Title

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Journal

Journal of Vascular Surgery, 73(4)

ISSN

0741-5214

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Publication Date

2021-04-01

DOI

10.1016/j.jvs.2020.07.106

Peer reviewed

HHS Public Access

Author manuscript

J Vasc Surg. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

J Vasc Surg. 2021 April ; 73(4): 1245–1252.e3. doi:10.1016/j.jvs.2020.07.106.

Lipoprotein(a) levels and risk of abdominal aortic aneurysm in the Women's Health Initiative

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ELC, SL: study conception and design, data interpretation and analysis, manuscript composition, critical revision; MP: data analysis; BH, MWM, MAH, JWW, MAA, RAW, AHS, RBW, LGS, MJE, MFC: manuscript composition, critical revision

Presentation Information: Accepted for presentation at the Society for Clinical Vascular Surgery 2020.

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Abstract

Objective—Few studies have prospectively examined associations of lipoprotein(a) [Lp(a)] levels with risk of abdominal aortic aneurysm (AAA), particularly in women. Accounting for commonly recognized risk factors, we investigated baseline Lp(a) levels with risk of AAA among postmenopausal women participating in the ongoing national Women's Health Initiative (WHI).

Methods—WHI participants with baseline Lp(a) levels who were beneficiaries of Medicare Parts A&B fee-for-service at study enrollment, or who aged into Medicare at any point, were included. Participants with missing covariate data or known AAA at baseline were excluded. Thoracic aneurysms were excluded due to different pathophysiology. AAA cases and interventions were identified by International Classification of Disease-9/10 codes and Current Procedural Terminology codes from claims data. Hazard ratios were computed using Cox proportional hazard models according to quintiles of Lp(a) (mg/dL).

Results—Among the 6,615 participants included in the analysis, the mean age was 65.3 years. 66.6% were non-Hispanic White, 18.9% Black, 7% Hispanic and 4.7% Asian/Pacific Islander. Compared to participants in the lowest quintile, those in higher quintiles were more likely to be overweight, Black, former or current smokers, hypertensive, hyperlipidemic, to have history of cardiovascular disease, use MHT and use statins.

During 65,476 person-years of follow-up, over a median of 10.4 years, 415 women were diagnosed with AAA and 36 required interventions. Over half required intervention for ruptured AAA. We failed to find a statistically significant association between Lp(a) and incident AAA. Additional sensitivity analyses by race, exclusion of statin users, and alternative categorizations of Lp(a) by log-transformed levels, tertiles and a cutoff of >50mg/dL were conducted and did not reveal any significant associations.

Conclusions—We found no statistically significant association between Lp(a) levels and risk of AAA in a large and well-phenotyped sample of postmenopausal women. Women with high Lp(a) levels were more likely to be overweight, Black, former or current smokers, hypertensive, hyperlipidemic, to have history of cardiovascular disease, or use hormone therapy and statins, compared to those with lower levels. These findings differ from previous prospective, case-control and meta-analysis studies which supported a significant relationship between higher Lp(a) levels and increased risk of AAA. Differences in association may be due to study limitations or sex differences.

TABLE OF CONTENTS SUMMARY

No association was found between lipoprotein(a) levels and risk of AAA in this post-hoc analysis of the large and well-phenotyped sample of 415 postmenopausal women from the ongoing, prospective Women's Health Initiative. Further investigation on hormone status in women on the different associations observed between Lp(a) and risk of AAA in men and women are needed.

Keywords

abdominal aortic aneurysm; lipoprotein a; women's health

ARTICLE HIGHLIGHTS

Type of Research: Post-hoc analysis of the prospective, multicenter Women's Health Initiative cohort study

Key Findings: During 65,476 person-years of follow-up, over a median of 10.4 years, 415 women were diagnosed with AAA. There was no association between Lp(a) level and risk of AAA in the Women's Health Initiative.

Take home Message: This study found no association between Lp(a) levels and risk of AAA. These findings differ from prior prospective, case-control and meta-analyses.

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a common, typically asymptomatic, and potentially devastating pathology that affects approximately 15,000 people per year.[1] The prevalence of AAA is estimated to be 0.5–1.3% in women compared to 1.7–4.5% in men.[1–3] AAAs in womem tend to develop at a later age than men, have a more aggressive course with more rapid expansion, and a higher tendency to rupture at smaller diameters with higher mortality after repair.[4] Women also account for 33% of ruptured AAA hospitalizations and 41% of AAA death.[5] Thus, although AAA has been a disorder considered to predominantly affect men, women bear a significant portion of its morbidity and mortality. Furthermore, specific criteria for screening and timing of elective repair in women remain uncertain.[6] Identifying high-risk patients for screening ultrasound by risk factors or biomarkers is critical to improving mortality and morbidity associated with AAAs, particularly among women.

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein that has long been associated with a higher risk of cardiovascular disease (CVD) but evidence in relation to AAA is limited.[7–12] Due to the many shared risk factors between CVD and AAA, emerging evidence suggests a direct relationship between Lp(a) levels and risk of AAA[13–15]. Variability of Lp(a) is thought to be mainly genetically determined, making it an attractive potential biomarker for risk stratification. Emerging literature, however, suggest that age, hormonal changes, environmental factors, and medications including menopausal hormone therapy (MHT) may contribute to Lp(a) levels as well.[16,17] In recent population-based studies, including the prospective Atherosclerosis Risk in Communities study (ARIC),[13] higher Lp(a) levels were found to be significantly associated with AAA in both women and men, but these analyses may not be applicable to postmenopausal women with varying estrogen statuses.[14,15,18]

Given the genetic, environmental and overall multifactorial etiology of AAAs,[19] we aimed to investigate the relationship between Lp(a) and AAA risk in a large racially diversified cohort of postmenopausal women.

METHODS

Study population

The study population consisted of participants of the Women's Health Initiative (WHI), which enrolled 161,808 post-menopausal women between 50–79 years of age from 1993 to 1998. The WHI consisted of three overlapping clinical trials (CT) evaluating low-fat versus high-fat eating patterns, menopausal hormone therapy, and calcium and vitamin D supplementation; and an observational study (OS) evaluating predictors and natural history of morbidity and mortality amongst its participants. WHI data were linked to Medicare enrollment and utilization data from Centers of Medicare and Medicaid Services (CMS). Detailed aspects of the WHI design, methods, medication variables and linkage with CMS have been extensively described.[20,21] Furthermore, validation studies investigating WHI Medicare Claims in relation to WHI adjudicated peripheral vascular diseases have been completed, with demonstration of good concordance.[20,21] The institutional review boards at each WHI site approved the study protocol, and all participants provided written informed consent.

Lipoprotein (a) and risk factor assessment

At baseline, all WHI participants provided fasting blood specimens following a standardized protocol previously described.[22] Briefly, blood samples were labeled, centrifuged and frozen in −70°C freezers and later shipped to the central WHI specimen repository. Lp(a) was measured in five different nested cardiovascular case-control studies and two random sample studies oversampled for minorities.[23–28] Lp(a) was quantified using an isoform independent bi-site ELISA assay procedure based on the linkage of apo(a) to apoB using the Hitachi 917 automated analyser (Roche Diagnostics - Indianapolis, IN) and reagents and calibrators from Denka Seiken (Niigata, Japan).[22,29,30]

Information on age, race, smoking status, physical activity and general health status were obtained by self-report questionnaires at baseline.[20] Trained staff measured weight and height at baseline using standardized protocols. Medication use was obtained at baseline by clinic interviewers. Diabetes status was determined by self-reported physician diagnosis of diabetes treated with either oral medication or insulin. Cardiovascular disease (CVD) was defined as a reported history of CVD, myocardial infarction, stroke, transitory ischemic attack, angina or revascularization. LDL-C, HDL-C and triglycerides were assayed as previously described.[31] LDL-C was calculated using the Friedewald formula for those with missing baseline values.[32]

Identification of AAA

AAA events were identified by International Classification of Diseases (ICD) 9 or 10 codes for AAA diagnosis or procedure. (Supplemental List 1) The event date was the first inpatient or outpatient Medicare claim with one of the AAA codes in any position. Thoracic aortic

aneurysms were not included due to different pathophysiology. Those with known personal history of AAA prior to enrollment in the WHI were excluded from analysis to evaluate incident AAA from baseline, postmenopausal Lp(a). The overall exposure period of analysis spanned the start of Medicare Fee for Service (FFS) Parts A and B until death or end of coverage. Medicare claims collected through 2017 were used.

Statistical analysis

From the entire WHI cohort (n=161,808), 13,068 participants had a baseline Lp(a) measurement. Exclusion criteria included: not enrolled in Medicare Fee for Service (FFS) A +B (n=4,046), missing covariates (n=3,048), or known or missing personal history of AAA (n=219). The final analytic cohort included 6,615 participants.

Descriptive statistics were reported by quintiles of (Lp(a)) with p-values reported for a linear trend across quintiles. Because (Lp(a)) levels were determined from subsamples of the overall WHI cohort consisting of several studies with different exclusion criteria, outcomes and designs, inverse probability weighting (IPW) and sandwich variance estimators were employed. Hazard ratios and 95% confidence intervals for incident AAA were estimated using Cox proportional hazard regression models.

Risk factors that may influence the association between Lp(a) with AAA, including age, race, BMI, smoking status (current, former or never), pack-years of smoking, history of HTN, history of diabetes, history of CVD, LDL, HDL, triglycerides and MHT use were assessed in the analysis as potential covariates and confounders.[15] Models were stratified by 5-year age interval, WHI study component (CT vs OS), hormone trial arm, and diabetes dietary modification trial arm with the adjustment for race/ethnicity. In the first set of models (Model 1), we additionally adjusted for BMI, smoking status, pack years of smoking, history of hypertension, history of treated diabetes, history of CVD, LDL-C (log-transformed), HDL-C (log-transformed), triglycerides (log-transformed), and MHT use (never user, past E-alone, past E+P, current E-alone, current E+P). In the second set of models (Model 2), additional adjustments for statin use, metformin use and physical activity (≤, >12 MET-hrs/week) were included.

The proportional hazards assumption was tested by including an interaction by age at menarche and menopause in all models. Significance was evaluated using the Wald chi-square statistic. Because of known differences in Lp(a) levels by race, we conducted race-specific analyses a priori in White and Black separately and an interaction test. However, small numbers of events precluded inclusion of other races in stratified analysis. Based on the size of the analyzed cohort there was 80% power to detect a difference in HR of 0.32 between the highest versus the lowest quintile of Lp(a) levels. An additional model was constructed using the log-transformed Lp(a) as a continuous variable.

Sensitivity analyses by exclusion of statin users, reproductive characteristics (age at menarche, age at menopause), and Lp(a) cutoffs were also conducted to evaluate potential interactions as described in the literature.[33] The Kaplan-Meier method was used to estimate the proportion of disease-free participants at any point during the follow-up period, adjusting for sampling criteria using inverse probability weighting.

RESULTS

Among the 6,615 participants included, the mean age was 65.3 years. 66.6% were non-Hispanic White, 18.9% Black, 7% Hispanic and 4.7% Asian/Pacific Islander. (Table 1) Median values of plasma Lp(a) for each quintile were 3.5, 10.0, 18.0, 33.0 and 68.0 mg/dL. (Table 2) Compared to participants in the lowest quintile, those in higher quintiles were more likely to be overweight, Black, former or current smokers, hypertensive, hyperlipidemic, to have history of cardiovascular disease, or use MHT and statins.

During 65,476 person-years of follow-up, over a median of 10.4 years, 415 women were diagnosed with AAA and 36 required interventions, reflecting an incidence of 63 cases and 5 interventions per 10,000 person years. 19 of the 36 (52.8%) women who underwent intervention had a diagnosis of ruptured AAA. Among 6,615 participants, 160 women (2.4%) were lost to follow-up. We failed to find any statistically significant association of Lp(a) level with risk AAA in any of the models. (Table 2, Supplemental Figure 1)

Given the reported variation of Lp(a) in different ethnic groups and races, subgroup analysis and tests for interaction was conducted by race, and no significant interaction was found ($p=0.98$).[34] (Supplemental Table 1A) To evaluate the negative association reported between diabetes and AAA, subgroup analysis was conducted for diabetes and no significant interaction was found ($p=0.37$). Sensitivity analysis by exclusion of statin users due to potential statin modification of Lp(a) level did not change findings. (Supplemental Table 1B) Categorizing Lp(a) levels by continuous log-transformed Lp(a) levels, by tertiles and the commonly used cutoff >50mg/dL was also conducted without significant association. (Supplemental Tables 1–4) Further analysis by reproductive factors, such as age at menarche and menopause, however, revealed significant interaction ($p=0.0098$) between age at menarche and the association between Lp(a) and incident AAA. (Figure 1) Amongst women who experienced menarche ≤12 years of age, higher Lp(a) levels did not associate with higher risk of AAA, compared with an increased risk among those who experienced menarche at >12 years of age. This interaction suggests that age at menarche and perhaps hormone exposure influences the association between Lp(a) levels and risk of AAA.

DISCUSSION

This, to our knowledge, is the first prospective cohort study of post-menopausal women investigating the association of plasma Lp(a) with risk of AAA. Although the 415 cases of incident AAA found in this analysis is comparable to the 505 incident cases described in the ARIC cohort of women and men,[13] we did not find a statistically significant association between Lp(a) levels and risk of AAA, although a linear trend was observed. These differences from prior studies may be due to limitations from our study or due to sex differences that may influence the association between Lp(a) levels and risk of AAA.[13,15,19] Hormone status within females may provide additional insight on the relationship, given the significant interaction found between age at menarche and the relationship between Lp(a) and AAA risk. Additionally, over half of the women who underwent intervention in our cohort had ruptured AAA. This high proportion of emergent repair warrants further investigation and replication in other cohorts, but is consistent with reported data.[35] These

findings highlight the need for sex-specific investigation of the etiology and identification of AAA.

Lp(a) levels have been described as highly heritable with minimal perturbation due to aging, environmental, or physiological factors.[9,36,37] There is growing evidence that Lp(a) is an independent risk factor and contributor in the pathogenesis of atherosclerotic CVD.[12,38] Therapeutically, however, there is limited evidence that specifically lowering Lp(a) levels reduces CVD risk, although it remains an area of exploration. The byproduct of certain hyperlipidemia medications, however, such as PCSK9-inhibitors, lower LDL-C and Lp(a).[39,40] Due to its heritability, one-time measurements of Lp(a) have been proposed as adequate to evaluate lifetime CVD risk for both sexes.[37] The potential interaction between age at menarche and the Lp(a)-AAA relationship (Figure 1), along with emerging studies investigating hormone status and risk of vascular diseases, suggests that Lp(a) levels may not be as static as previously thought.[41,42] Specifically, Lp(a) levels are lower in premenopausal women compared to postmenopausal women,[41,43,44] which may account for the difference between the WHI cohort compared to the ARIC cohort analysis and other case control studies.[13,15,19]

Furthermore, estrogen has been shown to lower plasma Lp(a) levels,[45] thus modifying the known relationship between elevated Lp(a) levels with cardiovascular disease risk. In fact, estrogen therapy has been shown to markedly attenuate the predictive utility of Lp(a).[18] While we accounted for MHT in the models used for analysis, we also sought to explore how reproductive history, such as age at menarche, as a surrogate for endogenous hormone exposure, may interact with the Lp(a)-AAA relationship. Early age of menarche (≤12 years of age) has been associated with higher risk of adverse cardiovascular outcomes, but there remains nearly no information on the potential association between early menarche and AAA risk, or early menarche on lifetime Lp(a) levels.[46] Emerging data supports that estrogen may induce increased uptake of Lp(a) by the LDL receptor, interact with cholesterol metabolites in the vasculature and reduce Lp(a) production by the liver.[47–49] Thus further investigation on the role and variability of hormone exposure within women and underrepresented populations is necessary to better delineate the utility of biomarkers traditionally evaluated in predominantly male populations.

Despite the use of a large, well-characterized, and diverse cohort of postmenopausal women who had extensive follow-up, there are several limitations of this study. Despite the large number of AAAs found in this cohort, a relatively small number of women underwent intervention. It is unknown if the rate is a true reflection of intervention rate, or if interventions were not adequately captured with claims data, or if there is insufficient follow-up to determine the true rate given the delayed presentation of AAA in women compared with men.[4] The National Death Index was used to determine if women died due to rupture prior to repair, but that number was low (n=3). Due to inconsistent practices for AAA screening in women, the criteria used diagnose women with AAA either via screening, or clinically was unknown. Although the WHI cohort has extensive baseline data, there is no information of family history of AAA, which is a well-known risk factor for AAA. Additionally, this is a post-hoc analysis of a prospective study using Lp(a) measurements from nested cardiovascular case-control studies and random studies for non-AAA outcomes.

Women enrolled in a Medicare HMO were excluded from analysis and women of lower socioeconomic status and minority women are underrepresented among fee-for service beneficiaries. It is unknown if these factors introduced bias. Information on kidney function and apolipoprotein(a) size was not available. Smaller apolipoprotein(a) isoforms and higher Lp(a) levels have been linked to incident cardiovascular disease, but their independent contributions are less clear. Moreover, reduced eGFR and elevated albuminuria have been independently associated with greater incidence of AAA and greater abdominal aortic diameter.[50] Finally, AAA diagnoses were not individually adjudicated and missing cases or errors in coding are always possible. Prior studies, however, have demonstrated adequate concordance.[21]

CONCLUSIONS

In a relatively large and well-phenotyped sample of postmenopausal women, we found no statistically significant association between Lp(a) levels and risk of AAA. Women with high Lp(a) levels were more likely to be overweight, Black, former or current smokers, hypertensive, hyperlipidemic, to have history of cardiovascular disease, or use hormone therapy and statins, compared to those with lower levels. These findings differ from prior prospective, case-control and meta-analyses. Further investigation on hormone status in women may provide additional information on the different associations observed between Lp(a) and risk of AAA in men and women. Candidate biomarkers predominantly investigated in men should be used and interpreted with caution in women, especially in pathologies with sexual dimorphic prevalence and outcomes such as AAA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

ELC is supported by National Institutes of Health, Grant/Award Number: T32HL007208. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C.

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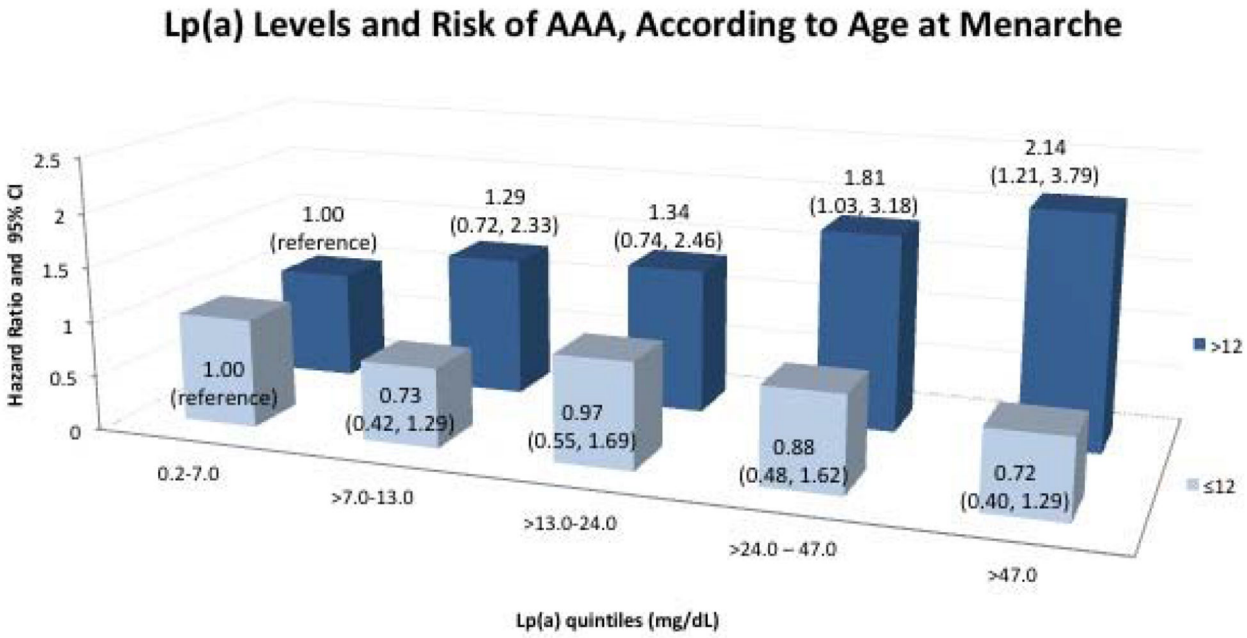

Figure 1. Lp(a) levels and risk of AAA by age at menarche

p= 0.0098, testing for an interaction between age at menarche (≤12 versus >12) and a linear term based on Lp(a) quintile categorization

Cox PH regression model stratified by 5-year age interval at WHI enrollment, WHI study component (CT vs OS), HT trial arm and DM trial arm, and adjusted for race/ethnicity, BMI, smoking status, pack years of smoking, history of hypertension, history of treated diabetes, history of CVD, LDL-C (log-transformed), HDL-C (log-transformed), triglycerides (log-transformed), and hormone therapy use (never user, past E-alone, past E +P, current E-alone, current E+P). Model used inverse probability weighting and “sandwich” variance estimators.

Table 1.

Baseline Characteristics by Quintiles of Lp(a) (mg/dL), N=6,615

	Total	**0.2–7.0**	**>7.0–13.0**	**>13.0–24.0**	**>24.0–47.0**	**>47.0**	**p-value for trend**
Participants, n		1479	1210	1312	1319	1295	
Age, mean (+/− SD)	65.3 (7.3)	66.0 (7.3)	65.3 (7.2)	65.1 (7.4)	64.8 (7.3)	65.4 (7.2)	0.0020
Race/ethnicity, %							
Non-Hispanic White	66.6	79.1	72.7	65.3	53.8	60.6	<0.0001
Non-Hispanic	18.9						
Black/African		4.9	9.1	17.6	34.0	30.0	
American							
Hispanic/Latina	7.0	8.0	9.2	6.9	5.7	5.3	
American	1.4	1.5	1.4	1.8	1.4	1.1	
Indian/Alaskan Native							
Asian/Pacific Islander	4.7	4.8	6.5	6.7	3.9	1.8	
Unknown	1.4	1.7	1.1	1.7	1.3	1.2	
BMI, mean (+/− SD)	28.5 (5.9)	27.6 (5.3)	28.4 (5.7)	28.8 (6.1)	29.1 (6.1)	28.9 (6.3)	<0.0001
Smoking status							
Never, %	52.8	54.1	53.4 %	54.6	51.6	50.3	0.0406
Current, %	8.0	6.2	9.2	7.6	8.8	8.7	
Pack-years smoking, mean (+/− SD)	10.1 (19.1)	10.0 (18.9)	10.9 (19.8)	10.2 (19.9)	9.9 (18.9)	9.9 (18.0)	0.5011
HTN, %							
Untreated	9.4	8.5	8.9	11.0	10.0	8.6	0.0004
T reated	31.6	28.8	29.7	30.4	34.9	34.4	
CVD ***, %	3.7	1.8	3.0	4.0	4.4	5.3	<0.0001
Statin use, %	7.8	5.5	7.2	7.3	9.0	10.3	<0.0001
Diabetes *, %	6.9	5.5	7.7	6.5	7.0	7.9	0.0861
Hormone replacement, %							
Never used	54.5	46.1	51.2	58.2	59.3	58.8	<0.0001
Current user	25.5	37.6	26.9	21.3	20.6	19.6	

	Total	0.2–7.0	>7.0–13.0	>13.0–24.0	>24.0–47.0	>47.0	p-value for trend
HDL-C, mg/dL [+]	54.5 (54.2, 54.9)	55.2 (54.4, 56.1)	54.3 (53.5, 55.2)	54.0 (53.3, 54.8)	54.2 (53.4, 54.9)	54.8 (54.1, 55.6)	0.3711
LDL-C, mg/dL [+]	132.1 (131.2, 133.0)	119.7 (117.9, 121.6)	127.9 (126.0, 129.8)	132.1 (130.2, 134.1)	138.2 (136.2, 140.2)	145.5 (143.6, 147.4)	<0.0001
Triglyceraides, mg/dL [+]	134.6 (133.1, 136.0)	139.2 (135.9, 142.5)	140.5 (136.9, 144.1)	133.2 (130.1, 136.5)	129.3 (126.3, 132.4)	130.9 (127.9, 133.9)	<0.0001

[*] treated diabetes with medication

[**] history of myocardial infarction, stroke or revascularization

[+] geometric mean (95% confidence interval)

Table 2.

Incident AAA[1] overall and by Lp(a) quintiles

	Total	Lp(a) quintiles (mg/dL) Median and range					P for trend[2]
		3.5 (0.2–7.0)	10.0 (>7.0–13.0)	18.0 (>13.0–24.0)	33.0 (>24.0–47.0)	68.0 (>47.0–229.7)	
N	6,615	1,479	1,210	1,312	1,319	1,295	
Person-years	65,476.2	1,5244.0	1,2155.4	1,3114.2	1,2616.1	1,2346.5	
Incident AAA	415	81	75	80	88	91	
HR[3]		1.00	1.00 (0.66–1.50)	1.13 (0.75–1.17)	1.30 (0.86–1.96)	1.31 (0.87–1.97)	0.1054
Model 1[4]		1.00	0.95 (0.63–1.44)	1.13 (0.74–1.72)	1.27 (0.83–1.97)	1.28 (0.84–1.97)	0.1332
Model 2[5]		1.00	0.94 (0.62–1.42)	1.10 (0.72–1.68)	1.22 (0.80–1.86)	1.23 (0.80–1.89)	0.1980

[1] AAA diagnosis code from inpatient or outpatient FFS A+B claims, or procedure code from inpatient claim (with or without corresponding diagnosis code).

[2] One degree of freedom test for linear trend based on quintile categorization.

[3] Cox PH regression model stratified by 5-year age interval at WHI enrollment, WHI study component (CT vs OS), HT trial arm and DM trial arm, and adjusted for race/ethnicity. Models use inverse probability weighting and “sandwich” variance estimators.

[4] Additional adjustment for BMI, smoking status, pack years of smoking, history of hypertension, history of treated diabetes, history of CVD, LDL-C (log-transformed), HDL-C (log-transformed), triglycerides (log-transformed), and hormone therapy use (never user, past E-alone, past E+P, current E-alone, current E+P).

[5] Stratified and adjusted as in model 1 with additional adjustment for statin use, metformin use and physical activity (≤, >12 MET-hrs/week).