Published in final edited form as:
Arterioscler Thromb Vasc Biol. 2008 September ; 28(9): 1666–1671. doi:10.1161/ATVBAHA.108.170431.

Lipoprotein Particle Concentrations May Explain the Absence of Coronary Protection in the Women's Health Initiative Hormone Trials

Judith Hsia, **James D. Otvos**, **Jacques E. Rossouw**, **LieLing Wu**, **Sylvia Wassertheil-Smoller**, **Susan L. Hendrix**, **Jennifer G. Robinson**, **Bernedine Lund**, **Lewis H. Kuller**, and **Women's Health Initiative Research Group**

Department of Medicine (J.H.), George Washington University, Washington, DC; Liposcience Inc (J.D.O.), Raleigh, NC; National Heart, Lung, and Blood Institute (J.R.), National Institutes of Health, Bethesda, Md; Fred Hutchinson Cancer Research Center (L.W., B.L.), Seattle, Wash; the Department of Epidemiology & Social Medicine (S.S.), Albert Einstein College of Medicine, Bronx, NY; the Department of Obstetrics and Gynecology (S.L.H.), Detroit Medical Center, Detroit, Mich; the Department of Medicine (J.G.R.), University of Iowa, Iowa City; and the Department of Epidemiology (L.H.K.), University of Pittsburgh, Pa.

Abstract

Objective—The Women's Health Initiative randomized hormone trials unexpectedly demonstrated an increase in early coronary events. In an effort to explain this finding, we examined lipoprotein particle concentrations and their interactions with hormone therapy in a case–control substudy.

Methods and Results—We randomized 16 608 postmenopausal women with intact uterus to conjugated estrogens 0.625 mg with medroxyprogesterone acetate 2.5 mg daily or to placebo, and 10 739 women with prior hysterectomy to conjugated estrogens 0.625 mg daily or placebo, and measured lipoprotein subclasses by nuclear magnetic resonance spectroscopy at baseline and year 1 in 354 women with early coronary events and matched controls. Postmenopausal hormone therapy raised high-density lipoprotein cholesterol and particle concentration and reduced low-density lipoprotein cholesterol (LDL-C; all $P<0.001$ versus placebo). In contrast, neither unopposed estrogen nor estrogen with progestin lowered low-density lipoprotein particle concentration (LDL-P).

Conclusions—Postmenopausal hormone therapy–induced reductions in LDL-C were not paralleled by favorable effects on LDL-P. This finding may account for the absence of coronary protection conferred by estrogen in the randomized hormone trials.

Keywords

lipoproteins; estrogen; women; coronary heart disease

The Women's Health Initiative randomized, controlled hormone trials unexpectedly demonstrated increased stroke risk with postmenopausal hormone therapy, and no coronary

Correspondence to Dr Judith Hsia, AstraZeneca LP, 1800 Concord Pike, Room C3C-123, PO Box 15437, Wilmington, DE 19850−5437. E-mail E-mail: judith.hsia@astrazeneca.com.

Disclosures

Dr Hsia is employed by and owns stock in AstraZeneca. Dr Otvos is employed by and owns stock in Liposcience. Dr Robinson has research grants from Abbott, Bristol–Myers Squibb, Merck/Schering-Plough, Merck, AstraZeneca, Hoffman LaRoche, Takeda, and Pfizer, is a member of the Merck/Schering-Plough speakers' bureau and advisory boards for AstraZeneca and Merck/Schering-Plough.

protection.[1,2] Among postmenopausal women with intact uterus, the primary efficacy outcome of myocardial infarction/coronary death (CHD) was more frequent among women randomized to active estrogen with progestin (E+P), with hazard ratio 1.81 in year 1, 1.34 in year 2, 1.27 in year 3, and 1.25 in year 4.[3] Among women with prior hysterectomy, unopposed conjugated estrogens (CEE) neither increased nor decreased CHD overall, with hazard ratio 1.11 in year 1, 1.20 in year 2, 0.89 in year 3 and 0.79 in year 4.[4]

Subgroup analyses failed to identify demographic or clinical characteristics which predicted who might safely take estrogen for vasomotor symptoms.[3,4] Lipoprotein particle concentrations predict coronary risk in older men and women[5,6] and may reflect hormone effects more accurately than lipoproteins measured by conventional enzymatic methods.[7] We measured lipoprotein particle concentrations by nuclear magnetic resonance (NMR) spectroscopy in a case–control substudy and evaluated their association with CHD.

Methods

The Women's Health Initiative included 2 randomized controlled trials of postmenopausal hormone therapy: the Estrogen Plus Progestin trial in women with intact uterus and the Estrogen Alone trial in women with prior hysterectomy. Eligibility criteria, recruitment methods, baseline data collection, randomization, and follow-up procedures for the trials have been previously reported.[8-10] The protocol and consent forms were approved by the institutional review boards of participating institutions, and written informed consent was obtained from all participants. The Estrogen Plus Progestin trial randomized 16 608 women, aged 50 to 79 years with intact uterus, to 0.625 mg of oral conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (Prempro, Wyeth) daily or to placebo. The Estrogen Alone trial randomized 10 739 women with prior hysterectomy to CEE 0.625 mg daily (Premarin, Wyeth) or to placebo.

Participants reported emergency room visits, overnight hospital stays, and outpatient coronary revascularization procedures semiannually. Medical records for all overnight hospitalizations and outpatient coronary revascularization procedures were scrutinized for potential outcomes of interest. Outcomes were classified by central physician adjudicators on the basis of medical record review. Myocardial infarction was defined using an algorithm which included symptoms, electrocardiographic findings, and cardiac enzymes.[10]

In the nested case–control study, for each of the hormone trials, cases of CHD occurring during the first 4 years after randomization were matched to controls on age, randomization date, and prevalent coronary disease. Using fasting blood samples collected at baseline and 1 year, lipid profiles were performed at Medical Research Laboratories (Highland Heights, Ky). Lipoprotein particle concentrations were assessed by NMR spectroscopy (Liposcience, Raleigh, NC).[11]

Statistical Analysis

Baseline characteristics of cases and controls were compared by *t* test and χ^2 (Table 1). Baseline biomarker values were log-transformed; differences from baseline to year 1 were analyzed on the original scale. Baseline and on-treatment lipoprotein levels are presented as medians and interquartile ranges; the association with CHD was compared in logistic regression models adjusted for treatment assignment (Table 2). Change in lipoprotein levels was compared between treatment groups by F test (Table 3). We evaluated the log-linearity relationship between lipoprotein levels and CHD in generalized additive models[12] adjusting for age, body mass index, current smoking, treated diabetes, and hypertension. For lipoprotein variables found to be nonlinear, a quadratic function was added to subsequent conditional logistic regression models evaluating the association between lipoproteins and CHD risk (Table 4).

Logistic models were adjusted for treatment assignment, age, current smoking at baseline, diabetes, alcohol use, and hypertension. Models evaluating the change of biomarker from baseline to year 1 included the (log-transformed) baseline biomarker. Interactions between treatment assignment and lipoproteins were evaluated by adding an interaction term to logistic regression models. From the 48 models, we would expect 2 probability values <0.05 by chance. Analyses were carried out using SAS System for Windows v 9.1. The authors had full access to the data and take responsibility for its integrity.

Results

Baseline characteristics for CHD cases and controls are shown separately for the 2 hormone trials (Table 1). CHD cases and controls were matched on age and prevalent cardiovascular disease at baseline. Smoking (P<0.001 for E+P and 0.003 for CEE) and hypertension (P=0.003 for E+P and 0.02 for CEE) were more prevalent, whereas Calcium/Vitamin D trial participation was less frequent (P=0.004 for E+P and 0.04 for CEE) among women with on-trial CHD events. CHD cases had greater waist circumference (P<0.04 for E+P and 0.003 for CEE).

Median levels and interquartile ranges for lipoproteins are shown separately for the 2 trials by case–control status (Table 2). After adjustment for treatment arm, high-density lipoprotein cholesterol (HDL-C) and particle concentration (HDL-P) were negatively associated with CHD (both P<0.001), whereas low-density lipoprotein cholesterol (LDL-C) and low-density lipoprotein particle concentration (LDL-P; both P<0.001), very low–density lipoprotein particle concentration (VLDL-P; P=0.005), and triglycerides (P<0.001) were positively associated with CHD. On-treatment, the associations with HDL-C and HDL-P remained strong. On-treatment LDL-C was not associated with CHD, whereas the association of LDL-P with CHD persisted. For none of the lipoproteins was change from baseline to year 1 significantly associated with CHD after adjustment for treatment arm (data not shown).

Changes in lipoproteins are shown by treatment group assignment (Table 3). For each trial, baseline lipoprotein levels were similar in the active treatment and placebo groups (data not shown). From baseline to year 1, HDL-C and HDL-P rose (P<0.001 for both) among women assigned to active E+P or CEE. LDL-C fell 16% among women assigned to active E+P and 12% among those assigned to active CEE (P<0.001 for both). In contrast, neither LDL-P nor LDL-P+VLDL-P were reduced by E+P or CEE.

Associations between lipoproteins and CHD after multivariable adjustment are shown separately for the 2 trials (Table 4). In the E+P trial at baseline, HDL-C was an independent negative predictor of CHD (OR 0.69, 95% CI 0.52 to 0.93, P=0.01). Positive predictors included LDL-P (OR 1.40, 95% CI 1.08 to 1.83, P=0.01), VLDL-P (OR 1.49, 95% CI 1.11 to 2.00, P=0.009), and triglycerides (1.39, 95% CI 1.08 to 1.79, P=0.01). At year 1, the associations of CHD with HDL-C, VLDL-P, and triglycerides persisted.

In the CEE trial at baseline, HDL-P was negatively associated with CHD (OR 0.64, 95% CI 0.44 to 0.93, P=0.02). LDL-C was an independent positive predictor of CHD (OR 1.61, 95% CI 1.13 to 2.30, P=0.008), but LDL-P and VLDL-P were not. At year 1, none of the lipoprotein levels were independently associated with CHD.

The interaction between postmenopausal hormone therapy and lipoprotein levels with regard to CHD was evaluated by formal interaction testing across the 4 treatment groups (data not shown). Interactions with randomized treatment assignment were identified for baseline HDL-P (P for interaction=0.05) and LDL-C (P for interaction=0.02). No significant interactions were identified between treatment assignment and lipoprotein levels at year 1 or with change in lipoprotein levels from baseline to year 1.

Discussion

Postmenopausal hormone therapy significantly reduced LDL-C and raised HDL-C and HDL-P, but did not alter LDL-P. In the E+P trial, on-treatment HDL-C was negatively associated, whereas triglycerides and VLDL-P were positively associated with CHD. In the E Alone trial, no on-treatment lipoprotein was an independent predictor of CHD.

Strengths of this analysis include the randomized, controlled design, large number of women in the randomized trials, and long duration of follow-up, diversity of the cohort, wide range of covariates available for analysis, and prospective collection of hard clinical end points. The predominant limitation is the number of CHD cases, which limited our ability to detect subtle associations, to evaluate combinations of lipoproteins and interactions with treatment assignment. No future randomized hormone trial, however, is likely to have a larger number of available cases. For example, the Women's International Study of long Duration estrogen after Menopause (WISDOM) was designed as a 22 300 woman trial with 15-year follow-up, but was terminated when the Women's Health Initiative results were announced after accruing only 7 CHD events.[13]

At baseline, participation in the Calcium/Vitamin D trial was less common among CHD cases than controls (50% versus 64%, P=0.004 in the E+P trial and 48% versus 60%, P=0.04 in the E Alone trial). This may be attributable to enrollment bias, as women with concurrent health issues may have been reluctant to join the Calcium/Vitamin D trial when invited at their first annual visit. In the randomized trial of calcium/vitamin D supplementation, we found no treatment effect on CHD.[14]

The goal of this case–control study was to explore mechanisms underlying the early CHD risk with postmenopausal hormones. Lipid modulating agents which raise HDL-C[15] or lower LDL-C,[16] and have parallel effects on lipoprotein particle concentrations,[17,18] have reduced CHD events in randomized trials. In the Women's Health Initiative randomized trials, postmenopausal hormone therapy raised HDL-C and lowered LDL-C, but did not reduce CHD.[3,4] This may be attributable to the fact that postmenopausal hormone therapy-induced changes in lipoprotein cholesterol concentrations did not consistently reflect changes in particle concentrations. For example, E+P reduced median LDL-C by 16% whereas LDL-P increased by 3%. Similarly, unopposed CEE reduced LDL-C by 12%, while increasing LDL-P by 5%. This dissociation is consistent with prior reports in nonrandomized cohorts.[7]

While LDL-C and LDL-P at baseline independently predicted CHD in our trials, we would expect estrogen's effects on CHD to be reflected in on-treatment levels. The association with LDL-C disappeared altogether on-treatment, and that with LDL-P was weaker. A possible explanation for this observation is that proinflammatory and thrombotic effects of postmenopausal hormone therapy[19] supersede the combination of favorable and unfavorable lipoprotein effects. Supporting this possibility is the apparent potentiation by progestins of the interleukin (IL)-6–mediated rise in C-reactive protein induced by estrogen.[20] The rise in CHD risk after initiating estrogen with progestin is prompt, with hazard ratio 1.81 in year 1 of the E+P trial[3] and relative hazard of 2.3 in the first 4 months of treatment in the Heart & Estrogen/progestin Replacement Study,[21] consistent with a fairly rapid mechanism.

Characteristics of women with incident CHD in our case–control study reflected typical predictors such as cigarette smoking and waist circumference. However, even the controls demonstrated some CHD risk characteristics such as body mass index above 25 kg/m^2, C-reactive protein above 3 mg/L, and LDL-P above 1500 nmol/L. These observations underscore the intrinsic limitations of estimating CHD event rates from risk factors, because we know the overall CHD event rates were low, 0.56%/yr for the E Alone trial and 0.33%/yr for the E+P

trial.[3,4] Ongoing genomic and proteomic studies from Women's Health Initiative samples are seeking novel biomarkers to improve current prediction models.

Because vasomotor symptoms remain a significant clinical issue for menopausal women, we carried out the interaction analyses to identify predictors of lower or higher CHD risk with hormones. Individuals perceived at higher risk could then be advised against taking exogenous estrogen for menopausal symptoms, whereas women lacking these characteristics could be reassured that their absolute and relative CHD risk with estrogen was low. In view of the possibility that the interactions we detected were attributable to chance, we cannot be confident that they distinguish women who can more safely take hormones.

This case–control study provides a plausible explanation for the lack of coronary protection with postmenopausal hormone therapy. The observed dissociation between hormone-induced changes in LDL-C and LDL-P supports the view that measures of atherogenic particles, either by NMR spectroscopy or apolipoprotein B levels, may be preferable to LDL-C as surrogate markers for CHD risk.

Sources of Funding

The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts N01WH22110, 24152, 32100−2, 32105−6, 32108−9, 32111−13, 32115, 32118−32119, 32122, 42107−26, 42129−32, and 44221.

References

1. Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. Principal Results From the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288:321–333. [PubMed: 12117397]
2. The Women’s Health Initiative Steering Committee. Effects of conjugated equine estrogen on postmenopausal women with hysterectomy: The Women's Health Initiative Randomized Controlled Trial. JAMA 2004;291:1701–1712. [PubMed: 15082697]
3. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M. Estrogen plus progestin and risk of coronary heart disease. N Engl J Med 2003;349:523–534. [PubMed: 12904517]
4. Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix S, Pettinger M, Caralis P, Crawford S, Eaton CB, Greep N, Heckbert SR, Kostis JB. Conjugated equine estrogens and the risk of coronary heart disease. Arch Intern Med 2006;166:357–365. [PubMed: 16476878]
5. Kuller L, Arnold A, Tracy R, Otvos J, Burke G, Psaty B, Siscovick D, Freedman DS, Kronmal R. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. Arterioscler Thromb Vasc Biol 2002;22:1175–1180. [PubMed: 12117734]
6. Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation 2002;106:1930–1937. [PubMed: 12370215]
7. Mackey RH, Kuller LH, Sutton-Tyrrell K, Evans RW, Holubkov R, Matthews KA. Hormone therapy, lipoprotein subclasses, and coronary calcification. The Healthy Women Study. Arch Intern Med 2005;165:510–515. [PubMed: 15767525]
8. The Women's Health Initiative Study Group. Design of the Women’s Health Initiative Clinical Trial and Observational Study. Control Clin Trials 1998;19:61–109. [PubMed: 9492970]
9. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women’s Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol 2003;13:S78–S86. [PubMed: 14575940]
10. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women’s Health Initiative. Ann Epidemiol 2003;13:S122–S128. [PubMed: 14575944]

11. Otvos JD, Jeyarajah EJ, Bennett DW, Krauss RM. Development of a proton nuclear magnetic resonance spectroscopic method for determining plasma lipoprotein concentrations and subspecies distributions from a single, rapid measurement. Clin Chem 1992;38:1632–1638. [PubMed: 1326420]
12. Hastie, TJ.; Tibshirani, RJ. Generalized Additive Models. Chapman and Hall; New York: 1990.
13. Vickers MR, MacLennan AH, Lawton B, Ford D, Martin J, Meredith SK, DeStavola BL, Rose S, Dowell A, Wilkes HC, Darbyshire JH, Meade TW, WISDOM team. Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomized controlled trial of hormone replacement therapy in postmenopausal women. BMJ 2007;335:239. [PubMed: 17626056]
14. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M, WHI Investigators. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:846–854. [PubMed: 17309935]
15. Robins SJ, Collins D, Wittes JT, Papdemetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA 2001;285:1585–1591. [PubMed: 11268266]
16. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. Lancet 2004;364:685–696. [PubMed: 15325833]
17. Otvos JD, Collins D, Freedman DS, Shalaurova I, Schaefer EJ, McNamara JR, Bloomsfield HE, Robins SJ. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation 2006;113:1556–1563. [PubMed: 16534013]
18. Soedamah-Muthu SS, Colhoun HM, Thomason MJ, Betteridge DJ, Durrington PN, Hitman GA, Fuller JH, Julier K, Mackness MI, Neil HAW. The effect of atorvastatin on serum lipids, lipoproteins and NMR spectroscopy defined lipoprotein subclasses in type 2 diabetic pateints with ischaemic heart disease. Atherosclerosis 2003;167:243–255. [PubMed: 12818407]
19. Kooperberg C, Cushman M, Hsia J, Robinson JG, Aragaki AK, Lynch JK, Baird AE, Johnson KC, Kuller lH, Beresford SAA, Rodriguez B. Can biomarkers identify women at increased stroke risk? The Women's Health Initiative Hormone Trials. PloS Clinical Trials 2007;2:e28. [PubMed: 17571161]
20. Reuben DB, Palla SL, Hu P, Reboussin BA, Crandall C, Herrington DM, Barrett-Connor E, Greendale GA. Progestins affect mechanism of estrogen-induced C-reactive protein stimulation. Am J Med 2006;119:167.e1–e8. [PubMed: 16443423]
21. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E, Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. JAMA 1998;280:605–613. [PubMed: 9718051]

Table 1

Baseline Characteristics

	Estrogen Plus Progestin Trial			Estrogen Alone Trial		
	Case (n=202) Mean (SD)	**Control (n=202) Mean (SD)**	***P* Value**	**Case (n=152) Mean (SD)**	**Control (n=152) Mean (SD)**	***P* Value**
Age, y	66 (7)	66 (7)	0.96	67 (6)	67 (6)	0.99
Body mass index, kg/m^2	29.0 (5.8)	27.8 (5.6)	0.04	30.2 (5.7)	29.6 (6.0)	0.37
Waist circumference, cm	91 (14)	87 (13)	0.008	95 (14)	90 (13)	0.003
C-reactive protein, mg/L	4.3 (4.4)	3.2 (4.0)	0.01	5.3 (5.3)	4.8 (9.1)	0.55
Total physical activity, MET-hr/week	10 (12)	12 (14)	0.09	9 (12)	9 (12)	0.59
	n (%)	n (%)		n (%)	n (%)	
Ethnicity						
White	180 (89)	178 (88)	0.52	116 (76)	123 (81)	0.26
Black	12 (6)	13 (6)		25 (16)	25 (16)	
Hispanic	5 (3)	7 (4)		6 (4)	2 (1)	
American Indian	1 (1)	1 (1)		0 (0)	1 (1)	
Asian/Pacific islander	0 (0)	2 (1)		3 (2)	0 (0)	
Unknown	4 (2)	1 (1)		2 (1)	1 (1)	
Treated diabetes	28 (14)	18 (9)	0.11	36 (24)	13 (9)	<0.001
Current smoking	42 (21)	15 (7)	<0.001	31 (20)	13 (9)	0.003
Hypertension	109 (54)	80 (40)	0.003	96 (63)	77 (51)	0.02
Prior MI/coronary revascularization	28 (14)	21 (10)	0.25	29 (19)	24 (16)	0.43
Alcohol consumption						
<1 drink/week	142 (70)	124 (61)	0.14	119 (78)	100 (66)	0.02
1 to <7 drinks/week	38 (19)	47 (23)		21 (14)	38 (25)	
7 or more drinks/week	19 (9)	28 (14)		7 (5)	12 (8)	
Statin/fibrate use at baseline	33 (16)	25 (12)	0.26	25 (16)	21 (14)	0.52
Dietary Modification trial participant	52 (26)	54 (27)	0.82	42 (28)	41 (27)	0.90
Calcium/Vitamin D trial participant	101 (50)	130 (64)	0.004	73 (48)	91 (60)	0.04

MET indicates metabolic equivalent; MI, myocardial infarction.

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2009 June 24.

Table 2

Baseline and On-Treatment Lipoprotein Levels in CHD Cases and Controls

	Estrogen Plus Progestin Trial				E Alone Trial				
	CHD		Control		CHD		Control		
Baseline	**n**	**Median (IQR)**	**n**	**Median (IQR)**	**n**	**Median (IQR)**	**n**	**Median (IQR)**	***P****
HDL-C, mmol/L	199	1.2 (0.4)	200	1.4 (0.5)	150	1.2 (0.4)	152	1.4 (0.5)	<0.001
HDL-P, nmol/L	202	29 (7)	200	31 (7)	149	30 (6)	149	31 (8)	<0.001
LDL-C, mmol/L	191	3.9 (1.1)	198	3.5 (1.1)	144	3.9 (1.2)	148	3.5 (1.0)	<0.001
LDL-P, nmol/L	202	1673 (603)	200	1513 (526)	149	1687 (611)	149	1525 (605)	<0.001
VLDL-P, nmol/L	202	95 (53)	200	90 (54)	149	98 (60)	149	87 (61)	0.005
LDL-P+VLDL-P, nmol/L	202	1791 (654)	200	1624 (550)	149	1799 (622)	149	1605 (662)	<0.001
Triglycerides, mmol/L	201	1.6 (1.2)	201	1.3 (1.0)	152	1.8 (1.1)	152	1.6 (1.1)	<0.001
Year 1									
HDL-C, mmol/L	122	1.3 (0.5)	123	1.5 (0.6)	95	1.3 (0.5)	94	1.4 (0.6)	<0.001
HDL-P, nmol/L	124	32 (9)	126	33 (10)	96	32 (8)	98	33 (9)	0.002
LDL-C, mmol/L	117	3.3 (1.1)	122	3.2 (1.2)	92	3.5 (1.5)	90	3.3 (1.1)	0.21
LDL-P, nmol/L	124	1639 (481)	126	1487 (540)	96	1739 (678)	98	1677 (701)	0.02
VLDL-P, nmol/L	124	86 (60)	126	77 (54)	96	91 (48)	98	86 (64)	0.02
LDL-P+VLDL-P, nmol/L	124	1723 (503)	126	1549 (546)	96	1826 (699)	98	1782 (738)	0.01
Triglycerides, mmol/L	122	1.8 (1.2)	123	1.5 (1.0)	95	1.9 (1.1)	94	1.6 (1.3)	0.007

IQR indicates interquartile range; HDL-C, high density lipoprotein-cholesterol; HDL-P, high density lipoprotein particle concentration; LDL-C, low density lipoprotein-cholesterol; LDL-P, low density lipoprotein particle concentration; VLDL-P, very low density lipoprotein particle concentration.

*Association between (log-transformed) biomarker and CHD from logistic regression models adjusted for treatment arm.

Table 3

Change in Lipoprotein Levels From Baseline to Year 1 by Treatment Group Assignment

	Estrogen Plus Progestin Trial					Estrogen Alone Trial				
	E+P		Placebo			CEE		Placebo		
Change, Baseline to Year 1	**n**	**Mean (SD)**	**n**	**Mean (SD)**	***P****	**n**	**Mean (SD)**	**n**	**Mean (SD)**	***P****
HDL-C, mmol/L	141	0.11 (0.20)	101	0.01 (0.22)	<0.001	97	0.23 (0.28)	90	−0.01 (0.17)	<0.001
HDL-P, nmol/L	144	4 (8)	105	0.5 (5)	<0.001	100	6 (8)	92	−1 (6)	<0.001
LDL-C, mmol/L	139	−0.62 (0.62)	94	−0.11 (0.72)	<0.001	89	−0.54 (0.73)	90	−0.02 (0.72)	<0.001
LDL-P, nmol/L	144	13 (316)	105	−56 (371)	0.11	100	66 (385)	92	18 (365)	0.38
VLDL-P, nmol/L	144	−13 (28)	105	−8 (30)	0.13	100	−10 (36)	92	0.3 (31)	0.04
LDL-P+VLDL-P, nmol/L	144	−1 (326)	105	−64 (386)	0.16	100	56 (403)	92	18 (378)	0.51
Triglycerides, mmol/L	142	0.06 (0.61)	101	−0.08 (0.88)	0.15	98	0.38 (1.33)	91	−0.05 (0.60)	0.01
Percent Change		% (SD)		% (SD)			% (SD)		% (SD)	
HDL-C	141	9 (16)	101	2 (16)	<0.001	97	18 (21)	90	0.1 (13)	<0.001
HDL-P	144	16 (25)	105	2 (17)	<0.001	100	20 (27)	92	−1 (20)	<0.001
LDL-C	139	−16 (15)	94	−1 (18)	<0.001	89	−12 (19)	90	1 (22)	<0.001
LDL-P	144	3 (20)	105	−0.4 (21)	0.25	100	5 (22)	92	4 (23)	0.63
VLDL-P	144	−12 (30)	105	−3 (33)	0.02	100	−2 (50)	92	5 (39)	0.35
LDL-P+VLDL-P	144	2 (19)	105	−1 (21)	0.36	100	4 (22)	92	4 (22)	0.78
Triglycerides	142	11 (30)	101	3 (31)	0.06	98	22 (45)	91	2 (26)	<0.001

*Change from baseline to year 1 assessed by F test.

Table 4

Adjusted CHD Risk (per SD Increase) and Lipoproteins

	Estrogen Plus Progestin Trial (n Pair=202)		Estrogen Alone Trial (n Pair=152)	
Baseline	**Odds Ratio (95% CI)***	***P* Value†**	**Odds Ratio (95% CI)***	***P* Value†**
HDL-C	0.69 (0.52, 0.93)	0.01	0.79 (0.58, 1.08)	0.14
HDL-P	0.87 (0.67, 1.13)	0.31	0.64 (0.44, 0.93)	0.02
LDL-C	1.29 (0.97, 1.73)	0.08	1.61 (1.13, 2.30)	0.008
LDL-P	1.40 (1.08, 1.83)	0.01	1.31 (0.97, 1.78)	0.08
VLDL-P	1.49 (1.11, 2.00)	0.009	1.02 (0.73, 1.41)	0.93
LDL-P+VLDL-P	1.44 (1.10, 1.89)	0.009	1.30 (0.96, 1.77)	0.09
Triglycerides	1.39 (1.08, 1.79)	0.01	1.06 (0.79, 1.43)	0.70
Year 1	(n pair=131)		(n pair=99)	
HDL-C	0.58 (0.38, 0.89)	0.01	0.79 (0.54, 1.17)	0.25
HDL-P	0.74 (0.48, 1.15)	0.19	0.77 (0.51, 1.16)	0.21
LDL-C	0.96 (0.65, 1.42)	0.84	1.07 (0.73, 1.57)	0.71
LDL-P	1.29 (0.90, 1.84)	0.17	1.13 (0.82, 1.55)	0.45
VLDL-P	1.73 (1.15, 2.59)	0.008	1.00 (0.68, 1.47)	>0.99
LDL-P+VLDL-P	1.36 (0.94, 1.97)	0.10	1.13 (0.82, 1.56)	0.45
Triglycerides	1.57 (1.08, 2.28)	0.02	1.11 (0.60, 2.69)	0.62

*Adjusted odds ratio and 95% CI from conditional logistic regression of per SD increase of log-transformed biomarker (according to controls), adjusted for age, treatment arm, current smoking at baseline, alcohol use, diabetes, and hypertension.

†One degree of freedom test for biomarkers (log-transformed from baseline and year 1) from conditional logistic regression models.