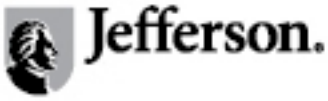

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Usefulness of Baseline Lipids and C-Reactive Protein in Women Receiving Menopausal Hormone Therapy as Predictors of Treatment-Related Coronary Events

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Abstract

Blood lipids and high sensitivity C-reactive protein (hsCRP) are altered by hormone therapy. The goal of the current study was to determine whether lipids and hsCRP have predictive value for hormone therapy benefit or risk for coronary heart disease (CHD) events in postmenopausal women without previous cardiovascular disease. A nested case-control study was performed in the Women's Health Initiative hormone trials. Baseline lipids and hsCRP were obtained from 271 incident CHD cases and 707 controls. In a combined trial analysis, a favorable lipid status at baseline tended to predict better CHD outcomes when taking conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA). Women with a low density lipoprotein (LDL)/high density lipoprotein (HDL) ratio <2.5 had no increase in risk of CHD when taking CEE with or without MPA (OR 0.60, 95%CI=0.34–1.06), whereas women with an LDL/HDL ratio ≥2.5 had an increased risk of CHD (OR 1.73, 95%CI=1.18–2.53) (p-value for interaction = 0.02). Low hsCRP levels added marginally to the value of LDL/HDL<2.5 when predicting CHD benefit on hormone therapy. In conclusion, postmenopausal women with undesirable lipid levels had excess CHD risk when using CEE with or without MPA; however, women with favorable lipid levels, especially an LDL/HDL ratio < 2.5, did not have an elevated risk of CHD with CEE with or without MPA, irrespective of hsCRP levels.

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Keywords

CHD; hormone therapy; lipids; cholesterol

It remains uncertain whether routinely available CHD biomarkers, such as lipids and hsCRP, may help to identify women at higher or lower risk of incident coronary events mediated by menopausal hormone therapy. The WHI conducted 2 clinical trials, assessing the effect of CEE alone in women without a uterus or CEE+MPA in postmenopausal women who had not undergone hysterectomy. Neither Women's Health Initiative trial showed an overall protective effect of hormone therapy for coronary events,[1, 2] in contrast to results of earlier observational studies.[3, 4] The reasons for this discrepancy are not yet determined but may be related to differences in baseline CHD risks of the study populations and the distributions of risk factors such as lipids and hsCRP. Because clinical trials have demonstrated a small overall increase in the absolute risk of short term hormone therapy use for CHD events in postmenopausal women, we asked whether commonly utilized biomarkers (lipids and hsCRP) could be useful for predicting hormone therapy-mediated CHD risk. We performed a nested case-control study of biomarkers obtained at baseline and 1 year follow-up in women from both WHI hormone trials. The goal of this study was to determine whether baseline lipids and hsCRP have predictive value for hormone therapy benefit or risk for CHD events.

Methods

Eligibility criteria and recruitment methods have been published for both Women's Health Initiative clinical trials.[5–7] From September 1993 to October 1998 generally healthy postmenopausal women aged 50 to 79 years were enrolled in 40 US clinical centers. Study participants provided informed consent via forms approved by each center's institutional review board. Eligible women with an intact uterus (n=16,608) were randomly assigned to receive 0.625 mg/d of CEE plus 2.5 mg/d MPA or a matching placebo. Eligible women who had undergone hysterectomy (n=10,739) were randomly assigned to receive 0.625 mg/d of CEE or a matching placebo.

A case-control biomarker study was nested within the 2 hormone clinical trials (note that lipid and hsCRP levels were performed only in a subset of participants in these trials). The current study represents a nested case-control analysis of biomarkers in 271 incident CHD cases and 707 controls. Reasoning that future hormone therapy use is likely to be discouraged for women with pre-existing cardiovascular disease, we included only those women without baseline cardiovascular disease. Outcome definitions and methods for ascertaining, documenting, and classifying outcomes have been published.[8] Women with a history of myocardial infarction, angina, coronary revascularization or stroke prior to study entry were excluded. Cases were defined as all incident acute myocardial infarction requiring overnight hospitalization and/or CHD death in either clinical trial that occurred in the first 4 years of follow-up. Incident myocardial infarction is defined as a clinical myocardial infarction presenting with chest discomfort, typical ECG changes, and elevation of cardiac-specific enzymes,, and does not include silent or possible silent myocardial infarctions. Case status was determined by central adjudication based on review of medical records. Controls are defined as women who did not experience a cardiovascular disease event during the entire duration of follow-up in the Women's Health Initiative clinical trial. The case/control selection process was done matching age at screening, randomization date and hysterectomy status.

Baseline and year 1 blood samples were obtained in a fasting state. The specimens were centrifuged, serum and plasma was frozen at −70°C, and shipped on dry ice to a central processing facility. Subjects who became cases within the first year of follow-up did not have their year 1 biomarkers measured. Lipids were measured in ethylenediaminetetraacetic acid -anticoagulated plasma at PPD Global Central Labs (Highland Heights, KY), formerly Medical Research Laboratories International, on a Hitachi 747 General Chemistry Analyzer. Triglycerides were measured by a chromogenic reaction after hydrolysis and oxidation. Total cholesterol was measured enzymatically utilizing cholesterol esterase and cholesterol oxidase. HDL cholesterol was measured after removal of chylomicrons, very low density lipoproteins and LDL from the plasma. LDL-cholesterol was calculated using the Friedewald formula (total cholesterol-HDL cholesterol-triglyceride/5). Lipoprotein(a) levels were measured by an enzyme immunoassay. hsCRP was measured in serum using the Dade Behring N Latex High Sensitivity hsCRP™ mono assay on the Behring Nephelometer II according to manufacturer's recommendations.

Means and frequencies are presented for demographic data. CHD cases and controls were compared using a 2-sample t-test (continuous variables) or a Chi-Square test (categorical variables). To account for the skewed distribution of the biomarker data, geometric means and standard deviations were calculated for the individual markers. For the ratio variables, which are normally distributed, standard means and deviations were calculated. Testing for descriptive tables was based on a t-test using the logged distribution for the individual biomarkers. All modeling was logistic with both odds ratios and p-values presented in the resulting tables. Interaction models were also fitted using logistic regression including terms for the main effects of the biomarker level of interest (e.g., high LDL/HDL ratio), treatment assignment, and their interaction. The resulting p-value for the interaction term is presented in the tables. All models were adjusted for age, year of randomization, history of hypertension (defined as self-report of pill usage or measured systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90), body mass index, current smoking, self report of cholesterol-lowering medication use, and self-report of treated diabetes. Additional logistic models were run to examine the linear trend of combinations of LDL/HDL ratio and hsCRP on CHD, assigning values to each LDL/HDL ratio and hsCRP combination. All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Results

Table 1 shows the baseline characteristics of the study subjects separated by clinical trial and for the trials combined. Increased BMI, current smoking, treated diabetes, and self-reported hypertension predicted case status in the combined trials. Mean baseline values for all biomarkers tended toward a "less desirable" direction in the women in the CEE trial compared to the women in the CEE+MPA trial, but only the mean triglyceride, lipoprotein(a) and hsCRP levels were significantly different between the 2 trials (Table 2). All biomarkers shown in Table 2 except lipoprotein(a) were associated with CHD risk, but the strength of the association varied by treatment group and clinical trial (see online Supplemental Tables).

We examined whether there were associations between the hormone therapy effect on incident CHD and the level of each lipid biomarker or hsCRP (Table 3). Subjects were grouped by desirable or undesirable HDL-cholesterol and triglyceride levels using ATP III recommended cut-offs,[9] and the median biomarker level of healthy controls for LDL-cholesterol, non-HDL-cholesterol, Lp(a) and the total cholesterol (TC)/HDL and triglyceride/HDL ratios. The cut-off for the LDL/HDL ratio was based on desirable values of 100 and 40, respectively. Women with higher levels of LDL-cholesterol, and the total cholesterol/HDL and LDL/HDL ratios had elevated risks of CHD when using CEE+MPA,

while women with lower levels of these biomarkers did not. A similar trend was observed for the LDL/HDL ratio in the CEE trial. When the trials were combined, there was a significant interaction between HT and the biomarker for LDL-cholesterol, non-HDL-cholesterol, the total cholesterol/HDL ratio and the LDL/HDL ratio. hsCRP showed a significant interaction with CEE alone but not CEE+MPA.

We utilized the baseline LDL/HDL ratio biomarker in combination with hsCRP in a combined trial analysis to evaluate CHD risk due to hormone therapy (Table 4). Women who had low LDL/HDL ratios at baseline did not experience an increased risk of CHD events on hormone therapy, regardless of hsCRP level, whereas women with elevated LDL/HDL ratios had increased risks of hormone therapy-mediated CHD, regardless of hsCRP levels.

Discussion

This study was designed to assess whether routinely available CHD biomarkers were useful for predicting the risk of incident myocardial infarction and/or CHD death in postmenopausal women without cardiovascular disease who had initiated CEE with or without MPA. The major findings were that several baseline lipid measurements, but especially the LDL/HDL ratio, interact with CEE with or without MPA to modify the risk for CHD. Specifically, women with baseline LDL/HDL ratios above 2.5 were at an increased CHD risk due to CEE with or without MPA, whereas there was no increased CHD risk due to CEE with or without MPA when the baseline LDL/HDL ratio was less than 2.5. We also found evidence that hsCRP added little or no additional predictive value beyond the LDL/HDL biomarker for predicting CHD risk for women using hormone therapy.

Women with baseline HDL-cholesterol <50, or with LDL-cholesterol, total cholesterol/HDL ratio and LDL/HDL ratio above the median control value, were at increased CHD risk when assigned to CEE+MPA, and similar trends were observed with unopposed CEE. Importantly, we found no clear evidence that either form of hormone therapy posed a risk for CHD events for women with baseline HDL-cholesterol ≥50, or with LDL-cholesterol, total cholesterol/HDL ratio and LDL/HDL ratio below the median control value. When analyzed using median control values for HDL and trigyceride (53 and 135, respectively) instead of the ATP III recommended cutoffs (50 and 150, respectively), the results were essentially the same.

Our analysis has provided a side-by-side comparison of the effect of biomarkers in the 2 Women's Health Initiative hormone trials. The odds ratios for the treatment effect by baseline LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol, the total cholesterol/HDL ratio and the LDL/HDL ratio were similar for both the CEE+MPA and CEE clinical trials. These similar responses provide support for combining the 2 trials in the analyses of these latter biomarkers. In the combined Women's Health Initiative hormone trial analysis, with an LDL/HDL ratio <2.5 the OR for hormone therapy effect of 0.6 (95%CI=0.34–1.06), underscoring the potential CHD safety of hormone therapy in women with a desirable, "healthy" lipid profile. These results were not materially affected when women using cholesterol-lowering drugs were excluded from the analyses (data not shown).

How might lipids and hormone therapy interact mechanistically to affect the risk for CHD? There is strong animal data that estrogen is cardioprotective in hyperlipidemic animals when administered at the time of menopause and/or prior to the development of atherosclerosis [10]. Our study specifically excluded women with prior CHD, yet we still observed an interaction between hormone therapy and baseline cholesterol levels for CHD risk even after adjusting for age. Recently, the cholesterol metabolite, 27-hydroxycholesterol, has been shown to

compete with estrogen for binding to vascular estrogen receptors, blocking the beneficial effects of estrogen (nitric oxide production and endothelial cell migration) on murine vascular cells [11]. This study by Umetani et al. suggests an attractive and testable hypothesis: that postmenopausal women with a poor lipid profile have elevated levels of 27-hydroxycholesterol, which disables a potential vascular benefit of estrogen. Conversely, the women in the Women's Health Initiative clinical trials with favorable lipids might experience no harm or even benefit from estrogen therapy if they have low levels of 27-hydroxycholesterol.

Since elevated plasma triglyceride levels are thought to be a risk factor for CHD in women[12] and hormone therapy increases triglyceride levels, it was important to consider the relationship between triglyceride and hormone therapy for CHD events. Our analyses showed high baseline levels of triglyceride were associated with CHD cases in only the CEE +MPA trial, but not the CEE trial (online supplemental data), but we observed no interaction between baseline triglyceride and CEE with or without MPA for CHD events. We also assessed whether the year 1 triglyceride levels or the change from baseline to year 1 triglyceride level were related to developing CHD events, but found no relationship.

The difference in study design between the current biomarker study and the overall Women's Health Initiative hormone trials should be noted. Only women developing CHD events within the first 4 years comprised cases for this biomarker study, and later events were not analyzed. Any conclusions from the current report only pertain to this time frame. Although this study is comparable in size to other large biomarker studies, the planned subgroup analysis nevertheless had relatively small numbers of cases, and we did not have a sufficient sample size to stratify by age.

Despite increasing information and understanding of the clinical benefits and risks of hormone therapy, practitioners are still challenged in making management choices for individual postmenopausal women. The Framingham risk prediction model specifically did not include estrogen replacement therapy use in formulating CHD risk assessment,[13] and no convincing data has previously defined whether hormone therapy modifies the CHD risk associated with increased lipid levels (or other biomarkers). This report has just considered the risks and benefits associated with CHD outcomes, and the decision to use postmenopausal hormones must consider the totality of health risks and benefits, including stroke, thrombosis and gall bladder disease. Women considering the use of postmenopausal hormone therapy should determine their overall cardiac risk and specifically their lipid profile. The absolute excess CHD risk is low or absent in younger women who take CEE with or without MPA.[14] Our study provides support that CEE with or without MPA may not increase the short term CHD risk among women with a favorable lipid profile.

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Table 1

Baseline characteristics of women in the Women's Health Initiative Coronary Heart Disease Biomarker Study.

	Estrogen+Progesterone (n=588)			Estrogen alone (n=390)			Combined Trials (n=978)		
	Cases (n=158)	Controls (n=430)		Cases (n=113)	Controls (n=277)		Cases (n=271)	Controls (n=707)	
Characteristic	**N (%)**	**N (%)**	**P***	**N (%)**	**N (%)**	**P***	**N (%)**	**N (%)**	**P***
Age at screen (mean years), (SD)	65.8 (7.3)	66.6 (6.8)	0.25	67.0 (6.6)	66.2 (6.5)	0.32	66.3 (7.0)	66.4 (6.7)	0.77
Race/ethnicity			0.26			0.41			0.78
White	141 (89.2%)	379 (88.1%)		86 (76.1%)	214 (77.3%)		227 (83.8%)	593 (83.9%)	
Black	7 (4.4%)	24 (5.6%)		16 (14.2%)	42 (15.2%)		23 (8.5%)	66 (9.3%)	
Hispanic	5 (3.2%)	17 (4.0%)		6 (5.3%)	14 (5.1%)		11 (4.1%)	31 (4.4%)	
Am Indian	1 (0.6%)	1 (0.2%)		0 (0.0%)	2 (0.7%)		1 (0.4%)	3 (0.4%)	
Asian/PI	0 (0.0%)	6 (1.4%)		3 (2.7%)	1 (0.4%)		3 (1.1%)	7 (1.0%)	
Unknown	4 (2.5%)	3 (0.7%)		2 (1.8%)	4 (1.4%)		6 (2.2%)	7 (1.0%)	
Hormone use			0.33			0.38			0.21
Never	116 (73.4%)	322 (74.9%)		69 (61.1%)	155 (56.0%)		185 (68.3%)	477 (67.5%)	
Past	36 (22.8%)	81 (18.8%)		36 (31.9%)	90 (32.5%)		72 (26.6%)	171 (24.2%)	
Current≠	6 (3.8%)	27 (6.3%)		8 (7.1%)	32 (11.6%)		14 (5.2%)	59 (8.3%)	
Body mass index (mean kg/m^2), (SD)	28.7 (6.0)	27.7 (5.8)	0.07	30.2 (6.1)	29.3 (5.5)	0.18	29.3 (6.1)	28.4 (5.7)	0.02
Smoking			<.001			0.001			<.001
Never	71 (44.9%)	239 (55.6%)		54 (47.8%)	147 (53.1%)		125 (46.1%)	386 (54.6%)	
Past	50 (31.6%)	154 (35.8%)		31 (27.4%)	99 (35.7%)		81 (29.9%)	253 (35.8%)	
Current	32 (20.3%)	32 (7.4%)		25 (22.1%)	22 (7.9%)		57 (21.0%)	54 (7.6%)	
Treated diabetes	16 (10.1%)	18 (4.2%)	0.006	23 (20.4%)	14 (5.1%)	<.001	39 (14.4%)	32 (4.5%)	<.001
Hypertension§	79 (50.0%)	158 (36.7%)	0.004	67 (59.3%)	127 (45.8%)	0.02	146 (53.9%)	285 (40.3%)	<.001
Treated cholesterol	26 (16.5%)	54 (12.6%)	0.28	18 (15.9%)	33 (11.9%)	0.48	44 (16.2%)	87 (12.3%)	0.14
Statin use	13 (8.2%)	23 (5.3%)	0.20	10 (8.8%)	20 (7.2%)	0.58	23 (8.5%)	43 (6.1%)	0.18

	Estrogen+Progesterone (n=588)			Estrogen alone (n=390)			Combined Trials (n=978)		
	Cases (n=158)	Controls (n=430)		Cases (n=113)	Controls (n=277)		Cases (n=271)	Controls (n=707)	
Characteristic	**N (%)**	**N (%)**	**P***	**N (%)**	**N (%)**	**P***	**N (%)**	**N (%)**	**P***
Aspirin use (≥80 mg/d)	31 (19.6%)	90 (20.9%)	0.73	25 (22.1%)	53 (19.1%)	0.50	56 (20.7%)	143 (20.2%)	0.88
History of bilateral oophorectomy	0 (0.0%)	1 (0.2%)	0.40	50 (44.2%)	112 (40.4%)	0.50	50 (18.5%)	113 (16.0%)	0.57

*Cases vs. Controls

‡Required a 3-month washout prior to randomization.

§Hypertension defined as self-report of treated hypertension ever, systolic BP ≥ 140, or diastolic BP ≥ 90.

Table 2

Baseline biomarker levels for all cases plus controls in the Women's Health Initiative biomarker study.

Biomarker	Trial				
	Estrogen+Progesterone (n=588)		Estrogen only (n=390)		
	N	Mean (SD)	N	Mean (SD)	P value
Lipids					
Total cholesterol * (mg/dL)	587	227.3 (36.4)	390	228.5 (38.6)	0.62
Low density lipoprotein * (mg/dL)	573	140.9 (33.5)	375	142.2 (35.0)	0.58
High density lipoprotein * (mg/dL)	585	52.6 (13.6)	387	51.1 (12.7)	0.08
Non-high density lipoprotein * (mg/dL)	585	171.3 (39.2)	387	174.6 (39.6)	0.20
Triglyceride * (mg/dL)	587	139.0 (65.3)	390	148.4 (69.8)	0.03
Lipoprotein (a) * (mg/dL)	561	17.0 (19.0)	371	19.7 (20.6)	0.04
Total cholesterol/high density lipoprotein ratio	585	4.5 (1.4)	387	4.7 (1.4)	0.13
Triglyceride/high density lipoprotein ratio	585	3.3 (2.6)	387	3.6 (2.8)	0.14
Low density lipoprotein/high density lipoprotein ratio	573	2.8 (1.0)	375	2.9 (1.0)	0.31
Inflammation					
high sensitivity C-reactive protein * (mg/dL)	570	2.0 (2.2)	377	2.6 (2.7)	<.001

* Geometric means

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Table 3

aseline Biomarker

	Estrogen+Progesterone trial				Estrogen alone trial				Combined trials			
	Hormone treatment	Placebo	O.R. (C.I.) for treatment effect†		Hormone treatment	Placebo	O.R. (C.I.) for treatment effect†		Hormone treatment	Placebo	O.R. (C.I.) for treatment effect†	
Cut-point*	Case/Control	Case/Control		P-Value‡	Case/Control	Case/Control		P-Value‡	Case/Control	Case/Control		P-Value‡
<130	11/85	19/75	0.47 (0.19, 1.13)	0.03	11/44	12/48	0.71 (0.22, 2.25)	0.33	22/129	31/123	0.66 (0.34, 1.27)	0.03
≥130	77/134	42/130	1.60 (0.99, 2.59)		45/88	38/89	1.28 (0.72, 2.26)		122/222	80/219	1.46 (1.02, 2.10)	
≥50	33/147	29/126	1.14 (0.64, 2.02)	0.34	18/82	24/83	0.78 (0.37, 1.61)	0.29	57/229	53/209	1.00 (0.64, 1.56)	0.11
<50	54/74	34/82	1.78 (1.00, 3.16)		42/53	27/58	1.37 (0.69, 2.72)		96/127	61/140	1.67 (1.09, 2.57)	
<169	23/122	23/101	0.84 (0.42, 1.67)	0.09	19/59	20/64	0.83 (0.37, 1.88)	0.24	42/181	43/165	0.88 (0.53, 1.47)	0.04
≥169	70/99	40/107	1.75 (1.05, 2.93)		41/76	31/77	1.50 (0.80, 2.82)		111/175	71/184	1.64 (1.11, 2.42)	
<150	52/148	33/127	1.64 (0.95, 2.83)	0.68	24/69	31/78	0.87 (0.45, 1.70)	0.30	76/217	64/205	1.27 (0.84, 1.91)	0.72
≥150	42/74	30/81	1.45 (0.78, 2.69)		37/66	21/64	1.49 (0.71, 3.11)		79/140	51/145	1.42 (0.90, 2.23)	
<20	45/106	24/112	1.89 (1.02, 3.48)	0.16	24/59	25/57	0.85 (0.41, 1.78)	0.22	69/165	49/169	1.38 (0.87, 2.19)	0.74
≥20	44/108	37/85	0.99 (0.57, 1.72)		34/69	25/78	1.49 (0.74, 3.01)		78/177	62/163	1.17 (0.77, 1.79)	
<4.182	23/124	25/102	0.79 (0.40, 1.54)	0.02	10/61	15/66	0.72 (0.29, 1.81)	0.26	33/185	40/168	0.76 (0.44, 1.29)	0.01
≥4.182	70/97	38/106	2.05 (1.22, 3.46)		50/74	36/75	1.33 (0.73, 2.42)		120/171	74/181	1.69 (1.15, 2.49)	
<2.551	36/122	24/106	1.76 (0.92, 3.35)	0.86	18/57	22/66	0.96 (0.44, 2.07)	0.62	54/179	46/172	1.32 (0.82, 2.12)	0.84
≥2.551	57/99	39/102	1.44 (0.84, 2.47)		42/78	29/75	1.21 (0.64, 2.31)		99/177	68/177	1.34 (0.89, 2.00)	
< 2.5	20/110	23/90	0.65 (0.32, 1.31)	0.01	9/55	15/54	0.46 (0.16, 1.26)	0.06	29/165	38/144	0.60 (0.34, 1.06)	0.002
≥2.5	68/109	38/115	1.96 (1.17, 3.29)		47/77	35/83	1.52 (0.84, 2.75)		115/186	73/198	1.73 (1.18, 2.53)	
<2.0	37/115	26/108	1.48 (0.81, 2.70)	0.96	15/63	20/50	0.47 (0.20, 1.11)	0.02	52/178	46/158	1.01 (0.63, 1.62)	0.16

	Estrogen+Progesterone trial				Estrogen alone trial				Combined trials			
	Hormone treatment	Placebo	O.R. (C.I.) for treatment effect†		Hormone treatment	Placebo	O.R. (C.I.) for treatment effect†		Hormone treatment	Placebo	O.R. (C.I.) for treatment effect†	
Cut-point*	Case/Control	Case/Control		P-Value‡	Case/Control	Case/Control		P-Value‡	Case/Control	Case/Control		P-Value‡
≥2.0	57/101	34/92	1.40 (0.80, 2.44)		44/68	30/87	1.88 (0.99, 3.58)		101/169	64/179	1.58 (1.05, 2.39)	

L and TGL, all cut-points based on median control values

ted from a logistic regression model with a response of case, explanatory variable of the treatment assignment, and adjusted for year of randomization, age, hysterectomy status, erol-lowering agents, body mass index, current smoking, and treated diabetes ever.

logistic regression model with a response of case, explanatory variables of treatment assignment, biomarker criterion of interest, and their interaction. This model is also zation, age, hysterectomy status, hypertension, use of cholesterol-lowering agents, body mass index, current smoking, and treated diabetes ever.

Table 4

Assessing the Coronary Heart Disease risk of low density lipoprotein/high density lipoprotein ratio in combination with C-reactive protein (Combined Trials).

Low density lipoprotein/high density lipoprotein ratio*	C-reactive protein*	Estrogen with or without progesterone Cases/ Controls	Placebo Cases/Controls	O.R. (C.I.) for treatment effect**
<2.5	<2.0	14/95	23/78	0.42 (0.19, 0.91)
<2.5	≥2.0	15/65	14/58	0.84 (0.34, 2.09)
≥2.5	<2.0	36/82	22/78	1.81 (0.93, 3.54)
≥2.5	≥2.0	76/101	47/115	1.75 (1.08, 2.86)

*Cut-points based on median control values

**OR's and 95% CI's computed from a logistic regression model with a response of case, explanatory variable of the treatment assignment, and adjust for year of randomization, age, hysterectomy status, hypertension, use of cholesterol-lowering agents, BMI, current smoking, and treated diabetes ever.