Review

Systematic Review of the Association between Lipoprotein -Associated Phospholipase A2 and Atherosclerosis

Jing Liu, MD, MPH;[1]* Yuling Hong, MD, PhD;[2] Yue Qi, MD, PhD;[1]
Fan Zhao, PhD;[1] Dong Zhao, MD, PhD[1]

[1]*Beijing An Zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China*
[2]*Division for Heart Disease & Stroke Prevention, Center for Disease Control and Prevention, Atlanta, Georgia*

Lipoprotein-associated phospholipase A2 (Lp-PLA_2) is a novel inflammatory biomarker. Basic research has shown that Lp-PLA_2 is involved in the pathogenesis of atherosclerosis. In the past decade, an increasing number of epidemiological studies have investigated the association of Lp-PLA_2 with atherosclerosis, but its roles in the different stages of atherosclerosis are not established. By undertaking a systematic review of the epidemiological studies on the relationship between Lp-PLA_2 and atherosclerotic cardiovascular disease (CVD)/subclinical atherosclerosis, we tried to evaluate the relationship between Lp-PLA_2 and the different stages of atherosclerosis. MEDLINE, Cochrane Library, and National Knowledge Infrastructure (CNKI) were searched up to September 1st, 2011. The references in all the located articles were manually searched. Epidemiological studies on the association of Lp-PLA_2 with CVD and subclinical atherosclerosis, with total CVD, coronary heart disease (CHD), stroke, and subclinical atherosclerosis as their observation endpoints or outcome variables, were included in this study. Studies which did not assess the hazard ratio (HR), relative risk (RR), or odds ratio (OR) of Lp-PLA_2 or which did not adjust for other known risk factors were excluded. The general information, study design, sample size, outcome variables and their definitions, follow-up duration, Lp-PLA_2 measurements, variables adjusted in the multivariate analysis and main results in the literatures were retrieved. Thirty-nine studies were enrolled in this systematic review. Thirty-three studies (49, 260 subjects) investigated the relationship between Lp-PLA_2 and CVD, among which 31 showed that increased Lp-PLA_2 is associated to high risk for incidence or mortality of CVD: HR/RR per 1 standard deviation (SD) increase = 1.17–1.40; RR for the highest as compared with the lowest quartile was 1.41–3.75 (1.8–2.5 in most studies). Six studies (four cross-sectional studies and two case-control studies, with an overall sample size of 5,537) explored the relationship between Lp-PLA_2 and subclinical atherosclerosis; among them, two studies demonstrated that Lp-PLA_2 was associated with coronary artery calcification in young adults and men. In conclusion, many epidemiological studies have demonstrated that Lp-PLA_2 increases the risk of clinical CVD events. However, whether there is a similar association between Lp-PLA_2 and subclinical atherosclerosis remains unclear. Whether Lp-PLA_2 exerts its effect during the occurrence of clinical events promoted by unstable plaques or at the early stage of atherosclerosis needs to be clarified in further prospective studies.
[N A J Med Sci. 2011;4(4):201-211.]

Key Words: *atherosclerosis, cardiovascular diseases, inflammation, biomarker*

INTRODUCTION

Atherosclerosis is a chronic, progressive and systemic pathologic process that frequently affects large- and medium-sized arteries, leading to severe cardiovascular disease (CVD) events such as coronary heart disease (CHD) and stroke. At least half million new events of myocardial infarction and 2 million new events of stroke occur in China annually.[1] This may be explained by the unsatisfactory prevention and control of conventional risk factors such as dyslipidemias, smoking, hypertension, and diabetes mellitus (DM). Nevertheless, studies have demonstrated that these conventional risk factors cannot fully explain the occurrence and development of atherosclerosis,[2] suggesting that there might be some emerging or novel risk factors of atherosclerosis. The pathological changes of atherosclerosis remain asymptomatic for decades before clinical events occur. Our previous study showed that one-third of Beijing residents aged 45–74 years have carotid plaques.[3] Therefore, further investigation of the risk factors of subclinical atherosclerosis will be important for the early prevention and treatment of CVD.

Received 10/14/2011; Revised 10/21/2011; Accepted 10/24/2011
***Corresponding Author:** Department of Epidemiology, Beijing An Zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, 2 Anzhen Road, Chaoyang District, Beijing, China 100029**. (**Email: jingliu0516@yahoo.com.cn)

Accumulated evidence has demonstrated that inflammatory reactions have key roles in the pathogenesis of atherosclerosis. Among various inflammatory factors, C-reactive protein (CRP) has been the most widely studied and confirmed to be associated with CVD. However, due to the lack of evidence from clinical trials, whether CRP can be treated as a therapeutic target remains uncertain. Furthermore, the atherosclerosis-related inflammatory reaction is a complex process involving multiple factors. For decades, scientists devoted untiring effort to discover more sensitive and more specific factors that cause atherosclerosis, with attempts to find new targets that can be used for the prevention and treatment of CVD. In recent years, the novel inflammatory biomarker lipoprotein-associated phospholipase A2 (Lp-PLA_2) has been found to be associated with the occurrence and development of atherosclerosis.

Lp-PLA_2 is an enzyme produced and secreted by monocyte-macrophages, T-lymphocytes, and other inflammatory cells. As a member of the phospholipase superfamily, it is also termed "platelet-activating factor acetylhydrolase (PAF-AH)" because of its ability to degrade platelet-activating factor (PAF) by hydrolysis of the sn-2 acetyl group. In humans, 80% of binds with low-density lipoprotein (LDL), 15%–20% with high-density lipoprotein (HDL), and the remaining with very-low-density lipoprotein (VLDL) and lipoprotein(a). In the circulation, hydrolyzes oxidized phosphatidylcholines in LDL, and produces lysophosphati-dylcholine and oxidized free fatty acids, two highly pro-inflammatory molecules. Research has shown that these hydrolyzed products can up-regulate the expressions of adherence factors and cytokines, as well as promote monocytes to aggregate from the lumen into the intima, where they develop into macrophages and lead to the formation of atherosclerotic plaques. Lysophosphati-dylcholine can also promote the release of arachidonic acid, which can affect the diastolic function of the vascular endothelium and induce cellular apoptosis, and thus damage the vascular endothelial cells and their protective mechanisms. As a result, the local inflammatory reaction becomes aggravated and plaques form.[4] Using combined in situ hybridization and immunocytochemistry, researchers have detected Lp-PLA_2 in atherosclerotic lesions in humans and rabbits. In addition, approximately six-fold higher activity was detected in the atherosclerotic aortas of Watanabe heritable hyperlipidemic rabbits compared with normal aortas from control rabbits.[5] All findings indicate that Lp-PLA_2 may play an important part during atherosclerosis. An increasing number of epidemiological studies have investigated the association of Lp-PLA_2 with atherosclerosis in the past decade, and have been reviewed to a certain extend in the literature.[6-11] However, most of the published reviews are traditional reviews, while only five systematic reviews (including meta-analyses) are available. The first two systematic reviews summarized the impact of Lp-PLA_2 levels on CVD in epidemiological studies, but the impacts on different types of CVD (CHD or stroke) were not reviewed,[12-13] while meta-analyses published by Casas JP, et al and Zheng GH, et al focused on the impact of genetic polymorphisms on CHD.[14-15] The Lp-PLA_2 Studies Collaboration conduced the largest meta-analysis and evaluated the association between plasma Lp-PLA_2 with both CHD and stroke.[16] However, none of the above systematic reviews have summarized the effect of Lp-PLA_2 on subclinical atherosclerosis. By carrying out systematic reviews on epidemiological studies focusing on the relationship between Lp-PLA_2 and different types of atherosclerotic cardiovascular disease/subclinical atherosclerosis, we tried to evaluate the relationship between Lp-PLA_2 and the different stages of atherosclerosis.

MATERIALS AND METHODS

Inclusion and exclusion criteria Epidemiological studies on the association of with total CVD, coronary heart disease (CHD), stroke, and subclinical atherosclerosis as their observation endpoints or outcome variables, were included in this study. Studies which did not assess the hazard ratio (HR) or relative risk (RR) of Lp-PLA_2 or which did merely univariable analysis and did not adjust for any other known risk factors (e.g., Framingham risk factors, including age, sex, smoking, blood pressure, diabetes, LDL-C, and HDL-C) were excluded.

Search strategy MEDLINE (from 1 January 1970), Cochrane library and National Knowledge Infrastructure (CNKI) were searched up to September 1st, 2011. All references in located articles were manually searched. We searched MEDLINE using the MeSHs of Cardiovascular Diseases OR atherosclerosis, AND the term "lipoprotein associated phospholipase A2" in all fields. In Cochrane library and CNKI, we used "lipoprotein associated phospholipase A2" in all fields or "Lp-PLA_2" in title to search. In addition, we checked the related references and complemented to the searching results. Only publications in English or Chinese were searched.

Review method all literature search results were imported into reference manager software with which excluded the repeated articles by checking the titles and authors. In addition, reviews and articles based on the same study data being published in different journals were excluded manually by reading the abstracts. We obtained the remains full text and identified the final including literatures which meet the criteria.

Reading the included articles, we extract the following information: authors, published year, study design, sample size, outcome variables and the definition, follow-up time (except case-control and cross-sectional studies), Lp-PLA_2 measurements, adjusted variables and main results in multivariate statistical analysis. Results data were mainly represented using RR, HR or OR and its 95% confidence interval (CI)

RESULTS

Results of the Literature Search

One hundred eighty nine English-language and 32 Chinese-language publications were identified. Eight of them that were repeatedly included from more than one search databases were excluded. Eighty seven review articles and one duplicated publication were further excluded after the

careful review of the abstracts. Among the remaining 125 articles, 64 did not report CVD or subclinical atherosclerosis outcomes, 22 did not assess the relationship between and CVD/subclinical atherosclerosis or conduct statistical analyses without adjusting for any known risk factors of CVD. Thirty nine studies are included in the final analysis (**Figure 1**).

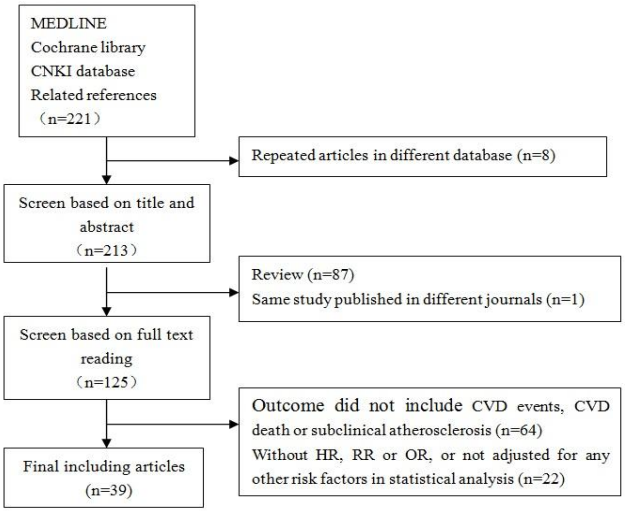

Figure 1. Flow chart of literature identification and selection process.

Basic Information of the Enrolled Studies

Thirty-three articles on the relationship between and clinical CVD events were retrieved: 21 prospective cohort studies (**Table 1**),[17-37] 6 case cohort studies/nested case control studies (**Table 2**),[38-44] and 5 case control studies (**Table 3**).[45-49] Among these 33 publications, 15 articles were on total CVD[18-20,22-26,28-30,33-35,39] (among which 1 article was also on CHD[25] and 1 article was also on stroke[20]), 17 articles were on CHD[17,21,25,27,31-32,36-38,40,42,44-49] (among which 1 article was also on total CVD[25] and 1 article was also on stroke[32]), and 4 articles were on stroke[20,32,41,43] (among which 1 article also on total CVD[20] and 1 article was also on CHD[32]). In total, 49, 260 subjects were enrolled in these 33 studies, among which 3 studies were done only among males[17,33,38] and 3 only among females.[39,43-44] In the remaining 27 studies, males accounted for over 50% in 17 studies. The age range of study subjects was from 21 to 84 years. Most of them were Caucasians, African Americans, Hispanics, and Asians (Koreans and Chinese). The length of follow-up ranged from 42 days to 18 years for the prospective studies. Fourteen studies measured Lp-PLA_2 concentrations, 13 detected its activities, and 6 determined both measurements. All studies carried out multivariate analyses and adjusted for all or some of the Framingham risk factors, including age, sex, smoking status, systolic blood pressure (SBP), DM, LDL-C, and HDL-C. Among them, 24 studies adjusted for CRP level.

Six articles (with a sample size of 5,537 subjects) on the relationship between and subclinical atherosclerosis were retrieved,[50-55] including two case control studies[50,55] and four cross-sectional studies.[51-54] Among the six studies, one study only measured mass, 3 only measured Lp-PLA_2 activities, and 2 had determined both measurements.

Relationship between Lp-PLA_2 and Atherosclerosis

Association of with CVD events

Among the 33 studies, 31 showed a positive association between increased Lp-PLA_2 and high risk for incidence or mortality of total CVD, CHD or stroke: hazard ratio/relative risk (HR/RR) per 1 standard deviation (SD) increase = 1.17–1.40; the RR or OR for the highest as compared with the lowest quartile was 1.41–3.75 (1.8–2.5 in 16studies). The remaining two did not find an association between Lp-PLA_2 and CVD.[25,39] Based on the observation endpoints or outcome variables, these 33 studies could be divided into the three categories described below.

Relationship between Lp-PLA_2 and Total CVD

Of the 15 studies on the association between Lp-PLA_2 and total CVD, 14 were prospective cohort studies, all of which had positive findings. The Malmo study from Sweden was the only study that examined first incident CVD event as all study subjects were free of CVD at baseline. After 10 years of follow-up, the risk of CVD events for the highest tertile of Lp-PLA_2 was 1.46-times (95% confidence interval (CI): 1.01–2.13) of that for the lowest.[29] Lp-PLA_2 was found to significantly increased the risk of recurrent CVD events in 8 cohort studies of all the patients with existing CVD at the baseline.[20,22-24,26,30,33-34] The remaining five studies enrolled both patients with and without CVD at the baseline. Their results showed that high baseline Lp-PLA_2 is associated with increased risk of the both first and recurrence CVD events.[18-19,25,28,35] However, no association was found between Lp-PLA_2 and total CVD in one nested case-control study based on the Women's Health Study (WHS).[39]

Relationship between Lp-PLA_2 and CHD

Among seventeen studies (eight cohort studies, four nested case-control studies or case-cohort studies, and five case-control studies) that examined the relationship between Lp-PLA_2 and CHD, 15 showed positive findings. However, two other studies showed that the association was no longer statistically significant after the other risk factors (especially cholesterol) were adjusted.[25,32]

Of eight cohort studies, five enrolled subjects free of CVD at baseline.[17,31-32,36-37] High Lp-PLA_2 was found to be associated with increased risk of incident CHD in three studies.[17,31,37] In one of the studies among patients with type 1 diabetes,[36] the association was only found in patients with specific genotypes. In another study Lp-PLA_2 was associated with stroke but not with CHD.[29] In one study among patients with history of myocardial infarction, the risk of recurrent CHD increased by 90% (95% CI: 31%–175%) in patients with the highest quartile of Lp-PLA_2 compared with those with the other three quartiles combined.[21] Of two studies that enrolled both patients with and without existing CVD, one showed that high Lp-PLA_2 was associated with increased risk for CHD deaths,[27] while no association was found in the other study after adjustment of LDL-C, HDL-C, and TG.[25]

Table 1. Prospective cohort studies for relationship of lipoprotein-associated phospholipase A2 (Lp-PLA_2) and cardiovascular disease (CVD).

Author (Year)	Parent Study	Subjects	Outcome Variables	Duration of Follow-up	Measurement of Lp-PLA_2	Variables Adjusted	Reults
Koenig[17] (2004)	MONICA /KORA	934 male without CVD, 45-64 yr	CHD (fatal or nonfatal MI, sudden death of CHD),[97]	14 yr	Mass	Age, SBP, TC/HDL-C, exercise, BMI, smoking, DM, alcohol, education, and CRP	HR for 1SD increase Lp-PLA_2: 1.21(1.01-1.45)
Brilakis[18] (2005)	Mayo	504 Coronary angiography patients (382 CAD) 60±11 yr, 62% male	CVD (MI, revascularization, stroke, death), [61]	4 yr	Mass	Age, sex, smoking, hypertension, TC, HDL-C, TG, and log-CRP	HR for 1SD increase in Lp-PLA_2: 1.30 (1.06–1.59)
May[19] (2006)	IMHS	1493 Coronary angiography patients (1012 CAD)	All-cause death, incidence and death of CVD (CAD death, non-CAD cardiac death, incidence of MI, stroke)	6.7 ±0.5 yr	Mass	Age, sex, hypertension, hyperlipidemia, DM, smoking, CAD family history, renal failure, No. of diseased vessels, (prior MI, CVA, CHF, SA, UA), (statin, ACE inhibitor, β-blocker, diuretic use), and CRP	Lp-PLA_2 quartiles for CV events (OR): 1.15 (0.78-1.71) 1.53 (1.02-2.31) 2.44 (1.58-3.79)
Elkind[20] (2006)	NOMASS	467 first-ever stroke, 45.4% male, 68.9±12.7 yr	Mixed endpoint of Recurrent stroke and CVD (recurrent 80, MI 18, non-vascular death 53)	5 yr (mean 4 yr)	Mass	Age, sex, hyperlipidemia, current smoking, race, CAD, DM, hypertension, AF, and CRP	Highest vs lowest quartile (Lp-PLA_2 mass): Recurrent stroke (HR): 2.08 (1.04-4.18) Combined endpoint (HR): 1.86 (1.01-3.42)
Corsetti[21] (2006)	THROMBO	766 post-myocardial infarction patients, 77% male, ≥21 yr, mean 58y	CHD (cardiac death, MI and UA)	26 mo	Activity	Age, sex, smoking, cholesterol, previous MI, pulmonary congestion, EF, apoB, BMI, factor VII, and MI index.	Highest vs Q1-Q3 quartile: Recurrent stroke (HR): 1.90 (1.31-2.75)
Koenig[22] (2006)		1051 patients with CHD, 30-70 yr	CVD (CHD death, nonfatal MI, stroke)	4 yr	Mass and activity	Age, sex, smoking, history of MI, DM, rehabilitation site, HDL-C, LDL-C, statin, ACE inhibitor use, cystatin C, NT-proBNP, and lipid-regulatory drugs	Highest vs lowest tertiles: (Lp-PLA_2) Mass HR 2.09 (1.10-3.96); Activity HR: 1.81 (0.94-3.49)
O'Donoghue[23] (2006)	PROVE IT - TIMI 22	3648 patients with ACS, 78% male, 29% ≥65 yr	CVD (death, MI, UA requiring hospitalization, revascularization, and stroke)	3 yr (mean 2 yr)	Mass and activity	Age, prior MI, renal disease, DM, treatment arm, LDL-C, index diagnosis, and CRP	Acute stage activity independent with recurrent CVD. Activity lower than baseline at 30 days Post-CVD Highest vs lowest quintiles: HR=1.33(1.01-1.74), *P*=0.002
Sabatine[24] (2007)	PEACE	3766 controlled CAD patients, 81% male, 64±8 yr	CVD (CVD death, MI, revascularization , UA and stroke)	4.8 yr	Mass	Age, sex, race, hypertension, DM, smoking, BMI, TC, GFR, prior MI, prior revascularization, β-blockers, lipid-regulatory therapy, randomized treatment arm	Lp-PLA_2 quartiles for CVD events (HR): 1.13 (0.94-1.36) 1.23 (1.02-1.48) 1.41 (1.17-1.70)
Allison[25] (2007)		508 received Lower Extremity Arterial Exam participants (189 CVD), 68.2 yr, 88% male	CVD death 167; CHD death 88	6.7 yr	Mass and activity	Age, sex, smoking, hypertension, DM, Premature CHD family history, PAD baseline and other CVD	Lp-PLA_2 activity increasing 1SD, CHD death: HR=1.37(1.00–1.89) LDL-C, TG and HDL-C adjusted HR=1.12(0.78–1.60)
Möckel[26] (2007)	NOBIS-II	429 suspect ACS participants 60.5±14.1 yr, 60.6% male	CVD combined endpoint (all-cause death, nonfatal MI, UA, HF or shock, PTCA, CABG, severely arrhythmia, or revascularization)	42 day	Mass	Tn-I, NT-proBNP, CRP, D-dimer	Lp-PLA_2>210 μg/L, RR=2.6 (1.1-6.6)
Winkler[27] (2007)	LURIC	2513 patients with CAD, 719 control; 70% male Male: 62±11 yr Female: 65±10 yr	Cardiac death 313 Death 501	5.5 yr	Activity	Age, sex, smoking, BMI, type 2 DM, hypertension, lipid-regulatory drugs, LDL-C, HDL-C, TG, CRP, NT-pro-BNP, angiographic CAD, and aspirin/antiplatelet agents	Tertiles of Lp-PLA_2 acivity for cardiac mortality (HR): 1.96 (1.37-2.80) 2.03(1.35-3.05) When CRP<3 and 3-10 *P*=0.001
Kiechl[28] (2007)	Bruneck	765 participants (77 CVD), 40-79 yr, 50.5% male	CVD combined endpoint (CVD death, MI, ischemic stroke, TIA), [82]	10 yr	Activity	Age, sex, smoking, previous CVD, SBP, DM, LDL-C, HDL-C, ferritin, fibrinogen, WHR, alcohol, social status, exercises, HOMA-IR, glucose, uric acid Lp-PLA_2, activity, α-1 antitrypsin, CRP, and urinary albumin	HR for 1SD increase Lp-PLA_2: 1.4 (1.1-1.4)

Persson[29] (2007)	MDCS	4480 participants without DM and CVD, 45-69 yr	CVD (stroke 130, MI 131)	10 yr	Mass and activity	Age, sex, LDL-C, smoking, statin, exercises, high alcohol, consumption, MS, and CRP	Tertiles for Lp-PLA_2 (RR): 1.08 (0.75-1.56) 1.46 (1.01-2.13) Activity high and with MS RR=1.97 (1.34-2.90) Activity high and without MS RR=1.40 (1.03-1.92) Only with MS, RR including 1
Raichlin[30] (2008)		112 heart transplants patients, 82% male, 47.6±15.9 yr	CVD (PTCA, CABG, LVEF≤45% secondary to CAV, and confirmed CVD death), [24]	5.1±1.6 yr	Mass	Age, sex, LDL-C, HDL-C, time after transplantation, Gesini Score, ischemic indication for transplantation, BMI, creatinine, TC, IDL, particle size, TG, and CRP	Lp-PLA_2>236 ng/mL HR=2.4 (1.16-5.19), *P*=0.012
Daniels[31] (2008)	Rancho Bernardo	1077 participants without CHD 46.4% male, 72 yr	CHD (MI, angina pectoris, revascularization), 228	16 yr	Mass	Age, sex, hypertension, LDL-C, HDL-C, SBP, FPG, TG, CRP, and DM	Quartiles for Lp-PLA_2 mass (HR): 1.43 (0.89-2.31) 1.96 (1.23-3.10) 1.75 (1.10-2.78)
Persson[32] (2008)	MDCS	5393 participants without CVD, 40% male, 46-68 yr,	CHD (MI, CHD death) 195 ischemic stroke 152	10.6±1.7 yr	Mass and activity	Age, sex, LDL-C, HDL-C, statin, BMI, CRP, smoking, DM, SBP, alcohol	Highest vs Lowest Tertiles for Lp-PLA_2 activity with stroke event RR: 1.94 (1.15-3.26); mass 1.92(1.20-3.10) CHD event: 1.48 (0.92–2.37); mass 0.95 (0.65–1.40)
Robins[33] (2008)	VA-HIT	1451 CVD patients (treat with gemfibrozil 725, Treat with placebo 726, 64.1±7.2 yr, low LDL-C, low HDL-C	combined endpoint (MI, stroke, CHD death), 320	5 yr	Activity	Age, hypertension, BMI, DM, smoking, medicine intake, LDL-C, HDL-C, triglycerides, CRP	HR for 1SD increase Lp-PLA_2: 1.17 (1.04-1.32)
Cucchiara[34] (2009)		167 TIA patients 62±14 yr, 45% male	CVD (stroke or death in 90 days, more than 50% stenosis of macrovascular or Cardiac embolism),[41]	90 days	Mass and activity	CRP	Highest vs Q1-Q3 quartiles for Lp-PLA_2 activity OR=3.75 (1.58-8.86), *P*=0.003
Tsimikas[35] (2009)	Bruneck	765 (77 CVD), 45-84 yr, 50.5% male	CVD combined endpoint (CVD death, MI, ischemic stroke, TIA) 108; extending endpoint (combined endpoint + revascularization +PVD),[82]	10 yr	Activity	Age, sex, smoking, previous CVD, SBP, DM, LDL-C, HDL-C, ferritin, fibrinogen, WHR, alcohol, social status, exercises, loge transformed levels of HOMA- IR, lipoprotein(a), CRP, and urinary albumin	Highest vs Lowest Tertiles for Lp-PLA_2 activity HR=2.2 (1.1-4.8) *P*=0.019 Extending endpoint: HR=2.0 (1.1-3.7)*P*=0.022
Miller[36] (2010)		96 type 1 DM patients with Microalbuminuria, 50% male, 29.5 yr	CHD (CHD death, MI, more than 50% stenosis or Revascularization, angina pectoris	18 yr (mean 11.5 yr)	Activity	CRP, DM course, sex, LDL-C, HbA1c, TG,	univariate analysis: HR=1.54 (1.11, 2.12), *P*=0.009 multivariate analysis for CAD: HR=2.40 (1.02, 5.64), *P*=0.05 (Haptoglobin genotype 2/1type)
Hatoum[37] (2010)	HPFS and NHS	740 male /777 female DM without CVD	CHD (CABG, PTCA, nonfatal MI, CHD death), 324	Male 10 yr, female 14 yr	Activity	Age, smoking, history of disease, HDL-C, LDL-C, CRP	Highest vs Lowest Tertiles for Lp-PLA_2 activity HR=1.39 (1.01-1.90, *P*=0.03)

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AMI = acute myocardial infarction; angio = angiographically; ApoB = apolipoprotein B; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CAV = coronary allograft vasculopathy; CHD = coronary heart disease; CHF = congestive heart failure; CHS = Cardiovascular Health Study; CRP = C-reactive protein; CVA = cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; EF = ejection fraction; ER = emergency room; FAST-MI = French Registry of Acute Stelevation Myocardial Infarction; GFR = glomerular filtration rate; HDL-C = high-density-lipoprotein cholesterol; HF = heart failure; HOMA-IR = homeostasis model assessment of insulin resistance; HPFS = the Health Professionals Follow-up Study; HR = hazard ratio; IDL = intermediate-density lipoprotein; IHCS = Intermountain Heart Collaborative Study; IMHS = InterMountain Heart collaborative Study; LDL-C = low-density-lipoprotein cholesterol; LURIC = Ludwigshafen Risk & Cardiovascular Health Study; MDCS = Malmö Diet & Cancer Study; MI = myocardial infarction; NHS = the Nurses' Health Study; NOBIS-II = North Wuerttemberg & Berlin Infarction Study; NOMASS = Northern Manhattan Stroke Study; NT-proBNP = N-terminal pro-brain natriuretic peptide; OR = odds ratio; PEACE = Prevention of Events with Angiotensin-Converting Enzyme Inhibition; PROVE IT–TIMI 22 = Pravastatin or Atorvastatin Evaluation & Infection Therapy–Thrombolysis in Myocardial Infarction; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; Q = quartile; RR = relative risk; SA = stable angina; SBP = systolic blood pressure; SD = standard deviation; TC = total cholesterol; TG = triglycerides; THROMBO = Thrombogenic Factors & Recurrent Coronary Events; TIA = transient ischemic attack; Tn-I = troponin I; UA = unstable angina; VA-HIT = Veterans Affairs High-density lipoprotein cholesterol Intervention Trial;

All the four nested case-control study on the relationship between Lp-PLA_2 and CHD demonstrated that high Lp-PLA_2 increased the risk of CHD.[38,40,42,44] The study by Packard et al. was the first population-based epidemiological study on the relationship between Lp-PLA_2 and CVD.[38] Framingham risk factors and CRP were adjusted in all these three studies. The RR for each increased SD of Lp-PLA_2 was 1.18 (95% CI = 1.05–1.33); RR ranged from 1.97 to 2.08 for the highest tertile/quartile versus the lowest).

There were five case-control studies on the relationship between Lp-PLA_2 and CHD,[45-49] in which all the patients were confirmed to have CHD by coronary angiography. All these five studies demonstrated that Lp-PLA_2 was associated with CHD (OR range of 1.39–1.92 for the highest quartile versus the lowest).

Relationship between Lp-PLA_2 and Stroke

Four studies on the relationship between Lp-PLA_2 and stroke were retrieved. All four studies demonstrated that Lp-PLA_2 was associated with the incidence or recurrence of ischemic stroke.[20,32,41,43] Two of the four were prospective cohort studies.

One study tracked subjects without CVD at the baseline for 10 years and found that increased Lp-PLA_2 activity was significantly associated with the risk of stroke (RR = 1.94 for the highest tertile versus the lowest; 95% CI = 1.15–3.26)

after the influence of conventional risk factors and CRP was adjusted for. The concentration of Lp-PLA_2 had a similar association with stroke (RR = 1.92 for the highest tertile versus the lowest; 95% CI = 1.20–3.10). In another study, 467 first-ever stroke patients was followed for 5 years, A strong association between increased Lp-PLA_2 concentration and high risk of stroke recurrence was reported (HR = 2.08 for the highest quartile versus the lowest; 95% CI = 1.04–4.18).[20] The positive association was also found in one case cohort study and one nested case-control.[41,43]

Table 2. Nested case-control and case-cohort studies for relationship of Lp-PLA_2 and CVD.

Author (Year)	Parent Study	Subjects	Outcome Variables	Duration of Follow-up	Measurement of Lp-PLA_2	Variables Adjusted	Results
Koenig[17] (2004)	MONICA /KORA	934 male without CVD, 45-64 yr	CHD (fatal or nonfatal MI, sudden death of CHD), 97	14 yr	Mass	Age, SBP, TC/HDL-C, exercise, BMI, smoking, DM, alcohol, education, and CRP	HR for 1SD increase Lp-PLA_2: 1.21(1.01-1.45)
Brilakis[18] (2005)	Mayo	504 Coronary angiography patients (382 CAD) 60±11 yr, 62% male	CVD (MI, revascularization, stroke, death), 61	4 yr	Mass	Age, sex, smoking, hypertension, TC, HDL-C, TG, and log-CRP	HR for 1SD increase in Lp-PLA_2: 1.30 (1.06–1.59)
May[19] (2006)	IMHS	1493 Coronary angiography patients (1012 CAD)	All-cause death, incidence and death of CVD (CAD death, non-CAD cardiac death, incidence of MI, stroke)	6.7±0.5 yr	Mass	Age, sex, hypertension, hyperlipidemia, DM, smoking, CAD family history, renal failure, No. of diseased vessels, (prior MI, CVA, CHF, SA, UA), (statin, ACE inhibitor, β-blocker, diuretic use), and CRP	Lp-PLA_2 quartiles for CV events (OR): 1.15 (0.78-1.71) 1.53 (1.02-2.31) 2.44 (1.58-3.79)
Elkind[20] (2006)	NOMASS	467 first-ever stroke, 45.4% male, 68.9±12.7 yr	Mixed endpoint of Recurrent stroke and CVD (recurrent 80, MI 18, non-vascular death 53)	5 yr (mean 4 yr)	Mass	Age, sex, hyperlipidemia, current smoking, race, CAD, DM, hypertension, AF, and CRP	Highest vs lowest quartile (Lp-PLA_2 mass): Recurrent stroke (HR): 2.08 (1.04-4.18) Combined endpoint (HR): 1.86 (1.01-3.42)
Corsetti[21] (2006)	THROMBO	766 post-myocardial infarction patients, 77% male, ≥21 yr, mean 58y	CHD (cardiac death, MI and UA)	26 mo	Activity	Age, sex, smoking, cholesterol, previous MI, pulmonary congestion, EF, apoB, BMI, factor VII, and MI index.	Highest vs Q1-Q3 quartile: Recurrent stroke (HR): 1.90 (1.31-2.75)
Koenig[22] (2006)		1051 patients with CHD, 30-70 yr	CVD (CHD death, nonfatal MI, stroke)	4 yr	Mass and activity	Age, sex, smoking, history of MI, DM, rehabilitation site, HDL-C, LDL-C, statin, ACE inhibitor use, cystatin C, NT-proBNP, and lipid-regulatory drugs	Highest vs lowest tertiles: (Lp-PLA_2) Mass HR 2.09 (1.10-3.96); Activity HR: 1.81 (0.94-3.49)
O'Donoghue[23] (2006)	PROVE IT -TIMI 22	3648 patients with ACS, 78% male, 29% ≥65 yr	CVD (death, MI, UA requiring hospitalization, revascularization, and stroke)	3 yr (mean 2 yr)	Mass and activity	Age, prior MI, renal disease, DM, treatment arm, LDL-C, index diagnosis, and CRP	Acute stage activity independent with recurrent CVD. Activity lower than baseline at 30 days Post-CVD Highest vs lowest quintiles: HR=1.33(1.01-1.74), *P*=0.002
Sabatine[24] (2007)	PEACE	3766 controlled CAD patients, 81% male, 64±8 yr	CVD (CVD death, MI, revascularization , UA and stroke)	4.8 yr	Mass	Age, sex, race, hypertension, DM, smoking, BMI, TC, GFR, prior MI, prior revascularization, β-blockers, lipid-regulatory therapy, randomized treatment arm	Lp-PLA_2 quartiles for CVD events (HR): 1.13 (0.94-1.36) 1.23 (1.02-1.48) 1.41 (1.17-1.70)
Allison[25] (2007)		508 received Lower Extremity Arterial Exam participants (189 CVD), 68.2 yr, 88% male	CVD death 167; CHD death 88	6.7 yr	Mass and activity	Age, sex, smoking, hypertension, DM, Premature CHD family history, PAD baseline and other CVD	Lp-PLA_2 activity increasing 1SD, CHD death: HR=1.37(1.00–1.89) LDL-C, TG and HDL-C adjusted HR=1.12(0.78–1.60)
Möckel[26] (2007)	NOBIS-II	429 suspect ACS participants 60.5±14.1 yr, 60.6% male	CVD combined endpoint (all-cause death, nonfatal MI, UA, HF or shock, PTCA, CABG, severely arrhythmia, or revascularization)	42 day	Mass	Tn-I, NT-proBNP, CRP, D-dimer	Lp-PLA_2>210 μg/L, RR=2.6 (1.1-6.6)
Winkler[27] (2007)	LURIC	2513 patients with CAD, 719 control; 70% male Male: 62±11 yr Female: 65±10 yr	Cardiac death 313 Death 501	5.5 yr	Activity	Age, sex, smoking, BMI, type 2 DM, hypertension, lipid-regulatory drugs, LDL-C, HDL-C, TG, CRP, NT-pro-BNP, angiographic CAD, and aspirin/antiplatelet agents	Tertiles of Lp-PLA_2 acivity for cardiac mortality (HR): 1.96 (1.37-2.80) 2.03(1.35-3.05) When CRP<3 and 3-10 *P*=0.001

Kiechl[28] (2007)	Bruneck	765 participants (77 CVD), 40-79 yr, 50.5% male	CVD combined endpoint (CVD death, MI, ischemic stroke, TIA), 82	10 yr	Activity	Age, sex, smoking, previous CVD, SBP, DM, LDL-C, HDL-C, ferritin, fibrinogen, WHR, alcohol, social status, exercises, HOMA- IR, glucose, uric acid Lp-PLA_2, activity, α-1 antitrypsin, CRP, and urinary albumin	HR for 1SD increase Lp-PLA_2: 1.4 (1.1-1.4)
Persson[29] (2007)	MDCS	4480 participants without DM and CVD, 45-69 yr	CVD (stroke 130, MI 131)	10 yr	Mass and activity	Age, sex, LDL-C, smoking, statin, exercises, high alcohol, consumption, MS, and CRP	Tertiles for Lp-PLA_2 (RR): 1.08 (0.75-1.56) 1.46 (1.01-2.13) Activity high and with MS RR=1.97 (1.34-2.90) Activity high and without MS RR=1.40 (1.03-1.92) Only with MS, RR including 1
Raichlin[30] (2008)		112 heart transplants patients, 82% male, 47.6±15.9 yr	CVD (PTCA, CABG, LVEF≤45% secondary to CAV, and confirmed CVD death), 24	5.1±1.6 yr	Mass	Age, sex, LDL-C, HDL-C, time after transplantation, Gesini Score, ischemic indication for transplantation, BMI, creatinine, TC, IDL, particle size, TG, and CRP	Lp-PLA_2>236 ng/mL HR=2.4 (1.16-5.19), *P*=0.012
Daniels[31] (2008)	Rancho Bernardo	1077 participants without CHD 46.4% male, 72 yr	CHD (MI, angina pectoris, revascularization), 228	16 yr	Mass	Age, sex, hypertension, LDL-C, HDL-C, SBP, FPG, TG, CRP, and DM	Quartiles for Lp-PLA_2 mass (HR): 1.43 (0.89-2.31) 1.96 (1.23-3.10) 1.75 (1.10-2.78)
Persson[32] (2008)	MDCS	5393 participants without CVD, 40% male, 46-68 yr,	CHD (MI, CHD death) 195 ischemic stroke 152	10.6±1.7 yr	Mass and activity	Age, sex, LDL-C, HDL-C, statin, BMI, CRP, smoking, DM, SBP, alcohol	Highest vs Lowest Tertiles for Lp-PLA_2 activity with stroke event RR: 1.94 (1.15-3.26); mass 1.92(1.20-3.10) CHD event: 1.48 (0.92–2.37); mass 0.95 (0.65–1.40)
Robins[33] (2008)	VA-HIT	1451 CVD patients (treat with gemfibrozil 725 , Treat with placebo 726, 64.1±7.2 yr, low LDL-C, low HDL-C	combined endpoint (MI, stroke, CHD death), 320	5 yr	Activity	Age, hypertension, BMI, DM, smoking, medicine intake, LDL-C, HDL-C, triglycerides, CRP	HR for 1SD increase Lp-PLA_2: 1.17 (1.04-1.32)
Cucchiara[34] (2009)		167 TIA patients 62±14 yr, 45% male	CVD (stroke or death in 90 days, more than 50% stenosis of macrovascular or Cardiac embolism), 41	90 days	Mass and activity	CRP	Highest vs Q1-Q3 quartiles for Lp-PLA_2 activity OR=3.75 (1.58-8.86), *P*=0.003
Tsimikas[35] (2009)	Bruneck	765 (77 CVD), 45-84 yr, 50.5% male	CVD combined endpoint (CVD death, MI, ischemic stroke, TIA) 108; extending endpoint (combined endpoint + revascularization +PVD), 82	10 yr	Activity	Age, sex, smoking, previous CVD, SBP, DM, LDL-C, HDL-C, ferritin, fibrinogen, WHR, alcohol, social status, exercises, loge transformed levels of HOMA- IR, lipoprotein(a), CRP, and urinary albumin	Highest vs Lowest Tertiles for Lp-PLA_2 activity HR=2.2 (1.1-4.8) *P*=0.019 Extending endpoint: HR=2.0 (1.1-3.7)*P*=0.022
Miller[36] (2010)		96 type 1 DM patients with Microalbuminuria, 50% male, 29.5 yr	CHD (CHD death, MI, more than 50% stenosis or Revascularization, angina pectoris	18 yr (mean 11.5 yr)	Activity	CRP, DM course, sex, LDL-C, HbA1c, TG,	univariate analysis: HR=1.54 (1.11, 2.12), *P*=0.009 multivariate analysis for CAD: HR=2.40 (1.02, 5.64), *P*=0.05 (Haptoglobin genotype 2/1type)
Hatoum[37] (2010)	HPFS and NHS	740 male /777 female DM without CVD	CHD (CABG, PTCA, nonfatal MI, CHD death), 324	Male 10 yr, female 14 yr	Activity	Age, smoking, history of disease, HDL-C, LDL-C, CRP	Highest vs Lowest Tertiles for Lp-PLA_2 activity HR=1.39 (1.01-1.90, *P*=0.03)

ARIC = Atherosclerosis Risk In Communities; BMI = body mass index; CABG = coronary artery bypass grafting; CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease; DM = diabetes mellitus; HaBPS = Hormones and Biomarkers Predicting Stroke; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SBP = systolic blood pressure; SD = standard deviation; TG = triglycerides; UA = unstable angina; WBC = white blood (cell) count; WHS = Women's Health Study; WOSCOPS = West Of Scotland Coronary Prevention Study

Relationship between Lp-PLA_2 and Subclinical Atherosclerosis

The relationship between Lp-PLA_2 and subclinical atherosclerosis was observed in six studies (**Table 4**),[50-55] among which four were cross-sectional studies51-54 and two case-control studies.50, 55 Coronary artery calcification (CAC) was used as an indicator for assessing subclinical atherosclerosis in four studies. Carotid plaques and intima-media thickness (IMT) was used in two studies.51, 55 Increased Lp-PLA_2 was found to be associated with high risk of CAC in the case-control study of young adult population (OR = 1.28; 95% CI, 1.03–1.60).[50] The association of increased Lp-PLA_2 with subclinical atherosclerosis was present if only the age was adjusted but disappeared if the cholesterol level was adjusted, according to the Rotterdam Study.[51-52] Lp-PLA_2 was associated with CAC only in men but not in women from the Dallas Heart Study.[53] No independent association between Lp-PLA_2 and subclinical atherosclerosis was found in patients with long-term DM54 or patients with metabolic syndrome.[55]

Table 3. Case-control studies for relationship of Lp-PLA_2 and CVD.

Author (Year)	Subjects	Case	Control	Lp-PLA_2 measurement	Variables Adjusted	Results
Blankenberg[45] (2003)	Case: 496 CAD, 76% male, 59.9±10 yr Control 477, 73% male 59.9±7.2 yr	>30% stenosis of at lease one coronary artery	Community people without CHD and normal ECG	Activity	Age, sex, hypertension, smoking, LDL-C, HDL-C, BMI, TG	Highest vs lowest quartiles for Lp-PLA_2 (OR): 1.8 (1.01-3.2)
Khuseyinova[46] (2005)	Case: 312 CAD, 86% male, 57.7±7.4 yr Control:479, 75% male, 55.8±7.2 yr	≥50% stenosis of at lease one coronary artery	Blood donor matching with age and sex	Mass	Age, sex, hypertension, smoking, TC, HDL-C, BMI, alcohol, DM, education, statin, VWF	Highest vs lowest quartiles for Lp-PLA_2 (OR): 1.91 (1.12-3.28)
Winkler[47] (2005)	Case: 2454,CAD, 85% male Control: 694, 52% male	>20% stenosis of at lease one coronary artery	Without stenosis of coronary artery	Activity	Age, sex, hypertension, smoking, LDL-C, DM, BMI, fibrinogen, WBC, SAA, ASA, CRP	Highest vs lowest quartiles for Lp-PLA_2 (OR): 1.39 (1.26-1.54) (excluding drug treatment)
Kim[48] (2008)	Case: 799 CAD (715 male) Control: 925 (805 male), 31-83 yr	≥50% stenosis of at lease one coronary artery, or prior MI	Without history of CHD and clinical CHD	Activity	Age, sex, BMI, SBP, DBP, smoking, alcohol, HDL-C, LDL-C, statin	Highest vs lowest quartiles for Lp-PLA_2 (OR): 1.92 (1.32-2.79)
Hou[49] (2009)	Case: 689 CHD Control: 416	AMI or ≥70% stenosis of at lease one coronary artery	Community people without CHD (disease history, normal ECG, clinical examination, Rose questionnaire), match with age and sex	Activity	Age, sex, BMI, smoking, alcohol, hypertension, DM, LDL-C, HDL-C	OR for 1SD increase Lp-PLA_2 With CHD: 1.27 (1.07-1.50) With MI: 1.27 (1.05-1.54)

ASA = acetylsalicylic acid; BMI = body mass index; CAD = coronary artery disease; CHD = coronary heart disease; CRP = C-reactive protein; DM = diabetes mellitus; ECG = electrocardiogram; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; OR = odds ratio; SAA = serum amyloid alpha; SD = standard deviation; TC = total cholesterol; TG = triglycerides; VWF = von willebrand factor; WBC = white blood (cell) count

Table 4. Studies for Lp-PLA_2 and subclinical atherosclerosis.

Author (Year)	Parent Study	Subjects	Measurement of subclinical atherosclerosis	Study type	Lp-PLA_2 measurement	Variables Adjusted	Results
Iribarren[50] (2005)	CARDIA	Case: 266 Coronary artery plaque calcification (33-45 yr) Control: 266 without plaque, match sex and race with 1:1	CAC	Case-control	Mass and activity	Age, education, alcohol, smoking, BMI, waistline, DM, hypertension, LDL-C, HDL-C, TG, CRP	OR for 1SD increase Lp-PLA_2 (mass) Coronary artery plaque 1.28 (1.03-1.60) Independent with activity.
Kardys[51] (2006)	Rotterdam	Randomized control sample 1820, 68.8 ± 8.7 yr, 34% male	Carotid IMT, plaque, ankle brachial index, Aortic calcification	Cross-sectional	Activity	Age, TC, HDL-C	Highest vs lowest teritles for Lp-PLA_2 Age-adjusted OR=1.77 (1.26-2.50) cholesterol-adjusted OR including 1
Kardys[52] (2007)	Rotterdam	520, 63.8 ± 5.3 yr, 45% male	CAC	Cross-sectional/Sample from 7 years ago	Activity	Age, non-HDL-C, HDL-C,	HR for 1SD increase Lp-PLA_2 Age-adjusted, 1.6 (1.1-2.4) non-HDL and HDL-C adjusted, HR including 1
Brilakis[53] (2008)	Dallas Heart Study	2171, 30-65 yr, 46% male	EBCT detected CAC, MRI detected AAP and AWT	Cross-sectional	Mass and Activity	Age, race, LDL-C, HDL-C, DM, smoking, hypertension, statin, CRP	OR for 1SD increase Lp-PLA_2: (mass) 1.20 (1.01-1.42) P=0.04 (male, CAC); OR including 1 in female
Saremi[54] (2009)	VADT test	306 patients with DM, 61±9 yr, DM course 12±8 yr, 98% male, 78% with hypertension, 60% intake statin	EBCT detected CAC and AAC	Cross-sectional	Mass	Age, race, DM course, hypertension, HbA1c, statin, IL-6	Lp-PLA_2 and CAC: Univariate linear regression β=0.000052, P=0.98.
Gong[55] (2011)		118 patients with metabolic syndrome, 70 age and sex matched controls	Maximal IMT	Case-control	Activity	Age, sex, BMI, WHR, BP, cholesterol, glucose, HOMA	Lp-PLA_2 and maximal IMT: β=0.146, P=0.097

IL-6 = interleukin 6; IMT = intima-media thickness; AAC = abdominal aortic calcification; AAP = abdominal aortic plaque; AWT = aortic wall thickness; CAC = coronary artery calcification; CARDIA = Coronary Artery Risk Development in Young Adults; CRP = C-reactive protein; EBTC = electron Beam Computed Tomography; HbA1c = haemoglobin A1C; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; SD = standard deviation; TC = total cholesterol; TG = triglycerides; DM = diabetes; VADT = Veterans Affairs Diabetes Trial

DISCUSSION

This systematic review suggests that Lp-PLA_2 is closely associated with CVD events from overwhelming majority of published studies. High Lp-PLA_2 was associated with increased risk for both first and recurrence of total CVD, CHD, and ischemic stroke. To understand the role of Lp-PLA_2 in the early prevention and treatment of CVD, elucidating the relationship between Lp-PLA_2 and subclinical atherosclerosis is very important. Studies on the relationship between Lp-PLA_2 and subclinical atherosclerosis are limited. Most of previous studies were cross-sectional or case-control in nature and often showed conflicting results.

Among 33 studies on the relationship between Lp-LPA_2 and CVD in this review, 31 studies demonstrated that increased Lp-PLA_2 could remarkably increase CVD risk. More specifically, of 17 studies that investigated the relationship between Lp-PLA_2 and CHD, 15 showed that increased Lp-PLA_2 increased the risk of CHD; of four studies that investigated the relationship between Lp-PLA_2 and ischemic stroke, all showed that increased Lp-PLA_2 increased the risk of ischemic stroke; and, of 15 studies that investigated the relationship between Lp-PLA_2 and total CVD, 14 showed that increased Lp-PLA_2 increased the risk of total CVD. Some other studies did not find an association of Lp-PLA_2 with CVD, which may be explained by the two main reasons. First, subjects had certain underlying diseases and the studies had too many confounding factors. For example, in the study by Allison et al., 508 individuals underwent examinations of arteries of the lower limbs;[25] and in the study by Miller et al., 96 patients with type 1 DM and microalbuminuria were assessed.[36] Therefore, no positive results were obtained from these two studies. Secondly, sample sizes were small and subjects belonged to low-risk populations. For example, in the study by Blake et al., only 123 female patients with CVD and 123 female normal controls were enrolled.[39] Female patients tend to have fewer risk factors for CVD and some of the women in that study used estrogen, so the results could have been confounded. Furthermore, the inconsistent spectrum of disease in the study groups (which may include CHD or stroke) can dramatically influence results (especially for case-control studies with relatively small sample sizes).

Majority of the studies demonstrated the association of Lp-PLA_2 with CVD events. CVD events are end-stage clinical manifestations of atherosclerosis. The initiation of the pathological changes of atherosclerosis usually starts decades prior to the occurrence of clinical events. Whether Lp-PLA_2 exerts its effect during the development of clinical events due to unstable plaques or at the early stage of atherosclerosis remains unclear. Although many studies have shown a relationship between Lp-PLA_2 and clinical events, the association between Lp-PLA_2 and subclinical atherosclerosis is uncertain. One hypothesis for this inconsistency is that the role of Lp-PLA2 in the development of atherosclerosis is different from its role in the occurrence of clinical CVD events. In fact, Kolodgie et al. investigated the expression of Lp-PLA_2 in coronary segments from 25 sudden coronary death patients, and found that early plaques do not stain intensely for Lp-PLA_2 whereas rupture-prone and ruptured plaques demonstrated intense Lp-PLA_2 staining, suggesting that Lp-PLA_2 might be a trigger of clinical events through plaque instability and rupture, but not an initiator of early development of atherosclerosis. Another possible explanation for the different findings from studies on clinical events and subclinical atherosclerosis is the difference in study designs. The association between Lp-PLA_2 and the development of clinical CVD events have been consistently shown by a number of prospective cohort studies, but few prospective studies has tested its association with the development of subclinical atherosclerosis. Ongoing studies have been mostly cross-sectional or case-control studies which are less powerful compared with prospective studies in hypothesis testing. As these studies used only one cross-sectional measurement for subclinical atherosclerosis, elucidation of its association with Lp-PLA_2 may not be possible. Prospective cohort studies are required to identify the relationship between Lp-PLA_2 and subclinical atherosclerosis. Additionally, most studies have been conducted in European and American populations,[50-54] and only one study with limited sample size has investigated the relationship between Lp-PLA_2 and subclinical atherosclerosis in Chinese population.[55] Whether there is any ethnic variety in the relationship is still unknown.

We also reviewed the pre-analytical phase and assay method for the studies included in the current study. Among the 39 studies, blood samples were collected at fasting stage in all but 5 studies,[17,39,42,51-52] and plasma were used for Lp-PLA_2measurements in all but 4 studies.[20,31,37,50] Lp-PLA_2 mass was assayed using a commercial ELISA kit (PLACIor PLACII) in 21 of 23 studies where Lp-PLA_2 mass were measured (including 8 studies measured both Lp-PLA_2 mass and activity). An in-house ELISA was used in the remaining two studies.[38-39] Lp-PLA_2 activity was measured in 24 studies, among which a colorimetric activity method was used in 16 studies, while a radiometric assay was applied in eight other studies.[23,29,32,42,45,48,51-52] Although the association between Lp-PLA_2 and CVD was rather consistent across the studies, the mean values of Lp-PLA_2 mass or activity varied considerably in different assays. An ELISA test has been cleared by the US Food and Drug Administration to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting the risk of CVD.[56]

In summary, high Lp-PLA_2 is associated with increased risk of clinical CVD events, while the association between Lp-PLA_2 and subclinical atherosclerosis remains uncertain. Further prospective cohort studies on the relationship between Lp-PLA_2 and subclinical atherosclerosis are warranted to determine whether Lp-PLA_2 may only play a role in the progression of subclinical atherosclerosis to clinical events or both the initiation of the atherosclerosis and the progressions towards to clinical outcomes.

ACKNOWLEDGMENT AND DISCLAIMER

This work is supported by grants from National Natural Science Foundation (81070226, 81000109) and Key Laboratory of Remodeling-Related Cardiovascular Diseases, Ministry of Education (110267).

The findings and conclusion in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

CONFLICT OF INTEREST

None.

REFERENCES

1. Center for the control of cardiovascular disease MoH. Report on Cardiovascular Disease in China (2008-2009). Encyclopedia of China Publishing House. 2009.
2. Spence JD. Point: uses of carotid plaque measurement as a predictor of cardiovascular events. Prev.Cardiol. 2005;8(2):118-121.
3. Liu J, Zhao D, Wang W. Association between baseline and 10-year change of lipid levels and corotid atherosclerosis in community population of Peking University. Chin Med J. 2006;86:1386-1389.
4. Khakpour H, Frishman WH. Lipoprotein-associated phospholipase A2: an independent predictor of cardiovascular risk and a novel target for immunomodulation therapy. Cardiol Rev. Sep-Oct 2009;17(5):222-229.
5. Hakkinen T, Luoma JS, Hiltunen MO, et al. Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase, is expressed by macrophages in human and rabbit atherosclerotic lesions. Arterioscler Thromb Vasc Biol. 1999;19(12):2909-2917.
6. Epps KC, Wilensky RL. - a novel risk factor for high-risk coronary and carotid artery disease. J Intern Med. 2011;269(1):94-106.
7. Ikonomidis I, Michalakeas CA, Lekakis J, Parissis J, Anastasiou-Nana M. The role of lipoprotein-associated phospholipase A2 (Lp-PLA) in cardiovascular disease. Rev Recent Clin Trials. 2011;6(2):108-113.
8. Yamamoto K, Isogai Y, Sato H, Taketomi Y, Murakami M. Secreted phospholipase A2, lipoprotein hydrolysis, and atherosclerosis: integration with lipidomics. Anal Bioanal Chem. 2011;400(7):1829-1842.
9. Stewart RA, White HD. The role of lipoprotein-associated phospholipase a as a marker and potential therapeutic target in atherosclerosis. Curr Atheroscler Rep. 2011;13(2):132-137.
10. Murakami M, Taketomi Y, Miki Y, Sato H, Hirabayashi T, Yamamoto K. Recent progress in phospholipase A research: from cells to animals to humans. Prog Lipid Res. 2011;50(2):152-192.
11. Mallat Z, Lambeau G, Tedgui A. Lipoprotein-associated and secreted phospholipases A in cardiovascular disease: roles as biological effectors and biomarkers. Circulation. 2010;122(21):2183-2200.
12. Garza CA, Montori VM, McConnell JP, Somers VK, Kullo IJ, Lopez-Jimenez F. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review. Mayo Clin Proc. 2007;82(2):159-165.
13. Madjid M, Ali M, Willerson JT. Lipoprotein-associated phospholipase A2 as a novel risk marker for cardiovascular disease: a systematic review of the literature. Tex Heart Inst J. 2010;37(1):25-39.
14. Casas JP, Ninio E, Panayiotou A, et al. PLA2G7 genotype, lipoprotein-associated phospholipase A2 activity, and coronary heart disease risk in 10 494 cases and 15 624 controls of European Ancestry. Circulation. 2010;121(21):2284-2293.
15. Zheng GH, Chen HY, Xiong SQ, Chu JF. Lipoprotein-associated phospholipase A2 gene V279F polymorphisms and coronary heart disease: a meta-analysis. Mol Biol Rep. 2011;38(6):4089-4099.
16. Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet. 2010;375(9725):1536-1544.
17. Koenig W, Khuseyinova N, Lowel H, Trischler G, Meisinger C. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. Circulation. 2004;110(14):1903-1908.
18. Brilakis ES, McConnell JP, Lennon RJ, Elesber AA, Meyer JG, Berger PB. Association of lipoprotein-associated phospholipase A2 levels with coronary artery disease risk factors, angiographic coronary artery disease, and major adverse events at follow-up. Eur Heart J. 2005;26(2):137-144.
19. May HT, Horne BD, Anderson JL, et al. Lipoprotein-associated phospholipase A2 independently predicts the angiographic diagnosis of coronary artery disease and coronary death. Am Heart J. 2006;152(5):997-1003.
20. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. Arch Intern Med. 2006;166(19):2073-2080.
21. Corsetti JP, Rainwater DL, Moss AJ, Zareba W, Sparks CE. High lipoprotein-associated phospholipase A2 is a risk factor for recurrent coronary events in postinfarction patients. Clin Chem. 2006;52(7):1331-1338.
22. Koenig W, Twardella D, Brenner H, Rothenbacher D. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. Arterioscler Thromb Vasc Biol. 2006;26(7):1586-1593.
23. O'Donoghue M, Morrow DA, Sabatine MS, et al. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trial. Circulation. 2006;113(14):1745-1752.
24. Sabatine MS, Morrow DA, O'Donoghue M, et al. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. Arterioscler Thromb Vasc Biol. 2007;27(11):2463-2469.
25. Allison MA, Denenberg JO, Nelson JJ, Natarajan L, Criqui MH. The association between lipoprotein-associated phospholipase A2 and cardiovascular disease and total mortality in vascular medicine patients. J Vasc Surg. 2007;46(3):500-506.
26. Mockel M, Muller R, Vollert JO, et al. Lipoprotein-associated phospholipase A2 for early risk stratification in patients with suspected acute coronary syndrome: a multi-marker approach: the North Wuerttemberg and Berlin Infarction Study-II (NOBIS-II). Clin Res Cardiol. 2007;96(9):604-612.
27. Winkler K, Hoffmann MM, Winkelmann BR, et al. Lipoprotein-associated phospholipase A2 predicts 5-year cardiac mortality independently of established risk factors and adds prognostic information in patients with low and medium high-sensitivity C-reactive protein (the Ludwigshafen risk and cardiovascular health study). Clin Chem. 2007;53(8):1440-1447.
28. Kiechl S, Willeit J, Mayr M, et al. Oxidized phospholipids, lipoprotein(a), lipoprotein-associated phospholipase A2 activity, and 10-year cardiovascular outcomes: prospective results from the Bruneck study. Arterioscler Thromb Vasc Biol. 2007;27(8):1788-1795.
29. Persson M, Hedblad B, Nelson JJ, Berglund G. Elevated levels add prognostic information to the metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. Arterioscler Thromb Vasc Biol. 2007;27(6):1411-1416.
30. Raichlin E, McConnell JP, Bae JH, Kremers WK, Lerman A, Frantz RP. Lipoprotein-associated phospholipase A2 predicts progression of cardiac allograft vasculopathy and increased risk of cardiovascular events in heart transplant patients. Transplantation. 2008;85(7):963-968.
31. Daniels LB, Laughlin GA, Sarno MJ, Bettencourt R, Wolfert RL, Barrett-Connor E. Lipoprotein-associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: the Rancho Bernardo Study. J Am Coll Cardiol. 2008;51(9):913-919.
32. Persson M, Berglund G, Nelson JJ, Hedblad B. activity and mass are associated with increased incidence of ischemic stroke: a population-based cohort study from Malmo, Sweden. Atherosclerosis. 2008;200(1):191-198.
33. Robins SJ, Collins D, Nelson JJ, Bloomfield HE, Asztalos BF. Cardiovascular events with increased lipoprotein-associated phospholipase A(2) and low high-density lipoprotein-cholesterol: the Veterans Affairs HDL Intervention Trial. Arterioscler Thromb Vasc Biol. 2008;28(6):1172-1178.
34. Cucchiara BL, Messe SR, Sansing L, et al. Lipoprotein-associated phospholipase A2 and C-reactive protein for risk-stratification of patients with TIA. Stroke. 2009;40(7):2332-2336.
35. Tsimikas S, Willeit J, Knoflach M, et al. Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: results from the Bruneck study. Eur Heart J. 2009;30(1):107-115.
36. Miller RG, Costacou T, Orchard TJ. Lipoprotein-associated phospholipase A2, C-reactive protein, and coronary artery disease in individuals with type 1 diabetes and macroalbuminuria. Diab Vasc Dis Res. 2010;7(1):47-55.

37. Hatoum IJ, Hu FB, Nelson JJ, Rimm EB. Lipoprotein-associated phospholipase A2 activity and incident coronary heart disease among men and women with type 2 diabetes. Diabetes. 2010;59(5):1239-1243.
38. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. N Engl J Med. 2000;343(16):1148-1155.
39. Blake GJ, Dada N, Fox JC, Manson JE, Ridker PM. A prospective evaluation of lipoprotein-associated phospholipase A(2) levels and the risk of future cardiovascular events in women. J Am Coll Cardiol. 2001;38(5):1302-1306.
40. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2004;109(7):837-842.
41. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med. 2005;165(21):2479-2484.
42. Oei HH, van der Meer IM, Hofman A, et al. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. Circulation. 2005;111(5):570-575.
43. Wassertheil-Smoller S, Kooperberg C, McGinn AP, et al. Lipoprotein-associated phospholipase A2, hormone use, and the risk of ischemic stroke in postmenopausal women. Hypertension. 2008;51(4):1115-1122.
44. Hatoum IJ, Cook NR, Nelson JJ, Rexrode KM, Rimm EB. Lipoprotein-associated phospholipase A2 activity improves risk discrimination of incident coronary heart disease among women. Am Heart J. 2011;161(3):516-522.
45. Blankenberg S, Stengel D, Rupprecht HJ, et al. Plasma PAF-acetylhydrolase in patients with coronary artery disease: results of a cross-sectional analysis. J Lipid Res. 2003;44(7):1381-1386.
46. Khuseyinova N, Imhof A, Rothenbacher D, et al. Association between and coronary artery disease: focus on its relationship with lipoproteins and markers of inflammation and hemostasis. Atherosclerosis. Sep 2005;182(1):181-188.
47. Winkler K, Winkelmann BR, Scharnagl H, et al. Platelet-activating factor acetylhydrolase activity indicates angiographic coronary artery disease independently of systemic inflammation and other risk factors: the Ludwigshafen Risk and Cardiovascular Health Study. Circulation. 2005;111(8):980-987.
48. Kim JY, Hyun YJ, Jang Y, et al. Lipoprotein-associated phospholipase A2 activity is associated with coronary artery disease and markers of oxidative stress: a case-control study. Am J Clin Nutr. 2008;88(3):630-637.
49. Hou L, Chen S, Yu H, et al. Associations of PLA2G7 gene polymorphisms with plasma lipoprotein-associated phospholipase A2 activity and coronary heart disease in a Chinese Han population: the Beijing atherosclerosis study. Hum Genet. 2009;125(1):11-20.
50. Iribarren C, Gross MD, Darbinian JA, Jacobs DR, Jr., Sidney S, Loria CM. Association of lipoprotein-associated phospholipase A2 mass and activity with calcified coronary plaque in young adults: the CARDIA study. Arterioscler Thromb Vasc Biol. 2005;25(1):216-221.
51. Kardys I, Oei HH, van der Meer IM, Hofman A, Breteler MM, Witteman JC. Lipoprotein-associated phospholipase A2 and measures of extracoronary atherosclerosis: the Rotterdam Study. Arterioscler Thromb Vasc Biol. 2006;26(3):631-636.
52. Kardys I, Oei HH, Hofman A, Oudkerk M, Witteman JC. Lipoprotein-associated phospholipase A2 and coronary calcification. The Rotterdam Coronary Calcification Study. Atherosclerosis. 2007;191(2):377-383.
53. Brilakis ES, Khera A, Saeed B, et al. Association of lipoprotein-associated phospholipase A2 mass and activity with coronary and aortic atherosclerosis: findings from the Dallas Heart Study. Clin Chem. 2008;54(12):1975-1981.
54. Saremi A, Anderson RJ, Luo P, et al. Association between IL-6 and the extent of coronary atherosclerosis in the veterans affairs diabetes trial (VADT). Atherosclerosis. 2009;203(2):610-614.
55. Gong HP, Du YM, Zhong LN, et al. Plasma lipoprotein-associated phospholipase A2 in patients with metabolic syndrome and carotid atherosclerosis. Lipids Health Dis. 2011;10:13.
56. Corson MA, Jones PH, Davidson MH. Review of the evidence for the clinical utility of lipoprotein-associated phospholipase A2 as a cardiovascular risk marker. Am J Cardiol. 2008;101(12A):41F-50F.