Published in final edited form as:
Am Heart J. 2007 January ; 153(1): 54–58. doi:10.1016/j.ahj.2006.10.019.

Absence of an interaction between the angiotensin converting enzyme (ACE) insertion-deletion polymorphism and pravastatin on cardiovascular disease in high-risk hypertensives: The GenHAT Study

Anke-Hilse Maitland-van der Zee, PharmD, PhD[1,2], **Eric Boerwinkle, PhD**[1], **Donna K. Arnett, PhD**[3], **Barry R. Davis, MD, PhD**[1], **Catherine Leiendecker-Foster, MS**[4], **Michael B. Miller, PhD**[3], **Olaf H. Klungel, PharmD, PhD**[2], **Charles E. Ford, PhD**[1], and **John H. Eckfeldt, MD, PhD**[4]

[1] University of Texas Health Science Center at Houston, School of Public Health, 1200 Hermann Pressler, Houston Tx 77030. Phone 713 500 9817, Fax 713 500 0900 Email: a.h.maitland@pharm.uu.nl [2] Department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, the Netherlands [3] University of Alabama at Birmingham, 1665 University Avenue, Birmingham, AL, 35294 [4] University of Minnesota, Department of Laboratory Medicine and Pathology, 420 Delaware Street SE MMC 609, Minneapolis, MN 55455

Abstract

Background—The aim of this study was to determine whether the ACE insertion-deletion (I/D) polymorphism interacts with pravastatin to modify the risk of CHD and other cardiovascular endpoints in a large clinical trial.

Methods—GenHAT is an ancillary study of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ACE ID genotyped population in the lipid lowering arm of ALLHAT included 9,467 participants randomly assigned to pravastatin (n=4741) or to usual care (n=4726). The efficacy of pravastatin in reducing the risk of primary outcome (all cause mortality), and secondary outcomes (fatal CHD and non-fatal MI, CVD mortality, CHD, stroke, other CVD, non-CVD mortality, stroke and heart failure) was compared between the genotype strata (dominant model ID+II versus DD, additive model II vs ID vs DD), by examining an interaction term in a Cox proportional Hazard model.

Results—The relative risk of fatal CHD and nonfatal MI among subjects randomized to pravastatin compared to subjects randomized to usual care was similar in subjects with the II genotype (HR 0.84 [95% CI 0.59–1.18]), the ID genotype (HR 0.84 [95%CI 0.68–1.03], and the DD genotype (HR 0.99 [95%CI:0.77–1.27]).

Conclusions—We found no evidence that ACE I/D genotype was a major modifier of the efficacy of pravastatin in reducing the risk of cardiovascular events.

Correspondence to: Anke-Hilse Maitland-van der Zee.

Introduction

The efficacy of cholesterol-lowering drug therapy in primary and secondary prevention has been firmly established. The combined results of 9 large long-term statin trials (including the ALLHAT-lipid lowering trial (ALLHAT-LLT)) showed a 27% reduction in coronary heart disease (CHD) events and a 14% reduction in all-cause mortality [1–9]. These reductions, however, were average effects of statin therapy for all patients included in the trials. Pharmacogenetic findings suggest that patients may differ in their response to statins because of their genetic constitution [10].

The angiotensin converting enzyme (ACE) is thought to play an important role in the development of coronary artery disease. Plasma and cellular levels of ACE are associated with a large insertion/deletion polymorphism located in intron 16 of the ACE gene. DD carriers have about twice the plasma levels of ACE compared with II carriers, while heterozygotes have intermediate levels [11]. In a meta-analysis including 145 reports with an overall sample size of 49,959, the excess risk in subjects with the DD genotype compared to subjects with the II genotype was 32% for coronary heart disease (30 studies) and 45% for myocardial infarction (20 studies) [12].

Contradictory results have been published on the influence of the ACE I/D polymorphism on the effectiveness of statins. In the Cholesterol And Recurrent Events (CARE) trial no effect was found for the ACE I/D polymorphism alone on the efficacy of pravastatin in reducing the primary endpoint [13]. In the Lipoprotein and Coronary Atherosclerosis (LCAS) study, subjects with the ACE DD genotype had the strongest reduction of coronary atherosclerosis with pravastatin. However, the distribution of clinical events among genotypes was not significantly different [14]. In an observational cohort study among subjects with hypercholesterolemia the beneficial effect of statins on coronary heart disease was different for men with different ACE genotypes. In men with two I alleles, the largest beneficial effects of statins were demonstrated while in men with two D alleles no beneficial effects were demonstrated [15]. The objective of this study was to determine whether the ACE I/D polymorphism interacts with pravastatin to modify the risk of CHD and other cardiovascular endpoints in a large randomized clinical trial of high-risk individuals.

Methods

Study Population and Design

GenHAT is an ancillary study of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The lipid lowering trial (LLT) component of ALLHAT was designed to evaluate the impact of large sustained cholesterol reductions on all-cause mortality in a hypertensive cohort with at least 1 other CHD risk factor and to assess CHD reduction and other benefits in populations that had been excluded or underrepresented in previous trials, particularly older persons, women, racial and ethnic minority groups, and persons with diabetes. A priori secondary outcomes included combination of CHD death [fatal CHD, coronary revascularization related mortality, previous angina or MI and no known potentially lethal non coronary disease process] and non-fatal MI, CVD mortality [mortality due to CHD, stroke, other treated angina, heart failure, peripheral disease], CHD [CHD death, coronary revascularization, hospitalized angina], fatal stroke, other CVD, non-CVD mortality, stroke [fatal and non-fatal] and heart failure. The design of ALLHAT including the LLT, and its participant and clinical site recruitment and selection have been reported elsewhere [9,16–18]. Briefly, ALLHAT-LLT was a randomized, non-blinded, large simple trial conducted from February 1994 through March 2002 at 513 clinical centers in the United States, Puerto Rico, US Virgin Islands, and Canada. The intervention was open-label pravastatin (40 mg/d) versus usual care. Participants were drawn exclusively from the ALLHAT antihypertensive trial. The

protocol of ALLHAT was approved by each participating center's Institutional Review Board. The GenHAT study was approved by the Institutional Review Boards of the University of Minnesota and The University of Texas Health Science Center at Houston.

Statistical methods

Participants were stratified according to genotype and baseline characteristics were compared using chi-square and t-tests. The efficacy of pravastatin in reducing the risk of the primary outcome (all-cause mortality) and of a-priori secondary outcomes is compared between the genotype strata (II + ID vs DD), using an interaction term in the Cox proportional Hazard model. These analyses were adjusted for potential confounding baseline factors: sex (men/women), race (black/white), current smoking status (yes/no), history of diabetes (yes/no), history of CHD (yes/no), visit 1 systolic blood pressure (mm Hg), and age (years).. Because on our previous finding that the interaction between the ACE I/D polymorphism and effectiveness of statins may be modified by gender [19] a 3-way interaction for gender-ACE genotype-statin therapy was included in the model to compare the interaction between men and women. We also included a three-way interaction for race-ACE genotype-statin therapy in the model to examine whether ethnicity accounted for differences in the pharmacogenetic effect of the ACE ID genotype on the primary and secondary outcomes.

Results

The genotyped population in the lipid lowering arm of ALLHAT included 9,467 participants. Of these 4,741 were in the pravastatin treatment group, and 4,726 were in the usual care group. In Table 1 baseline characteristics according to ACE ID genotype for subjects randomized to pravastatin and subjects in the usual care group are shown.

The proportions and characteristics within each of the three genotypes assigned to each treatment (pravastatin versus usual care) were well balanced. The total number of trial events and the cumulative 6-year Kaplan-Meier event rates of clinical outcomes by ACE genotype and treatment are shown in Table 2. The effects of ACE ID on the clinical outcomes (regardless of pravastatin treatment assignment) can be found in Table 3. Subjects with the ID genotype had a statistically significant lower risk of fatal and nonfatal stroke compared with subjects with the II genotype (HR_{adj} =0.76 [95% CI 0.59–0.99]). This finding was marginally significant for fatal strokes alone (p =0.051).

Hazard ratios of the effect of statin use are shown, by genotype, in Table 4. Three-way analyses of the ACE I/D genotypes, treatment and primary clinical outcome (all-cause mortality) identified no differences in efficacy of pravastatin between subjects with the II and DD genotype (interaction hazard ratio 0.81 [95% CI 0.58–1.14] p=0.31), or between subjects with the ID and DD genotype (interaction hazard ratio 0.90 [95% CI 0.69–1.17] p=0.42) (Table 4). The secondary endpoints were consistent with these negative findings. No significant gene drug interactions were found. We evaluated gene-drug interactions in relation to the primary and secondary outcomes in subgroups based on gender and on race. There were no apparent gene-treatment interactions across gender-gene-drug or race-gene-drug subgroups (data not shown).

Discussion

The GenHAT-LLT study is a large pharmacogenetic trial of pravastatin versus usual care. Based on genotype data collected from almost 10,000 individuals, who were followed for cardiovascular events using standard, well-defined definitions for cardiovascular outcomes, we found no compelling evidence that ACE I/D genotype is a major determinant of the efficacy of pravastatin in reducing the risk of cardiovascular events. We did not find any significant

interactions in the response to therapy, despite the large number of tests performed. We did observe that participants with the II and ID genotypes tended to fare better on pravastatin than usual care for most of the outcomes examined, while the opposite was true for the DD participants. The IIvs DD and the ID vs DD interaction hazards ratios were below 1.00 for all outcomes except heart failure, ranging from 0.47 for fatal strokes (II vs DD) to 0.98 for CHD (ID vs DD). This is in concordance with what would be expected based on a previous study [15].

The GenHAT study selected individuals based on pre-existing coronary risk factors and hypertension. Therefore there is some uncertainty about the applicability of the findings of this study to the association in subjects without these risk factors.

In the ALLHAT study no overall beneficial effect of pravastatin was demonstrated on the primary outcome. After 6 years of follow-up 26% of subjects in the usual care arm used statins, and 16% in the pravastatin arm did not use a lipid lowering drug anymore. There was no significant differential in crossovers among ACE genotypes, and therefore would not affect the interaction between pravastatin and the ACE polymorphism.

Our finding that the ACE I/D polymorphism did not modify the efficacy of statins were in concordance with three studies [13,14,19]. Results were different from the results of the Rotterdam study that found a significant interaction in men [15]. Even though no statistically significant interaction was found in GenHAT, there was a trend towards better efficacy in the subjects with the II and ID genotype compared with the DD genotype. For example, subjects with the ID genotype tended to fare better on pravastatin than usual care for fatal CHD and nonfatal MI (HR_{adj} 0.84 [95% CI 0.68–1.03]), while there was no effect of pravastatin in subjects with the DD genotype (adjusted HR 0.99 [95% CI 0.77–1.27]). This result is similar to the findings in the Rotterdam study. However, we did not find evidence that there were differences in efficacy between men and women as was found in the Rotterdam Study. The physiological role of the renin-angiotensin system varies with sodium intake, age and disease status [20]. Since this trial included high risk hypertensives, while the Rotterdam cohort study included a hypercholesterolemic subset of the general population, this might be an explanation for the different findings in men. A strength of the GenHAT study, however, is that it was performed in a large clinical trial with reasonable event rates in both subjects randomized to pravastatin and in subjects randomized to usual care. Furthermore since only the I/D polymorphism was studied an effect of other polymorphisms in the ACE gene on pravastatin cannot be ruled out. These pharmacogenetic analyses of the ALLHAT-LLT in combination with results from earlier studies provide no rationale for using ACE I/D genotype to guide decisions about treatment with pravastatin. Since there was a trend towards less efficacy in subjects with the DD genotype, more research in larger settings, possibly combinations of different trials/cohort studies, is necessary.

References

1. Anonymous. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. Lancet 1994;344:1383–1389. [PubMed: 7968073]
2. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, McFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Eng J Med 1995;333:1301–1307.
3. Sacks F, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwals E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Eng J Med 1996;335:1001–1009.
4. Anonymous. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Eng J Med 1998;339:1349–1357.

5. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA 1998;279:1615–1622. [PubMed: 9613910]
6. Anonymous. MRC/BHF Heart protection study of cholesterol lowering with simvastatin in 20,536 high risk individuals; a randomized placebo controlled trial. Lancet 2002;360:7–22. [PubMed: 12114036]
7. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997;336:153–162. [PubMed: 8992351]
8. Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;287:3215–22. [PubMed: 12076217]
9. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. JAMA 2002;288:2998–3007. [PubMed: 12479764]
10. Maitland-van der Zee AH, Klungel OH, Stricker BHCh, Verschuren WMM, Kastelein JJP, Leufkens HGM, de Boer A. Genetic polymorphisms: importance for response to HMG-CoA reductase inhibitors. Atherosclerosis 2002;163:213–222. [PubMed: 12052467]
11. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 1990;86:1343–1346. [PubMed: 1976655]
12. Staessen JA, Wang JG, Ginocchio G, Petrov V, Saavedra AP, Soubrier F, Vlietinck R, Fagard R. The deletion/insertion polymorphism of the angiotensin converting enzyme gene and cardiovascular-renal risk. J Hypertens 1997;15:1579–92. [PubMed: 9488209]
13. Bray PF, Cannon CP, Goldschmidt-Clermont P, Moye LA, Pfeffer MA, Sacks FM, Braunwald E. The platelet Pl(A2) and angiotensin-converting enzyme (ACE) D allele polymorphisms and the risk of recurrent events after acute myocardial infarction. Am J Cardiol 2001;88:347–352. [PubMed: 11545752]
14. Marian AJ, Safavi F, Ferlic L, Dunn JK, Gotto AM, Ballantyne CM. Interactions between angiotensin-I converting enzyme insertion/deletion polymorphism and response of plasma lipids and coronary atherosclerosis to treatment with fluvastatin: the lipoprotein and coronary atherosclerosis study. J Am Coll Cardiol 2000;35:89–95. [PubMed: 10636265]
15. Maitland-van der Zee AH, Stricker BH, Klungel OH, Kastelein JJ, Hofman A, Witteman JC, Leufkens HG, Duijn CM, Boer de A. Effectiveness of HMG-CoA reductase inhibitors is modified by the ACE insertion deletion polymorphism. Atherosclerosis 2004;175:377–379. [PubMed: 15262195]
16. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT Jr, Cushman WC, Grimm RH, LaRosa J, Whelton PK, Perry HM, Alderman MH, Ford CE, Oparil S, Francis C, Proschan M, Pressel S, Black HR, Hawkins CM. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. Am J Hypertens 1996;9:342–360. [PubMed: 8722437]
17. Pressel S, Davis BR, Louis GT, Whelton P, Adrogue H, Egan D, Farber M, Payne G, Probstfield J, Ward H. Participant recruitment in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Control Clin Trials 2001;22:674–686. [PubMed: 11738123]
18. Wright JT Jr, Cushman WC, Davis BR, Barzilay J, Colon P, Egan D, Lucente T, Nwachuku C, Pressel S, Leenen FH, Frolkis J, Letterer R, Walsh S, Tobin JN, Deger GE. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): clinical center recruitment experience. Control Clin Trials 2001;22:659–673. [PubMed: 11738122]
19. Marques-Vidal P, Bongard V, Ruidavels JB, Fauvel J, Perret B, Ferrieres J. Effect of apolipoprotein E alleles and angiotensin converting enzyme insertion/deletion polymorphisms on lipid and lipoprotein markers in middle aged men and in patients with stable angina pectoris or healed myocardial infarction. Am J Cardiol 2003;92:1102–1105. [PubMed: 14583365]

20. Danser AH, Schunkert H. Renin-angiotensin system gene polymorphisms: potential mechanisms for their association with cardiovascular diseases. Eur J Pharmacol 2000;410:303–316. [PubMed: 11134678]

Table 1

Baseline characteristics of the pravastatin and usual care subgroups, according to ACE insertion/deletion genotype.

	ACE Genotype					
	II		ID		DD	
Characteristic	**Pravastatin**	**Usual care**	**Pravastatin**	**Usual care**	**Pravastatin**	**Usual care**
Sample size	951 (20.1)	922 (19.5)	2376 (50.1)	2336 (49.4)	1414 (29.8)	1468 (31.1)
Age	65.95 (7.5)	66.13 (7.8)	66.64 (7.7)	66.17 (7.4)	66.32 (7.8)	66.34 (7.6)
Race						
White	551 (57.9)	567 (61.5)	1358 (57.2)	1367 (58.5)	778 (55.1)	806 (54.9)
Black	304 (32.0)	274 (29.7)	897 (37.8)	824 (35.3)	572 (40.4)	587 (40.0)
Other	96 (10.1)	81 (8.8)	121 (5.0)	145 (6.2)	64 (4.5)	75 (5.1)
Gender (Male)	481 (50.6)	471 (51.1)	1218 (51.3)	1185 (50.7)	735 (52.0)	747 (50.9)
Lipid Meds in last year	14 (1.5)	19 (2.1)	38 (1.6)	33 (1.4)	27 (1.9)	20 (1.4)
SBP, mm Hg	145 (13.9)	146 (14.2)	145 (14.1)	145 (13.9)	145 (13.7)	145 (14.1)
DBP, mm Hg	84 (9.7)	84 (9.9)	84 (10.0)	84 (9.7)	84 (9.6)	84 (10.0)
Smoker	211 (22.2)	245 (26.6)	548 (23.1)	525 (22.5)	353 (25.0)	339 (23.1)
History of diabetes	359 (37.8)	286 (31.0)	843 (35.5)	834 (35.7)	477 (33.7)	501 (34.1)
History of MI or Stroke	164 (17.3)	145 (15.7)	397 (16.7)	408 (17.5)	248 (17.5)	268 (18.3)
History of CHD	131 (13.8)	146 (15.8)	333 (14.0)	344 (14.7)	178 (12.6)	227 (15.5)
BMI	30.1 (6.0)	29.7 (6.2)	29.8 (5.9)	29.9 (6.1)	29.8 (5.9)	30.2 (6.2)
Total cholesterol	224.7 (26.2)	223.1 (26.3)	223.2 (27.3)	223.5 (26.3)	223.5 (26.9)	223.9 (26.6)
HDL cholesterol	47.0 (13.6)	46.9 (13.5)	47.6 (13.4)	47.2 (13.2)	47.9 (13.3)	47.7 (13.9)
LDL cholesterol	145.5 (20.5)	144.9 (20.9)	145.2 (21.9)	145.3 (21.4)	145.8 (21.1)	145.5 (21.3)
Antihypertensive treatment group						
Doxazosin	180 (18.9)	194 (21.0)	497 (20.9)	508 (21.8)	316 (22.3)	309 (21.1)
Chlorthalidone	367 (38.9)	348 (37.7)	838 (35.3)	850 (36.4)	513 (36.3)	516 (35.2)
Amlodipine	196 (20.6)	197 (21.4)	536 (22.6)	501 (21.5)	292 (20.7)	315 (21.5)
Lisinopril	208 (21.9)	183 (19.9)	505 (21.3)	477 (20.4)	293 (20.7	328 (22.3)

Table 2

Total number of trial events and cumulative 6-year Kaplan-Meier risk estimates of clinical outcomes by ACE genotype and lipid treatment group.

			ACE Insertion/Deletion Genotype					
	ALL		II		ID		DD	
Trial Outcome	**Prav**	**UC**	**Prav**	**UC**	**Prav**	**UC**	**Prav**	**UC**
Sample Size	4,741	4,726	951	922	2,376	2,336	1,414	1,468
All-cause mortality	584	566	101	108	302	286	181	172
	0.1441	0.1402	0.1328	0.1409	0.1482	0.1460	0.1462	0.1363
CVD deaths	273	272	45	55	145	139	83	78
	0.0685	0.0670	0.0570	0.0666	0.0732	0.0704	0.0686	0.0617
CHD	149	150	24	27	82	78	43	45
	0.0371	0.0372	0.0309	0.0314	0.0397	0.0399	0.0377	0.0356
Stroke	48	49	9	15	19	17	20	17
	0.0120	0.0127	0.0125	0.0219	0.0088	0.0088	0.0173	0.0139
Other CVD	76	73	12	13	44	44	20	16
	0.0208	0.0184	0.0145	0.0149	0.0263	0.0232	0.0151	0.0134
Non-CVD mortality	277	259	50	46	141	131	86	82
	0.0711	0.0694	0.0684	0.0693	0.0719	0.0709	0.0720	0.0719
Fatal CHD and nonfatal MI	349	392	61	70	172	198	116	124
	0.0904	0.1031	0.0830	0.0921	0.0864	0.1063	0.1032	0.1032
Fatal and nonfatal stroke	192	212	38	50	84	90	70	72
	0.0552	0.0510	0.0537	0.0727	0.0469	0.0449	0.0593	0.0615
Heart failure (hospitalized or fatal)	229	232	40	50	128	107	61	75
	0.0604	0.0616	0.0541	0.0650	0.0677	0.0555	0.0505	0.0678

ACE = Angiotensin converting enzyme; Prav = pravastatin; UC = usual care; CVD = cardiovascular disease; CHD= coronary heart disease; MI = myocardial infarction.

Am Heart J. Author manuscript; available in PMC 2009 October 24.

Table 3

Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) of the ID and DD genotypes relative to the II genotype for combined randomized groups.

	II reference	ID		DD	
		HR (unadjusted) 95% CI	HR (adjusted)[1] 95% CI	HR (unadjusted) 95% CI	HR (adjusted) [1] 95% CI
All Cause Mortality	1	1.12 (0.96, 1.31)	1.11 (0.94, 1.29)	1.09 (0.91, 1.29)	1.08 (0.91, 1.29)
CVD mortality	1	1.13 (0.90, 1.42)	1.12 (0.89, 1.41)	1.04 (0.81, 1.33)	1.03 (0.80, 1.33)
CHD	1	1.25 (0.91, 1.71)	1.25 (0.91, 1.71)	1.11 (0.79, 1.57)	1.10 (0.78, 1.56)
Stroke	1	0.59 (0.35, 1.00)	0.59 † (0.35, 0.99)	1.00 (0.60, 1.67)	0.96 (0.57, 1.61)
Other CVD	1	1.40 (0.90, 2.19)	1.36 (0.87, 2.13)	0.93 (0.56, 1.56)	0.95 (0.57, 1.58)
Non-CVD mortality	1	1.13 (0.89, 1.42)	1.11 (0.88, 1.40)	1.13 (0.88, 1.45)	1.14 (0.88, 1.46)
Fatal CHD and nonfatal MI	1	1.13 (0.92, 1.38)	1.14 (0.93, 1.39)	1.19 (0.96, 1.48)	1.20 (0.97, 1.49)
Stroke (fatal and nonfatal)	1	0.78 (0.61, 1.01)	0.76 ‡ (0.59, 0.98)	1.04 (0.80, 1.36)	1.00 (0.76, 1.31)
Heart Failure (hospitalized or fatal)	1	1.04 (0.81, 1.32)	1.03 (0.81, 1.31)	0.98 (0.75, 1.27)	0.98 (0.75, 1.28)

[1] Adjusted for treatment group (pravastatin/usual care), sex (male/female), race (black/white), and eight baseline variables: current smoking status (yes/no), history of diabetes (yes/no), history of CHD (yes/no), systolic blood pressure level (mm Hg), and age (years).

† p = 0.047

‡ p = 0.038

Table 4

Adjusted hazard ratios (HR_{adj}) and 95% confidence limits of the effect of pravastatin versus usual care on study outcomes, according to II, ID, and DD genotype strata. In addition, the adjusted interaction hazard ratios [1] (IHR_{adj}) of the II versus the DD genotype and the ID versus DD genotype are given. The interaction hazard ratio estimates for a given outcome were obtained from respective Cox proportional hazards models incorporating treatment, genotype (II/DD and ID/DD), treatment by genotype interactions, and seven baseline covariates.

Trial Outcome	HR_{adj} (95% CI) II	HR_{adj} (95% CI) ID	HR_{adj}(95% CI) DD	IHR_{adj} (95% CI) II vs DD, p-value[2]	IHR_{adj} (95% CI) ID vs DD, p-value[2]
All-Cause Mortality	0.90 (0.68, 1.18)	0.99 (0.84, 1.16)	1.09 (0.89, 1.35)	0.81 (0.58, 1.14), 0.23	0.90 (0.69, 1.17), 0.42
CVD Mortality	0.79 (0.53, 1.18)	0.98 (0.78, 1.24)	1.10 (0.81, 1.50)	0.70 (0.42, 1.15), 0.16	0.87 (0.59, 1.29), 0.49
CHD	0.84 (0.48, 1.46)	1.00 (0.73, 1.37)	1.01 (0.66, 1.53)	0.82 (0.41, 1.64), 0.58	0.98 (0.58, 1.65), 0.94
Fatal Stroke	0.60 (0.26, 1.39)	1.02 (0.53, 1.97)	1.22 (0.64, 2.33)	0.47 (0.16, 1.34), 0.16	0.83 (0.33, 2.10), 0.70
Other CVD	0.93 (0.42, 2.05)	0.91 (0.60, 1.39)	1.22 (0.63, 2.36)	0.71 (0.26, 1.99), 0.52	0.71 (0.33, 1.55), 0.39
Non-CVD Mortality	1.04 (0.69, 1.55)	1.00 (0.79, 1.27)	1.09 (0.81, 1.48)	0.95 (0.58, 1.57), 0.85	0.92 (0.63, 1.35), 0.67
Fatal CHD and nonfatal MI	0.84 (0.59, 1.18)	0.84 (0.68, 1.03)	0.99 (0.77, 1.27)	0.84 (0.55, 1.29), 0.43	0.85 (0.61, 1.17), 0.31
Stroke (fatal and nonfatal)	0.73 (0.48, 1.11)	0.88 (0.66, 1.19)	1.03 (0.74, 1.43)	0.69 (0.41, 1.19), 0.18	0.86 (0.55, 1.35), 0.52
Heart Failure (hospitalized or fatal)	0.75 (0.50, 1.14)	1.15 (0.89, 1.48)	0.85 (0.61, 1.20)	0.87 (0.51, 1.49), 0.61	1.32 (0.86, 2.02), 0.20

Adjusted for differences in sex (male/female), race (black/white), and five baseline variables: current smoking status (yes/no), history of diabetes (yes/no), history of CHD (yes/no), systolic blood pressure level (mm Hg), age (years).

[1] The interaction hazard ratio is a ratio of ratios: Prav/UC for II stratum over Prav/UC for DD stratum, and similarly for ID versus DD.

[2] Test of null hypothesis: $IHR_{adj} = 1.0$.