

# Hormone Therapy and Coronary Heart Disease: The Role of Time since Menopause and Age at Hormone Initiation

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## ABSTRACT

**Background:** Apparently discrepant findings have been reported by the Women's Health Initiative (WHI) trial compared with observational studies of postmenopausal hormone therapy (HT) and coronary heart disease (CHD).

**Methods:** We prospectively examined the relation of HT to CHD, according to timing of hormone initiation relative to age and time since menopause. Participants were postmenopausal women in the Nurses' Health Study, with follow-up from 1976 to 2000. Information on hormone use was ascertained in biennial, mailed questionnaires. We used proportional hazards models to calculate multivariable adjusted relative risks (RR) and 95% confidence intervals (CI). We also conducted sensitivity analyses to determine the possible influence of incomplete capture of coronary events occurring shortly after initiation of HT.

**Results:** Women beginning HT near menopause had a significantly reduced risk of CHD (RR = 0.66, 95% CI 0.54-0.80 for estrogen alone; RR = 0.72, 95% CI 0.56-0.92 for estrogen with progestin). In the subgroup of women demographically similar to those in the WHI, we found no significant relation between HT and CHD among women who initiated therapy at least 10 years after menopause (RR = 0.87, 95% CI 0.69-1.10 for estrogen alone; RR = 0.90, 95% CI 0.62-1.29 for estrogen with progestin). Among women who began taking hormones at older ages, we also found no relation between current use of estrogen alone and CHD (for women aged 60+ years, RR = 1.07, 95% CI 0.65-1.78), although there was a suggestion of possible reduced risk for combined HT (RR = 0.65, 95% CI 0.31-1.38). In sensitivity analyses, we found that the incomplete capture of coronary events occurring shortly after initiation of HT could not explain our observation of a reduced risk of coronary disease for current users of HT.

**Conclusions:** These data support the possibility that timing of HT initiation in relation to menopause onset or to age might influence coronary risk.

## INTRODUCTION

**O**BSERVATIONAL STUDIES OF POSTMENOPAUSAL hormone use report substantially lower

coronary heart disease (CHD) rates with the use of either estrogen plus progestin or estrogen alone.<sup>1</sup> In contrast, the Women's Health Initiative (WHI), a randomized trial of postmenopausal

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hormone therapy (HT), reported a possible increase in CHD for women assigned to estrogen with progestin compared with placebo<sup>2,3</sup> and no relation between estrogen alone and CHD.<sup>4</sup>

Numerous hypotheses have been suggested to explain these apparent discrepancies.<sup>5</sup> In addition to the potential for uncontrolled confounding in the observational studies, another methodological limitation of the observational studies is the inability to capture clinical events occurring shortly after initiation of HT (as most studies update subjects' hormone use infrequently). Moreover, there are important differences between the age at enrollment in WHI and the age at hormone initiation in most observational investigations.

The vast majority of subjects in WHI were older women, more than a decade past menopause. The mean age at randomization in both the combined therapy<sup>3</sup> and estrogen only<sup>4</sup> studies was about 63 years, when many of the women likely already had underlying atherosclerosis. In observational studies, most women began HT near the onset of menopause. Trials in oophorectomized monkeys show coronary benefits with HT started at menopause but not later,<sup>6</sup> and indeed, the WHI trials of estrogen alone and of combined therapy suggested differing effects of HT with increasing time since menopause<sup>2</sup> or age at initiation.<sup>4</sup>

Many other important issues about hormone use remain. There are still relatively few data regarding combined HT, and data addressing the relationship between lower estrogen doses and risk of CHD are almost nonexistent. Although we have previously provided data on both these issues,<sup>7</sup> the current analyses include 4 further years of follow-up. With over 200 additional cases of CHD, our statistical power to examine specific associations is substantially enhanced. Thus, in the current paper, we explore the relation of heart disease to type of hormones used and dose of estrogen, in addition to the possible influences of women's CHD risk factor profile, the timing of their HT initiation, and incomplete capture of early clinical events.

## MATERIALS AND METHODS

### *The Nurses' Health Study cohort*

The Nurses' Health Study began in 1976, when 121,700 female nurses, aged 30–55 years, returned a mailed questionnaire including detailed infor-

mation on menopause and postmenopausal hormone use, as well as diagnosis of cardiovascular disease (CVD) and cardiovascular risk factors. We update health and lifestyle information with biennial follow-up questionnaires. Dietary and physical activity questionnaires were added in 1980. Information on cholesterol-lowering drugs was first requested in 1988, and specific information on statin drugs was requested in 1994, 1996, and thereafter. Cohort follow-up is >90%.

### *Ascertainment of postmenopausal hormone use*

On each biennial questionnaire, women were asked details about postmenopausal HT, including current use (within the last month), duration of use, type of hormones taken, and dose of oral conjugated estrogen (data on estrogen dose were first collected in 1980).

### *Identification of coronary heart disease*

We identified first occurrences of nonfatal myocardial infarction (MI) and fatal coronary disease between the return of the 1976 questionnaire and June 1, 2000. Nurses who reported a nonfatal MI were asked for permission to review their medical records. Nonfatal MIs were confirmed by hospital records if they met the World Health Organization (WHO) criteria<sup>8</sup> (symptoms plus either cardiac enzyme elevations or diagnostic electrocardiograms). Infarctions requiring hospitalization and 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 not included.

Most deaths were reported by the participants' families. We searched the National Death Index to identify deaths among the nonrespondents to each 2-year questionnaire; the mortality follow-up was more than 98% complete.<sup>9</sup> For all deaths possibly attributable to coronary disease, we requested permission from relatives (subject to state regulations) to review the medical records. Deaths were considered due to coronary disease if medical records or autopsy findings confirmed a fatal MI. 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 subjects with no other plausible cause of death besides coronary disease was also included. Physician investigators, blinded to subjects' reports of hormone use on the biennial questionnaires, conducted all medical record reviews.

The category of major CHD combines nonfatal MI (74%) and coronary death (26%). Confirmed and probable cases in each category were analyzed together (80% of cases were confirmed); in separate analyses, results for probable cases were similar to those for confirmed cases.

### *Population for analysis*

In primary analyses, women who reported stroke, MI, angina, coronary revascularization, or cancer (except nonmelanoma skin cancer) on the 1976 questionnaire were excluded because these are among the most common major diseases that may have caused subjects to alter their hormone use. These exclusions have been incorporated into previous Nurses' Health Study analyses of HT and CVD.<sup>7</sup> 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.

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 for nonsmokers). The women's reports of age at<sup>10</sup> and type of menopause<sup>11</sup> were highly accurate in this cohort.

Primary analyses included follow-up from 1976 to 2000 and included only women with no prior history of coronary disease. In secondary analyses, we included women who reported previous coronary disease (defined as MI, angina, or coronary revascularization); these analyses were conducted to provide similar inclusion criteria to the WHI study, in which a small proportion of women with existing coronary disease were included (e.g., in the combined therapy trial,<sup>2,3</sup> WHI included 1.8% of women with previous MI, 2.9% with history of angina, 1.3% with revascularization surgery). As in WHI, women with prevalent

coronary disease in our cohort represented a small proportion of the population in these analyses; among current users of estrogen alone or estrogen with progestin, a total of 5.7% of the person-time was among women with prevalent coronary disease.

We also explored the effects of initiating HT at varying intervals since menopause and at different ages. First, we examined women at least 10 years beyond menopause to provide an analysis similar to that of the WHI (in the WHI combined therapy trial, for example, 87% of CHD cases were among women randomized to therapy at least 10 years after menopause). In comparison, in order to separately provide data for women initiating hormones near menopause, we examined women who began hormone use within 4 years of menopause; we chose a cutoff of 4 years to define "near" menopause because our follow-up occurs in 2-year intervals, and we believed that a 2-year cutoff was excessively short and a 6-year cutoff was too long. In these analyses, we excluded women with unknown age at menopause (e.g., those with no uterus, but intact ovaries). In addition, we examined women initiating HT at  $\geq 60$  years, and compared them to women who never used hormones. Finally, we conducted analyses stratifying women by major cardiovascular risk factors.

### *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). We specifically assessed oral conjugated estrogen with or without oral medroxyprogesterone acetate, as these two 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 period. In order to maintain the prospective nature of the study, hormone status during each 2-year period was defined based on women's reports at the start of the period. However, in sensitivity analyses, we evaluated the effect of varying degrees of misclassification of HT for those subjects who initiated therapy subsequent to the start of a given 2-year follow-up period.

Follow-up for a participant ended with a first diagnosis of CVD, or death or June 1, 2000, whichever came first. In analyses stratified by

cholesterol-lowering drugs, we began follow-up in 1988 (when we first asked about these drugs) and applied information on cholesterol-lowering drugs provided in 1988 to the 1990 and 1992 follow-up periods; in 1994 and thereafter, we used the specific data on statin drugs.

Analyses are based on incidence rates using person-months of follow-up as the denominator. We used relative risk (RR) as the measure of association, defined as the incidence rate of coronary events among women in various categories of hormone use divided by the rate among women who never used hormones. We computed age-specific rates using 5-year categories and calculated age-adjusted RRs using Mantel-Haenszel rate ratios,<sup>12</sup> with 95% confidence intervals (CIs).<sup>13</sup> For evaluating statistical differences in the effect of hormones among women who initiated therapy near menopause vs. many years after menopause, we calculated a *p* heterogeneity.

We calculated adjusted RRs with Cox proportional hazards models, controlling for age (continuous), BMI (<21 kg/m<sup>2</sup>, 21–22, 23–25, 26–29, 30–31, 32+), cigarette smoking (never, past, current smoker of 1–14 cigarettes/day, 15–24, 25–34, 35+), history of hypertension (yes, no), diabetes (yes, no), and elevated cholesterol (yes, no), and parental MI before age 60 (yes, no). For certain analyses, alcohol use (none, <5 g/day, 5–14.9, 15+), vitamin E supplementation (yes, no), multivitamin use (yes, no), regular aspirin use (none, 1–6/week, 7+/week), and physical activity (quintiles of MET hours of activity) were added to the model; in these analyses, follow-up began in 1980 when that information was first collected and included only women in the diet cohort (approximately 80% of the subjects). In those models, we also adjusted for husband's education as an additional measure of socioeconomic status. We do not have specific data on household income; however, among these nurses with relatively uniform education and income, husband's education likely well represents variability in household income. Finally, adjusting for hysterectomy status had no impact on our results; thus, we did not include this variable in our models.

#### *Analyses of early clinical events*

We ask subjects about hormone use and about CHD events every 2 years. In our prospective analyses, we categorize HT according to women's

reports on the questionnaire before their event; this induces up to a 2-year lag between the identification of hormone status and the CHD event. Thus, we have limited opportunity to identify acute effects of HT. To address the extent to which this issue may impact our results, we conducted sensitivity analyses. First, in our cohort, 17 cases of nonfatal CHD occurred in which women reported never having used hormones on the questionnaire prior to their event, with current or past hormone use on the first questionnaire after their event. In the primary analyses, all of these cases were categorized as "never users." Some of these women likely began hormone therapy just before their CHD event, and some were certainly prescribed hormones after their event to prevent a recurrence. In the sensitivity analyses, we considered the extreme assumption that all 17 women had initiated HT prior to their CHD event, as well as the more plausible assumption that half had initiated hormones before and half after their event. Additionally, as we were unable to identify such women among those who had had a fatal event (because they died before being able to report their hormone use), we assumed that the ratio of nonfatal/fatal CHD cases would be similar among the whole cohort and among those who recently initiated hormone use (i.e., a ratio of approximately 3:1). Thus, for example, if 17 nonfatal cases may have been misclassified, 6 fatal cases may also have been misclassified.

Second, we recalculated the RR of CHD for current compared with never hormone use by calculating a weighted average of the RR for overall current use (from Table 1) and the RR for short-term hormone use (from the WHI data<sup>2,4</sup>). The weights in these calculations were determined by the estimated percentages of new initiators vs. all others among the current hormone users.

The study was funded by NIH, which had no role in the design of the study, the collection, analysis, and interpretation of the data, or the decision to approve publication of the finished report. This study was approved by the Institutional Review Board of Partners Healthcare.

## RESULTS

For estrogen alone, the age-adjusted RR of major CHD for current users was 0.57, compared

TABLE 1. RISK FOR MAJOR CORONARY HEART DISEASE AMONG CURRENT POSTMENOPAUSAL HORMONE USERS COMPARED TO WOMEN WHO NEVER USED HORMONES

	<i>Cases</i>	<i>Person-years</i>	<i>Age-adjusted model RR</i>	<i>Multivariate-adjusted: model A<sup>a</sup> RR</i>	<i>Multivariate-adjusted: model B<sup>b</sup> RR (95% CI)</i>
Analyses excluding women with prevalent heart disease					
Never used hormones	795	429,032	1.0 (reference)	1.0 (reference)	1.0 (reference)
Current estrogen alone	225	206,383	0.57	0.65	0.71 (0.61–0.83)
Current estrogen + progestin	112	118,735	0.49	0.64	0.68 (0.55–0.83)
Analyses similar to WHI inclusion criteria— including women with and without prevalent heart disease <sup>c</sup>					
Never used hormones	922	449,599	1.0 (reference)	1.0 (reference)	1.0 (reference)
Current estrogen alone	274	220,368	0.58	0.66	0.72 (0.62–0.82)
Current estrogen + progestin	131	124,391	0.50	0.64	0.69 (0.57–0.83)

<sup>a</sup>Model A includes follow-up from 1976 to 2000 and adjusts for age (continuous), BMI (<21 kg/m<sup>2</sup>, 21–22, 23–25, 26–29, 30–31, 32+), hypercholesterolemia (yes, no), hypertension (yes, no), parental history of premature heart disease (yes, no), diabetes (yes, no), cigarette smoking (never, past, current of 1–14, 5–24, 25–34, 35+ cigarettes/day).

<sup>b</sup>Model B includes follow-up from 1980 to 2000 and includes the 80% of subjects who provide dietary data. Model B adjusts for the same variables as model A, in addition to husband’s education (high school or less, college, advanced graduate degree), alcohol intake (none, <5 g/day, 5–14.9, 15+), physical activity (none, at least once/week), vitamin E supplementation (yes, no), multivitamin supplementation (yes, no), aspirin use (none, 1–6/week, 7+ /week).

<sup>c</sup>The WHI inclusion criteria permitted inclusion of about 4%–6% of women with prevalent coronary disease, and these analyses in the NHS include about 6% of women with prevalent coronary disease.

with women who never used HT (Table 1). For combined HT, this RR was 0.49. Adjustment for a wide variety of potential confounding factors attenuated these estimates: the RR for estrogen alone rose to 0.71, and the RR for estrogen with progestin rose to 0.68. For both regimens, the vast majority of attenuation was noted after control for the major known CHD risk factors (model A: smoking, high blood pressure, hypercholesterolemia, diabetes, family history of premature heart disease, BMI); additional adjustment for husband’s education as a marker of socioeconomic status had no influence on results. Adjustment for dietary factors, physical activity, and regular aspirin use also had little impact on RR estimates (model B, Table 1), and risk of CHD among current hormone users remained significantly lower than among women who never used hormones in all statistical models. In addition, as in the WHI, findings were similar when we did not exclude the small percentage of women with prevalent heart disease (Table 1).

We found a strong inverse relation between HT and CHD for women who began hormone use near menopause, in analyses both excluding and

including subjects with prevalent heart disease (Table 2). Only a small proportion of women in our cohort began hormones long after menopause. Overall, 16% of current estrogen use was among women who had initiated HT 10 or more years after menopause, and this proportion was 10% for combined therapy. However, the RRs of CHD appeared to increase somewhat with later initiation of HT (for estrogen alone, RR = 0.76, 95% CI 0.57–1.00; for combined therapy, RR = 0.80, 95% CI 0.53–1.23). These estimates increased somewhat further in analyses in which we used inclusion criteria similar to those of WHI and included a small percentage of women with existing CHD. We found an RR of 0.87 (95% CI 0.69–1.10) for estrogen alone and an RR of 0.90 (95% CI 0.62–1.29) for estrogen with progestin. We specifically compared our RR estimates from analyses similar to most observational studies (i.e., women without prevalent heart disease who began therapy near menopause; RR = 0.66 for unopposed estrogen and RR = 0.72 for combined therapy) with our estimates from analyses similar to those of WHI (i.e., women with and without prevalent heart disease who began therapy

TABLE 2. RISK FOR MAJOR CORONARY HEART DISEASE, ACCORDING TO CURRENT HORMONE USE AND TIMING OF HORMONE THERAPY INITIATION WITH RESPECT TO ONSET OF MENOPAUSE

	Cases	Person-years	Age-adjusted model <sup>a</sup> RR	Multivariate-adjusted model <sup>b</sup> RR (95% CI)
Analyses excluding women with prevalent heart disease				
Near menopause <sup>b</sup>				
Never	666	329,604	1.0 (reference)	1.0 (reference)
Initiated estrogen alone	116	133,194	0.48	0.66 (0.54–0.80)
Initiated estrogen + progestin	78	91,985	0.45	0.72 (0.56–0.92)
10+ years after menopause				
Never	400	152,205	1.0 (reference)	1.0 (reference)
Initiated estrogen alone	59	34,000	0.68	0.76 (0.57–1.00)
Initiated estrogen + progestin	23	11,945	0.70	0.80 (0.53–1.23)
Analyses similar to WHI inclusion criteria—including women with and without prevalent heart disease <sup>c</sup>				
Near menopause <sup>b</sup>				
Never	773	346,219	1.0 (reference)	1.0 (reference)
Initiated estrogen alone	130	140,515	0.46	0.62 (0.52–0.76)
Initiated estrogen + progestin	89	95,847	0.45	0.71 (0.56–0.89)
10+ years after menopause				
Never	481	164,537	1.0 (reference)	1.0 (reference)
Initiated estrogen alone	84	37,978	0.78	0.87 (0.69–1.10)
Initiated estrogen + progestin	31	13,133	0.78	0.90 (0.62–1.29)

<sup>a</sup>Age-adjusted model includes follow-up from 1976 to 2000. Multivariate-adjusted model includes follow-up from 1980 to 2000, includes only the 80% of women who provide dietary data, and adjusts for age, BMI, hypercholesterolemia, hypertension, parental history of premature heart disease, diabetes, cigarette smoking, husband's education, alcohol intake, physical activity, vitamin E supplementation, multivitamin supplementation, aspirin use.

<sup>b</sup>Near menopause defined as within 4 years of menopause.

<sup>c</sup>The WHI inclusion criteria permitted inclusion of about 4%–6% of women with prevalent coronary disease, and these analyses in the NHS include about 6% of women with prevalent coronary disease.

10+ years after menopause; RR = 0.87 for unopposed estrogen and RR = 0.90 for combined therapy). For estrogen alone, we found a borderline statistically significant difference between the two estimates ( $p$  heterogeneity = 0.07), but there was not a significant difference for estrogen with progestin ( $p$  heterogeneity = 0.4).

We also examined the relation of HT to CHD in women who initiated HT at older ages. For women aged 60+ years at initiation of hormone use, we found no relation between estrogen alone and CHD (adjusted RR = 1.07, 95% CI 0.31–1.38 among women without prevalent CHD; RR = 1.03, 95% CI 0.65–1.64 among women with and without prevalent CHD). We found significant differences when directly comparing the estimate most consistent with the WHI analyses (RR = 1.03) to the estimate most consistent with observational analyses (women aged 50–59 years, no prevalent CHD: RR = 0.51, 95% CI 0.32–0.82;  $p$  heterogeneity < 0.05). For estrogen with prog-

estin, there was a nonsignificant decreased CHD risk among the older women (adjusted RR = 0.65, 95% CI 0.31–1.38 among women without prevalent CHD; RR = 0.68, 95% CI 0.35–1.31 among women with and without prevalent CHD).

We found no appreciable difference in the relations of HT to CHD across strata of major CHD risk factors or use of cholesterol-lowering drugs (Table 3). In analyses of estrogen dose (Table 4), we combined estrogen alone and estrogen with progestin, as RRs of CHD were similar across regimens. Although relatively few women used either low or high estrogen doses, we generally found reduced risks of CHD across estrogen doses (0.3 mg: RR = 0.74; 0.625 mg: RR = 0.70; 1.25 mg: RR = 0.80).

Finally, we explored the potential impact of incomplete capture of early clinical events. We based these calculations on the data in Table 1 for the analyses with similar inclusion criteria as WHI. Thus, the sensitivity analyses included a to-

TABLE 3. RISK FOR MAJOR CORONARY HEART DISEASE AMONG CURRENT POSTMENOPAUSAL HORMONE USERS COMPARED TO WOMEN WHO NEVER USED HORMONES, STRATIFIED BY CORONARY DISEASE RISK FACTORS AND USE OF CHOLESTEROL-LOWERING DRUGS

<i>Hormone use</i>	<i>Cases</i>	<i>Person-years</i>	<i>Age-adjusted RR</i>	<i>Multivariate-adj.<sup>a</sup> RR (95% CI)</i>
Current estrogen alone				
High cholesterol <sup>b</sup>				
Yes	125	76,665	0.60	0.73 (0.59–0.91)
No	100	129,718	0.49	0.69 (0.56–0.86)
Use of cholesterol-lowering drugs <sup>b,c</sup>				
Yes	21	9,058	0.65	0.67 (0.36–1.24)
No	158	123,381	0.63	0.77 (0.63–0.94)
High blood pressure <sup>b</sup>				
Yes	144	71,589	0.57	0.78 (0.64–0.96)
No	81	134,794	0.51	0.63 (0.49–0.80)
Type 2 diabetes <sup>b</sup>				
Yes	36	8,317	0.53	0.67 (0.46–0.99)
No	189	198,066	0.61	0.72 (0.61–0.85)
Family history of premature CHD <sup>b</sup>				
Yes	54	32,332	0.51	0.65 (0.47–0.89)
No	171	174,052	0.58	0.73 (0.62–0.87)
Current smoking <sup>b</sup>				
Yes	66	33,346	0.58	0.66 (0.50–0.86)
No	159	172,639	0.64	0.76 (0.63–0.91)
Current estrogen + progestin				
High cholesterol <sup>b</sup>				
Yes	72	52,036	0.54	0.74 (0.57–0.97)
No	40	66,700	0.37	0.59 (0.43–0.82)
Use of cholesterol-lowering drugs <sup>b,c</sup>				
Yes	12	6,119	0.52	0.67 (0.35–1.29)
No	97	104,233	0.53	0.72 (0.58–0.91)
High blood pressure <sup>b</sup>				
Yes	60	35,303	0.49	0.67 (0.51–0.89)
No	52	83,432	0.51	0.69 (0.51–0.92)
Type 2 diabetes <sup>b</sup>				
Yes	14	3,865	0.44	0.54 (0.30–0.96)
No	98	114,871	0.54	0.71 (0.57–0.88)
Family history of premature CHD <sup>b</sup>				
Yes	29	18,392	0.49	0.66 (0.44–0.99)
No	83	100,343	0.49	0.68 (0.54–0.87)
Current smoking <sup>b</sup>				
Yes	27	15,498	0.47	0.51 (0.34–0.77)
No	85	102,994	0.60	0.79 (0.62–1.00)

<sup>a</sup>Adjusted for age, BMI, hypercholesterolemia, hypertension, parental history of heart disease <60 years, diabetes, cigarette smoking, husband's education, alcohol intake, physical activity, vitamin E supplementation, multivitamin supplements, aspirin use.

<sup>b</sup>Reference group is women in a given strata who never used hormones.

<sup>c</sup>For analyses stratified by cholesterol-lowering drugs, follow-up is from 1988 to 2000.

tal of 405 cases of CHD among women who were currently taking HT (either estrogen alone or combined therapy). In the extreme assumption that all women who had initiated HT near their CHD event had begun taking hormones prior to the event, we estimated that 23 such cases were included in our dataset (17 nonfatal and 6 fatal cases). If these 23 women were considered current rather than never users of HT, they would represent 5% of the cases among the current users

(23 per 405 + 23) = 5%). Thus, if we used an RR of 0.71 for 95% of the women currently taking HT (the overall adjusted RR we found for current hormone use in Table 1) and an RR of 1.8 for the 5% of new initiators (the RR found in the WHI trial of combined therapy in the first year of follow-up,<sup>2</sup> this would yield an RR of 0.76. If we used an RR of 1.2 for the new initiators (the RR found in the WHI trial of estrogen alone in the first year<sup>4</sup>), this would yield an RR of 0.73. If we

TABLE 4. RISK FOR MAJOR CORONARY HEART DISEASE AMONG CURRENT POSTMENOPAUSAL HORMONE USERS COMPARED TO WOMEN WHO NEVER USED HORMONES, ACCORDING TO ESTROGEN DOSE

	<i>Cases</i>	<i>Person-years</i>	<i>Age-adjusted model RR</i>	<i>Multivariate-adjusted model<sup>a</sup> RR (95% CI)</i>
Dose of oral conjugated estrogen (mg) <sup>b</sup>				
0.3	32	26,690	0.56	0.74 (0.52–1.06)
0.625	195	188,102	0.50	0.70 (0.59–0.83)
1.25+	56	50,453	0.62	0.80 (0.60–1.06)

<sup>a</sup>Adjusted for age, BMI, hypercholesterolemia, hypertension, parental history of heart disease <60 years, diabetes, cigarette smoking, husband's education, alcohol intake, physical activity, vitamin E supplementation, multivitamin supplements, aspirin use.

<sup>b</sup>These analyses combine use of estrogen alone and estrogen plus progestin. Reference group is women who never used hormone therapy. Data on dose were missing for 54 cases and 59,873 person-years.

consider the more likely scenario that half of the new initiators had begun HT before their CHD event, these RRs would be 0.73 for combined therapy and 0.72 for estrogen alone.

## DISCUSSION

Overall, after adjusting for a wide variety of potential confounding factors, we found approximately a 30% lower risk of CHD for women using estrogen alone or combined HT compared with postmenopausal women who never used hormones. Findings were similar across various doses of oral conjugated estrogen and across women with and without numerous CVD risk factors. Although the large majority of women in our cohort initiated HT near menopause, there was a suggestion that the apparent benefits of hormones, especially unopposed estrogen, decreased when therapy was initiated long after menopause or at older ages. Finally, sensitivity analyses exploring the potential impact of incomplete capture of early clinical events indicated that this hypothesis could not plausibly explain any apparent differences between the relation of HT to CHD in our cohort vs. the WHI.

Our data regarding the similar associations between CHD and estrogen alone or estrogen combined with progestin are consistent with other observational studies.<sup>1</sup> However, very limited research has been conducted on the relation of hormone dose to risk of CHD, and available data on the benefits of low-dose estrogen are unclear. For example, lower estrogen doses may raise

high-density lipoprotein (HDL) similarly to the 0.625-mg dose but may not decrease low-density lipoprotein (LDL) comparably to the higher dose estrogen.<sup>14,15</sup> In contrast, low-dose estrogen may not increase certain inflammatory or thrombotic markers to the same extent as higher doses.<sup>15</sup> Interestingly, we found a nearly identical RR of CHD associated with 0.3 and 0.625 mg estrogen. Clearly, substantially more data are needed on the cardiovascular effects of 0.3 mg estrogen, as this dose has now become standard in clinical practice.

In interpreting these data, several important issues should be considered. First, we found that adjustment for potential confounding factors substantially attenuated associations between postmenopausal HT and heart disease (range 25%–39% attenuation), raising the possibility that the relation might be further attenuated with either more accurate data on known confounding factors or additional data on currently unknown confounding factors. However, as most confounding in our study resulted from the major known coronary risk factors (smoking, high blood pressure, high cholesterol, diabetes, family history of heart disease, and higher BMI), substantial residual confounding seems unlikely. (1) These factors are all relatively simple to measure, and validation studies in our cohort have established the high accuracy<sup>16,17</sup> of risk factor reporting among these registered nurses, and (2) adjustment for numerous additional factors (e.g., diet, socioeconomic status, physical activity, aspirin use) had little impact on the RR estimates, rendering it less plausible that unknown con-

founders spuriously produced a 30% lower risk of CHD among hormone users. We recognize, nonetheless, that it is not possible to fully eliminate confounding in an observational study.

Second, we had limited data for reaching firm conclusions about the potential cardiovascular impact of beginning HT at older ages or at increasingly longer intervals since menopause. However, our data suggested that such use may be associated with reduced CHD benefits. These findings are supported by animal studies.<sup>6,18</sup> For example, conjugated estrogen had no effect on coronary artery plaque in monkeys randomized to estrogen alone or combined with medroxyprogesterone acetate beginning 2 years after oophorectomy (equivalent to approximately 6 human years) and, thus, substantially after establishment of atherosclerosis. In a separate study, HT caused a 50% reduction in plaque extent when given immediately after oophorectomy to younger monkeys in the early stages of atherosclerosis.<sup>6</sup> Similarly, in a small randomized trial of HT in postmenopausal women, several cardiovascular risk factors (e.g., hypertension, vascular resistance) improved in subjects close to menopause (<5 years), whereas the effect appeared less marked in those farther from menopause (5+ years).<sup>19</sup>

Similarly, in subgroup analyses, the WHI report<sup>2</sup> for combined hormones suggested greater risk with initiation of therapy at longer intervals since menopause: RR = 0.89 for <10 years since menopause; RR = 1.22 for 10–19 years; RR = 1.71 for 20+ years. Although no significant interaction between hormone assignment and time since menopause was reported ( $p$  interaction = 0.33), in a reanalysis of the estimates presented, we found a significant trend of increasing risk of CHD with increasing time since menopause ( $p$  trend = 0.036;  $p$  trend calculated in a meta-regression analysis using the command “metareg” in STATA statistical software). Likewise, in subgroup analyses of the unopposed estrogen trial, the WHI reported an RR of 0.56 with initiation of hormones at age 50–59 years (similar to our estimate of 0.51 for women beginning unopposed estrogen at age 50–59). The RR rose to 0.92 at age 60–69 years (again, similar to our estimate of 1.07 for women aged 60+ years) and 1.04 at age 70–79 years. There was a borderline significant interaction between hormone assignment and age ( $p$  interaction = 0.1).

Third, the inability to assess acute effects of

hormone use is a limitation of our study. Indeed, the issue of incomplete capture of early clinical events in observational studies has been suggested as a possible explanation for the apparent discrepancy between observational studies and the WHI. We do not have sufficient data to identify women who had begun HT shortly before their coronary event, and in our primary analyses, these subjects would be generally categorized among those who had never taken HT. Nonetheless, we have adequate information to determine the number of nonfatal CHD cases who had initiated hormone use near their coronary event. We used that information to conduct sensitivity analyses to estimate the approximate effect such cases may have had on our RR estimates. We recognize that these calculations were limited and included many assumptions about the subjects' use of HT. Nonetheless, even with very conservative assumptions, these calculations indicated that incomplete capture of early clinical events could not have plausibly resulted in RRs that which were substantially different from those reported in our primary analyses.

In summary, our findings in the Nurses' Health Study support the possibility that timing of hormone initiation in relation to menopause onset or age might influence coronary risk. However, with existing data, we cannot draw firm conclusions regarding these associations because few women in trials of HT were randomized soon after menopause, whereas in our cohort and other observational studies, only a small proportion of subjects initiated hormones long after menopause. Most importantly, although newly menopausal women are more likely to be appropriate candidates for HT because of vasomotor symptoms, the clear risks of postmenopausal hormones (e.g., increases in stroke,<sup>4,7,20</sup> pulmonary embolism,<sup>3,4,21</sup> and possibly breast cancer<sup>3,22</sup>) in both randomized trials and observational studies rule out a general indication for their long-term use in chronic disease prevention.

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