Internal and Emergency Medicine (2019) 14:621–625
https://doi.org/10.1007/s11739-019-02082-8

CE - RESEARCH LETTER TO THE EDITOR

Impact of lipoprotein(a) levels on recurrent cardiovascular events in patients with premature coronary artery disease

Felice Gragnano[1,2] · Fabio Fimiani[2] · Marco Di Maio[2] · Arturo Cesaro[1,2] · Giuseppe Limongelli[2] · Davide Cattano[3] · Paolo Calabrò[1,2]

Received: 18 February 2019 / Accepted: 25 March 2019 / Published online: 30 March 2019

Keywords Lipoprotein(a) · Dyslipidemia · Acute coronary syndrome · Coronary artery disease · Percutaneous coronary intervention

Introduction

Lipoprotein(a) [Lp(a)] is an independent risk factor for atherosclerotic cardiovascular disease, acting by either accelerating atherosclerosis progression or inducing a prothrombotic/antifibrinolytic systemic milieu [1–3]. Several studies support the relevant role of Lp(a) in the occurrence of coronary events, especially in patients with premature coronary artery disease (CAD) [4–6]. However, the association of elevated Lp(a) levels with the risk of recurrent cardiovascular events in patients with a prior coronary event optimally treated with statins remains controversial [7]. We sought to assess the impact of Lp(a) levels on the recurrence of cardiovascular events in patients with premature CAD treated with percutaneous coronary intervention (PCI).

Methods

This prospective single-center study enrolled consecutive young patients (aged less than 50 years) undergoing first-ever PCI for stable CAD (SCAD) or acute coronary syndrome (ACS) (both ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation acute coronary syndrome [NSTE-ACS]), from 2013 to 2017. As Lp(a) can behave as an acute-phase reactant, patients were screened for Lp(a) in clinically stable conditions at least 8 weeks after PCI, by blood samples collected after 12 h fasting. Lp(a) was measured at a single core laboratory using enzyme-linked immunosorbent assay, as previously reported [8]. Lp(a) concentration was reported in mg/dL, and a serum concentration ≥ 30 mg/dL was considered elevated [9]. Based on Lp(a) concentration, the study population was divided into three groups defined as 'normal' (< 30 mg/dL), 'high' (≥ 30 and < 60 mg/dL), or 'very high' (≥ 60 mg/dL) Lp(a). All patients were followed up with clinical visits or phone contact until June 2018. To evaluate the recurrence of major cardiovascular events at follow-up in the three study groups, a survival analysis was performed. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, stroke, coronary revascularization, and hospitalization for cardiovascular causes. Secondary endpoints consisted of the individual components of the primary endpoint. We analyzed categorical variables by Chi square test or Fisher test, and continuous data by *t* test, ANOVA, and Mann–Whitney *U* test (as appropriate). Survival analysis was performed with Cox regression and log-rank test. Event rates were expressed as event per person-years. p values < 0.05 (two-tailed) were considered significant. Analyses were performed using R (R Foundation for Statistical Computing). The study protocol followed ethical guidelines of the Helsinki Declaration, and informed consent was obtained from all participants.

Results

We prospectively evaluated 63 consecutive patients with premature CAD undergoing PCI, receiving a diagnosis of SCAD (14.3%), STEMI (61.9%), or NSTE-ACS (23.8%).

✉ Paolo Calabrò
paolo.calabro@unicampania.it

1 Division of Cardiology, A.O.R.N. Sant'Anna e San Sebastiano, F. Palasciano, 81100 Caserta, Italy

2 Division of Cardiology, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", L. Bianchi 1, 80131 Naples, Italy

3 McGovern Medical School, UTHealth at Houston, 6431 Fannin, Houston, TX 77030, USA

Mean follow-up was 3.4 years, not differing among study groups ($p = 0.248$). Population baseline and procedural characteristics are detailed in Table 1. None of the patients was on lipid-lowering therapy before the qualifying PCI. At the time of blood samples for Lp(a), all patients were on optimal medical therapy, receiving high-dose statins, ezetimibe, and fibrates in 100%, 11.1% and 6.3% of cases, respectively. In the overall population, mean Lp(a) levels were 31.3 mg/dL (median 22.0 mg/dL; interquartile range: 6.00-54.5), resulting elevated (≥ 30 mg/dL) in 42.9% of patients. Based on Lp(a) concentration, 57.1% of patients were allocated to 'normal' Lp(a) (< 30 mg/dL), 23.8% to 'high' Lp(a) (≥ 30 mg/dL and < 60 mg/dL), and 19.1% 'very high' Lp(a) (≥ 60 mg/dL) groups. The event rates (expressed as event per person-years) during follow-up was 0.023, 0.054, and 0.226 for 'normal', 'high' Lp(a), and 'very high' Lp(a) groups, respectively. Survival analysis showed a significantly higher rate of primary endpoint events in patients with 'very high' Lp(a) compared with those with 'normal' Lp(a) [hazard ratio (HR) 9.91; 95% CI 2.53–38.84; $p < 0.001$], but no significant difference between patients with 'high' versus 'normal' Lp(a) [(HR 2.36, 95% CI 0.47–11.76); $p = 0.284$)] (p value for log-rank test < 0.001). The Kaplan–Meier estimates showed a 2-year event-free survival rate for primary endpoint of 91.1% in 'normal' Lp(a) (95% CI 82.0–100%; 3 follow-up

Table 1 Population baseline and procedural characteristics

	Overall population $N = 63$	Normal Lp(a) (< 30 mg/dL) $n = 36$ (57.1%)	High Lp(a) (≥ 30 and < 60 mg/dL) $n = 15$ (23.8%)	Very high Lp(a) (≥ 60 mg/dL) $n = 12$ (19.1%)	p value
Age	42.94 ± 4.6	43.4 ± 5.2	42.8 ± 4.1	41.7 ± 3.4	0.286
Body mass index	28.7 ± 5.3	28.4 ± 5.6	30.1 ± 4.0	28.1 ± 6.0	0.871
Male sex	54 (85.7%)	32 (88.9%)	13 (86.7%)	9 (75.0%)	0.489
Smokers	41 (65.1%)	27 (75.0%)	8 (53.3%)	6 (50.0%)	0.160
Previous smokers	9 (14.3%)	4 (11.1%)	3 (20.0%)	2 (16.7%)	0.687
Diabetes	6 (9.5%)	1 (2.8%)	2 (13.3%)	3 (25.0%)	0.064
Hypertension	35 (55.6%)	19 (52.8%)	11 (73.3%)	5 (41.7%)	0.226
Dyslipidaemia	23 (35.9%)	10 (27.8%)	8 (53.3%)	4 (33.3%)	0.217
Familiar history of coronary disease	35 (55.6%)	18 (50.0%)	10 (66.7%)	7 (58.3%)	0.538
Chronic kidney disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
TOT-C (mg/dL)	181.3 ± 60.1	181.9 ± 70	194.4 ± 36.7	163.2 ± 49.5	0.530
LDL-C (mg/dL)	119.5 ± 52.9	121.1 ± 62.7	128.9 ± 31.7	103.2 ± 39.7	0.453
HDL-C (mg/dL)	41.1 ± 13.9	40.1 ± 12.9	42.7 ± 14.0	42.0 ± 17.2	0.597
Triglycerides (mg/dL)	135.8 ± 62.0	136.1 ± 60.0	140.3 ± 65.1	119.3 ± 65.3	0.592
STEMI	39 (61.9%)	24 (66.7%)	9 (60.0%)	6 (50.0%)	0.580
NSTE-ACS	15 (23.8%)	9 (25.0%)	2 (13.3%)	4 (33.3%)	0.464
SCAD	9 (14.3%)	3 (8.3%)	4 (26.7%)	2 (16.7%)	0.226
Treated vessels	63 (100%)	36 (100%)	15 (100%)	12 (100%)	–
LAD	39 (60.9%)	21 (58.3%)	9 (60%)	9 (75.0%)	0.580
RCA	26 (41.3%)	14 (38.9%)	7 (46.7%)	5 (41.7%)	0.879
LCX	15 (23.8%)	8 (22.2%)	4 (26.7%)	3 (25.0%)	0.938
LM	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Multi-vessel disease	17 (27.0%)	8 (22.2%)	4 (26.7%)	5 (41.7%)	0.421
Number of stents					
0	3 (4.8%)	3 (8.3%)	0 (0%)	0 (0%)	0.307
1	30 (47.6%)	16 (44.4%)	7 (46.7%)	7 (58.3%)	0.704
2	18 (28.6%)	9 (25.0%)	5 (33.3%)	4 (33.3%)	0.769
3	10 (15.9%)	6 (16.7%)	3 (20.0%)	1 (8.3%)	0.698
4	2 (3.2%)	2 (5.6%)	0 (0%)	0 (0%)	0.461

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *STEMI* ST-segment elevation myocardial infarction, *NSTE-ACS* non-ST-segment elevation acute coronary syndromes, *SCAD* stable coronary artery disease, *LAD* left anterior descending artery, *RCA* right coronary artery, *LCX* left circumflex artery, *LM* left main coronary artery, *TOT-C* total cholesterol

events), 79.4% in 'high' Lp(a) (95% CI 61.2–100%; 3 follow-up events), and 45.7% in 'very high' Lp(a) (95% CI 23.9–89%; 9 follow-up events) groups (Fig. 1). Results for secondary endpoints are reported in Table 2. An additional survival analysis, including Lp(a) as a continuous variable, confirmed that Lp(a) was an independent predictor of primary endpoint in the overall population (HR 1.03, 95% CI 1.01–1.04; p value = 0.003), and in STEMI patients (HR 1.03, 95% CI 1.01–1.05; p value = 0.006), but not in NSTE-ACS (HR 1.03, 95% CI 0.99–1.06; p value = 0.126) nor SCAD patients (HR 1.00, 95% CI 0.93–1.07; p value = 0.909).

Discussion

In the present study, we investigated the prognostic impact Lp(a) in patients with premature CAD treated with PCI. We showed that elevated Lp(a) can be found in a not negligible proportion of patients with premature CAD, while very high Lp(a) levels (above the threshold of 60 mg/dL) was associated with a higher recurrence of cardiovascular events compared with lower levels. Our findings suggest the importance of Lp(a) measurement in young 'high-risk' patients to improve risk stratification, and potentially influence dedicated therapeutic strategies (i.e.,

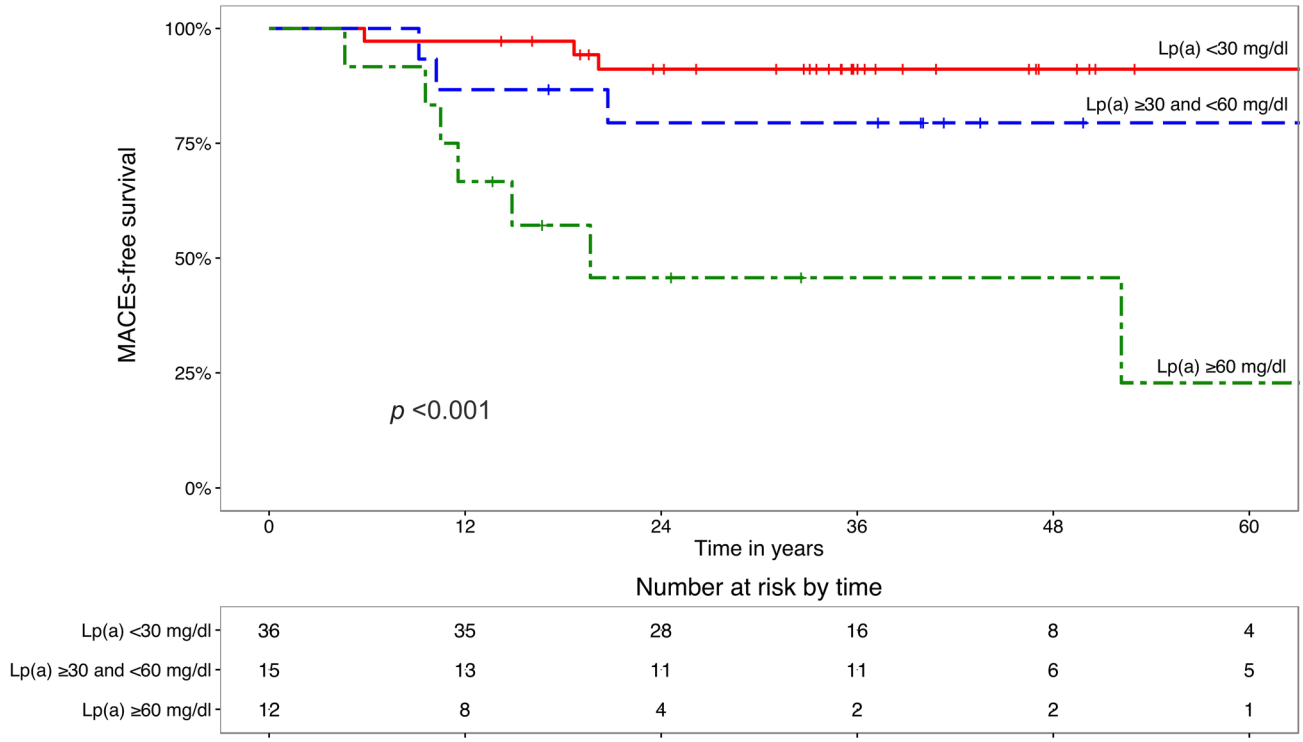

Fig. 1 Event-free survival curves for the primary endpoint. The study population was divided into three groups defined as 'normal' (< 30 mg/dL), 'high' (≥ 30 and < 60), and 'very high' (≥ 60 mg/dL) Lp(a) levels

Table 2 Event-free survival rates at 2-year follow-up for primary and individual secondary endpoints

	Primary endpoint	Death (%)	Stroke (%)	Myocardial infarction	Coronary revascularization	Rehospitalisation for cardiovascular cause
Lp(a) < 30 mg/dL	91.1% [95% CI 82.0–100]	100	100	100%	100%	91.1% [95% CI 82.0–100]
Lp(a) ≥ 30 and < 60 mg/dL	79.4% [95% CI 61.2–100]	100	100	100%	100%	79.4% [95% CI 61.2–100]
Lp(a) ≥ 60 mg/dL	45.7% [95% CI 23.5–89.0]	100	100	72.7% [95% CI 45.2–100]	55.4% [95% CI 30.1–100]	82.5% [95% CI 63.1–100]

lipoprotein apheresis). Several considerations can be made regarding secondary endpoints analysis. First, no cardiovascular death occurred probably due to the young age of patients; a more extended follow-up might be necessary to detect differences in mortality. Second, 'hard' coronary events (namely new myocardial infarction and/or coronary revascularization), exclusively occurred in patients with Lp(a) higher than 60 mg/dL. Patients with lower Lp(a), only experienced hospitalization for cardiovascular cause without receiving any coronary interventions, possibly suggesting a lower risk for CAD progression. Moreover, a sub-group analysis confirmed Lp(a) as an independent predictor of outcomes in STEMI, but not in NSTE-ACS and SCAD patients. This result probably led the low number of patients and events in each sub-group, although a different prognostic impact of Lp(a) per clinical presentation cannot be excluded. Numerous studies indicated Lp(a) as an independent risk factor for atherosclerotic disease [1, 5, 10], and similar to low-density lipoprotein cholesterol (LDL-C), this relation seemed to be continuous [4, 9]. However, evidence on the prognostic role of Lp(a) in patients with previous coronary events treated with optimal medical therapy (mainly statins) remains conflicting [7, 9]. A recent study-level analysis of three large trials suggested that high Lp(a) levels were similarly associated with a higher residual cardiovascular risk in patients on statins and with controlled LDL-C [9]. Conversely, a case–cohort analysis of the dal-Outcomes trial failed to demonstrate any associations between Lp(a) and the risk of recurrent cardiovascular events [7], questioning the use of specific Lp(a)-lowering therapies in patients on statins. In the dal-Outcomes trial [7], mean patients' age was 63 years, possibly masking (at least in part) the impact of Lp(a) on outcomes. Indeed, in a previous study, elevated Lp(a) (> 50 mg/dL) was associated with a significant threefold increase in the risk of coronary events in patients aged less than 45 years [5]. However, this association was weaker (twofold increased risk) in individuals with 45–60 years and entirely abolished after 60 years, suggesting a negative trend with aging [5]. In line with these results, our data showed a significant impact of Lp(a) on the recurrence of events in patients with a premature CAD, suggesting an 'age dependency' in the effect of Lp(a) on cardiovascular outcomes. Recent guidelines highlighted the importance of Lp(a) testing in patients with early cardiovascular disease presentation, to quantify more accurately their risk [11]. Our results confirm the relevance of Lp(a) screening in patients with premature CAD to stratify the risk of future events further and potentially identify candidates to Lp(a)-lowering strategies. In recent years, a growing awareness has emerged in the importance of developing effective Lp(a)-lowering drugs. Oral lipid-lowering medications demonstrated modest effects in lowering the Lp(a) levels [9], and only niacin showed to reduce Lp(a) of ~ 30% [9]. Recent reports also indicated a ~ 30% reduction in Lp(a) levels with the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [12, 13]. To date, lipoprotein apheresis is the only treatment reporting consistent Lp(a) levels reduction and potential benefits on cardiovascular outcomes [14]. However, in young patients with hyperlipoproteinemia, the decision to undergo apheresis is of great psychological and social impact, and informing patients requires the knowledge of principles of informative counseling. Novel antisense oligonucleotides targeting apolipoprotein(a) showed a potent Lp(a)-lowering effect (60–90% reduction) and this sounded promising for the future [15], but additional data are needed to confirm their efficacy and safety.

Our study has several limitations. First, the modest sample size (due to the difficulties in recruiting these special patients), and single-center design might be potential sources of bias, limiting the generalizability of our results. Second, other risk factors for premature CAD (including homocysteine, and genetic prothrombotic risk factors) were not evaluated, but evidence suggests that they have only a minor contribution in the development of early CAD [4, 5]. Third, Lp(a) measurements were performed in patients on lipid-lowering therapy. Although this approach might have influenced Lp(a) levels, their impact on Lp(a) concentration is relatively modest as discussed.

In conclusion, our findings suggest that elevated levels of Lp(a) can be detected in a consistent proportion of patients with premature CAD undergoing PCI in real-world practice. Moreover, 'very high' Lp(a) levels (above the threshold of 60 mg/dL) showed a significant association with recurrent cardiovascular events in these patients, mainly due to new myocardial infarction and coronary revascularization. Hence, systematic screening for elevated plasma Lp(a) can help clinicians in the understanding and management of patients with premature coronary atherosclerosis by (1) improving prognostic assessment; (2) intensifying the control of traditional risk factors; and (3) proposing additional Lp(a)-lowering treatment, including lipoprotein apheresis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The study was carried out according to Declaration of Helsinki.

Informed consent Patients gave their informed consent to participate to the study.

References

1. Ferretti G, Bacchetti T, Johnston TP et al (2018) Lipoprotein(a): a missing culprit in the management of athero-thrombosis? J Cell Physiol 233:2966–2981. https://doi.org/10.1002/jcp.26050
2. Gragnano F, Calabrò P (2018) Role of dual lipid-lowering therapy in coronary atherosclerosis regression: evidence from recent studies. Atherosclerosis 269:219–228. https://doi.org/10.1016/j.atherosclerosis.2018.01.012
3. Fogacci F, Cicero AF, D'Addato S, D'Agostini L, Rosticci M, Giovannini M, Bertagnin E, Borghi C, Brisighella Heart Study Group (2017) Serum lipoprotein(a) level as long-term predictor of cardiovascular mortality in a large sample of subjects in primary cardiovascular prevention: data from the Brisighella Heart Study. Eur J Intern Med 37:49–55. https://doi.org/10.1016/j.ejim.2016.08.018
4. Scanu AM (1992) Lipoprotein(a): a genetic risk factor for premature coronary heart disease. JAMA, J Am Med Assoc 267:3326–3329. https://doi.org/10.1001/jama.267.24.3326
5. Rallidis LS, Pavlakis G, Foscolou A et al (2018) High levels of lipoprotein (a) and premature acute coronary syndrome. Atherosclerosis 269:29–34. https://doi.org/10.1016/j.atherosclerosis.2017.12.011
6. Marcucci R, Brunelli T, Fedi S et al (2005) Relevance of post-methionine homocysteine and lipoprotein (a) in evaluating the cardiovascular risk in young CAD patients. Eur J Clin Invest 35:1–7. https://doi.org/10.1111/j.1365-2362.2005.01439.x
7. Schwartz GG, Ballantyne CM, Barter PJ et al (2018) Association of lipoprotein(a) with risk of recurrent ischemic events following acute coronary syndrome: analysis of the dal-outcomes randomized clinical trial. JAMA Cardiol 3:164–168. https://doi.org/10.1001/jamacardio.2017.3833
8. Milionis HJ, Filippatos TD, Loukas T et al (2006) Serum lipoprotein(a) levels and apolipoprotein(a) isoform size and risk for first-ever acute ischaemic nonembolic stroke in elderly individuals. Atherosclerosis 187:170–176. https://doi.org/10.1016/j.atherosclerosis.2005.08.036
9. Tsimikas S (2017) A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol 69:692–711. https://doi.org/10.1016/j.jacc.2016.11.042
10. Chiarugi L, Prisco D, Antonucci E et al (2001) Lipoprotein (a) and anticardiolipin antibodies are risk factors for clinically relevant restenosis after elective balloon percutaneous transluminal coronary angioplasty. Atherosclerosis 154:129–135
11. Catapano AL, Graham I, De Backer G et al (2016) 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 37:2999–3058l. https://doi.org/10.1093/eurheartj/ehw272
12. Shapiro MD, Minnier J, Tavori H, Kassahun H, Flower A, Somaratne R, Fazio S (2019) Relationship between low-density lipoprotein cholesterol and lipoprotein(a) lowering in response to PCSK9 inhibition with evolocumab. J Am Heart Assoc 8:e010932. https://doi.org/10.1161/JAHA.118.010932
13. Gragnano F, Natale F, Concilio C et al (2018) Adherence to proprotein convertase subtilisin/kexin 9 inhibitors in high cardiovascular risk patients: an Italian single-center experience. J Cardiovasc Med 19:75–77. https://doi.org/10.2459/JCM.0000000000000611
14. Schettler VJJ, Neumann CL, Peter C et al (2017) Current insights into the German lipoprotein apheresis registry (GLAR)—almost 5 years on. Atheroscler Suppl 30:50–55. https://doi.org/10.1016/j.atherosclerosissup.2017.05.006
15. Viney NJ, van Capelleveen JC, Geary RS et al (2016) Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet 388:2239–2253. https://doi.org/10.1016/S0140-6736(16)31009-1