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Original Article

Association of Lp-PLA2 mass and heart failure in a cohort of Nantong population

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Abstract: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a useful inflammatory marker which correlated with the development of coronary artery disease (CAD). Inflammatory cytokines may be involved in the pathogenesis of ventricular dysfunction which contributes to the severity of heart failure (HF). However, the role of Lp-PLA2 in HF was not clear. We evaluated the association of Lp-PLA2 mass levels with the severity of HF with or without CAD and assessed this enzyme involved in these pathophysiologic processes in relation to left ventricular ejection fraction. Plasma Lp-PLA2 mass were measured in 652 HF patients with or without CAD and evaluated along with known risk indicators. Lp-PLA2 mass dramatically increased in advanced HF compared to mild/moderate HF ($P<0.05$). A negative correlation was found between Lp-PLA2 mass and left ventricular ejection fraction (LVEF) level in HF ($r=-0.287$, $P<0.0001$) and in HF without CAD ($r=-0.306$, $P<0.0001$). Lp-PLA2 mass was significantly associated with advanced HF after adjusted with age, gender, hypertension, diastolic blood pressure, statins, inclusion diagnosis of CAD and atrial fibrillation (95% CI=1.01-1.02, $P<0.05$). In conclusion, Lp-PLA2 mass was strongly and independently associated with advanced HF in this community-based cohort of patients.

Keywords: Lipoprotein-associated phospholipase A2 mass, heart failure, epidemiology

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by exercise intolerance, fatigability, dyspnea and volume retention. A lot of processes are involved in the evolution of HF: neurohormonal activation, extracellular matrix remodeling, myocyte injury, and renal dysfunction. Recently, several studies have reported that inflammation plays a role in the pathophysiology of heart failure. Elevated inflammatory markers, such as interleukin-6 [1], tumor necrosis factor-α [2], and C-reactive protein [3], have been proved to be associated with heart failure. Furthermore, a correlation has been discovered between high blood levels of these inflammatory markers and worsening functional New York Heart Association (NYHA) class [4], increased hospitalization rates, and poorer survival of heart failure patients.

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase (PAF-AH), is a novel inflammatory biomarker specific for vascular inflammation [5-8], which is mainly produced by monocytes and macrophages and mainly binds to low-density lipoprotein (LDL) cholesterol. Less than 20% Lp-PLA2 is associated with high-density lipoprotein (HDL) cholesterol [9]. Lp-PLA2 hydrolyzes phospholipids on LDL to lyso-phospholipid and oxidized fatty acids which are pro-inflammatory lipid mediators [7]. It is reported that Lp-PLA2 associated with LDL cholesterol, atherosclerotic disease and incident of coronary heart disease [6, 10]. Therefore, Lp-PLA2 involves in the progress of vascular inflammation.

Evidence demonstrates that inflammation is an underlying pathophysiology of HF [11]. Epidemiological studies and meta-analyses also consistently show that increased plasma level of Lp-PLA2 is associated with an augmented risk of cardiovascular events [12-15]. The role of LP-PLA2 in cardiovascular pathophysiol-

ogy has been well demonstrated both *in vitro* and in animal models. Rotterdam study found that Lp-PLA2 is an independent predictor of heart failure in healthy people [16]. However, far less is known about the potential association of Lp-PLA2 with HF. Lp-PLA2 were measured by activity assay or antigenic (mass) assay in previous epidemiological studies [16, 17]. The Rotterdam Study reported that Lp-PLA2 activity associated with risk of CHF over 6.7 years [16]. Whereas Takeki Suzuki et. al. indicated that Lp-PLA2 mass, but not activity, was associated with increased risk of future chronic HF in older people without CVD or CHF at baseline [18]. Therefore, in the present study, we aimed to assess possible association between Lp-PLA2 mass levels and NYHA HF class.

Materials and methods

Study population

We conducted a cross-sectional study within the Department of Cardiology of the Affiliated Hospital of Nantong University (Nantong, China), from April 2014 to December 2015. This study was approved by the ethics committee at Affiliated Hospital of Nantong University, and informed consent was obtained from all patients and control subjects. Patients who had serious pulmonary, hepatic, or renal insufficiency; malignant tumor or autoimmune disease; abnormal thyroid function at enrollment were excluded from the study.

Patient enrollment was determined by the medical records of inpatients from the Department of Cardiology. Functional capacity of HF was defined by the mild/moderate HF (NYHA classification system I-II) and advanced HF (NYHA classification system III-IV). Cardiac systolic function was classified by left ventricular ejection fraction (LVEF) level (preserved LVEF >50%, reduced LVEF ≤50%) upon admission [19]. The NYHA classification increases in severity from Class I to Class IV [20]. All cases were manually reviewed to validate the diagnosis of HF using NYHA criteria and the standard criteria recommended by the European Society [4, 21]. All patients were contacted directly.

Patients with coronary artery disease (CAD) were determined by medical records which included acute coronary syndrome (ACS) and chronic stable angina (CSA). The ACS cases included ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI) and unstable angina [22]. Patients are defined as STEMI when they present with biomarkers of myocardial necrosis (i.e. typical rise and gradual fall of troponin or more rapid rise and fall of creatine kinase MB) and at least one of the following criteria: clinical history of ischemic type chest pain; development of pathologic Q waves on the electrocardiogram (ECG); ECG changes indicative of ischemia. Patients are defined as UA/NSTEMI when they present with three possible types of chest pain [i.e. new onset (2 months) angina that is severe and/or frequent (>3 episodes per day), accelerating angina and/or angina at rest] with ECG changes (ST segment depression >0.05 mV or T-wave inversion >0.2 mV in the precordial leads). NSTEMI is differentiated from UA by the presence of elevated serum cardiac markers.

Measurement of demographic characteristics

At enrollment, the characteristics of patients were determined in medical records in admission. Age, gender, smoking status and statins therapy were recorded [23-26]. Diabetes mellitus was defined by the American Diabetes Association diagnostic criteria [27]. Height and weight were measured with patients in light indoor clothes. Body mass index (BMI) is a value derived from the mass (weight) and height of an individual and BMI ≥28 kg/m^2 was considered as obesity in China [28]. Blood pressure (BP) was measured twice in the sitting position on the right arm using standard mercury sphygmomanometer on admission. Hypertension is defined as the resting blood pressure above 140/90 mmHg [29]. Fasting venous blood was drawn in the early morning hours before breakfast at the next day of admission for the assessment of fasting blood glucose (FBG), brain natriuretic peptide (BNP), total cholesterol, triglyceride, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apoprotein in B (apoB) [30-32].

Measurement of Lp-PLA2 mass

The following standardized examinations were performed: Fasting venous blood was collected in EDTA tubes in the early morning before breakfast at the next day of admission. Plasma level of Lp-PLA2 at admission was evaluated

Table 1. Basic characteristics of study population in the whole study sample, advanced HF and mild/moderate HF (mean ± standard deviation for continuous variables, proportion for classified variables)

	All subjects	Mild/moderate HF	Advanced HF	t/χ^2	P
N	652	425	227		
Age [years]	64.9±13.2	62.8±13.6	68.9±11.4	-6.034	0.000
Gender [% of males]	395 (60.6)	234 (55.1)	161 (70.9)	15.598	0.000
Current smoking [%]	162 (24.8)	102 (24.0)	60 (26.4)	0.469	0.277
Hypertension [%]	345 (52.9)	230 (54.1)	115 (50.7)	0.710	0.224
Diabetes mellitus [%]	161 (24.7)	104 (24.5)	57 (25.1)	0.033	0.464
Systolic blood pressure [mmHg]	135.3±23.0	135.1±22.5	135.6±24.0	-0.283	0.778
Diastolic blood pressure [mmHg]	78.4±14.8	76.7±13.2	81.6±17.1	-3.727	0.000
Body mass index ≥28 kg/m^2 [%]	86 (13.2)	55 (12.9)	31 (13.7)	0.066	0.443
Total cholesterol [mmol/l]	4.35±1.06	4.42±1.06	4.22±1.05	2.236	0.026
Triglycerides [mmol/l]	1.46±1.17	1.58±1.32	1.24±0.76	2.072	0.054
HDL-cholesterol [mmol/l]	1.20±0.43	1.20±0.34	1.21±0.56	-0.381	0.703
LDL-cholesterol [mmol/l]	2.35±0.78	2.34±0.71	2.35±0.78	-0.117	0.904
ApoB [mmol/l]	76.2±21.3	76.0±20.8	76.6±22.3	-0.361	0.718
Fasting glucose [mmol/l]	5.76±2.08	5.77±2.13	5.75±1.98	-0.085	0.934
Statins [%]	156 (27.4)	129 (30.4)	27 (11.9)	23.566	0.000
Brain natriuretic peptide	423.2±718.7	154.5±262.3	926.2±984.4	-11.593	0.000
Inclusion diagnosis [% of CAD]	185 (28.4)	152 (35.8)	33 (34.5)	32.807	0.000
Atrial fibrillation [%]	182 (27.9)	80 (18.8)	102 (44.9)	50.133	0.000
LP-PLA2 mass [ng/ml]	233.6±96.0	207.3±89.0	282.8±89.0	-10.313	0.000

by enzyme-linking immune-absorbent assay (Shanghai Yueyan Biological) according to its manual.

Analysis of LV function

The LV function was analyzed by echocardiography. For the purpose of determining whether increased plasma level of Lp-PLA2 was associated with the severity of HF, all participants were divided into four different subgroups according to the categories of New York Heart Association class assessment or left ventricular ejection fraction.

Statistical analyses

SPSS21.0 software was used for all statistical analyses. Before statistical analysis, continuous data was presented as mean ± SD and categorical data was presented as percentage. Differences between two groups were compared by student's *t*-test and *Chi*-square test. Univariate logic regression was used to analyze the associations between HF and baseline characteristics. Risk factors found significant on univariate analysis were entered into multivariate logistic regression model. All statistical tests were 2-tailed, and a significance level (P) of 0.05 was used. Stepwise multivariate logic regression was performed to evaluate the relationship between Lp-PLA2 value and the severity of HF. The details are mentioned in relevant sections. Kolmogorov-Smirnov test was used to evaluate whether the variables were Gaussian distributed. Spearman's correlation analysis (for continuous distribution with non-Gaussian distributed) was used to compute the correlation of Lp-PLA2 mass and LVEF level.

Results

Baseline characteristics of study population

Baseline clinical characteristics of the study population were shown in **Table 1**. A total of 652 patients including 185 (28.4%) with CAD and 467 (71.6%) non-CAD were enrolled in the present study. Average age was 64.9±13.2 years and New York Heart Association (NYHA) functional class was separated in mild/moderate HF (Class I/II) and advanced HF (class III/IV): 425/227. As expected, age and diastolic blood pressure in the advanced HF patients was significantly higher (P<0.05) than in mild/moderate HF. The advanced HF patients were

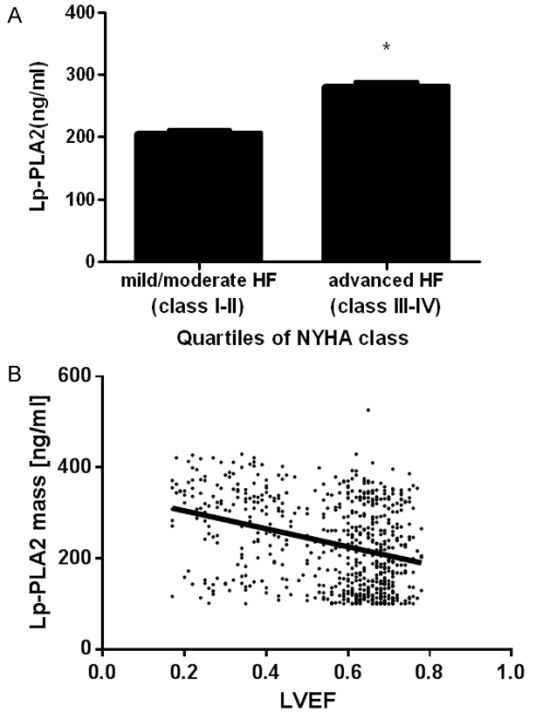

Figure 1. LP-PLA2 levels in HF patients with different cardiac function. A. Difference in LP-PLA2 levels between HF patients with different NYHA grade. *; P<0.05. B. Correlation between LP-PLA2 levels and EF level in HF patients. r=-0.287, P<0.0001.

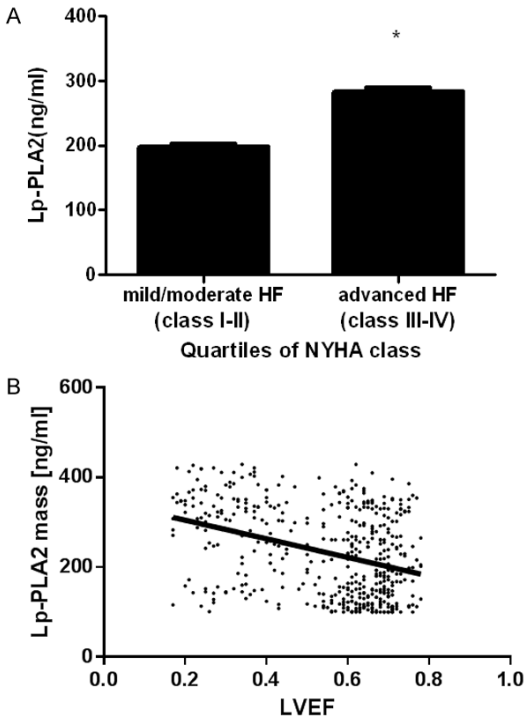

Figure 2. LP-PLA2 levels in HF patients without CAD with different cardiac function. A. Difference in LP-PLA2 levels between HF patients without CAD with different NYHA grade. *; P<0.05. B. Correlation between LP-PLA2 levels and EF level in HF patients without CAD. r=-0.306, P<0.0001.

more likely to occur in the male patients with a history of atrial fibrillation and abnormal Lp-PLA2 mass. Patients of advanced HF had significantly low (P<0.05) level of HDL-cholesterol as compared to controls. The proportion of patients with CAD and treated by statins were higher in mild/moderate HF. There were no significant statistical differences in proportion of current smoking, hypertension and diabetes mellitus. There was no significant difference in levels of body mass index, total cholesterol, HDL, LDL, apoB and fasting glucose.

Association between Lp-PLA2 mass and cardiac function

Lp-PLA2 mass dramatically increased in advanced HF compared to mild/moderate HF (P<0.05, **Figure 1A**). Kolmogorov-Smirnov test showed that Lp-PLA2 mass and LVEF level were continuous distribution with non-Gaussian distributed (P<0.0001). A negative correlation was found between Lp-PLA2 mass and LVEF level by Spearman's correlation analysis (r=-0.287, P<0.0001, **Figure 1B**). These relationships remained after we excluded participants with CAD (**Figure 2**). As **Figure 2** demonstrates, Lp-PLA2 mass levels elevated significantly in advanced HF compared to mild/moderate HF (P<0.05, **Figure 2A**). Kolmogorov-Smirnov test showed that Lp-PLA2 mass and LVEF level were continuous distribution with non-Gaussian distributed (P<0.0001). A negative correlation was found between Lp-PLA2 mass and LVEF level by Spearman's correlation analysis (r=-0.306, P<0.0001, **Figure 2B**).

Associations between Lp-PLA2 mass and incident HF

As seen in **Table 2**, we used univariate regression to analyze the associations between advanced HF and baseline characteristics. Advanced HF has no significant association with Current smoking, diabetes mellitus, Body mass index, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol and ApoB. Advanced HF was positively associated hypertension (95% CI=0.48-0.97, P<0.05), diastolic blood pressure (95% CI=1.01-1.03, P<0.05), statins therapy (95% CI=0.20-0.48, P<0.05), BNP (95% CI=1.01-1.02, P<0.05), CAD inclu-

Table 2. Association of HF and basic characteristics

	Odds ratios (95% CI)	P
Current smoking [%]	0.89 (0.59-1.36)	0.595
Hypertension [%]	0.68 (0.48-0.97)	0.031
Diabetes mellitus [%]	0.90 (0.61-1.33)	0.609
Systolic blood pressure [mmHg]	1.00 (0.99-1.00)	0.353
Diastolic blood pressure [mmHg]	1.02 (1.01-1.03)	0.000
Body mass index ≥28 kg/m^2	1.34 (0.81-2.20)	0.225
Total cholesterol [mmol/l]	0.93 (0.79-1.10)	0.381
Triglycerides [mmol/l]	0.83 (0.75-1.01)	0.108
HDL-cholesterol [mmol/l]	1.17 (0.79-1.72)	0.432
LDL-cholesterol [mmol/l]	1.14 (0.93-1.44)	0.258
ApoB [mmol/l]	1.01 (0.99-1.01)	0.140
Fasting glucose [mmol/l]	0.97 (0.89-1.05)	0.410
Statins [%]	0.31 (0.20-0.48)	0.000
Brain natriuretic peptide	1.01 (1.01-1.02)	0.000
Inclusion diagnosis [% of CAD]	0.24 (0.16-0.37)	0.000
Atrial fibrillation [%]	3.31 (2.27-4.82)	0.000
LP-PLA2 mass [ng/ml]	1.01 (1.01-1.02)	0.000

Age and gender were adjusted.

Table 3. Association of HF and LP-PLA2 mass

	Odds ratios (95% CI)	P
Age [years]	1.03 (1.02-1.05)	0.001
Gender [% of males]	2.14 (1.36-3.39)	0.001
Hypertension [%]	0.88 (0.55-1.40)	0.582
Diastolic blood pressure [mmHg]	1.01 (0.99-1.02)	0.108
Statins [%]	0.83 (0.46-1.50)	0.537
Inclusion diagnosis [% of CAD]	0.29 (0.16-0.53)	0.000
Brain natriuretic peptide	1.01 (1.01-1.02)	0.000
Atrial fibrillation [%]	2.35 (1.48-3.74)	0.000
LP-PLA2 mass [ng/ml]	1.01 (1.01-1.02)	0.000

sive diagnosis (95% CI=0.16-0.37, P<0.05), atrial fibrillation (95% CI=2.27-4.82, P<0.05) and LP-PLA2 mass(95% CI=1.01-1.02, P<0.05) after adjusted with age and gender.

In order to determine whether LP-PLA2 mass was independently associated with advance HF, hypertension, diastolic blood pressure, statins therapy, BNP, CAD inclusive diagnosis and atrial fibrillation were adjusted by stepwise multivariate regression. **Table 3** showed that Lp-PLA2 mass was strongly associated with advanced HF (95% CI=1.01-1.02, P<0.05).

Discussion

This study demonstrates that Lp-PLA2 mass is increased in HF patients, and highlights the positive association between Lp-PLA2 level and NYHA HF grade. Furthermore, our study has shown that this positive association existed not only in HF patients with CAD, but also in HF patients without CAD even though we excluded participants with coronary heart disease. After adjustment for age and sex, similar findings remained. We also found that Lp-PLA2 mass was inversely associated with left ventricular ejection fraction in HF patients in our study. To our knowledge, Lp-PLA2 plays a causal role in atherogenesis [33, 34] and augments the risk of cardiovascular events such as myocardial infarction and ischemic stroke [10, 24, 35]. On the other hand, Takeki Suzuki and colleagues found that Lp-PLA2 antigen was associated with risk of chronic HF in older people without CAD [18]. In the Rotterdam Study, Laura C. van Vark and colleagues reported that Lp-PLA2 activity is independently associated with incident heart failure after excluding subjects with prevalent coronary heart disease at baseline and censored subjects with incident coronary heart disease during follow-up [16].

There are several plausible mechanisms linking Lp-PLA2 with HF. On one hand, Lp-PLA2 is primarily secreted by macrophages in sclerotic plaque. When released, it binds (by 80%) to the apolipoprotein B moiety on low-density lipoprotein (LDL) particles, whereas about 15% is bound to HDL, and the remaining amount to very low density lipoprotein (VLDL). Moreover, its biosynthesis and secretion can be modulated by cytokines, which are increased in heart failure [36]. On another hand, Lp-PLA2 exerts a negative inotropic effect in the heart, generates arrhythmias, and induces secretion of atrial natriuretic peptide in rat cardiomyocytes [37]. Owing to interaction between Lp-PLA2 and heart failure, we observed that Lp-PLA2 mass increased in patients with HF.

Plasma Lp-PLA2 can effectively hydrolyze oxidized phospholipids, yielding the proinflammatory and proatherogenic products, lysophosphatidylcholine and oxidized nonesterified fatty acids. These bioactive products play critical

roles in the induction of chemotactic response, endothelial cell dysfunction, and smooth muscle cell apoptosis [38]. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death [39]. It is conceivable that improving endothelial function may exert beneficial effects in heart failure patients. Interestingly, statins can improve endothelial function and have demonstrated to improve survival post-infarction through an eNOS-dependent mechanism [40].

Lp-PLA2 mass may serve as biomarker of HF, and may be a potential treatment target. However, the specific inhibitor of Lp-PLA2 activity, darapladip failed to obtain any significant benefit in the prevention of CAD risk from the STABILITY trial [41]. While Karabina S and Ninio E indicated that plasma PLA2G7 genetic variability influenced the effect of darapladib on clinical trials [42]. Furthermore, clinical and basic research is needed to investigate pharmacological and physiological effect of Lp-PLA2 on HF.

In conclusion, our investigation showed that Lp-PLA2 mass levels were increased in HF patients and Lp-PLA2 mass was positively related to the worse NYHA class level including even when excluding patients with CAD. Lp-PLA2 mass seems to be a biomarker and novel therapeutic target in patients with HF.

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Disclosure of conflict of interest

None.

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References

[1] Hirota H, Izumi M, Hamaguchi T, Sugiyama S, Murakami E, Kunisada K, Fujio Y, Oshima Y, Nakaoka Y and Yamauchi-Takihara K. Circulating interleukin-6 family cytokines and their receptors in patients with congestive heart failure. Heart Vessels 2004; 19: 237-241.

[2] Deswal A, Petersen NJ, Feldman AM, Young JB, White BG and Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation 2001; 103: 2055-2059.

[3] Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, Signorini S, Mocarelli P, Hester A, Glazer R, Cohn JN; Val-HeFT Investigators. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation 2005; 112: 1428-1434.

[4] New York Heart Association. Criteria Committee. and New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston: Little, Brown; 1979.

[5] Caslake MJ and Packard CJ. Lipoprotein-associated phospholipase A2 (platelet-activating factor acetylhydrolase) and cardiovascular disease. Curr Opin Lipidol 2003; 14: 347-352.

[6] Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, Macphee CH, Suckling KE, Krishna M, Wilkinson FE, Rumley A and Lowe GD. 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: 1148-1155.

[7] Zalewski A and Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. Arterioscler Thromb Vasc Biol 2005; 25: 923-931.

[8] Lavi S, McConnell JP, Rihal CS, Prasad A, Mathew V, Lerman LO and Lerman A. Local production of lipoprotein-associated phospholipase A2 and lysophosphatidylcholine in the coronary circulation: association with early coronary atherosclerosis and endothelial dysfunction in humans. Circulation 2007; 115: 2715-2721.

[9] Karabina SA, Liapikos TA, Grekas G, Goudevenos J and Tselepis AD. Distribution of PAF-acetylhydrolase activity in human plasma low-density lipoprotein subfractions. Biochim Biophys Acta 1994; 1213: 34-38.

[10] Daniels LB, Laughlin GA, Sarno MJ, Bettencourt R, Wolfert RL and 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: 913-919.

[11] Yndestad A, Damas JK, Oie E, Ueland T, Gullestad L and Aukrust P. Systemic inflammation in heart failure-the whys and wherefores. Heart Fail Rev 2006; 11: 83-92.

[12] May HT, Horne BD, Anderson JL, Wolfert RL, Muhlestein JB, Renlund DG, Clarke JL, Kolek MJ, Bair TL, Pearson RR, Sudhir K and Carlquist JF. Lipoprotein-associated phospholipase A2 independently predicts the angiographic diagnosis of coronary artery disease and coronary death. Am Heart J 2006; 152: 997-1003.

[13] Jenny NS, Solomon C, Cushman M, Tracy RP, Nelson JJ, Psaty BM and Furberg CD. Lipoprotein-associated phospholipase A(2) (Lp-PLA(2) and risk of cardiovascular disease in older adults: results from the Cardiovascular Health Study. Atherosclerosis 2010; 209: 528-532.

[14] Lp PLASC, Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, Kaptoge S, Ballantyne C, Cannon CP, Criqui M, Cushman M, Hofman A, Packard C, Thompson SG, Collins R and Danesh J. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 2010; 375: 1536-1544.

[15] Dohi T, Miyauchi K, Okazaki S, Yokoyama T, Ohkawa R, Nakamura K, Yanagisawa N, Tsuboi S, Ogita M, Yokoyama K, Kurata T, Yatomi Y and Daida H. Decreased circulating lipoprotein-associated phospholipase A2 levels are associated with coronary plaque regression in patients with acute coronary syndrome. Atherosclerosis 2011; 219: 907-912.

[16] van Vark LC, Kardys I, Bleumink GS, Knetsch AM, Deckers JW, Hofman A, Stricker BH and Witteman JC. Lipoprotein-associated phospholipase A2 activity and risk of heart failure: the Rotterdam study. Eur Heart J 2006; 27: 2346-2352.

[17] Iribarren C, Gross MD, Darbinian JA, Jacobs DR Jr, Sidney S and 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: 216-221.

[18] Suzuki T, Solomon C, Jenny NS, Tracy R, Nelson JJ, Psaty BM, Furberg C and Cushman M. Lipoprotein-associated phospholipase A(2) and risk of congestive heart failure in older adults: the Cardiovascular Health Study. Circ Heart Fail 2009; 2: 429-436.

[19] Farmakis D, Koeck T, Mullen W, Parissis J, Gogas BD, Nikolaou M, Lekakis J, Mischak H and Filippatos G. Urine proteome analysis in heart failure with reduced ejection fraction complicated by chronic kidney disease: feasibility, and clinical and pathogenetic correlates. Eur J Heart Fail 2016; 18: 822-9.

[20] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW; American College of Cardiology F and American Heart A. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009; 53: e1-e90.

[21] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; Task Force for the Diagonsis; Treatment of Acute; Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14: 803-869.

[22] Anguita M, Comin J, Almenar L, Crespo M, Delgado J, Gonzalez-Costello J, Hernandez-Madrid A, Manito N, Perez de la Sota E, Segovia J, Segura C, Alonso-Gomez AM, Anguita M, Cequier A, Comin J, Diaz-Buschmann I, Fernandez-Lozano I, Fernandez-Ortiz A, Gomez de Diego JJ, Pan M, Worner F, Alonso-Pulpon L, Bover R, Castro A, Diaz-Molina B, Gomez-Bueno M, Gonzalez-Juanatey JR, Lage E,

Lopez-Granados A, Lupon J, Martinez-Dolz L, Munoz R, Pascual D, Ridocci F, Roig E, Varela A and Vazquez de Prada JA. Comments on the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. A report of the Task Force of the Clinical Practice Guidelines Committee of the Spanish Society of Cardiology. Rev Esp Cardiol (Engl Ed) 2012; 65: 874-878.

[23] Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM and Vasan RS. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002; 347: 1397-1402.

[24] Gerber Y, McConnell JP, Jaffe AS, Weston SA, Killian JM and Roger VL. Lipoprotein-associated phospholipase A2 and prognosis after myocardial infarction in the community. Arterioscler Thromb Vasc Biol 2006; 26: 2517-2522.

[25] Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P and Gapstur SM. 50-year trends in smoking-related mortality in the United States. N Engl J Med 2013; 368: 351-364.

[26] Fukuta H, Goto T, Wakami K and Ohte N. The effect of statins on mortality in heart failure with preserved ejection fraction: a meta-analysis of propensity score analyses. Int J Cardiol 2016; 214: 301-306.

[27] Woodward M, Zhang X, Barzi F, Pan W, Ueshima H, Rodgers A, MacMahon S; Asia Pacific Cohort Studies Collaboration. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. Diabetes Care 2003; 26: 360-366.

[28] He W, Li Q, Yang M, Jiao J, Ma X, Zhou Y, Song A, Heymsfield SB, Zhang S and Zhu S. Lower BMI cutoffs to define overweight and obesity in China. Obesity (Silver Spring) 2015; 23: 684-691.

[29] Poulter NR, Prabhakaran D and Caulfield M. Hypertension. Lancet 2015; 386: 801-812.

[30] Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, Woodward M; Asia Pacific Cohort Studies Collaboration. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation 2004; 110: 2678-2686.

[31] Coffman E and Richmond-Bryant J. Multiple biomarker models for improved risk estimation of specific cardiovascular diseases related to metabolic syndrome: a cross-sectional study. Popul Health Metr 2015; 13: 7.

[32] Pistulli R, Hammer N, Rohm I, Kretzschmar D, Jung C, Figulla HR and Yilmaz A. Decrease of circulating myeloid dendritic cells in patients with chronic heart failure. Acta Cardiol 2016; 71: 165-172.

[33] MacPhee CH, Moores KE, Boyd HF, Dhanak D, Ife RJ, Leach CA, Leake DS, Milliner KJ, Patterson RA, Suckling KE, Tew DG and Hickey DM. Lipoprotein-associated phospholipase A2, platelet-activating factor acetylhydrolase, generates two bioactive products during the oxidation of low-density lipoprotein: use of a novel inhibitor. Biochem J 1999; 338: 479-487.

[34] Karabina SA, Elisaf M, Bairaktari E, Tzallas C, Siamopoulos KC and Tselepis AD. Increased activity of platelet-activating factor acetylhydrolase in low-density lipoprotein subfractions induces enhanced lysophosphatidylcholine production during oxidation in patients with heterozygous familial hypercholesterolaemia. Eur J Clin Invest 1997; 27: 595-602.

[35] Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Heiss G and Sharrett AR. 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: 837-842.

[36] Bussolino F, Camussi G, Tetta C, Garbarino G, Bosia A and Baglioni C. Selected cytokines promote the synthesis of platelet-activating factor in vascular endothelial cells: comparison between tumor necrosis factor alpha and beta and interleukin-1. J Lipid Mediat 1990; 2 Suppl: S15-22.

[37] Montrucchio G, Alloatti G and Camussi G. Role of platelet-activating factor in cardiovascular pathophysiology. Physiol Rev 2000; 80: 1669-1699.

[38] Yang EH, McConnell JP, Lennon RJ, Barsness GW, Pumper G, Hartman SJ, Rihal CS, Lerman LO and Lerman A. Lipoprotein-associated phospholipase A2 is an independent marker for coronary endothelial dysfunction in humans. Arterioscler Thromb Vasc Biol 2006; 26: 106-111.

[39] Fischer D, Rossa S, Landmesser U, Spiekermann S, Engberding N, Hornig B and Drexler H. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. Eur Heart J 2005; 26: 65-69.

[40] Greer JJ, Kakkar AK, Elrod JW, Watson LJ, Jones SP and Lefer DJ. Low-dose simvastatin improves survival and ventricular function via eNOS in congestive heart failure. Am J Physiol Heart Circ Physiol 2006; 291: H2743-2751.

[41] O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP; SOLID-TIMI 52 Investigators, Steen DL. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA 2014; 312: 1006-1015.

[42] Karabina S and Ninio E. Plasma PAFAH/PLA2G7 genetic variability, cardiovascular disease, and clinical trials. Enzymes 2015; 38: 145-155.