Moderately elevated lipoprotein (a) levels are associated with an earlier need for percutaneous coronary intervention in recurrent cardiovascular disease

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Abstract. A significant number of cardiovascular disease (CVD) patients, with the target lipid levels, as set by the guidelines, achieved, continue to remain at risk. In this setting, lipoprotein (Lp) a role in CVD prognosis is regaining interest. Although Lp(a) is related to the arteriosclerotic process, there is not currently an adequate amount of data for the inclusion of Lp(a) levels as a primary therapeutic target in the treatment of coronary artery disease (CAD) patients. In this framework, the current retrospective study aims to investigate the association of Lp(a) levels with the adverse cardiovascular (CV) events presented in a 10 year follow-up of CVD patients with dyslipidemia and its association with the major CV risk factors. A statistically significant reduction in Lp(a) levels was observed during the follow-up period (72.8±45.6 vs. 68.3±41.8 mg/dl; McNemar test; P<0.001). The vast majority of patients who suffered a new acute myocardial infarction during the follow up period had Lp(a) levels >30 mg/dl (24/28 patients, mean ± standard deviation Lp(a), 83.1±36.6 mg/dl, P=0.001). Kaplan-Meier survival analysis did not find statistically significant differences in a percutaneous coronary intervention (PCI) time occurrence during the follow-up period between patients with low (≤30 mg/dl) and high (>30 mg/dl) Lp(a) levels (log-rank P=0.305). On the other hand, when a second and third PCI conducted during the monitoring period were included in the Kaplan Meier analysis as events, the mean time for a PCI was significantly shorter (7.2%; P=0.01) for patients with Lp(a) levels >30 mg/dl. In conclusion, the current study reported that patients with high Lp(a) values are more prone to the occurrence of new myocardial infarction, while the Lp(a) cut-off value of 30 mg/dl was linked in CVD patients to an earlier need for PCI, especially in the most vulnerable group of patients with more than one (recurrent) revascularizations.

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Introduction

Lipoprotein (a) [Lp(a)] is a low-density, cholesterol-containing Lp, whose role in cardiovascular disease (CVD) is currently being re-evaluated. Lp(a) is different from other low-density lipoproteins, as its structure comprises apolipoprotein(a) attached to surface apolipoprotein B100 (1). Increasing evidence suggests that serum Lp(a) levels are genetically determined, remain unaltered for years on a given individual and are not affected by diet or exercise (2).

In clinical practice, a significant number of CVD patients, with the target lipid levels set by the guidelines achieved, continue to remain at risk. In this setting, Lp(a) role in CVD prognosis is regaining interest. In a large Japanese study, Lp(a) levels >30 mg/dl were reported to confer additional risk for worse prognosis after percutaneous coronary intervention (PCI), despite the fact that those patients had reached the target lipid levels according to current guidelines at the time the study was conducted, i.e., low-density lipoprotein (LDL) <100 mg/dl (3). It is notable that 90% of healthy Japanese present Lp(a) values <30 mg/dl (4).

Among acute myocardial infarction (AMI) patients submitted to primary PCI within 24 h of its onset, those with Lp(a) levels >40 mg/dl presented higher major adverse cardiac events (MACE), specifically cardiac death, myocardial infarction and/or revascularization during the following 5 years. Lp(a) levels were an independent predictor of revascularization of new coronary (non-culprit) lesions (5), while revascularization for new lesions was the main component driving MACE incidence.

Although Lp(a) is related to the arteriosclerotic process (6), there is currently no adequate amount of data for the inclusion of Lp(a) levels as a primary therapeutic target in the treatment of coronary artery disease (CAD) patients. In this framework, the current retrospective study aimed to investigate the association of Lp(a) levels with the adverse cardiovascular events presented in a 10 year follow-up of CVD patients with dyslipidemia and its association with the major cardiovascular risk factors.

Materials and methods

In the present retrospective cohort study, consecutive CVD patients, including CAD patients, who were monitored as outpatients at the lipidology clinic of the Onassis Cardiac Surgery Center for a period of ~10 years (2000-2010), were included. A total of more than 3,000 files were originally screened (Table I). Data collection was recorded at two distinct time intervals: at baseline and at the end of the follow-up period. Only patients with Lp(a) values recorded at both time intervals were enrolled in the study. Patients with fewer than 4 years follow-up sessions, as well as those who died during the monitoring period, were excluded. Age was not considered as an exclusion criterion (Fig. 1).

The current study was approved by the Ethics and Bioethics Committee of Onasseio Cardiac Surgery Center, Athens (reference no. 368/05.09.2008; Management Board approval 14.01.2009).

All study participants were informed in detail and agreed at the time of their evaluation to the publication of associated data as appropriate, fully respecting their anonymity and medical ethics.

Biochemical analysis. Almost all subjects in the study had had a complete determination of the lipid profile, which included, apart from Lp(a), levels of total serum cholesterol, high density lipoprotein (HDL)- and LDL-cholesterol, triglycerides, apolipoprotein A1 and apolipoprotein B 100 levels. Blood glucose levels, fibrinogen, homocysteine, and C-reactive protein (CRP) were also measured as part of the inflammatory profile of individuals with dyslipidemia and coronary heart disease.

Total cholesterol and triglycerides were determined by CHOD Abell-Kendall and Lipase/GPO-PAP enzyme chromatographic methods, respectively, using an automated biochemical analyzer, while LDL cholesterol, according to the Friedewald formula (triglycerides needed to be <400 mg/dl). HDL-C was enzymatically determined from the supernatant after precipitation of the remaining lipoproteins using phosphotungstic acid and magnesium chloride. Apolipoprotein A1, apolipoprotein B and CRP were calculated by an immunoenzymatic assay using nephelometry (mg/dl) and homocysteine by chemiluminescence.

All measurements were performed on Roche Integra Biochemical analyzer (Roche Diagnostics) with the commercially available kits (Roche). The laboratory is subject to external quality control Randox International Quality Assessment Scheme (RIQAS) of the company RANDOX with a monthly 'certificate of acceptable performance' and an ISO 9001 certificate.

For Lp(a) determination, all measurements were typically performed after an overnight fasting, the nephelometric method (INA) was applied with the help of particles coated with specific Lp(a) antibody (Dade Behring Marburg GmbH, USA) (7).

Statistical analysis. Continuous variables were expressed with the use of mean values and standard deviation, while nominal variables were expressed by frequencies and percentage frequencies. A paired samples t-test was used to identify differences between values of the same continuous variable at two different time points. Differences in mean values of different continuous variables were estimated with the use of independent samples t-test.

The Kruskal-Wallis non-parametric test followed by Dunn's test was used to compare differences between >2 groups of continuous non-normally distributed independent variables. Spearman's correlation coefficient was used to explore non-linear correlations, as depicted by Scatter plots, between two variables. McNemar test was used for the estimation of changes in independent variables between two measurements of the same variable. Graphical representation of continuous variables was made with the use of box plots and scatter plots. Kaplan-Meier survival curves were produced and the log-rank test was used to study the need (risk) for PCI over time (event of interest) in relation to Lp(a) levels. Statistical analysis was performed with the use of IBM SPSS Statistics 23 statistical package (IBM Corp.). $P<0.005$ was considered to indicate a statistically significant difference.

Results

Demographics, biochemical markers and treatment. A total of 860 CVD patients were finally enrolled in the study, including CAD patients and patients with high lipid levels. The demographics of the study population at baseline are summarized in Table I. It is worth noting that upon the end of the follow-up, smokers were reduced by 12.6%, with ex-smokers raising to 47.9% of all patients.

Biochemical markers levels at baseline and at the end of the follow-up are presented in Table II.

A statistically significant reduction in Lp(a) levels was observed during the follow up period (72.8±45.6 vs. 68.3±41.8 mg/dl; $P<0.001$), (Fig. 2).

Lp(a) levels according to anti-lipidemic treatment. Table III presents the anti-lipidemic treatment applied in the study population.

Lp(a) levels at baseline were higher with the use of statins (75.3±45.4 mg/dl) compared with the rest of the study population (both those with other anti-lipidemic treatment and those with no treatment) (54.1±40.3 mg/dl in the rest of the study population; $P=0.027$). Similar results were obtained at the end

Table I. Demographics, somatometrics and clinical history of the study population.

Parameter	Mean ± standard deviation		Range
Age			
Baseline	57.5±10.3		26-80
Follow-up	67.9±10.3		38-90
Height (cm)	170.1±8.7		150-191
Weight (kg)	79.6±13.4		52-115
Systolic blood pressure (mmHg)			
Baseline	132±14.2		100-170
Follow-up	132±12.2		100-176
Diastolic blood pressure (mmHg)			
Baseline	79.3±8.10		60.0-100
Follow-up	79.6±7.45		60.0-100
BMI (kg/m^2)	27.3±3.4		19.6-38.8
Sex			
Male (n, %)	628, 73.0		
Female (n, %)	232, 27.0		
Parameter	**Baseline**	**Follow-up**	**P-value**
Smoking (n, %)			
Yes	260, 30.2	108, 12.6	**0.015**
No	344, 40.0	340, 39.5	0.567
Ex-smoker	256, 29.8	412, 47.9	**0.009**
Xanthomas (n, %)	32, 3.7	40, 4.72	0.500[a]
Lp(a) (mg/dl) (± standard deviation)	104±31.5	95.5±36.4	
Intermittent claudication (n, %)	20, 2.32	52, 6.04	**0.039**[a]
Lp(a) (mg/dl) (± standard deviation)	91.3±31.9	76.4±66.0	
Arterial hypertension (n, %)	400, 47.6	492, 57.2	**0.005**[a]
Lp(a) (mg/dl) (± standard deviation)	71.3±44.3	63.7±41.3	
Diabetes mellitus (n, %)	116, 13.5	208, 24.2	**<0.001**[a]
Lp(a) (mg/dl) (± standard deviation)	73.6±44.3	59.9±37.1	
Myocardial infarction (n, %)	72, 8.4	100, 11.6	**<0.001**[a]
STEMI	44	51	
Non STEMI	28	49	
Lp(a) (mg/dl) (± standard deviation)	74±41.8	74.2±41.9	

STEMI, ST elevation myocardial infarction; P-value, comparison between baseline and follow-up values; [a]comparison between baseline and follow-up values with Mc Nemar test; statistically significant differences at P≤0.05 are highlighted in bold font.

of the follow-up period (Lp(a)=70.2±41.4 mg/dl in the statin group vs. 53.6±42.0 mg/dl; P=0.031). Fibrates and nicotinic acid derivatives lower Lp(a) levels at the end of the follow-up by ~10% with no statistical significance.

Lp(a) levels and clinical history of patients. The clinical history of the patients and the respective Lp(a) levels at the two monitored time intervals of the present study are also summarized in Table I. Patients that presented xanthomas increased non-statistically significantly by eight patients (0.9% of the patients) at the end of the follow-up period (McNemar test; P=0.5). Intermittent claudication diagnosis, on the other hand, was not verified in four (0.5%) of these patients in the second evaluation, but appears at another 32 patients (3.7%; McNemar test; P=0.039). New presentation of arterial hypertension at the end of the follow-up was reported for 92 patients (10.7%) (McNemar test; P=0.005), while another 92 patients were diagnosed with increased blood glucose levels at the second evaluation (diabetes mellitus, 24.2%) (McNemar test; P<0.001). The increase in the frequency of high blood pressure and diabetes mellitus at the end of the follow-up is statistically significantly associated with the Lp(a) levels at that time interval (bivariate correlation, P=0.02 and P=0.046, respectively), while there was no statistically significant correlation between the incidences of hypertension and diabetes and Lp(a) values or the change in Lp(a) values at baseline and at the end of the follow-up period.

Table II. Biochemical profile of the study population.

Parameter	No. of patients	Baseline values		Follow-up		P-value
		Mean	Standard deviation	Mean	Standard deviation	
Glucose (mg/dl)	856	98.4	15.9	104	19.7	**<0.001**
Creatinine (mg/dl)	664	1	0.3	1.6	3.9	0.054
Urea (mg/dl)	629	39	15.2	43	24	0.004
Uric acid (mg/dl)	524	6	1.7	6.1	1.4	0.459
Homocysteine (μmol/l)	480	13.7	5.6	11.3	3.3	**<0.001**
CRP (mg/l)	584	2.0	0.2	2.0	0.5	0.592
Total cholesterol[a] (mg/dl)	740	186.4	32.4	169.8	26.4	**<0.001**
Triglycerides[1] (mg/dl)	647	119	48.4	113.1	44.8	0.074
HDL[a] (mg/dl)	668	43.5	10.8	46.4	11.4	**<0.001**
LDL[a] (mg/dl)	664	117.6	28	101.8	23.4	**<0.001**
CPK (U/l)	513	99.1	52.7	109.8	54	**0.009**
Lp(a) (mg/dl)	860	72.8	45.2	68.3	41.8	**<0.001**

[a]Levels at baseline after initiation of therapy treatment; P-value, comparison between baseline and follow-up values; statistically significant differences at P≤0.05 highlighted in bold; the no. of patients represents the actual number of patients with data on the specific biochemical parameter in the patients records reviewed.

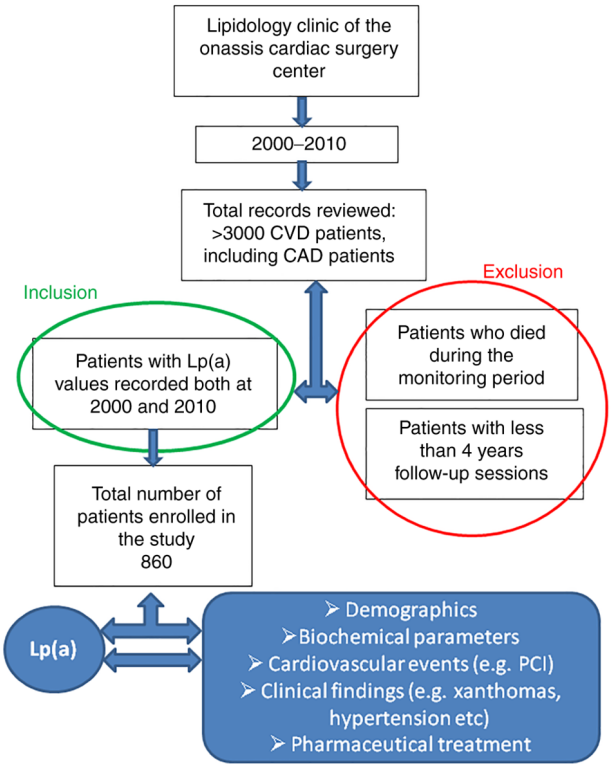

Figure 1. Study flow chart. Lp, lipoprotein.

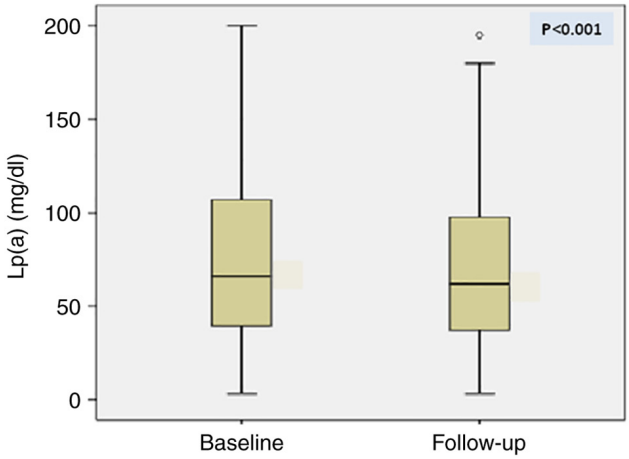

Figure 2. Lp(a) levels change between first and second measurement (paired samples t-test). Lp, lipoprotein.

Lp(a) correlations. Lp(a) levels both at baseline and at the end of the follow-up were weakly and negatively correlated with body mass index (BMI) (Spearman's correlation r=-0.171, P=0.022; r=-0.153, P=0.040, respectively; Fig. 3).

Lp(a) values correlation to biochemical and hematological measurements are presented in Table IV. Fasting glucose levels and hematocrit were significantly but weakly inversely correlated to Lp(a) values both at baseline and at the end of the follow up period. Total cholesterol and LDL levels were correlated significantly but not strongly to Lp(a) values both at baseline and at study end. No sex-related differences regarding Lp(a) levels were found in our study population.

Lp(a) levels and AMI, PCI. The vast majority of patients who suffered a new AMI during the follow up period had Lp(a) levels >30 mg/dl (24/28 patients, mean ± standard deviation Lp(a), 83.1±36.6, P=0.001). Women appeared to develop AMI later than men (58.8±8.02 vs. 50.6±9.08 years of age).

At baseline, patients already submitted to PCI (n=272) had significantly higher Lp(a) compared with the rest of study patients (83.4±45.1 vs. 67.7±44.5 mg/dl, P=0.016). Similar findings were observed at the end of the follow-up (PCI patients n=424, mean ± standard deviation, 76.7±41.8

Table III. Anti-lipidemic treatment applied in the study population.

Variable	Statins	Fibrates	Nicotinic acid derivatives/n-3 fatty acids	No treatment[a]
Number of patients treated	756	11	9	22
Co-administration	-	7[c]	9[c]	
Lp(a), mg/dl[b]	75.3±45.4	52.8±48.6	65.0±54.8	
Active substances (number of patients treated)	Atrovastatin (271) Simvastatin (280) Pravastatin (133) Fluvastatin (64) Rosuvastatin (8)	Bezafibrate (4) Fenofibrate (6) Gemfibrozil (1)	Acipimox (8) Eicosapentaenoic acid (1)	

[a]For 62 patients no relevant data on anti-lipidemic treatment were included in the reviewed records; [b]at baseline; [c]co-administered with statins.

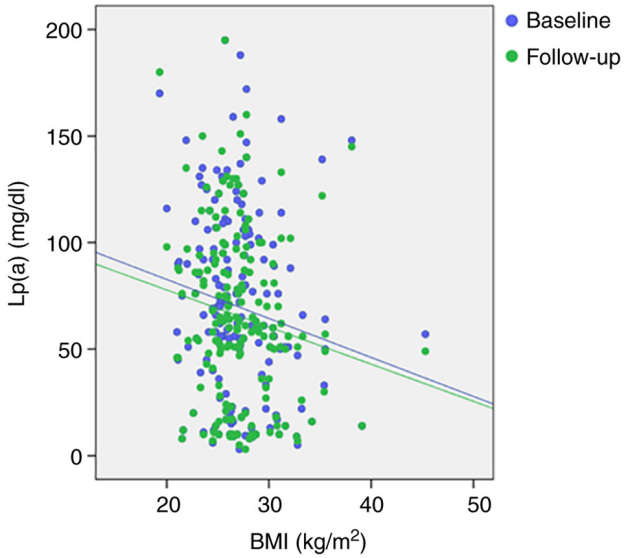

Figure 3. Correlation of Lp(a) with BMI (Spearman's correlation). Lp, lipoprotein.

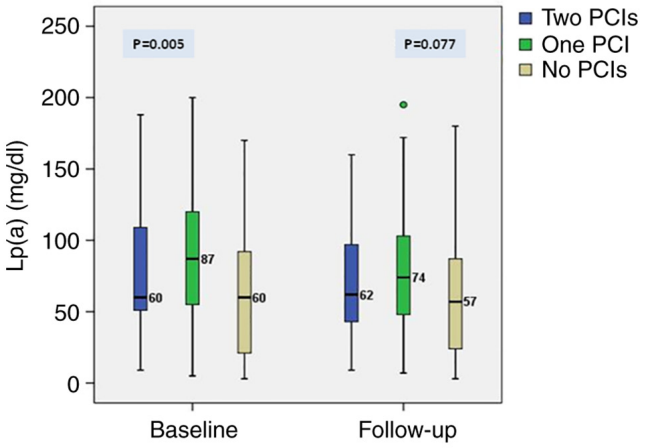

Figure 4. Lp(a) values differences in patients with previous history of no, 1 or 2 PCIs (Kruskal Wallis test followed by Dunn's test). Lp, lipoprotein, PCI, percutaneous coronary intervention.

vs. 64.1±41.3 mg/dl, P=0.038). At baseline Lp(a) levels were significant different between patient with a clinical history of one, two or no PCI in their clinical history. At study end, the said differences in Lp(a) seemed to be attenuated (Fig. 4).

Kaplan-Meier survival analysis. Kaplan-Meier survival analysis did not find statistically significant differences in the event time (occurrence of a PCI until the second evaluation) between patients with low Lp(a) levels (≤30 mg/dl compared with patients with higher Lp(a) levels (>30 mg/dl; log-rank P=0.305; Fig. 5). In addition, no significant differences were found by Kaplan-Meier survival analysis when the threshold for Lp(a) was set to 50 mg/dl (log-rank P=0.866). Even a higher Lp(a) cut-off value of 80 mg/dl did not lead to significantly different results in the time a PCI should occur (log-rank P=0.145) (data not shown).

On the other hand, Kaplan-Meier analysis for patients with at least one PCI in the monitoring period including as events in the analysis (second or third PCIs in the monitoring period), the mean event time for a PCI during the study period was significantly shorter (10.2 years vs. 11 years, P=0.01) for patients with Lp(a) levels >30 mg/dl (Fig. 6), suggesting that when taking into account the most vulnerable coronary patients with more than one PCI, Lp(a) values >30 mg/dl are associated with shorter need for revascularization.

Discussion

Mendelian randomization studies offer new evidence for Lp(a) role in promoting CVD (6,8). Genetic polymorphisms leading to increased Lp(a) levels are in fact associated with CVD and its adverse events, such as MI (9). The effects of anthropometric parameters and everyday activities on Lp(a) levels have also been studied. Reports of a non-fully explained rise of Lp(a) with diet and exercise exist in literature (10). At the same time, it is found that an interaction with additive effect exists between BMI and Lp(a) in the risk for a first MI (11). In the current study, Lp(a) levels decreased significantly during the follow-up period, while a weak inverse relationship was observed between Lp(a) levels and BMI.

Lp(a) is causally linked to atherosclerotic disease progression. Pathophysiology describes the ability of Lp(a)

Table IV. Correlation of Lp(a) levels with clinical parameters monitored during the study.

	Baseline Lp(α) values		Follow-up Lp (α) values	
Parameter	R_s[a]	P-value	R_s[a]	P-value
SBP (mmHg)	-0.004	0.954	-0.140	0.072
DBP (mmHg)	-0.047	0.503	-0.098	0.210
Fasting glucose (mg/dl)	**-0.151**	**0.027**	**-0.202**	**0.003**
Creatinine (mg/dl)	0.104	0.152	0.042	0.576
Urea (mg/dl)	-0.069	0.351	-0.004	0.957
Uric acid (mg/dl)	-0.081	0.334	0.063	0.457
Hematocrit (%)	**-0.202**	**0.003**	**-0.143**	**0.037**
Blood Platelets (per μl)	0.014	0.833	0.132	0.054
Homocysteine (μmol/l)	0.112	0.192	0.044	0.624
CRP (mg/l)	-0.021	0.790	0.007	0.931
Total cholesterol[b] (mg/dl)	**0.200**	**0.006**	**0.269**	**<0.001**
Triglycerides[b] (mg/dl)	0.028	0.706	-0.015	0.837
HDL[b] (mg/dl)	-0.061	0.415	-0.134	0.068
LDL[b] (mg/dl)	**0.218**	**0.003**	**0.287**	**<0.001**
Apolipoprotein A[b] (mg/dl)	0.061	0.562	0.014	0.968

[a]R_s, Spearman's rank correlation coefficient; [b]levels at baseline after initiation of therapy treatment; statistically significant differences at P≤0.05 highlighted in bold font.

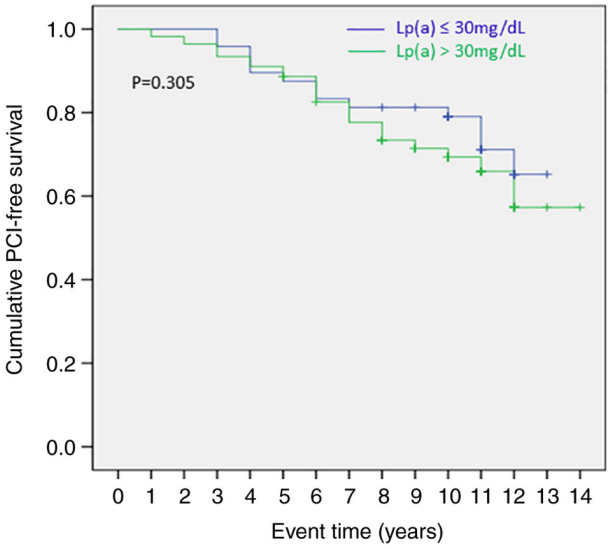

Figure 5. Kaplan Meier survival curve addressing the need of PCI of study patients based on their Lp(a) levels (cut-off Lp(a) value=30 mg/dl) (Kaplan Meier survival analysis). PCI, percutaneous coronary intervention; Lp, lipoprotein.

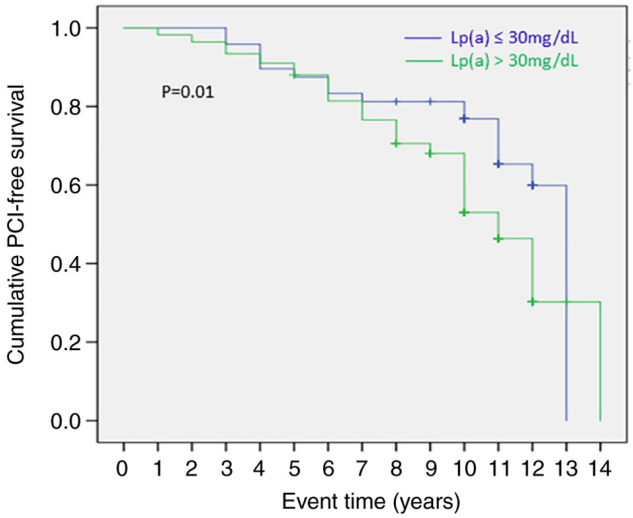

Figure 6. Kaplan Meier survival curve presenting time for at least 1 PCI (taking into account recurrent PCIs in the monitoring period) in study patients based on their Lp(a) levels (cut-off Lp(a) value=30 mg/dl) (Kaplan Meier survival analysis). PCI, percutaneous coronary intervention; Lp, lipoprotein.

to enter the vessel wall and accumulate in the macrophages along with cholesterol, thus leading to the formation of foam cells, fatty streaks and atherosclerotic plaques. At the same time, Lp(a) inactivates transforming growth factor and augments smooth muscle cell proliferation in atherosclerotic lesions (5,12).

Lp(a) ability to promote atherosclerosis is mediated also by oxidized phospholipids (OxPL) of which Lp(a) is the preferential carrier (13). The role of OxPL is thought to be crucial in plaque destabilization. OxPl are immunogenic and are found in atherosclerotic lesions. OxPL modify Lp(a) primarily by covalent binding to its unique apo(a) component and promote inflammation, endothelial dysfunction and calcification. Plaque vulnerability, evident by thin cap fibroatheroma, a state with augmented potential for plaque rupture, is linked to OxPL and Lp(a) presence. In advanced 'vulnerable' human carotid artery thin-cap fibroatheroma the 2 molecules were found to co-exist (14). At the same time Apo(a) possesses

unique properties leading to arterial wall inflammation and atherosclerosis progression (14).

Rapid angiographic progression of CAD could be attributed in part to Lp(a) as a study with repetitive coronary angiography on average 60 days from each other described (15). The partial structural homology of Lp(a) with plasminogen was pinpointed but also intracoronary plaque rupture and thrombosis through the plasminogen-like apo(a) moiety could be the missing link. Lp(a) preferentially enters and deposits to the vessel wall as a result of apo(a) binding to extracellular matrix proteins (16). An apolipoprotein(a) antisense oligonucleotide ended phase 2 trials showing promising results in safe reduction of Lp(a) (17). However today no drugs specifically aimed at lowering Lp(a) are currently clinically available (18). With the approval of the antisense oligonucleotide for clinical use, individuals with established CVD will probably be selected as the first recipients in an effort to minimize recurrent CVD events to them (19).

It is estimated that Lp(a) levels >25-30 mg/dl are present in ~30% of Caucasians and 60-70% of African Americans (i.e., 100,000,000 Americans) (14).

Regarding secondary vascular events in CAD patients, Lp(a) cut-off values as low as 19 mg/dl are important in discriminating patients with a higher probability of MACE for a follow-up period of 3 years post MI (20). Konishi *et al* (3) report that in patients on statin therapy undergoing PCI for the first time, lp(a) levels >21.5 mg/dl were linked to higher rates of MACE, namely cardiac mortality and acute coronary syndromes. In the present study, on the other hand, Lp(a) levels >30 mg/dl were significantly linked to an earlier need of revascularization, only when repeated revascularizations in the study monitoring period were included in the Kaplan Meier survival analysis. It is interesting to note that LDL levels in the study population of the present study were close enough to current guidelines at the time the study was conducted.

It is known that niacin and estrogens lower Lp(a) up to 30%, but that statins either have no effect or increase Lp(a) levels, occasionally significantly (21). In the current study, statin treatment led to higher Lp(a) levels both at baseline and at the end of the follow-up.

In the primary care setting, when the findings of two former large studies, the European Prospective Investigation of Cancer (EPIC)-Norfolk prospective population study and the Copenhagen City Heart Study (CCHS) prospective population study, were re-analyzed, at LDL-C levels below <96 mg/dl, the risk associated with elevated Lp(a) was attenuated (22). No significant interaction existed between corrected LDL and Lp(a) levels on CVD risk, thus meaning that both high Lp(a) and LDL levels contribute to CVD occurrence independently. It is interesting to note that in the said studies the cut-off Lp(a) of 50 mg/dl represents different percentile values: the 87th percentile in EPIC-Norfolk and the 80th percentile in CCHS cohort. In the current study with mean LDL values slightly over 100 mg/dl, different Lp(a) cut-off values were weakly able to discriminate progressive CAD evident by the need for revascularization.

New evidence from meta-analysis of large community trials suggests that a 10 mg/dl lower plasma Lp(a) was associated with a multifactorial adjusted hazard ratio for MACE of 0.96 (95% CI, 0.94-0.98) during 5 years of follow-up in patients with CVD (19). In addition, in the most recent Plaque at RISK study, patients with symptomatic carotid artery stenosis were characterized by increased Lp(a) which was associated with degree of stenosis and other vulnerable plaque characteristics (23).

In conclusion, the current study reported that patients with high Lp(a) values are more prone to the occurrence of 5 MI, while the Lp(a) cut-off value of 30 mg/dl is linked in CVD patients to an earlier need for PCI, especially in the most vulnerable group of patients with more than one (recurrent) revascularizations.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AH and KT organized and performed the research, collected relevant information, wrote the manuscript and performed overall project management. AH and GK confirm the authenticity of all the raw data. CT performed the statistical analysis, data assessment and manuscript preparation. GK, AV, IH and DAS performed the statistical analysis and the evaluation of the results, and were involved in the preparation and writing of the research article. HM, ME and ST reviewed the manuscript and comprehensively assessed the study design and the data analysis, prepared and wrote the manuscript, organized the references and reviewed the current study. All authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

The current study was approved by the Ethics and Bioethics Committee of Onasseio Cardiac Surgery Center, Athens (reference no. 368/05.09.2008; Management Board approval 14.01.2009). All procedures were in accordance with the ethical standards of the patient's evaluation reports (institutional and national) and in agreement with the Helsinki Declaration of 1964 and later versions. All the data were original, used in the current study with anonymity and confidentiality. Informed consent was obtained from all study participants at the time of their evaluation. All study participants were informed in detail and agreed at the time of their evaluation to the publication of associated data as appropriate, fully respecting their anonymity and medical ethics.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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