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A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease

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Background: **Most primary prevention studies have found that long-term users of postmenopausal hormone therapy are at lower risk for coronary events, but numerous questions remain. An adverse influence of hormone therapy on cardiovascular risk has been suggested during the initial year of use; however, few data are available on short-term hormone therapy. In addition, the cardiovascular effects of daily doses of oral conjugated estrogen lower than 0.625 mg are unknown, and few studies have examined estrogen plus progestin in this regard.**

Objective: **To investigate duration, dose, and type of postmenopausal hormone therapy and primary prevention of cardiovascular disease.**

Design: **Prospective, observational cohort study.**

Setting: **Nurses' Health Study, with follow-up from 1976 to 1996.**

Patients: **70 533 postmenopausal women, in whom 1258 major coronary events (nonfatal myocardial infarction or fatal coronary disease) and 767 strokes were identified.**

Measurements: **Details of postmenopausal hormone use were ascertained by using biennial questionnaires. Cardiovascular disease was established by using a questionnaire and was confirmed by medical record review. Logistic regression models were used to calculate relative risks and 95% CIs, adjusted for confounders.**

Results: **When all cardiovascular risk factors were considered, the risk for major coronary events was lower among current users of hormone therapy, including short-term users, compared with never-users (relative risk, 0.61 [95% CI, 0.52 to 0.71]). Among women taking oral conjugated estrogen, the risk for coronary events was similarly reduced in those currently taking 0.625 mg daily (relative risk, 0.54 [CI, 0.44 to 0.67]) and those taking 0.3 mg daily (relative risk, 0.58 [CI, 0.37 to 0.92]) compared with never-users. However, the risk for stroke was statistically significantly increased among women taking 0.625 mg or more of oral conjugated estrogen daily (relative risk, 1.35 [CI, 1.08 to 1.68] for 0.625 mg/d and 1.63 [CI, 1.18 to 2.26] for ≥1.25 mg/d) and those taking estrogen plus progestin (relative risk, 1.45 [CI, 1.10 to 1.92]). Overall, little relation was observed between combination hormone therapy and risk for cardiovascular disease (major coronary heart disease plus stroke) (relative risk, 0.91 [CI, 0.75 to 1.11]).**

Conclusions: **Postmenopausal hormone use appears to decrease risk for major coronary events in women without previous heart disease. Furthermore, 0.3 mg of oral conjugated estrogen daily is associated with a reduction similar to that seen with the standard dose of 0.625 mg. However, estrogen at daily doses of 0.625 mg or greater and in combination with progestin may increase risk for stroke.**

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Whether to take hormone therapy is one of the most difficult medical decisions that healthy postmenopausal women face. The apparent coronary benefits (1) of hormone use are an important part of that decision. Although the data appear consistent in suggesting long-term coronary benefits, the Heart and Estrogen/progestin Replacement Study (2) showed an increased risk for coronary events during the first year of therapy in women with existing heart disease; we also found such an elevated risk in an examination of secondary prevention in the Nurses' Health Study (3). More recently, a report from the Women's Health Initiative, an ongoing randomized clinical trial of hormone therapy for primary prevention of cardiovascular disease, suggested similar findings in healthy women (National Institutes of Health. Press release). However, additional data on short-term effects of hormone use in women without previous cardiovascular disease are sparse.

Many further questions also remain. Among them is the cardiovascular effect of daily doses lower than the standard 0.625 mg of oral conjugated estrogen. Recent studies suggest that lower doses of hormone therapy provide bone benefits (4) and, compared with higher doses, might decrease the risk for thromboembolism (5) and reduce endometrial hyperplasia (4). However, few data are currently available on the relation between low-dose estrogen and primary prevention of heart disease and stroke.

In an earlier report, we examined the relation between postmenopausal hormone therapy and primary prevention of cardiovascular disease based on 16 years of

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follow-up from the Nurses' Health Study (6). In the current analysis, we have almost 50% more follow-up time among women taking daily doses less than 0.625 mg and more than 800 additional cases of cardiovascular disease, allowing more precise assessment of specific associations. Thus, we now report on the relation among low-dose estrogen, short-term hormone use, and cardiovascular events in 70 533 postmenopausal women with no previous cardiovascular disease who were followed for up to 20 years. We also provide additional information on the effects of estrogen combined with progestin.

METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study began in 1976 when 121 700 female nurses 30 to 55 years of age completed a mailed questionnaire about their postmenopausal hormone use and medical history, including cardiovascular disease and its risk factors. We update information with biennial follow-up questionnaires. Dietary and physical activity questionnaires were added in 1980. Cohort follow-up is greater than 90%.

Ascertainment of Hormone Use

In 1976, women were asked about use and duration of hormone therapy after menopause. Beginning in 1978, we collected information on type of hormones taken, and starting in 1980, we asked about the dose of oral conjugated estrogen. All information is updated biennially.

Identification of Cardiovascular Disease

We identified first occurrences of nonfatal myocardial infarction, fatal coronary disease, and fatal and nonfatal stroke between the return of the 1976 questionnaire and 1 June 1996. Nurses who reported a nonfatal infarction or stroke were asked for permission to review their medical records. Nonfatal myocardial infarctions were confirmed by hospital records if they met World Health Organization criteria (7) (symptoms plus either elevated levels of cardiac enzymes or diagnostic electrocardiograms). Infarctions that required hospitalization and were corroborated by interview or letter but for which medical records were unobtainable were included as "probable." Infarctions of indeterminate age discovered on routine examination were excluded.

Nonfatal strokes were confirmed by review of medical records if they were characterized by a typical neurologic deficit, were rapid in onset, lasted at least 24 hours, and met the criteria of the National Survey of Stroke (8). We classified strokes as ischemic (thrombotic or embolic occlusion of a cerebral artery), subarachnoid hemorrhage, or intraparenchymal hemorrhage. We excluded subdural hematomas and strokes caused by infection or neoplasia. Strokes that required hospitalization and were corroborated by letter or interview but for which medical records were unavailable were included as "probable."

Most deaths were reported by the participants' families. We searched the National Death Index to identify deaths among nonrespondents to each 2-year questionnaire; mortality follow-up was more than 98% complete (9). For all deaths possibly attributable to cardiovascular causes, we requested permission from relatives (subject to state regulations) to review the medical records. Deaths were considered to be due to coronary disease if medical records or autopsy findings confirmed a fatal myocardial infarction. We also included coronary disease listed on the death certificate as the underlying cause without another, more plausible cause, if the nurse was known (from hospital records, family, or other sources) to have had coronary disease before death. In no case was the cause listed on the death certificate used as the sole criterion for coronary death. Sudden death within 1 hour of the onset of symptoms in participants with no other plausible cause of death besides coronary disease was also included. Fatal strokes were documented by autopsy or hospital records or if stroke was listed as the underlying cause on the death certificate.

The category of "major coronary heart disease" combines nonfatal myocardial infarction and coronary death; similarly, "total stroke" includes nonfatal and fatal cases. The category of "combined cardiovascular disease" includes major coronary heart disease and stroke. Confirmed and probable cases in each category were analyzed together (80% of major coronary events and 73% of strokes were confirmed). In this and previous analyses (6), results for probable cases were similar to those for confirmed cases. The investigators conducted all interviews and record reviews without knowledge of participants' hormone use status.

Population for Analysis

Women who reported stroke, myocardial infarction, angina, coronary revascularization, or cancer (except nonmelanoma skin cancer) on the 1976 questionnaire were

excluded because their disease may have caused them to alter their hormone use. Similarly, women who reported such diagnoses on a subsequent questionnaire were excluded from further analysis. Thus, at the start of each 2-year interval, the base population included no women reporting these diagnoses.

Our own studies (6, 10) and other studies (11) have suggested that hormone therapy may differentially affect incident and fatal strokes; thus, we separately examined deaths due to stroke. In these analyses, we excluded women with cancer and cardiovascular disease at baseline but did not update the exclusions because the women who develop cardiovascular disease during follow-up are those most likely to die of stroke.

We classified women as postmenopausal from the time of natural menopause or hysterectomy with bilateral oophorectomy. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for smokers and 56 years for nonsmokers). In this cohort, the women's reports of age at menopause (12) and type of menopause (13) were highly accurate.

In 1976, 21 947 postmenopausal women entered the analysis, and 48 586 women were added during follow-up as they became postmenopausal, for a total of 70 533 participants; 808 825 person-years of follow-up were accrued from 1976 to 1996.

Statistical Analysis

For each participant, person-months were allocated to hormone categories according to the 1976 data and were updated every 2 years (for estrogen dose, follow-up began in 1980). For analyses of type of hormone therapy, we assigned the regimen reported on the 1978 questionnaire to women who reported hormone use in 1976. Analyses of type of hormone therapy were limited to users of oral conjugated estrogen with or without oral medroxyprogesterone acetate, since these were the most common hormone regimens. If no data were available on hormones in a given time period, women were assigned to a missing category for that time period. To maintain the prospective nature of the study, hormone use (including duration) during each 2-year period was established from women's reports at the start of the period; thus, we probably underestimate duration of use by an average of 1 year. Follow-up for a participant ended at the first diagnosis of cardiovascular disease, death, or 1 June 1996, whichever came first.

The primary analysis is based on incidence rates for which person-months of follow-up were used as the denominator. We used relative risk as the measure of association, defined as the incidence of cardiovascular events among women in various categories of hormone use divided by the incidence among women who never used hormones. We computed age-specific rates by using 5-year categories (14) and age-adjusted relative risks by using Mantel–Haenszel rate ratios (15) with 95% CIs (16).

We used pooled logistic regression across the ten 2-year time periods to adjust simultaneously for potential confounding factors (17). In this approach, independent blocks of person-time are pooled for regression analysis, and time-varying covariates are readily accommodated by assigning successive blocks of person-time to the covariate values at the start of each follow-up cycle. The dependence of the incidence rates on time is modeled nonparametrically with indicator variables. Simulation studies have established the asymptotic equivalence of pooled logistic regression to Cox regression with time-dependent covariates (18). The necessary conditions for this equivalence include relatively short time intervals and small probability of the outcome during each interval, both of which are satisfied here. Information on most variables was updated biennially, including age (5-year categories), body mass index (<21 kg/m^2, 21 to 22 kg/m^2, 23 to 25 kg/m^2, 26 to 29 kg/m^2, 30 to 31 kg/m^2, or ≥ 32 kg/m^2), cigarette smoking (never; past; or current smoker of 1 to 14 cigarettes/d, 15 to 24 cigarettes/d, 25 to 34 cigarettes/d, or ≥ 35 cigarettes/d), self-reported history of hypertension (yes or no), diabetes (yes or no), and elevated cholesterol level (yes or no). The following confounding variables were not updated: type of menopause (natural or surgical), age at menopause (<50 years, 50 to 53 years, or ≥ 54 years), parental myocardial infarction before 60 years of age (yes or no), and previous oral contraceptive use (yes or no). For certain analyses, saturated fat intake (quintiles), alcohol use (none, <5 g/d, 5 to 14.9 g/d, or ≥ 15 g/d), vitamin E supplementation (yes or no), multivitamin use (yes or no), aspirin use (none, 1 to 6 per week, or ≥ 7 per week), and physical activity (none or at least once per week) were added to the model; information on these variables was updated every 4 years, with

Table 1. **Rates of Cardiovascular Disease among Women Who Never Used Postmenopausal Hormone Therapy, Nurses' Health Study, 1976–1996**

Age	Major Coronary Heart Disease	Stroke
	cases/100 000 person-years	
<50 y	114	20
50–54 y	114	57
55–59 y	174	64
60–64 y	264	121
65–75 y	308	229

follow-up from 1980 to 1996. We used SAS software for all analyses (SAS Institute, Inc., Cary, North Carolina).

We calculated rate differences based on the rate of cardiovascular disease for postmenopausal Nurses' Health Study participants 55 to 59 years of age who never used hormone therapy. We multiplied this rate by the multivariate-adjusted relative risks to obtain the cardiovascular disease rate in various categories of hormone use. We subtracted the rates estimated for hormone use categories from the rate among women who never took hormones to obtain rate differences, or the number of cardiovascular disease cases that could be avoided with hormone use.

Role of the Funding Source

The current analysis was funded by the National Institutes of Health, which had no role in the study design, conduct, or reporting of results.

RESULTS

From 1976 to 1996, we identified 953 nonfatal myocardial infarctions, 305 coronary deaths, and 767 strokes (432 ischemic, 174 hemorrhagic, and 161 other or unspecified type); 119 deaths were due to stroke. Rates of coronary heart disease and stroke increased dramatically with age (**Table 1**). Never-users of hormones represented 44.3% of the follow-up time, current users accounted for 32.8%, and past users accounted for 22.9%.

Risk for Major Coronary Events

Overall, current use of hormone therapy was associated with an age-adjusted relative risk for major coronary event of 0.54 (95% CI, 0.46 to 0.62) (**Table 2**). Adjustment for additional cardiovascular risk factors attenuated the relative risk slightly to 0.61 (CI, 0.52 to 0.71), largely because current users tended to be leaner and to smoke less. Further control for dietary variables, use of vitamin supplements, aspirin use, and physical activity had only a small additional influence on the relative risk estimate (relative risk, 0.64 [CI, 0.54 to 0.76]); thus, we did not consider these factors in subsequent analyses because it would require us to limit the follow-up (this information was first requested in 1980). Duration of hormone use had little influence on the observed inverse association. The risk for a major coronary event was reduced in short-term users compared with never-users (relative risk, 0.40 [CI, 0.21 to 0.77]); however, our ability to assess the impact of hormone therapy in the first months of use is limited because we established duration of therapy at the start of each 2-year follow-up period and probably underestimated its duration during follow-up by an average of 1 year.

Risk for Stroke

We found little association between current use of hormone therapy and risk for stroke (**Table 3**). Overall, the relative risk was 1.13 (CI, 0.94 to 1.35) for current users of hormone therapy and 1.32 (CI, 0.76 to 2.32) for short-term users compared with never-users, although we had limited statistical power to estimate short-term effects. The results were similar when we separately examined ischemic and hemorrhagic strokes, although the risk for ischemic stroke was increased significantly in current users compared with never-users (relative risk, 1.26 [CI, 1.00 to 1.61]). For deaths due to

Table 2. **Risk for Major Coronary Heart Disease among Current Postmenopausal Hormone Users and Nonusers, Nurses' Health Study, 1976–1996**

Hormone Use	Person-Years of Follow-up	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*
Never	358 125	662	1.0 (referent)	1.0 (referent)
Past	185 497	337	0.88 (0.77–1.00)	0.82 (0.72–0.94)
Current	265 203	259	0.54 (0.46–0.62)	0.61 (0.52–0.71)
<1 y†	20 091	9	0.30 (0.16–0.58)	0.40 (0.21–0.77)
1–1.9 y†	19 155	9	0.32 (0.16–0.61)	0.41 (0.21–0.80)
2–4.9 y†	78 928	60	0.47 (0.36–0.61)	0.53 (0.41–0.70)
5–9.9 y†	77 435	74	0.51 (0.40–0.65)	0.58 (0.45–0.74)
≥10 y†	69 594	107	0.69 (0.56–0.85)	0.74 (0.59–0.91)

* Adjusted for age, body mass index, history of diabetes, hypertension, high cholesterol level, age at menopause, cigarette smoking, and parental history of premature heart disease.
† Duration of use is underestimated by an average of 1 year, since duration during each 2-year follow-up period was established at the start of each period.

Table 3. **Risk for Stroke among Postmenopausal Current Users of Hormone Therapy and Nonusers by Duration of Therapy, Nurses' Health Study, 1976–1996**

Hormone Use	Person-Years of Follow-up	All Stroke			Ischemic Stroke			Hemorrhagic Stroke		
		Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*
Never	358 125	312	1.0 (referent)		170	1.0 (referent)		79	1.0 (referent)	
Past	185 497	217	1.11 (0.93–1.33)	1.02 (0.85–1.24)	120	1.06 (0.84–1.34)	1.01 (0.79–1.30)	45	1.07 (0.74–1.55)	0.95 (0.65–1.40)
Current	265 203	238	1.03 (0.87–1.22)	1.13 (0.94–1.35)	142	1.13 (0.90–1.41)	1.26 (1.00–1.61)	50	0.89 (0.62–1.27)	0.93 (0.64–1.34)
<1 y†	20 091	13	1.05 (0.60–1.85)	1.32 (0.76–2.32)	6	0.94 (0.40–2.20)	1.07 (0.44–2.61)	5	1.39 (0.57–3.38)	1.56 (0.63–3.90)
1–1.9 y†	19 155	10	0.85 (0.45–1.60)	1.04 (0.55–1.97)	6	1.03 (0.46–2.32)	1.32 (0.58–3.00)	2	0.54 (0.13–2.28)	0.63 (0.15–2.59)
2–4.9 y†	78 928	61	1.08 (0.82–1.43)	1.14 (0.86–1.52)	36	1.25 (0.87–1.79)	1.31 (0.90–1.92)	14	0.87 (0.49–1.55)	0.95 (0.54–1.67)
5–9.9 y†	77 435	63	0.94 (0.71–1.23)	1.05 (0.79–1.38)	42	1.14 (0.81–1.60)	1.36 (0.96–1.92)	12	0.73 (0.40–1.34)	0.74 (0.40–1.36)
≥10 y†	69 594	91	1.09 (0.85–1.39)	1.17 (0.91–1.49)	52	1.02 (0.74–1.39)	1.17 (0.84–1.63)	17	1.11 (0.66–1.87)	1.03 (0.59–1.78)

* Adjusted for age, body mass index, history of diabetes, hypertension, high cholesterol level, age at menopause, cigarette smoking, and parental history of premature heart disease.
† Duration of use is underestimated by an average of 1 year, since duration during each 2-year follow-up period is established at the start of each period.

stroke, the relative risk was 0.81 (CI, 0.54 to 1.22) for current users compared with never-users. When we combined cardiovascular diseases (major coronary heart disease plus stroke), we found a lower rate of cardiovascular disease among current users than never-users (relative risk, 0.77 [CI, 0.69 to 0.87]); however, these results are influenced by the preponderance of coronary heart disease end points in this cohort.

Estrogen Dose and Cardiovascular Risk

We observed a decreased risk for major coronary disease in women taking 0.625 mg of estrogen daily (relative risk, 0.54 [CI, 0.44 to 0.67]) and those taking 0.3 mg daily (relative risk, 0.58 [CI, 0.37 to 0.92]) compared with women who had never taken hormones (**Table 4**). However, risk for stroke was increased modestly but statistically significantly among women who took 0.625 mg daily (relative risk, 1.35 [CI, 1.08 to 1.68]) and those who took 1.25 mg or more daily (relative risk, 1.63 [CI, 1.18 to 2.26]) (**Table 4**). Women who took 0.3 mg/d seemed to experience a decrease in risk (relative risk, 0.54 [CI, 0.28 to 1.06]), although this finding was not statistically significant. The increased risk at a daily dose of 0.625 mg was similar when we separately analyzed ischemic strokes and hemorrhagic strokes. These relative risks appeared to be somewhat attenuated for deaths due to stroke (relative risk, 1.01 [CI, 0.59 to 1.71] for women taking 0.625 mg/d and 1.25 [CI, 0.57 to 2.77] for those taking ≥1.25 mg/d). Overall, compared with never-users, risk for combined cardiovascular disease (major coronary heart disease plus stroke) was reduced among women taking 0.3 mg of estrogen daily (relative risk, 0.57 [CI, 0.39 to 0.83]); the reduced risk was smaller among women taking higher doses (relative risk, 0.81 [CI, 0.70 to 0.95 for women taking 0.625 mg/d and 0.95 [CI, 0.76 to 1.20] for those taking ≥1.25 mg/d).

Type of Hormone Therapy and Cardiovascular Risk

We found a similar reduction in risk for coronary heart disease among women taking oral conjugated estrogen alone (relative risk, 0.55 [CI, 0.45 to 0.68]) and those taking estrogen plus progestin (relative risk, 0.64 [CI, 0.49 to 0.85]). These results are consistent with those of our previous report based on 16 years of follow-up (6); however, the current estimate is substantially more precise because more than twice as many person-years of combined hormone use were included. We found little association between stroke and use of oral conjugated estrogen alone (relative risk, 1.18 [CI, 0.95 to 1.46]), but we observed a 45% higher risk for stroke among women taking estrogen combined with progestin than in those who had never taken hormone therapy (relative risk, 1.45 [CI, 1.10 to 1.92]). These results did not appear to be confounded by the dose of estrogen; when we confined the analysis to women taking 0.625 mg of oral conjugated estrogen daily, the relative risks were 1.24 (CI, 0.95 to 1.62) for estrogen alone and 1.54 (CI, 1.12 to 2.11) for estrogen plus progestin. For fatal strokes, relative risk seemed to be

Table 4. **Risk for Major Coronary Heart Disease and Stroke among Postmenopausal Current Users of Hormone Therapy and Nonusers by Dose of Oral Conjugated Estrogen, Nurses' Health Study, 1980–1996**

Hormone Use	Person-Years of Follow-up	Coronary Heart Disease			All Stroke		
		Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*
Never	313 661	609	1.0 (referent)		290	1.0 (referent)	
0.3 mg	19 964	19	0.46 (0.29–0.72)	0.58 (0.37–0.92)	9	0.43 (0.22–0.83)	0.54 (0.28–1.06)
0.625 mg	116 150	99	0.44 (0.35–0.54)	0.54 (0.44–0.67)	124	1.11 (0.90–1.37)	1.35 (1.08–1.68)
≥1.25 mg	39 026	41	0.62 (0.45–0.84)	0.70 (0.51–0.97)	46	1.58 (1.16–2.15)	1.63 (1.18–2.26)

* Adjusted for age, body mass index, history of diabetes, hypertension, high cholesterol level, age at menopause, cigarette smoking, and parental history of premature heart disease.

lower among current users of estrogen alone (0.81 [CI, 0.49 to 1.34]) and users of combined therapy (1.22 [CI, 0.65 to 2.28]). When we combined heart disease and stroke end points, we found a 25% reduced risk for cardiovascular disease among current users of estrogen alone (relative risk, 0.75 [CI, 0.65 to 0.87]) but little relation between current use of combined hormone therapy and cardiovascular disease (relative risk, 0.91 [CI, 0.75 to 1.11]).

Absolute Effect of Hormone Use on Cardiovascular Disease

To assess the absolute effect of hormone use on cardiovascular disease, we calculated rate differences to measure the number of cardiovascular disease cases that could be avoided with postmenopausal hormone use. According to data from this Nurses' Health Study cohort, if 100 000 postmenopausal women 55 to 59 years of age were given hormone therapy, 55 fewer cases of cardiovascular disease per year would be expected. For estrogen alone, 60 fewer cases would be expected, and with combined therapy, 21 fewer cardiovascular disease events would be expected.

DISCUSSION

In this large observational, prospective study, the risk for major coronary events appeared to be substantially decreased among current users of hormone therapy. For women taking oral conjugated estrogen, daily doses of 0.625 mg and 0.3 mg were both associated with a reduced risk for heart disease, as was estrogen, alone or in combination with a progestin. However, we observed a modest increase in risk for stroke among women taking 0.625 mg or more of conjugated estrogen daily and those taking estrogen plus progestin.

The Heart and Estrogen/progestin Replacement Study (2) was the first large-scale randomized clinical trial of hormone use and secondary prevention of cardiovascular disease. These data indicated that combined hormone therapy in women with previous heart disease increased their risk for a subsequent event by 52% during the first year of use. In a comparable examination of 2489 women with previous coronary disease from the Nurses' Health Study (3), we also found a higher rate of recurrent events with short-term hormone use.

In their trial of primary prevention, the Women's Health Initiative recently reported that risk for cardiovascular disease may be increased during the initial year of hormone use (National Institutes of Health. Press release); however, additional data on the impact of short-term hormone use in healthy women are sparse. In the Leisure World Study (19), which included a prospective observational cohort, the relative risk was 0.73 (CI, 0.46 to 1.16) for recent hormone use of 3 or fewer years' duration, although their estimate of duration was based on a single assessment of hormone use at baseline. In a small prospective study, Avila and colleagues (20) found little relation between less than 1 year of current hormone use (relative risk, 0.9 [CI, 0.4 to 1.9]) and myocardial infarction in women without previous heart disease. In a case–control study, Heckbert and coworkers (21) reported that current hormone use of less than 1.8 years was not related to myocardial infarction (relative risk, 0.91 [CI, 0.60 to 1.38]), and Sidney and associates (22) observed no association between current hormone use of less than 1 year and primary prevention of myocardial infarction (relative risk, 0.95 [CI, 0.37 to 2.45]). In a hospital-based case–control study of primary prevention (23), short-term hormone use appeared to have adverse cardiac effects (relative risk, 1.9; $P < 0.05$).

Table 4. **Continued**

Ischemic Stroke			Hemorrhagic Stroke		
Cases, *n*	**Age-Adjusted Relative Risk (95% CI)**	**Multivariate-Adjusted Relative Risk (95% CI)***	**Cases, *n***	**Age-Adjusted Relative Risk (95% CI)**	**Multivariate-Adjusted Relative Risk (95% CI)***
160	1.0 (referent)		69	1.0 (referent)	
4	0.33 (0.12–0.89)	0.43 (0.16–1.16)	2	0.45 (0.11–1.85)	0.51 (0.13–2.10)
73	1.15 (0.87–1.52)	1.44 (1.07–1.93)	31	1.22 (0.80–1.87)	1.41 (0.91–2.19)
29	1.86 (1.25–2.76)	2.00 (1.32–3.05)	9	1.20 (0.60–2.39)	1.18 (0.58–2.38)

In most of these studies, the CIs are wide and are compatible with a substantial decrease in risk for heart disease as well as a modest increase. In our primary prevention study, we found a lower rate of heart disease among women who were short-term users of hormone therapy than among women who never used hormone therapy; this decrease was statistically significant ($P = 0.006$) and the upper bound of the 95% CI was 0.80, indicating a negligible likelihood that our data could be compatible with an increased risk similar to that observed for secondary prevention in the Heart and Estrogen/progestin Replacement Study. However, duration of hormone use during a 2-year follow-up cycle was established at the start of each follow-up period; therefore, we probably underestimated duration and have restricted ability to assess the impact of hormone therapy in the initial months of use.

Nonetheless, we found an elevated rate of coronary heart disease with short-term hormone use in our study of secondary prevention in nurses (3); thus, we suspect that any increase for primary prevention is less than that for secondary prevention, or that the initial increase is more quickly reversed in primary prevention. Unfortunately, even biennial follow-up is rare in large prospective, observational studies, and it is unlikely that many investigations will be able to provide further information on cardiovascular risks associated with initiation of hormone therapy. Even the experimental data in healthy women have largely identified acute benefits of estrogen on cardiovascular variables. For example, Bourne and colleagues (24) reported improved blood flow in a study lasting 2.5 months, Gangar and associates (25) observed reduced arterial impedance after 9 weeks of estrogen therapy, and Sack and coworkers (26) found that women given estrogen for 3 weeks had prolonged lag time of low-density lipoprotein oxidation by 16% ($P < 0.01$ compared with before treatment). Thus, although an elevation in C-reactive protein level with hormone therapy was recently established (27), it remains unclear exactly how postmenopausal hormone use might increase risk for cardiovascular disease, particularly in women with no previous coronary condition.

The cardiovascular effects of various estrogen doses are also not clear. To our knowledge, only one other epidemiologic study examined less than 0.625 mg of oral conjugated estrogen and primary prevention of heart disease. Avila and colleagues (20) reported a lower risk for myocardial infarction among women taking 0.625 mg of estrogen daily compared with nonusers (relative risk, 0.5 [CI, 0.2 to 1.3]) and no relation among those taking 0.3 mg daily (relative risk, 1.0 [CI, 0.3 to 2.5]), but the latter result was based on four patients using estrogen and the CI was wide. Our data strongly suggest a reduced risk for heart disease with 0.3 mg of estrogen daily.

Likewise, few data specifically address the issue of estrogen dose and primary prevention of stroke. Pfeffer (28) reported no relation between estrogen and stroke, regardless of the dose taken (although the data on dose were not presented), and Paganini-Hill and colleagues (11) found a similarly decreased but nonsignificant risk for fatal stroke among women taking 0.625 mg of estrogen or less daily (relative risk, 0.73 [CI, 0.32 to 1.66]) and those taking 1.25 mg or more (relative risk, 0.49 [CI, 0.19 to 1.27]); however, these latter estimates are based on seven and five patients with stroke who took those respective doses. In this study and our previous analyses (6) of primary prevention, we observed a strong dose–response relation of estrogen to risk for stroke.

The influence of added progestin on risk for cardio-

vascular disease is still not well understood. Experimental data have established that oral progestin attenuates but does not obliterate the increase in high-density lipoprotein cholesterol induced by estrogen alone (29), and it may inhibit improvement of blood flow (30) in estrogen users. Although epidemiologic data on primary prevention of heart disease with combined therapy are limited, almost all studies (1) indicate similarly decreased risks among long-term users of estrogen alone and combined with progestin, including our examinations of primary (6) and secondary (3) coronary heart disease prevention. Fewer studies have assessed the effect of combination hormone therapy on primary prevention of stroke, but these have generally reported null results, regardless of hormone regimen (31–33). For example, in one of the largest stroke studies, Pedersen and coworkers (31) reported odds ratios of 1.16 (CI, 0.86 to 1.58) for current use of estrogen alone and 1.17 (CI, 0.92 to 1.47) for estrogen combined with progestin. In a case–control study of ischemic stroke, Petitti and associates (32) found an odds ratio of 1.04 (CI, 0.60 to 1.10) for estrogen alone and 0.60 (CI, 0.31 to 1.16) for estrogen with progestin.

Our data on hormone therapy and primary prevention of cardiovascular disease are observational; participants in the Nurses' Health Study choose whether to take hormone therapy. Several studies have reported that in the general population, hormone users differ from nonusers in ways that could affect their risk for cardiovascular disease (34, 35). However, the Nurses' Health Study is not a general population study; it is a cohort of registered nurses, all of whom have knowledge about and access to health care. We have found few substantial differences in lifestyle factors, including screening habits, diet, and exercise, between women who take hormones and those who do not (6). All of our analyses were carefully adjusted for potential confounders, including the two variables that seem to be most important: cigarette smoking and body mass index. In numerous analyses in which we have isolated samples of even more homogeneous participants (for example, only those who report regular physician visits or only those with no cardiovascular risk factors) (6), our results have been consistently almost identical to those in the entire cohort, which strongly suggests that confounding by lifestyle or health practice probably does not explain our observations.

Ongoing randomized clinical trials such as the Women's Health Initiative will provide additional data in the coming years, but women today must make informed decisions about their hormone use. Furthermore, clinical trials usually cannot provide information on diverse hormone doses or regimens. The Nurses' Health Study investigation of primary prevention indicates that hormone therapy may be associated with coronary benefits and that low doses of estrogen as well as estrogen combined with progestin may be equally effective in providing these benefits. However, the risk for stroke appears to be increased with hormone use. In addition, hormone therapy is related to increased risk for breast cancer (36). Clearly, alternatives should be considered that promote healthy aging and pose no risks, such as physical activity, a healthy diet, and smoking cessation (37).

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