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Authors

Garg, Parveen K
Norby, Faye L
Polfus, Linda M
et al.

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Lipoprotein-associated phospholipase A_2 and risk of incident peripheral arterial disease: Findings from The Atherosclerosis Risk in Communities study (ARIC)

Parveen K. Garg[a,*], **Faye L. Norby**[b], **Linda M. Polfus**[c], **Eric Boerwinkle**[c], **Richard A. Gibbs**[d], **Megan L. Grove**[c], **Aaron R. Folsom**[b], **Pranav S. Garimella**[e], **Kunihiro Matsushita**[f], **Ron C. Hoogeveen**[g,h], and **Christie M. Ballantyne**[g,h]

[a]Division of Cardiology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

[b]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA

[c]University of Texas Health Sciences Center at Houston, Houston, TX, USA

[d]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

[e]Division of Nephrology-Hypertension, University of California San Diego, La Jolla, CA, USA

[f]Department of Epidemiology, The Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[g]Section of Atherosclerosis and Vascular Medicine, Baylor College of Medicine, Houston, TX, USA

[h]The Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart Center, Houston, TX, USA

Abstract

Background and aims—Results from prospective studies evaluating the relationship between elevated lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity and incident peripheral arterial disease (PAD) have been mixed. We investigated whether higher Lp-PLA_2 levels are associated with increased risk of incident PAD and whether *PLA2G7* gene variants, which result in lower Lp-PLA_2 levels, are associated with reduced risk of incident PAD.

*Corresponding author. 1510 San Pablo St. Suite 322, Los Angeles, CA 90033, USA, parveeng@med.usc.edu (P.K. Garg).

Author contributions

PKG and FNL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: all authors.

Acquisition, analysis and interpretation of data: all authors.

Drafting of the manuscript: PKG.

Critical revision of the manuscript: all authors.

Statistical analysis: FNL.

Study supervision: PKG, CMB.

Conflict of interest

Dr. Hoogeveen received funding from diaDexus. The funding sources did not have a role in the design, analysis or approval of the manuscript. The other authors have nothing to disclose.

Method—Our analysis included 9922 participants (56% female; 21% African-American; mean age 63 years) without baseline PAD at ARIC Visit 4 (1996–1998), who had Lp-PLA_2 activity measured and were subsequently followed for the development of PAD, defined by occurrence of a PAD-related hospitalization, through 2012. Cox proportional hazard models were performed to determine the association of Lp-PLA_2 levels and *PLA2G7* gene variants with incident PAD.

Results—During a median follow-up of 14.9 years, we identified 756 incident cases of PAD. In analyses adjusting for age, race, and sex, each standard deviation increment in Lp-PLA_2 activity (62 nmol/ml/min) was associated with a higher risk of developing PAD (hazard ratio (HR) 1.17; 95% confidence interval (CI) 1.09, 1.26). This association remained significant after additional adjustment for risk factors, other cardiovascular disease, and medication use, but was strongly attenuated (HR: 1.09; 95% CI 1.00, 1.20). *PLA2G7* variants were not associated with a lower risk of PAD in both white carriers (HR: 1.21; 95% CI: 0.17–8.56) and African-American carriers (HR: 0.83; 95% CI: 0.41–1.67), although statistical power was quite limited for this analysis, particularly in whites.

Conclusions—While higher Lp-PLA_2 activity was associated with an increased risk for incident PAD, it is likely a risk marker largely represented by traditional risk factors.

Keywords

Inflammation; Epidemiology; Peripheral artery disease; Lipoprotein-associated phospholipase A_2

1. Introduction

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme highly expressed by macrophages in atherosclerotic lesions and is responsible for the hydrolysis of oxidized phospholipids on LDL particles [1,2]. Although the relationship of both higher Lp-PLA_2 mass and activity with greater risk of incident cardiovascular disease (CVD) is well-established [3–8], only two prospective studies have evaluated its association with incident peripheral arterial disease (PAD) [9,10]. These two studies obtained conflicting results, leaving uncertainty regarding this association.

Individuals with PAD have high mortality rates [11]. Eleven percent of US adults older than 40 years and over 200 million people worldwide are estimated to have PAD [12,13]. Prevalence of PAD is nearly twice as high in African-Americans compared to non-Hispanic whites, and established risk factors alone do not explain ethnic-specific variations in PAD prevalence [14–16]. Building upon the existing literature to better define whether a relationship between Lp-PLA_2 levels and incident PAD exists is important. If an association is observed, future studies could investigate whether individuals with high baseline Lp-PLA_2 levels would benefit from more intensive cardiovascular risk modification to reduce their risk of incident PAD.

We prospectively examined the relationship between Lp-PLA_2 activity and the development of PAD in The Atherosclerosis Risk in Communities (ARIC) study, a large population-based cohort with long-term follow-up. To better understand possible mechanisms of associations,

we also examined the relationship between *PLA2G7* gene variants, which results in lower Lp-PLA_2 levels, and risk for incident PAD.

2. Materials and methods

The ARIC study included 15,792 men and women aged 45–64 years sampled from four U.S. communities in 1987–1989 [17]. Participants were re-examined in 1990–1992 (93% response), 1993–1995 (86%), 1996–1998 (80%), and 2011–2013 (65%) and followed for cardiovascular events. Due to the availability of Lp-PLA_2 activity data, participants in ARIC Visit 4 (1996–98) served as the eligible cohort and baseline Visit for the present analysis. Institutional review boards at each participating institution (University of Minnesota, Johns Hopkins University, University of North Carolina, and University of Mississippi Medical Center) approved the study, and all participants gave written informed consent at each study Visit.

2.1. Lp-PLA_2 activity measurement

Lp-PLA_2 activity was assessed from stored plasma at Visit 4 by an automated Colorimetric Activity Method (CAM) assay (diaDexus Inc., South San Francisco, CA) using a Beckman Coulter (Olympus) AU400e autoanalyzer. The Lp-PLA_2 activity assay had an inter-assay variation coefficient of 4.4% and a reliability coefficient (R) of 0.92, based on 419 blinded replicate samples.

Determination of *PLA2G7* gene mutations associated with a loss of Lp-PLA_2 activity function among ARIC participants has been described previously [18]. DNA sequencing was previously performed on Illumina HiSeq 2000 after exome capture with NimbleGen's VCRome2.1 on ARIC participants consenting to genomic use [19]. Whole exome sequencing was performed in 6325 ARIC participants to determine genetic variants that lower Lp-PLA_2 activity. There were 4 *PLA2G7* gene loss-of-function (LOF) variants observed on whole exome sequencing in white participants, of which one variant was already present on Illumina's HumanExome BeadChip array, rs140020965 Q287X. LOF variants were defined as mutations resulting in premature stop codons, splice sites, and small indels, which were predicted to disrupt protein production. Joint genotype calling on the exome chip with improved calling of rare variation was previously described [20]. There was 1 rare nonsynonymous *PLA2G7* mutation noted in African-American participants, which also was present on the exome chip, rs34159425 L389S. These two exome chip variants (one LOF stop codon and one nonsynonymous) along with sequenced LOF variants were used for the analysis.

2.2. Peripheral artery disease

The diagnosis of PAD was determined by ankle-brachial index (ABI) measurement, administration of the Rose Questionnaire, or confirmation of PAD-related hospitalizations.

The ABI was measured by trained technicians on nearly all participants at Visit 1 (96%) and on a selected random number of participants at Visits 3 (n = 4197) and 4 (n = 5882), using the Dinamap Model 1846 SX, an oscillometric device that obtains repeated blood pressure measurements automatically [21]. Trained technicians measured the ankle blood pressure at

the posterior tibial artery in a randomly selected leg, and the brachial artery systolic blood pressure was measured in the right arm. Both were measured while the patient was in the supine position. The ABI was defined as the ratio of a single ankle SBP in one leg to a single brachial BP. According to a previous study, the reliability of the ABI based on single ankle and arm systolic blood pressure was 0.61 (95% confidence interval (CI) 0.50, 0.70) [22].

The Rose Questionnaire was used to evaluate whether participants had developed intermittent claudication, which was defined as exertional leg pain relieved within 10 min by resting [23]. Interviewers contacted participants by telephone annually through 1998 to directly identify intermittent claudication symptoms.

PAD-related hospitalizations were determined through use of ICD-9 codes. A trained abstractor obtained and recorded all ICD-9 hospital discharge diagnoses when a hospitalization occurred. All records with an ICD-9 code of 443.9 (peripheral vascular disease, unspecified), 440.2 (atherosclerosis of native arteries and extremities), 440.3 (atherosclerosis of bypass graft of the extremities), 440.4 (chronic total occlusion artery extremities), 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below-knee amputation), 84.17 (above-knee amputation), 38.18 (leg endarterectomy), 39.25 (aorto-iliac-femoral bypass), 39.29 (leg bypass surgery), and 39.50 (percutaneous transluminal angioplasty of non-coronary vessels) qualified as hospitalized PAD. Surveillance for all hospitalizations including revascularization procedures and amputations occurred through the year 2012.

We defined prevalent PAD as an ABI ≤0.9 at Visit 1, 3 or 4, a positive Rose Questionnaire through Visit 4, or a diagnosis of hospitalized PAD through Visit 4. These individuals were excluded from the study (n = 1381). Given the caveats of ABI measurements (nearly all participants but only single leg at Visit 1, only on a subsample and single leg [sometimes different leg than Visit 1] at Visits 3 and 4) and that the Rose Questionnaire was not administered beyond the time Visit 4 ended, we defined incident PAD as a hospital discharge diagnosis consistent with PAD.

Because *PLA2G7* LOF variants are rare exposures that are present throughout the entire life span, Visit 1 served as the baseline (instead of Visit 4) for the Lp-PLA_2 LOF analysis and exclusion criteria were applied to this visit only. As a result, new diagnoses of hospitalized PAD occurring between Visit 1 and Visit 4 were counted as incident PAD in this analysis (as opposed to prevalent PAD for the Lp-PLA_2 activity analysis). For this reason, more cases of incident PAD were observed in the LOF analysis.

2.3. Baseline covariates

All covariates were assessed at Visit 4 (1996–98) and included age (years), sex, race/ARIC clinic site, body mass index (BMI), education level (<12 years or ≥12 years), smoking status (current, former, or never), alcohol consumption (drinks/week), physical activity, medication use (anti-hypertensive, aspirin, and statin), diabetes (self-reported physician diagnosis, medication use, fasting blood glucose ≥126 mg/dL, or random glucose≥200 mg/dL), atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), systolic and diastolic

blood pressure, HDL and total cholesterol, estimated glomerular filtration rate (eGFR), and plasma high-sensitivity C-reactive protein (CRP).

BMI was calculated as weight in kilograms divided by height in meters squared. Education level and smoking status (never, former, current) were determined from interviews. Physical activity was scored from 1 (lowest) to 5 (highest) based on answers to a modified Baecke Physical Activity questionnaire [24,25]. Medications use was ascertained by asking participants to bring containers of current medications. Prevalent ASCVD was defined at Visit 1 as a self-reported history of physician diagnosed myocardial infarction (MI), stroke, and prior coronary revascularization or evidence of a previous MI by electrocardiogram. ASCVD at subsequent visits was ascertained and adjudicated by the ARIC Morbidity and Mortality Classification Committee, using data from follow-up calls, hospitalization records, and death certificates [26,27]. Prevalent HF was defined at each visit as the reported use of HF medication in the previous 2 weeks, the presence of HF according to the Gothenburg criteria (Visit 1 only), or having developed incident HF from the previous visit [28]. Incident HF was defined as the presence of ICD-9 code 428 in any hospitalization during follow-up [29]. The eGFR was calculated based on serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration [30]. CRP was measured by the CRP-Latex (II) high sensitivity assay from Denka Seiken (Tokyo, Japan). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times and the average of the last two measurements was used. Details have been previously described for measurement of plasma lipids [31–33].

2.4. Statistical analysis

Supplemental Fig. 1 shows the flow of participants eligible for the analysis. Baseline characteristics were compared across quartiles of baseline Lp-PLA_2 activity. Analysis of variance for continuous variables and a χ^2 test for dichotomous variables were used to test differences between quartiles.

Cox proportional hazards models were used to investigate the association of baseline Lp-PLA_2 activity with incident PAD. In this analysis, Lp-PLA_2 activity was modeled continuously (per SD increment) and also categorized into quartiles (lowest quartile as referent category). Models were initially adjusted for age, sex, race/ARIC clinic site (Model 1). Additional adjustment included smoking, alcohol consumption, diabetes, systolic and diastolic blood pressure, ASCVD, HF, total and HDL cholesterol, BMI, education, physical activity, eGFR, CRP, anti-hypertensive use, aspirin use, and statin use (Model 2). An area under the curve (AUC) comparison was calculated for the predictive ability of Lp-PLA_2 activity beyond variables adjusted for in Model 2. This analysis was repeated stratified by race, sex and also after excluding individuals with baseline ASCVD or HF. Cox proportional hazards models were also used to investigate associations of *PLA2G7* gene variants and incident PAD stratified by race and adjusted for age and sex.

3. Results

3.1. Participant characteristics

Over a median follow-up of 14.9 years, of 9922 participants included in the analysis, a total of 756 (8.0%) participants developed incident PAD. Compared to participants in the lowest quartile of Lp-PLA_2 activity, those in higher quartiles were older, less likely to be African-American or on anti-hypertensive medication, and more likely to be male, to smoke, to have ASCVD, and to be on statin medications (Table 1). Baseline alcohol consumption, physical activity, TC, and CRP were higher while systolic blood pressure, eGFR, and HDL-c were lower in participants in higher quartiles of Lp-PLA_2 activity.

3.2. Lp-PLA_2 activity levels and incident PAD

Fig. 1 shows the continuous association of Lp-PLA_2 activity with incident PAD using a restricted cubic spline model risk and suggests the risk of developing PAD is most pronounced in those with very high baseline levels of Lp-PLA_2 activity. Table 2 shows the hazard ratios for developing clinical PAD according to Lp-PLA_2 activity levels. Adjusting for age, sex, race/ARIC clinic site, smoking, alcohol consumption, diabetes, systolic and diastolic blood pressure, ASCVD, HF, total and HDL cholesterol, BMI, education, physical activity, eGFR, CRP, anti-hypertensive use, aspirin use, and statin use, each higher standard deviation of Lp-PLA_2 activity (62 nmol/min/ ml) was associated with 9% greater risk of PAD (hazard ratio (HR) 1.09; 95% CI: 1.00, 1.20). Excluding patients with a history of ASCVD or HF mildly attenuated these findings (HR 1.07; 95% CI: 0.96, 1.19). Risk prediction did not change with addition of Lp-PLA_2 activity: comparing model 2 with and without Lp-PLA_2 activity, c-statistic remained 0.807 (95% CI: 0.787–0.826).

3.3. *Stratified analyses for the associations of Lp-PLA_2 levels with incident PAD*

Lp-PLA_2 activity levels were lower in African-American participants compared to white participants (197.1 nmol/min/ml *vs.* 237.2 nmol/min/ml, $p < 0.01$). There was no significant interaction between Lp-PLA_2 activity and race for the outcome of incident PAD ($p = 0.39$) in adjusted analysis. Similarly, there was also no significant interaction between Lp-PLA_2 activity and sex for the outcome of incident PAD ($p = 0.08$) in adjusted analysis.

3.4. PLA2G7 gene variants and risk of PAD

There were 7 white participants and 82 African-American participants with *PLA2G7* gene variants. Lp-PLA2 activity levels were significantly lower in these individuals (111.2 nmol/min/ml *vs.* 238.7 nmol/min/ml, $p < 0.0001$ for white participants; 114.1 nmol/ min/ml *vs.* 199.3 nmol/min/ml, $p < 0.0001$ for African-American participants). No significant differences in baseline characteristics were associated with these variants (Supplemental Table 1). Using Visit 1 as the baseline, there were 1116 incident cases of PAD over an average of 15.9 years of follow-up (848/1 among white noncarriers/ carriers; 259/8 among African-American noncarriers/carriers). *PLA2G7* gene variants were not significantly associated with a lower risk of PAD in both white carriers (HR: 1.21; 95% CI: 0.17–8.56) and African-American carriers (HR: 0.83; 95% CI: 0.41–1.67) in age and sex adjusted analyses.

4. Discussion

In this large community-based sample, higher baseline Lp-PLA_2 activity was associated with an increased risk of incident PAD. The association was attenuated but remained significant with adjustment for other PAD risk factors, with evidence of a dose-response. There was no evidence of effect modification by race.

Lp-PLA_2 has been previously proposed as an inflammatory marker involved in the atherosclerotic process [34]. Lp-PLA_2 is bound to cholesterol in the circulation and activates when LDL undergoes oxidation within the arterial wall. It is expressed particularly within the necrotic core and fibrotic cap of ruptureprone plaques [35]. Upon LDL oxidation, the enzyme becomes capable of hydrolyzing oxidized phospholipids located on lipoprotein cell membrane, resulting in the creation of lysophosphatidylcholine and oxidized free fatty acids [2]. These free fatty acids, in turn, play a role in inflammatory processes critical to atherosclerotic development, including the expression of adhesion molecules and cytokines, recruitment of monocytes and T-lymphocytes, and stimulation of macrophage proliferation [36–38].

Prior investigation into the prospective relationship of Lp-PLA_2 levels with incident PAD has been conflicting. Both higher Lp-PLA_2 mass and Lp-PLA_2 activity were associated with incident PAD in the Cardiovascular Health Study (CHS) whereas neither Lp-PLA_2 mass nor Lp-PLA_2 activity were associated with incident PAD in MESA [9,10]. The rates of incident PAD in ARIC and CHS were nearly two times that reported in MESA and it is possible that the considerably lower number of events in MESA may have contributed to the lack of an association found in that cohort. The prevalence of PAD is closely related to age, co-existing cardiovascular disease, and ethnicity, all of which varied across cohorts, and may explain why higher incidence rates were seen in ARIC and CHS.

Although the association between Lp-PLA_2 and incident PAD was statistically significant, *PLA2G7* variants were not associated with a lower risk of PAD in this cohort. A prior study has already demonstrated that *PLA2G7* variants were not associated with a lower risk of coronary heart disease and randomized trials showed no benefit of Lp-PLA_2 pharmacologic inhibition in reducing cardiovascular events [18,39–42]. In ARIC, the association of Lp-PLA_2 with PAD was modest, and further attenuated after adjustment for traditional risk factors and CRP. Lp-PLA_2 activity did not significantly improve the c-statistic for incident PAD risk prediction. Taken together, these findings suggest that, although a positive association exists between Lp-PLA_2 activity and risk of PAD, Lp-PLA_2 is a risk marker that largely reflects traditional risk factors and may not have a causal role in PAD development. Additional gene variant analyses in more adequately powered larger cohorts will help provide better clarification.

Considering the mixed results reported in prior studies, the results from this study help establish that higher Lp-PLA_2 has a considerably weaker association with PAD than it does with CVD [5–10]. PAD is a separate form of atherosclerosis and nearly 40% of people with PAD have no coexistent coronary or cerebrovascular disease [43]. The relationship of other inflammatory markers with risk of PAD has also been reported to differ from their

relationships to other cardiovascular diseases. While CRP and fibrinogen are consistently associated with an increased risk of PAD, other ones such as interleukin-6 or adhesion molecules have not been [44–46]. Additionally, certain traditional risk factors, particularly cigarette smoking and diabetes mellitus, have much stronger associations with the development of PAD compared to other forms of atherosclerotic disease and may explain why associations of novel risk factors with PAD are relatively weaker as compared to other cardiovascular diseases [47,48].

Our study has limitations. Only Lp-PLA_2 activity was measured at Visit 4 for ARIC participants and we could not report any associations for Lp-PLA_2 mass and incident PAD in this cohort. We did not include low ABI as an end point, so our findings do not apply to asymptomatic PAD. We also did not capture less severe forms of symptomatic PAD that did not require hospitalization. Consequently, the actual incidence rate of PAD was underestimated and overall association of Lp-PLA_2 with incident PAD may have been biased. Gene variant analysis was underpowered and interpretation of these results is limited. In conclusion, these results demonstrate that while higher Lp-PLA_2 activity was significantly associated with an increased risk for incident PAD, it does not improve risk prediction and is likely a risk marker that is largely represented by traditional risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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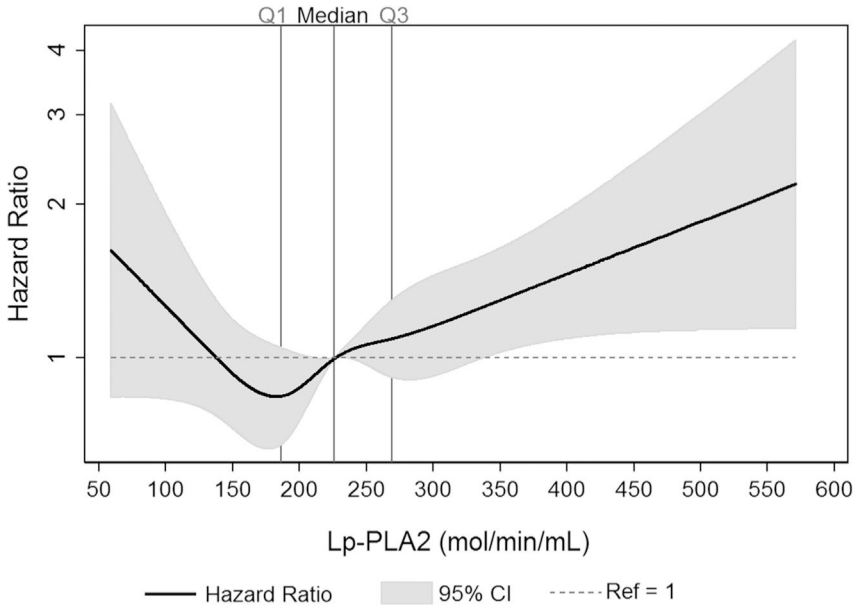

Fig. 1.

Continuous Lp-PLA_2 activity (nmol/min per liter) at baseline, in relationship to incident peripheral arterial disease, using adjusted restricted cubic splines to show hazard ratios (95% confidence intervals).

Lp-PLA_2, lipoprotein-associated phospholipase A_2Q, quartile.[a]

[a]Model adjusted for age (years), sex, race/ARIC clinic site, smoking, alcohol consumption, diabetes, systolic and diastolic blood pressure, ASCVD, CHF, total and HDL cholesterol, BMI, education, physical activity, eGFR, CRP anti-hypertensive use, aspirin use, and statin use.

Table 1

Baseline characteristics of ARIC participants according to baseline quartiles of Lp-PLA$_2$ activity, 1996–1998[a]

Characteristics	Lp-PLA$_2$ activity quartiles (nmol/min/ml)				*p*-value[b]
	1st quartile (≤184)	2nd quartile (185–225)	3rd quartile (226–268)	4th quartile (≥269)	
Age	61.8 (5.6)	62.6 (5.7)	63.0 (5.6)	63.4 (5.6)	<0.01
Male, %	338 (14%)	776 (30%)	1373 (55%)	1885 (76%)	<0.01
African-American, %	888 (37%)	570 (22%)	378 (15%)	213 (9%)	<0.01
Education, % ≥12 years	1989 (82%)	2099 (82%)	2043 (82%)	2043 (82%)	0.99
Smoking status, %					<0.01
Never	1233 (51%)	1127 (44%)	945 (38%)	890 (36%)	
Former	911 (38%)	1075 (42%)	1164 (47%)	1192 (48%)	
Current	274 (11%)	344 (14%)	369 (15%)	398 (16%)	
Alcohol use, # drinks/week	2.2 (5.6)	2.3 (5.5)	3.0 (6.9)	2.7 (5.9)	<0.01
ASCVD, %	118 (5%)	203 (8%)	240 (10%)	266 (11%)	<0.01
Heart failure, %	114 (5%)	126 (5%)	99 (4%)	104 (4%)	0.33
Diabetes, %	330 (14%)	388 (15%)	397 (16%)	397 (16%)	0.07
SBP, mmHg	127.6 (19.0)	127.3 (19.2)	127.4 (18.8)	126.1 (18.0)	0.01
DBP, mmHg	71.4 (10.3)	70.9 (10.1)	71.2 (10.5)	70.8 (10.0)	0.13
Body mass index, kg/m^2	28.6 (6.3)	28.7 (5.8)	28.8 (5.2)	28.7 (4.6)	0.89
Physical activity index, mean	2.4 (0.8)	2.5 (0.8)	2.5 (0.8)	2.6 (0.8)	<0.01
Total cholesterol, mg/dl	192.3 (33.7)	200.7 (36.7)	203.3 (36.9)	207.0 (37.4)	<0.01
HDL cholesterol, mg/dl	62.5 (18.5)	52.8 (15.1)	46.1 (12.8)	40.2 (10.5)	<0.01
eGFR, ml/min/1.73 m^2	90.1 (16.1)	86.4 (16.1)	85.1 (15.8)	82.5 (16.3)	<0.01
C-reactive protein, mg/L	3.6 (1.4–7.4)	2.4 (1.1–5.4)	2.0 (0.98–4.4)	1.9 (0.96–4.2)	<0.01
Anti-hypertensive use, %	1069 (44%)	1035 (41%)	1020 (41%)	950 (38%)	<0.01
Aspirin use, %	1330 (55%)	1422 (56%)	1382 (56%)	1397 (56%)	0.83
Statin use, %	242 (10%)	292 (11%)	292 (12%)	219 (9%)	<0.01

ASCVD, atherosclerotic cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$.

[a]Continuous variables are expressed as mean (SD) or median (Q1-Q3). Categorical variables are N (percent).

[b] p-value for trend across increasing quartiles of Lp-PLA2 activity.

Table 2

Associations between Lp-PLA$_2$ activity (nmol/min/ml) and incident peripheral arterial disease in ARIC (n = 9922)[a], 1996–2012.

	Incident Cases	Incidence rate[b] (95% CI)	Model 1[c]	Model 2[d]
			HR (95% CI)	HR (95% CI)
1st quartile(≤184)	138	4.1 (3.5–4.8)	1(Referent)	1(Referent)
2nd quartile(185–225)	168	4.8 (4.1–5.6)	1.11 (0.88–1.39)	0.92 (0.72–1.16)
3rd quartile(226–268)	208	6.2 (5.4–7.1)	1.35 (1.07–1.71)	1.07 (0.84–1.38)
4th quartile(≥269)	242	7.6 (6.7–8.6)	1.55 (1.22–1.98)	1.18 (0.89–1.55)
Per SD (62)			1.17 (1.09–1.26)	1.09 (1.00–1.20)
P value (linear)			<0.001	0.05

[a]Results of multivariable proportional hazards regression models are shown by quartiles of the distribution, with each Lp-PLA$_2$ quartile compared with the 1st quartile (referent quartile), and per standard deviation increment (62 nmol/min/ml).

[b]Rates are per 1000 person years.

[c]Model 1 adjusted for age (years), sex, race/ARIC clinic site.

[d]Model 2 adjusted for Model 1 þ smoking, alcohol consumption, diabetes, systolic and diastolic blood pressure, ASCVD, HF, total and HDL cholesterol, BMI, education, physical activity, eGFR, CRP, anti-hypertensive use, aspirin use, and statin use.