questions about diet and physical activity. Follow-up data were available for over 90 percent of the cohort.

Ascertainment of Hormone Use

In 1976, the study participants were asked whether they used hormones after menopause and, if so, the duration of use. Beginning in 1978, we collected information on the type of hormone therapy, and beginning in 1980, we also asked about the dose of oral conjugated estrogen.

Documentation of Cardiovascular Disease

Cardiovascular disease was defined as nonfatal myocardial infarction, fatal coronary disease, coronary-bypass surgery or angioplasty, and fatal or nonfatal stroke occurring during the period between the return of the 1976 questionnaire and June 1, 1992. Nurses who reported a nonfatal infarction or stroke were asked for permission to review their medical records. Nonfatal myocardial infarctions were confirmed if the information in the medical records met the criteria of the World Health Organization[8] (symptoms plus either elevated cardiac-enzyme levels or diagnostic findings on electrocardiograms). Infarctions for which medical records were unavailable were defined as probable and included in the analysis if they required hospitalization and were corroborated by an interview or a letter from the subject. Infarctions of indeterminate age discovered on routine examination were not included. Data on coronary-artery surgery were obtained from the study participants' reports alone.

Nonfatal strokes were confirmed if they were characterized in the medical records as typical neurologic deficits that were rapid in onset and lasted at least 24 hours and if they met the criteria of the National Survey of Stroke.[9] We classified strokes as ischemic strokes (defined as thrombotic or embolic occlusion of a cerebral artery), subarachnoid hemorrhages, or intraparenchymal hemorrhages. We excluded subdural hematomas and strokes caused by infection or neoplasia. Strokes for which the medical records were unavailable were defined as probable strokes and included in the analysis if they required hospitalization and were corroborated by letter or interview.

Most deaths were reported by the participants' families. We searched the National Death Index[10] to identify deaths among the nonrespondents to each two-year questionnaire; data on mortality were more than 98 percent complete. For all deaths possibly attributable to cardiovascular causes, we requested permission from family members (subject to state regulations) to review the medical records. A death was considered to be due to coronary disease if the medical records or autopsy report confirmed a fatal myocardial infarction or if coronary disease was listed on the death certificate as the underlying cause of death without another, more plausible cause and if the nurse was known (from hospital records, a family member's report, or another source) to have had coronary disease before death. In no case was the cause listed on the death certificate used as the sole criterion for death due to coronary disease. Fatal strokes were confirmed on the basis of autopsy reports, hospital records, or death certificates listing stroke as the underlying cause.

The category of major coronary heart disease includes nonfatal myocardial infarction and death due to coronary disease; similarly, the category of total stroke includes nonfatal and fatal cases of stroke. Confirmed and probable cases in each category were analyzed together; in this and previous analyses, the results for probable cases were quite similar to those for confirmed cases.[2] Eighty percent of the cases of major coronary disease and 73 percent of the cases of stroke were confirmed. All interviews and reviews of medical records were conducted by investigators without knowledge of the category of hormone use.

Study Population

Women who reported stroke, myocardial infarction, angina, or cancer (except skin cancer other than melanoma) on the 1976 questionnaire were excluded from the analysis, because the disease may have caused them to alter their use of hormones. Similarly, women who reported such conditions on a subsequent questionnaire were excluded from further analysis. Thus, at the start of each two-year interval, the base population included no women reporting these conditions.

We classified women as postmenopausal from the time of natural menopause or a hysterectomy with a bilateral oophorectomy. Women who underwent a hysterectomy without a bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90 percent of the cohort (54 years among the smokers and 56 years among the nonsmokers).[11] The reported age at the time of menopause and the type of menopause were highly accurate in this cohort.[12]

In 1976, a total of 21,726 postmenopausal women were included in the analysis, and 37,611 women were added during follow-up as they became postmenopausal; 662,891 person-years of follow-up were accrued from 1976 to 1992.

Statistical Analysis

For each participant, person-months were allocated to categories of hormone use according to the 1976 data and updated every two years (for progestin use and estrogen dose, follow-up began in 1978 and 1980, respectively). Follow-up ended when cardiovascular disease was first diagnosed, the participant died, or the last questionnaire was returned.

The primary analysis was based on incidence rates, with person-months of follow-up used as the denominator. We used relative risk as the measure of association; the relative risk was defined as the incidence rate of cardiovascular disease among women in various categories of hormone use divided by the incidence rate among women who never used hormones. We computed age-specific rates using five-year categories and calculated age-adjusted relative risks with 95 percent confidence intervals.[13] Tests of trends across categories of exposure were calculated by treating the levels of exposure as a continuous, ordinal variable in the regression model.

Proportional-hazards models[14] were used to calculate relative risks, with adjustments for age, age at menopause, body-mass index (the weight in kilograms divided by the square of the height in meters), cigarette smoking, hypertension, diabetes, elevated cholesterol levels, myocardial infarction in a parent before the age of 60 years, prior use of oral contraceptives, type of menopause (natural or surgical), and two-year interval (eight categories). For certain analyses, saturated-fat intake (in quintiles), alcohol use (none, <5 g, 5 to 14.9 g, or ≥15 g per day), use of vitamin E (none, <100 IU, 100 to 299 IU, 300 to 599 IU, or ≥600 IU per day) or multivitamins (yes or no), use of aspirin (none or 1 to 6 pills or ≥7 pills a week), and physical activity (none or at least once per week) were added to the model (with follow-up from 1980 to 1992, because information on these additional variables was not available before 1980). Rate differences (the excess number of cases attributable to the nonuse of hormones per 100,000 person-years) were calculated in strata of risk groups (e.g., cigarette smokers and nonsmokers) as the difference between the incidence rates

among hormone users and nonusers (i.e., those who had never used hormones), standardized to the age distribution among nonusers without the specified risk factor (e.g., nonsmokers).

RESULTS

We documented 584 nonfatal myocardial infarctions, 186 deaths due to coronary disease, 572 strokes (285 ischemic events, 155 subarachnoid hemorrhages, and 132 other or unspecified types), and 553 instances of coronary surgery or angioplasty. Women who had never used hormones accounted for 49.0 percent of the person-years of follow-up, current users for 25.1 percent (three fourths of whom used estrogen alone, and one fourth estrogen with progestin), and past users for 22.7 percent; information was missing for 3.2 percent of the follow-up time.

Current hormone users, regardless of whether they used estrogen alone or with progestin, tended to have a better risk profile than women who had never used hormones (Table 1). Fewer current users had a parental history of myocardial infarction, had diabetes, or smoked cigarettes. Current users also took multivitamins, vitamin E, and aspirin more often than women who had never used hormones, were slightly younger and leaner, and drank more alcohol. However, current users reported a greater intake of saturated fat and were more likely to have high serum cholesterol levels.

Among current users of oral conjugated estrogen alone, as compared with women who had never used hormones, the age-adjusted relative risk of major coronary disease was 0.45 (95 percent confidence interval, 0.34 to 0.60) (Table 2). With adjustment for cardiovascular risk factors, the relative risk was 0.60, largely because current users were leaner and less likely to smoke. However, adjustment for age as a continuous variable did not further change the estimates of relative risk. Among the women who used estrogen with progestin, there was also a marked decrease in the risk of major coronary disease (multivariate adjusted relative risk, 0.39; 95 percent confidence interval, 0.19 to 0.78).

We found little association between the risk of stroke of any type and current use of estrogen alone (relative risk, 1.27, as compared with women who had never used hormones) or estrogen with progestin (relative risk, 1.09). There was an increase in the risk of ischemic stroke among current users of estrogen alone (relative risk, 1.63; 95 percent confidence interval, 1.10 to 2.39) and current users of the combined regimen (relative risk, 1.42; 95 percent confidence interval, 0.73 to 2.75). For subarachnoid hemorrhage, we found no decrease in risk among current users of estrogen alone (relative risk, 1.35); among users of estrogen with progestin, there was a nonsignificant decrease in the risk of hemorrhagic stroke (relative risk, 0.53), but the data were based

TABLE 1. AGE-STANDARDIZED DISTRIBUTION OF CHARACTERISTICS OF WOMEN PARTICIPATING IN THE NURSES' HEALTH STUDY IN 1990, ACCORDING TO THE USE OR NONUSE OF POSTMENOPAUSAL HORMONES.

CHARACTERISTIC	HORMONE USE			
	NEVER USED (N=27,034)	USED IN PAST (N=12,503)	CURRENTLY USED	
			Estrogen Alone (N=7776)	Estrogen with Progestin (N=6224)
Parental MI before the age of 60 yr (%)*	29.6	26.7	21.8	20.6
Hypertension (%)	32.9	35.9	35.6	27.3
Diabetes mellitus (%)	5.8	5.6	3.8	2.7
High serum cholesterol level (%)	35.6	41.9	43.9	41.6
Moderate smoker (%)†	9.4	8.9	5.5	4.6
Bilateral oophorectomy (%)	4.2	27.6	47.9	8.9
Past use of oral contraceptives (%)	30.6	37.9	42.0	46.4
Multivitamin use (%)	24.6	29.0	41.1	42.2
Vitamin E use (%)	9.5	11.6	17.4	18.1
Aspirin use (%)	33.6	36.7	46.9	48.3
Mean age (yr)	60.1	61.6	58.5	56.7
Mean age at menopause (yr)	50.9	46.3	44.7	49.2
Mean body-mass index	26.3	25.9	25.1	24.3
Mean alcohol consumption (g/day)	4.7	5.5	6.4	6.0
Mean consumption of saturated fat (g/day)	31.2	34.4	41.9	41.4

*MI denotes myocardial infarction.

†Moderate smokers were defined as women who smoked 15 to 24 cigarettes per day.

on only three cases of stroke among women using the combined regimen.

In subsequent analyses, we combined the data on use of estrogen alone and use of estrogen with progestin, since the results were similar for the two types of hormone therapy. The multivariate adjusted relative risk of major coronary disease was 0.60 for current hormone use, but 0.85 for past use (Table 3). These findings are similar to the results of our follow-up at 10 years.[2] Additional adjustment for dietary variables, use of vitamin supplements, use of aspirin, and physical activity did not substantially alter these estimates (relative risk of major coronary disease among current users, 0.65; 95 percent confidence interval, 0.50 to 0.84). We did not include these factors in further analyses, because we would have had to limit the follow-up, since dietary information was first requested in 1980. There was no relation between coronary bypass or angioplasty and current hormone use (relative risk, 0.99; 95 percent confidence interval, 0.78 to 1.26), as was also noted in our 10-year follow-up.[2]

We found no decrease in the risk of stroke among

TABLE 2. RELATIVE RISK OF CARDIOVASCULAR DISEASE AMONG CURRENT USERS OF CONJUGATED ESTROGEN ALONE OR WITH PROGESTIN AS COMPARED WITH NONUSERS, 1978 TO 1992.*

HORMONE USE	PERSON-YEARS	MAJOR CORONARY DISEASE			STROKE (ALL TYPES)		
		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)	
			Age Adjusted	Multivariate Adjusted†		Age Adjusted	Multivariate Adjusted†
Never used	304,744	431	1.0		270	1.0	
Currently used							
Estrogen alone	82,626	47	0.45 (0.34–0.60)	0.60 (0.43–0.83)	74	1.13 (0.88–1.46)	1.27 (0.95–1.69)
Estrogen with progestin	27,161	8	0.22 (0.12–0.41)	0.39 (0.19–0.78)	17	0.74 (0.45–1.20)	1.09 (0.66–1.80)

*CI denotes confidence interval.

†The analysis was adjusted for age (in five-year categories), time (in two-year categories), age at menopause (in two-year categories), body-mass index (in quintiles), diabetes (yes or no), high blood pressure (yes or no), high cholesterol level (yes or no), cigarette smoking (never, formerly, or currently [1 to 14, 15 to 24, or 25 or more cigarettes per day]), past oral-contraceptive use (yes or no), parental history of myocardial infarction before the age of 60 years (yes or no), and type of menopause (natural or surgical).

current or past hormone users, as compared with nonusers; there was the suggestion of an increased risk of ischemic stroke among current users (Table 3).

Among current users, a longer period of use was not associated with any apparent trend toward a further reduction in the risk of either major coronary disease or stroke (P for trend, 0.73 for both). With less than 2 years of current use, the relative risk of coronary disease was 0.53 (95 percent confidence interval, 0.31 to 0.93), and with 10 or more years of use, the risk was 0.70 (95 percent confidence interval, 0.47 to 1.04). The relative risk of a stroke of any type among the long-term users was 1.01 (95 percent confidence interval, 0.69 to 1.46). The data on the duration of use are available elsewhere.*

The benefit of hormone use in providing protection against coronary disease appeared to diminish somewhat 3 or more years after the cessation of hormone use (Fig. 1): the relative risk of coronary disease among women who had stopped using hormones less than 3 years earlier as compared with women who had never used hormones was 0.69 (95 percent confidence interval, 0.48 to 1.00), and it was 0.81 (95 percent confidence interval, 0.54 to 1.21) for those who had stopped using hormones 3 to 4.9 years earlier (P for trend, 0.05).

We also examined the risk of coronary disease according to the current dose of oral conjugated es-

*See NAPS document no. 05320 for 2 pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) $7.75 for photocopies or $4 for microfiche. Outside the U.S. and Canada, add postage of $4.50 ($1.75 for microfiche postage). There is a $15 invoicing charge for all orders filled before payment.

trogen (Table 4). There was an inverse association between coronary disease and estrogen therapy at doses of 0.3 and 0.625 mg (relative risk, 0.57 and 0.53, respectively), but this association was diminished at higher doses. Although we found little apparent overall relation between the risk of stroke and the dose of oral conjugated estrogen, there was a trend toward an increased risk with higher doses (P for trend, 0.047).

We performed an analysis to determine whether the effect of hormones on the risk of major coronary disease varied in specific subgroups of women (Table 5). The protective effect appeared to be similar in most subgroups. Even among women who were 60 to 71 years old, the risk of coronary disease was lower among current users than among nonusers (relative risk, 0.66); in our 10-year follow-up,[2] we had found a nonsignificant increase in the risk among the women in this age group, although the numbers were small. In addition, estrogen use was inversely related to the risk of coronary disease among women, regardless of whether they had diabetes or a parental history of heart disease, used aspirin daily, or exercised regularly. Among low-risk women (those who had a body-mass index in the first to fourth quintiles; did not have diabetes, hypertension, or hypercholesterolemia; and were not current smokers), the relative risk of coronary disease was 0.67 (95 percent confidence interval, 0.34 to 1.32) for current hormone users, as compared with women who had never used hormones.

Women who use hormones must see a physician, which may account, in part, for the apparent benefit of hormones. In 1978, 1988, and 1990, however, we asked the study participants whether they had

TABLE 3. RELATIVE RISK OF CARDIOVASCULAR DISEASE AMONG CURRENT AND PAST HORMONE USERS
AS COMPARED WITH NONUSERS, 1976 TO 1992.*

HORMONE USE	PERSON-YEARS	MAJOR CORONARY DISEASE			STROKE (ALL TYPES)			ISCHEMIC STROKE			SUBARACHNOID HEMORRHAGE		
		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)	
			Age Adjusted	*Multivariate Adjusted†*		*Age Adjusted*	*Multivariate Adjusted†*		*Age Adjusted*	*Multivariate Adjusted†*		*Age Adjusted*	*Multivariate Adjusted†*
Never used	324,748	452	1.0		279	1.0		133	1.0		79	1.0	
Currently used	166,371	98	0.47 (0.38–0.58)	0.60 (0.47–0.76)	121	0.93 (0.75–1.16)	1.03 (0.82–1.31)	73	1.19 (0.89–1.57)	1.40 (1.02–1.92)	33	0.89 (0.59–1.34)	0.90 (0.57–1.41)
Used in past	150,238	195	0.90 (0.76–1.07)	0.85 (0.71–1.01)	152	1.08 (0.89–1.32)	0.99 (0.80–1.22)	75	1.09 (0.82–1.45)	1.01 (0.74–1.36)	32	0.86 (0.57–1.30)	0.81 (0.52–1.25)

*Information on hormone use was missing for 21,534 person-years, 25 cases of coronary heart disease, and 20 cases of stroke (4 ischemic strokes, 11 subarachnoid hemorrhages, and 5 other or unknown types of stroke). CI denotes confidence interval.

†The analysis was adjusted for age (in five-year categories), time (in two-year categories), age at menopause (in two-year categories), body-mass index (in quintiles), diabetes (yes or no), high blood pressure (yes or no), high cholesterol level (yes or no), cigarette smoking (never, formerly, or currently [1 to 14, 15 to 24, or 25 or more cigarettes per day]), past oral-contraceptive use (yes or no), parental history of myocardial infarction before the age of 60 years (yes or no), and type of menopause (natural or surgical).

visited a physician in the previous two years; in the subgroup of women who reported a visit in each period (accounting for 50 percent of the follow-up time), the relative risk of major coronary disease among the current hormone users was 0.52 (95 percent confidence interval, 0.37 to 0.74), as compared with the women who had never used hormones.

Even though the relative risks were similar regardless of the presence or absence of coronary risk factors, the number of cases of coronary disease per 100,000 women-years that could have been avoided if hormones had been used was higher among the women with risk factors than among those without risk factors (Table 5).

DISCUSSION

In this large prospective study, the risk of major coronary disease was substantially decreased among current users of estrogen and progestin, as well as among current users of estrogen alone. Neither estrogen alone nor combined therapy substantially affected the risk of stroke, although there was a suggestion of an increased risk in the subgroup of women taking the highest doses of oral conjugated estrogen. The associations were unrelated to the duration of hormone use, and the protective benefit diminished somewhat three years after cessation of hormone therapy. In general, women with risk factors for heart disease and those without risk factors had similar relative risks, but the absolute rate differences were greater among the women with risk factors.

Although we did not validate self-reported hormone use, we believe the reports were accurate, be-

cause all the study participants are registered nurses with a demonstrated interest in medical research. Moreover, the prospective design eliminates recall bias, which can be a problem in case–control studies.

A primary concern is whether hormone users are different from nonusers (i.e., women who have never used hormones) in ways that may influence the risk of heart disease. Women who take hormones see a physician regularly, and these visits may themselves result in a decreased risk of coronary disease. For example, in a study of upper-middle-class women, estrogen users reported undergoing more screening tests, such as blood cholesterol measurements and
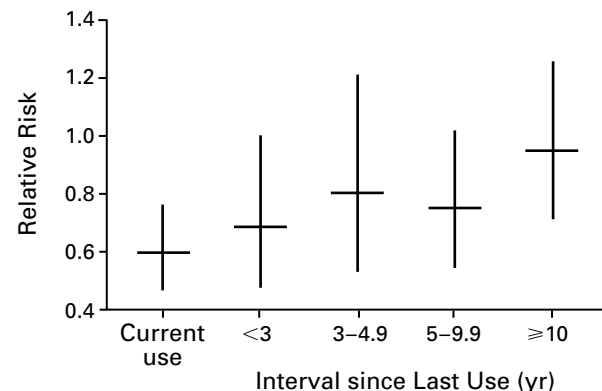

Figure 1. Relative Risk of Major Coronary Heart Disease among Current Hormone Users and among Past Users, According to the Interval since Last Use.

Data are for the period from 1976 to 1992. Horizontal bars indicate relative risks, and vertical bars 95 percent confidence intervals.

TABLE 4. RELATIVE RISK OF CARDIOVASCULAR DISEASE AMONG CURRENT HORMONE USERS
AS COMPARED WITH WOMEN WHO NEVER USED HORMONES,
ACCORDING TO THE DOSE OF ESTROGEN, 1980 TO 1992.*

DOSE (mg)	PERSON-YEARS	CORONARY HEART DISEASE			STROKE (ALL TYPES)		
		NO. OF CASES	RELATIVE RISK (95% CI)		NO. OF CASES	RELATIVE RISK (95% CI)	
			Age Adjusted	Multivariate Adjusted†		Age Adjusted	Multivariate Adjusted†
0.3	13,900	8	0.40 (0.20–0.79)	0.57 (0.28–1.16)	7	0.53 (0.25–1.12)	0.64 (0.30–1.36)
0.625	61,512	29	0.35 (0.25–0.50)	0.53 (0.36–0.78)	54	1.01 (0.75–1.35)	1.24 (0.90–1.70)
1.25	25,895	19	0.62 (0.40–0.98)	0.82 (0.51–1.33)	26	1.38 (0.93–2.06)	1.44 (0.94–2.22)
>1.25	2,238	2	0.79 (0.20–3.15)	0.92 (0.23–3.72)	3	1.99 (0.64–6.10)	1.86 (0.59–5.90)
P for trend			0.22			0.047	

*CI denotes confidence interval.

†The analysis was adjusted for age (in five-year categories), time (in two-year categories), age at menopause (in two-year categories), body-mass index (in quintiles), diabetes (yes or no), high blood pressure (yes or no), high cholesterol level (yes or no), cigarette smoking (never, formerly, or currently [1 to 14, 15 to 24, or 25 or more cigarettes per day]), past oral-contraceptive use (yes or no), parental history of myocardial infarction before the age of 60 years (yes or no), and type of menopause (natural or surgical).

mammography, than nonusers.[15] In our study, however, the proportions of women who reported having had blood pressure and blood cholesterol checks in 1988 were only slightly larger among the hormone users (83 percent and 72 percent, respectively) than among the nonusers (78 percent and 61 percent, respectively). Furthermore, when we limited our analysis to women who reported a visit to a physician in 1978, 1988, and 1990, the results still showed a strong protective effect of hormone use.

Women who take hormones are a self-selected group and usually have healthier lifestyles with fewer risk factors than women who do not take hormones. In general-population samples, hormone users, as compared with nonusers, have more years of education, are leaner, drink more alcohol, and participate in sports more often,[16] even before starting to use hormones.[17] However, these characteristics are due primarily to socioeconomic factors, since women who take hormones can generally afford medical care. Participants in the Nurses' Health Study are relatively homogeneous in terms of education. Although the current hormone users had a somewhat better risk profile, an analysis adjusted for many risk factors still yielded a strong inverse association between current hormone use and major coronary disease. Unknown confounders may have influenced our results, but to explain the apparent benefit on the basis of confounding variables, one must postulate unknown risk factors that are extremely strong predictors of disease and closely associated with hormone use.

A substantial body of biologic data supports the role of estrogen in reducing the risk of coronary dis-ease,[4,18-24] but the effect of progestin added to estrogen is less clear. Miller et al.[18] found that the estrogen-induced elevation in HDL cholesterol levels was attenuated by 14 to 17 percent with the addition of progestin, although there was little change in the estrogen-induced reduction in LDL cholesterol levels. In the Postmenopausal Estrogen/Progestin Interventions trial,[5] 875 women were randomly assigned to receive placebo, oral estrogen alone, or one of three estrogen–progestin regimens. HDL cholesterol levels were increased and LDL cholesterol levels were decreased in all the treatment groups. The decreases in LDL cholesterol levels were similar for all regimens, but the HDL cholesterol levels were significantly less elevated in the women who took estrogen with medroxyprogesterone acetate than in those who took estrogen alone.

In a study of monkeys given either estrogen alone or estrogen combined with progestin, there was a reduction of approximately 50 percent in the extent of coronary atherosclerosis after 30 months in both groups, as compared with monkeys given placebo.[25] In addition, cholesterol-fed rabbits given estrogen alone or estrogen with progestin had similar decreases in aortic cholesterol accumulation, as compared with rabbits given placebo.[26] In ovariectomized ewes, however, estrogen-induced increases in uterine blood flow were reduced by 20 to 35 percent with the addition of progestin; the withdrawal of progestin immediately restored the flow.[6]

The few epidemiologic studies of estrogen with progestin for the most part found an inverse association between combined therapy and the risk of coronary disease. In two British studies, compounds

TABLE 5. RELATIVE RISK OF CORONARY HEART DISEASE AND RATE DIFFERENCES AMONG CURRENT HORMONE USERS AS COMPARED WITH WOMEN WHO NEVER USED HORMONES, ACCORDING TO CATEGORIES OF RISK FACTORS.

VARIABLE	PERSON-YEARS	NO. OF CASES	MULTIVARIATE-ADJUSTED RELATIVE RISK (95% CI)*	RATE DIFFERENCE (CASES PREVENTED/ 100,000 WOMEN/YR)†
Age				
<50 yr				
Never used	29,881	22	1.0	
Currently used	35,379	4	0.18 (0.05–0.60)	61
50–59 yr				
Never used	213,636	272	1.0	
Currently used	92,922	61	0.71 (0.52–0.96)	37
60–71 yr				
Never used	81,231	158	1.0	
Currently used	38,070	33	0.66 (0.44–1.01)	66
Smoking status				
Current smoker				
Never used	92,337	253	1.0	
Currently used	35,734	36	0.43 (0.29–0.62)	168
Nonsmoker				
Never used	136,279	106	1.0	
Currently used	72,177	22	0.55 (0.34–0.91)	35
Type of menopause				
Surgical				
Never used	20,755	26	1.0	
Currently used	77,175	38	0.52 (0.31–0.88)	75
Natural				
Never used	266,375	371	1.0	
Currently used	63,555	40	0.61 (0.43–0.85)	54
Body-mass index				
<23.0				
Never used	88,979	83	1.0	
Currently used	65,494	28	0.52 (0.33–0.84)	45
23.0–28.9				
Never used	126,367	140	1.0	
Currently used	69,535	40	0.67 (0.46–0.98)	36
≥29.0				
Never used	55,476	116	1.0	
Currently used	18,976	20	0.67 (0.40–1.13)	65
Blood pressure				
High				
Never used	88,526	241	1.0	
Currently used	43,502	54	0.68 (0.48–0.95)	84
Normal				
Never used	236,222	211	1.0	
Currently used	122,869	44	0.54 (0.38–0.76)	41
Cholesterol level				
High				
Never used	49,636	113	1.0	
Currently used	34,367	37	0.63 (0.41–0.97)	83
Normal				
Never used	275,112	339	1.0	
Currently used	132,004	61	0.60 (0.45–0.81)	49

*The analysis was adjusted for age (in five-year categories), time (in two-year categories), age at menopause (in two-year categories), body-mass index (in quintiles), diabetes (yes or no), high blood pressure (yes or no), high cholesterol level (yes or no), cigarette smoking (never, formerly, or currently [1 to 14, 15 to 24, or 25 or more cigarettes per day]), past oral-contraceptive use (yes or no), parental history of myocardial infarction before the age of 60 years (yes or no), and type of menopause (natural or surgical). In the subgroup analyses of body-mass index, blood pressure, cholesterol level, cigarette smoking, and type of menopause, the risk factor being examined was not included in this model. CI denotes confidence interval.

†To calculate the rate difference, incidence rates for coronary heart disease (cases per 100,000 women per year) were directly standardized to the age distribution among women who never used hormones and did not have the specified risk factor.

other than conjugated estrogen were frequently used; Hunt et al. reported a lower risk in hormone users than in the general population,[27] whereas Thompson et al. reported null findings in a case–control study.[28] In a clinical trial involving 168 women, Nachtigall et al.[29] reported a lower incidence of myocardial infarction in women given estrogen and cyclic progestin than in those given placebo (relative risk, 0.32; P>0.05), although there was only one case of infarction in the treatment group. In a population-based case–control study, Psaty et al.[30] reported similarly decreased risks of myocardial infarction among current users of estrogen alone (relative risk, 0.69; 95 percent confidence interval, 0.47 to 1.02) and current users of estrogen with progestin (relative risk, 0.68; 95 percent confidence interval, 0.38 to 1.22). In a prospective analysis of health care records in Uppsala, Sweden, Falkeborn et al. found that women given a prescription for an estradiol–levonorgestrel combination had a 50 percent lower risk of myocardial infarction than women in the general population of that region[31]; among the women given a prescription for estrogen alone, the relative risk was 0.74.

The data on stroke are unclear. In the Leisure World study,[32] the relative risk of mortality from stroke was 0.3 among current estrogen users as compared with women who had never used estrogen (P<0.05). Falkeborn et al.[33] reported that the relative risk of stroke was 0.72 among women taking estrogen and 0.61 among those taking combined hormones. In our study, however, there was no decrease in the risk of stroke among hormone users, regardless of whether they used estrogen alone or with progestin, and there was the suggestion of an increased risk associated with the use of high doses of estrogen. Similarly, a large prospective study in Copenhagen, Denmark,[34] found little association between the risk of stroke and hormone use (relative risk, 0.8; 95 percent confidence interval, 0.4 to 1.4). At present, the data are still too sparse to clarify the effect of hormones on the risk of stroke.

In conclusion, the addition of progestin to estrogen does not appear to attenuate the cardioprotective effects of hormone therapy in relatively young postmenopausal women. This issue will be addressed more directly in the next decade, when the results of clinical trials, such as the Women's Health Initiative, are known. Any cardiovascular benefits of postmenopausal hormone use, however, must be evaluated in the light of possible risks, such as an increased risk of breast cancer, particularly among long-term current users and older women.[35]

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