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Lipoprotein (a)—We Know So Much Yet Still Have Much to Learn . . .

Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA

Lipoprotein(a) (Lp[a]) has been identified as an independent, causal risk factor for cardiovascular disease (CVD).[1,2] Lp(a) has a structure similar to low-density lipoprotein (LDL) in its lipid core composition in addition to a molecule of apolipoprotein B_{100} (apoB), but also contains a unique glycoprotein—apo(a), with strong structural homology with plasminogen.[2] Apo(a) contains anything from 3, to more than 50 identically repeated plasminogen-like kringle IV domains, which gives rise to the heterogeneity in isoform size reported in the population.[3] There is a general inverse correlation between the size of the apo(a) isoform and the Lp (a) plasma concentration.[2,3] The variation in the concentration of Lp(a) is primarily controlled by the level of synthesis rather than catabolism, with as much as 90% of the variation being genetically determined based on variation in the gene encoding apo(a) (*LPA*) located on chromosome 6q26-27.[3,4]

The mechanism and sites of Lp(a) catabolism still remain obscure.[2,3] Uptake via the LDL receptor (LDLR) may not be a major pathway of Lp(a) metabolism (however, the studies in familial hypercholesterolemia patients with null LDLR allele confirmed the important role of the receptor), and very low-density lipoprotein receptor, LDL receptor-related protein 1, megalin/gp33018, scavenger receptor class B type 1, and plasminogen receptors might also play an important role.[3] The catabolism pathway of Lp(a) is therefore mainly sustained by the liver, spleen, and kidney.[3,4] Lp(a) concentrations are also dependent on the rate of hepatic apo(a) and $apoB_{100}$ secretion, what might also be the mechanism (together with the metabolism with LDLR) responsible for the Lp(a) reducing effect of proprotein convertase subtilisin/kexin type 9 inhibitors.[3,5]

Aside from its role as a recognized independent CVD biomarker, the physiological function of Lp(a) still is not completely understood.[1–4,6] Because of its structural similarity to plasminogen and tissue plasminogen activator, it competes with plasminogen for its binding site, leading to reduced fibrinolysis, and as a result of the stimulation of secretion of plasminogen activator inhibitor-1, Lp(a) leads to thrombogenesis.[1–3] Lp(a) also carries cholesterol and binds atherogenic proinflammatory oxidized phospholipids, which attract inflammatory cells to vessel walls and leads to smooth muscle cell proliferation. In consequence, Lp(a) strongly contributes to the process of atherogenesis.[1–4]

Despite the recognition of the role of Lp(a) as an independent risk factor of CVD events, irrespective of other coexisting risk factors, physician knowledge regarding Lp(a) is limited. Consequently, Lp(a) is measured infrequently. One of the reasons for this is associated with the lack of clear recommendation associated with the Lp(a) cut-off values, another relates to the cost and difficulties associated with diagnostic methods, and a third reason is the lack of recommendations on management and therapy of patients with high levels of this biomarker.[2,6] The first guideline relating to the management of high levels of Lp(a) was the Consensus Paper of European Society of Atherosclerosis (EAS; 2010).[2] The authors recommended the measurement of Lp(a) once in all subjects at intermediate or high risk of CVD/CHD who present with premature CVD and/or familial hypercholesterolemia, a family history of premature CVD and/or elevated Lp(a), recurrent CVD despite statin treatment, ≥3% 10-year risk of fatal CVD, and ≥10% 10-year risk of fatal and/or nonfatal CHD.[2] They suggested repeat measurement only if treatment for high Lp(a) levels is initiated, in order to evaluate the therapeutic response. For reduction of plasma Lp(a) as a secondary priority after reduction in low-density lipoprotein cholesterol (LDL-C), the experts recommended a desirable level below 50 mg/dL.[2] Almost at the same time (2011) the experts from the National Lipid Association presented a comprehensive study on the utility of the selected biomarkers in CVD risk stratification.[6] The authors suggested that initial Lp(a) measurement before the therapy might be considered in selected patients with intermediate

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From the Department of Hypertension, Chair of Nephrology and Hypertension and Healthy Aging Research Centre (HARC), Medical University of Lodz, Poland; Polish Mother's Memorial Hospital Research Institute, Lodz, Poland.

Correspondence to: Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA, Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland. E-mail: maciejbanach@aol.co.uk

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risk (5–20% 10-year CHD event risk) or CHD or a CHD equivalent. They also suggested measurement would be reasonable for many patients with a family history of premature CHD or in patients with established CHD with a history of recurrent events despite appropriate therapy.[6] Having access to the Lp(a) measurements of patients already on treatment may be useful when considering on-treatment management decisions in selected patients with CHD (or a CHD risk equivalent), premature family history, or a history of recurrent coronary events.[6] Both of these recommendations started the discussion on Lp(a), which has become even louder within the context of trials of cholesteryl ester transfer protein and proprotein convertase subtilisin/kexin type 9 inhibitors, which are very effective at lowering Lp(a) concentrations.[5] This discussion is increasingly important as we see more and more patents with complex dyslipidemias, including elevated Lp(a), as well as individuals with isolated Lp(a) elevations, who are at high and very high cardiovascular risk, and we need to consider suitable management for these patients.[2,6]

Interestingly, in addition to the role of high Lp(a) levels in various vascular diseases, low concentrations also seem to be important in vascular medicine.[7] Some authors have suggested the existence of a *J-curved* phenomenon for Lp(a) concentration with a slight increase of cardiovascular and cerebrovascular outcomes in the group of patients with very low levels and a larger increase in the group of patients with significantly increased Lp(a) levels.[7] Available studies have also suggested that decreased values of Lp(a) have been associated with carotid atherosclerosis and have been proposed as markers of cerebral hemorrhage risk.[8] There are several hypotheses relating to this phenomenon: one associated with the induction of angionecrosis and impaired nutritional metabolism within the vessels, another with the impaired metabolism of scavenging oxidized lipids.[8] On the other hand, elevated Lp(a) has been confirmed as a causal factor for CVD including myocardial infarction, and aortic stenosis.[1–4,6] Some studies have also suggested its important role in patients with abdominal aortic aneurysm (AAA).[9] In the recent Lipid and Blood Pressure Meta-analysis Collaboration Group meta-analysis, Kotani et al[9] aimed to evaluate the association between circulating Lp(a) levels and the presence of AAA. Meta-analysis of 9 studies showed that patients with AAA were found to have a significantly higher level of Lp(a) compared to the controls (standard mean deviation: 0.87, 95% CI: 0.41–1.33, $P<0.001$), which might suggest the causality of high Lp(a) with the presence of AAA.[9]

Taking the abovementioned into account, the study by Afshar et al[10] in this issue of the *Journal of the American Heart Association* (*JAHA*) is of special interest and importance. The authors verified the current recommendations for Lp(a) and suggested that treatment should focus on the control of other risk factors first, including lowering LDL-C, and assumed that identifying interactions between Lp(a) and other risk factors could identify individuals at increased risk for Lp(a)-mediated disease.[10] They included 939 participants at median age of 49 (range 18–55) from the GENdEr and Sex determInantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary Syndrome (GENESIS-PRAXY) study.[10] The study population included individuals who developed symptoms consistent with acute cardiac ischemia within the first 24 hours of hospital admission. These individuals were considered to have an acute coronary syndrome (ACS), which included unstable or intermediate coronary syndromes and/or acute myocardial infarction. The authors showed a higher prevalence of elevated Lp(a) levels (>50 mg/dL) in study participants as compared to the general population from the Copenhagen General Population Study (31% versus 20%; $P=1.643e-10$). Lp(a) was strongly associated with LDL-C (adjusted β 0.17; $P=2.072e-5$), and individuals with high Lp(a) were more likely to have LDL-C >2.5 mmol/L, indicating a synergistic interaction (adjusted odds ratio 1.51; 95% CI 1.08–2.09; $P=0.015$). The interaction with high Lp(a) was stronger at increasing LDL-C levels (LDL-C >3.5, adjusted odds ratio 1.87; LDL-C >4.5, adjusted odds ratio 2.72), and became attenuated at LDL-C ≤3.5 mmol/L (OR 1.16; $P=0.447$). No other risk factors investigated, such as age, sex, smoking, hypertension, diabetes, familial hypercholesterolemia, and body mass index were associated with high Lp(a).[10] The authors confirmed that in relatively young ACS patients (<55 years), high Lp(a) was strongly associated with high LDL-C levels, and Lp(a) confers greater risk for premature ACS when LDL-C is elevated. Therefore, especially in individuals with high Lp(a) (>50 mg/dL) and concomitant elevations in LDL-C >3.5 mmol/L, intensive LDL-C lowering may be warranted to reduce the risk of premature ACS.[10] Obviously this study needs to be confirmed in larger well-designed controlled trials; however, even based on these results, we can say that Lp(a) might be an important predictor of premature ACS in young patients with cardiovascular risk.[10] This study clearly confirms that elevated Lp(a) might often be present in relatively young individuals without any other important risk factors. Thus, it is always extremely important to ask patients about family history of CHD. The authors also demonstrated that Lp(a) appears to be strongly associated with LDL-C in young ACS cases, confirming the physiological link between Lp(a) and LDL/LDLR, and emphasizing the potential importance of LDL-C in these patients.[10] Finally, taking into account that previous studies have confirmed that Lp(a) and LDL-C are not associated in the general population, the authors' finding that Lp(a) and LDL-C are strongly associated in young ACS individuals suggest that Lp(a) excess may promote initiation and early development of atheromatous plaques, which may be accelerated by the

presence of a high level of LDL-C (especially above 3.5 mmol/L).[10]

In addition to the discussion about the role of Lp(a) as an important biomarker of CVD, we are faced with the very great challenge of treating patients with high Lp(a) levels. Currently, the appropriate management of high Lp(a) is not known and there are limited therapeutic options to lower Lp(a) directly.[2,6] Niacin reduces Lp(a) levels by up to 30% to 40% in a dose-dependent manner and in addition exerts other potential beneficial effects by reducing LDL-C, total cholesterol, triglycerides, and remnant cholesterol and by raising high-density lipoprotein cholesterol (HDL-C); however, the available trials did not show any cardiovascular benefit with niacin administration as an agent to reduce residual risk of increasing high-density lipoprotein cholesterol. Therefore, niacin is not commonly available in many European countries.[2,6,11] New agents, such as cholesteryl ester transfer protein and proprotein convertase subtilisin/kexin type 9 inhibitors, are also very effective; however, they are not still available. In the case of cholesteryl ester transfer protein inhibitors, the studies with torcetrapib, dalcetrapib, and evacetrapib were terminated prematurely and we await the results of the Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib (DEFINE) trial with anacetrapib, which seems to be the most potent agent, both increasing high-density lipoprotein cholesterol by even 140%, and significantly reducing LDL-C and Lp(a).[12,13] Proprotein convertase subtilisin/kexin type 9 inhibitors have been approved by the US Food and Drug Administration and the European Medicines Agency, but due to the lack of reimbursement in most countries as well as the high cost of the therapy they are also still not commonly available.[5,14] Therefore, according to the current recommendations and expert opinions, statins should be considered as a first-line therapy in case of high level of Lp(a), despite their limited efficacy, because such therapy is aimed to reduce overall cardiovascular risk.[2,5,6] There are also other drugs as well as nutraceuticals/functional foods that may be effective in Lp(a) lowering. Within the Lipid and Blood Pressure Meta-analysis Collaboration Group, Kotani et al[15] investigated the effects of tibolone treatment on circulating Lp(a) levels in postmenopausal women through systematic review and meta-analysis of available randomized controlled trials. Meta-analysis of 12 trials suggested a significant reduction of Lp(a) levels following tibolone treatment (weighted mean difference: −25.28%, 95% CI: −36.50, −14.06; $P<0.001$), and the effect remained significant both for the doses <2.5 (−17.00%) and ≥2.5 mg/day (−29.18%), as well as in the subsets of trials with follow-up either <24 (−26.79%) or ≥24 months (−23.10%).[15] The same group has recently evaluated the effect of L-carnitine supplementation on Lp(a) concentrations.[16] The meta-analysis showed a significant reduction of Lp(a) levels following L-carnitine supplementation (weighted mean difference: −8.82 mg/dL, 95% CI: −10.09, −7.55, $P<0.001$), especially when L-carnitine was administrated orally (−9.00 mg/dL) but not intravenously (−2.91 mg/dL).[16] In another meta-analysis from the Lipid and Blood Pressure Meta-analysis Collaboration Group, Serban et al investigated the effect of garlic on Lp(a) concentrations; however, they did not show any effect of garlic supplementation on the reduction of Lp(a) levels.[17]

In conclusion, the available literature supports the predictive value of Lp(a) on CVD outcomes—mainly myocardial infarction, and aortic stenosis. Clinical studies and meta-analysis also suggest that it might be important to predict the risk of AAA, and the present study by Afshar et al[10] further extends the current knowledge suggesting that high Lp(a) might be an important biomarker of premature ACS in young individuals (<55 years), especially with simultaneous high LDL-C levels. Further studies are still required to enable an understanding of all of the aspects of Lp(a) (patho)physiology, its functions, predictive values in different conditions, the "gold standard" method for its measurement, and whether it is possible to reduce the cost of this method to enable its widespread use. We also need to determine the cut-off value for the risk increase (as some studies suggest that the cardiovascular risk might be increased even with Lp(a) values over 25–30 mg/dL[18]), and finally we need to know the most effective methods of therapy for elevated Lp(a) levels. We know so much yet still have much to learn . . .

Disclosures

None.

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